More effective for you, a real alternative for her.

Surgery can be a daunting prospect for her; that's why Philips has designed Sonalleve MR-HIFU. It takes non-invasive MR-HIFU treatment to a new level with advanced planning, real time temperature monitoring and volumetric ablation. This combination of MR and HIFU allows fast and targeted ablation of uterine fibroids. Improve your healthcare services while restoring her balance. Discover how MR-HIFU can benefit both her and you at www.philips.com/Sonalleve.

The Philips Sonalleve MR-HIFU uterine fibroid therapy system is not for sale in North America.
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- Verasonics

**Sponsors:**
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- Electronics & Innovation
- Precision Acoustics
- Sonic Concepts
- JJ&A Instruments

---

**InSightec Advantages By The Numbers**

- 11,000 patients treated worldwide
- 180 physicians use the technology worldwide
- 100 systems installed in 20 countries
- 185 peer reviewed clinical publications
- 30 research centers
- 20 completed global clinical trials
- 10 new indications being treated in clinical research
- 5 indications CE marked
- 5 generations of transducers
- 2 FDA approvals
## Wed April 2

### Pre-Meeting Educational Sessions

<table>
<thead>
<tr>
<th>Time</th>
<th>Clinical Track</th>
<th>Basic Science Track</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 AM</td>
<td>MR-Guided IFU Therapy: Clinical Introduction Young-Sun Kim, MD</td>
<td>Science Primer on Therapeutic Ultrasound: Wave Physics and Bioeffects Vera Khokhlova, PhD and Jean-François Aubry, PhD</td>
</tr>
<tr>
<td>8:30 AM</td>
<td>US IMAGING IN CLINICAL FUS TREATMENTS Shin-ichiro Umemura, MD</td>
<td></td>
</tr>
<tr>
<td>9:00 AM</td>
<td>HiFU for Prostate cancer: Current Status and Future Trends Christian Chaussy, MD</td>
<td>Can We Unleash the Power of Anti-Tumor Immunity Through Thermal/Ultrasound Therapies? Elizabeth Repasky, PhD</td>
</tr>
<tr>
<td>9:30 AM</td>
<td>Tips and Trick for Successful Focused Ultrasound Treatment of Symptomatic Uterine Fibroids Elizabeth Stewart, MD and Gina Hesley, MD</td>
<td>FUS: Principles and Instrumentation Design Kullervo Hynynen, PhD</td>
</tr>
<tr>
<td>10:00 AM</td>
<td>Ultrasonic Imaging in Clinical Focused Ultrasound Treatments Lian Zhang, MD</td>
<td>Delivering the Right Dosage in US Treatments: Measurements and Standards Gail ter Haar, PhD</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>Lunch Provided in the Exhibit Hall</td>
<td></td>
</tr>
<tr>
<td>12:00 PM</td>
<td>HIFU for Emerging Applications-Overview Yael Inbar, MD</td>
<td>Cavitation and its Role in Therapeutic Ultrasound Larry Crum, PhD</td>
</tr>
<tr>
<td>1:00 PM</td>
<td>Treatment of Painful Bone Metastases Using MR Guided High Intensity Focused Ultrasound Pejman Ghanouni, MD</td>
<td>Enabling Targeted Drug Delivery to the BBB Via US-Induced BBB Disruption, and Sonothrombolysis Nathan McDannold, PhD and Stephen Meairs, MD</td>
</tr>
<tr>
<td>3:00 PM</td>
<td>MR Guided Focused Ultrasound for Current Neurosurgical Indications and Future Potential for Other Indications Stephen Monteith, MD</td>
<td>US-Mediated Drug and Gene Delivery Kathy Ferrara, PhD</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>Lithotripsy: State of the Art Robin Cleveland, PhD</td>
<td>Microbubbles as Carrier Systems: Application for Ultrasound-Triggered Drug and Gene Delivery Alexander Klibanov, PhD</td>
</tr>
<tr>
<td>4:30 PM</td>
<td>US Therapy at Low Intensity: Non-Thermal Bioeffects and Biophysics Alfred Yu, PhD</td>
<td></td>
</tr>
<tr>
<td>5:00 PM</td>
<td>Q&amp;A With the Speakers</td>
<td></td>
</tr>
<tr>
<td>6:00 PM</td>
<td>Reception</td>
<td></td>
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</table>

### Thurs April 3

### Scientific Sessions Day 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Scientific Sessions: Prostate</th>
<th>Scientific Sessions: Transducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 AM</td>
<td>Plenary Lecture -- Wady Gedroyc, MD MRgFUS of the Body</td>
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<tr>
<td>9:00 AM</td>
<td>Plenary Lecture -- Jeff Elias, MD Transcranial MRgFUS for the Treatment of Neurologic Disease</td>
<td></td>
</tr>
<tr>
<td>10:00 AM</td>
<td>Scientific Sessions: Clinical Applications and Treatment Assessment Florentine Ballroom I/II</td>
<td>Scientific Sessions: Therapeutic Agent Delivery Florentine Ballroom III/IV</td>
</tr>
<tr>
<td>1:15 PM</td>
<td>Poster Session 1 Roman Ballroom I/II</td>
<td></td>
</tr>
<tr>
<td>2:15 PM</td>
<td>Scientific Sessions: Brain Florentine Ballroom I/II</td>
<td></td>
</tr>
<tr>
<td>3:35 PM</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td>4:00 PM</td>
<td>Scientific Sessions: Transducers Florentine Ballroom III/IV</td>
<td></td>
</tr>
<tr>
<td>5:30 PM</td>
<td>Adjourn</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Fri April 4</td>
<td>Sat April 5</td>
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<tr>
<td></td>
<td><strong>Scientific Sessions Day 2</strong></td>
<td><strong>Scientific Sessions Day 3</strong></td>
</tr>
<tr>
<td>8:30 AM</td>
<td>Announcement of 2014 Lizzi and Fry Award Winners</td>
<td>Announcement of Student Awards</td>
</tr>
<tr>
<td></td>
<td><strong>2013 ISTU Award Plenary Lectures</strong> Pompeian Ballroom</td>
<td><strong>Plenary Lectures: From Basic Science to The Clinical Future</strong> Pompeian Ballroom</td>
</tr>
<tr>
<td>8:40 AM</td>
<td>2013 Lizzi Award Lecture -- Hao Li Liu, Ph.D. FUS BBB Opening and CNS Drug Delivery: An Overview</td>
<td>8:40 AM</td>
</tr>
<tr>
<td></td>
<td>Plenary Lecture -- Mark Dewhirst, D.V.M., Ph.D. Combining Thermosensitive Liposomes with Ultrasound</td>
<td></td>
</tr>
<tr>
<td>9:10 AM</td>
<td>2013 Fry Award Lecture -- Feng Wu, MD Is HIFU Therapy an Emerging Discipline in Medicine?</td>
<td>9:10 AM</td>
</tr>
<tr>
<td></td>
<td>Plenary Lecture -- Willem Mali, M.D., HIFU Amidst other minimal and non-invasive treatments</td>
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</tr>
<tr>
<td>9:40 AM</td>
<td>Coffee Break</td>
<td>9:40 AM</td>
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<tr>
<td></td>
<td>10:10 AM Scientific Sessions: Monitoring Methods Florentine Ballroom I/II</td>
<td>10:10 AM</td>
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<tr>
<td></td>
<td>Scientific Sessions: BBB Opening Florentine Ballroom III/IV</td>
<td>Scientific Sessions: Other Hardware and Systems Florentine Ballroom I/II</td>
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<tr>
<td></td>
<td>10:10 AM Scientific Sessions: Monitoring Methods Florentine Ballroom I/II</td>
<td>Scientific Sessions: Sonothrombolysis and Other Microbubble-Enhanced Therapies Florentine Ballroom III/IV</td>
</tr>
<tr>
<td>12:00 PM</td>
<td>Break for Lunch</td>
<td>11:30 AM</td>
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<tr>
<td></td>
<td>12:00 PM Break for Lunch</td>
<td>12:30</td>
</tr>
<tr>
<td>1:15 PM</td>
<td>Poster Session 2 Roman Ballroom I/II</td>
<td>Adjourn</td>
</tr>
<tr>
<td>2:15 PM</td>
<td>Scientific Sessions: Modeling Florentine Ballroom I/II</td>
<td>Scientific Sessions: Sonoporation Florentine Ballroom II/IV</td>
</tr>
<tr>
<td>3:35 PM</td>
<td>Coffee Break</td>
<td></td>
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<tr>
<td>4:00 PM</td>
<td>Scientific Sessions: Lithotripsy and Histotripsy Florentine Ballroom I/II</td>
<td>Scientific Sessions: Treatment Planning Florentine Ballroom II/IV</td>
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<tr>
<td>5:30 PM</td>
<td>Adjourn</td>
<td></td>
</tr>
<tr>
<td>18:00</td>
<td>Dinner Gala at the Stratosphere</td>
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</tbody>
</table>
Dear ISTU Colleagues and Friends,

It is a great pleasure and privilege to welcome you to the 14\textsuperscript{th} International Symposium on Therapeutic Ultrasound (ISTU’14) in Las Vegas on April 2 – 5, 2014. Our Annual meeting provides an excellent forum for basic scientists, clinicians, and physicists/engineers from industry to meet face-to-face, exchange ideas, and renew friendships. We are proud of the high level of participation by students and young scientists and engineers at this meeting. We hope that our young scientists will take advantage of this meeting to develop their professional networks as they enrich the meeting with their fresh ideas that will define the future of the field.

ISTU continues to attract members from all parts of the world with major participation from Asia, Europe, and North America. Our meeting this year is held in coordination with the AIUM Annual Convention following a very successful experiment in 2011. We believe this will be a beneficial model for the memberships of ISTU and AIUM as well as the larger biomedical ultrasound community. For this first time this year, ISTU’14 will feature a pre-meeting educational day covering physical principles and clinical aspects of therapeutic ultrasound. Dr. Butts-Pauly initiated and planned this meeting with help from Dr. Arik Hananel and Dr. Alfred Yu. The Society is grateful for these efforts and we hope this becomes a permanent feature of ISTU meetings in the future.

Meetings like ISTU’14 are the fruit of volunteer work of many individuals who give generously of their time and energy. ISTU is fortunate to have the outstanding efforts of Dr. Kim Butts Pauly, the ISTU’14 Chair and the Organizing Committee, Dr. Joo-Ha Hwang (Sponsorship/Exhibits Chair), Dr. Jean-Francois Aubry (Student Travel Award Chair), our AIUM support team and many others who continue to work towards a successful completion of ISTU’14.

ISTU’14 promises to be one of our most successful meetings in terms of providing an excellent integration between of basic science, engineering, and clinical practice. The addition of the educational day on April 2 will provide an opportunity for students and practitioners alike to develop a deeper understanding of the physics, bioeffects, and clinical aspects of focused ultrasound. This event is included in the registration fee and outstanding speakers in the field will present the lectures. We encourage you to take advantage of this excellent opportunity.

Finally, we hope that you will enjoy the venue and the other activities including the welcome reception and the ISTU Special Event Dinner. I am looking forward to seeing many of you in Las Vegas.

Emad S Ebbini  
President of the International Society for Therapeutic Ultrasound  
Professor of Electrical and Computer Engineering  
University of Minnesota
Dear Colleagues,

Welcome to the 2014 ISTU Meeting in Las Vegas!

This meeting has been in the planning for over a year. I’d like to thank the many people who helped make it possible. This includes the program committee members, the reviewers, the education course speakers, and the moderators. Thank you all.

In addition, I’d like to thank the AIUM/ISTU office for their contributions, including Jenny Clark, Brenda Kinney, Danielle Delanko, and Angela Marinelli.

Most importantly, I’d like to thank my assistant Kellison Pack who did yeoman’s work pulling together the program book on the very tight schedule.

Please enjoy the meeting, including the Friday party at the Stratosphere, which should be thrilling.

-Kim Butts Pauly

Program Committee

Alfred Yu
Arik Hananel
Beat Werner
Brian Fowlkes
Chris Diederich
Chrit Moonen
Cyril Lafon
Dennis Parker
Emad Ebbini
Feng Wu
Guofeng Shen
Jean-François Aubry
Joo Ha Hwang
Juan Plata
Mike Marx
Nathan McDannold
Patrick Ye
Rachelle Bitton
Ron Watkins
Sham Sokka
Stephen Meairs
Urvi Vyas
Vera Khokhlova
Viola Rieke
Wen-Shiang Chen
Yoichiro Matsumoto
Yufeng Zhou

Reviewers

Adam Maxwell
Adam Shaw
Alfred Yu
Allison Payne
Arik Hananel
Aurea Pascal-Tenorio
Beat Werner
Bradford Wood
Brian Fowlkes
Charles Cain
Chris Diederich
Christy Holland
Chrit Moonen
Chuck Dumoulin
Constantin Coussios
Craig Meyer
Cyril Lafon
David Cranston
Dennis Parker
Doug Christiansen
Eitan Kimmel
Emad Ebbini
Ernst Martin
Feng Wu
Gail Ier Haar
Gerald Harris
Greg Clement
Hao-Li Liu
Jahan Tavakkoli
Jason Stafford
Jean Yves Chapelon
Jean-François Aubry
Joo Ha Hwang
Juan Plata
Kathy Ferrarra
Kullervo Hynynen
Larry Crum
Leonid Gavrilov
Lili Chen
Mario Ries
Mathieu Pernot
Matsumoto Yoichiro
Max Wintermark
Michael Bailey
Michael Canney
Nathan McDannold
Nick Todd
Nico de Jong
Oleg Sapožnikov
Patrick Ye
Rachelle Bitton
Rajiv Chopra
Rares Salomir
Robert Staruch
Robin Cleveland
Ron Watkins
Seung-Schik Yoo
Sham Sokka
Stephen Meairs
Urvi Vyay
Vera Khokhlova
Viola Rieke
Volker Wiikens
Wayne Kreider
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- Enhanced drug delivery study
- Opening the blood brain barrier (BBB)

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Declaration of Financial Interests or Relationships

**Presenter Without Financial Interests or Relationships**

Jean-François Aubry, PhD  
Christian Chaussy, MD  
Robin Cleveland, PhD  
Larry Crum, PhD  
Kathy Ferrara, PhD  
Vera Khokhlova, PhD  
Young-Sun Kim, MD  
Nathan McDonald, PhD  
Stephen Meairs, MD  
Stephen Monteith, MD  
Elizabeth Repasky, PhD  
Gail ter Haar, PhD  
Shin-ichiro Umemura, MD  
Alfred Yu, PhD

**Presenter With Financial Interests or Relationships**

Pejman Ghanouni, MD  
Grants: GE and Insightec

Gina Hesley, MD  
Grants: NIH and Insightec

Alexander Klibanov, PhD  
Grant: Philips and AstraZeneca-UVA; Ownership Interest: Targeson Inc.

Elizabeth Stewart, MD  
Clinical Trial Investigator: InSightec; Consultant: Abbott, Bayer, Gynesonics;  
Royalties: UpToDate, Johns Hopkins University Press

Lian Zhang, MD  
Consulting Fee: Chongqing Haifu

Kullervo Hynynen, PhD: Financial Interests Unknown  
Yael Inbar, MD: Financial Interests Unknown
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<thead>
<tr>
<th>Time</th>
<th>Clinical Applications and Treatment Assessment</th>
<th>Florentine Ballroom I/II</th>
<th>Moderators: Young-Sun Kim &amp; Viola Rieke</th>
<th>Presenters</th>
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</thead>
<tbody>
<tr>
<td>10:00 AM</td>
<td>CYCLOCOAGULATION BY HIFU FOR TREATING GLAUCOMA: MECHANISTIC STUDY IN RABBITS AND RESULTS OF MULTICENTRIC CLINICAL TRIALS IN 52 PATIENTS</td>
<td>CYCLOCOAGULATION BY HIFU FOR TREATING GLAUCOMA: MECHANISTIC STUDY IN RABBITS AND RESULTS OF MULTICENTRIC CLINICAL TRIALS IN 52 PATIENTS</td>
<td>Cyril Lafon</td>
<td></td>
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<tr>
<td>10:10 AM</td>
<td>CLINICAL APPLICATION OF HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION IN GYNECOLOGY: SAFETY ANALYSIS</td>
<td>CLINICAL APPLICATION OF HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION IN GYNECOLOGY: SAFETY ANALYSIS</td>
<td>Lian Zhang</td>
<td></td>
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<tr>
<td>10:30 AM</td>
<td>HIGH INTENSITY FOCUSED ULTRASOUND APPLIED TO THE PLACENTAL UNIT/ PRELIMINARY RESULTS OF AN IN VIVO STUDY</td>
<td>HIGH INTENSITY FOCUSED ULTRASOUND APPLIED TO THE PLACENTAL UNIT/ PRELIMINARY RESULTS OF AN IN VIVO STUDY</td>
<td>David Melodelima</td>
<td></td>
</tr>
<tr>
<td>10:40 AM</td>
<td>IN-OFFICE RAPID VOLUMETRIC ABLATION OF UTERINE FIBROIDS UNDER ULTRASOUND IMAGING GUIDANCE: PRECLINICAL AND EARLY CLINICAL EXPERIENCE WITH THE MIRABILIS TRANSABDOMINAL HIFU TREATMENT SYSTEM</td>
<td>IN-OFFICE RAPID VOLUMETRIC ABLATION OF UTERINE FIBROIDS UNDER ULTRASOUND IMAGING GUIDANCE: PRECLINICAL AND EARLY CLINICAL EXPERIENCE WITH THE MIRABILIS TRANSABDOMINAL HIFU TREATMENT SYSTEM</td>
<td>Jessica Parsons</td>
<td></td>
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<tr>
<td>10:50 AM</td>
<td>TREATMENT OF EXTRA-ABDOMINAL DESMOID TUMORS USING MR GUIDED HIGH INTENSITY FOCUSED ULTRASOUND: PRELIMINARY RESULTS AFTER FIVE PATIENTS</td>
<td>TREATMENT OF EXTRA-ABDOMINAL DESMOID TUMORS USING MR GUIDED HIGH INTENSITY FOCUSED ULTRASOUND: PRELIMINARY RESULTS AFTER FIVE PATIENTS</td>
<td>Pejman Ghanouni</td>
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<tr>
<td>11:00 AM</td>
<td>OSTEOID OSTEOMA: MRGFUS FOR ENTIRELY NON-INVASIVE TREATMENT. A PROSPECTIVE DEVELOPMENTAL STUDY.</td>
<td>OSTEOID OSTEOMA: MRGFUS FOR ENTIRELY NON-INVASIVE TREATMENT. A PROSPECTIVE DEVELOPMENTAL STUDY.</td>
<td>Alessandro Napoli</td>
<td></td>
</tr>
<tr>
<td>11:10 AM</td>
<td>HYPERTHERMIA AND TISSUE ABLATION TREATMENTS IN THE HEAD AND NECK REGION USING MRGHIFU: AN IN VIVO FEASIBILITY STUDY</td>
<td>HYPERTHERMIA AND TISSUE ABLATION TREATMENTS IN THE HEAD AND NECK REGION USING MRGHIFU: AN IN VIVO FEASIBILITY STUDY</td>
<td>Samuel Pichardo</td>
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<tr>
<td>11:20 AM</td>
<td>A FULLY INTEGRATED, REAL TIME 2-D HIFU MONITORING SYSTEM USING HARMONIC MOTION IMAGING FOR FOCUSED ULTRASOUND (HMIFU)</td>
<td>A FULLY INTEGRATED, REAL TIME 2-D HIFU MONITORING SYSTEM USING HARMONIC MOTION IMAGING FOR FOCUSED ULTRASOUND (HMIFU)</td>
<td>Gary Hou</td>
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<tr>
<td>11:30 AM</td>
<td>NON-INVASIVE TISSUE PARAMETER ESTIMATION WITH DUAL-MODE ULTRASOUND ARRAYS.</td>
<td>NON-INVASIVE TISSUE PARAMETER ESTIMATION WITH DUAL-MODE ULTRASOUND ARRAYS.</td>
<td>Alyona Haritonova</td>
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<tr>
<td>11:40 AM</td>
<td>T1RHO MAPPING FOR THE MRI-BASED EVALUATION OF HIGH INTENSITY FOCUSED ULTRASOUND TUMOR TREATMENT</td>
<td>T1RHO MAPPING FOR THE MRI-BASED EVALUATION OF HIGH INTENSITY FOCUSED ULTRASOUND TUMOR TREATMENT</td>
<td>Stefanie Hectors</td>
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<tr>
<td>11:50 AM</td>
<td>MAGNETIC RESONANCE AND HISTOLOGICAL FINDINGS FOLLOWING HIGH INTENSITY FOCUSED ULTRASOUND ABLATION</td>
<td>MAGNETIC RESONANCE AND HISTOLOGICAL FINDINGS FOLLOWING HIGH INTENSITY FOCUSED ULTRASOUND ABLATION</td>
<td>Brett Fite</td>
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**Therapeutic Agent Delivery**

<table>
<thead>
<tr>
<th>Time</th>
<th>Therapeutic Agent Delivery</th>
<th>Florentine Ballroom III/IV</th>
<th>Moderators: Elisa Konofagou &amp; Natasha Rapoport</th>
<th>Presenters</th>
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<tbody>
<tr>
<td>10:00 AM</td>
<td>POTENTIATING THE ANTITUMOR EFFECTS OF CHEMOTHERAPY WITH THE ANTIVASCULAR ACTION OF ULTRASOUND STIMULATED MICROBUBBLES</td>
<td>POTENTIATING THE ANTITUMOR EFFECTS OF CHEMOTHERAPY WITH THE ANTIVASCULAR ACTION OF ULTRASOUND STIMULATED MICROBUBBLES</td>
<td>David Goertz</td>
<td></td>
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<tr>
<td>10:10 AM</td>
<td>HYPERTHERMIA TRIGGERED DRUG DELIVERY IN A PANCREATIC CANCER MOUSE MODEL USING MR-GUIDED FOCUSED ULTRASOUND</td>
<td>HYPERTHERMIA TRIGGERED DRUG DELIVERY IN A PANCREATIC CANCER MOUSE MODEL USING MR-GUIDED FOCUSED ULTRASOUND</td>
<td>Navid Farr</td>
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<tr>
<td>10:20 AM</td>
<td>LOW-INTENSITY CONTINUOUS ULTRASOUND AND A CLINICAL DOSING REGIMEN OF Zoledronate PRODUCE ANTITUMOR EFFECTS IN MOUSE MODELS OF BREAST TUMOR XENOGRAFT AND BONE METASTASIS.</td>
<td>LOW-INTENSITY CONTINUOUS ULTRASOUND AND A CLINICAL DOSING REGIMEN OF Zoledronate PRODUCE ANTITUMOR EFFECTS IN MOUSE MODELS OF BREAST TUMOR XENOGRAFT AND BONE METASTASIS.</td>
<td>Sophie Tardoski</td>
<td></td>
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<tr>
<td>10:30 AM</td>
<td>MAGNETIC ALBUMIN-SHELLED PERFLUOROCARBON MICROBUBBLES AS MULTIFUNCTIONAL ULTRASOUND/MRI AND DRUG DELIVERY AGENTS</td>
<td>MAGNETIC ALBUMIN-SHELLED PERFLUOROCARBON MICROBUBBLES AS MULTIFUNCTIONAL ULTRASOUND/MRI AND DRUG DELIVERY AGENTS</td>
<td>Juntu</td>
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<tr>
<td>10:40 AM</td>
<td>ENHANCED ACCUMULATION OF CU-DOXORUBICIN NANOPARTICLES WITH MR GUIDED FOCUSED ULTRASOUND THERMAL ABLATION</td>
<td>ENHANCED ACCUMULATION OF CU-DOXORUBICIN NANOPARTICLES WITH MR GUIDED FOCUSED ULTRASOUND THERMAL ABLATION</td>
<td>Andrew Wong</td>
<td></td>
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<tr>
<td>10:50 AM</td>
<td>A NEW GOLD-NANOPARTICLE-BASED COATING TO ENHANCE ULTRASOUND-MEDIATED DELIVERY OF NANOMEDICINES TO TUMOURS</td>
<td>A NEW GOLD-NANOPARTICLE-BASED COATING TO ENHANCE ULTRASOUND-MEDIATED DELIVERY OF NANOMEDICINES TO TUMOURS</td>
<td>Constantin Coussios</td>
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<tr>
<td>11:00 AM</td>
<td>ULTRASOUND AND MICROBUBBLES DIRECTED GENE DELIVERY OF FACTOR IX PLASMID FOR HEMOPHILIA B THERAPY</td>
<td>ULTRASOUND AND MICROBUBBLES DIRECTED GENE DELIVERY OF FACTOR IX PLASMID FOR HEMOPHILIA B THERAPY</td>
<td>Shuxian Song</td>
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<tr>
<td>11:10 AM</td>
<td>IBUPROFEN AND ETANERCEPT (TNFA RECEPTOR PROTEIN) INTERFERES WITH THE ENHANCED TARGETED MESENCHYMAL STEM CELL HOMING INDUCED BY PULSED FUS (PFUS): IMPLICATIONS FOR CELL THERAPY</td>
<td>IBUPROFEN AND ETANERCEPT (TNFA RECEPTOR PROTEIN) INTERFERES WITH THE ENHANCED TARGETED MESENCHYMAL STEM CELL HOMING INDUCED BY PULSED FUS (PFUS): IMPLICATIONS FOR CELL THERAPY</td>
<td>Joseph Frank</td>
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<tr>
<td>11:20 AM</td>
<td>ULTRASOUND-TRIGGERED REGULATION OF BLOOD GLUCOSE LEVELS USING INJECTABLE NANO-NETWORK</td>
<td>ULTRASOUND-TRIGGERED REGULATION OF BLOOD GLUCOSE LEVELS USING INJECTABLE NANO-NETWORK</td>
<td>Jin Di</td>
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<tr>
<td>11:30 AM</td>
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<td>IN VIVO CAVITATION ENHANCED DELIVERY OF DOXORUBICIN IN MOUSE PANCREATIC TUMORS</td>
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### Sonothrombolyis and Other Microbubble-Enhanced Therapies

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High-intensity focused ultrasound (HIFU) therapy induces temperature elevation of the target tissue by focusing ultrasound waves with high energy into a small spot. Temperature can be elevated to the degree where the target tissue is immediately necrotized (i.e., ablation therapy), or where the target tissue gets susceptible to chemo-radiation therapy or the low temperature-sensitive liposome vehicle releases its drug contents (i.e., mild hyperthermia). Because ultrasound waves are propagated through the body, HIFU therapy can be performed in a completely non-invasive way, which provides a great clinical benefit. In clinical applications, HIFU therapy is guided and monitored by either ultrasonography (US) or magnetic resonance (MR) imaging. As compared to US-guidance, MR-guided HIFU therapy has merits in terms of a capability of MR thermometry and the better image quality which are likely to contribute to more efficient and safer treatment. However, MRI is inferior to US in terms of cost effectiveness. Determination of guiding modality between US and MR should be made based on clinical weighting of its advantages and disadvantages in the specific organ targeted. Clinical applications of HIFU therapy have the longest history in the treatment of uterine fibroids and the prostate cancer, and its indications are being widened. MR-guidance is already actively used for treating the diseases of the uterus, the bone, the prostate gland, the breast and the brain, or is under investigation for being used for the diseases of the liver, the kidney and the pancreas. Clinically-available MR-guided HIFU systems are adopting either point-by-point sonication technique or volumetric sonication technique. Whereas volumetric ablation technique is known to be able to treat more volume within a given time owing to its mechanism of action, the risk of causing near field thermal injury (such as skin burn) is also increased. Stable monitoring of the temperature at the target tissue is an essential part of mild hyperthermia therapy, therefore MR-guided HIFU seems to be the only solution for this purpose. Volumetric ablation technique is more favorable for inducing localized mild hyperthermia than point-by-point technique. In this presentation, the basic principles of HIFU therapy as well as MR monitoring technology which are necessary for clinicians to understand this therapeutic modality will be introduced, and the clinical applications of MR-HIFU ablation therapy will be overviewed. In addition, a potential clinical use of localized mild hyperthermia by MR-HIFU will also be discussed.

- Principles of HIFU therapy
- MRI in HIFU therapy
  - Roles of MRI
  - MR thermometry
  - MR-ARFI
- Clinical MR-HIFU therapy
  - Ablation therapy
  - Localized mild hyperthermia
- Conclusion
8:30 AM
ULTRASONIC IMAGING IN CLINICAL FOCUSED ULTRASOUND TREATMENTS
Shin-ichiro Umemura
Biomedical Engineering, Tohoku University, Sendai, Miyagi, Japan.

Ultrasonic imaging in ultrasound guided HIFU (high intensity focused ultrasound) treatment has two roles: 1) aiming the target tissue and 2) monitoring the tissue change. In the roll of aiming, ultrasound has an advantage over other imaging modalities such as MRI, in that both imaging beam and therapeutic beam reflect in a similar way under a nonuniformity of sound speed and therefore the aiming is self-adjusted. In addition to this, ultrasonic imaging is real time, compact, and affordable. Ultrasonic imaging is inferior to other imaging modalities in whole-body scale imaging, but technologies to navigate ultrasonic imaging using 3D X-ray or MRI image taken prior to the treatment are available. The change in tissue should be monitored both in the HIFU focal zone and in its outside. It should be monitored for the efficacy of the treatment in the focal zone, and for preventing potential adverse effects in its outside. MRI is superior to ultrasound imaging in monitoring unwanted hot spots outside the focal zone, but ultrasound imaging is superior to MRI in detecting unwanted cavitation events outside the focal zone. B-mode ultrasonic imaging can detect boiling in the focal zone in real time although MRI is superior to ultrasonic imaging in measuring the temperature rise in the focal zone. In a typical ultrasound guided HIFU treatment of prostate tumor, HIFU intensity and exposure time is adjusted so that boiling is slightly detected at the focal point [1]. The space between the focal points of consecutive two exposures is set so that the resulting two coagulation volumes should make a contiguous volume. Researches and developments are underway to ultrasonically detect the tissue change due to thermal coagulation [2,3], which occurs at much lower temperature than boiling. Ultrasonic backscatter significantly changes during tissue coagulation [4] although the change is too small to be detected by conventional B-mode imaging. Ultrasonic detection of the shear strain induced by ARFI (acoustic radiation force impulse) can be a powerful tool to detect the result of tissue coagulation [5]. The changes in absorption as well as speed of sound also have a potential to be used to detect temperature rise due to HIFU exposure. [6] These researches and developments will enhance the efficacy, efficiency, and safety of ultrasound guided HIFU treatments in clinics in the near future.

9:00 AM
HIFU FOR PROSTATE CANCER: CURRENT STATUS AND FUTURE TRENDS
Christian G Chaussy 1, 3, Stefan J.M. Thueroff 2, 3
1. Urology, University Regensburg, Regensburg, Germany. 2. Urology, Harlaching Hospital, Munich, Germany. 3. Harlaching Krebshilfe, Munich, Germany.

Over the past 25 years, the average life expectancy for men has increased almost 4 years, and the age of prostate cancer detection has decreased an average of 10 years with diagnosis increasingly made at early-stage disease where curative therapy is possible. These changing trends in the age and extent of malignancy at diagnosis have revealed limitations in conventional curative therapies for prostate cancer, including a significant risk of aggressive cancer recurrence, and the risk of long-term genitourinary morbidity and its detrimental impact on patient quality of life (QOL). Greater awareness of the shortcomings in radical prostatectomy, external radiotherapy and brachytherapy have prompted the search for alternative curative therapies that offer comparable rates of cancer control and less treatment-related morbidity to better preserve QOL. High intensity focused ultrasound (HIFU) possesses characteristics that make it an attractive curative therapy option. HIFU is a non-invasive approach that uses precisely-delivered ultrasound energy to achieve tumor cell necrosis without radiation or surgical excision. In current urological oncology, HIFU is used clinically in the treatment of prostate cancer, and is under experimental investigation for therapeutic use in renal and breast malignancies. Clinical research on HIFU therapy for localized prostate cancer began in the 1990s, and there have now been approximately 30,000 prostate cancer patients treated with HIFU, predominantly with the Ablatherm (EDAP TMS, Lyon, France) device. Transurethral resection of the prostate (TURP) has been combined with HIFU since 2000 to reduce prostate size, facilitate tissue destruction, and to minimize side effects. Advances in imaging technologies are expected to further improve the already superior efficacy and morbidity outcomes, and ongoing investigation of HIFU as a focal therapy and in salvage and palliative indications are serving to expand the role of HIFU as a highly versatile non-invasive therapy for prostate cancer.
TIPS AND TRICK FOR SUCCESSFUL FOCUSED ULTRASOUND TREATMENT OF SYMPTOMATIC UTERINE FIBROIDS
Gina Hesley 2, Elizabeth Stewart 1

Targeting uterine fibroids with any therapy is challenging. First the size range of fibroids is more extreme than in most other lesions; symptomatic disease can range from a centimeter in size to over 20 cms. Additionally there can be a single dominant fibroid or dozens of individual lesions. There is also considerable symptomatic variability. Women can have isolated heavy menstrual bleeding (HMB), complaints related to the size and the position of the fibroids (including abdominal distention, urinary frequency, bowel dysfunction and pelvic pain) or both. Finally the point in a woman’s reproductive lifespan where she requires therapy affects the treatment plan, especially her plans for future pregnancy and her proximity to menopause. There is increasing data that clinical variables affect outcomes of MRgFUS. This talk will discuss the published literature on this topic and place it in the context of other minimally invasive fibroid therapies including endoscopic myomectomy, uterine artery embolization and laparoscopic RF ablation. In addition, specifics on how to maximize focused ultrasound treatment will be discussed. Imaging features of fibroids including signal intensity, heterogeneity, and enhancement all play a role in how to plan treatment. Characteristics of fibroids ideal for treatment as well as tips on how to maximize treatment effect in patients who have challenging fibroid characteristics or intervening bowel or scars will be presented.

References
11:00 AM
ULTRASONIC IMAGING IN CLINICAL FOCUSED ULTRASOUND TREATMENTS
Lian Zhang 1, 2
1. Clinical Center for Tumor Therapy of 2nd Hospital, Chongqing Medical University, Chongqing, China. 2. State Key Laboratory, College of Biomedical Engineering, Chongqing Medical University, Chongqing, China.

Ultrasonic imaging in ultrasound guided HIFU (high intensity focused ultrasound) treatment has two roles: 1) aiming the target tissue and 2) monitoring the tissue change. In the role of aiming, ultrasound has an advantage over other imaging modalities such as MRI, in that both imaging beam and therapeutic beam reflect in a similar way under a nonuniformity of sound speed and therefore the aiming is self-adjusted. In addition to this, ultrasonic imaging is real time, compact, and affordable. Ultrasonic imaging is inferior to other imaging modalities in whole-body scale imaging, but technologies to navigate ultrasonic imaging using 3D X-ray or MRI image taken prior to the treatment are available. The change in tissue should be monitored both in the HIFU focal zone and in its outside. It should be monitored for the efficacy of the treatment in the focal zone, and for preventing potential adverse effects in its outside. MRI is superior to ultrasound imaging in monitoring unwanted hot spots outside the focal zone, but ultrasound imaging is superior to MRI in detecting unwanted cavitation events outside the focal zone. B-mode ultrasonic imaging can detect boiling in the focal zone in real time although MRI is superior to ultrasonic imaging in measuring the temperature rise in the focal zone. In a typical ultrasound guided HIFU treatment of prostate tumor, HIFU intensity and exposure time is adjusted so that boiling is slightly detected at the focal point [1]. The space between the focal points of consecutive two exposures is set so that the resulting two coagulation volumes should make a contiguous volume. Researches and developments are underway to ultrasonically detect the tissue change due to thermal coagulation [2,3], which occurs at much lower temperature than boiling. Ultrasonic backscatter significantly changes during tissue coagulation [4] although the change is too small to be detected by conventional B-mode imaging. Ultrasonic detection of the shear strain induced by ARFI (acoustic radiation force impulse) can be a powerful tool to detect the result of tissue coagulation [5]. The changes in absorption as well as speed of sound also have a potential to be used to detect temperature rise due to HIFU exposure. [6] These researches and developments will enhance the efficacy, efficiency, and safety of ultrasound guided HIFU treatments in clinics in the near future.

1:00 PM
HIFU FOR EMERGING APPLICATIONS-OVERVIEW
Yael Inbar
Diagnostic Imaging, Sheba Medical Center, Ramat-Gan, Israel.

HIFU is a promising non-invasive therapy for prostate and liver cancer, symptomatic uterine fibroids, painful bone metastasis and functional neurosurgery. However, over the years, HIFU has been evaluated as a potential therapy for other indications that are either at an earlier stage of research or are less common and known. These indications will be covered in this talk. The information presented will be based on survey of recent literature and input received from relevant device manufactures. I'll be reviewing the current technological aspects as well as the clinical state of HIFU for the treatment of breast cancer and breast fibroadenoma, pancreatic and kidney cancer, benign thyroid nodules, hyperparathyroidism, hypertension, glaucoma, back pain, osteoarthritis and osteoid osteoma. Once session is over participants are expected to have a firm grasp of the high level clinical and technological status of HIFU treatment for the discussed indications.
2:00 PM
TREATMENT OF PAINFUL BONE METASTASES USING MR GUIDED HIGH INTENSITY FOCUSED ULTRASOUND
Pejman Ghanouni
Radiology, Stanford University, Stanford, CA, United States.

Bone metastases in patients with advanced cancer are a common cause of cancer-related pain and diminished quality of life. Standard therapies, including radiation, systemic chemotherapy, and analgesics, do not relieve pain in a up to one-third of patients. MR guided high intensity focused ultrasound provides a means of precise localized tumor treatment, and has been approved by the FDA for the palliation of painful bone metastases.

The goals of this session are to:
- review the results of the Phase 3 randomized controlled trial using MR guided focused ultrasound to treat bone metastases that led to FDA approval.
- discuss clinical criteria for patient selection for this treatment using case examples
- describe the treatment process, including screening, treatment planning, treatment, and post-treatment imaging
- correlate typical patient post-procedural outcomes with imaging findings seen after treatment
- present practical examples of the risks and benefits of the procedure
MR Guided Focused Ultrasound is a rapidly emerging field in neurosurgery. Focused Ultrasound has the potential to treat a range of neurological conditions that are traditionally treated with invasive surgical therapies. The number of neurological conditions that have now been treated successfully with MRgFUS continues to expand. Transcranial MRgFUS has now been used in the treatment of movement disorders (Parkinson’s disease and essential tremor), and the treatment of chronic pain. The treatment of OCD and metastatic brain tumors are now in clinical trials.

The combination of high quality MR imaging and the latest transcranial transducer technology lends itself to many intracranial applications that have not yet been explored in clinical trials. This session will discuss the unmet clinical needs in the intracranial space which MRgFUS has the potential to address in the future. Some of these disorders include benign brain tumors, neuro-endocrine disease, epilepsy, hydrocephalus, ischemic and hemorrhagic stroke, and psychiatric disorders. Obstacles and limitations with existing technology will be discussed as well as some of the unique ways in which MRgFUS may be used in the future to augment neurosurgical practice.
4:00 PM
LITHOTRIPSY: STATE OF THE ART
Robin Cleveland
Engineering Science, University of Oxford, Oxford, United Kingdom.

Shock wave lithotripsy (SWL) is a clinical procedure whereby shock waves, generated outside the body, are used to break-up kidney stones. First introduced in 1980 it revolutionized the treatment of renal calculi and at it is still the first line modality for treating kidney stones in the UK. Despite its widespread use it is recognized that a clinical dose of shock waves will induce renal injury in most, if not all, treated kidneys. This talk will address the underlying physics of lithotripsy and discuss the current understanding as to how shock waves fragment kidney stones and produce tissue damage. Based on analysis of the physics methods by which shock waves can be delivered that enhance stone fragmentation and limit tissue damage will be described. The talk will conclude with emerging technology for improving lithotripsy, such as using HIFU to expel remaining fragments and a combination of HIFU and shock waves to accelerate shock wave damage.
8:00 AM
SCIENCE PRIMER ON THERAPEUTIC ULTRASOUND: WAVE PHYSICS AND BIOEFFECTS
Vera Khokhlova 1, 2, Jean-François Aubry 3, 4
1. Department of Acoustics, Faculty of Physics, Moscow State University, Moscow, Russian Federation. 2. Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, WA, United States. 3. Institut Langevin, ESPCI ParisTech, CNRS, INSERM, Paris, France. 4. Department of Radiation Oncology, University of Virginia, Charlottesville, VA, United States.

Therapeutic Ultrasound is currently emerging into many clinical applications. Major developments include the use of High Intensity Focused Ultrasound for treating tumors, neurological diseases, acoustic haemostasis and thrombolysis, targeted drug and gene delivery, nerve and brain stimulation. Other high pressure ultrasound-based therapies as lithotripsy and shock wave therapies utilize single shock pulses for stone comminution and tissue revascularisation. New low intensity treatments are used for healing of bone fractures and joints. Biological and therapeutic effects of ultrasound are determined in the first place by the in situ ultrasound field parameters. Understanding wave propagation effects in tissue, developing methods to predict in situ pressures from characterization measurements in water for medical devices, and physical mechanisms of ultrasound interaction with tissue that result in specific bioeffects are therefore critical initial steps in successful development of therapeutic ultrasound. Correspondingly, this lecture is divided into three parts. Basic ultrasound wave phenomena are considered first in water where calibration measurements are typically carried out. Acoustic quantities that are used as metrics of therapeutic fields are introduced. Wave propagation models, methods of calculating acoustic pressure distributions, and typical ultrasound fields generated by HIFU medical transducers are overviewed. Setting a boundary condition to the modelling using measurements for a specific transducer is discussed. The effects of diffraction, focusing, and nonlinear propagation on the maximum values of ultrasound field parameters and their spatial distributions in water are shown. Physical effects of ultrasound propagation and interaction with soft biological tissue are overviewed next. Acoustic properties of different tissues are discussed: sound velocity, attenuation, absorption, scattering, and nonlinearity. Propagation of longitudinal waves is considered in detail; however some properties of shear waves are also presented. Major wave phenomena responsible for different biological effects in tissue are discussed introduced: acoustic energy attenuation and absorption, acoustic radiation force and streaming, nonlinear propagation, formation of shocks and enhanced tissue heating. Reflection and scattering from soft tissue layers and inhomogeneities are considered as well as the effects of strong obstacles like skull bones and ribs. Ultrasound-induced bioeffects are presented in the third part of the lecture. Thermal ablation of tissue, which is a major approach in current HIFU technologies, is overviewed. The concept of thermal dose is introduced. Thermal ablation of tissue caused by interaction of microsecond-long shock pulses with cavitation clouds (histotripsy) or by millisecond-long shock wave pulses with boiling bubbles induced by shock wave heating (boiling histotripsy) is presented. Thermal and cavitation effects and typical ultrasound field parameters for approaches that involve the use of contrast agents, nanoparticles, and nanoemulsions, are given. Optimal choice of ultrasound frequency based on frequency dependence of attenuation and cavitation thresholds are discussed for particular therapeutic applications. Diagram of a typical HIFU therapy configuration; vibrational pattern of a therapeutic transducer, reconstructed experimentally using acoustic holography, to be used as an input to modeling; transmission of ultrasound energy through intercostal spaces between ribs using a multi-element array with special modulation of amplitude and phase of its elements; different HIFU induced bioeffects: a purely thermal lesion, a thermal lesion with vaporized cavities caused by HIFU-induced boiling, and a mechanically fragmented lesion.
9:00 AM
CAN WE UNLEASH THE POWER OF ANTI-TUMOR IMMUNITY THROUGH THERMAL/ULTRASOUND THERAPIES?
Elizabeth A. Repasky
Immunology, Roswell Park Cancer Institute, Buffalo, NY, United States.

The goal of this educational session is to summarize some recent discoveries in cancer immunology and use this information to examine the immunological and clinical rationale for combination therapies involving HIFU (or ionizing radiation) and immunotherapy. This summary will include a discussion of concepts such as “cancer immunoediting” and “immune evasion” as well as research which has defined some of the major cellular players in tumor immunity. The typical treatment protocol for high-intensity focused ultrasound (HIFU) aims to produce a localized thermal lesion to eliminate the tumor mass. However, evidence is accumulating suggesting that, similar to ionizing radiation, ultrasound can act “systemically” by triggering potentially useful changes in the environment of tumors that stimulate various arms of a complex network of interacting cells and soluble factors that comprise tumor immunity. Some of these effects derive from inflammatory signals which occur following HIFU and from in situ activation of macrophages and antigen presenting cells that can infiltrate the dying tumor mass where newly released tumor antigens may be available. These and other pre-clinical data strongly suggest the exciting possibility that HIFU can potentiate the efficacy of immunotherapy. Data will be presented that reveals the existence of a dynamic balance between pro-tumorigenic (immunosuppressive) cells and anti-tumor effector cells that ultimately shapes the outcome of cytotoxic therapy. This information will be used to identify the rationale for new clinical trials which aim to combine immunotherapy with HIFU or ionizing radiation.
10:00 AM
FUS: PRINCIPLES AND INSTRUMENTATION DESIGN
Kullervo Hynynen
Physical Sciences, Sunnybrook Research Institute, Toronto, ON, Canada.

Abstract Unavailable.
11:00 AM
DELIVERING THE RIGHT DOSAGE IN US TREATMENTS: MEASUREMENTS AND STANDARDS
Gail ter Haar
Division of Radiotherapy & Imaging, The Institute of Cancer Research, London, United Kingdom.

The widespread acceptance of any promising new medical therapy will depend to some extent on the accuracy and reproducibility with which a treatment can be delivered. In order to ensure the high quality of ultrasound treatments it is thus necessary to establish standardised measurement methods and protocols for characterisation of acoustic fields. This will allow comparison of treatments not only between different patients in one hospital, but also between clinical sites. These measurements are also essential if therapeutic effects are to be correlated with exposure conditions. The field of ultrasound therapy suffers from a lack of a true dosimetric parameter, with treatments being described in terms of the acoustic power emitted by the therapy source, or some measure of pressure intensity, usually measured under free field conditions in water. None of these approaches informs the clinicians directly about the associated biological effect in tissue. Unlike other energy forms, ultrasound produces cell killing by two distinct principle mechanisms: cavitation and heating. While dose parameters have been proposed for each mechanism, there has been no attempt to combine these into a single unit. The high power, tightly focused fields used in High Intensity Focused Ultrasound (HIFU) present a number of measurement challenges. For example, the increased probability of the occurrence of acoustic cavitation in regions of high negative pressure amplitude means that many of the small sensors used for mapping pressure fields cannot be used in a beam’s focus without the risk of their irreversible damage. Rapid quality assurance (QA) techniques that have been used include test objects capable of measuring temperature at the focal peak using a temperature sensor implanted in a phantom material and a rapid beam visualisation method based on acoustically induced optical diffraction. For more detailed calibration, automated beamplotting and calorimetry systems are used for pressure field and acoustic power output measurements, respectively. Calibrated membrane, fibre optic and needle hydrophones are used for measuring pressure distributions. Phase measurement techniques have been developed to verify the correct angular alignment of the HIFU beam. Acoustic power measurements can be performed using a combined radiation force and “buoyancy” method which involves measuring the apparent weight change of a castor oil target which is expanded due to heating from ultrasound energy absorption. Focal peak intensities can be inferred from the total power. There is an international effort to produce standards for the measurement of high intensity therapy ultrasound (HITU). This work is carried out through the International Electrotechnical Commission (IEC). In this lecture, existing dose parameters will be discussed, as will methods for characterising ultrasound exposures and for calibrating therapeutic devices used in the clinic. Finally, the standards that exist, or are in development will be introduced.
CAVITATION AND ITS ROLE IN THERAPEUTIC ULTRASOUND

Larry Crum
Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, Seattle, WA, United States.

Therapeutic ultrasound, by its very nature, usually involves acoustic intensities considered to be relatively high, and thus acoustic cavitation can be produced. Cavitation is the generation of gas and/or vapor filled cavities in the liquid/tissue due to the high negative acoustic pressures amplitudes. Once such a cavity is created, and driven into violent pulsations, significant mechanical forces are generated that can disrupt tissues and induce measurable local damage. Thus, in many cases, cavitation is to be avoided, and techniques have been developed to detect the presence of cavitation by a variety of means. On the other hand, often it is desirable to have a strong mechanical force that would disrupt the local tissue environment; e.g., to disrupt the blood-brain barrier. In these cases, techniques have been developed that permit the enhancement of cavitation, and in some cases, even to control its effects. In this lecture, a brief review of the physics of acoustic cavitation will be given, followed by a description of measurement techniques to detect its presence. Examples also will be given of cases where it is to be avoided, and cases in which it is essential to the therapeutic effect desired.
ENABLING TARGETED DRUG DELIVERY TO THE BRAIN VIA ULTRASOUND-INDUCED BLOOD-BRAIN BARRIER DISRUPTION
Nathan McDannold
Radiology, Brigham and Women's Hospital, Boston, MA, United States.

The physiology of the vasculature in the central nervous system (CNS), which includes the blood-brain barrier (BBB) and other factors, complicates the delivery of most drugs to the brain. Different methods have been used to bypass the BBB, but they have limitations such as being invasive, non-targeted or requiring the formulation of new drugs. Focused ultrasound (FUS), when combined with circulating microbubbles, is a noninvasive method to locally and transiently disrupt the BBB at discrete targets. This review will provide insight on the current status of this unique drug delivery technique, experience in preclinical models, and potential for clinical translation. If translated to humans, this method would offer a flexible means to target therapeutics to desired points or volumes in the brain, and enable the whole arsenal of drugs in the CNS that are currently prevented by the BBB.

SONOTHROMBOLYSIS
Stephen Meairs
Neurology, Heidelberg University, Mannheim, Germany.

Ultrasound applied as an adjunct to thrombolytic therapy improves recanalization of occluded vessels and microbubbles can amplify this effect. New data suggests that the combination of ultrasound and microbubbles without t-PA may achieve recanalization with less risk of hemorrhage. Further possibilities are specific targeting of thrombus with immunobubbles, as well as local drug delivery with ultrasound-sensitive liposomes. Clinical studies support the use of ultrasound for therapy of ischemic stroke, and first trials of enhancing sonothrombolysis with microbubbles have been encouraging. One emerging clinical application is sonothrombolysis of intracranial hemorrhages for clot evacuation. Ultrasound and microbubbles may also improve flow to the microcirculation irrespective of recanalization, thus opening new opportunities for application of sonothrombolysis in acute ischemic stroke. Understanding the mechanisms of therapeutic action and relating this knowledge to issues of efficacy and safety are important objectives of ongoing research. This course will discuss the translational capacities of in vitro studies and preclinical research, and attempt to elucidate the merits and pitfalls of various models used in sonothrombolysis research.
3:00 PM
US-MEDIATED DRUG AND GENE DELIVERY
Katherine W Ferrara
Biomedical Engineering, UC Davis, Davis, CA, United States.

Our objective in this presentation is to explore the mechanisms and technologies that are exploited to enhance drug and gene delivery with ultrasound. Physical mechanisms including cavitation, radiation force and hyperthermia can alter the local concentration of the drug or gene or enhance transport across the vascular surface and cell membrane. Delivery can also be enhanced by molecular targeting, particularly using a ligand that increases cellular internalization. In addition, we will describe the technologies for guiding and assessing delivery, including direct imaging of the therapeutic cargo with positron emission tomography or optical imaging, temperature estimation and control, imaging of the mechanical properties of tissue and imaging of tissue perfusion. Finally, we will summarize the delivery vehicle technologies that are showing promise for improving therapeutic efficacy.

We will demonstrate that ultrasound can effectively increase drug and gene delivery.

We conclude with future applications of these technologies.
Microbubble contrast agents are rapidly becoming established as intravascular tools for the localized deposition of acoustic energy. In response to the ultrasound wave application, microbubbles compress and expand and thus locally deposit ultrasound energy in proximity to the microbubble surface. Typical microbubble design includes a thin flexible shell (typically, a monomolecular layer, several nm thick) that entraps a low-solubility fluorinated gas, most often a perfluorocarbon. Microbubble preparations can be very stable on storage, sometimes for several years. However, circulation time of microbubbles in the bloodstream is short (minutes): gas diffuses out through the thin shell and is exhaled via the lungs, resulting in the bubble collapse and loss of the acoustic activity. Microbubbles are already applied as blood pool contrast agents for clinical ultrasound imaging, both in cardiology and radiology, so it may be practical to expand their use in therapy. Microbubbles can be co-administered with a drug or a drug carrier (a liposome or another nanoparticle). Ultrasound action on the microbubbles in the vasculature of the insonated tissue results in the enhanced drug delivery to the endothelial cells that cover the vessel wall. Insonation also leads to the increased permeability of the endothelial lining, for a period up to hours. Thus, circulating drug or a drug carrier can exit the bloodstream in this high-permeability area, and accumulate in the interstitial space, for enhanced therapeutic action.

Even more interesting is to associate the drug with the microbubbles, so that drug release from the microbubble due to ultrasound action can occur close to the vessel wall, and the drug concentration by the endothelial layer is high. The drug can be retained in the microbubble shell by hydrophobic interaction (that only works for hydrophobic drugs, e.g., paclitaxel or rapamycin). Genetic material can be attached to the shell by electrostatic forces. Hydrophilic drugs (doxorubicin, or enzyme therapeutics) that cannot be part of a shell are instead entrapped inside the liposome inner core. Liposomes are placed on the bubble shell, e.g., by a specific streptavidin-biotin linkage. Thus a pendant microparticle structure is created: each particle complex can carry up to a picogram of a drug in the bubble-associated liposomes. Microbubbles and microbubble complexes can be targeted to the vascular endothelium markers of disease, e.g., in the areas of angiogenesis or inflammation, via antibodies (e.g., anti-VCAM-1). Upon ultrasound action, the bubble is destroyed, and drugs, nucleic acid therapeutics or the drug-liposome complexes are released. They can be embedded in the vessel wall, creating a drug depot; some of the entrapped drug is also released from liposomes into the surrounding medium, so that the therapeutic action can be enhanced locally. Overall, drug and gene delivery can be selectively enhanced by ultrasound action. Development of the novel generation of carrier system may lead to a new generation of targeted personalized treatments with the improved therapeutic index, lower toxicity and better efficacy.
4:30 PM
ULTRASOUND THERAPY AT LOW INTENSITY: NON-THERMAL BIOEFFECTS AND BIOPHYSICS
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The therapeutic applicability of ultrasound is perhaps well demonstrated with the advent of high-intensity focused ultrasound (HIFU) that works by rapidly heating tissues to induce ablation. Ultrasound also holds tremendous therapeutic potential at low intensities that are near or below the clinical diagnosis limit (720 mW/cm² spatial-peak time-averaged intensity, as set forth by FDA), presumably acting through a mechanical interaction pathway. This talk shall present the non-thermal wave-matter interactions of low-intensity ultrasound and how they can be harnessed for therapeutic applications. The biophysical interactions between low-intensity ultrasound and living cells will first be demonstrated through a series of direct observations acquired using live optical and confocal microscopy tools. In particular, findings will be shown on how low-intensity ultrasound pulsing would give to a dynamic course of cytomechanical perturbations at both the membrane and nucleus levels. Next, the associated downstream bioeffects will be highlighted by reviewing various bioassay results reported in the literature. One particular phenomenon that will be described is that, if applied on the order of minutes, low-intensity ultrasound pulsing would reversibly perturb the physical and subcellular structures of living cells. We shall show how low-intensity ultrasound would induce temporary cell size reduction that would recover after the end of ultrasound exposure. These morphological changes are volumetric in nature, and the nucleus is concomitantly contracted over the process. Unlike HIFU where the biological outcome is typically instant cell death, low-intensity ultrasound may induce stimulatory outcome in the long run, even though the short-term impact may be morphologically suppressive. To strengthen our current scientific understanding on this topic, it would be vital to pursue further interdisciplinary investigations that seek to unify the physical principles of ultrasound with current knowledge in mechanobiology.
8:30 AM
MR GUIDED FOCUSED ULTRASOUND OF THE BODY
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The largest area of FUS application has been of uterine fibroids. These benign tumours are extremely common and responsible for huge expenditure each year. FUS can provide a completely non-invasive way of treating women with fibroids in an outpatient manner with negligible complications and very minor post-operative pain. Selecting appropriate patients is vital and will be discussed together with methods of assessing success. Improved technology can now speed up fibroid treatment with ablation spots up to 7 cm in length that can be rapidly moved from one point to another minimizing heating in front of the focal spot whilst treating multiple areas. Current follow-up studies suggest that if a nonperfused volume of greater than 60% is achieved symptomatic response is well over 80% at one year and that the requirement for further fibroid related treatment is 11% at two years. Because of the outpatient non-invasive nature of the procedure FUS becomes a highly cost-effective method for the treatment of fibroids with no requirement for inpatient stays on need for open surgery. Percutaneous destruction of liver tumours in a completely non-invasive manner would change therapy to the liver radically. MRgFUS holds out such a prospect but the technological improvements required to our current machinery are substantial. The barrier of the FUS absorbing rib cage is hard to overcome and to date MR guided focused ultrasound has only been able to treat lesions that are not covered by ribs. The movement produced by respiration presents a significant problem currently addressed by controlled ventilation during FUS. Technological improvements are slowly being implemented to address these areas to try and speed the introduction of this approach into this complex area in which therapeutic options are relatively limited at the moment. New endorectal MR guided transducers which can ablate areas of the prostate under accurate MR targeting and thermal control are in phase 1 studies treating low risk prostate carcinoma and looking at safety and early efficacy. These results will be discussed but early results indicate safety and effectiveness. A brief discussion of MR guided focused ultrasound application to the breast and soft tissue tumours will also be presented but this is early case-by-case material.
9:00 AM
TRANSCRANIAL MR-GUIDED FOCUSED ULTRASOUND FOR THE TREATMENT OF
NEUROLOGIC DISEASE
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Stereotactic lesioning has proven effective for the treatment of movement disorders, but it fell out of favor in the 1960s with the discovery of dopamine replacement and then again in the 1980s with the advent of deep brain stimulation. Therapeutic uses of ultrasound have long been of interest but were never really applied to the brain because of limitations with transcranial sonication. Today advances in ultrasound technology are enabling precise delivery of acoustic waves through the skull while MRI allows for precise targeting and continuous monitoring of the treatment. An FDA-approved (IDE#100169) phase 1 clinical trial was designed to test the safety and potential efficacy of MR guided focused ultrasound thalamotomy for the treatment of medically-refractory, essential tremor. A series of incremental sonations is targeted by MRI to the Vim nucleus while patients were continuously monitored clinically and with real-time MRI and MR thermography. Standard clinical assessments of tremor, potential adverse events, and MR imaging were obtained at baseline and posttreatment: 1 day, 1 week, 1 month, 3 months. Clinical trials are now underway to treat essential tremor and Parkinson's disease. Additional applications are being explored with neuropathic pain, brain tumors, and obsessive-compulsive disorder. MR guided focused ultrasound technology allows for precise targeting of deep brain structures. The treatment is transcranial and can be monitored continuously with clinical assessment and MR thermal imaging. Neuromodulation of deep brain targets is likely possible prior to lesioning.
CYCLOCOAGULATION BY HIFU FOR TREATING GLAUCOMA: MECHANISTIC STUDY IN RABBITS AND RESULTS OF MULTICENTRIC CLINICAL TRIALS IN 52 PATIENTS

Florent Aptel 1, Aurélie Béglé 2, Arash Razavi 2, Fabrice Romano 2, Thomas Charrel 2, Jean-Yves Chapelon 3, 4, Philippe Denis 5, Cyril Lafon 3, 4
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To study the short- and long-term effects on the ciliary body and the aqueous outflow pathways of high-intensity focused ultrasound cyclocoagulation in rabbit eyes and to evaluate the efficacy and safety of the procedure with one year of follow-up in humans.

The Eyeop1 (EyeTechCare, Rillieux-la-Pape, France) device is made of six cylindrical transducers operating at 21MHz for modulating and producing sharp zones of ablation in the ciliary body (CB). Each transducer generated sequentially an ultrasonic beam at an acoustic power of 2.45W for 4 to 8s.

Methods for the mechanistic study on rabbits: 34 eyes of 21 rabbits were sonicated for 8s per transducer. The rabbits were followed for up to 180 days, with regular intraocular pressure (IOP) measurements and ophthalmic examinations. Microscopy and corrosion casts after intravascular injection of methacrylate resin were used to study the CB anatomy and vasculature changes.

Methods for the clinical trials: A prospective non comparative interventional clinical study was performed in 9 French glaucoma centers. Fifty-two eyes of 52 patients with refractory glaucoma, intraocular pressure (IOP) > 21 mmHg, an average of 1.7 failed previous surgeries and an average of 3.7 hypotensive medications were exposed. 24 patients (group 1) were treated with a 4s exposure time for each shot and 28 patients (group 2) with a 6s exposure time. Patients were examined before the procedure and followed for a year. Primary outcomes were surgical success (defined as IOP reduction from baseline ≥ 20% and IOP > 5mmHg) at the last follow-up visit, and vision-threatening complications. Secondary outcomes were mean IOP at each follow-up visits compared to baseline, medication use, complications, and re-interventions.

Results for the mechanistic study on rabbits: IOP dropped from a mean value of 10.4 ± 1.5 mmHg before treatment to a mean value of 7.3 ± 0.9 mmHg at 180 days after treatment. No macroscopic abnormalities were evidenced. At the microscopic level, histological examinations showed acute inflammatory and necrotic changes ranging from stromal edema and vascular congestion in the CB. In the long term, when present, CB appeared atrophied and covered by nonfunctional epithelium. Microscopy showed focal interruption of the CB microvasculature and, in most animals, a fluid space between the sclera and the CB and between the sclera and the choroid adjacent to treated areas.

Results of the clinical trials: IOP was significantly reduced in both groups, from a mean preoperative value of 30.3 ± 7.8 mmHg in group 1 and 29 ± 7.4 mmHg in group 2 to a mean value of 20.0 ± 6.9 mmHg in group 1 and 19.0 ± 6.7 mmHg in group 2 at last follow-up. Success (IOP reduction >20%) was achieved in 63.2% of eyes of the group 1 and 44% of eyes of the group 2 at last follow-up. Seven patients were retreated. No major intra- or post-operative complications occurred.

From our histological study in rabbits, we speculate that the decrease of IOP is the result of the combined effect of CB destruction and increase of aqueus humour outflow. Clinically, the treatment was also well-tolerated and significant IOP decrease could be obtained and maintained for a year.

Work funded by EyeTechCare SA - Aptel, Chapelon, Denis and Lafon are scientific consultants for EyeTechCare SA
CLINICAL APPLICATION OF HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION IN GYNECOLOGY: SAFETY ANALYSIS
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The clinical application of noninvasive ultrasound ablation, which started in late 20th century in China, has provided a new option to patients with benign and malignant tumors. The first clinical use of ultrasound ablation for uterine fibroids adopting Chongqing Haifu technology was published in 2002. Clinical signs and symptoms of uterine fibroids or adenomyosis were found to have been effectively alleviated in 90% of the patients undergoing HIFU ablation. Since then, clinical application of this technology to treat benign uterine diseases have been steadily broadened and demonstrated unparalleled clinical benefits compared with conventional surgery. Meanwhile, increasing attention has been drawn to the study of its safety. This study was to analyze the safety of this technique in clinical practice. From July, 2006 to June, 2013. A total of 10078 patients with uterine fibroids or adenomyosis from ten centers were treated with ultrasound-guided HIFU. All patients were treated under conscious sedation. All the adverse effects were retrospectively analyzed. Immediately after HIFU procedure, 12.7% (1281/10078) of patients experienced either abnormal vaginal secretion, lower abdominal pain, leg or buttock pain, dysuria, vomit, uterus bleeding, urinary retention, fever. Skin blisters, leg or buttock pain, uterus bleeding occurred in 0.51% (51/10078) of patients. Major complications, which have previously led to substantial morbidity and disability corresponding to unified standardized SIR grading system, did not occur in this study. Based on the evidence, USgHIFU can be considered a safe treatment modality in clinical practice in gynecology.
SEMIQUANTITATIVE PERFUSION MRI ENABLES PREDICTION OF THE INTRA-PROCEDURAL AND IMMEDIATE POST-PROCEDURAL TREATMENT EFFICIENCIES OF MR-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION OF UTERINE FIBROIDS

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It has been known that a high T2 signal intensity or a high Ktrans value on dynamic contrast-enhanced (DCE)-MRI limits the ability of MR-HIFU (MR-guided high-intensity focused ultrasound) ablation to achieve a high non-perfused volume ratio. Although T2-weighted imaging is one of essential parts of virtually all MRI studies, but DCE-MRI is more difficult to acquire and interpret, thus not commonly included in routine screening MR exams. Therefore, as a substitute of DCE-MRI, semiquantitative perfusion MRI which uses time-signal intensity curves instead of time-concentration curves could be considered as a clinical routine.

The purposes of this study were to determine whether semiquantitative perfusion MRI can predict therapeutic efficacy of MR-HIFU ablation of uterine fibroids and which semiquantitative perfusion parameters are associated with treatment efficiency. A total of 77 women (mean age, 43.3 years) with 119 fibroids (mean diameter, 7.5 cm) who were treated with MR-HIFU ablation were analyzed. The correlations between semiquantitative perfusion MR parameters (peak enhancement, relative peak enhancement, time to peak, wash-in rate, and wash-out rate), and heating and ablation efficiencies (lethal thermal dose volume based on MR thermometry and non-perfused volume based on immediate contrast-enhanced image, respectively, divided by intended treatment volume) were evaluated using a linear mixed model on a per-fibroid basis. The specific value of the significant parameter that substantially affected the treatment efficiency was determined. Peak enhancement, relative peak enhancement, time to peak, wash-in rate, and wash-out rate of the analyzed fibroids were 1293.1 ± 472.8 (570.2-2477.8), 271.4 ± 57.2% (170.6-470.2%), 137.2 ± 119.8 sec (20.0-300.0sec), 79.5 ± 48.2/sec (12.5-236.7/sec) and 11.4 ± 10.1/sec (0-39.3/sec), respectively. Relative peak enhancement was found to be independently significant for both heating and ablation efficiencies (B=-0.002, p<0.001 and B=-1.230, p=0.002, respectively). Both efficiencies showed the most abrupt transitions at 320% of relative peak enhancement. Relative peak enhancement in semiquantitative perfusion MRI was significantly associated with treatment efficiency of MR-HIFU ablation of uterine fibroids, and a value of 320% (i.e., an approximately three-fold increase in signal intensity compared to the precontrast images) or less is suggested as a screening guideline for more efficient treatment.

Definitions of semiquantitative perfusion MR parameters.
Relative peak enhancement refers to a peak enhancement value relative to a reference dynamic.
Demonstrate the feasibility of high intensity focused ultrasound (HIFU) applied to the placental unit using a toroidal-shaped transducer with possible application to the treatment of the twin-to-twin transfusion syndrome using a monkey pregnant model. A toroidal HIFU transducer working at 3 MHz and composed of 32 ring-shaped emitters was used. An ultrasound probe working at 7.5 MHz was placed in the center of the HIFU transducer. The imaging plane was aligned with the HIFU acoustic axis. The acoustic parameters used during HIFU exposures were selected according to preliminary simulations taking into account the attenuation coefficient of placentas, measured previously. Ex vivo experiments were then performed. An animal abdominal wall simulated the maternal wall was used and placed at the top of placenta. Single and juxtaposition of HIFU lesions were created. A monkey pregnant for a gestational age of 63 days, was then included and exposed to the HIFU treatment determine from previous ex vivo trials. A single HIFU lesion was performed after maternal anesthesia, and monitoring of maternal and fetal parameters such as subcutaneous and amniotic fluid temperature, maternal and fetal heart rate and maternal oxygen saturation. These parameters were recorded continuously during the treatment. The resulting HIFU lesion was studied on sonogram, macroscopically and microscopically. Attenuation coefficients of 12 human placentas were measured in vitro and ranged from 0.07 to 0.10 Np.cm⁻¹.MHz⁻¹ according to the gestational age (17 to 40 weeks). Thirty-three human placentas (from 17 to 40 weeks) were included and exposed to HIFU. 25 single HIFU lesions were obtained, with an average diameter and depth of 7.1±3.2 mm, and 8.2±3.1mm respectively. Eight placentas were used for juxtaposing 6 HIFU lesions. The average diameter of these HIFU lesions was 23±5 mm and the average depth was 11±5 mm. The average thickness of the abdominal wall was 10.5±1.8 mm. No lesions or damage were observed in intervening tissues. In-vivo, a single HIFU lesion has been created in the placenta with a diameter of 10 mm and a depth of 5 mm. No lesions or damage were observed in intervening tissues not in the fetus. Ultrasound examination revealed a hyperechoic HIFU lesion in the placenta. The diameter and the depth of the HIFU lesion measured in ultrasound images were 10.0 and 4.4 mm respectively. During the HIFU exposure, no significant variation of maternal and fetal parameters was observed. The subcutaneous and intra-amniotic fluid temperature were 25°C (24.9-26) and 34°C(33.4-34.5) respectively. The fetal heart rate was 124 (122-125). This study demonstrates the feasibility, the reproducibility, the harmlessness and the effectiveness of HIFU applied to the placental unit within an in vivo model using a toroidal transducer. These results remain to be confirmed using a significant population of pregnant monkeys.
IN-OFFICE RAPID VOLUMETRIC ABLATION OF UTERINE FIBROIDS UNDER ULTRASOUND IMAGING GUIDANCE: PRECLINICAL AND EARLY CLINICAL EXPERIENCE WITH THE MIRABILIS TRANSABDOMINAL HIFU TREATMENT SYSTEM

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Mirabilis Medica (Bothell, WA) is commercializing a HIFU technology platform that enables gynecologists to deliver rapid noninvasive ablation of uterine fibroids in their offices using ultrasound imaging guidance. The Mirabilis treatment is transabdominal and can be performed in less than 10 minutes using only oral analgesia. The objectives of this research were to determine the safety profile in preclinical models and subsequently to monitor the safety and acute efficacy in a clinical pilot study of the device. Preclinical development and safety evaluation were conducted in an in vivo porcine lower extremity model and an excised human uterus model. The treatment approach utilized two orthogonal ultrasound images produced by an imaging probe embedded in the HIFU applicator to position a treatment volume of selectable size (1-4 cm in diameter) and depth (3-10 cm) in the region desired for ablation. These bi-plane ultrasound images and all system controls were displayed on a Graphical User Interface. HIFU energy was delivered using a proprietary pulsed-wave technique that leverages nonlinear heating effects and biases energy delivery to the perimeter of the treatment volume without insonating its core. In the subsequent single-arm clinical pilot study, 37 women scheduled to undergo hysterectomy who met certain eligibility criteria received transabdominal HIFU treatment. Most subjects received only sublingual tramadol/ketorolac prior to treatment (N=29). Intra-procedural pain was assessed on a numerical scale. A subset of 19 subjects received post-treatment gadolinium-enhanced MRI to assess acute HIFU-mediated perfusion deficits. All subjects then underwent scheduled hysterectomies at variable times ranging from 0 to 155 days after treatment, and the excised uteri were assessed by a pathologist. Subjects were followed for adverse event episodes for a minimum of two weeks post-treatment. In total, 178 animals and 108 human uteri were evaluated during the course of preclinical development. Of these, 30 animals were used for safety validation of final clinical treatment parameters. During safety validation testing, no skin burns or other unexpected effects were observed. In both models, HIFU lesions were proportional to the acoustic powers and energy doses delivered and occurred in the expected locations. During the clinical pilot study, an excellent safety record was maintained. There were no observations of skin burns or collateral tissue injury. No serious or unanticipated adverse device effects were reported. Among subjects receiving only oral analgesia, the average intra-procedural pain score was 2.4 ± 2.5 out of 10 (mean ± std. dev., N=29). The average active treatment time was 3.5 ± 1.9 minutes (N=37). Post-treatment MRI revealed discrete non-perfused volumes (NPVs) consistent with the targeted regions. The average length and diameter spanning the NPVs were 3.5 ± 2.0 cm and 3.5 ± 1.0 cm, respectively (N=19). Pathological assessment showed sharp demarcation between viable and non-viable tissue and dimensional consistency with the NPV appearance on MRI. Ablation was achieved through a combination of coagulation and secondary ischemic necrosis. The Mirabilis HIFU Treatment System shows promise as a novel approach for managing uterine fibroids that enables rapid in-office HIFU treatment. These preliminary data indicate that the treatment can be delivered safely, that the procedure is well tolerated, and that clinically relevant ablation volumes can be achieved in dramatically shorter time frames than other treatment alternatives.
TREATMENT OF EXTRA-ABDOMINAL DESMOID TUMORS USING MR GUIDED HIGH INTENSITY FOCUSED ULTRASOUND: PRELIMINARY RESULTS AFTER FIVE PATIENTS

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The treatments were approved by the Stanford Hospital Innovative Care and Ethics Committees. The benefits and risks of the procedure were discussed with the patient, all questions were answered, and written informed consent was obtained. The patient was transferred to lie on the ExAblate 2100 focused ultrasound MR table, using a special gel mold for patient positioning and for coupling to the transducer. The gel mold was modified to conform to the shape of the desmoid. MR images were obtained to define the desmoid volume and surrounding critical structures in preparation for therapy. Sonication planning was initiated by the ExAblate software, and then manually modified. Individual sonications were adjusted to avoid heating the skin, nerves, or other non-targeted tissues. Thermal dose maps were monitored to confirm heating in the desmoid. Energy was adjusted to avoid tissue cavitation. Post-treatment and post-contrast images were then obtained. The patient was then transferred to the recovery area in SHC and monitored prior to discharge. Five patients were treated, with a median age of 17 years (range 14 to 60 years). One to three desmoid tumors was treated per patient, with two patients treated twice. The desmoid tumors were located in the popliteal fossa, the buttock and medial thigh, the posterior ankle, the lateral aspect of the knee, and the anterior upper abdominal wall. The average tumor volume was 242 cc (range 39 cc in the posterior ankle to 760 cc in the left anterior upper abdomen). The ExAblate 2100 transducer was operated at 1.1 MHz. Average focal depth was 12 cm. The average number of sonications per treatment was 104 (range 42 - 235), with an average of 146 sonications per patient (range 42 - 356). Average treatment time was 4 hours 39 minutes (range 2 hours 6 minutes to 7 hours 52 minutes). Patients were treated while receiving general anesthesia, epidural anesthesia (popliteal fossa), or after peripheral nerve blockade (posterior ankle). The average power used for each sonication was 66 W (range 40 - 110 W). Mean sonication spot energy was 1398 J (range from 802 - 2128 J), with mean spot energies ranging from a minimum of 435 J to a maximum of 2495 J. The maximum energy used for a sonication during these 5 treatments was 4898 J. Typical predicted sonication spot sizes (diameter x length) used for a procedure range from 5 x 17 mm to 7 x 35 mm. The averages of the median values of temperatures achieved during individual sonications were 57°C (average temperature) and 69°C (maximum temperature). The average predicted ablated volume based on thermal dose calculations was 33 cc (range 11 - 70 cc). The average non-perfused volume was 166 cc (range 23 - 645 cc). The average ratio of the non-perfused volume to the total tumor volume (NPVR) was 0.58 (range 0.36 - 0.86). Complications of the procedures included a first degree skin burn, muscle ablation, temporary distal paresthesia, and acute pancreatitis. No serious adverse events occurred. MR guided high intensity focused ultrasound is a promising means of achieving thermal ablation of extra-abdominal desmoid tumors. Potential advantages over existing approaches include the ability to target the treatment while minimizing the risk to skin, nerves, muscles and vessels. In addition, treatments may be repeated to maintain tumor control. The procedure must be improved to reduce treatment time, and to improve the accuracy of the estimated ablated volume based on MR thermal dose calculations.

Pre-treatment axial T2 weighted fat saturated image (left) demonstrates a left popliteal fossa 6.6 x 4.4 x 5.9 cm desmoid tumor, delineated by the white boundary. Post-contrast T1 weighted (right) fat-suppressed image obtained after treatment, with the white boundary demarcating the ablated, non-enhancing portion of the tumor. The mid and lateral portion of the tumor were targeted, while the medial portion was spared because of concern for injury to the tibial nerve. A total of 44% of the tumor volume was no longer perfused after ablation. There was no clinical evidence of injury to the tibial nerve after treatment.
11:00 AM
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To determine the effect of acoustic energy delivered during MR guided Focused Ultrasound (MRgFUS) treatment of symptomatic osteoid osteomas. This prospective, IRB approved study involved 15 consecutive patients (11 m; 4f; mean age, 21) with clinical and imaging diagnosis of Osteoid Osteoma; all patients underwent MRgFUS ablation (ExAblate, InSightec; Discovery 750 MR unit, GE). Lesions located in the vertebral body were excluded, while lesions in proximity to joints or neurovascular bundles were included. Treatment success was determined at clinical and imaging follow-up at 1, 6 and 12 months post-treatment. A visual Analog Pain Score (VAS) was used to assess changes in symptoms. Bone changes at nidus site were evaluated on the basis of CT and dynamic ce-MR imaging (Gd-Bopta; Bracco) pre- and post-treatment. Treatment was carried out using a variable number of sonications (mean 4±1.8) with a mean energy deposition of 866±211 J. There were no treatment- or anesthesia-related complications. A statistically significant (p=0.001) difference was noted between the overall pre- and post-treatment mean VAS scores (8.3±1.6 and 0.6±1.5, respectively). Two treatments were conducted in patients with prior CTgRFA failure and needed two different session for achieving complete clinical successful. At imaging, edema and hyperemia associated with typical osteoid osteoma, gradually disappeared in all lesions. No apparent relationship between nidus vascular extinction and successful outcome was found. Variable reabsorption degree of sclerotic reaction was observed with nidus disappearance in 4 cases (27%). Treatment of osteoid osteoma using MR guided Focused Ultrasound can be performed safely with a high rate of success and without treatment related morbidity; our results indicated also a positive trend to bone rearrangement after treatment.

Dynamic Contrast Enhanced MR study performed before MRGFUS treatment shows a hyper vascular subcortical nodular lesion compatible with Osteoid Osteoma. Same image set acquired post-treatment shows absence of nidus perfusion. Effective Treatment time was 20 seconds using single sanitation. Overall treatment time was 35 min including sedation. Patient underwent MRgFUS as an out-patient basis and had symptoms relieve in 2 days with pain free at 9 months.
11:10 AM
HYPERTERMIA AND TISSUE ABLATION TREATMENTS IN THE HEAD AND NECK REGION USING MRgHIFU: AN IN VIVO FEASIBILITY STUDY
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Tumours in head and neck represent a challenge in oncology because the important presence of critical organs in that area. A more targeted treatment is desired to reduce risks of morbidity. This paper presents preliminary results to establish the feasibility of performing ablation and hyperthermia treatments in the neck area with Magnetic Resonance-guided High Intensity Focused Ultrasound (MRgHIFU) using an acute pig model. Six 17-18-kg pigs were treated in the omohyoid muscle at the middle section of the neck area. The protocol was approved by the local animal care committee. Experiments were performed using an MRgHIFU system Sonalleve V2 and a 3T Achieva scanner (Philips Healthcare). Animal was under anesthesia (Isofluorine 2%) and breathing rate was set to 20 breaths per minute and a volume of 200 mL. Thermometry maps were calculated using a technique based on the water-proton resonance frequency shift. Baseline temperature was measured with an optic fiber inserted in the gluteus muscle. Prior to euthanasia, contrast enhancement imaging was performed using a gadolinium-based agent (Magnevist, Bayer). The right size of the neck was treated with hyperthermia with a target temperature of 41 C during 30 minutes. A target region of 16-mm diameter and 34-mm in length was used to cover the muscle region. First 3 pigs were treated using the automatic control algorithm included in the standard Sonalleve software (V3.1.1010.343). The remaining 3 pigs were treated with a manual control of the sonication using real-time toolboxes for the control of the MRgHIFU system and MR scanner. Ultrasound frequency was set to 1.2 MHz. The left side of the neck was treated with a cluster of individual HIFU lesions, each with a diameter of 8 mm and a length of 20 mm. Duration of exposure of was set to 20 s and frequency to 1.2 MHz. The standard Sonalleve software was used to induce the HIFU lesions. Hyperthermia. Compared to the automatic method, the user-controlled approach managed to deliver temperatures closer to the target goal of 41C and with inferior peak temperatures. Noise was observed by the respiratory motion in the head-foot direction. With the automatic algorithm, initial power was set to 40W, which was later modulated without user intervention. In the user-controlled algorithm, power was initially set to 20 W and power has to be increased up to 50W to sustain the hyperthermia level. The required time of temperature to return to baseline values ranged from 100 to 200 s. Lesion formation. Three (3) experiments were conducted with a target power level of 110W and the 3 remaining with a power level of 140W. The number of individual lesions ranged from 4 to 12 to cover the target zone with an expected treated volume ranging from 3.52 to 10.56 mL. Experiments with a power of 110W showed very low success rate when compared to high power. One experiment at 140W developed post-focal region in the adjacent muscle. In all experiments the lesion volume observed in contrast imaging was inferior to the planned volume for all experiments. Exposures located in proximity of the carotid artery were unable to produce lesions regardless the applied power. HIFU lesions were clearly observable in gadolinium-contrast imaging as a reduction in intensity on the left side of the neck where HIFU lesions were intended, while no observable difference in contrast was observed in the right side treated with hyperthermia. Macroscopic analysis of tissue corroborated contrast-imaging findings. Results indicated that it is feasible to both induce lesions and sustain hyperthermia levels in the neck area using MRgHIFU.

Transverse (left) and coronal (right) plans of the middle section of the neck where treatments regions are shown by green contours. HIFU lesions were performed on the left side of the neck and hyperthermia on the right side of the neck.
A FULLY INTEGRATED, REAL TIME 2-D HIFU MONITORING SYSTEM USING HARMONIC MOTION IMAGING FOR FOCUSED ULTRASOUND (HMIFU)
Gary Yi Hou 1, Jean Provost 1, Julien Grondin 1, Shutao Wang 1, Yang Han 1, Fabrice Marquet 1, Elisa Konofagou 1, 2

Harmonic Motion Imaging for Focused Ultrasound (HMIFU) is a recently developed high-intensity focused ultrasound (HIFU) treatment monitoring method. HMIFU utilizes an Amplitude-Modulated (AM frequency = 25 Hz) HIFU beam to induce a focal oscillatory motion, namely HMI displacement, which is tracked simultaneously by a confocally-aligned diagnostic probe. The objectives in this chapter are first to develop a 2-D HMIFU system using a fully-integrated, clinically relevant commercial ultrasound scanner with high frame rate real time imaging capability by incorporating a GPU-based reconstruction algorithm. The completed platform is aimed at providing a quantitative real time 2D monitoring feedback during the HIFU treatment directly back to the user. We also aim at demonstrating initial feasibility of the 2-D HMIFU in HIFU treatment monitoring in tissue-mimicking phantoms and in vitro tissue experiments. In this study, a 93-element and 4.5 MHz center frequency custom therapeutic transducer was used to induce a focal displacement while a coaxially-aligned 64-element 2.5 MHz center frequency phased array diagnostic probe was operated using a four-board Verasonics ultrasound system for radio-frequency (RF) channel data acquisition, beamforming, and displacement map construction. A flash transmit sequence was used to perform imaging with 1000 frames/second, across a field of view varying from 30 to 90° and receiving using 32 to 128 beams. Beamforming was performed using a new method consisting on multiplying a reconstruction matrix by the RF data matrix. The reconstruction matrix is a sparse matrix containing the contribution of each point of the RF data matrix to the points of the beamformed signals at 80 MHz sampling frequency using the sum and delay method. Axial HMI displacements were then estimated from beamformed RF signals using a 1-D normalized cross-correlation algorithm and streamed at a graphic user interface in real time. Thermocouple monitoring was performed by inserting a T-type bare wire thermocouple with diameter of 25 µm inside the tissue. HMIFU monitoring was performed on 5 locations across a 10 kPa gelatin phantom and 18 locations across five in vitro canine liver specimens. The estimated displacement across five locations on the gelatin phantom were 22.5±1.25 µm. The estimated focal displacements before and after HIFU treatment were 8.36±3.51 µm and 4.40±1.11 µm, respectively, indicating the system’s ability to estimate and monitor the stiffness change in real time. In addition, 16 of the 18 cases exhibited displacement increase-then-decrease mechanism, indicating tissue initial-softening-then-stiffening phase change. The increasing and decreasing slopes with respect to temperature were 0.73±0.69 %/°C and 2.03±0.93%/°C, respectively. In this study, a fully-integrated, clinically relevant ultrasound imaging platform was developed for 2D real-time HIFU monitoring using HMIFU with implementing a GPU-based sparse-matrix reconstruction algorithm capable of providing 2D real-time streaming during HIFU treatment up to 15 Hz without interruption. Reproducible HMI displacements were imaged and highlighted a clear excitation region across multiple locations, and 18 HIFU treatment monitoring cases showed clear decrease in focal displacements upon lesion formation with 16 cases also showed consistent successful monitoring of tissue-softening-then-stiffening phase change with thermocouple monitoring. This study was funded by NIH R01EB014496.
11:30 AM
NON-INVASIVE TISSUE PARAMETER ESTIMATION WITH DUAL-MODE ULTRASOUND ARRAYS.
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Dual-mode ultrasound array (DMUA) systems offer unique advantages in image-guided HIFU in surgical applications. The key advantage of the DMUA approach is the inherent registration between the imaging and therapeutic coordinate systems. In addition, the high degree of focusing of DMUA imaging beams allows for quantitative tissue property measurements with high degree of localization. In this paper, we present experimental results demonstrating the feasibility of localized tissue property measurement using highly focused DMUA imaging beams. We also show that the focusing gain of DMUA imaging increases both the sensitivity and specificity of tissue property changes compared to diagnostic beams used by conventional imaging probes on diagnostic scanners. In particular, we present results from in vitro experiments in bovine heart tissue where we estimated the local absorption before and after the formation of thermal lesions. Imaging and therapy were performed using a 3.5MHz DMUA (Imasonic, France). First, thermocouple calibration measurement was performed in tissue mimicking phantom and bovine heart tissue to ensure proper exposure during subtherapeutic shot delivery. After the calibration a set of 1 second subtherapeutic shots was delivered 12-mm deep inside the tissue with the following ultrasonic watt density [20 mW/cm²; 40 mW/cm²; 60mW/cm²; 90mW/cm²; 120mW/cm²]. Subtherapy shots were repeated twice in the forward and reverse directions, to ensure repeatability. After the first set of subtherapy shots an electronically steered volumetric lesion was formed which composed of 5 electronically steered foci spaced .55mm apart (1350mW/cm²), with a total duration of 5 seconds. After the completion of therapy subtherapeutic shots were repeated. The slope of the temperature rise curve during the initial heating phase was used as a measure of local absorption. Experiments completed in tissue like phantom and bovine heart tissue confirm a linear relationship between acoustic power absorbed and the initial slope of the subtherapeutic temperature profile. Figure 1 summarizes data in the form of boxplots for five different subtherapeutic exposures. Slopes for four out of five subtherapeutic exposures, with the exclusion of the 20mW/cm² group, showed statistically significant difference when measured before and after therapy (p<0.05 for 40mW/cm² and p<0.01 for 60mW/cm², 90mW/cm², 120mW/cm² ). The mean slope value for the four out of five exposures differed according to the following trend: 18%, 20%, 16%, and 19% (% difference is summarized in the order of increasing subtherapy exposure). When analyzing axial-temporal temperature maps going through the focus of the lesion, higher relative absorption was observed both at the center of the lesion and also axially along the lesion (~3mm axial extent). Significant changes in absorption coefficient before and after therapy formation were estimated through the use of STF imaging using DMUA. The mean in absorption changed by 16-20%, allowing the user to infer quantitative information indicative of the permanent damage due to thermal coagulation. Axial-temporal profiles of absorption proved to be very helpful in highlighting the HIFU focus and enabled the user to precisely locate the lesion. This property can be used to characterize the tissue response to HIFU at sub-therapeutic levels without compromising critical tissues. As a result, we are working to outline the lesion extent from the axial profiles of the temperature estimates, carefully done gross photography of the lesions will corroborate our findings.

Slopes for five different subtherapeutic exposures are summarized as boxplots for before and after therapy groups.
T1rho mapping for the MRI-based evaluation of high intensity focused ultrasound tumor treatment

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For the clinical application of HIFU for ablation of malignant lesions, it is of key importance that the extent and severity of HIFU-induced tissue damage can be accurately identified. We have recently shown that amide proton transfer imaging and multiparametric MR analysis based on T1, T2 and Apparent Diffusion Coefficient data are promising MRI methods for segmentation of HIFU-treated and non-treated tumor tissue. Another MRI method with potential sensitivity to HIFU-induced changes in the tumor tissue is T1ρ imaging. Changes in tumor T1ρ after gene therapy and chemotherapy have been reported. The aim of the present study was to assess if T1ρ provides contrast between HIFU-treated and non-treated tumor tissue and at which time point after HIFU treatment this contrast is manifested. MRI (7T) of tumor-bearing (CT26 colon carcinoma in hind limb) Balb/c mice was performed 1 day before (n=13), directly after (n=13) and 3 days after (n=7) HIFU treatment. Partial tumor treatment was performed outside the MR system with an 8-element therapeutic ultrasound transducer (TIPS, Philips). Ablation settings were: power 12 W, frequency 1.4 MHz, duty cycle 50 %. The multislice MRI protocol consisted of T2-weighted imaging and T1ρ mapping at various spin-lock strengths (B1=0, 100, 250, 500, 750, 1000, 1500, 2000 Hz). The T1ρ map at B1=0 Hz is equivalent to a T2 map. Animals were sacrificed directly after the last MR examination and subsequently the tumors were processed for NADH-diaphorase and H&E staining. Representative MRI results are shown in Fig A. HIFU treatment did not lead to contrast in the T2-weighted images. This was confirmed by absence of visible changes after HIFU in the T1ρ maps at B1=0 Hz, which essentially represent T2 maps. At both time points after HIFU, a large region of decreased T1ρ was observed at B1=2000 Hz. Histology confirmed extensive necrosis in the tumor (Fig B). There was a significant effect of spin-lock strength on the ΔT1ρ between 3 days after and before HIFU (Fig C). The ΔT1ρ values at B1 strengths above 100 Hz were significantly lower (more negative) than at B1=0 Hz. Moreover, the ΔT1ρ value at 2000 Hz was significantly lower than the ΔT1ρ values at B1 strengths between 0 and 1000 Hz. Significant changes in tumor T1ρ were observed after HIFU treatment. T1ρ imaging may thus be suitable for HIFU treatment evaluation. Clinical translation seems feasible, since significant contrast between HIFU-treated and non-treated tissue was already observed at B1=100 Hz, which is well below clinical SAR limits.


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High intensity focused ultrasound (HIFU) is capable of rapidly, and noninvasively, delivering a controlled thermal dose for ablative therapies. Under MR guidance, precise temperature measurements can be made in real time. The resulting thermal dose maps can be used to gauge treatment efficacy and determine collateral tissue damage. We sought to examine tumor tissue response to HIFU ablation and evaluate the correlation between histological findings (haematoxylin and eosin (H&E)) and several common MR imaging protocols as to their ability to assess the extent of thermal tissue damage. An MR compatible therapeutic ultrasound system (IMASONIC SAS, Voray sur l'Ognon, France) consisting of a 16 element annular array capable of 100 acoustic watts was used in conjunction with a 7T MR scanner (Bruker Biospec 70/30, Bruker BioSpin MRI, Ettlingen, Germany). Animals (n = 24, female FVB mice bearing bilateral NDL tumors) were insonated under MR guidance. Only one tumor per animal was insonated, with the contralateral tumor used as a control. Between one and five spots were insonated per tumor, with each spot receiving an approximate acoustic dose of 75 J. MR thermometry was used to measure the temperature change peri-ablation, and thermal dose maps were generated from this data. The animals were divided into 3 groups: 0hr, 24hr, and 48hr. Prior to insonation, T1 weighted (T1w) images were collected in addition to T2, T2* and apparent diffusion coefficient (ADC) maps. Following insonation, animals were again imaged using the same protocols. However, a post gadolinium (Gd-HPDO3A, 0.5 µmol/g) T1w scan was added to assess tumor perfusion. Animals in the 0 hour group were sacrificed following this series of scans while animals in the 24 or 48 hour groups were also imaged at 24 or 48 hours respectively prior to sacrifice. Following sacrifice, both the treated and contralateral tumors were removed. The tumor samples were then divided into two halves. One half was flash frozen, sliced into 20 µm sections and used for NADH-diaphorase staining. The other half was preserved in formalin and used for H&E and caspase staining. There was good correlation between the MR findings and NADH diaphorase histological results. Generally, the region of tissue death, as indicated by the NADH diaphorase staining, was larger at the later time points, which was also supported by contrast enhanced T1w images. Diffusion weighted images appeared to underestimate tissue death, while T2 and T2* images did not show any obvious correlation. Conversely, setting a thermal dose threshold of CEM43 ≥ 240 seemed to overestimate the extent of lethality. Contrast enhanced T1w MRI yields good correlation with NADH diaphorase histological sections. The extent of cell death following HIFU can increase dramatically within 24 hours. Thus, the true efficacy of the treatment may not be reflected immediately in standard MRI protocols.

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POTENTIATING THE ANTITUMOR EFFECTS OF CHEMOTHERAPY WITH THE ANTIVASCULAR ACTION OF ULTRASOUND STIMULATED MICROBubbles

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Considerable efforts are being directed towards investigating the use of ultrasound stimulated microbubbles (USMBs) to promote the uptake of anticancer agents in tumors. It has also been shown that, under relatively low exposure conditions, USMBs can induce a rapid shutdown of the tumor vasculature. This effect can be accompanied by tumor growth inhibition but eventually there is a degree of flow recovery along with the resumption of tumor growth. These effects parallel those observed for small molecule vascular disrupting agents, which have shown the most effective antitumour effects when combined with other chemotherapeutic agents. In this presentation we will describe work that has been conducted combining antivascular USMB effects with chemotherapeutic agents. All work was carried out on tumors that were subcutaneously implanted in mice. 1 MHz ultrasound was employed using a series of 50ms bursts transmitted at 20s intervals to permit reperfusion between exposure sequences (0.00024 duty cycle). Exposures were conducted for a period of 2 minutes following the systemic injection of microbubbles. Pressure levels ranged from 1.4-1.65 MPa (peak negative pressure), which produced significant levels of inertial cavitation. Flow within the tumors was monitored during treatments with ultrasound contrast imaging. For each treatment type, both longitudinal growth experiments were conducted along with acute experiments to acquire tissue for histologic analyses (apoptosis, necrosis, proliferation and perfusion). Experiments were carried out with the taxanes docetaxel and paclitaxel on PC3 (prostate cancer) and EMT6 (breast cancer) tumor cell lines to assess the combination of USMBs with single low doses of chemotherapy. Experiments were also carried out combining USMB treatments with metronomically administered cyclophosphamid on MDA-231 tumors to investigate their use in conjunction with an antiangiogenic therapy strategy. For all cell lines, the USMB treatments produced a vascular shutdown within the tumors and resulted in growth inhibition relative to the control (sham treatment) groups. For the longitudinal taxane therapy experiments, the combined USMB+drug groups had profound and significant growth inhibition relative to both the USMB-only and drug-only groups. A histologic analysis of the tumors from the acute experiments (24 hour point) revealed a higher level of apoptosis and necrosis and lower levels of proliferation and perfusion in the combined versus individual treatment groups. A subset of experiments examining EMT6 tumor tissue acquired post-treatment indicated that the USMB treatments were not associated with increased drug uptake. For the cyclophosphamid experiments, the combined treatment group also produced strongly increased tumor growth inhibition relative to the individual treatment groups. Collectively these results suggest the potential of combining antivascular USMB treatments with chemotherapy. This is a strategy that is distinctly different from the conventional approach of employing microbubbles to promote the uptake of drugs into tumor tissue. This approach may be of relevance to a range of anticancer agents whose activity is not inhibited by their ability to extravasate from the tumor blood supply.
10:10 AM
HYPERTHERMIA TRIGGERED DRUG DELIVERY IN A PANCREATIC CANCER MOUSE MODEL USING MR-GUIDED FOCUSED ULTRASOUND
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Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. Current treatment options are of limited benefit with a five year survival rate following diagnosis of less than 5%. Dense stromal tissue and poor vascular perfusion limits drug penetration and uptake into the tumor tissue. Growing evidence suggests that hyperthermia can decrease drug resistance by enhancing cellular uptake. Hyperthermia treatments in combination with temperature sensitive liposomal (TSL) can lead to increased organ perfusion and drug extravasation resulting in high local drug concentration. MR-guided heating methods enable accurate and precise spatial and temporal control of heating, and when coupled with TSLs, could result in tightly targeted drug delivery. The goal of the study was to evaluate enhanced drug delivery using Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) in conjunction with a heat triggered drug delivery system. Two different mouse models of pancreatic ductal adenocarcinoma were used for these studies: a transgenic mouse model (KPC) and an induced orthotopic model. An animal positioning system with an integrated 4-channel small animal Magnetic Resonance Imaging (MRI) coil (Philips Medical Systems, Helsinki, Finland) was used with the MR-HIFU system (Sonalleve®, Philips Healthcare) to hold, image and treat the mice assigned to the experimental group. Defined tumor tissue was treated by targeted sonications (1.2 MHz frequency, 7W acoustic power) in 5-10 minute increments with a total time of 30 minutes after injection of free doxorubicin (Dox) or TSLs loaded with Dox (ThermoDox®, Celcion Corporation). Temperature elevation during sonications was monitored by a gradient echo based echo planar imaging (EPI) sequence with EPI factor 5, TE/TR 16/25 ms, flip angle 20 degree, dynamic scan time 1.8 s. A small gel phantom placed beside the mouse was used to monitor the magnetic drift for temperature correction. Mice were flushed before sacrifice and tumor tissue was removed for evaluation. Tumor drug uptake was evaluated by fluorescence microscopy and high performance liquid chromatography (HPLC). Fluorescence evaluation of the tumor tissue revealed increased focal nuclear uptake of Dox in regions treated with MR-HIFU hyperthermia with systemically administered Dox loaded TSLs. Quantitative measurement of tissue drug concentrations using HPLC indicated an increase in Dox uptake from TSL compared to free drug and drug without hyperthermia application. This method provides precise and non-invasive hyperthermia treatment in a small animal using a clinically available MR-HIFU system. The combination of hyperthermia with TSL resulted in higher concentration of doxorubicin by a factor between 2 and 8 fold. These results are encouraging as we move in to survival studies. The clinical translation would offer a new non-invasive and local treatment option in this type of cancer.
LOW-INTENSITY CONTINUOUS ULTRASOUND AND A CLINICAL DOSING REGIMEN OF ZOLEDRONATE PRODUCE ANTITUMOR EFFECTS IN MOUSE MODELS OF BREAST TUMOR XENOGRAFT AND BONE METASTASIS.

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Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and have demonstrated clinical utility in the treatment of patients with bone metastases. There is also preclinical evidence suggesting that bisphosphonate zoledronic acid (ZOL) exhibits antitumor effects. However, high doses of ZOL used in most animal studies are incompatible with the dosing regimen that has been approved for the treatment of bone metastases. Mild hyperthermia (42 -45°C) is known to enhance membrane cell permeability, increase intratumoral blood flow and decrease intratumoral pressure. Low intensity ultrasound delivered in continuous mode can induced mild hyperthermia as well as mechanical effect such as acoustic radiation force which is known to help the penetration of drugs into cells. We first assessed if the chosen parameters for producing low intensity ultrasound are able to create and maintained a temperature of 43°C in tissues without creating cavitation. We also examined whether US could maximize the effects of a clinically relevant dose of ZOL. A plane transducer working at a frequency of 2.9 MHz was used. The free field acoustic power was 7 watts applied for 30 minutes to produce thermal effects in bone tumors. US treatments were performed each day for fifteen days. Human cancer cells were used in nude mice. In a first set of in vivo experiments, tumor xenograft were created by injecting cancer cells subcutaneously. Experimental bone metastases were created by injecting cells into the tail vein. Once tumor-bearing mice had palpable tumors (xenograft) or radiographically detectable bone metastases, animals were randomly assigned to different groups (vehicle, ZOL, US, ZOL+daily US). Clinically relevant dose of ZOL (0.1 mg/kg) was used. Osteolytic lesions were detected by radiography. Tumor angiogenesis and tumor cell proliferation were assessed by immunohistochemistry. IPP accumulation within tumor cells and unprenylated Rap1A, two surrogate markers of the penetration of ZOL into tumor cells was measured respectively by mass spectrometry and Western Blot. With the acoustic parameters used, no detection of wideband emission and harmonics of the fundamental frequency considered as signatures of inertial and non-inertial cavitation were found. The temperature in tumors was 42.0±2.8°C during US treatment. No lesion was observed in surrounding tissues. US alone did not have any effect on bone metastasis and tumor outgrowth, compared with vehicle-treated animals. ZOL+daily US statistically significantly (p< 0.01) decreased bone destruction (1.3±0.4 mm2) compared with ZOL alone (3 ± 0.4 mm2). This difference was accompanied with a sharp reduction in the tumor volume (TB/STV ratio: 11%) compared with ZOL-treated metastatic mice (TB/STV ratio: 46%), as determined by histomorphometry. ZOL+ US treatment also inhibited growth of subcutaneous tumors in animals, when compared with ZOL alone. For both protocols, tumor angiogenesis and tumor cell proliferation were substantially reduced. Analysis of bone marrow flush and tumor extract showed an increase of unprenylated Rap1A suggesting a penetration of ZOL into the tumors and cells of the bone marrow due to US. US facilitates the uptake of ZOL by tumor cells, thereby promoting its antitumor effects in vivo. US enhance membrane cell permeability and acoustic radiation force as well as the bioavailability of ZOL for tumor cells. Importantly, clinical doses of ZOL and US were used, suggesting that clinical application of such therapy is possible.
Integrating multiple functions on a micro/nanometer scale particles is a key focus in both biomedical engineering and nanotechnology, which will have far-reaching impact on medical imaging and therapies. However, constructing safe and efficient multifunctional agents, which can combine multiple capabilities of individual micro/nanometer components to support different diagnostic and therapeutic modalities, has been recognized to be a great challenge. In this paper, superparamagnetic iron oxide nanoparticles (SPIO) were coupled to perfluorocarbon-filled microbubbles encapsulated with albumin shell (referred as SPIO-albumin MBs) to enable multimodal imaging and therapeutic applications. The properties of SPIO-albumin MBs (e.g., size distribution, effective stiffness, acoustic scattering and magnetic response) were systematically assessed based on magnetization assessment, TEM Imaging, EDX spectra, US and MR imaging, as well as US-facilitated VEGF transfection. The results show that: (1) SPIOs could be successfully loaded to albumin-shelled perfluorocarbon MBs; (2) significant SPIO concentration dependence was observed for the physical, acoustic and magnetic responses of these MBs; (3) an optimized US-facilitated VEGF transfection outcome was achieved by adopting SPIO-albumin MBs with an appropriate concentration of 114.7 µg/ml.

In summary, by coupling SPIOs into albumin-shelled MBs, a new type of multifunctional imaging and therapeutic agents was synthesized to take the advantages of good biocompatibility, adjustable shell properties, intensified acoustic and magnetic contrast and significantly enhanced gene transfection efficiency. With these merits, these MBs could be guided by the dual-modality imaging system to specific locations of interest to provide complementary vascular/tissue information with improved temporal and spatial resolution or controllable therapeutic applications. It might also open new possibilities to develop more ideal non-invasive controllable treatment strategies that can simultaneously provide accurate imaging information and efficient therapies in intracerebral hemorrhage diagnosis, gene/drug delivery, cancer treatment, blood-brain barrier opening, etc.
ENHANCED ACCUMULATION OF CU-DOXORUBICIN NANOPARTICLES WITH MR GUIDED FOCUSED ULTRASONIC THERMAL ABLATION

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Magnetic resonance guided focused ultrasound (MRgFUS) treatment protocols provide noninvasive imaging of soft tissue for therapeutic guidance as well as real-time three-dimensional monitoring of thermal dose. However, incomplete ablation is a concern for achieving complete response in malignancy. Adjuvant chemotherapy can potentially destroy the remaining tumor. We have previously demonstrated that ultrasound hyperthermia can enhance nanoparticle accumulation. Therefore, we hypothesize that adjuvant nanoparticle chemotherapy can improve the effectiveness of MRgFUS for breast cancer. MRgFUS was performed on a Bruker BioSpec 7T small animal system (Ettlingen, Germany) and 16 element annular FUS transducer (3Mhz center frequency, 300kHz bandwidth, 120 W peak acoustic power, 85° aperture, 48 mm diameter, 1 x 1 x 2 mm FWHM focus size) from IMASONIC (Voray sur l'Ognon, France) and positioning system from Image Guided Therapy (Pessac, France). 42 female FVB mice implanted with murine NDL mammary carcinomas were used. 20 mice were followed for four weeks after biweekly treatment with 6 mg/kg copper-doxorubicin long circulating liposomes (CuDox-LCL) and weekly treatment with singlespot MRgFUS (7 s, >70 °C at the focus) then sacrificed for histology. 10 mice were treated with CuDox-LCL and singlespot MRgFUS and followed until tumors reached an endpoint of 1.5 cm diameter in the longest dimension. Twelve tumors were treated with CuDox-LCL and singlespot MRgFUS, imaged with microPET/CT using 64Cu-long circulating liposomes at (64Cu-LCL) 6, 24, and 48 hours, and then sacrificed for gamma counting and histology. Tumors treated with combination CuDox-LCL and singlespot MRgFUS were below the detection threshold of diagnostic US after four weeks of treatment. Median survival time increased from 43 ± 1 to 46.5 ± 14.5 to 62 ± 0 to 114 ± 19 days for untreated, singlespot MRgFUS only, CuDox-LCL only, and singlespot MRgFUS + CuDox-LCL treated mice (median ± median absolute deviation n = 5, 10, 3, 5). One mouse experienced sustained remission of over 100 days. While nonenhancing regions on contrast enhanced MRI were observed immediately following ablation and contrast administration, PET/CT of 64Cu-LCL reveals enhanced accumulation of nanoparticle doxorubicin in MRgFUS tumors as early as 6 hours after therapy (7.8 ± 1.24 vs. 4.1 ± 0.26 %ID / cc mean ± standard error of the mean for MRgFUS treated vs. untreated tumors). Adjuvant nanoparticle chemotherapy is a viable means to enhance efficacy of MRgFUS therapy of cancer. Increased intensity or duration of therapy may increase rate of sustained remission.

(A) MicroPET/CT demonstrates enhanced accumulation of 64Cu-LCLs in MRgFUS treated tumor. (B) MR imaging demonstrates tumor location (C) as well as successful singlespot thermal ablation. (D) Following therapy, tumor demonstrates region of nonenhancement with MR contrast enhanced imaging. (E) This nonenhancing region correlates with NADH Diaphorase viability stain.
A NEW GOLD-NANOPARTICLE-BASED COATING TO ENHANCE ULTRASOUND-MEDIATED DELIVERY OF NANOMEDICINES TO TUMOURS
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Delivery of systemically delivered nanomedicines to tumors is hindered by poor circulation kinetics, typically addressed through chemical modification using poly(ethylene glycol) (PEG) or poly[N-(2-hydroxypropyl)methacrylamide] (PHPMA) polymers. Even with such stealth and exploitation of the enhanced permeability retention effect (EPR), limited extravasation of the nanomedicine from the vasculature into the tumour mass typically results in less than 2% of the injected dose reaching the tumour. Here we introduce a novel nanomedicine modification based on gold nanoparticles and PEG specifically designed both to improve stealth and enhance tumour penetration of therapeutics when co-delivered with ultrasound and SonoVue microbubbles. Highly-PEGylated gold nanoparticles (AuPEG) were linked to a model nanomedicine, adenovirus (Ad), by a single reduction cleavable bond, providing both excellent steric shielding and a three-fold increase in the effective density of the adenovirus. An OptiCell tissue-mimicking material comprising a flow channel was initially used to compare the relative extravasation of Ad, Ad-PHPMA and Ad-AuPEG when co-injected with SonoVue microbubbles and exposed to 0.5 MHz ultrasound at peak rarefractional pressures of 180 kPa and 1250 kPa, resulting in either ultraharmonic or broadband emissions being detected by a passive cavitation detector. The same exposure parameters and viral vectors were then used in BALB/c mice bearing CT26 tumours to quantify accumulation of each therapeutic in the tumour, and in CD1 mice bearing HepG2 xenografts to assess therapeutic efficacy. The in vitro OptiCell results showed that, in the presence of inertial cavitation, 8.7% of the AuPEG dose extravasated, compared to 1.5% for Ad and Ad-PHPMA for the same conditions, with the greatest increase observed 4-6 mm away from the flow channel. In vivo, AuPEG resulted in dramatically enhanced circulation (59%) at 30 minutes compared to Ad (6.8%) and Ad-PHPMA (31%), and under inertial cavitation conditions accumulated in tumours at 100x the concentration of Ad. A previously unmatched level of 12% of the injected dose was thus recovered from tumors of mice treated with adenovirus-gold-PEG, ultrasound and SonoVue microbubbles, ultimately improving treatment efficacy. The proposed gold-PEG-based surface modification is widely applicable to all nanomedicines, whether they are liposomes, virotherapeutics or antibodies, and has been demonstrated to greatly improve not only circulation but also accumulation and penetration in tumours during inertial-cavitation-enhanced ultrasonic delivery. It is hypothesized that the increase in density underpins the observed improvements but the underlying mechanism requires further investigation.
ULTRASOUND AND MICROBUBBLES DIRECTED GENE DELIVERY OF FACTOR IX PLASMID FOR HEMOPHILIA B THERAPY

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Hemophilia B is a genetic blood clotting disorder that is caused by a deficiency of blood clotting factor IX (FIX), which is the second most common form of hemophilia. In order to develop therapeutic gene treatment for hemophilia B, we previously explored ultrasound (US) combined with microbubbles (MBs) mediated reporter gene delivery in murine models, which has shown significant enhancement of gene transfer efficiency. Here we report further studies of US/MB mediated therapeutic gene delivery of a human FIX (hFIX) plasmid encoding a hFIX variant protein with 5-10 fold higher activity than the wild-typed hFIX in mouse and rat models. In the mouse model, the whole liver was injected with plasmid and MBs through portal vein, and simultaneously treated with an unfocused therapeutic US transducer H158 for 60sec. In the rat model, one or two liver lobes were individually treated with US and targeted injection through portal vein branch for 90sec. Based on our previous reporter gene transfer studies, the optimized treatment protocols of pulse-train US exposure with acoustic pressure of 2.0-2.7MPa at 1 MHz and 5% NuvOx neutral MBs were employed. Blood samples were collected on day 1, 4, 7, 14, 21, 28 following treatment to evaluate hFIX expression levels in plasma and potential liver damages by ELISA and transaminase assays, respectively. Liver tissues were also collected at different time points for histological examinations. We first delivered hFIX plasmid/MB mixture into the livers of C57BL/6 normal mice via portal vein injection, up to 100ng/ml hFIX levels were obtained on day 1 following US treatment, however the levels gradually fell to ~6ng/ml on day 28. In subsequent rat experiments, we investigated gene transfer efficiency with US/MB treatment targeting one or two liver lobes. We found that more significant enhancement of hFIX expression was achieved in rats with two liver lobes treated with US/MB gene delivery compared with rats with only one treated liver lobe. Furthermore, in a hemophilia B mouse model, up to ~100ng/ml of hFIX variant expression was achieved on day 1 following delivery of the hFIX variant plasmid and US/MB treatment, which is significantly higher than hFIX levels detected in plasmid only treated or untreated hemophilia B mice. Most significantly, therapeutic activity levels (6-10%) of FIX are more persistent than those in normal mice over 28 days following treatment (duration of the experiment). Most recently, we have incorporated a newly designed codon-optimized hFIX variant cDNA into our liver-specific vector in order to further increase hFIX gene expression levels. Our data showed that hFIX variant expression can reach up to 200ng/ml on day 1 by using this new plasmid. Transient short-term liver damages were observed in both mice and rats following US/MB treatment as shown by increased transaminase levels with higher levels in rats with multiple lobes treatment than single lobe treatment; both transaminase levels and histological staining showed that these damages recovered within 10-28 days. In summary, we have successfully enhanced hFIX gene delivery efficiency in mice and rats, and in particular, achieved persistent and high levels of hFIX activities in hemophilia B mice. These results demonstrated that US/MB mediated gene transfer is a promising strategy for therapeutic treatment of hemophilia B.
IBMUPROFEN AND ETANERCEPT (TNFA RECEPTOR PROTEIN) INTERFERES WITH THE ENHANCED TARGETED MESENCHYMAL STEM CELL HOMING INDUCED BY PULSED FOCUSED ULTRASOUND (PFUS): IMPLICATIONS FOR CELL THERAPY
Joseph Alan Frank, Pamela Tebebi, Sage Kim, Scott Burks, Ben Nguyen
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Recent studies have demonstrated the utility of noninvasive pulse focused ultrasound (pFUS) in enhanced homing permeability and retention (EHPR) of stem cells to targeted tissues. The purpose of this study is to demonstrate that pretreatment with ibuprofen (IB) a cyclooxygenase (COX) inhibitor or etanercept (ET), a tumor necrosis alpha receptor binding protein inhibits the EHPR effects of pFUS by altering the molecular zip code as well as decreased homing of infused mesenchymal stem cells (MSC) to targeted muscle (M) or kidney (K). Mice (n=6 per time point) were pretreated with IB 30mg/kg PO or ET 100µg IP prior to pFUS using a Sonoblate or VIFU 2000 system with 1Mhz transducer. pFUS exposures was set at 8.9 MegaPascals (MPa); pulse repetition frequency, 5 Hz; duty cycle, 5%; 100 pulses per site and 6-8 points. To determine the effect of IB or ET on cytokines chemokines and trophic factors (CCTF) and cell adhesion molecules (CAM) after pFUS, mice were euthanized unto 10 points following pFUS. IB or ET were also given to mice prior to pFUS followed by 10e6 MSC iv and animals cell counts to targeted tissues was compared to contralateral M or K. pFUS induces a unique expression of CCTF for either M or K with an increase in TNF(4.5x) at 10min following exposure without elevation in Heat Shock Protein 70. Both pro and anti-inflammatory CCTF remained elevated for 48 hour pFUS along with cell adhesion molecules. Following either IB or ET, there was almost complete suppression of all CCTF following pFUS over 48hrs. Coupling intravenous infusion of mesenchymal stem cells (MSC) either before or up to 16 hours after pFUS resulted in 5-8 times (ANOVA p<0.01) more of infused cells homing to M or K as compared to contralateral control. Treatment with either IB or ET prior to pFUS and MSC resulted in significant decrease in homing to contralateral tissue. Pulsed FUS exposure in COX2-/- knockout mice resulted in no differences in number of MSC homing to treated muscle compared to contralateral tissue. pFUS without micro bubbles induced a complex array of alterations in the tissue milieu by provoking a transient molecular zip-code of increased CCTF and CAM. The effects of the transient molecular zip code resulted in enticing IV MSC to actively home and subsequently facilitate transmigration from vascular in pFUS treated areas. Pretreating mice with IB commonly used in treating muscle overexertion or ET used clinically for arthritis resulted in the almost complete suppression of the mechanical effects of pFUS resulting in a decrease homing of MSC to targeted tissues. pFUS induction of CCTF appears to be through COX mediated pathways within tissue. pFUS can be used to evaluate drug-host interactions through interference of pathways and have an important impact on cell homing and therapy.
11:20 AM
ULTRASOUND-TRIGGERED REGULATION OF BLOOD GLUCOSE LEVELS USING INJECTABLE NANO-NETWORK

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Diabetes mellitus is a major public health problem currently affecting 371 million people across the world. Conventional blood glucose (BG) regulation methods are based on subcutaneous injection of insulin multiple times a day by hypodermic needles, insulin pens, or catheters. These methods are painful/invasive, and can cause inconvenience and poor patient compliance, leading to suboptimal BG management. We aim to develop an approach that would allow for long-time sustained, on-demand insulin delivery. We mix positively and negatively charged nanoparticles which form a 3-dimensional (3D) cohesive gel-like nano-network via electrostatic forces. Such a nano-network allows for convenient subcutaneous injections. We expect that dissociation of nano-network upon the trigger of focused ultrasound promotes the release of the “accumulated drug” stored in the unique porous structure of the nano-network. It is expected that, like an insulin arsenal, the subcutaneously injected nano-network can maintain underneath the skin for a certain period and effectively release insulin for multiple times and regulate BG levels by triggering of ultrasound. We found that integration of an injectable nano-network with a focused ultrasound system (FUS) can remotely regulate insulin release both in vitro and in vivo. A maximum of 80-fold increase in the insulin release rate was observed when the nano-network was exposed to the irradiation of ultrasound for 30 sec in vitro. In vivo studies validated that this method provided repeatable and spatiotemporal regulation of blood glucose levels in Type 1 diabetic mice. A single subcutaneous injection of the nano-network with intermittent FUS administration facilitated reduction of the blood glucose levels for up to 10 days. In summary, we have developed a new ultrasound-triggered controlled drug delivery means comprised of injectable nano-network. The gel-like 3D scaffold of nano-network can be effectively triggered to release insulin upon ultrasound-mediated administration. This system provides an unprecedented useful tool for noninvasive, rapid and pulsatile regulation of blood sugar levels of diabetics.

Schematic of the focused ultrasound (FUS)-mediated insulin delivery using nano-network. a) Nanoparticles (NPs) encapsulating insulin are made of PLGA and coated with chitosan and alginate, respectively. b) Nano-network (NN) is obtained by mixing oppositely charged nanoparticles together. The FUS triggers the dissociation of NN and promotes insulin release from the formulation. c) Schematic envision of noninvasive based long-term drug delivery triggered by the FUS after a subcutaneously injection of NN.
11:30 AM
COUPLING MESENCHYMAL STEM CELLS AND PULSED FOCUSED ULTRASOUND BETTER PREVENTS ACUTE KIDNEY INJURY AND RESCUES FUNCTION DURING ONGOING RENAL INSUFFICIENCY
Scott R Burks 1, Ben Nguyen 1, Pamela Tebebi2, Sage Kim1, Jonathan M Street3, Peter S.T. Yuen3, Robert A Star3, Joseph Alan Frank 1
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Pulsed focused ultrasound (pFUS) can noninvasively enhance homing of i.v. infused mesenchymal stem cells (MSC) to healthy pFUS-treated kidneys. This study examined pFUS as a tool to enhance homing to murine kidneys during cisplatinum (CIS)-induced acute kidney injury (AKI). Experimental MSC models and clinical MSC trials administer cells early in disease and attempt to prevent subsequent renal failure. However, most clinical AKI requires treatment as an established disease--an arena where therapeutic development has lagged. Thus, dialysis is the only clinical option and mortality rates remain high. Therefore, we investigated pFUS-enhance MSC homing to kidneys during early AKI (to further improve current MSC approaches) and we also investigated delayed administration of pFUS and MSC until injury was clinically obvious and attempted to rescue renal function. C3H mice received CIS i.p. (15 mg/kg) and pFUS/MSC as described previously (Ziadloo et al. Stem Cells 30:1216). Five groups of mice were used: AKI, AKI+pFUS, AKI+MSC, AKI+pFUS+MSC, and healthy controls. For early treatment (like previous studies), CIS was given on Day 0 with pFUS/MSC on Day 1. Disease developed until Day 4 when renal function (blood urea nitrogen [BUN] and serum creatinine [SC]), morphology, apoptosis, and Ki67 expression were measured. To treat established renal failure, mice received CIS on Day 0 and MSC/pFUS on Day 3. Renal function was measured on Days 4 and 6, and survival was recorded through Day 7. ANOVAs were used for multiple comparisons and log-rank tests compared survival data. pFUS treatment at Days 1 (early) or 4 (late) post-CIS enhanced homing of i.v.-injected MSC by 2-3 fold at either day. To examine improvements over previous MSC therapies for AKI, MSC and/or pFUS were given 1 day post-CIS. MSC alone provided modest protection against AKI, improving BUN clearance and tubular necrosis. While pFUS alone had no effects on AKI outcomes, enhanced MSC homing through pFUS provided additional protection against injury. pFUS+MSC further improved BUN and SCr clearance (Fig 1A), as well as tubular necrosis/apoptosis and Ki67 expression. To examine the more clinically-relevant scenario of intervention during established renal failure, pFUS/MSC treatment was delayed until Day 3 post-CIS. Renal function was measured at Days 4 (24h post-treatment) and 6 (72h post-treatment) and only MSC with pFUS improved BUN clearance. MSC alone (no pFUS) modestly improved survival through Day 7, but pFUS-enhanced MSC homing yielded additional significant increases in survival (Fig 1B). 1) These pFUS exposures have previously been shown to be benign in kidney tissue and they alter the AKI microenvironment to create a "molecular zip code" where MSC preferentially home. 2) Enhanced MSC homing during early AKI further improves MSC protection against AKI and may be the preferred therapeutic approach when AKI is foreseeable (e.g. surgery or chemotherapy). 3) MSC alone improve survival when administered during ongoing renal failure and even greater survival rates are achieved with enhanced MSC homing through pFUS. Therapies have largely failed for AKI that is unforeseeable (e.g. from trauma, sepsis, inadvertent toxicity) and requires treatment after renal function declines. Therefore, MSC or MSC coupled with pFUS represent novel and lone potential therapeutic options to treat established AKI.

Fig 1. A) MSC and pFUS better protect against AKI than MSC alone. AKI was induced by CIS injection on Day 0. MSC with or without pFUS were administered on Day 1 and renal function (BUN and SCr) was measured on Day 4. Symbols indicate statistical differences from all groups with different symbols. B) MSC alone improve the 7-day survival of mice with AKI when treatment is delayed until Day 3 (as opposed to Day 1 in A), during clinically obvious renal insufficiency. Additional improvements in survival are observed by coupling pFUS and MSC infusions.
ULTRASOUND-ENHANCED DELIVERY OF ANTIBIOTICS AND ANTI-INFLAMMATORY DRUGS INTO THE EYE

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1. Electrical and Computer Engineering, George Washington University, Washington, DC, United States.

Delivery of sufficient amounts of therapeutic drugs into the eye in treatment of various ocular diseases is often a challenging task. Our research describes applying ultrasound for increasing corneal permeability for several ocular drugs while generating some changes in corneal structure. Initial studies were carried out using unfocused ultrasound transducers in ultrasound- and sham-treated New Zealand rabbit corneas in vitro in a standard diffusion cell set-up. In these studies, ultrasound application (frequencies of 400 kHz-1 MHz, intensities of 0.3-1.0 W/cm², and exposure duration of 5 min) was tested to overcome the barrier properties of cornea. Permeability of ophthalmic drugs, Tobramycin and Dexamethasone Sodium Phosphate, and Sodium Fluorescein, a drug-mimicking compound, was investigated. Light microscopy observations of histology slides were used to determine ultrasound-induced structural changes in the cornea. After in vitro studies were completed, an in vivo study was designed using the most effective parameters from in vitro experiments. In the in vivo studies, the eye cup filled with drug solution (Dexamethasone Sodium Phosphate) was placed on the rabbit cornea. Ultrasound at frequencies of 400 kHz and 600 kHz, intensity of 0.8 W/cm², and exposure duration of 5 min was applied. Drug concentration in aqueous humor samples, collected after 60 min, was determined using chromatography methods. After animal was sacrificed, corneas were dissected and fixed for histology observations. Theoretical simulations were performed using a finite element modeling software to further understand the temperature changes during ultrasound application and establish the safety of the proposed application. Results from in vitro showed an increase of 32-47% for Tobramycin, 46-126% (p < 0.05) for Sodium Fluorescein, and 32-109% (p < 0.05 except for 1-MHz ultrasound application) for Dexamethasone Sodium Phosphate in corneal permeability. Histological analysis showed some structural changes in the cornea due to ultrasound application, which were limited to epithelial layer, with no changes observed in stroma and endothelium. Results for in vivo study showed that increase in drug concentration in aqueous humor samples was 2.8 times (p < 0.05) at frequency of 400 kHz and 2.4 times (p < 0.01) at frequency of 600 kHz, as compared to sham treated samples. Histological analysis showed that minor structural changes were present in first layers of corneal epithelium. Investigating the thermal and mechanical effects of ultrasound in enhancing ocular drug delivery showed that one of the key mechanism was cavitation activity, especially presence of inertial cavitation. Results for modeling study showed the maximum temperature was approximately 38.5°C and 39.5°C in the lens (increase of 1.5-2.5°C from base temperature of 37°C) at frequency of 400 kHz and 600 kHz respectively at 0.8 W/cm² intensity. The simulation results showed that temperature was elevated at higher frequencies, and lens was the most affected eye structure. Ultrasound application provided enhancement of drug delivery, increasing the permeability of the cornea, and has a potential to provide effective and safe method for ocular drug delivery in treatment of eye infections and inflammations.
IN VIVO CAVITATION ENHANCED DELIVERY OF DOXORUBICIN IN MOUSE PANCREATIC TUMORS
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1. Center for Industrial and Medical Ultrasound, University of Washington, Seattle, WA, United States. 2. Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, WA, United States.

Pancreatic ductal adenocarcinoma is characterized by stromal desmoplasia and vascular dysfunction, which critically impairs drug delivery. In order for chemotherapeutic agents to be effective, they must penetrate through the stromal tissue, otherwise, cancer cells will not be exposed to sufficient drug. Pulsed high intensity focused ultrasound (pHIFU) induced acoustic cavitation and the subsequent disruption of capillaries and stromal tissue have been found to play a key role in enhancing drug penetration and uptake. However, the ideal pHIFU parameters are tissue specific and still controversial. In this study, pHIFU treatment was applied to induce cavitation in a genetically engineered mouse model of naturally occurring pancreatic ductal adenocarcinoma and to promote the penetration of chemotherapeutic agent doxorubicin (Dox) into the tumor. The goal of this study was to correlate the presence and degree of cavitation activity to the enhancement of drug delivery by the tumor cells. pHIFU exposures of varying intensities were applied to the pancreatic tumor in transgenic KPC mice. Two HIFU transducers with center frequencies of 1.1MHz (peak negative pressures 1.6-12MPa) and 1.5MHz (peak negative pressures 2.2-19.6MPa) were used in different groups of animals to evaluate the effect of frequency on cavitation activity during treatment. The following cavitation metrics were calculated from the acquired PCD signals: cavitation probability, cavitation persistence and broadband noise level.

Doxorubicin was administered during or post pHIFU treatment. The enhancement of drug uptake in the treated area of the tumor was evaluated by multispectral imaging, fluorescence microscopy and high-pressure liquid chromatography (HPLC). The untreated area of the same tumor was used as an internal control. As evident from multispectral imaging of the tumor, Dox uptake was notably enhanced in the treated area for the pressure levels that exceeded cavitation threshold. The fluorescent microscopy suggested the tumor vasculature was disrupted and drug penetrated through the dense structure of stromal tissue in the treated regions. The HPLC results showed that the ratio of drug concentration in treated and non-treated tumor tissue increases with the applied peak negative pressure. The relative Dox concentration in treated tumor area was significantly different from the control group when peak negative pressure exceeded cavitation threshold level, i.e. cavitation occurred during every delivered HIFU pulse, irrespective of focus location in the tumor, and the broadband noise level during each pulse was significantly higher than at lower peak negative pressure levels. The results demonstrate that reliable and intense cavitation correlates with enhanced (2-4 fold) Dox uptake beyond tumor vasculature. Cavitation threshold is considerably higher at 1.5MHz than 1.1 MHz HIFU frequency. However, due to a smaller focal area, the 1.5 MHz transducer allowed to minimize collateral damage to the animal and was therefore more efficient overall. Work is supported by the NIH grant R01CA154451 and 1K01EB015745.
RADICAL HIFU IN LOCALIZED PROSTATE CANCER
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High intensity focused ultrasound (HIFU) as therapy for localized prostate cancer is combined with TURP to standardize prostatic volume for complete prostatic ablation with HIFU. To evaluate efficacy and side effects three treatment strategies were analyzed: A) “HIFU Monotherapy” (without TURP), B) “TURP and HIFU in one session” and C) “TURP one month before HIFU”. The prospective monocentric “Harlaching HIFU Database” (n > 2,300, since 96) was the primary data source (managed independently by HKH Cancer foundation). Only T1-2, N0, M0 patients with sufficient follow up were included: Group A) 1998-2000, group B) 2001-2004, group C) 2005-2010. None of the patients had previous long term PCa/PSA influencing therapy. All patients were treated completely with Ablatherm® (EDAP-Lyon-France). No patients with focal or partial HIFU treatments were included. During a median follow up time of 5.5 years (range 0.5 – 15 years) a PSA Nadir < 0.1 ng/ml and a PSA velocity of < 0.05 ng/ml/year was observed. Patients showed median PSA levels of < 0.3 ng/ml after median 5 years of follow up. Side effects were moderate, infravesical stenosis was the most frequent one (24%) with the need for 2nd TURP.

<table>
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<tr>
<th>Ablatherm® device:</th>
<th>Prototype</th>
<th>Maxis</th>
<th>Integrated imaging</th>
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<tr>
<td>evaluable T1-2 patients</td>
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<td>358</td>
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<td>45</td>
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<td>PSA at diagnosis (median)</td>
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<td>5.4</td>
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<td>PSA Nadir (median)</td>
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<td>Prostate volume final (cc)</td>
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<table>
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<th>Rate of side effects</th>
<th>Prototype</th>
<th>Maxis</th>
<th>Integrated imaging</th>
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<td>Incontinence &lt; 3 months (%)</td>
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<td>4.2</td>
<td>3.1</td>
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<td>Incontinence &gt; 3 months (%)</td>
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<td>Recto-urethral fistula (%)</td>
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<td>Others perioperative (%)</td>
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<td>2nd endouro intervention (%)</td>
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<td>Others in follow up (%)</td>
<td>1.26</td>
<td>0.0</td>
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</table>

TURP before HIFU resolves technical restrictions, expands indications, standardizes any prostate.

PSA Nadir < 0.1 ng/ml, PSA velocity/year of 0.05, last median PSA levels after 5 years of 0.3 ng/ml showed a high oncological efficacy. Retreatment rate for recurrent PCa decreased to 15% within the last 5 years.
2:25 PM
PHASE I CLINICAL TRIAL OF THE PAD-105 MRI-GUIDED TRANSURETHRAL ULTRASOUND ABLATION SYSTEM FOR THE TREATMENT OF LOCALIZED PROSTATE CANCER: INITIAL OUTCOMES OF A MULTI-CENTRE PROSPECTIVE STUDY
Mathieu Burtnyk 1, Michele Billia 2, Cameron Wright 1, Matthias Roethke 3, Sascha Pahernik 4, James Relle 5, Heinz-Peter Schlemmer 3, Joseph Chin 2
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MRI-guided transurethral ultrasound ablation (TULSA) is an emerging minimally-invasive technology for the treatment of prostate cancer, which aims to provide local disease control with low morbidity. A transurethral ultrasound device generates a continuous volume of thermal coagulation that is shaped precisely to the prostate using real-time MR thermometry and active temperature feedback control. A phase I clinical trial of MRI-guided TULSA was initiated with the world's first primary-care patient treatment in March 2013. Primary objectives of this multi-centre, prospective study are to determine the safety and feasibility of MRI-guided TULSA using the PAD-105 (Profound Medical Inc., Canada). Secondary objective is to assess its efficacy for treatment of localized prostate cancer. This ethics-approved study is enrolling a total of 30 patients with biopsy-proven, low-risk, localized prostate cancer: age ≥ 65 years, clinical stage T1c/T2a, PSA ≤ 10ng/ml, Gleason Score ≤ 3+3 (3+4 max in Canada only). MR imaging is performed using a 3T clinical magnet (Siemens, Germany) and an 18-channel phased-array coil. The transurethral device is inserted under general anaesthesia and positioned precisely in the prostatic urethra with direct feedback from an MRI-compatible positioning system and MR imaging. Treatment planning is performed with the therapeutic intent of whole-gland ablation. Ultrasound treatment is delivered in one session under 3D active MR thermometry feedback control (PRF-shift method, EPI sequence, FOV 26cm, matrix 128x128, slice 4mm, gap 1mm, TE 8ms, TR 350ms, 12 image slices acquired in 5.9sec), where targeted prostate tissues are heated to ≥55°C (acute ablation volume). To conform the acute ablation volume to the prostate, the rotation rate of the transurethral device as well as the ultrasound power and frequency of each transducer element are adjusted during treatment by the active temperature feedback control algorithm (linear array of 10 independent planar rectangular transducers, each 4.5x5.0mm^2, operating at 4 or 14MHz continuous wave, acoustic power ≤ 4W per element SATA). After treatment, the patient recovers as an outpatient procedure. Safety and feasibility endpoint follow-up is 12 months, with complete study follow-up to 5 years. Comprehensive clinical monitoring includes adverse event assessment, prostate MRI, serial PSA, TRUS biopsy and quality-of-life questionnaires. MRI-guided TULSA was well-tolerated by all 18 patients treated to-date. There were no cases of urinary incontinence, fistula or rectal injury reported, and normal urinary function returned after catheter removal. Median (range) prostate volume and treatment time were 44cc (33-95cc) and 30min (24-61min), respectively. MR thermometry measurements depict a continuous region of heating and a high degree of spatial control of the acute ablation volume to within ±0.1±1.3mm, with over- and under-targeted volumes of 0.4cc (0.0-1.4cc) and 1.2cc (0.1-2.7cc), respectively, and Dice Similarity Coefficient of 0.94 (0.90-0.96). In all cases, the acute ablation volume correlated well with the NPV on CE-MRI. Successful treatment was further indicated by a PSA decrease at 1-month of 90% (60-99%) to 0.7ng/ml (0.1-3.3ng/ml), with the nadir expected by 6 months. Preliminary results of this phase I clinical trial indicate that MRI-guided TULSA for whole-gland ablation of the prostate is feasible, safe, accurate and precise. MRI-guidance enables accurate planning, real-time dosimetry and control, and post-treatment assessment of the thermal ablation volume.
COMPARISON BETWEEN HIGH-INTENSITY FOCUSED ULTRASOUND DEVICES FOR THE TREATMENT OF PATIENTS WITH LOCALIZED PROSTATE CANCER

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High-intensity focused ultrasound (HIFU) is minimally invasive surgical treatment for prostate cancer. In this study, we aimed to evaluate the long-term outcomes of patients with prostate cancer who underwent HIFU, comparing between the devices used in terms of risk stratification and complication rates. The study subjects comprised 937 patients with stage T1c-T3N0M0 prostate cancer treated with Sonablate (SB) devices from 1999 to 2013. All patients were followed up for more than 2 years. The 3 treatment groups were as follows: group 1, SB200/SB500 (412 patients treated from 1999 to 2006); group 2, SB500 ver. 4 (253 patients from 2005 to 2009); and group 3, SB 500 TCM (275 patients from 2007 up to the present). A Kaplan-Meier analysis was performed to determine the overall, cancer-specific, and biochemical disease-free survival (bDFS) rates according to the Phoenix definition. The mean follow-up periods in groups 1, 2, and 3 were 55, 53, and 42 months, respectively. The 10-year overall and cancer-specific survival rates were 88% and 98%, respectively. The 5-year bDFS rates in groups 1 - 3 were 49%, 61%, and 75%, respectively (p < 0.0001). The 10-year bDFS rates in the low-, intermediate-, and high-risk groups were 63%, 54%, and 30%, respectively (p < 0.0001), whereas the 5-year bDFS rates in group 3 were 92%, 79%, and 65%, respectively (p = 0.0186). The overall negative biopsy rate was 87%. Multivariate analysis revealed that pretreatment PSA levels, neoadjuvant hormonal therapy, stage, HIFU devices (p < 0.0001), and Gleason score (p = 0.0094) were statistically significant variables. Urethral stricture was observed in 18.6% of the cases. Grades I and II stress incontinence were observed in 1.6% and 0.5% of the cases, respectively. The improvement of the clinical outcomes was device dependent. Thus, technological advances that are continually being made for the improvement of treatment devices in terms of accuracy, ease of use, and safety.

![Biochemical Disease-free Survival Rates with Each Device](image-url)
To utilize in situ temperature measurements, acoustic and biothermal modeling, and data fitting techniques in the analysis of heat distributions generated during clinical interstitial ultrasound hyperthermia (HT) treatments of locally advanced prostate cancer. Thermal dosimetry analyses from a clinical pilot study where ultrasound hyperthermia was administered to the prostate in conjunction with high-dose rate (HDR) brachytherapy are presented here. As part of a clinical pilot study, HT was administered to patients with locally advanced prostate cancer. HT was delivered by ultrasound applicators from within multiple 13-g brachytherapy catheters implanted along the posterior periphery of the gland. The heating applicators were linear arrays of sectored tubular transducers (~7 MHz), with independently powered array elements which were capable of energy deposition with 3D spatial control. Heat treatments were administered following radiation therapy. Typical exposures employed time-averaged peak acoustic intensities of 1 – 3 W/cm² and lasted for 60 – 70 minutes. Throughout the treatments, temperature was monitored using multi-junction thermocouples, placed within available brachytherapy catheters in mid-gland prostate. The mid-gland region was also identified as the hyperthermia target volume (HTV). Clinical constraints allowed placement of 8 – 12 thermocouple sensors in the HTV. 3D temperature profiles obtained during the hyperthermia treatments were estimated using a modified patient-specific thermal treatment planning platform (finite element methods used to evaluate Pennes bioheat transfer models) previously designed for catheter-based ultrasound devices. The applied power levels were based on transient data recorded during the treatments. The patient anatomy, heating device positions, orientations, and thermometry junction locations were obtained from patient CT scans and HDR treatment planning software. Six hyperthermia treatments, representing two implants per patient, were simulated using finite element methods (FEM). Tissue properties such as perfusion and acoustic absorption were varied within physiological ranges such that squared-errors between measured and simulated temperatures were minimized. This data-fitting was utilized to estimate volumetric temperature distributions in the HTV and surrounding anatomy devoid of thermocouples. For these treatments, the measured and simulated T50 values in the hyperthermia target volume (HTV) were between 40.1 – 43.9 °C and 40.3 – 44.9 °C, respectively. Transient changes in temperature correlated consistently between measurement and simulation. Maximum temperatures between 46.8 – 49.8 °C were measured during these treatments and the corresponding range obtained from simulation was 47.3 – 51.1 °C. The simulations also estimated an EM43oC thermal dose between 7.3 – 10 min. in more than 50% of the HTV. Based on the simulations, the maximum temperatures in the bladder and the rectum were below 41.7 °C and 41.1 °C, respectively. Real-time embedded thermometry and model-based data fitting techniques were employed to evaluate clinical HT delivery to the prostate with interstitial ultrasound, applied from within HDR implant catheters. Temperature measurements and simulations confirmed that therapeutically relevant temperatures could be established and sustained in mid-gland prostate, with tolerable thermal dose to the surrounding tissue (NIH R01 CA 122276).

Comparison between T50 calculated from thermocouple measurements and numerical simulations for all patient cases.
2:55 PM  
FOCAL TREATMENT OF PROSTATE CANCER USING A DYNAMIC FOCUSING HIFU PROBE AND AN ELASTIC MR-US REGISTRATION SYSTEM: PILOT STUDY RESULTS  
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To evaluate the ability of a new high-intensity focused ultrasound (HIFU) device with a dynamic focusing probe (Focal One®, Edap-TMS, France) to perform HIFU therapy of the prostate. In addition, a new method of treatment planning for focal treatment of the prostate using elastic registration of magnetic resonance and ultrasound (MR-US) imaging was demonstrated. Focal One® is a device designed for the focal therapy of Prostate Cancer combining the necessary software tools to visualize, target, treat and validate the treatment. MR images acquired prior to treatment are first used to define the contours of the prostate as well as the regions of interest (ROI) that have been confirmed with biopsy as cancerous tissue. The same contouring of the prostate is performed on a live ultrasound volume acquired by the transrectal probe during the treatment procedure. The Focal One software then performs an “elastic fusion” of the two acquired images: the live Ultrasound volume is considered as the reference volume and the MR volume is smoothly deformed to match it. The same 3D elastic transformation is applied to the ROIs initially indicated on the MR image so that they appear at the adequate position on the live Ultrasound Image, guiding the planning process. The Focal One® is equipped with a new generation of HIFU probe able to electronically steer the focal point along the acoustic axis using a multi-element annular HIFU array. During the HIFU treatment step, the operator views a live ultrasound image of the zone being treated and, if necessary, can readjust the treatment planning. At the end of the treatment process, a Contrast-Enhanced Ultrasound (CEUS) volume is acquired showing the de-vascularized areas. This image volume can furthermore be superimposed with the treatment planning as well as the initial MR image showing the theoretical lesions obtained. This pilot study was approved by the local ethics committee. Ten (10) patients with small focal low or intermediate risk localized prostate cancer were treated using the Focal One® between March and November 2013. Patients were not candidates for active surveillance (Priass criteria). All tumors were precisely localized with MRI and targeted biopsies. The mean age was 66.9 ±4.8, the mean PSA value was 4.72 ±2.8 ng/ml and the mean prostate volume before treatment was 51 ±23 cc. The mean treated volume was 14.3 cc (28% of the prostate volume). In all patients treated, complete destruction of the targeted tumor was demonstrated using CEUS performed during the HIFU session. Contrast-enhanced MRI and targeted biopsies inside and at the rime of the treated area performed between day 2 and day 30 after the HIFU session respectively also showed destruction that agreed well with CEUS. The Focal One® device can be used for complete destruction of small focal prostate cancer using an elastic magnetic resonance-ultrasound (MR-US) registration system for tumor location and HIFU treatment planning.
Focal magnetic resonance guided intensity focused ultrasound treatment offers a novel strategy that targets the cancer rather than the prostate in an attempt to preserve tissue and function. Its aim is to achieve long-term cancer control with minimal morbidity. A prospective, ethics committee approved trial was conducted to determine the side effects of focal magnetic resonance guided intensity focused ultrasound treatment on ExAblate 2100 (InSightech). The purpose of this study was to evaluate the safety and initial effectiveness of focal ExAblate MR-guided focused ultrasound treatments for the treatment of organ-confined low risk prostate cancer (LRPC). 22 adult males between the age of 49 and 73 were underwent 23 focal treatments for locally confined LRPC. One patient underwent two treatments due to two different foci. 5 SAE’s were reported; 4 of them were treatment-related. 3 treatment-related SAE’s were acute urinary retention, and one was chronic stricture of the urethra and bladder neck that required further intervention for resolution. Urinary tract symptoms were reported in the questionnaires by 9 patients out of 23 (39%) during their last follow-up visit; 2 of them were reported as SAE’s. Urinary Incontinence was reported by 2 patients in their self-reported QoL questionnaires. In one patient it was part of the urinary obstructive symptoms (overflow incontinence) until he underwent TURP. The other patient had no urinary obstructive symptoms, and specific investigation by the PI did not reveal any clinical incontinence. 3 out of 18 (17%) patients that were potent or partially potent before procedure had impaired sexual function after treatment compared to baseline. Biopsy results after 6 months of follow-up are available for 23 patients. 2 patients dropped out of the study prior to completion of their follow-up periods (one patient due to disease progression and the second patient due to non-clinical reasons). At 6-mo follow-up 9 out of 23 biopsies (39%) were positive; all of them were in newly detected foci (from sectors that were negative at screening); 2 of these biopsies comprised stage upgrading as compared to baseline, (i.e., Gleason 7). This work shows that Focal ExAblate treatment has a promising safety profile and adverse events are mild and transient. However, cancer localization improvement is crucial for tumor control.
FOCAL THERAPY FOR LOCALIZED UNIFOCAL AND MULTIFOCAL PROSTATE CANCER: A PROSPECTIVE DEVELOPMENT STUDY USING REAL TIME MR GUIDED FOCUSED ULTRASOUND

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To assess safety and feasibility of non-invasive high intensity 3T MR guided focused ultrasound (MRgFUS) treatment of localized prostate cancer in an exploratory designed study. Men aged 45–80 years were eligible for this prospective study if they had low-risk localized prostate cancer (prostate specific antigen [PSA] ≤10 ng/mL, Gleason score ≤ 3 + 3), with no previous androgen deprivation or treatment for prostate cancer, and who could safely undergo multiparametric MRI (Discovery 750, GE; Gd-Bopta, Bracco) and have a spinal anesthetic. Patients underwent focal therapy using real time MR guided high intensity focused ultrasound (MRgFUS), delivered to all known cancer lesions, with a margin of normal tissue. Primary endpoints were adverse events (serious and otherwise) and urinary symptoms and erectile function assessed using patient questionnaires. 8 men were recruited between June 2011 and June 2012. After treatment, one man was admitted to hospital for acute urinary retention. Another patient had self-resolving, mild, intermittent dysuria (median duration 5.0 days). Urinary tract infection was not reported. Urinary debris occurred in 6 men (75%), with a median duration of 12 days. Median overall International Index of Erectile Function-15 (IIEF-15) scores were similar at baseline and at 6 to 12 months (p=0.060), as were median IIEF-15 scores for intercourse satisfaction (p=0.433), sexual desire (p=0.622), and overall satisfaction (p=0.256). There was an improvement in lower urinary tract symptoms, assessed by International Prostate Symptom Score (IPSS), between baseline and 6 to 12 months (p=0.026). All 8 men with no baseline urinary incontinence were leak-free and pad-free by 9 months. No histological evidence of cancer was identified in 7 of 8 men biopsied at 6 months (87.5%); overall, the entire population (8 patients) was free of clinically significant cancer and had no evidence of disease on multi-parametric MRI at 6 to 12 months. MR guided Focused Ultrasound focal therapy of individual prostate cancer lesions, whether multifocal or unifocal, leads to a low rate of genitourinary side-effects and an encouraging rate of early absence of clinically significant prostate cancer.
PILOT EVALUATION OF A NON-INVASIVE ULTRASOUND LIQUID MOLECULAR BIOPSY:
BOILING HISTOTRIPSY INDUCED RELEASE OF CANCER ASSOCIATED MIRNAS IN A RAT PROSTATE CANCER MODEL

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Prostate biopsy for prostate cancer (PCA) is invasive with associated morbidity and several diagnostic limitations, suggesting the need for a new approach. The ability of moderate intensity ultrasound to stimulate release of cancer-specific extracellular protein biomarkers was recently reported. In order to induce the release of intracellular biomarkers, exposures optimized for mechanical disruption of cells may be desirable. One possible approach is to induce targeted tumor tissue lysis with boiling histotripsy (BH). BH is a high-intensity focused ultrasound (HIFU) technique utilizing ms long pulses to create boiling bubbles via rapid shockwave heating. Interaction of shocks with the ensuing vapor cavity fractionates tissue with negligible thermal effect. The resulting tissue-lysis/permeabilization may induce the release of intracellular biomarkers into the circulation for detection. Tumor-associated microRNAs (miRNAs) are one class of intracellular biomarkers that have been observed circulating in cell-free form and are diagnostic and prognostic biomarkers for cancer, but are often present in low abundance. As a result, we evaluated the ability of two different HIFU strategies (hyperthermia and non-thermal cell-lysis by BH) to release PCA specific miRNAs in a rat PCA model. Putative miRNA biomarkers were identified using RT-PCR array profiling (Exiqon) of the syngeneic MatLyLu rat PCA cell line. Adult intact male Copenhagen rats were surgically modified with implanted jugular-vein catheters to enable serial, puncture-free blood collection. Rats were then subcutaneously grafted with syngeneic prostate cancer cells (MatLyLu). When tumors were >1cm, the rats were divided into one of two separate HIFU treatment groups: HIFU optimized for sub-lethal gentle heating (120 W/cm2, 50% duty cycle, N=7), BH (~30KW/cm2, 1% duty cycle, N=8) or a sham procedure (N=5) using a 1.5 MHz transducer under ultrasound image guidance. Blood was collected immediately prior to treatment and serially over a 24-hour time course. Specimens were immediately processed into plasma and miRNA extracted Plasma concentrations of candidate tumor-derived miRNAs were measured via quantitative real-time polymerase chain reaction (qRT-PCR). Relative plasma concentrations (RPC) of miRNAs were compared with ANOVA and the Mann-Whitney test. Following treatment with thermal HIFU and sham procedures, no significant changes were observed in the relative plasma concentrations of any evaluated miRNA. Conversely, following BH treatment, the relative plasma concentrations of the putative PCA-derived miRNAs miR-34c and miR-196a increased significantly while the relative concentration of the broadly expressed, non-PCa specific miR-16 was not significantly altered by BH (1.24-fold peak increase). PCA-derived miRNA concentrations peaked at 0.25 hr (miR-34c: 23.4-fold, p=0.0127 vs sham; miR-196a: 10.2-fold, p=0.0007 vs sham) from initiation of BH treatment, remained significantly elevated for 3 hours (p= 0.008, p=0.0047, respectively vs sham), and then returned to baseline within 24 hrs (see figure). BH can efficiently increase the release of putative PCA-derived plasma miRNAs in the syngeneic rat PCA model. Further studies will optimize exposures and establish the minimum-required lysed tumor volume for further development of BH “biopsy”.

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THERMAL EFFECTS OF MIXED PERFLUOROCARBON NANODROPLETS ON HIGH INTENSITY FOCUSED ULTRASOUND ABLATION IN LIVER AND TUMORS
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High intensity focused ultrasound (HIFU) ablation is FDA-approved for ablation of both uterine fibroids and bone metastases. It is also under pre-clinical evaluation for the treatment of a variety of cancers including breast, prostate, liver, pancreas, and brain. Due to the small treatment volume of HIFU, these procedures can require hours of treatment. Perfluorocarbon contrast agents, or microbubbles, are known to enhance the speed and volume of lesion creation during HIFU. Microbubbles, however, can result in superficial skin heating, and remain in circulation on the order of minutes, minimizing their clinical translation. We have designed a mixed-perfluorocarbon nanodroplet that offers a lower acoustic threshold to induce heating, while maintaining focused heating. This a perfluorocarbon nanodroplet agent (1:1 decafluorobutane, and dodecofluoropentane) that activates only at the higher pressures present at the acoustic focus. We hypothesized that this dual-perfluorocarbon nanodroplet formulation would 1) enhance HIFU thermal deposition and, 2) remain effective in vivo longer than microbubbles. HIFU ablation was assessed in Sprague-Dawley rats (~200g) either in the liver, or in C6 glioma flank tumors. Microbubbles (2.1 +/- 0.5 µm) and nanodroplets (240 +/- 65 nm) were prepared in house and injected into rats (n=3 per group). Under magnetic resonance guidance, continuous wave HIFU (1MHz, 15 seconds) was focused into each liver or tumor either 5, 15, or 95 minutes after the injection of the nanodroplets. The HIFU intensity was set to 15W for livers. Since the tumors were superficial, a HIFU beam intensity of 12W was applied to the tumors at the latest time point in order to avoid skin burns. Thermal enhancement throughout both tissues was assessed by magnetic resonance thermometry via phase mapping of the proton resonance frequency shift. Without the presence of any agents, HIFU induced temperature rises of 13 +/- 6 deg. C in liver, and 14 +/- 10 deg. C in tumors. The nanodroplets enhanced HIFU heating at all three time points in the livers, resulting in peak temperature rises of 52 +/- 14 deg. C 95 minutes after their injection. The average HIFU and nanodroplet-induced temperature rise observed in the tumors was 34 +/- 5 deg. C at 15W after 15 minutes. Applying only 12 W to tumors 95 minutes after injection of the nanodroplets did not result in a significant increase in thermal enhancement compared to agent-free controls. This result may partially be due to the lower acoustic intensity applied and/or the different physiology of the tumors compared to the livers. The nanodroplets provided enhanced ablation in the liver for least 95 minutes whereas microbubbles typically circulate for less than 15 minutes. Although enhanced ablation was observed in both the liver and tumors, the effective ablation time was shorter in the tumors. A greater range of time points will be evaluated in the future. The liver may preferentially filter the nanodroplets resulting in a higher dose within the liver compared to the tumors. Comparison studies are underway to assess the effective HIFU-ablation lifetime of microbubbles in vivo. These mixed-perfluorocarbon nanodroplets may offer a longer-lasting, safe method of ablation enhancement by HIFU, as demonstrated by the increased thermal deposition combined with a reduced pressure requirement to induce ablation.
Phase-shift Nano-emulsion (PSNE) with a small initial diameter in nanoscale has the potential to leak out of the blood vessels and to accumulate at target point of tissue. At desired location, PSNE can undergo acoustic droplet vaporization (ADV) process, change into gas bubbles and enhance focused ultrasound efficiency. The aim of this work was to provide spatial and temporal information on PSNE induced cavitation and ablation effects during pulsed high intensity focused ultrasound (HIFU) exposure. The PSNE was composed of dodecafluoropentane (DDFP) and bovine serum albumin (BSA), and then uniformly distributed in a transparent polyacrylamide phantom. The Sonoluminescence (SL) method was employed to visualize the cavitation distribution and formation process of PSNE induced cavitation. For the phantom which was used for ablation observation, heat sensitive BSA was added. When the temperature generated by ultrasound exposure was high enough to denature BSA, the transparent phantom would turn out white lesions. The shape of the lesion and the formation process were compared with those of cavitation. Each of the pulse contained 12 cycles for a duration of 10µs. And the duty cycle changed from 1:10 to 1:40. The total on time of HIFU was 2s. PSNE can evidently accelerate cavitation emitting bright SL in pre-focal region. The cavitation was generated layer by layer towards the transducer. The formed bubble wall can block acoustic waves transmitting to the distal end. And the lesion appeared to be separated into two parts. One in pre-focal region stemmed from one point and grew quickly toward the transducer. The other in focal region was formed by merging some small white dots, and grew much slower. The influence of duty cycle has also been examined. The lower duty cycle with longer pulse-off time would generate more intense cavitation, however, smaller lesion. Bubble cloud gradually developed within phantom would greatly influence the cavitation and ablation process. One hand, the evaporated bubbles could enhance both the cavitation and thermal effects of HIFU. The other hand, outside layer bubbles would block the acoustic wave transmission, inducing distinctive cavitation and ablation formation process. The spatial distribution of cavitation and lesion organized into special structures under different acoustic parameters.
CHARACTERISATION OF A CAVITATION CLOUD IN TISSUE USING ULTRAFAST ULTRASOUND IMAGING
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The local application of ultrasound is known to improve drug intake by tumors. The appearance of cavitating bubbles is one of the contributing effects. Due to the random aspect of the cavitation activity there is a need to monitor its intensity and spatial extent to ensure proper treatment of the targeted volume of tissue. Ultrafast ultrasound imaging should allow studying the appearance and evolution of the cavitation cloud in tissue. A setup where two ultrasound transducers are placed confocally is used to generate cavitation in ex vivo chicken filet. The transducers emit a series of short pulses with high amplitude at a low pulse repetition frequency to create cavitation and avoid excessive heating. As a sequence of pulse is transmitted, the creation and evolution of the cavitation activity is monitored using an ultrafast ultrasound imaging system. This system provides several tens of images between consecutive pulses. The post-processing of the obtained sequence of images computes the correlation between two consecutive images. The area of the image that is decorrelated provides an estimate of the zone where cavitation is present. Further analysis determines the evolution of the area of cavitation and of its geometrical center throughout the transmission of the pulse sequence. The post-processed sequence of images reveals that once bubbles have been created in the tissue, they remain for a short time even when no ultrasound is applied. In some cases, the cavitation cloud remains visible until the next pulse is transmitted. The evolution of the size and geometrical center of the cavitation cloud between pulses shows a repeatable pattern through a pulse sequence. The size of the cavitation cloud is maximum just after the transmission of a pulse and decreases exponentially until the next pulse. From a state of rest, the size of the cavitation cloud following the transmission of a pulse increases for the first pulses until it reaches a nominal size that it keeps through the remaining pulses. The creation and evolution of the cavitation cloud in ex vivo tissue was observed using ultrafast ultrasound imaging. It allows an estimation of the size of the cavitation cloud and its position within the tissue. It also shows that cavitation bubbles remain for some time after ultrasound stimulus has stopped. This method of monitoring cavitation activity could potentially be used in devices aimed at enhancing drug delivery using ultrasound and cavitation. It allows a quantification of the extent of the cavitation cloud and of its geometrical center.
NANOPARTICLES FOR INDUCING INERTIAL CAVITATION ON-DEMAND WITHIN TUMOURS
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Inertial cavitation has been shown to play a key role in oncological applications of therapeutic ultrasound, ranging from direct tumour ablation to ultrasound-triggered drug release and ultrasound-enhanced drug delivery. The elevated inertial cavitation threshold of tissue requires either the use of high therapeutic ultrasound intensities, or the injection of artificial nuclei, such as ultrasound contrast agent microbubbles. However, these gaseous particles are unable to pass through leaky tumor endothelium into tumours due to their large size, typically between 1-10 micrometers in diameter. Furthermore, microbubbles are rapidly destroyed by inertial cavitation and thus require continuous infusion, a process limited by the maximum tolerated dose. There is thus an urgent need for nanoscale agents capable of inducing repeatable inertial cavitation on demand. Here we present two novel formulations of crevasse-type nanoparticles (< 600 nm) that entrap nanobubbles on their outer surface as opposed to encapsulation of gas. The nanoparticles are first fully characterised for size, zeta potential, and cytotoxicity. Additionally, the cavitation behaviour of both types of nanoparticles is modelled using a modified Rayleigh-Plesset equation that was adapted to account for nanoscale crevasses. Inertial cavitation thresholds, defined as the lowest peak rarefractional pressure to result in the onset of broadband acoustic emissions, are finally determined experimentally at excitation frequencies of 0.5 and 1.6 MHz using passive cavitation detection techniques under both static and flowing conditions. Experimental results demonstrate that both types of nanoparticles, which are in the size range 100 - 600 nm, induce inertial cavitation at both low (0.5 MHz) and high (1.6 MHz) frequencies at modest peak rarefractional pressure amplitudes (< 3 MPa). Inertial cavitation thresholds are accurately predicted by the modified Rayleigh-Plesset model. Both types of nanoparticles exhibit different cavitation responses compared to the conventional ultrasound contrast agent Sonovue, remaining active over hundreds of incident pulses with only modestly decaying responses. The unique size characteristics and repeatable cavitation behaviour enable these nanoparticles to extravasate into tumours, and to provide intratumoural cavitation on demand for both surgical and drug delivery applications. Lastly, the ability to model their cavitation response and modify their size and surface characteristics during manufacturing suggests the possibility of tuning their response to specific excitation frequencies.
Ultrasound-induced inertial cavitation has been used extensively for non-invasive surgeries. Nucleation thresholds are reached using low-frequency ultrasound, with concomitant target sizes of a few millimeters at best. A new type of theranostic nanoagent has been developed as a combined ultrasound/photoacoustic agent for both molecular imaging and targeted therapies. Its small size (100 nm) and reduced cavitation threshold could permit targeted therapies with great potential for sono-trombolysis since the nanoagent can diffuse within the clot. This work aims to quantify cavitation thresholds with combined light and ultrasound exposures. The theranostic nanoagent is composed of a nanoemulsion core encapsulated with a layer of gold nanospheres at the water/oil interface. The optical absorption spectrum is broadened up to 1100 nm, enabling 1064 nm pulsed laser excitation of cavitation nuclei, which can also be excited using ultrasound alone only at a high mechanical index. If light is delivered to the target at peak negative pressure during ultrasound exposure, cavitation thresholds can be greatly reduced. A 1.24 MHz, spherical, single-element transducer (Sonic Concepts, Seattle) has been used with a portable 1064 nm fiber-laser (HM 40W G3.1, SPI, South Hampton, UK) to insonify/illuminate a 1.6mm tube filled with nanoemulsion. Cavitation was detected with a broadband PVDF transducer recording the ultrasonic scattered wavefield. Laser-induced cavitation activity was prolonged with ultrasound exposure, allowing a more significant therapeutic effect. Inertial cavitation was clearly identified using broadband noise measurements. Bubble nucleation appears at lower exposure when light is delivered at peak negative pressure. A parameter sweep of laser fluence and acoustic pressure was performed to determine the cavitation probability for each condition, distinguishing between stable and inertial cavitation. Cavitation probability can be raised from 0% to at least 80% at 1 MPa using a laser fluence under 100 mJ/cm2. In vitro thrombolysis was achieved with this new emulsion. This work presents a potential solution for laser-assisted sonothrombolysis using a nanoemulsion composite. Since exposure levels are greatly reduced by the proper combination of laser and ultrasound, safe therapeutic targeting can potentially be achieved without damaging surrounding tissue (e.g., blood vessels). Further work will aim to optimize in vitro clot breakage, measure the size of resulting debris, and develop treatment monitoring modalities.
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INSTIGATION AND REAL-TIME MAPPING OF CAVITATION FROM NANOPARTICLES USING A DIAGNOSTIC IMAGING PLATFORM
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Inertially cavitating bubbles have been recently shown to enable enhanced extravasation and improved intratumoral distribution during ultrasound-mediated delivery of anti-cancer agents, acting as micropumps to overcome the barriers presented by elevated interstitial pressure and heterogeneous tumor vascularization. Commonly used nucleation agents, micron-scale ultrasound contrast agents (UCAs), suffer from the inability to accumulate in tumors via the enhanced permeability and retention (EPR) effect due to their size, and their rapid destruction upon exposure, requiring frequent replenishment. Cavitation-inducing nanoparticles (NPs) sized for endothelial gaps in leaky tumor vasculature (100-500 nm) can provide tumor-selective nucleating agents that yield sustained cavitation activity upon ultrasound exposure at intensities achievable by a conventional diagnostic ultrasound scanner. This creates the possibility of a single-low cost ultrasound platform which enables B-mode imaging for treatment guidance, instigation of therapeutic cavitation, and real-time passive acoustic mapping (PAM) of the location and extent of therapeutic delivery. An open-source ultrasound platform (V-1, Verasonics, Inc) using an abdominal diagnostic imaging probe (ATL C4-2, fc=3MHz, 128elements, 50.2mm aperture) was operated to transmit interlaced therapy and B-mode imaging pulses while PAM was employed to detect and image cavitation in real-time on an overlaid display. To deal with nonlinear propagation, limited probe bandwidth, and removal of transmission pulse, novel PAM algorithms were developed. Therapy pulses were 5 cycles of 2MHz ultrasound in the range 1-5MPa peak negative. Custom polymeric nanocups (NCs) and mesoporous carbon nanoparticles (CNPs), sized between 100-500nm, were suspended in filtered, deionized water flowing through an agar-based vessel phantom. A separate passive cavitation detector (Olympus Corp., fc=15MHz, focus 75mm) was used to verify the presence of inertial cavitation. Experimental results confirm the strong presence of inertial cavitation when US is combined with NCs and CNPs but no cavitation with just US alone. Cavitation is reliably and repeatedly instigated at pressures below 1.5MPa with both particles. CNPs display an extended presence of cavitation energy that does not diminish, while NCs bubble nuclei deplete on excitation. The US system was found to be capable of real-time adjustment of the therapy focus in depth and angle. Simultaneously, the system allowed for B-mode US image guidance as well as real-time overlaid PAM that displayed only cavitation in the vessel when NPs were present. Adjustment of focus and PAM feedback allowed for complete treatment coverage of the vessel volume. Use of an open-platform US system allowed for the rapid development of a complete US enhanced drug delivery system yielding image guidance, therapy delivery, and real-time monitoring of delivery. Formulated NPs significantly lower the cavitation threshold permitting the use of a diagnostic imaging system and providing a mechanism for treatment monitoring. Through real-time focusing and PAM an entire volume can be covered over the course of a treatment cycle, increasing chances of complete therapeutic agent delivery. Future work focuses on correlating release of therapeutic agents with cavitation maps in in vivo preclinical models.
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SIZE DISTRIBUTION ESTIMATION OF CAVITATION BUBBLE CLOUD VIA BUBBLES DISSOLUTION USING AN ULTRASOUND WIDE-BEAM METHOD AND ITS APPLICATIONS
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The performance and efficiency of numerous cavitation enhanced applications in a wide range of areas of science, including both fundamental and applied ultrasonic and interfacial science, depend on the cavitation bubble size distribution. Therefore, bubble size estimation and control would be beneficial for cavitation enhanced applications. In this study, an acoustic method using a wide beam with low pressure is proposed to acquire the time intensity curve of the dissolution process for the cavitation bubble population and then determine the bubble size distribution. Dissolution of the cavitation bubbles in saline and in phase-shift nanodroplet emulsion diluted with undegassed or degassed saline was obtained to quantify the effects of pulse duration (PD) and acoustic power (AP) or peak negative pressure (PNP) of focused ultrasound on the size distribution of induced cavitation bubbles. In addition, condensation of cavitation bubble produced in diluted suspension of phase-shift nanodroplet emulsion was involved in the calculation to discuss the effect of bubble condensation in the bubble size estimation in acoustic droplet vaporization. It was found that an increase of PD will induce large bubbles while AP had only a little effect on the mean bubble size in saline. It was also recognized that longer PD and higher PNP increases the proportions of large and small bubbles, respectively, in suspensions of phase-shift nanodroplet emulsions. Moreover, degassing of the suspension tended to bring about smaller mean bubble size than the undegassed suspension. Furthermore, it was shown that calculation without considering the condensation might underestimate the mean bubble size and the calculation with considering the condensation might have more influence over the size distribution of small bubbles, but less effect on that of large bubbles. Without or with considering bubble condensation, the accessible minimum bubble radius was 0.4 or 1.7 μm and the step size was 0.3 μm. This acoustic technique provides an in situ approach to estimate the size distribution of generated cavitation bubbles and might be a promising tool for applications where it is desirable to tune the ultrasound parameters to control the size distribution of generated cavitation bubbles. The optimization of acoustic parameters to limit the majority cavitation bubbles within the active size range in pulsed-HIFU induced applications such as thrombolysis and drug delivery is under way.
A NEW ACTIVE CAVITATION MAPPING TECHNIQUE FOR PULSED HIFU APPLICATIONS – BUBBLE DOPPLER
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Pulsed high intensity focused ultrasound (pHIFU) therapy is a modality used in such clinical applications as drug and gene delivery, where mild mechanical disruption of tissue by bubbles is desired, and thermal effects are to be avoided. Therefore, pHIFU treatment protocols consist of short pulses, delivered at low pulse repetition frequency, to induce transient bubble activity. The current gold standard for detecting and monitoring that transient activity is passive cavitation detection (PCD), which provides minimal information on the spatial distribution of the bubbles. B-mode imaging can detect hyperecho formation, but has very limited sensitivity, especially to small-size, transient microbubbles. Here, we propose and evaluate the feasibility of a new method for pHIFU induced microbubble detection based on a fusion of two Doppler techniques, that were previously developed for imaging of ultrasound contrast agents – Doppler decorrelation and pulse inversion Doppler. This approach, that we term “bubble Doppler” can both spatially map the presence of transient bubbles and to estimate their sizes and the degree of nonlinearity. The pHIFU exposures of tissue mimicking gel phantoms, ex vivo tissues and small animals in vivo were performed using a 1 MHz focused transducer emitting 0.1-1 ms pulses at 1 – 3 kHz pulse repetition frequency with peak negative pressure amplitude within 1 – 12 MPa range. The cavitation activity was monitored using three high speed camera imaging (in the case of transparent gels), recording of the broadband emissions by a confocally aligned focused PCD transducer and the bubble Doppler method. An ultrasound imaging probe (ATL L7-4) controlled by Verasonics Ultrasound Engine (VUE) was operated in flash mode, and Doppler ensemble pulses with interchanging polarities were transmitted after each HIFU pulse. The raw signals received by the probe were post-processed to obtain maps of bubble presence from signal decorrelation between HIFU pulses, and the degree of bubble nonlinearity from pulse inversion processing across the received Doppler pulse ensemble. The bubble Doppler method proposed here was shown to provide accurate maps of pHIFU-induced bubbles, as verified by the high speed camera videos. The sensitivity of the bubble Doppler method to the mere presence of small, non-violently oscillating bubbles was found to be better than that of PCD. The degree of bubble nonlinearity estimated from pulse inversion algorithm corresponded to the level of broadband emissions recorded by the PCD. Figure 1(a) shows an image from conventional Doppler imaging and Figure 1(b) shows an example image reconstructed by the bubble Doppler method overlaid on a B-mode image in a gel phantom. The method produced maps of cavitation activity induced in the organs of small animals, in the presence of cardiac and breathing motion. A new ultrasound imaging protocol was developed to detect microbubbles induced by pHIFU using a modification of Doppler processing. This imaging modality was shown to provide the sensitivity superior to that of existing cavitation detection methods, and at the same time has high spatial resolution inherent to the conventional Doppler imaging. Work supported by RFBR and NIH (EB007643, 1K01EB015745, and R01CA154451).

(a) Conventional Color Doppler image of the distribution of bubbles induced by pHIFU in a gel phantom. (b) Bubble Doppler image reconstructed using the raw signals. Both images are overlaid on top of a Bmode image.
4:00 PM
A CADAVERIC STUDY TO DEFINE THE TREATMENT ENVELOPE FOR TRANSCRANIAL MR-GUIDED FOCUSED ULTRASOUND ABLATION
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The objective of this study is to determine the treatment envelope for transcranial MR-guided focused ultrasound. MR-guided FUS has been used to produce thalamic lesions for the treatment of chronic pain and essential tremor. The thalamus lies near the geometric center of the skull in relative coaxial alignment with the skull convexity. This reduces the computational challenges of transcranial acoustic refocusing and avoids potential concerns regarding energy dissipation at the skull in non-perpendicular incident angles. It is unclear whether these factors will affect acoustic focusing and the accompanying therapeutic thermal tissue heating at other potential intracranial targets outside the thalamus. Two cadaveric experiments were conducted to assess the efficiency of MR-guided FUS heating in the thalamus, globus pallidum, hypothalamus, anterior limb of the internal capsule, cingulate gyrus, hippocampus, and corpus callosum. In experiment 1, each structure was sonicated in four cadavers using the same sonication parameters. The maximal temperature rise was measured at each target using MR thermography. In experiment 2, custom-molded phantom gels were cast in the skulls from experiment 1. Phantom MR imaging was co-registered with ex-vivo MR imaging to target the regions corresponding to the anatomical structures from experiment 1. All phantom targets were sonicated with the same parameters, and MR thermography was used to measure heating. In experiment 1, sonication of the thalamus resulted in peak temperature increases between 23-39 degrees C. Average temperature increases in the pallidum were 93% of thalamic heating with the same sonication energy. Averaged heating of the accumbens nucleus, hypothalamus, hippocampus, cingulate gyrus and corpus callosum ranged from 71-79% of thalamic heating. In experiment 2, similar trends in heating were observed in gel phantoms, although absolute temperatures were generally lower for all locations. Targeting of subcortical structures outside the central regions of the brain with MR-guided FUS is feasible, but may require additional acoustic energy to reach therapeutic temperatures.
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ORIGINS OF ULTRASOUND NEURAL STIMULATION IN THE RETINA

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Focused high-frequency ultrasound has recently been shown to be effective at stimulating retinal neurons with high spatial and temporal precision, and thus has potential both for basic studies and for use in a neural prosthesis. The physical mechanism of ultrasound energy delivery and the biophysical mechanism of transduction are unknown. Two possibilities for the mechanism of energy delivery are cavitation and radiation pressure due to absorption of the acoustic wave. In order to make inferences about possible neurostimulation mechanisms, we imaged the retina at millisecond temporal resolution to determine if focused ultrasound physically moves the retina. Ultrasound stimuli at an acoustic frequency of 43 MHz were delivered from a piezoelectric transducer and focused to a spot diameter of 90 μm in the isolated intact salamander retina. To stain cell membranes the retina was bathed in the dye FM 4-64. We measure fluorescence from cell membranes with a two-photon laser-scanning microscope while modulating ultrasound at a stimulus frequency of 0.5 Hz. By repeating the stimulus at different times relative to the image scan, the average response to the ultrasound stimulus across the entire frame was reconstructed at a spatiotemporal sampling of ~1 μm and ~10 ms. We observed that retinal cells near the ultrasound focus moved away from the transducer 2 - 4 μm in response to the ultrasound stimulus, whereas lateral movement was observed adjacent to the focal center. This motion occurred at power levels similar to that at which ultrasound elicits ganglion cell action potentials (~1 W/cm²). The displacement was maintained throughout the 1 s period that ultrasound was turned on, and relaxed at stimulus offset. Motion was observed at different levels of the retina, but the ganglion cell layer, which was in contact with the recording chamber, moved the least. The dynamics of motion involved multiple time constants, but contained a prominent very fast component (<10 ms) consistent with the short latencies of ultrasound stimulation. We conclude that radiation pressure underlies retinal motion and is likely responsible for ultrasound neurostimulation. These measurements place further constraints on whether the biophysical transduction mechanism is mechanosensitive ion channels, synaptic vesicle fusion, or a nonspecific effect on the membrane. The lack of observed ganglion cell motion when mounted upon a rigid surface may account for the previous result that ganglion cells in our preparation are not stimulated directly. A better understanding of how ultrasound stimulates an intact neural circuit will make ultrasound a more powerful tool for noninvasive neurostimulation for both basic research and clinical applications.
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CALCULATION AND SIMULATION-BASED STEERING APPROACHES FOR TRANSCRANIAL FOCUSED ULTRASOUND
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Transcranial FUS (tcFUS) is an attractive noninvasive modality for neurosurgical interventions. The presence of the skull, however, compromises the efficiency of tcFUS therapy, as its heterogeneous nature and acoustic characteristics induce significant distortion of the acoustic energy deposition, shifting of the focus and thermal gain decrease. Phased-array transducers featuring hundreds of elements allow for the partial compensation of skull-induced aberrations by calculation and application of appropriate phase and amplitude corrections. Precise focusing however, remains a necessity, especially at high acoustic frequencies. A numerical framework allowing for 3D full-wave, linear and nonlinear acoustic and thermal simulations has been developed and applied to transcranial sonication. Simulations were performed to investigate the impact of skull aberrations, compare different aberration correction approaches to achieve refocusing, extend the treatment envelope of tcFUS therapy, and explore acoustic and thermal secondary effects of the treatment. The simulated setup consisted of an idealized model of a commercial tcFUS system, InSightec ExAblate 4000 operated at 230 kHz, and the detailed anatomical head model of a 34-year old male segmented from MR data. Four different approaches were employed to calculate aberration corrections including analytical calculation of the aberration corrections disregarding tissue inhomogeneities, a semi-analytical ray-casting approach compensating for the presence of the skull while ignoring soft tissues, and two simulation-based time-reversal approaches with and without pressure amplitude corrections which take into account the entire anatomy. These approaches were evaluated for 22 targets in the brain and their impact on the resulting pressure and temperature distributions was compared. In addition, the impact of acoustic nonlinearity on the pressure distribution and temperature increase and the effect of temperature-dependent perfusion and vascular shutdown on the temperature distribution were also explored. Automatized iterative connected-component analyses were performed on all calculated 3D pressure and temperature distributions to analyze the acoustic and thermal performance of the different approaches for each target in a consistent manner. They yielded the full-width half-maximum (FWHM) size of the focal regions or thermal lesions, the distance between these regions and the intended target, as well as their shape and volume. While the (semi-)analytical approaches failed to induced high pressure values or ablative temperatures in any but the targets in the close vicinity of the geometric focus, the simulation based approaches allowed for considerable extension of the treatment envelope (including targets below the transducer level and to locations up to 8 cm from the geometric focus), generation of sharper foci (factor of 5), and increased targeting accuracy. This study suggests that utilizing simulation-based approaches to calculate aberration corrections for tcFUS therapies may significantly extend the treatment envelope of such treatments as well as predict and avoid possible secondary effects of these procedures, e.g., standing waves and skull heating. Utilization of modern but affordable computer hardware, combined with state-of-the-art high-performance computing techniques, enables realistic acoustic and thermal simulations in complicated setups to be performed within minutes. Thus, due to their superior performance, simulation-based correction approaches may soon replace their analytical counterparts.
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ULTRASHORT ECHO-TIME MRI VERSUS CT FOR SKULL ABERRATION CORRECTION IN MR-GUIDED TRANSCRANIAL FOCUSED ULTRASOUND
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Clinical MR-guided focused ultrasound (MRgFUS) brain treatment systems compensate for skull-induced beam aberrations by adjusting the phase and amplitude of individual transducer elements. These corrections are currently calculated based on a pre-acquired CT scan of the patient’s head. Ultrashort echo-time (UTE) MRI is an emerging technique that can image the weak, short-lived MR signal from cortical bone. The objective of the work presented here is to demonstrate the feasibility of using UTE MRI instead of CT to calculate and apply aberration corrections on a clinical MRgFUS system. Phantom experiments were performed in three de-fleshed cadaver skulls filled with tissue-mimicking hydrogel (ATS Laboratories, Bridgeport CT, USA). Each skull phantom was imaged with both CT and UTE MRI. The MR images were then segmented into “skull” and “not-skull” pixels using a computationally efficient, threshold-based algorithm. The resulting three-dimensional binary skull map was converted into a series of two-dimensional virtual CT images, by assigning +1000 Hounsfield units to skull pixels and −1000 Hounsfield units to not-skull pixels. The virtual CT images were saved as dicom files with appropriate CT header entries, so that they would be accepted as valid CT scans by the MRgFUS system. Each skull was mounted in the head transducer of a clinical MRgFUS system (ExAblate Neuro, Insightec, Israel), and transcranial sonications were performed using a power setting of 750 Acoustic Watts at 2 to 4 different target locations within the electronic steering range of the transducer. Each target location was sonicated three times: once using aberration corrections calculated from the actual CT scan, once using corrections calculated from the MRI-derived virtual CT scan, and once without applying any aberration correction. MR thermometry was performed in conjunction with each 10-second sonication, and the highest single-pixel temperature rise and surrounding-pixel mean were recorded for each sonication. In all three skull phantoms, the observed temperature rises were significantly larger for the aberration-corrected sonications than for the non-corrected sonications, but there was no significant difference between the temperatures achieved using CT-based and MRI-based aberration correction. Figure panels a and b show the measured temperature rises for each correction method, averaged over all three phantom experiments. Representative skull images are shown in panels c-e. These results suggest that it is entirely feasible to use UTE MRI instead of CT to implement aberration corrections for transcranial focused ultrasound. The MR acquisition and image segmentation procedure demonstrated here would add less than 15 minutes to a clinical MRgFUS treatment session.

Average measured temperature rise (a) at natural focus of transducer and (b) electronically steered 1 cm off center. Each bar in (a) represents the average of 3 sonications, and each bar in (b) represents the average of at least 7 sonications. Error bars represent one standard deviation. A representative UTE MR image and derived virtual CT image from one of the skull phantoms are shown in (c) and (d). The threedimensional UTE images were acquired at 1.25 mm isotropic resolution using a 3 Tesla whole-body scanner (Siemens Trio). An actual CT image of the same skull is shown in (e) for comparison.
Spatial heterogeneities of the cranium cause aberrations in the location and shape of the beam’s focus. Modifications to the element’s phases are required to ensure that all elements add constructively at the focus after transcranial propagation. CT imaging is used clinically for corrections due to its superior density contrast and the ease of automatic segmentation. The computation is fast and CT-based techniques have been shown to recover much of the focal intensity, although not all of it. In this work we compare the effect of CT voxel size on the accuracy of the phase correction estimates. Additionally, we compare the estimated phase aberrations when considering only the cortical components of the bone (HU>2100). We assess the utility of ultra-short echo time (UTE) imaging for TCMRgFUS in the brain, specifically using rapid automatic segmentation of cranial contours to provide phase-aberration correction. We compare UTE-derived aberrations to those predicted from CT images of the comparable voxel sizes. 3D beam propagation simulations were calculated using the Hybrid Angular Spectrum method, which rapidly simulates the effect of reflection, refraction and attenuation in complex heterogeneous media. A CT and a UTE scan were obtained on a patient to be treated with TC MRgFUS. A 3D UTE pulse sequence acquired four echoes at 0.042ms, 1.442ms, 2.242ms, and 3.642ms. The imaging parameters were 28 cm x 28 cm x 39.2 cm FOV, 1.1mm isotropic resolution, 18 flip angle, 125 kHz BW, 8ms TR and 7.5 min. scan time. The CT slices were acquired at a 0.5 mm isotropic resolution and downgraded successively to 0.75 mm, 1.1 mm and 1.15 mm resolution using linear interpolation. The phase corrections from the 0.5mm slice resolution were used as reference. The effect of increasing voxel size was quantified using both the estimated phase correction and the simulated focal intensity. To quantify the effect of the cortical bone on phase corrections, the 0.5mm CT images were used, first calculating the aberrations due to the entire range of the CT using properties shown in Table 1 and then using only the aberrations caused by the cortical components of the CT (HU>2100). Finally, the UTE-derived and CT-derived phase corrections were compared for the 1.1 mm resolution data sets, using only the cortical bone components. A bone contour map was segmented from the UTE images using R2* values and region-growing and thresholding algorithms, with voxels with an R2*>0.5ms-1 classified as cortical bone. The phase aberrations and resulting focal intensity from the CT and UTE cortical bone contour maps were compared.

Figure 1a shows the decrease in focal pressure when using phase corrections estimated from lower-resolution CT scans. Figure 1b compares the phase aberrations on one plate of the InSightec brain transducer using the entire CT scan, the cortical-only CT scan and the cortical-only UTE. Figure 1c compares the UTE-derived and CT-derived aberrations for one plate of the clinical brain system. Lowering the resolution of CT voxel size reduces the focal intensity recovered after phase correction. Cortical components of the bone correct more than 90% of the CT-based phase aberrations, while cortical-only UTE images correct 75% of the phase aberration. Future work will compare CT images downgraded to the effective UTE resolution (not nominal) to compare phase aberration corrections.
FEASIBILITY AND SAFETY OF MR-GUIDED FOCUSED ULTRASOUND LESIONING AFTER DEEP BRAIN STIMULATION ELECTRODE PLACEMENT

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Patients with movement disorders often exhibit asymmetric symptoms and may be treated with unilateral deep brain stimulation. If safe, focused ultrasound lesioning could be available to treat progressive ipsilateral or contralateral symptoms. The objective of this study is to test the feasibility and safety of MR-guided focused ultrasound lesioning after deep brain stimulation electrodes have been implanted. Three preclinical experiments were designed to assess the feasibility and safety of MR-guided FUS lesioning in the presence of an intracranial electrode and implanted impulse generator. In experiment 1, two cranial phantom gels were implanted with an electrode. FUS lesions were made 22 mm from the electrode, and MR thermography was used to assess temperature around the electrode. In experiment 2, thalamic electrodes were implanted in two intact human cadavers, and FUS lesions were made in the contralateral thalamus. The temperature surrounding the intracranial electrode and subcutaneous extension wiring was monitored with MR thermography. In the third experiment, four piglets had neurostimulating electrodes implanted and underwent contralateral FUS lesions. Post-procedural radiographic evaluation was conducted postoperatively and at 48 hours for all four piglets. Histological analyses of the FUS lesion and electrode tract were performed at 48 hours in two piglets and at 1 month in two piglets. In experiment 1, a 15 sec, 250-Watt sonication centered 22 mm from the electrode resulted in gel heating to 64 °C at the target and no observed temperature rise surrounding the implanted electrode. Similar results were observed in cadavers in experiment 2 as there was no evidence of electrode or lead extension heating during sonications. In experiment 3, there was no evidence of T2 weighted MR signal change around the electrode in three of four animals immediately after the procedure and at 48 hours. One piglet had imaging evidence of hemorrhage around the neurostimulation electrode during implantation, and subsequent FUS lesioning did not result in further changes. Histological analysis at 48 hours and at 1 month after the procedure showed no evidence of damage surrounding the electrode tracts in three of four animals. A small hemorrhage was seen along the tract in one animal. Histologically, FUS lesions appeared to have the appropriate volume and target. Transcranial focused ultrasound for subcortical lesioning is feasible in the setting of deep brain stimulation. These experiments did not reveal heating of the electrodes during the FUS; however, caution should be used in cases of recently implanted electrodes.
Classical trigeminal neuralgia (tic douloureux) is a neurological condition characterized by jolts of intense, sharp, stabbing or electric facial pain. There are effective medications that alleviate tic, but they can induce various side effects, ranging from nausea to impaired cognition to hepatic failure. Medications tend to lose their effect over time. There are excellent surgical options but they, too, lose their effect. The best treatment is microvascular decompression (MVD) of the trigeminal nerve at or near the root entry zone, but it is the most invasive and is only suitable for healthy individuals (Stiles et al., 2007). It is postulated that MVD may be effective because it causes damage to the nerve (Hurt et al., 2009). The efficacy of less invasive surgical procedures tends to be shorter lived. Gamma knife radiosurgery is non-invasive, but at best, affords lasting relief to fewer than 60% of patients (Petit et al., 2009, de Lotbiniere, 2009). MR-guided Focused Ultrasound Surgery (MRgFUS) has recently proven successful in the treatment of essential tremor (Lipsman et al., 2013, Elias et al., 2013). It is postulated that the treatment of trigeminal neuralgia is within the targeting range of MRgFUS. An elementary study has shown that it is possible to obtain a good focus at the root entry zone, the cisternal segment, and the distal segment of the trigeminal nerve (Monteith et al., 2012). Using a novel amplitude control algorithm, it is demonstrated through phantom and simulation studies that a sufficient thermal dose for damage can be obtained safely on the trigeminal nerve, in effect, non-invasively duplicating an MVD. Using clinical imaging data of five patients, a finite difference grid ultrasound propagation method is used to simulate the results of the treatment on the trigeminal nerve, and a novel amplitude control algorithm is used to safely administer a thermal dose to the target without overheating bone structures in the proximity. It is shown that the thermal dose away from the focus remains below 1 equivalent minute at 43°C, which has been formulated as a safety threshold in the literature (McDannold et al., 2004). Phantom studies using the Insightec ExAblate 4000 Therapy device paired with a 3T MR imaging system are also performed with a soft-tissue mimicking phantom-filled skull. Incorporating the amplitude controls specified in the simulation studies, it is again shown that the thermal dose away from the focus remains below 1 minute. In the simulation studies, a focal temperature of 55°C is achieved at the focus over a 10s sonication, while the maximum temperature away from the focus remains below 47°C, and hence below 1 minute thermal dose. Without invoking amplitude controls, the same treatment will have temperatures in tissue exceeding 50°C away from the focus, particularly at the base of the skull. Figure 1 demonstrates the treatment inside the phantom before and after the amplitude controls. The focal temperature in both cases is 49°C, however, the peak temperature away from the focus decreases from 48 to 40°C before and after amplitude controls, respectively. The treatment of trigeminal neuralgia using noninvasive methods would be an extremely desirable addition to the clinician's toolbox, avoiding side effects from invasive surgery and medication. We demonstrate that it is possible to treat the location of the trigeminal nerve safely and effectively, by using a novel amplitude control, thereby reducing the overall distribution of heat away from the focus.

The uncorrected (A) and corrected (B) temperature maps through the focus in the sagittal plane.
While transcranial FUS thermal ablation in the brain has reached clinical trials, tumors at the skull base are still challenging due to limitations imposed by skull heating. Previous work in rats demonstrated that we can ablate tissue at the skull base directly adjacent to the optic tract without evidence of functional loss by combining FUS exposure with an injected ultrasound contrast agent (USCA). The microbubbles concentrate the FUS-induced effects on the blood vessels, producing vascular damage throughout the targeted regions and tissue necrosis. This method does not cause significant heating of the brain or skull. In a large animal model, we studied whether this ablation is possible at deep brain targets without producing damage along the beam path. In 4 rhesus macaques, brain structures at the skull base adjacent to the optic tract were ablated using a clinical transcranial MRI-guided FUS (TcMRgFUS) system (ExAblate 4000, 220 kHz, InSightec). FUS exposures were applied for 5min combined with IV injection USCA. The acoustic power (3.5-6.4 W, peak negative pressure amplitude: 420-560 kPa), was set to be above the inertial cavitation threshold measured at each target using passive cavitation detectors. Acoustic emissions were recorded during the sonications, spectral analysis was performed and emission signals were integrated over harmonic, sub/ultraharmonic and broadband emissions. Tissue effects were evaluated in CE T1-weighted MRI to identify regions of BBB disruption (BBBD) and 3D T2*-weighted MRI for hypointense areas produced by red blood cell extravasations due to microvascular damage that occurs in the case of inertial cavitation. Animals were euthanatized at different time points after sonication and the brains were evaluated in histology. The inertial cavitation threshold, as indicated by the concurrent appearance of sub- and ultra-harmonic and broadband emissions, was equal to 430±90 kPa peak negative pressure. Sonications above this threshold coincided with the production of hypoechoic spots in T2*-weighted MRI suggesting red blood cell extravasations, and resulted in discrete lesions in all targeted regions that were consistent with our prior experience in rats. Even though the targeted regions in some cases partly overlapped the optic tract, the tract itself appeared mostly intact without the gross damage observed in the adjacent sonicated areas such as putamen and amygdala. Some blood-brain barrier disruption (BBBD) and petechiae along the ultrasound beam path and a few small areas with tissue damage (micro-necrosis) beyond the targeted regions were identified. The results suggest that this technique can selectively destroy blood supply and produce discrete lesions that evolve to tissue infarction, while the close association of the tissue damage to cavitation activity might provide the means to optimize this type of ablation. While BBBD and minor damage were observed near the lesion in the beam path, and thus more work is needed to optimize the exposures, these results are highly encouraging and demonstrate that ablation can be achieved with this TcMRgFUS system at the skull base without overheating the bone and damaging surrounding large white matter tracts and other structures. This result would not be possible with thermal ablation. Future work is needed to develop methods to monitor the procedure and to avoid the minor beam path effects observed here. The technique offers a potential way to expand the “treatment envelope” where TcMRgFUS ablation can be applied.
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NEURON ACTIVITY MODULATION VIA MICROBUBBLE-FACILITATED FOCUSED-ULTRASOUND INDUCED BLOOD-BRAIN BARRIER OPENING IN SMALL ANIMAL

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Focused ultrasound (FUS) with the presence of microbubbles has been confirmed to be able to induce blood-brain barrier (BBB) opening. Somatosensory evoked potential (SSEP) and function magnetic resonance imaging (fMRI) currently serves as a useful tool to monitor the neuron activity. Since brain function modulation follow BBB disruption may not yet been fully explored, this study attempts to employ the measurement of SSEP and fMRI signals to observe brain anatomical/functional modulation during FUS BBB-opening. Eleven Sprague-Dawley rats were sonicated in left S1FL somatosensory cortex by using a 400-kHz focused ultrasound in three groups (Group 1: sham control; Group 2: 0.35 MPa; Group 3: 0.47 MPa), and were post-operationally monitored by using 7-T MRI for anatomical and functional observation. For functional MRI scans, a gradient-echo EPI sequence was used during stimulation. The other twenty SD rats induced identical same three parameters of FUS and characterized its brain activity by measuring SSEP signal in one hour. Results showed that neuronal modulation accompanied with BBB disruption at the exposure site. Low FUS exposure induced BOLD value reduction as well as SSEP signal transient suppression but recovered one hour after FUS exposure. For high pressure exposure, a more profound SSEP signal reduction was noticed and the recovery duration was prolonged. Also, latency of SSEP signal which represents neuron activity showed more profound suppression in high pressure group. Lower pressure exposure made an unchanged latency in time course. Results observed infer that the cavitation decreased different degrees of neuron loses in activity effectiveness at S1FL area for both 0.35 and 0.47 MPa exposure. This study provides observation of brain neuron active change during FUS BBB-opening, and first provide evidence showing this CNS intervention may also have potential in modulating local neuron activity. Detail correlations and mechanism between neuron activity and FUS BBB-opening should be further investigated.

Upper: Temporal changes of SSEPs waveforms

Lower:
left: Temporal change of P1 wave of SSEPs
right: The cross-correlation mapping of BOLD images
FIRST IN-VIVO EXPERIMENTS OF CARDIAC ABLATION USING AN ULTRASOUND-GUIDED TRANSSESOPHAGEAL HIFU DEVICE
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Atrial fibrillation (AF) is the most frequent cardiac arrhythmia. Endocardial ablation is currently performed to treat this disease. The main target of this procedure is to isolate the pulmonary veins (PV) by thermal ablation. However procedures must often be repeated to be effective because of difficulties to create transmural lesions. These procedures can even be ineffective on patients with well-settled AF. High-Intensity Focused Ultrasound (HIFU) devices have been proposed to improve the transmurality of the lesions but they all require invasive interventions. Transesophageal HIFU probes are currently under development but none of them integrate imaging system to guide the procedure. Our team has developed an ultrasound-guided transesophageal HIFU device to perform ultimately a more complex procedure, called the HIFU “mini-Maze”. It was made with a 3 MHz 8-ring HIFU transducer with a spherical truncated shape. This HIFU transducer includes in its center a commercial 5 MHz 64-element planar phased-array imaging transducer used for transesophageal echocardiography. Preliminary simulation investigations showed the ability to focus the ultrasound (US) beam over a broad range of depths from 17 to 55 mm to perform lesions in various areas, while preserving intervening tissues. The aim of the present study was to demonstrate experimentally the feasibility to achieve precise transesophageal cardiac ablation under US guidance on pig model ex-vivo/in-situ and in-vivo. The first trial was carried out ex-vivo/in-situ on a 40-kg pig. In realistic anatomical conditions, transesophageal HIFU exposures were performed in interventricular septum under 2D US guidance to create an in-plane single line of ablation. Then, in-vivo experiments were performed on 5 anesthetized 90-kg pigs. The probe was inserted under endoscopic video and US guidance provided simultaneously. HIFU treatment planning was determined according to the heart structures which appear accessible on the transesophageal US image. The ex-vivo/in-situ study showed the ability to perform accurately fine lines of lesions in deep seated cardiac tissues transesophageally and under US guidance in realistic anatomical conditions. During the in-vivo experiments, the four cardiac cavities were clearly visible on the US images provided by the on-board imaging transducer allowing to perform lesions in atria and ventricles. Two areas of treatment were precisely targeted per animal. Elementary lesions were juxtaposed by 2°-rotations of the probe and dynamic focusing to create lines of lesions. Lesions were performed at 9 W/cm² over a range of depths from 31 mm to 49 mm. Biological damages were created on cardiac tissues in the areas located on US images and confirmed by anatomopathological analyses. These first results confirmed the ability to target specific areas in cardiac tissues in-vivo using the on-board imaging transducer but also to create damage on cardiac tissues using the transesophageal HIFU transducer. In-vivo tests are ongoing to create more intense necrosis. These preliminary in-vivo experiments gave encouraging results for future development of a complete HIFU Mini-Maze procedure.

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EXPERIMENTAL INVESTIGATIONS OF AN ENDOLUMINAL ULTRASOUND APPLICATOR FOR MR-GUIDED THERMAL THERAPY OF PANCREATIC CANCER
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To validate the feasibility of performing volumetric thermal therapy from within the gastric tract using endoluminal ultrasound applicators, integrated with MR-enabled real-time device localization and MR temperature monitoring. Endoluminal applicators were constructed with two 8x10 mm planar ultrasound transducers (4.4 or 5.6 MHz) mounted onto a 12 mm diameter 3D printed fixture secured at the distal end of a catheter. These fixtures contained an air-backed stage for the transducers, channels for water flow and wiring connections, platforms for active tracking coils, and were surrounded by custom shaped water-filled collapsible PET balloons for acoustic coupling and surface cooling. RF tracking coils (2-5 mm diameter) for active MR tracking, based on flat spiral coil designs, were placed in single or dual configuration on the underside of the fixture, as shown in Figure 1. Experiments in ex vivo porcine carcass were performed under MR guidance to validate the ability to determine the position and orientation of the applicator, perform preliminary determination of the feasibility of heating targets through luminal walls, and to ensure successful integration with a real-time MR tracking and temperature monitoring platform customized specific to this device. All experiments were performed using a 3T GE Discovery MRI Scanner. In each experiment, an applicator was surgically introduced into the porcine esophagus, and manually directed towards the liver or soft tissue surrounding the spine for sonication (surrogate for human sized pancreas). Following applicator insertion, T2-weighted anatomical images were taken and used to determine position and orientation of the applicator, and sonication was performed under MRTI guidance for 10-12 min at 5 W/cm². Phantom experiments were also performed in the MRI scanner to evaluate the capacity for real-time device tracking and temperature monitoring of applicators with single or dual-tracking coil configurations. The applicator position and orientation in ex vivo porcine studies were clearly visualized using integrated tracking coils, and the signal intensity of the tracking coil was well localized to within one slice-thickness. Substantial volumetric heating (>150°C) was observed in liver, and heating penetration extended 20-25 mm from the applicator, as shown in Figure 2. These therapeutic temperatures were achieved in non-perfused tissues using ~ 40% of the maximum allowable applied power, indicating additional power can be applied in vivo to accommodate perfusion effects. The active tracking coils were successfully integrated with the MR guidance platform, demonstrating real-time applicator localization based on tracking coil signals and fast setup for real-time monitoring of temperature during sonication. Individual tracking coil signals from dual-coil applicators were differentiated during phantom experiments and could be localized in real-time, allowing for automatic prescription of imaging slices transverse to the applicator for temperature monitoring. A prototype endoluminal ultrasound applicator with active MR tracking coils has been fabricated and preliminary experiments have demonstrated both heating capability as well as compatibility with real-time device localization and MR temperature monitoring. Further development of this technology, including in vivo studies, will be directed towards endoluminal thermal therapy of pancreatic cancer. (Supported by NIH P01 CA159992)

Figure 1: A: Top view of endoluminal applicator with dual-planar 5.6 MHz transducers. B: Spiral RF tracking coil mounted on underside of fixture.

Figure 2: MRTI during liver ablation through GI tract in ex vivo porcine carcass. 10 min ablation at 5 W/cm² for 5.6 MHz transducer. TE = 5 ms.
4:20 PM
1D MULTI-ELEMENT CMUT ARRAY FOR INTERSTITIAL ULTRASOUND THERMAL THERAPY
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Interstitial therapeutic ultrasound devices have the potential to enable greater spatial control of the heat deposition as compared to current minimally-invasive interstitial heating strategies (laser, radiofrequency, cryoablation), while allowing fast treatments of large volumes of tissue. For improving the treatment control, the ability to modify driving parameters (acoustic power, frequency) or to multiply the number of independent ultrasound elements on a therapeutic system is critical. Conventional ultrasound transducer technologies, however, may be limited for increasing the density of elements on interstitial catheters (few millimeters in diameter) or to modulate continuously acoustic parameters (discrete working frequencies). Capacitive Micromachined Ultrasound Transducers (cMUTs) exhibit potential advantages such as the possibility for extreme miniaturization (cell size: few dozens of microns), inherit broad bandwidth (several MHz) and high electro-acoustic efficiency. In the biomedical field, cMUTs have been primarily proposed for performing imaging, but their characteristics could also be interesting for therapeutic applications in continuous wave (CW) mode. In the presented study, further investigations have been conducted to evaluate the interest of using cMUTs to generate high intensity ultrasound and perform thermal ablations in biological tissues. Two designs of cMUT arrays have been studied: (i) a 1D 128-element planar-cMUT array originally dedicated to abdominal ultrasound imaging purposes (central frequency: 5 MHz, element size: 0.3 × 8.0 mm2); (ii) a new 12-element linear-array, 32.4-mm long and 0.8-mm wide, developed specifically for minimally-invasive interstitial therapeutic applications (element size: 2.7 × 0.8 mm2). The acoustical characteristics of those cMUT linear-arrays were investigated experimentally and compared with simulations. Simulations were also performed to evaluate the ability to generate thermal lesions in soft tissues with: (i) 1 single linear array, (ii) a combination of multiple linear arrays positioned on a cylindrical catheter. With this later configuration, the feasibility of conformal interstitial ultrasound treatments was investigated by integrating the geometry of real human brain metastases segmented from clinical MR-images as target volumes. Experimental investigations performed with the cMUT imaging array showed the ability to generate surface acoustic intensities (Iac) up to 20 W.cm-2 and to generate intense centimetric thermal lesions in in-vitro turkey breast tissues. Preliminary characterizations conducted on the new cMUT array dedicated to interstitial therapy showed that the elements had a frequency-bandwidth at -3dB of greater than 12 MHz. At 6 MHz, a single element was able to generate in water a maximum peak pressure of > 0.5 MPa. The pressure field distribution measured for a single element was well collimated along the 1D-array direction and no electro-mechanical coupling was observed between neighboring elements. In simulations, the ability to use various power levels and frequencies on independent elements, as well as combinations of multiple linear-arrays offered sufficient flexibility to achieve a wide variety of thermal ablation patterns in 3D. Simulated ablation volumes could be controlled to cover accurately non-symmetrical volumes of brain metastases. In conclusion, cMUT arrays show interesting characteristics, which may open new perspectives of spatial control for conformal interstitial thermal therapy with miniaturized multi-element therapeutic ultrasound catheters. This project was supported by the French National Research Agency (ANR) through the 2010 campaign.

Thermal ablation induced in in-vitro turkey breast tissues with a cMUT transducer in therapy mode of operation. (a) Localized necrotic aspect on the upper surface (tissue surface observed by an IR camera); (b) Temperature distribution measured with an IR camera.
In previous years, we have demonstrated the feasibility of capacitive micromachined ultrasonic transducers (CMUTs) for thermal ablation using a single-element unfocused transducer and a concentric ring transducer array. Improving over the approaches of previous years, the aim of this work is to develop a fully populated 2-D CMUT array for high intensity focused ultrasound (HIFU) treatment. We designed and fabricated a 2-D CMUT array for HIFU applications using a Thick-Buried-Oxide (BOX) process. The array consists of 20×20 square CMUT elements with an element pitch of 1 mm. This CMUT array is flip-chip bonded onto a custom fan-out board, and then assembled on a custom interface board that can provide various array configurations depending on desired applications. In this work, the interface board groups the CMUT elements in the array into 8 channels, based on the phase delay from the array element to the targeted focal point. An 8-channel phase generating system supplies continuous waves with equally spaced 8 different phases to the 8 groups of the CMUT array through 8 bias-tees. The beam profile and the thermal dose of this array configuration are simulated in a water-tissue medium using Field II and K-Wave. We measured the electrical input impedance of individual CMUT elements and the 8 groups of the CMUT array in air. Each channel is tuned with a series inductor at an operational frequency of 1 MHz. At a targeted focal depth of 19.6 mm, the peak acoustic intensity is expected to be 1031 W/cm², assuming the output pressure at the surface of the CMUT element of 1 MPa. According to the simulations, the volume of the lesion and the peak heat power are expected to be 0.22 cm³, 140 W/cm³, respectively. We successfully fabricated a 20×20-element 2-D CMUT array, and assembled it with an 8-channel phase generating system using a custom interface board. The simulation result shows a promising thermal distribution inside the tissue. Currently, we are performing experiments to measure the output pressure in immersion and to test ex vivo tissue ablation.
4:40 PM
NON-INVASIVE TRANSCRANIAL SURGERY WITH DUAL-MODE ULTRASOUND ARRAYS.
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Dual-mode ultrasound arrays (DMUAs) offer the promise of optimal focusing and localization of therapeutic beams in complex media, including transcranial applications. Extensive 3D imaging was completed to visualize anatomical landmarks with DMUA and MRI. Localized pulsed focused ultrasound (pFUS) shots were next placed through the skull of the animal, allowing us to visualize focal thermal changes as a result of the shots. After the completion of therapy we transected the skull and examined the brain tissue for visual changes. First set of experiments was completed in sacrificed rats, where upper half of rat's skull was shaved and positioned under 3.5MHz DMUA (Imasonic, France) submerged inside a water tank with degassed deionized water. To capture 3D volume of SA images we secured rat onto a 3D stepper motor controlled translation stage and moved in fine increments to capture region extending from the eye socket to the occipital bone. After the completion of 3D anatomical mapping, we formed subtherapeutic shots at a subset of varying intensities followed by a therapy delivery. SA images were collected prior and post therapy, STF imaging with PRF of 100 was recorded at the time of shot delivery. After the completion of DMUA therapy, a T2-weighted scan with a 9.4T MRI scanner was performed. The second set of experiments, consisted of in vivo imaging of rat's skull under 3.5MHz DMUA encased inside a water bolus. This set of animals suffered a traumatic brain injury, we collected SA and STF images prior and post injury. Completing of comparative scan between SA images and MRI scan revealed important anatomical landmarks apparent on the SA images (Figure). The dorsal aspect of the skull was clearly visualized, where we captured frontal, parietal, interparietal and occipital bones. Floor of cranial cavity and cheek muscles were also clearly outlined on the SA images. The subtherapeutic shot delivery allowed us to visualize localized temperature changes at the focal location after processing STF images. These are the first documented temperature estimates tracked through an intact skull of an animal model. Lastly, after analyzing the in vivo data we observed prominent pulsation appearing inside the brain of the rat. Localization of pulsation and blood vessels enables us to navigate the HIFU beam very selectively around anatomical landmarks localized and identified on DMUA imaging. Transcranial DMUA images of rodent brains were collected postmortem as well as in vivo. These images showed anatomical detail of the brain and surrounding tissue consistent with MRI and gross histology. Furthermore, DMUA echo signals from brain tissue were shown to produce fully developed speckle suitable for speckle tracking. This was shown to allow for the implementation of transcranial ultrasound thermometry which has demonstrated the formation of localized HIFU focus near the intended target point. Methods for image-based transcranial refocusing of DMUAs are currently being investigated.

Experimental set up and example MR (top right) and DMUA (bottom right) images.
The brain tissue produced fully-developed speckle signal suitable for speckle tracking and temperature estimation.
AN INTEGRATED IMAGE-GUIDED FOCUSED ULTRASOUND SYSTEM FOR NONINVASIVE SURGERY
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We present the system architecture of an integrated Ultrasound-guided HIFU (USgHIFU) system for image-guided surgery. Real-time monitoring and guidance of HIFU can be performed using a diagnostic scanner with imaging frames synchronized with the pulsed HIFU (pHIFU) bursts. In addition, the system is capable of driving the therapeutic array in both imaging and therapy modes. The dual-mode ultrasound array (DMUA) imaging is also synchronized with the pHIFU bursts and the diagnostic imaging. Real-time ultrasound thermography data is superimposed on B-mode and DMUA data, which allows for real-time monitoring and guidance of pHIFU beams. The system is capable of operating with multiple frontends, current implementation has a SonixRP for imaging and a custom designed dual mode ultrasound array (DMUA) system (32Tx/32Rx) for imaging/therapy. The highlights of the system include a fully-programmable, multiple data stream capable data processing engine, and an arbitrarily programmable high power array driver that is able to synthesize complex beam patterns in space and time. The data processing engine features a pipeline-style design that can be programmed on-the-fly by re-arranging the pre-verified GPU-accelerated high performance pipeline blocks, which cover an extensive range from basic functions such as filtering to specialized processing like speckle tracking. Furthermore, the pipeline design also has the option of bringing in MATLAB as part of the processing chain, thus vastly increase the capability of the system. By properly balancing the processing load between GPU-enabled routine and MATLAB script. This allows one to achieve a high degree of flexibility while meeting real-time constraints. Results are presented from in vivo rat experiment. Where low dose of therapeutic ultrasound was delivered into the hind limb of the Copenhagen rats using DMUA and temperature was tracked using a linear probe (HST, Ultrasonix). The data is processed in realtime with MATLAB in the loop to perform temperature regularization. Other real-time signal processing is also used to characterize the changes in echogenicity with millisecond and sub-millimeter temporal and spatial resolutions, respectively. In vivo results show that we can reliably track small temperature changes in the presence of motion artifacts (respiration and pulsation). The temperature data can be explored in real time using multiple views which allow for exploring the temperature field with high temporal and spatial resolutions.
In the applications of ultrasonic diagnosis or therapies, the acoustic resolution is always restricted by the diffraction limit. The applications of recent metamaterial designs are limited especially for therapeutic ultrasound. To achieve an ultrasonic spot of "super resolution", ultrasonic source should be of sub-wavelength in size. We have designed a new structure that can converge plane acoustic waves with the help of a multiple Fabry-Perot (FP) resonance effect. The designed structure integrates several folded and straight apertures, as is shown in Fig. 1(a). The lengths of the apertures are integral multiples that of the shortest one, which enables FP resonances to exhibit in all the apertures simultaneously. This effect can cause extraordinary acoustic transmission (EAT) effects in the apertures. The evascent waves (EWs) can be generated at the intersection sites of different apertures. The combination of EWs and EAT effects can induce a focal spot of sub-wavelength scale at the outlet of the structure. To further enhance the generation efficiency of EWs, the inlet array is extended by putting subwavelength cavities on the structure's left surface. The transmission of acoustics waves through the proposed structure is illustrated in Fig. 1(b). As a plane acoustic wave incidents from the left, the acoustic energies pass through the apertures and form a focal spot of sub-wavelength scale at the outlet. At the known FP resonance frequencies, the spot diameter ranges from 0.37λ to 0.68λ. After the inlet array has been extended, an extra transmission peak is observed, indicating the cooperation of surface resonance and FP resonances. The spot size can then be reduced to 0.35λ. A transmission gain of about 7 decibel is obtained in the focal region. The achieved sub-wavelength focusing can be further optimized by increasing the acoustic impedance ratio between the matrix and the aperture materials. We have proposed a novel structure, which enables a multiple FP resonance effect. With plane acoustic waves incident, EWs are generated, amplified and then converged from multiple inlets to a single outlet, and a focal spot of sub-wavelength scale is achieved. A smallest focal width is observed to be 0.35λ, which can be even reduced by adopting different materials. The results might open a new door for various acoustic applications such as acoustic microscopy or biomedical ultrasound. This work is supported by the National Basic Research Program 973 (No. 2011CB707900) and the National Natural Science Foundation of China (No. 11104140).
5:10 PM
ARRAY TRANSDUCER ELEMENT UTILIZING CORESONANCE BETWEEN HEMISPHERICAL PZT SHELL AND WATER SPHERE
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Cavitation bubbles can efficiently induce therapeutic effects of ultrasound. They play the main role in cavitation enhanced heating as well as histotripsy. A short highly-focused ultrasound pulse with an extremely high intensity can generate them in a well spatially controlled manner. It requires high-voltage amplifiers to drive the highly-focused ultrasonic transducer. Using a typical array transducer in a thickness mode, the voltage reaches several hundred volts, which is almost the limit of commercially available power FETs in the MHz range. The objective of this study is to provide a focused array transducer which can generate such extremely-high-intensity ultrasound at a much lower drive voltage. A thin spherical ceramic shell and a water sphere with the same diameter have almost the same resonant frequency. This is a lucky coincidence which can lead a solution to provide a transducer of the objective. A thin hemispherical PZT shell with electrodes on both surfaces, and with its concave surface attached to water, can utilize the coresonance not only to provide naturally good acoustic coupling with water but also to reduce its electrical as well as mechanical impedance at the resonant frequency. First, finite element simulation was performed using PzFlex to determine the optimum diameter and thickness of the PZT shell and to predict the behavior as an array transducer element with an operating frequency around 0.5 MHz. Based on the prediction, a double-scale prototype transducer element was fabricated. The air-backed concave hemispherical PZT shell has an inner diameter of 8 mm and a thickness of 0.7 mm. Its electrical impedance at 0.1-0.4 MHz was measured in air and in water. Both amplitude and phase of the two-dimensional acoustic field transmitted by the prototype transducer element were measured in water. Then, the acoustic fields produced by an array transducer consisting of the prototype array elements were numerically simulated in the manner of acoustic holography. Figure 1 shows the magnitude and phase of the electrical impedance of the prototype transducer element. At 0.24 MHz, the impedance is real and equal to 170 ohms. From this, it is estimated that only 40 Vp-p or less is needed to generate an acoustic power of 1 W per element. Acoustic fields produced by a focused array transducer consisting of the 696 prototype elements with a spherical curvature of 300 mm were simulated. Degradation of the focal beam in strength and width was ignorable and the acoustic noise level was not significantly more than -20 dB even at a beam steering angle of 0.2 rad. Although 2-4 times larger both in wavelength and size suitable for typical HIFU treatment, the prototype transducer element clearly demonstrated the potential of an array transducer of the proposed concept to generate a focal ultrasonic field suitable for cavitation induced or enhanced HIFU treatment at a drive voltage level significantly lower than a conventional thickness mode transducer.
5:20 PM
INTRAMUSCULAR HEATING AND BIO-REGULATORY EFFECTS PRODUCED BY LONG DURATION LITUS
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A wearable long-duration low intensity therapeutic ultrasound (LITUS) device was developed for sustained therapy for up to 4 hrs. Prior to this study, it was unknown whether an ultrasound device could maintain therapeutic intramuscular (IM) heating for a long duration without overheating human tissues. This study measured IM temperature during long duration LITUS therapy, and compared the heating effect from 1 or 2 transducers each emitting continuous 3 MHz, 0.132 W/cm2 intensity ultrasound with a BNR of <5:1 and ERA of 6 cm2. In an IRB-approved, randomized crossover study, 26 subjects (Male = 16 and Female = 10, age = 23.0 ± 2.1 years, height = 1.74 ± 0.09 m, mass = 73.48 ± 14.65 kg) received 3 hr ultrasound treatments from the LITUS device over the triceps surae muscle. Over the course of the treatment, subjects received 7,020 or 14,040 J of energy from 1 or 2 transducers, respectively. IM temperature was measured by two MT-26/6 needle thermocouples horizontally inserted into the left triceps surae muscle at depths of 1.58 ± 0.15 and 2.91 ± 0.16 cm from the posterior surface of the calf. Thermocouples were positioned underneath a single transducer or the intersection of two transducers placed side-by-side. Surface skin temperature on the opposite leg was measured by a PT-6 thermocouple. Temperatures were recorded at 5 min intervals throughout the treatment and for 30 min post-treatment. The resulting temperature profiles were analyzed in 3 phases: 1) heating, 2) steady-state, and 3) cooling. Repeated measures (condition x time) ANOVA was used to determine the significance between treatment conditions. At 1.5 cm, the device heated tissues 4.45 ± 1.52° and 3.86 ± 1.10° C using 1 and 2 transducers, respectively. At 3 cm, the device heated tissues 3.19 ± 0.90° and 3.24 ± 0.95° C using 1 and 2 transducers, respectively. Peak temperatures were maintained for approximately 2 hrs during the steady-state phase. Dual transducers provided an equivalent peak IM temperature increase while also treating 2X the tissue volume than 1 transducer (p=0.99). IM temperature measured in placebo subjects decreased by 3.45 ± 1.38° C at 1.5cm depth and 3.75 ± 0.62° C at the 3cm depth during the long duration treatment. The wearable LITUS device provided sustained tissue heating throughout a 3 hr treatment without over-heating the tissue.
8:40 AM
FOCUSED-ULTRASOUND BLOOD-BRAIN BARRIER OPENING AND CNS DRUG DELIVERY: AN OVERVIEW
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Focused ultrasound (FUS) technology, which appears half century ago, has got more and more attention on its clinical therapeutic potential in recent years. Recently, focused ultrasound with the presence of microbubbles has been noticed to be capable of locally and reversibly open the blood-brain barrier (BBB). This FUS application has been validated its feasibility to transcranially and temporally, enhance the molecule delivery larger than 400 Da into CNS, particularly potential for those therapeutic agents penetration (> 90% among all approved) which are intrinsically cannot cross BBB, and brings new route for CNS disease treatment. On the other hand, current advanced nanotechnology brings opportunity to design novel nano-carriers to serve both as an image indicator and therapeutic agents to allow simultaneous diagnostic imaging and drug delivery monitoring in vivo in real time. Here, we overview the current preclinical studies which demonstrate the reports by using FUS with MB-facilitated drug delivery technology for brain drug delivery, which here we specifically emphasized for anticancer drug delivery for brain tumor treatment. Also, we report the current progress on the in-vivo animal testing as the proof-of-concept. Novel nanoparticles (including diagnostic and therapeutic nanoparticles) will be introduced about their participation of the procedure (including safety, biodistribution, agent quantification, and treatment evaluation) among different imaging platforms (including MRI, ultrasound, nuclear imaging) and their efficacy will be discussed. At last, we also review recently developed multifunctional theranostic MBs for FUS-induced BBB opening for brain tumor therapy.
9:10 AM  
IS IMAGE-GUIDED HIFU THERAPY AN EMERGING DISCIPLINE IN MEDICINE?  
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Over the past ten years, image-guided HIFU therapy has become one of the fastest growing areas in the field of minimally-invasive cancer treatment. It is being used clinically to treat a wide variety of tumours in the human body. This presentation aims to provide an up-to-date overview of clinical applications of imaged-guided HIFU therapy, and discusses an enormous potential to establish a new academic discipline in medicine. Image-guided HIFU has been clinically used to treat both malignant and benign tumours, including those of the prostate, liver, breast, kidney, pancreas, uterus, bone, soft tissue, brain and thyroid. Although short- and long-term clinical results are very encouraging, a coordinated research effort is definitely needed across scientific disciplines to develop the best treatment approach and strategic research plan for HIFU therapy in the future. The definition of this new academic discipline will cover current knowledge of physical and technical sides, device manufacture, biomedical science, imaging, HIFU treatment plan and exposure, and multiple cancer treatments. It is a multidisciplinary community, which is made up of people from different disciplines and professions who are engaged in working together. It will help to address and decompose common challenges in scientific and clinical aspects, establish the global standards of HIFU technology, manufacture and device, clinical application and education. Image-guided HIFU therapy is an exciting and fast expanding field. The number of diseases and organs treated, and the numbers of patients to whom HIFU is being offered are increasing quickly. As the technology and clinical devices are undergoing extremely rapid evolutions, a multifaceted approach, using the best knowledge available from medical physics, engineering, biomedical science, multidisciplinary cancer specialties including surgery, interventional radiology, oncology and radiation oncology, is in the best interest of the patient.
10:10 AM
A 3D MULTI-CONTRAST PULSE SEQUENCE FOR ACQUISITION OF MR ACOUSTIC RADIATION FORCE IMAGING CONCURRENTLY WITH PROTON RESONANCE SHIFT THERMOMETRY
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The 3D multi-contrast MRI pulse sequence presented here is a novel method for performing Acoustic Radiation Force Imaging (mcMR-ARFI) simultaneously with Proton Resonance Frequency (PRF) thermometry and would be especially beneficial for MR guided Focused Ultrasound (MRgFUS) as a method for safely localizing the ultrasound focal spot in all three dimensions while simultaneously measuring the induced temperature rise. A 3D Gradient Echo segmented EPI pulse sequence was modified to include a bipolar Motion Encoding Gradient (MEG), with multiple contrasts achieved by repeating the EPI readout multiple times during the TR interval. Optionally, the readout uses a ‘flyback’ scheme (figure 1a). An ultrasound burst is synchronized with the second lobe of the MEG via an optical trigger emitted by the sequence. The phase change for any given voxel is given by: Δφ = γ B0(ΔT × αTE) + γ ∫ MEGamp(t) × ΔD(t) × dt, where γ is the gyromagnetic ratio (2π × 42.577 MHz/T), α is the constant -0.01 ppm/°C, ΔT is temperature rise in °C, MEGamp is the MEG amplitude in mT/m, and ΔD is tissue placement in μm. To separate the phase change due to temperature versus displacement, the complex phase difference is taken between one image acquired with no ultrasound and a second with ultrasound, and, for each voxel, a linear least-squares fit, weighted by signal magnitude, is made to the measured phase at each contrast's echo time (figure 1b). The line's slope is the phase induced by a change in temperature while the intercept at t = 0 s is the phase induced due to tissue displacement. Experiments were performed in a gelatin phantom with a phased array transducer (256-channel, f = 1MHz) and a 3T MRI scanner. Simultaneous 3D ARFI and temperature maps were acquired in a 160x120x36 mm volume at 1.25x1.25x2 mm resolution and zero-fill-interpolated to 0.5x0.5x0.5 mm voxel spacing. TR = 160 ms, TE = [39, 72, 105, 139] ms, ETL = 7, BW = 752 Hz/px, FA = 60°, MEGamp = 28 mT/m, MEGdur = 10.2 ms, time/meas = 49 s, US power = 150 W, δ = 10 ms (6.25% duty cycle). The focal spot was electronically steered to (0, -5, 0) mm. The ARFI and temperature maps derived simultaneously are shown in figure 1c-f. The location of peak ARFI displacement occurred at (13, -5, -5.5) mm, while the peak temperature rise (3.8°C) occurred at (13.5, -5, -2.5) mm, a difference of (0.5, 0.0, 3.0) mm. Figure 1c and 1d show coronal slices (perpendicular to the beam) through maximum displacement and maximum temperature rise respectively. Figure 1e and 1f show sagittal slices (along the beam) at x = 13 mm, with the transducer to the left of the figure. Line plots through figure 1c and 1d along y = -5 mm (white arrow in 1c) are shown in figure 1g where we see the expected broader ARFI pattern and peak locations matching closely. Similarly, figure 1h shows the line through the sagittal slices at y = -5 mm (black arrow in 1f) which demonstrates how the displacement profile is shifted closer to the transducer than the temperature profile. This shift, observed in multiple experiments, could have important implications for using ARFI to predict the location of peak temperature rise along the direction of beam propagation. This new 3D multi-contrast sequence simultaneously measured displacement and temperature distributions in a large volume and at high spatial resolution. These features are beneficial for beam characterization and focusing, while providing temperature feedback to ensure safety with no time penalty.
High-intensity focused ultrasound (HIFU) ablation is a promising, noninvasive method for treatment of bone tumors and palliation of pain (Li C, Cancer 2010). MR thermometry allows for a physician to monitor temperature changes during HIFU treatment to ensure proper heat deposition to the targeted tumor and to prevent unwanted damage to healthy tissues. However, conventional proton resonance frequency (PRF)-based MR thermometry (Ishihara Y, Magn Reson Med 1995) is not suitable for cortical bone due to its short T2* relaxation time. Recently, it was shown that temperature changes in cortical bone can be depicted with ultrashort echo-time (UTE) MRI through signal intensity changes (Miller W, Int Symposium on FUS 2012). In this work, we demonstrate the ability of 3D UTE imaging to characterize T1 changes due to temperature rises in cortical bone. An ex vivo study was conducted with a diaphysis segment of bovine femur on a Discovery MR 750w 3T scanner (GE Healthcare, Waukesha, WI) using an eight-channel phased-array wrist coil (Invivo, Gainesville, FL). Heating was performed by using a 7.7 MHz catheter-cooled interstitial ultrasound applicator with two-sectored cylindrical transducers (Diederich CJ, IEEE Trans Ultrason Ferroelectr Freq Control 1999). The applicator was inserted into the fatty yellow bone marrow in the medullary cavity and produced high intensity ultrasound energy with a 180° directional heating pattern toward the cortical bone (12 W/cm² transducer surface intensity). Two ablations (each 25 min duration) with varying applicator locations were performed to heat different regions of the cortical bone, having a 30 min cooling period in between. Before starting each ablation, 3D UTE imaging incorporating a non-selective hard pulse excitation and 3D radial acquisitions was performed using a 11 ms TR, 76 μs TE, 1 mm isotropic spatial resolution, 9 x 9 x 7.8 cm³ FOV, and RF spoiling. UTE images with two flip angles of 8° and 44° were acquired, each with a 4.3 min scan time. From these UTE images, baseline T1 maps were calculated by using a variable flip angle scheme (Christensen KA, J Phys Chem 1974). During ablation, transient temperature changes in bone marrow were monitored by quantifying T2 by using a double-echo 2D fast spin-echo sequence. The scan parameters used were 35.6 ms and 185 ms TEs, 666 ms TR, echo train length of 40, 10 x 10 cm² FOV, 128 x 128 matrix size, and 4 mm slice thickness. Temperature was assumed to reach steady state at 10 min after the ablation began, and UTE images with the two flip angles were acquired again to calculate T1 for the heated bone. The maps of T1 changes in the cortical bone and those of T2 changes in the bone marrow due to heating are illustrated in Figure 1. The T2-change maps visualized heated bone marrow regions as T2 increases with temperature increase in fat (Ghandi S, ISMRM 1998). In the cortical bone, T1 increase of up to 40 ms was measured, which was an approximately 20% increase from baseline. Actual temperatures were not measured during this study, but we expect that the highest temperature increase in bone marrow was approximately 43°C assuming a T2-temperature coefficient of 5.72 ms/°C, measured in a separate experiment. We have shown the feasibility of using UTE imaging to detect T1 changes in cortical bone for temperature mapping. Direct quantification of temperature changes in bone can provide more accurate monitoring of thermal dose than the extrapolation of temperature information in surrounding soft tissues, improving the safety and efficacy of bone tumor ablation. Future work includes quantification of T1-temperature dependence in cortical bone.

UTE images of the bovine femur segment at baseline (a,d) and maps of T1 changes (b,e) from the two ablations. The T2-change maps in the bone marrow at the matching locations are shown in (c,f). Increases in T1 are observed in the cortical bone adjacent to the heated bone marrow with high T2 changes.
10:30 AM
MONITORING TEMPERATURE RISE AND CAVITATION DURING HIGH INTENSITY FOCUSED ULTRASOUND THERAPY WITH PASSIVE ACOUSTIC MAPPING AND MAGNETIC RESONANCE IMAGING
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High intensity focused ultrasound (HIFU) is a promising method for non-invasive treatment of tumours by thermal ablation and targeted release and enhanced delivery of drugs. HIFU is hampered by long treatment times and a lack of an effective, affordable technique for noninvasive monitoring in real-time. Passive Acoustic Mapping (PAM) is a new ultrasound-based technique for monitoring thermal and non-thermal HIFU therapies, which uses acoustic emissions received on an ultrasound (US) array to monitor the location and strength of the incident HIFU field as well as any regions of acoustic cavitation. PAM has been shown to enable prediction of the temperature rise and subsequent ablation in ex-vivo tissue due to acoustic cavitation (Jensen et al. Radiology 2012; Jensen et al. PMB 2013), and monitor drug release and delivery (Choi et al. ISTU 2012). The aim of the study is twofold: first, to compare the ability of PAM to predict temperature rises in the absence of cavitation against the current gold standard for thermal HIFU therapy monitoring, MR thermometry; secondly, to determine whether PAM is able to image short bursts of acoustic cavitation in the absence of heating, of the kind suitable for drug delivery applications, which is difficult to visualize by MR. We also investigate the potential for US and MR to be combined. A silica-agar-gel phantom is treated by HIFU in two distinct regimes: continuous-wave below the inertial cavitation threshold and short tone bursts that cause inertial cavitation but no heating. The two experiments are performed inside a small-bore 4.7T MRI scanner to produce gradient-recalled-echo phase images of a volume 50x50x24mm at a temporal resolution of 1.7Hz and voxel size 1x1x2mm that can be converted into 3-D temperature images to within 1 degree C. The two insonifications are repeated outside the MRI machine with a clinical Zonare US imaging system facing the transducer, which creates PAM maps of sources of harmonic emissions, which map the incident HIFU field, and broadband emissions, yielding maps of cavitation activity. The energy in the HIFU maps is converted into acoustic energy and used as an input to a 3-D heat equation to determine temperature rise. Temperature rises recorded in gel with a thermocouple and by MR thermometry agree well with each other and a thermal simulation using the measured HIFU intensity. Below the cavitation threshold PAM creates a map where the harmonic energy relates to the intensity of the incident HIFU beam. This can be compared to measured heat deposition based on measurement or simulation of the HIFU field, and used to predict temperature rise. Above the cavitation threshold short tone bursts of 20 cycles create cavitation activity that can be detected and mapped by PAM, however this is not expected to be detectable in MR images. To investigate the feasibility of simultaneous PAM and MR thermometry, the Zonare was inserted into the MR scanner and US and MR images recorded. There is no significant degradation of MR or US images with the US imaging system placed inside the scanner. Our preliminary data suggests that PAM has the potential to monitor HIFU in real-time, and match the performance of MR thermometry even in the absence of acoustic cavitation. Where HIFU is being used to generate cavitation with minimal heating, PAM monitors the activity in real-time whereas MR thermometry cannot. This is significant for drug delivery applications where mechanical rather than thermal effects of acoustic cavitation underpin the treatment. The results also suggest that a combined PAM/MR system can be developed.
10:40 AM
STRATEGY OF HIGH EFFICIENCY AND REFINED HIGH-INTENSITY FOCUSED ULTRASOUND AND ULTRASOUND MONITORING IMAGING OF THERMAL LESION AND CAVITATION
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High-intensity focused ultrasound (HIFU) has been developed as a noninvasive technique to selectively and locally produce therapeutic effects in biological tissue deep into the interior of the body while sparing surrounding tissue from harmful exposure. High efficiency and refined HIFU therapeutic methods for reducing the acoustic intensities and duration of treatment will be of benefit in the application of HIFU. The use of HIFU for the treatment of tumors located in various tissues is being investigated due to the development of the medical imaging techniques for targeting and monitoring HIFU during recent years, such as magnetic resonance imaging and ultrasound imaging. Ultrasound imaging presents a number of advantages such as its portability, low-cost, real-time imaging capability, simple integration with the HIFU system and its extensive availability. In our work, we proposed that high efficiency and refined HIFU could be achieved by using a splitting transducer with various frequencies and focusing patterns, and explored the feasibility of using ultrasonic Nakagami imaging, passive cavitation imaging (PCI) and ultrafast active cavitation imaging (UACI) for monitoring of HIFU. To map cavitation bubbles with high spatial-temporal resolution and high SNR and better capture transient cavitation bubble behavior, an ultrafast active cavitation imaging method combining plane wave transmission, minimum variance adaptive beamforming, and coherent factor weighting was proposed. 2-D RF data backscattered from lesions were captured by a linear array imaging probe of a modified diagnostic US machine during HIFU and were processed to obtain ultrasonic Nakagami images. By analyzing the receiving signal, it illustrated that cavitation bubble shielding was supposed to cooperate with the temperature rise to induce a decrease in the signal, which was accompanied by an increase in cavitation events. The UACI was compared with conventional B-mode ACI from the SNR level and the resolution gain. Although the SNR of UACI was a little lower than the conventional B-mode ACI, the lateral resolutions and axial resolution were increased. The use of HIFU splitting transducer had the potential to increase the size of the thermal lesion in a shorter duration and may improve the ablation efficiency of HIFU and would shorten the exposure duration significantly. Compared with B-mode image, the ultrasonic Nakagami image was not subject to the significant shadowing effects of bubbles. Consequently, this feedback information from PCI would provide an appropriate approach to monitor the cavitation activity and then help to accomplish the HIFU treatment. UACI may realize high spatial-temporal resolution imaging of cavitation bubbles.
ADAPTIVE LESION FORMATION USING DUAL MODE ULTRASOUND ARRAY SYSTEM

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We present the results from an ultrasound-guided focused ultrasound platform designed to perform real-time monitoring and control of lesion formation. Real-time signal processing of echogenicity changes during lesion formation allows for identification of signature events indicative of tissue damage. The detection of these events triggers the cessation or the reduction of the exposure (intensity and/or time) to prevent overexposure. A dual mode ultrasound array (DMUA) is used for forming single- and multiple-focus patterns in a variety of tissues. The DMUA approach allows for inherent registration between the therapeutic and imaging coordinate systems providing instantaneous, spatially-accurate feedback on lesion formation dynamics. The beamformed RF data has been shown to have high sensitivity and specificity to tissue changes during lesion formation, including in vivo. In particular, the beamformed echo data from the DMUA is very sensitive to cavitation activity in response to HIFU in a variety of modes, e.g. boiling cavitation. This form of feedback is characterized by sudden increase in echogenicity that could occur within milliseconds of the application of HIFU (see http://youtu.be/No2wh-ceTLs for an example). The real-time beamforming and signal processing allowing the adaptive control of lesion formation is enabled by a high performance GPU platform (response time within 10 msec). We present results from a series of experiments in bovine cardiac tissue demonstrating the robustness and increased speed of volumetric lesion formation for a range of clinically-relevant exposures. Gross histology demonstrate clearly that adaptive lesion formation results in tissue damage consistent with the size of the focal spot and the raster scan in 3 dimensions. In contrast, uncontrolled volumetric lesions exhibit significant pre-focal buildup due to excessive exposure from multiple full-exposure HIFU shots. Stopping or reducing the HIFU exposure upon the detection of such an event has been shown to produce precisely controlled lesions with no evidence of overexposure even when fast raster scan of volumetric HIFU lesions is attempted. We also show that the DMUA beamformed echo data is capable of detecting underexposure condition at the target location, e.g. due to the obstruction of the HIFU beam resulting from cavitation activity in the path of the beam. The results clearly demonstrate the advantage of adaptive lesion formation in reducing the treatment time while confining the tissue damage to the target volume.
11:00 AM
ULTRASOUND THERMOGRAPHY: A NEW TEMPERATURE RECONSTRUCTION MODEL AND IN-VIVO RESULTS
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Ultrasound has shown high sensitivity to small localized temperature changes when used for monitoring and guidance of the sub-therapeutic HIFU beams. The estimated temperature field based on the widely used thermal strain model, however, can be highly distorted either due to propagation artifacts (e.g. thermal lens effect, reverberation etc.) or by natural motions. We have recently presented a new model in which by incorporating the low-pass nature of the thermal expansion process in the model derivation, non-mechanical artifacts can be effectively reduced without further filtering. A digital filter realization of the new temperature reconstruction model is presented in which the filter parameters are defined by the tissue properties. Natural motions, in the other hand, cause non-thermal deformations in the underlying tissue which in turn create artifacts in the same spatial-temporal bandwidth as the true temperature field. An adaptive filter approach is presented which takes advantage of the global (spatial) availability of the deformation field before and after the HIFU operation and the fact that most of the natural motions are quasi-periodic in time. A new ultrasound temperature reconstruction filter was applied to the echo shift data obtained from RF imaging data of sub-therapeutic HIFU in the hind limb of Copenhagen rats in vivo. The animals were anesthetized without breathing control and sporadic gasping occurred during data collection. In order to reduce the effect of natural motions on the displacement data, an adaptive filter was trained before administrating the HIFU shot. Points with significant mechanical strain and from outside the converging region of the HIFU beam were chosen for adjusting the coefficients of the adaptive filter. During sub-therapeutic shot, the data from selected points and trained coefficients were used to eliminate the effect of natural motions using a spatial interference cancellation filter. Figure 1 shows the axial-temporal temperature profiles computed using the new ultrasound-temperature model before (a) and after (b) motion compensation during sub-therapeutic HIFU shot in the hind limb of a Copenhagen rat in vivo. As it is seen the ripple artifact usually seen in the post focal region is greatly reduced by the new model and the temperature rise is well localized near 40 mm (the geometric focus of the HIFU array). The lateral extent of the estimated temperature field is affected by the wide point spread function of the imaging probe. It is also seen that the new model has effectively reduced the ripple artifact due to the thermal lens effect which is usually present in the post focal region. The sporadic gasping induced erroneous temperature change which is effectively eliminated by the adaptive filtering technique. The results presented here show the effectiveness of the new model in reducing the ripple artifacts due to the thermal lens effect. We also showed that effective use of adaptive filtering can help in mitigating interferences which share spatial-temporal bandwidth with the temperature field. The overall improvements confirm the suitability of ultrasound for in vivo thermography.

Figure 1: Axial-temporal temperature profiles computed using the new ultrasound-temperature model before (a) and after (b) motion compensation during sub-therapeutic HIFU shot in the hind limb of a Copenhagen rat in vivo.
11:10 AM
REAL-TIME RNN-BASED ACOUSTIC THERMOMETRY WITH FEEDBACK CONTROL
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A major obstacle to the widespread adoption of HIFU therapy is the development of a suitable method of monitoring the ablation therapy in real-time. Recently, MR-thermometry has emerged as a promising method for HIFU therapy monitoring. We have previously demonstrated the potential of acoustic thermometry, by using a recurrent neural network (RNN), to estimate changes in tissue temperature during HIFU ablation therapies. A limitation of this method is that an excessive therapeutic dose can cause multiple, non-linear changes within the ultrasound data, resulting in unreliable temperature estimates from the RNN. Accordingly, we propose a revised method of dosing wherein closed loop feedback is used to provide a specific dose--not only to ensure the creation of a lesion, but also to preserve the integrity of the ultrasound image, thereby producing accurate temperature estimates from the RNN.

This investigation of controlling the thermal dose using feedback was performed on ex vivo bovine liver. The acoustic parameters used as inputs to the RNN were: changes in integrated backscatter intensity, thermal strain, and correlation. The therapeutic dose was delivered using a 1.1 MHz, 2D-array HIFU transducer transmitting at regular intervals during a 40-second dose. Interleaved between these regular HIFU dose intervals, volumetric ultrasound images were also acquired on a Siemens ACUSON SC2000, with a 4Z1c probe. Feedback was introduced to the system by varying the HIFU duty cycle, in order to minimize the difference between a desired temperature curve (assigned a priori) and the estimated focal temperature values. Two methods were used for estimating the focal temperature: first, using a 75-micron copper-constantan thermocouple embedded within the liver sample, and second as calculated from the RNN-based output temperatures estimated from the ultrasound data. The ability of each method to deliver a controlled, therapeutic dose was compared. We have demonstrated a method of feedback controlled dosing that both creates a lesion (an indicator of assured cell death), and also sustains the integrity of the ultrasound features in imaging to ensure accurate temperature estimates. While thermocouple derived focal temperature estimates are more precise than the temperature estimates derived from RNN-based acoustic thermometry, we were still able to achieve effective therapeutic doses which created thermal lesions and maintained ultrasound feature quality. This approach to incorporating feedback in real-time RNN-based acoustic thermometry appears promising as a potential method of HIFU therapy monitoring.
11:20 AM ✭ Invited Speaker ✭

IMPROVING TEMPERATURE MONITORING IN PALLIATIVE TREATMENT OF BONE METASTASES BY FOCUSED ULTRASOUND

Yuexi Huang 1, Nichlas Ellens 2, Charles Mougenot 3, Gregory Jan Czarnota 4, Kullervo Hynynen 1, 2

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Magnetic resonance guided focused ultrasound (MRgFUS) has shown promising results in the palliative treatment of bone metastases. Despite its clinical effectiveness, temperature monitoring by MR thermometry proved challenging due to motion artifacts and non-uniform heating at the bone-muscle interface. In this study, ex vivo experiment and computer simulation were performed to optimize the treatment/imaging protocol; patient data from a clinical trial were processed retrospectively to investigate algorithms for minimizing motion artifacts. FUS heating on the femur bone of ex vivo porcine thighs were performed on a clinical MRgFUS system (Philips Sonalleve, Finland). The FUS array was 12 cm in diameter, f number of 1, operating at 1.2 MHz under a 3T MR scanner (Achieva, Philips). The focus was either placed at or behind the bone surface with 4 mm cells, or at the surface with 12 mm cells. Image resolution of MR thermometry was either 2.5x2.5x7.0 mm, or higher at 1.5x1.5x5.3 mm. Incident angle at the bone interface was 0 or 30 degrees. Computer simulations of flat and circular bone interface were performed with similar parameters as in the ex vivo study. MR thermometry data from a clinical trial were re-processed to minimize motion artifacts by subtracting only matched pairs of images. Both ex vivo experiments and simulation showed more uniform heating with 12 mm cell focusing at the bone surface than 4 mm cell focusing behind the bone at similar energy levels, especially at 30 degree incident angle. Higher image resolution of MR thermometry visualized heating with better accuracy. By subtracting only matched pairs of images, transient motion artifacts were avoided in some cases and temperature information were restored. In palliative treatment of bone metastases, ablation targets are the nerves in the periosteum at the bone surface. Therefore, focusing and steering at the bone surface with low to medium power levels provides more uniform and controllable heating than focusing behind the bone with high power levels. Motion in this application is often transitory due to pain reaction, therefore subtracting only matched pairs, or using a multi-baseline approach, may minimize motion artifacts in MR thermometry.
11:30 AM
3D TREATMENT ENVELOPE EVALUATION IN TRANSCRANIAL MRgFUS
Henrik Odén 1, 2, Nick Todd 1, Josh de Bever 3, Scott Almquist 3, Allison Payne 1, MarJanna Dahl 4, Kurt H Albertine 4, Douglas A. Christensen 5, 6, Dennis L Parker 1
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Recent clinical trials utilizing transcranial MR-guided focused ultrasound (tcMRgFUS) for thermal ablations targeted areas near the geometric center of the skull convexity [1]. This minimizes the challenges of US focusing through the skull in terms of beam aberration and unintended near-field heating. Areas where therapeutic levels of US can be achieved have been evaluated in a treatment envelope study using 2D MR temperature imaging (MRTI), monitoring only the focal spot [2]. Here we present a proof-of-concept 3D treatment envelope evaluation, monitoring the fully insonified field-of-view in a lamb model. Beam aberration is evaluated with hydrophone scans. A 3D segmented EPI pulse sequence, with k-space subsampling (R=4) in the phase encode direction, was used for MRTI using the PRF shift method. Imaging parameters were: voxel size=1x1x2 mm (zero-filled interpolated to 0.5x0.5x1.0 mm), FOV=192x144x60 mm, TR/TE=36/11 ms, ETL=9, 4.3 s per time frame. All data were reconstructed with a temporally constrained reconstruction algorithm [3-4]. 32 US sonications (32 acoustic watts, 17.3 s) were performed in two axial planes through a lamb skull using a phased-array transducer (256 elements, 1 MHz, 13 cm radius of curvature). The transducer was mechanically moved and electronically steered +/- 5 mm in x and y, for 10 mm in-plane sonication spacing. Post-heating hydrophone scans were performed through the skullcap with all soft tissue removed, FOV and resolution were 20x20 mm and 0.25x0.25 mm, respectively. Fig. 1a-b shows coronal and sagittal views of temperature maps from sonications in the distal plane overlaid on magnitude images. 2D thin-slab MIP of near-field heating for one sonication in the distal plane is shown in 1c. The ratio between the hottest focal spot voxel and mean of ten hottest near-field voxels (i.e., relative skull heating) was calculated for all sonications, and is extrapolated to the full intracranial volume in 1d-e (coronal and sagittal views, respectively). Fig 1 a-c indicates substantial near-field heating in all sonications, resulting from the application-specific non-optimal transducer design; due to the large US focus depth (13 cm) and the small size of the brain, the energy entering the skull is spread over a relatively small area. This, in combination with high US frequency (1 MHz), results in large near-field energy deposition. Hydrophone scans (data not shown) indicate slight phase aberration and substantial intensity drop, which agree well with MRTI. This work describes proof-of-concept methods for 3D treatment envelope evaluation that simultaneously monitor the focal spot and all near- and far-field tissue-bone interfaces. Increased FOV coverage for human applications without sacrifices in spatio-temporal resolution can be achieved with higher values of R. R’s of 6-12 have been shown to result in temperature errors below 0.5 °C [4]. 3D treatment envelope evaluations can be useful in evaluating existing transducer designs and validating new designs aimed at expanding the treatable volume in tcMRgFUS.


Fig 1. a-b) Combined temperature maps for heatings in the distal plane (relative to the transducer). c) Near-field heating for one sonication in distal plane. d-e) Ratio of focal spot to skull heating, extrapolated to the full intracranial volume.
Conventionally, MRI temperature monitoring during HIFU ablation is performed with 2DFT GRE imaging. To achieve high SNR with fast sequence times, very low sampling bandwidths are used (~11 kHz). Because of the low bandwidth, off-resonance can cause shift artifacts in the image. Off-resonance created by ablative heating can cause shifts greater than half of a pixel, affecting the accuracy of treatment monitoring. Five SPGR sequences were implemented and tested on a 3T GE scanner using developmental builds of SpinBench and RTHawk (HeartVista, Inc. Menlo Park, CA USA), and a healthy volunteer was scanned with each sequence. High-order shims were calculated and applied prior to imaging, to reduce B0 variation. All sequences used a 28 cm FOV, 3 mm slice thickness, and TBW=4 excitation. The first sequence "Single 2DFT" was designed to mimic the sequence being used for monitoring in brain HIFU applications. "Multi-echo 2DFT" acquired 9 echoes using 11 times higher bandwidth. Three multi-echo spiral sequences were designed to independently optimize resolution, speed, or accuracy, while keeping the other two parameters constant. "ME Spiral, Resolution" reduced voxel volume by a factor of 2. "ME Spiral, Speed" reduced sequence time as much as possible while maintaining speed and accuracy. "ME Spiral, Accuracy" minimized temperature uncertainty for the original voxel volume and acquisition time. For each sequence, at least 20 frames were collected. 3 frames were averaged to obtain a baseline, which was used to estimate temperature changes for the remaining frames. Mean temperature (0 order polynomial fit) was subtracted from each frame to remove B0 drift. Temperature uncertainty was calculated as the voxel-wise standard deviation through all frames, and was averaged over an ROI. Temperature uncertainty maps are shown in the attached figure, with reduced FOV. The title for each figure gives the sequence used, the mean uncertainty, resolution, and acquisition time. The ROI for mean uncertainty is displayed as a black box in the "Multi-echo 2DFT" image. For the Cartesian sequences, resolution was 1.09 mm x 2.19 mm, which is equivalent in volume to a 1.55 mm isotropic voxel. Multi-echo 2DFT had 17% higher uncertainty than single-echo, which was slightly worse than the 11% increase expected from reduced sampling time. The improved resolution ME Spiral sequence doubled the resolution of the original sequence without sacrificing temperature accuracy or sequence time. The improved speed sequence reduced acquisition time from 3.6 seconds to 1.1 seconds without reducing accuracy. Finally, the improved accuracy sequence improved temperature uncertainty by 2.7x as compared to the original sequence. Higher bandwidth temperature imaging was successfully demonstrated using multiple-echo sequences. With proper reconstruction, multiple-echo 2DFT thermometry performed similarly to single-echo 2DFT after accounting for reductions in sampling time. Using multi-echo spiral acquisitions allowed for significantly improved resolution, speed, and accuracy. Future temperature monitoring applications can choose other design points to best take advantage of the improved design space for their specific needs.
11:50 AM
TREATMENT PLANNING AND STRATEGIES FOR ACOUSTO-OPTIC GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND THERAPIES
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Real-time acousto-optic (AO) sensing has been shown to non-invasively detect changes in the optical properties of ex vivo tissue during high-intensity focused ultrasound (HIFU) exposures. The technique is particularly appropriate for monitoring non-cavitating lesions that offer minimal acoustic contrast. This work employs a multi-physics numerical model to: improve the AO sensing of lesion formation during HIFU therapy, develop treatment strategies for the ablation of large volumes, and assess the technique’s viability and robustness in a clinical setting. The angular spectrum method is used to model the acoustic field from the HIFU source. The resulting temperature field, due to the absorption of ultrasound, is modeled using a finite-difference time-domain solution to the Pennes bioheat equation. Changes in tissue optical properties are calculated using a thermal dose model, calibrated using experimental data. The diffuse optical field is modeled using an open-source, GPU-accelerated Monte Carlo algorithm. The Monte Carlo algorithm is modified to account for light-sound interactions and to account for AO signal detection. AO signals are presented in the context of a photorefractive-crystal-based detection scheme, and are compared to signals obtained using standard optical detectors. Detected AO signals show a dependence on the geometry of the illumination and detection configuration, as well as the optical wavelength. Optimal contrast is observed when the tissue is illuminated normal to the direction of ultrasound propagation and light is detected in transmission mode. In this configuration, AO sensing of lesion formation is more sensitive and more robust than purely optical sensing for every investigated case. Additionally, it is shown that AO sensing can be effectively used to monitor the formation of lesion arrays for the ablation of large volumes by employing an appropriate treatment strategy. AO sensing is a robust method for monitoring the formation of both single and arrays of HIFU lesions when an appropriate illumination and detection configuration scheme and an appropriate treatment strategy are employed. AO sensing is also more sensitive than purely optical sensing for the scenario investigated. The study suggests that AO sensing is a promising modality for real-time monitoring of HIFU.
Acoustically driven stable and inertial microbubble oscillations (acoustic cavitation) exert forces that, among others, have been shown to activate cell's mechanoreceptors, disrupt cellular and vascular membranes and lyse blood clots. While numerous investigations that explore these unique properties of acoustic cavitation have recently demonstrated very promising results for a wide range of applications, there is a need to develop new and noninvasive methods that will lead to i) deeper understandings of the interactions involved, ii) their optimal use for therapy or diagnosis, and iii) ultimately their translation to the clinics. Here we combine the distinct information provided by three different medical imaging modalities (US, MR and CT) with three-Dimensional Finite Difference Time Domain (3D-FDTD) simulations to assess, visualize and, by extension, harness this nonlinear process transcranially. In the present work, acoustic cavitation is studied in the context of focused ultrasound (FUS) induced blood brain barrier permeabilization. Here, it is performed with a clinical MR guided FUS system (MRgFUS) in non-human primates (NHP). A US imaging research system (Verasonics), operated in passive mode and programmed to perform passive acoustic mapping (PAM), was also integrated to the MRgFUS system. The integrated system (US&MRgFUS) was used to acoustically assess and visualize acoustic cavitation experimentally. In addition, from CT datasets, we also extracted the skull acoustic properties (density, speed of sound, and absorption) and incorporated them to the PAM back-projection algorithm in order to account for spatially varying wave propagation effects of the recorded acoustic emissions, such as refraction and diffraction. The US, MR, and CT datasets were co-registered using the 3D slicer program (CT to MR datasets) and fiducial markers (US to MR). The derived acoustic properties and the location of the targets determined by the CT and MRI data respectively were then used as input to 3D-FDTD simulations that we developed. At these locations, point sources derived by microbubble dynamics models were incorporated and propagated towards a virtual US array. With these simulations we assessed the losses and aberrations involved to the propagation of diverging pressure waves towards the receivers and compared the PAMs generated by the simulated and experimental data. Finally, using clinical CT and MR datasets and the FDTD model we demonstrate the clinical utility of the proposed framework. The 3D-FDTD simulations suggest that the microbubbles' pressure waves propagating through the skull lose 97% of their strength as compared to propagation in water-only (78% due to reflections and scatter and 19% due to absorption). Further, the incorporation of variable speed of sound to the PAM back-projection algorithm indeed corrects aberration and significantly improves the resolution, which was reduced by only 17% and 28% than water-only propagation in transverse and axial directions respectively. More than 94% agreement in FWHM between the simulated and experimentally determined axial and transverse line profiles was observed. Finally, the simulations with the clinical datasets indicate that PAM of acoustic cavitation will be possible with our current experimental set-up. The proposed approach provides a clinically relevant framework for developing a comprehensive treatment planning, monitoring and assessment of the therapeutic and diagnostic applications that harness acoustic cavitation in the brain and elsewhere. It may also enrich our understandings and provide more control over this inherently nonlinear process.
FOCUSED ULTRASOUND-INDUCED BLOOD-BRAIN BARRIER OPENING IN NON-HUMAN PRIMATES WITH TRANSCRANIAL CAVITATION DETECTION IN VIVO

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Focused ultrasound (FUS) with microbubbles has shown great promise in assisting brain drug delivery by noninvasively and locally opening the blood-brain barrier (BBB). Real-time monitoring of the treatment with transcranial passive cavitation detection (PCD) is critical to assess efficacy and safety without requiring online MRI. The objective of this study is to investigate the consistency of PCD monitoring and opening threshold during BBB opening at different targeting regions and across non-human primates of different ages. The experiments were performed in four rhesus macaques (9 years old (n=2) and 23 years old (n=2)) with pre-planned targeting at the caudate nucleus, putamen, and thalamus. During the experiment, in-house microbubbles (lipid-shell and monodisperse with a median diameter of 4-5 µm) were injected intravenously at the beginning of sonication (frequency: 0.5 MHz, peak negative pressure: 200–600 kPa, pulse length: 10 ms), with a confocal hydrophone serving as a passive cavitation detector to real-time monitor the PCD signals. After sonication, pre- and post-contrast enhanced 3D T1-weighted, 3D T2-weighted, and susceptibility weighted MRI were used to confirm the opening and potential damage. The harmonic, ultraharmonic, and broadband signals within 1-5 MHz were separately filtered for quantifying the stable cavitation dose (SCD) and inertial cavitation dose (ICD), which were used to correlate the opening volume and enhancement quantified from MR images. A total of 25, 29, and 6 sonications were performed at the caudate nucleus, putamen, and thalamus, respectively. Real-time PCD monitoring showed that the ICD and SCD were at the same level for different targets (caudate nucleus, putamen, and thalamus). By correlating the SCD to the opening results, it was found that the MRI enhancement (related to the concentration of the contrast agent) correlated well with the SCD while the opening volume did not. This implies that the SCD could be used to assess the amount of model drug been delivered, while lack of correlation between opening volume and SCD may be due to the white vs. gray matter distribution and various anatomical structures in the brain. By comparing the opening results, the non-human primates across two age groups, it was found that the pressure thresholds of opening were 250 kPa and 350 kPa in young and old animals, respectively. This may be due to the age-related skull characteristics such as thickness or density that affects skull attenuation. The PCD showed consistency in non-human primates at different targeting regions despite the thicker skull and inhomogeneous brain tissue, while the SCD could be used to assess the amount of drug molecules been delivered. The pressure thresholds of opening were found to increase with animal age, and could be due to the age-related skull characteristics.
MODELING LOCALIZED DELIVERY OF DOXORUBICIN TO THE BRAIN UPON FOCUSED ULTRASOUND ENHANCED PERMEABILITY OF BLOOD-BRAIN BARRIER

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Despite its well-established antitumor effect for chemotherapy of the central nervous system (CNS), Doxorubicin (DOX) with molecular weight of 544Da has limited access into the parenchyma due to the presence of blood-brain barrier (BBB). Treatment of CNS malignancies with DOX typically fails to reach cytotoxic levels at the targeted intracellular compartment. However, recent preclinical studies have demonstrated that focused ultrasound (FUS)-induced blood-brain barrier disruption (BBBD) can improve localized delivery of DOX to the brain [Aryal et al, 2013; Treat el al, 2012; Yang et al, 2012]. Therefore, it would be beneficial to establish a mathematical framework to predict the effect of enhanced BBB permeability on the spatial and temporal distribution profiles of DOX concentration at the treatment area. To closely depict sonication conditions resulting from a typical half-MHz ultrasound frequency used for transcranial FUS-induced BBBD on rat (Fig.A), we considered a 2D idealized model geometry with the sonicated area and surrounding tissue dimensions detailed in Fig.B. Spatially- and temporally-dependent DOX concentrations are described for 3 compartments: plasma (Cp), extravascular-extracellular (Ce), and extravascular-intracellular (Ci).

Plasma concentration Cp(t) after a bolus injection of 5mg/kg (clinical dose) is described as a triexponential function and used as an input for the model. To account for its high affinity to albumin, DOX plasma concentration is partitioned into free DOX (544Da - Cfp) and bound DOX (70kDa - Cbp). In the extravascular compartment, their size-dependent permeability kinetics (illustrated in Fig.C) and mass transport parameters (diffusion, elimination, association, dissociation) are reflected in rate equations of Cfe and Cbe. Finally, the uptake and efflux of free DOX by brain cells are considered in the rate equation of the intracellular concentration Ci, which is used as a measure of therapeutic efficacy. To solve these 3 coupled partial-differential equations (Cfe(r,t) - Cbe(r,t) - Ci(r,t)), we implemented a finite element method in COMSOL for 48hr time range and 50sec time step. To validate our model against previously published experimental results [Park et al, 2012], 3 distinct sonication schemes (single-sonication (SS), 10min double-sonication (DS10), 120min double-sonication (DS120)) are simulated and their corresponding Ci outputs are compared. Spatial-temporal distribution of Ci(r,t) in response to single-sonication (SS) with 0.01min-1 Ktrans is illustrated in Fig.D. Highest intracellular concentration occurs between 6-12hrs post-sonication. In comparing the 3 sonication schemes given the same injection dose of DOX, we found that DS10 yields the greatest drug deposition at targeted region (Fig.E). Finally, we survey the effect of BBB permeability enhancement on the overall therapeutic level by calculating the temporally-peaked spatially-averaged Ci as a function of Ktrans (Fig.F). A mathematical model is established for DOX delivery to the brain upon localized BBBD. When compared to experimental data by Park et al, our simulation consistently verifies that DS10 is superior to other 2 sonication schemes (SS and DS120). Ultimately, this model can provide a framework to predict the treatment efficacy of a specific therapeutic agent underlined by FUS-induced BBBD.
The blood brain barrier (BBB) protects the brain by preventing entry of large molecules, but this poses a major obstacle to the development of drug therapies for various neurological disorders. High-intensity focused ultrasound (HIFU) has become a promising research area enabling non-invasive and transient opening of the blood brain barrier (BBB) using microbubble ultrasound contrast agents. When this technique is combined with a drug treatment, the potential for targeted therapies in the brain becomes possible. Traditionally, HIFU research is conducted under MRI guidance, which is expensive and poses physical limitations due to the magnetic field. A system that could allow research investigators to test brain therapies outside of the MR environment could facilitate and accelerate translational research. In this study, we present a novel HIFU system that uses a custom-built HIFU generator mounted to a motorized stereotaxis unit with brain atlas to target blood brain barrier disruption (BBBD) without MR-guidance. The spatial accuracy of the ultrasound system was calibrated using an optically-transparent tissue-mimicking phantom containing bovine serum albumin, gellan gum, salt and degassed water. Continuous high-power exposures were used to coagulate the albumin causing a localized change in the optical properties of the gel. Animal studies using a rat model were performed to evaluate whether localized BBBD could be achieved through the intact skull using atlas-based targeting. Anesthetized animals were mounted in the motorized stereotaxis system and the skull suture landmarks were identified. Brain targets were identified for each of the animals using a commercially-available rat brain atlas (StereoDrive, Neurostar Tubingen Germany). A lightweight water reservoir with an acoustically transparent polyimide membrane at the base was then placed over the skull with the HIFU probe submerged. The mounted ultrasound probe was moved to the target location by the motorized system. 2% Evans Blue dye (3 ml/kg) was injected intravenously as a marker to visualize BBBD. For each target, a bolus injection of 30ul/kg of Optison® was injected intravenously. Immediately after injection, the HIFU transducer was driven at its fundamental frequency (1.05MHz) or 3rd harmonic frequency (3.23MHz), with a peak negative focal pressure estimated to be 0.54MPa through the skull. The pulse signal was set to be 10ms pulse width, 1Hz repetition frequency and 120s duration. The rat was sacrificed immediately after sonication. Tissue-mimicking phantom studies were able to demonstrate that the system could accurately target two regions within 0.5mm +/- 0.1mm. In rat studies, upon brain dissection and histology, Evans blue dye was visualized in the targeted brain regions, indicating BBB permeability and successful disruption. With this dedicated small animal motorized stereotaxis HIFU system, we achieved accurate targeting in the brain. This system can be used as an alternative to MRI-guided HIFU in order to perform non-invasive localized BBBD with or without drug delivery. This system offers researchers the ability to perform high-throughput studies in a conventional laboratory environment.
A NEW MOTORIZED MR-GUIDED ULTRASOUND SYSTEM FOR THE CONTROLLED DELIVERY OF LARGE MOLECULES TO THE RODENT BRAIN
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Short sonifications of circulating microbubbles have shown its capability to disrupt the Blood Brain Barrier (BBB) locally, transiently and non-invasively, allowing large molecules to access the central nervous system. To do so, MRI guidance ensures a precise control of the disruption location and deposited acoustic intensity prior to BBB opening. MRI also enables to visualize and quantify its extent through the use of MR contrast agents injected after disruption. In the framework of pharmacology studies for brain diseases, being able of targeting specific brain regions while keeping the rest of the brain untreated is of great interest. We developed a motorized setup for rodent transcranial experiments which allows the displacement of the ultrasound transducer within high field MRI preclinical systems. After head shaving, Sprague Dawley rats (n=5) were maintained under isoflurane anesthesia in stereotactic position inside a 7T preclinical scanner (Pharmascan, Bruker). A single channel spherically focused transducer (1.5 MHz, F/D=0.8, F= 20 mm) was coupled to the head. A catheter was inserted in the caudal vein. Anatomy T2-weighted, T1-weighted and T1-mapping reference scans were acquired. The position of the ultrasound focal point was monitored using a MR-acoustic radiation force imaging sequence. We programmed an arbitrary spatial pattern for BBB opening (see Figure) by moving the focal point (displacement of the transducer) and varying the emitted acoustic intensity from outside the magnet. 200 µL of Sonovue (Bracco) were injected intravenously via the catheter and the sonication was performed following the defined trajectory. 200 µL of gadolinium (Gd) chelate (Guerbet) were then injected. A T1-weighted sequence was performed to visualize the contrast enhancement at the sonoporated regions (frame a), while a T1-mapping sequence (frame b) allowed, after post-processing, calculating quantitative Gd concentration maps at the disruption sites (frame c). Due to T1 shortening effect induced by the presence of Gd chelate, a contrast enhancement is visible at the expected locations compared to the rest of the brain (see Figure a), confirming that the BBB has been opened along the planned trajectory. No Gd chelate penetration was observed for acoustic pressures below the opening threshold, estimated to be around 0.3 MPa (frame a). We obtained BBB disruptions for different spatial patterns (circle, square, cross, dotted line). The acquisition of a T1 map (frame b) then enables to quantify drug uptake in brain tissue (frame c). Above 0.5 MPa at focus, no significant difference was found in the maximum Gd concentration that was measured although the width of the disrupted line was increased as expected. Frequent hemorrhages were observed at histology for pressures exceeding 0.5 MPa. This study demonstrates that this new MR guided motorized device can be used to deliver drugs to arbitrarily chosen regions in the rodent brain after a unique systemic injection. The delivered concentration can be tuned by adjusting the acoustic pressure, and measured using quantitative MRI sequences. Our setup also offers the unique possibility to test on the same animal different acoustic conditions (pressure, shot duration) or the influence of physiological parameters such as anesthesia and vascular density on BBB opening efficiency. It may result in a significant reduction of the number of animals and the acquisition time required for drug delivery experiments, and may also offer a real gain of reproducibility by planning precisely the disruption location.
**PROTOCOL OPTIMIZATION IN A PIG MODEL FOR BLOOD-BRAIN BARRIER DISRUPTION BY TRANSCRANIAL FOCUSED ULTRASOUND**

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Blood-brain barrier disruption (BBBD) by focused ultrasound has been demonstrated in many pre-clinical animal models including non-human primates. In preparation for a clinical trial, however, the ultrasound parameters and microbubble dosage need to be optimized according to the properties of the human skull and the capabilities of the current clinical device. In this study, a BBBD protocol was developed in a pig model with human applications in mind. Wide craniotomies were performed on six pigs. The skin was closed and the surgical site filled with degassed saline. A partial human skull was positioned over the pig’s head. The sonication protocol was developed on an ExAblate 4000 system (InSightec, Israel) at 230kHz. Sonications were steered over a 3x3 grid of 9 spots at 3mm spacing. For each spot, the pulse was 2ms ON, 28ms OFF, for 300ms. Total sonication time was 50s. Acoustic power levels from 3 to 10 W were tested. As multiple sonications with stepwise increases in power are anticipated in humans to determine individual BBBD thresholds, both one-tenth (2ul/kg) and one-fifth (4ul/kg) of the maximum dose (20ul/kg on the label) were investigated for each set of sonication parameters. Microbubbles were injected simultaneously with the start of the sonication. Acoustic emission signals were recorded by two hydrophones. Gd-enhanced FSE T1 was acquired post sonication to verify BBBD. Histology was performed to assess for hemorrhage or tissue damage. At 3W, using either 2ul/kg or 4ul/kg of Definity, no BBBD was revealed in the Gd-T1 images. Only very small and transient wide-band emission signals were observed. At 5W, 2ul/kg Definity, delayed Gd enhancement (20 min post sonication) was observed. Wide-band emission signal was higher but still sporadic. At 4W and 5W with 4ul/kg Definity, BBBD was observed immediately post sonications (Figure 1). The BBBD volume was about 1cm in diameter, close to the designed steering pattern. No obvious hemorrhage was seen on histology. Wide-band emissions were observed frequently over the sonication time. At 10W, 2ul/kg Definity, Gd leakage in an extended area (bleeding) was observed in the cortex, with strong cavitation signals. With one-fifth of the maximum dose of Definity and 4 to 5 W acoustic power, BBBD was achieved over the steered volume. The intensity of wide-band emission can be used as a confirmation of the optimal power level for successful BBBD, and as a safety measure to terminate the sonication should excessive cavitation occur. Future studies will be performed to gain a statistical measure of the cavitation threshold as a function of the acoustic emissions.

Figure 1 Gd-T1 MR image showing BBBD at 4W (right) and 5W (left) with 4 ul/kg Definity boluses.
BEHAVIORAL EFFECTS OF TARGETED DRUG DELIVERY VIA NON-INVASIVE FOCUSED ULTRASOUND BLOOD BRAIN BARRIER OPENING IN NON-HUMAN PRIMATES
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It has been shown that the blood brain barrier (BBB) can be transiently opened in non-human primates (NPHs) with the application of non-invasive focused ultrasound (FUS) coupled with the IV administration of microbubbles. We aim at demonstrating that the responses of NHPs to a decision making task can be modulated with the delivery of pharmacological agents to specific brain regions targeted by FUS BBB opening. Under general anesthesia (isoflurane) NHPs (n = 4) were placed into a stereotax for targeted FUS treatment. In house prepared microbubbles (4-5 um) were administered IV and a single element transducer (500 kHz, 0.3-0.4 MPa, 10 ms pulse length, 120 second duration) was used for the FUS treatment. The putamen was targeted for all behavioral experiments and the stereotactic target coordinates were generated with atlas-based developed targeting methodologies. There was a three hour recovery period post FUS treatment for the effects of general anesthesia to dissipate before administering an IM injection of haloperidol (0.01mg/kg), a D2 antagonist. The NHPs then completed a reaching-reward magnitude bias with dot coherence task for water reward. NHPs were allowed to work until satiated. One day post FUS treatment and behavioral task the BBB opening at the target site was confirmed using contrast-enhanced T1-weighted MRI. FUS treatment MRIs confirmed BBB opening in the putamen in our target region for each subject. Administration of haloperidol does have a significant effect on the behavioral responses of the NHPs post BBB opening compared to control (IM saline with BBB opening). No significant difference from control (IM saline) was observed for haloperidol without BBB opening. Reaction times were significantly increased on the contralateral side of BBB opening compared to the ipsilateral side for haloperidol with BBB opening only. There was a decrease in accuracy for the low reward choice for both sides as well as a loss in significant difference between high and low reward reaction times to the initial cue when comparing haloperidol injection with BBB opening to haloperidol injection without BBB opening. All effects from haloperidol with BBB opening were transient, i.e., only lasting 20 min on average post injection. We have shown that we can modulate the behavioral responses of NHPs to a reaching decision making task with the delivery of pharmacological agents coupled with BBB opening. Haloperidol was shown to have significant effects on motivation, motion bias and reaction time in the cases after opening of the BBB in the putamen. These findings support the potential of targeted drug delivery enhancement through non-invasive FUS mediated BBB opening as well as dose dependent responses with BBB opening.
11:20 AM
SAFETY AND EFFICACY OF BLOOD-BRAIN BARRIER DISRUPTION WITH FOCUSED ULTRASOUND IN A MOUSE MODEL OF ALZHEIMER’S DISEASE
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Focused ultrasound (FUS)-mediated drug delivery has been shown to effectively reduce amyloid plaque load in the cortex of a mouse model of Alzheimer’s disease (AD). However, commonly in AD, amyloid is also found deposited in vessel walls, disrupting cerebrovascular regulation and increasing the susceptibility of the vessels to hemorrhage. Therefore, further investigation into the safety and effectiveness of FUS as a method for drug delivery through the blood-brain barrier (BBB) in the presence of amyloid pathology is required. Here, we used a transgenic (Tg) mouse model of AD and their non-transgenic littermates at 8 months of age, which corresponds to late-stage AD characterized by behavioral deficits and compromised vasculature. The mice received weekly MRI-guided FUS treatments to temporarily open the BBB in the hippocampus and were evaluated using cognitive tests and histology. Further, we used real-time, two-photon microscopy to characterize FUS-induced changes in BBB permeability in the presence of cerebral amyloid deposits. Using the Y maze with novel arm, untreated Tg mice were found to spend significantly less time in the novel arm compared to their non-Tg littermates. Following FUS treatment, Tg mice performed as well as their non-Tg counterparts. These results indicate that repeated FUS treatments are safe and may improve cognitive behavior, even in a model of late-stage AD. The behavior data corresponded to a reduction in plaque load and increase in neuronal plasticity in the hippocampus. From two-photon studies, we observed that leakage through the BBB occurred at similar acoustic pressures in Tg and non-Tg mice but the Tg mice displayed slower leakage kinetics. Further analysis determined that vessels containing amyloid plaque are much less permeable than healthy vessels after FUS treatment suggesting that hemorrhage is unlikely. Together this data suggests that FUS-mediated BBB opening is safe and effective for improving drug delivery in the presence of amyloid pathology.
11:30 AM
NON-INVASIVE, NEURON-SPECIFIC GENE THERAPY CAN BE ACHIEVED BY FOCUSED ULTRASOUND AND RECOMBINANT ADENO-ASSOCIATE VIRUS
Shutao Wang 1, Oluyemi O Olumolade 1, Tao Sun1, Geshimani Samiotaki 1, Elisa Konofagou 1, 2

Recombinant adeno-associated virus (rAAV), a gene therapy vehicle, promises the potential cure for neurodegenerative diseases (such as Parkinson’s Disease). The existence of the blood-brain barrier (BBB), however, hinders efficient delivery of the viral vectors. Focused Ultrasound (FUS) in combination with microbubbles (MB) has been shown capable of inducing reversible blood-brain barrier (BBB) opening. This study aimed at investigating the feasibility of using FUS to non-invasively deliver rAAV through the opened BBB in mice to achieve neuron-specific transgene expression. A total of 13 mice (strain: C57BL/6) were used in this study and were divided into four groups: FUS+rAAV1 (n=5), FUS only (n=5), and sham (n=3). A single element FUS transducer (center frequency 1.5 MHz) was used for all the ultrasound treatments. The acoustic parameters used in this study were: peak rarefractional pressure 0.45 MPa, pulse length 20 ms, pulse repetition frequency 5 Hz, and treatment duration of 300 s. FUS targeting was performed using a metallic grid and the FUS focus was placed in the Caudate-Putamen (CPu) region. Immediately before the sonication, a 100 μl mixture of rAAV1-synapsin-GFP vectors (1.2×10^11 GC/animal) and in-house polydispersed microbubble (~2.5×10^7 #/animal) was administrated via the tail vein. For the sham and FUS only groups, saline was used instead of rAAV1 vectors. The targeting and BBB disruption was verified with T1-weighted contrast-enhanced magnetic resonance imaging (MRI). Behavior testing (rotarod performance test and vertical poll test) was carried out weekly for four weeks, starting from one day post the FUS treatment. Upon the end of the survival time, mice were sacrificed and transcardially perfused with 30 mL PBS and 60 mL 4% paraformaldehyde. The brains and four critical organs (heart, lung, liver and kidney) were collected for immunostaining and imaging. The brains were frozen and sectioned at 40 μm for both immunohistochemistry and immunofluorescent staining. The number of neurons transducted by rAAV was quantified using a custom-written program in MATLAB (Mathworks). The T1-weighted images revealed that FUS and MB treatments induced localized BBB opening in the intended CPu region. In the rAAV1 treated group, profound transgene (GFP) expression was found in the FUS targeted region from immunohistochemistry (DAB) staining results. The numbers of rAAV1 transducted cells were counted for eight series brain sections (200 μm inter-section distance) and was fit with a Gaussian distribution (R^2 = 0.759). The total number of rAAV1 transducted cells were calculated by interpolating the numbers based on the Gaussian distribution. It was found that FUS treated sides had significantly more transducted cells than the contralateral side (P = 0.012). The types of rAAV1 transducted cells were identified by co-localizing the GFP positive and NeuN positive or GFAP positive cells. It was concluded that the rAAV1 transducted cells are virtually exclusively neurons (mean 96.3%). Finally, no significant histological or behavioral deficits were observed from the combined the treatment regime. FUS in combination with MB provide a non-invasive and targeted approach for gene delivery to the brain. This study demonstrated the feasibility of delivering rAAV1-synapsin-GFP for neuron-specific gene therapy demonstrating the safety and efficacy of the technique.
11:40 AM

MULTIPLE SESSIONS OF LIPOSOMAL DOXORUBICIN AND FOCUSED ULTRASOUND MEDIATED BLOOD-BRAIN BARRIER DISRUPTION: SAFETY STUDY

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Previously we demonstrated that multiple treatments with liposomal doxorubicin (DOX) delivered via disruption of the blood-tumor and blood-brain barriers (BTB/BBB) by FUS combined with an ultrasound contrast agent (USCA) can effectively inhibit tumor growth and improve outcomes in the 9L rat glioma model. However, some adverse events were observed, including tissue loss at the tumor site, damage (infarct) in neighboring tissue, and in one animal, hemorrhage. We could not determine whether these effects were due to the sonications, the chemotherapy, or the tumor itself, which in some cases reached a substantial volume before it began to resolve. Here, we tested whether multiple sessions of DOX administration and FUS-mediated BBB disruption (FUS-BBBD) induces similar adverse events in normal brain tissue. FUS-BBBD was produced in one hemisphere in 10 male Sprague-Dawley rats (250-350g); the other hemisphere served as a control. In five animals we evaluated the effects of three weekly treatments with i.v injected liposomal doxorubicin (DOX) after FUS-BBBD. Sonications (0.69 MHz; 0.55-0.81 MPa; 10 ms bursts; 1 Hz PRF; 60s duration) were performed over three weeks in a grid pattern at 5, 9, and 12 targets, respectively, which mimicked the three weekly treatments we administered in our previous study. Each sonication was combined with an i.v. injection of Definity (10 μl/kg). DOX (5.67 mg/kg) was administered in fractions before each sonication. Contrast enhanced T1-weighted MRI and T2*-weighted imaging were used to confirm BBBD and detect hemorrhage in the targeted areas, respectively. The animals’ health was monitored regularly, and MRI was obtained to evaluate treatment effects. Seven weeks after the last treatment, animals were sacrificed, and the brains were sectioned and stained for histological analysis. To confirm that we were delivering DOX liposomes across the BBB, five additional animals were sacrificed four hours after sonication (0.55 MPa; nine targets in a 3×3 grid) and DOX concentrations were measured in both hemispheres (sonicated and non-sonicated) using fluorometry. BBB permeabilization was confirmed in all targeted regions in contrast-enhanced MRI. T2*-weighted imaging detected small hypointense spots, presumably small petechiae. These spots persisted and were observed at 31 and 45 days after the last sonications; they included the brain ventricle in three animals. Histological evaluation found evidence of small areas of prior necrosis in the focal plane (vacuolation, macrophages, and in three animals, small scars). In animals sonicated four hours after FUS, the mean DOX concentration in areas of the brain with BBB disruption was 4146 ± 284 ng/g. In areas with BBB disruption and evident petechiae, a higher DOX concentration (8686 ± 298 ng/g) was observed. Overall, this work demonstrates that multiple sessions of DOX delivery combined with FUS-mediated BBB disruption does not result in hemorrhage and the other significant damage in the normal brain around the tumor that was observed in our previous study. The effects we did observed may have been produced by vascular damage induced by sonication above the inertial cavitation threshold, DOX delivery across the BBB, DOX delivery to the microvasculature, or by a combination of effects. This study suggests that aggressive sonication and DOX delivery to sensitive brain structures should be performed with caution.
11:50 AM
TARGETED INTRANASAL DRUG DELIVERY TO THE BRAIN USING FOCUSED ULTRASOUND-INDUCED BLOOD-BRAIN BARRIER OPENING
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Focused ultrasound (FUS) in the presence of microbubbles has been shown to increase the permeability of the blood-brain barrier (BBB), thus allowing targeted delivery of therapeutic agents for the treatment of central nervous system diseases. Intravenous (IV) injection currently is the only delivery route used to administer the drugs. However, it requires systemic circulatory exposure, thus significantly decreasing the bioavailability of the therapeutic agents while increasing the potential of undesired immune response. Previous researches have demonstrated that intranasal (IN) route of administration provides an effective approach for drug delivery to the brain with minimized systemic exposure. But such delivery is not target-specific. In the present study, we tested the feasibility to combine IN administration with FUS-induced BBB opening for targeted drug delivery in the brain, thus providing an alternative route to IV injection for rapid delivery of therapeutic agents that have short circulation half-lives while minimizing systemic exposure. Fluorescently-labeled 40-kDa dextran was used as the model drug to signify BBB opening. It was administered via either the IN or the IV route before FUS was applied to target the left caudate putamen of C57/BL mice in the presence of microbubbles. The acoustic pressure was kept constant at 0.45 MPa to be clinically relevant. The fluorescence enhancement was quantified to compare the delivery efficiency. Passive cavitation detection was used to ensure that the same acoustic emission was achieved during sonication so that any variations seen in the BBB opening were due to the different dextran administration routes. Both administration routes successfully delivered 40-kDa dextran to the targeted location: IN route induced 5.89-folds fluorescence enhancement while IV route induced 37.5-folds increase between the control and the sonicated hemispheres. Surprisingly, no significant difference in the intensity level was detected between the targeted regions for the two groups. The apparent low enhancement level of the IN cohort was due to the significant dextran diffusion in the non-targeted right hemisphere. Histological evaluation revealed minor damage as represented by isolated spots of red blood cell extravasation regardless the dextran administration route. The present study demonstrated the feasibility of targeted intranasal drug delivery to the brain using FUS-induced BBB opening for the first time. Our results highlighted the potential of this technology to encompass a wide range of therapeutic agents with reduced systemic toxicity. Future studies are needed to further illustrate the advantages of this targeted drug delivery method to achieve higher delivery efficiency of therapeutic agents with short circulatory persistence.
VALIDATION OF A THREE-DIMENSIONAL MR-ACOUSTIC RADIATION FORCE IMAGING SIMULATION ALGORITHM

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The in situ characterization of focal spot location and quality is critical in magnetic resonance-guided focused ultrasound (MRgFUS) treatments. MR acoustic radiation force imaging (MR-ARFI) is a technique that can measure the tissue displacement caused by the concentrated force of the ultrasound beam. MR-ARFI can both assess the focus and targeting quality of the ultrasound beam as well as be used to correct for phase aberrations. This abstract presents a new technique to model the displacements caused by the radiation force of an ultrasound beam in a homogeneous tissue model mapped to a Cartesian grid. The theory behind the technique and experimental validation in several homogeneous phantom models is presented. The force distribution due to the radiation force of the ultrasound beam is found by summing the forces due to absorption in each voxel and due to reflection at the interface between two voxels. The beam intensity pattern is found using the Hybrid Angular Spectrum method. When a steady-state point-source force acts internally in an infinite homogeneous medium, the displacement of the material in all directions is given by the Somigliana elastostatic tensor. Assuming the displacement is predominantly in the direction of the ultrasound beam and assuming linear isotropic properties, a nearly incompressible medium and steady-state conditions, the displacement $w$ in the direction of beam propagation reduces to Equation 1 seen below, which is a convolution of the force field pattern and a 3D Green's function $g(r)$, where $\mu$ is the Lamé shear constant, $r$ is the distance from the point source to the location of $w$, and $z$ is the projection of $r$ onto the z-axis. Experimental validation used gelatin-based phantoms of varying mechanical stiffness (125-, 175- and 250-bloom). The Young's modulus and attenuation values for each phantom type were obtained using independent measurement techniques. All experiments were performed with a pre-clinical MRgFUS system with a 1-MHz 256-element phased-array transducer in a Siemens Trio 3T scanner. Displacements in the phantoms were measured using a 3D spin echo segmented-EPI sequence with unbalanced-bipolar motion encoding gradients and flyback readout (TR = 250 ms, TE = 50 ms, fat saturation, FA = 90°, EPI = 7, 256x128x36-mm FOV, 2x2x3-mm ZFI’d to 0.5-mm3 spacing, motion encoding amplitude (MEamp) = 30 mT/m, USdur = 10 ms, USpower = 60 W, acquisition time = 64 s, Nave = 4). Slice views of the displacement in both the in-plane and slice directions for the 125-bloom phantom are shown in Figure 1. The 3D MR-ARFI sequence used in this work allows for a thorough evaluation of the presented simulation theory. While the general trends and shape of the ARFI displacement patterns agree between experiment and simulation, there are discrepancies in the peak displacement (2.7-6.5 µm error). In addition, the simulated displacement pattern has a steeper descent than what is observed experimentally. This may be due to discrepancies in the property measurements or the assumption of homogeneous, linear isotropy. The presented 3D MR-ARFI simulation algorithm and accompanying experimental validation demonstrates the potential to use quantitative MR-ARFI displacement data in MRgFUS therapies.
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ULTRASOUND SHEAR WAVE ELASTOGRAPHY SIMULATION BASED ON NONLINEAR WAVE PROPAGATION AND WIGNER-VILLE TIME FREQUENCY ANALYSIS
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Ultrasound shear wave elastography has been investigated in several studies to differentiate abnormal tissue from normal tissue by estimating the local shear and viscosity properties of the medium. In this paper, a time-frequency numerical algorithm based on the Wigner-Ville distribution (WVD) is proposed to detect the shear wave induced by Acoustic Radiation Force Impulses (ARFI) in a viscoelastic homogeneous material. The method provides estimations of the shear wave speed at each local point as well as the frequency of the shear wave and the local shear attenuation coefficient of the medium. Knowing this information, the shear elasticity and the shear viscosity of the medium is estimated based on the Voigt model. In this work, we first simulate the particle displacement at different points of the medium resulted from an ARFI induced by a typical HIFU transducer. Then, a time-frequency numerical algorithm based on the WVD is used to detect the shear wave at different points by analyzing the particle displacement data. Finally, the results from the WVD analysis are compared with the mechanical properties of the medium assumed in the simulation. In the numerical simulation part, first the ultrasound intensity of the HIFU beam is calculated in nonlinear regime based on the KZK wave equation; then, the acoustic radiation force is calculated from nonlinear acoustic intensity at focal point of the transducer. The particle displacement resulted from ARFI is simulated based on a numerical solution of the Navier’s equation. This equation is first solved for a point-like source by introducing relevant Green’s functions. In order to find the particle displacement, the time convolution of the Green’s functions and the acoustic radiation force is calculated. In our approach, we generalize this solution by considering the superposition of the terms generated from the acoustic radiation force from the HIFU transducer in time. The time profile of shear waves in each local point is analyzed by the WVD using Equation 1. The shear wave peak amplitudes are detected for each local point separately to estimate the time of arrival of the shear wave at each location which results in estimating the shear wave propagation speed. The shear attenuation coefficient is also estimated by analyzing the variations of the amplitude of the shear wave. Moreover, the average of all detected shear wave frequencies at different locations is considered as the average frequency of the shear wave. The shear elasticity and viscosity are calculated based on the Voigt model by solving Equations 2 and 3, knowing the shear wave frequency, shear wave propagation speed, and the medium’s shear attenuation coefficient and density. The shear elasticity and shear viscosity resulted from the WVD algorithm along with the Voigt model show good agreement with the initial parameters defined in the numerical simulation based on the Navier’s equation. The estimated medium’s mechanical properties resulted from the WVD analysis are compared with the simulation parameters to numerically validate the performance of the developed algorithm. The comparison demonstrates the potentials of the WVD algorithm to detect shear wave and estimate the mechanical properties of tissue. The proposed algorithm is therefore a promising method to detect shear elasticity changes of the HIFU thermal lesions, and can potentially be used as a real-time HIFU lesion detection and characterization method.

\[ W_s(t,f) = F_{f 	o t} \{ z(t + \tau/2) \tilde{z}^* (t - \tau/2) \} \]  
\[ c_s(\omega_s) = \frac{2(\mu_1^2 + \omega_s^2 \mu_2^2)}{\sqrt{\rho(\mu_1 + \sqrt{\mu_1^2 + \omega_s^2 \mu_2^2})}} \]  
\[ \alpha_s(\omega_s) = \frac{\rho \omega_s^2 (\sqrt{\mu_1^2 + \omega_s^2 \mu_2^2} - \mu_2)}{2(\mu_1^2 + \omega_s^2 \mu_2^2)} \]
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SIMULATIONS OF NONLINEAR CONTINUOUS WAVE PRESSURE FIELDS IN FOCUS
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The Khokhlov - Zabolotskaya - Kuznetsov (KZK) equation is a parabolic approximation to the Westervelt equation that models the effects of diffusion, attenuation, and nonlinearity. Although the KZK equation is only valid in the far field of the paraxial region for mildly focused or unfocused transducers, the KZK equation is widely applied in medical ultrasound simulations. For a continuous wave input, the KZK equation is effectively modeled by the Bergen Code [J. Berntsen, Numerical Calculations of Finite Amplitude Sound Beams, in M. F. Hamilton and D. T. Blackstock, editors, Frontiers of Nonlinear Acoustics: Proceedings of 12th ISNA, Elsevier, 1990], which is a finite difference model that utilizes operator splitting. The Bergen Code has recently been converted into C++, a few new features have been added, and the resulting program has been interfaced to FOCUS, the 'Fast Object-Oriented C++ Ultrasound Simulator' (http://www.egr.msu.edu/~fultras-web) to calculate nonlinear pressure fields generated by axisymmetric flat circular and spherically focused ultrasound transducers. This new routine complements an existing FOCUS routine that models finite amplitude ultrasound propagation with a nonlinear angular spectrum approach [P. T. Christopher and K. J. Parker, J. Acoust. Soc. Am. 90, 488–499 (1991)]. Results obtained from these two nonlinear ultrasound simulation approaches are evaluated without the nonlinear terms and then compared to continuous wave linear simulation results calculated with the fast nearfield method in FOCUS. All three simulation results match closely in the farfield of the paraxial region, but the KZK results differ elsewhere. Results obtained from the two nonlinear simulation approaches are also compared. The nonlinear simulation results agree in the farfield of the paraxial region, but the results in other locations are different. For each simulation approach, the computation time is also evaluated. The simulation of the first 10 harmonics of the nonlinear pressure field generated by a flat circular transducer with a radius of 7.5mm and a peak surface pressure of 1.5MPa radiating in a lossless medium with $\beta = 1$ is completed in 2 seconds with the nonlinear 2D finite difference approach, whereas the nonlinear 3D angular spectrum simulation takes 18 minutes. The fundamental and the next three harmonics obtained with the finite difference simulation are shown in the figure below. Thus, although the nonlinear simulation results are not in agreement everywhere, these two related nonlinear simulation approaches are now included with FOCUS to enable convenient simulations of nonlinear pressure fields on desktop and laptop computers.
The objective of this project is to model and simulate the physical characteristics and behavior of cavitation bubbles generated by shockwave lithotripsy or histotripsy in order to optimize the bubble removal process. Although the formation of cavitation bubbles on the surface of urinary stones can cause desirable erosion and aid in stone fragmentation, shockwaves can also produce pre-focal bubbles which may have a shielding effect and potentially induce collateral tissue damage. Instead of waiting for these bubbles to dissolve away before applying the next shockwave, we are exploring using low amplitude acoustic waves to actively remove residual nuclei from the surrounding fluid by bubble coalescence. The goal of this work is to create a simulation which can be used to optimize the supplemental acoustic field for fast and efficient removal of residual bubbles. A bubble dynamic simulation was created in MATLAB. Through this program, an initial population of bubbles can be generated with any user-defined size and number of bubbles. Initial cavitation bubble population may also be generated by image processing of given image/video to approximate an actual experiment. It is assumed that the medium, e.g., water, is under an acoustic field with a user-defined frequency and amplitude which can be set to a standing wave, traveling wave or a given map of pressure field. The simulation then applies radiation forces: oscillation, primary and secondary Bjerknes radiation forces as well as Stokes’ drag force, and real time coalescing of bubbles and active and passive dissolution. Experiments were conducted in partially degassed water using a transducer setup optimized for high speed photography at 20kfps of the microscopic nuclei produced during histotripsy (residual nuclei ~3 um radius). The following general pulse scheme was used: (A) Cavitation Bubble Initiation Pulse: Primary cavitation bubbles were initiated by a 2 MHz histotripsy transducer using a single very short intense pulse (P > 30MPa). (B) Bubble Removal (BR) Pulse: Residual bubble nuclei were sonicated using a 5 ms pulse from a 1 MHz transducer to stimulate coalescence. Pulse amplitudes 350kPa and 600kPa were applied. The simulation results were found to be largely in agreement with experiment results for applied bubble removal fields where primary or secondary Bjerknes forces were the dominant factors and the bubble behavior was stable. Fig1(left) shows normalized backlit area of cavitation bubbles as a function of time as a quantitative measure to compare simulation prediction (bottom-left) to experimental results(top-left). It can be observed, from experimental results, that with higher pressure, 600kPa, cavitation bubbles start to coalesce faster than 350kPa case and there is a large drop in backlit area within the first 100µs, and after about 2500µs of bubble removal pulse the backlit area reaches its minimum; the same trend is predicted by simulation as well. The pattern of congregation of bubbles in pressure nodes due to the effect of primary Bjerknes forces are shown in one snapshot (t=1.5ms) of captured video and simulation in Fig1 (right). For this initial study, the bubble coalescence model was found to agree with experimental results within the range of amplitudes tested. The model does not currently incorporate any transient cavitation behavior which we expect to degrade coalescence ability for a given sequence where the mechanical index is high. However, since we plan to use this model to design a coalescence sequence to reduce collateral tissue damage, the acoustic parameters will most likely have to be constrained to a range avoiding transient cavitation.
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CAVITATION-ENHANCED BACK PROJECTION FOR ACOUSTIC RIB DETECTION AND ATTENUATION MAPPING
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A method for on-the-fly detection of attenuating structures in abdominal HIFU interventions to determine transducer apodization laws. Current methodology for the detection of attenuating structures in abdominal HIFU interventions requires lengthy, elaborate image analysis which is undesired in a clinical setting. The proposed method employs an ultrasound pulse sequence similar to the methods used for tissue harmonic imaging (THI): In THI, two subsequent pulse-echo experiments with opposite polarity are performed and the resulting echoes are summed to suppress reflections from structures in the ultrasonic beam path at the transducer’s principle frequency and to enhance echoes subject to non-linear acoustic propagation. The idea of the proposed method is to exploit this approach on a high-power therapeutic phased array transducer with transmit/receive capabilities. When the acoustic power of the employed THI pulses is increased, non-inertial cavitation in the focal region is induced. If the two pulse echo-experiments are performed sufficiently close in time, then the second pulse is subject to scattering by the cavitation bubble-cloud of the first pulse. Since the diameter of the bubbles is orders of magnitude smaller than the acoustic wavelength, these reflections are scattered incoherently and omni directionally. Since the incoming acoustic energy from all elements is mixed during the scattering process, the received signal strength for each element for the return path can be used as a measure of the attenuation due to structures between the respective element and the focus. Using this technique, an attenuating structure in the reflected beam path will be projected onto the transducer. The proposed method thus provides intensity maps displaying the amount of attenuation that each element encounters in its respective beam path to the focus. This method has been validated ex vivo on a porcine tissue sample containing ribs for five different shot positions by comparing obtained binary apodization laws to those obtained using a method based on MR image analysis and ray tracer simulations. Signal excitation and detection was performed using a Verasonics ultrasound acquisition system, which was connected to a 256-element high power phased array transducer integrated in a clinical Philips Sonalleve platform. The transducer has nominal frequencies between 1.2 and 1.45 MHz and element diameters of 6.6 mm. A single-cycle pulse with a frequency of 1.25 MHz was used for all transmissions. The average similarity in apodization between the proposed method and the method based on ray tracer simulations was 88.7%, with approximately 130 active elements. Several methods for beam path validation have been suggested in the past, either relying on anatomical 3D data derived from MRI, or ultrasonic A-mode imaging. The drawback of these approaches is the requirement to detect obstacles as anatomical structures in the image data. This is generally a lengthy and/or error prone process. In comparison, the proposed method for rib detection in intercostal HIFU therapy provides very similar results. However, the proposed method is very fast, insensitive to motion, and requires no user input or elaborate image analysis. This allows the proposed method to derive synthetic transducer apertures on-the-fly for different shot positions. Future work will include the evaluation of the proposed method in vivo. Additionally, methods to ensure that the applied focal pressure stays within the non-inertial cavitation regime will be investigated, in order to prevent potentially harmful inertial cavitation events from taking place.

Example of an acoustically obtained transducer apodization map. Elements are clustered as either obstructed (black) or non-obstructed (grey). With the proposed method, the acquisition of such a map is done in less than 5 seconds.
Cavitation has been shown to cause tissue damage in therapeutic and diagnostic ultrasound. The precise damage mechanisms, however, remain poorly understood. Experimental observations of cavitation in tissue are hindered by available spatial and temporal resolution, as well as optical access. While theoretical models of gas bubbles in water are well-established, the viscoelasticity of tissue significantly complicates the analysis. We developed a numerical model to simulate bubble dynamics in such media. Taking laboratory ultrasound waveforms and measured viscoelastic properties as inputs, our objective is to identify potential bubble-tissue damage mechanisms. A spherical bubble dynamics model was used to predict the response of bubbles to analytical and experimental pressure waveforms. The Keller-Miksis equation governs the bubble dynamics, and the energy equation describes the internal bubble temperature. Kelvin-Voigt and Zener models that include viscosity, elasticity and relaxation are used as the viscoelastic constitutive relationship. A spectral collocation method is used to solve the energy equations and obtain the viscoelastic stress fields, along with a Dormand-Prince algorithm for time marching. Using laboratory waveforms, reasonable agreement was found between simulated and experimentally-measured maximum bubble radii. The simulations were consistent with experimentally observed trends in the tissue elasticity- and ultrasound frequency-dependence on bubble growth. The bubble response in tissue produced an order-of-magnitude higher deviatoric stresses than comparable bubble oscillations would in water. By contrast to cavitation in water, small strains in tissue can generate large deviatoric stresses (causing changes in shape but not volume) due to the viscoelastic properties of the medium. Furthermore, we found that tissue may permit bubble oscillations about a large radius (see figure) and that neighboring particles (e.g., cells) would thus be closer to the regions of high stresses, that is, nearer to the bubble wall at collapse. A spherical bubble dynamics model has been developed to investigate ultrasound-induced cavitation in tissue-like viscoelastic materials and produces reasonable agreement with experiments. The simulations reveal two potential damage mechanisms in tissue: high deviatoric stresses due to both viscoelastic material properties and geometrical effects.

Radial response of a spherical gas bubble when subjected to a 3-MHz, 400-kPa sinusoidal acoustic pressure in a linear Zener media. The material viscosity is 30 cP, the rigidity is 10 kPa, and the relaxation time is 106 ns. The bubble radius as a function of time, normalized with respect to the initial radius, is given by the boundary between the white and colored regions. The pseudocolor in the surrounding field gives the logarithmically-scaled radial deviatoric stress. The black curves trace out the path of Lagrangian points as a semblance of cell location. The large collapse radii of the bubble causes high stresses to occur near such points.
NUMERICAL INVESTIGATION OF SCANNING APPROACHES, VASCULATURE IMPACT AND STANDING-WAVE EFFECTS IN HIFU BASED TUMOR ABLATION

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HIFU offers advantages over conventional modalities in the ablation of solid malignancies, due to the prospect of achieving sharply demarcated, precise lesions in an otherwise noninvasive procedure. However, the long treatment times resulting from the necessity to overlap multiple such lesions and ensure good tumor coverage can be limiting. In this study, a line-focused transducer (based on the SonoKnife which generates a ‘blade’-like focal region, thus producing larger lesions and potentially decreasing the treatment time) is used to investigate various potentially complicating factors involved in the ablation process, particularly when targeting larger tumors. The SonoKnife has been previously evaluated both numerically and experimentally in in-vitro, ex-vivo, and in-vivo setups on live piglets. Acoustic and thermal simulations are used to investigate a realistic but challenging setup, involving a head and neck squamous cell carcinoma (HNSCC) implanted into an anatomical model. This model is used to investigate the impact of scanning approaches, the presence of vasculature in the tumor vicinity, and standing-wave effects on therapy efficacy. A model of a HNSCC tumor segmented from CT data was implanted into an anatomical model generated from MR data. It was positioned in the immediate vicinity of the vertebral column and the mandible while surrounding the jugular vein and lying in close proximity to the carotid artery. The SonoKnife was modeled as an array of 450 elements operating at 1 MHz. Simulations in water were successfully compared against measurements and simulations with FOCUS. Acoustic and thermal simulations of tumor ablation were performed where beam steering (both analytical and simulated time-reversal approaches) was applied to the array to overlap multiple focal regions and ensure coverage of the entire tumor. Multiple ablation approaches, including sequential volume scanning and volumetric ablation were investigated. In addition, the treatment parameters, i.e., sonication duration and intensity, pause duration between sonications, scanning scheme etc., were varied and their impact on the treatment outcome was quantified by calculating CEM43 and applying thresholds to delimit damaged/ablated regions. Analytically calculated phase steering resulted in a prominent distortion and shift of the focal region, which could be improved using simulation-based time-reversal techniques. Improper choice of the acoustic window can lead to collateral damage due to standing wave effects from strong reflections at the bones (and skin), which can’t be avoided even with time-reversal focusing approaches. For sequential scanning, the scanning order had only a minimal impact, but volumetric ablation approaches achieved similar treatment quality with reduced damage to the intervening tissues. The presence of major vasculature in the vicinity of the treated volume resulted in non-ablated tumor areas close to the vessel wall and between vessels. In order to maximize tumor exposure while sparing healthy tissue, optimization of the input power, sonication duration, scanning scheme, and potentially frequency may be necessary on a per-sonication basis. Challenging targets lying in the immediate vicinity of bone structures can require alternative acoustic windows to be defined in order to noninvasively ablate the tumor. High-resolution acoustic and thermal simulations allow for entire HIFU ablation process to be modeled in detail. Parameters pivotal to the treatment can be easily evaluated and optimized, while full-wave modeling permits for secondary effects to be predicted and possibly compensated for.
ACCURATE QUANTIFICATION AND DELIVERY OF THERMAL DOSE TO CELLS IN CULTURE

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HIFU treatments involve raising the temperature of target tissue above 60°C in short (~2s) bursts. It is known that as tissue temperature is progressively increased above physiological levels, shorter exposure times are required to induce a given deleterious effect. The Sapareto-Dewey thermal dose equation links time taken to produce a biological effect at one temperature to time taken to produce an equivalent effect at another. However, experimental evidence on the validity of this relationship is lacking for short exposures of the order of seconds. To investigate the validity of this relationship for short (seconds) high temperature exposures, a heating chamber was developed to deliver controlled thermal doses to cells in culture under differential interference contrast microscopy observation. The system comprised of a cell culture well and cover slip coated with a transparent electrode inserted into a microscope stage with integral electrical contacts. Thermal doses were delivered to cells in monolayer culture using a proportional-integral-derivative (PID) controller to raise and maintain the temperature of the chamber above 37°C while monitoring with fine wire thermocouples. To obtain valid results from this type of experiment, accurate determination of the thermal dose is critical. This relies on the ability to accurately and precisely measure the temperature that the cells are exposed to; small uncertainties in temperature contribute much larger uncertainties in thermal dose. Fine-wire thermocouple measurements were compared to reference temperature measurements made using thin-film thermocouples in order to validate the measurement methods. A thermal model of the system in COMSOL (COMSOL Multiphysics, COMSOL Ltd., Cambridge, UK) was also used to investigate the spatial and temporal variation of heating. Both of these methods were used to help quantify sources of uncertainty in temperature with the aim of reaching an uncertainty of less than 20% in thermal dose. HeLa cells in monolayer culture were imaged before, during and after heating. Changes in cell shape and adhesion began shortly after raising the temperature to 45°C or more and progressed during a heating period of 20 minutes, continuing after the cells were returned to 37 °C. No such changes were observed in control cells. Fluorescent stains for the nuclei, cell membrane and actin filaments were used to show the differences between heated and control cells. It is possible to directly observe changes in cells due to heating at relatively high temperatures. Results from experiments using a range of temperatures and times to deliver thermal dose will be presented.
The formation of aspecific pores in the cell membrane is well-known to contribute to ultrasound mediated drug delivery. However, more recently, ultrasound enhanced endocytosis was also suggested to occur. Remarkably, papers reporting endocytosis applied relatively low acoustic pressures. Therefore, our aim is to investigate if the uptake mechanism is dependent on the ultrasound settings used, e.g., acoustic pressure. In addition, it was observed that there are subpopulations in cells showing uptake after ultrasound treatment. However, the reason for the existence of these subpopulations was never addressed. We hypothesize there might be a link with the mechanism of uptake. 2 MDa FITC-dextrans, used as model drugs, and microbubbles were added to BLM cells. Immediately afterwards, cells were exposed to ultrasound with increasing acoustic pressure. FITC-dextran uptake and cell viability, by calcein AM staining, was quantified by flow cytometry. Based on the levels of FITC-dextran uptake, cell populations were separated via Fluorescent Activated Cell Sorting (FACS). After sorting, the intracellular localization of FITC-dextran was analyzed by confocal microscopy. In the fluorescence intensity plots, 2 subpopulations can be distinguished in the cells having FITC-dextran uptake after ultrasound treatment, i.e., a low and a high fluorescence intensity population (Fig. A). At 100 kPa, cells mainly belong to the low uptake subpopulation. When increasing the acoustic pressure, the fraction of cells having a high uptake increases. Moreover, after cell sorting, confocal images show that cells of the low intensity population had a dotted fluorescence pattern (Fig. B). This indicates that FITC-dextrans were located in endocytotic vesicles. In contrast, the high intensity population showed a diffuse pattern, suggesting uptake via pores. Our data show that ultrasound delivery occurs both by enhanced endocytosis and by pore formation. However, by adjusting the acoustic pressure, one of both mechanisms can be favored.

Figure. (A) Flow cytometry plots (Forward scatter – FITC-fluorescence intensity). The left plot shows cells not incubated with FITC-dextran and not treated with ultrasound. The right plot depicts cells incubated for 15 min with FITC-dextran and exposed to ultrasound of 500 kPa (other ultrasound parameters include: center frequency of 1 MHz, pulse length of 2000 cycles, pulse repetition frequency of 125 Hz and exposure time of 5 sec). The low and the high intensity subpopulations were gated as marked on the plots. (B) Confocal images. The left image shows two cells of the low intensity population, which have a dotted fluorescence pattern. In contrast, cells of the high intensity population have a diffuse fluorescent signal over the whole cytoplasm (right image).
Sonoporation promises a local gene/drug delivery with a high therapeutic efficacy and low toxicity level. However, the mechanisms orchestrating the molecules uptake are still unclear. Here, we investigate the effects of sonoporation on the plasma membrane of U-87 MG cells, either immediately or at different times post-sonoporation, using electron microscopy, and also the implication of cytoskeleton during the sonoporation process. In our set-up, the U-87 MG cells were seeded on 18 mm diameter cover slips, placed in 24-well plates. The acoustic exposure conditions consisted of ultrasound pulses at 1 MHz, 1W/cm² with duty cycle of 20% during 60 seconds. BR14® microbubbles were added at a microbubble/cell ratio of 5. These acoustic parameters were obtained as a result of a prior optimization experiments. Membrane permeabilization after sonoporation was assessed using SYTOX® Green dye (1 μM), as a model drug which does not cross the membrane of normal cells. The cell mortality was measured with propidium iodide staining. The alterations on the plasma membrane after sonoporation were monitored by scanning electron microscopy (SEM). The cell samples were processed immediately (0 min) and every 5 min up to 60 min post-sonoporation and coated by platinum sputtering (5 nm). For immunofluorescence experiments, the cells were fixed with 4% paraformaldehyde, and then incubated with TRITC−labeled Phalloidin, used to stain the actin cytoskeleton. Tubulin antibody Alexa Fluor® 555 conjugate was used to label the microtubules. Our results showed that immediately after ultrasound and microbubble exposure, dark and spherical structures appear on the plasma membrane. These structures have a diameter ranging from few nanometers to 160 nm. These structures are named here "permeation structures". The permeation structures are transient, since 15 min post-sonoporation, almost half of these structures disappeared. The decrease in the number of permeation structures is accentuated over time to be fully resorbed 60 min post-sonoporation, consequently the cells still metabolically active. Moreover, flow cytometry results show a positive correlation between membrane permeabilization and the number of permeation structures (60% of SYTOX® Green incorporation is achieved immediately after sonoporation, to decay over time and therefore as a function of the presence of permeation structures on the cell membrane). To define the nature of these structures the cells were treated with Genistein, an inhibitor of caveolae-mediated endocytosis. Scanning Electron microscopy images showed a significant diminution of the number of permeation structures for cells incubated with Genistein, suggesting that a part of these structures are caveolae mediated. Moreover, immunofluorescence analysis showed a depolymerization of both actin and tubulin cytoskeleton. This depolymerization is accompanied with a massive uptake of SYTOX® Green, while the use of cytochalasin D and Nocodazole (inhibitors of actin and tubulin polymerization) induced a decrease in the percentage of SYTOX® Green incorporation. In conclusion, our findings reveal the reversibility of sonoporation effects on the cell membrane, and show that the caveolae-mediated endocytosis is a dominant pathway involved in the sonoporation process of U-87 MG cells, with a probable involvement of other endocytic and non-endocytic pathways. In addition, cytoskeleton is also implicated during endocytic process (entry and transport of molecules).
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ENDOPLASMIC RETICULUM STRESS ACTIVATION: A DOWNSTREAM CELLULAR RESPONSE TO SONOPORATION

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The use of cavitational means to create transient membrane pores on living cells (i.e., sonoporation) may potentially induce a broad range of downstream bioeffects that disrupt the functioning of various organelles. The endoplasmic reticulum (ER) is one particular organelle that can be affected in view of its pivotal role in facilitating protein folding, lipid synthesis, and intracellular calcium ion regulation. In this work, our aim is to perform the first investigation on the role that ER may assume in sensing and mediating sonoporation-induced cellular stress.

Calibrated ultrasound exposure experiments performed on HL-60 cells in the presence of lipid-shelled microbubbles (1:1 cell-to-bubble ratio; 1 MHz frequency; 0.45 MPa in-situ peak negative pressure; 100-cycle pulse length; 1 kHz pulse repetition frequency; 60 s exposure period). Multivariate flow cytometry was performed to assess the ER mass of sonoporated cells (labeled using ER-Tracker Green; co-labeled with Sytox-Red sonoporation tracer and Sytox-Blue viability dye). Four different post-sonoporation time points were considered (0 to 6 h). Western blot analysis was also conducted over a longer timeframe (0 to 24 h) to assay for various ER-related proteins. Focus was given to: 1) protein folding enzymes (PDI, Ero1); 2) ER membrane stress sensors (PERK, IRE1); 3) ER-induced pro-apoptotic signals (CHOP, JNK). To obtain comparative insight, caspase-9 apoptosis initiator proteins were also assayed as a probe into the terminal bioeffects of sonoporation. Sonoporated cells were found to exhibit a progressive loss of functional ER mass over a 6 h period. Also, post-exposure Western blot assays (between 0-24 h) revealed various indications of post-sonoporation ER stress: (i) upregulation of ER-resident enzymes responsible for catalyzing protein folding; (ii) activation of trans-ER-membrane stress sensors; (iii) increased expression of ER-induced regulatory proteins that mediate pro-apoptotic signals to the mitochondria. These results corresponded with flow cytometry observations that depicted a progressive depolarization of a sonoporated cell’s mitochondrial outer membrane potential. They were also consistent with another Western blot assay that showed, in sonoporated cells, a time-lapsed increase of caspase-9 (a mitochondrial-activated apoptosis initiator protein). Taken together, our findings show that an ER stress response can be elicited in sonoporated cells. They serve to highlight the need for further efforts to more controllably achieve sonoporation whilst curtailing its downstream bioeffects.
NEW CATIONIC LIPOSOMAL MICROBUBBLES FOR NUCLEIC ACIDS TRANSFER

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Ultrasound and microbubbles-mediated gene transfer is a non-invasive, targetable and controlled DNA delivery technique. Under ultrasound microbubbles are known to interact with cells and to permeabilize the plasma membrane leading to sonoporation. The main limitation of this technique is the low transfection efficiency of the commercially available microbubbles. Our project concerns the design of cationic microbubbles with the aim of binding DNA on the microbubble shell and having the capacity to fuse with cellular membranes. Several microbubble formulations were produced using three kinds of cationic lipids: Lipid 1 (triple cationic lipid), Lipid 2 (mono charged cationic lipid) and Lipid 3 (fusogenic lipid). Microbubble stability was assessed by optical observations, counting, sizing and flow cytometry. Their acoustic activity and interaction in the presence of cells has also been measured by attenuation measurements and high-speed imaging microscopy. Microbubbles produced by mechanical shaking showed required properties: a proper stability up to 3 hours, a size distribution centered at 1.9 μm and a resonance frequency around 1.5 MHz. Microbubbles produced presented a Zeta potential of +45 mV when lipid 1 was used and +12 mV with lipid 2. Plasmid DNA molecules were found on the microbubble surface when observed by confocal microscopy and atomic force microscopy. Flow cytometry and confocal microscopy analyzes showed a good DNA binding capacity. In vitro sonoporation of HeLa cells using the produced microbubbles resulted in almost 30% of GFP transfected cells. In vivo, gene transfer was achieved on a previous animal model developed on the Achilles tendon and liver by either local or systemic injection. A stable luciferase expression lasting over two weeks was obtained after local injection of microbubbles bearing DNA and sonoporation. Further experiments on in vivo ultrasound microbubble imaging and DNA delivery after systemic injection are in progress. The use of microbubbles bearing plasmid DNA is possible for gene transfer applications in vitro, in vivo by local and systemic injection.
NEW OBSERVATIONS ON THE RECOVERY OF SONOPORATION SITES: MEMBRANE BLEBBING

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How cells recover after a sonoporation episode is an important question that remains poorly understood at present. While observations of membrane resealing after sonoporation have been reported, the mechanistic steps involved in the process still remain to be unknown grounds with the exception of a few hypotheses based on site patching and membrane self-reunion arguments. In this work, our aim is to gain insight into post-sonoporation recovery strategies by acquiring new observations on the membrane dynamics of sonoporation sites. Individual sonoporation episodes were generated in this work through single-pulse ultrasound triggered collapse of a single targeted microbubble (MB) resting on the cell membrane. Targeted MBs were fabricated in-house using an avidin-biotin conjugation approach. It first involved sonication of a mixture containing DSPC phosphocholine and DSPE-PEG2000-biotin in the presence of C3F8 gas, and avidin and biotinylated IgG antibodies were added onto the MBs after that. Our MBs were made specific to VEGF (vascular endothelial growth factor) receptors residing on ZR-75-30 breast carcinoma cells, whose membrane was labeled using a membrane-specific dye (CellMask). The MBs were introduced to a ZR-75-30 cell monolayer seeded within a cell chamber (a glass cover slip mounted onto a base holder). After flushing unbound MBs, the cell chamber was mounted onto a customized experimental platform that coupled a waveguided ultrasound exposure apparatus to a confocal microscopy system for real-time cellular observations. The ultrasound apparatus consists of a 1”-diameter, 1 MHz piston transducer and a leg-shaped waveguide, and a single-shot 30-cycle pulse was used as the transmission waveform. The free-field peak negative pressure at the planar cross-section of the waveguide’s leg base was measured to be 0.45 MPa on average (sufficient to induce MB rupture - i.e. inertial cavitation). A series of z-stack images of the whole cell was acquired before the ultrasound exposure. To capture the moments during and after ultrasound exposure, time lapse imaging of the cells were obtained at interval of 5 seconds throughout duration of 15 minutes. Sonoporation episodes were tracked by concurrently observing Sytox influx through the sonoporation site. Subsequently, a z-scan was performed again to obtain images of the entire cell after ultrasound exposure. At MB binding sites, post-sonoporation blebbing of the cellular membrane was evident. The feature was especially apparent when the microbubble size is large. In a sonoporation case induced by the collapse of a 4.7 um diameter microbubble, a significant bleb measuring 24 um in apical height and 22 um in diameter can be observed shortly after the onset of sonoporation (1 min). Synchronized with this action, sonoporation tracer influx plateaued as a result, thereby indicating that the sonoporation site is resealed. This feature was not observed in the unsonoporated cell. As the morphology of membrane blebs generally resembles a local herniation of the plasma membrane, it matched well with previous observations that showed membrane protrusions in some cells that were exposed to acoustic cavitation. More interestingly, sonoporation site was found to be resealed as a result of this bleb formation. Thus, we can infer that membrane blebbing is potentially a repair maneuver to facilitate recovery of sonoporation sites, especially for sites that are larger in size as generated by MBs situated adjacent to the cell membrane.
Ultrasound and microbubble treatment (USMB) can generate transient nonselective pores in the cell membrane through a process known as sonoporation. These pores allow molecules to move across the cell membrane. Studies have shown that USMB can enhance the intracellular uptake of molecules, which otherwise would be excluded, through USMB-mediated membrane disruption and enhanced endocytosis. However, the effect of USMB on extracellular delivery (the outward movement of molecules from cells) is not well understood. This study investigates the effects of USMB on the extracellular delivery of molecules from specific compartments including cytoplasm, lysosomes, and recycling endosomes. In vitro ARPE-19 (RPE henceforth) and MDA-MB-231 cells were used. MDA-MB-231 cells were loaded with the nano-sized fluorescent molecules: FITC-dextran and Alexa fluor- transferrin as markers for the lysosomes and recycling endosomes, respectively. In addition, LAMP-1 antibody was used to detect the fusion of lysosomes with the plasma membrane and GFP-transfected RPE cells were used to examine the extracellular delivery of GFP from the cytoplasm. Subsequently, cells were exposed to USMB (1x10^6 cells/mL, 300 kPa peak negative pressure, 1 min treatment duration, and 20 μL/mL Definity microbubbles). Following USMB, the extracellular delivery of the fluorescent markers was examined at 0, 10, and 20 minutes. The mean fluorescent intensity (MFI) of untreated and USMB treated samples was measured using flow cytometry and confocal fluorescent microscopy. USMB increased the extracellular delivery of GFP molecules from the cytoplasm; the MFI of USMB treated GFP-transfected RPE cells decreased by 65% immediately following the treatment. Additionally, the MFI of intact cells stained with LAMP-1 antibody increased by 51% immediately after USMB treatment, indicating lysosome exocytosis. This was confirmed by observing the post USMB extracellular delivery of FITC-dextran from the lysosomes with fluorescent microscopy. Furthermore, the MFI of cells loaded with fluorescent transferrin decreased by 13% after USMB treatment, indicating a significant increase in transferrin recycling to the cell membrane. USMB can enhance extracellular delivery of molecules from the cytoplasm, lysosomes, and recycling endosomes.
CHARACTERIZATION OF JET FORMATION AND FLOW FIELD PRODUCED BY TANDEM Bubbles
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Tandem bubble interactions have been shown to produce directional jetting flow and vortex flow that can be used to create localized membrane poration on single cells. This study aims to characterize the jet formation and the flow field produced in a microfluidic channel by the interaction of tandem bubbles. Anti-phase tandem bubbles with maximum projected diameters in the range of 40 to 60 μm were generated by two Nd: YAG pulsed lasers of 532 nm wavelength and 5 ns duration in a PDMS-glass microfluidic channel with a nominal height of 25 μm. The transient interaction of the tandem bubbles and the resultant jet formation were captured by two high-speed video cameras with framing rates up to 10 M frames/sec. The tandem bubble interactions were also analyzed numerically using the BEM module of 3DYNAFS©. In addition, the flow field around the tandem bubble was characterized by using Particle Imaging Velocimetry (PIV) technique with polystyrene beads of 1 or 2 μm seeded in the medium. The average jet speed from the asymmetric collapse of the first bubble was found to vary in the range of 20 to 60 m/s, increasing amount linearly with the maximum diameter of the second bubble. In contrast, the size of first bubble affected predominantly the dimension and shape of the jet. These features were confirmed by the results of numerical simulations. For 50-μm tandem bubbles, the maximum flow velocity along the jet axis was found to vary with the standoff distance (10 to 50 μm) in the range of 5.0 m/s to 8.6 m/s in the middle plane of the channel, compared to 2.9 m/s to 4.9 m/s near the bottom of the channel. At both locations, the maximum flow velocities were measured at a standoff distance of about 30 μm. Furthermore, the maximum vorticity was found to decay from 2240 to 817 to 322 kHz in the middle plane of the channel, compared to 800 to 345 to 127 kHz near the bottom of the channel at approximately 6, 12, and 20 μs, respectively, following the tandem bubble interaction. The interaction of tandem bubbles produces jetting flow with distinct characteristics. The first bubble influences the jet shape while the second determines the jet speed. The resultant vortex flow changes with standoff distance, which may correlate with the varying bioeffects produced in single cells present in their vicinity.
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TEMPERATURE EFFECT ON SONOPORATION EFFICACY FOR CERVICAL CANCER DRUG DELIVERY IN VITRO
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It has been observed that when performing hyperthermia drug uptake can be enhanced, but the mechanism behind this response has not been completely elucidated. A hypothesis is that an increased temperature can enhance cell permeability. In this case, ultrasound-mediated drug delivery or sonoporation should have an increased efficacy when the temperature of the media is increased. The objective of this study was to investigate this possibility and utilize temperature as an adjuvant to enhance sonoporation drug delivery. Sonoporation efficacy and cell viability were examined at different media temperatures. Sonoporation and sham treatments were performed on cervical cancer CaSki cells at temperatures of 37°C, 39.5°C, and 42°C (n=3 per group). CaSki cells were seeded (0.6x10^6) and cultured overnight on a gas-permeable, cell culture treated polystyrene membrane (Opticell, Nunc); then plasmid DNA expressing green fluorescent protein (GFP; 250 μg) and ultrasound contrast agent (Definity(R); 0.33% v/v) were added to the cell culture chamber and exposed to pulsed ultrasound (total duration of 30 seconds; 1 MHz; 1 MPa; 4.8% duty cycle; 1.6 kHz pulse repetition frequency). GFP expression was used to evaluate transfection efficiency. Two control groups were used which either received ultrasound exposure without contrast agent present or did not receive ultrasound exposure but had contrast agent. The cells were imaged prior to and following treatment to assess cell loss. The cells were fixed 24 hours after ultrasound exposure and stained for nuclei (DAPI), cytoplasmic GFP presence (GFP anti-body), and early apoptosis (cleaved PARP) to obtain cell count, GFP expression and apoptosis rates, respectively. GFP expression was quantified using Cell Profiler over a total of 25 fields of view per Opticell. A cell was considered expressing GFP if its green signal was above a defined threshold (background intensity + 3 standard deviations). Apoptosis was quantified by a similar method using PARP red signal images. The percentage of GFP-expressing cells was significantly higher for the ultrasound exposure group with contrast agent compared to the two control groups for all temperatures (p<0.001 @37°C; @39.5°C and @42°C). However, no significant effects on GFP expression due to temperature or mixed effects were observed. Additionally, no significant effects on apoptosis or cell loss were observed due to treatment, temperature, or mixed effects. Sonoporation efficacy does not seem to be related to the temperature of the media. However, temperature has no negative effect on cell viability. The enhanced drug delivery reported by previous groups when temperature is increased could be related to vascular response and not cell membrane effects.
BURST WAVE LITHOTRIPSY: A NEW METHOD TO FRAGMENT KIDNEY STONES WITHOUT SHOCK WAVES
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Shock wave lithotripsy is a common treatment for kidney stones. However, stone free rates with this therapy are low compared with other treatment options, and stones often remain incompletely fragmented. We are developing a new method of stone comminution using broadly-focused, sinusoidal ultrasound bursts rather than shock waves. This presentation describes preliminary in vitro experiments and the fragmentation mechanisms for burst wave lithotripsy. Cylindrical artificial stones with acoustic properties similar to calcium oxalate monohydrate (Begostone, 6 mm diameter x 10-12 mm length) and several types of natural stones (uric acid, struvite, calcium oxalate monohydrate, cystine) were tested in this work. A focused ultrasound transducer was electrically driven by a custom high-voltage amplifier at 170 kHz to produce 10-cycle bursts with ≤ 6.5 MPa focal pressure amplitude. The stone was placed in a degassed water bath in a fixed position, adhered to a polyester membrane. The transducer was positioned to center the focus on the stone, and bursts were delivered at a pulse repetition frequency of 200 Hz. Time to achieve complete fragmentation was recorded and fragments were collected and sieved after treatment to obtain fragment size distribution. To examine the mechanisms of stone comminution under this modality, a linear elastic wave model was employed that simulated the stresses generated by bursts inside the stone. The position of stresses was compared with observed fracture points and fragment sizes of artificial stones. Stones exposed to bursts formed periodic fractures along their surface, leading to small fragments separating from the stone. Fragmentation usually began at the surface nearest to the transducer and progressed distally until the stone was completely disintegrated. Artificial stones fractured at pressure amplitudes ≥ 2.8 MPa. At 6.5 MPa, artificial stones could be completely fragmented in 9.7 ± 2.8 minutes (mean ± standard deviation, n = 12 stones). All natural stones treated could be fragmented, but the time to achieve comminution varied greatly by stone type. For instance, those composed of uric acid (n = 3) required 0.2 – 1.4 minutes while cystine stones (n = 3) required 10.3 – 21 minutes (Fig. 1). The largest fragments were ~3 mm for all stone types treated at 170 kHz. However, artificial stones treated with higher-frequency bursts produced proportionately smaller fragments.

Simulations of the stresses inside the stone indicated that surface waves are created by bursts, generating spatially-periodic stresses along the stone. This result is consistent with the observed fracture patterns and frequency-dependent fragmentation of stones. Stones treated in castor oil did not fragment, indicating cavitation is also an important factor to stone comminution. Burst wave lithotripsy effectively fragments artificial and natural stones in vitro without shock waves. Results suggest bursts can achieve comminution over a time frame comparable to shock wave lithotripsy, and for certain stones, much faster. Additionally, the mechanism of fracture and corresponding relationship between fragment size and frequency presents a method to optimize the therapy to exclusively produce small, passable stone fragments. These results demonstrate the feasibility of burst wave lithotripsy as a treatment method for stones and suggest benefits over the use of shock waves. Work supported by NIH 2T32 DK007779-11A1, R01 EB007643, P01 DK043881, R01 DK092197, and NSBRI through NASA NCC 9-58.

Figure 1. A cystine stone before (left) and after (right) a 12.7 minute exposure to 170 kHz bursts.
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A PRELIMINARY ASSESSMENT OF THE POTENTIAL FOR KIDNEY INJURY BY BURST WAVE LITHOTRIPSY
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Shock wave lithotripsy (SWL) is a common treatment for kidney stones that relies on the delivery of high-amplitude shocks to break stones into passable fragments. Despite its popularity as a noninvasive option, SWL treatments lead to relatively poor stone-free rates and involve measurable kidney injury on the order of 1% of functional renal volume. A new noninvasive treatment approach has been proposed that relies on short bursts of sub-megahertz ultrasound: burst wave lithotripsy (BWL). Although BWL uses much lower pressure amplitudes than SWL, pulses are delivered more rapidly so that energy is delivered to the stones and tissue at higher rates than in SWL. To complement work showing that BWL can effectively break real and artificial stones, this effort aims to provide a preliminary assessment of the potential for injury associated with BWL. Kidneys from four pigs (55-60 kg) were exposed to BWL treatments at 170 kHz with pressure amplitude sufficient to break stones. The transducer possessed a central hole in which an ultrasound imaging probe was mounted for the collection of B-mode images. Because of the short focal distance of this transducer, treatments were applied intra-abdominally, using a degassed saline solution for direct coupling to each kidney. When possible, separate exposures were applied to target the collecting system in both the upper and lower poles of each treated kidney. Based on experience with SWL in which injury is typically associated with cavitation activity, B-mode images were monitored during each exposure to identify hyperechoic regions that appeared to represent bubble activity. Exposures comprised bursts of 10 cycles of ultrasound at a pulse repetition frequency of 40 Hz. Exposures lasted either 10 or 25 minutes, during which the ultrasound amplitude was adjusted to avoid excitation of hyperechoic bubble activity. After completing treatments in a given pig, kidneys were perfusion-fixed for evaluation. Overall, the volume of hemorrhagic injury was quantitated in a single kidney, while others were evaluated by gross examination. For comparison, additional exposures were performed at a pressure/PRF for which hyperechoes persisted throughout; these kidneys were evaluated on both gross examination and histology. Cavitation activity identified in B-mode images consistently started in the collecting space and progressed proximally toward the transducer. From 9 exposures in 6 different kidneys, the cavitation threshold based on B-mode images remained between 4.9 and 5.5 MPa. In all cases, no more than one or two amplitude adjustments were needed to remain below the threshold. From gross examination, little or no hemorrhagic injury was identified. For one kidney exposed to a 10-minute treatment in the lower pole and a 25-minute treatment in the upper pole, the volume of hemorrhagic injury was quantitated (Figure 1) and found to be insignificant. Kidneys exposed to BWL with persistent cavitation exhibited more substantive injury characterized by subcapsular hematomas on both proximal and distal surfaces of the kidney as well as focal cellular and vascular damage from histological evaluation. If cavitation activity that is readily identifiable on B-mode ultrasound is avoided, burst wave lithotripsy exposures at 170 kHz appear to induce negligible kidney injury. This result suggests that a range of safe BWL treatment parameters can be used to noninvasively break kidney stones without significant tissue injury. Results from this initial study are promising, but further studies are needed. Work supported by NIH 2T32 DK007779-11A1, R01 EB007643, P01 DK043881, R01 DK092197, and NSBRI through NASA NCC 9-58.

Figure 1: Gross image of sectioned kidney used in the volumetric quantitation of hemorrhagic injury. With a BWL pressure amplitude of 4.9 MPa, the kidney was exposed to a 25-minute treatment in the upper pole and a 10-minute treatment in the lower pole. Though small sites of hemorrhage were identified in the upper pole (arrow), the total lesion volume was determined to be less than 0.1% of functional renal volume, which is the measurable resolution of the technique. This technique for injury quantitation was developed for evaluating kidneys exposed to SWL, which typically produces lesions on the order of 1% of functional renal volume.
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ELIMINATION OF CAVITATION-RELATED ATTENUATION IN SHOCK WAVE LITHOTRIPSY
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The prevalence of kidney stone disease in the United States has doubled over the past 30 years. Shock wave lithotripsy (SWL) uses a few thousand focused acoustic pulses to break a kidney stone into fragments without surgical intervention. Previous research has shown that a shockwave's tensile phase can be strongly attenuated by bubble proliferation in the coupling medium along the lithotripter propagation path. In this study we investigate the effects of removing bubble nuclei in the coupling cushion on stone comminution and pressure field at the lithotripter focus. We examine the relationship between tensile attenuation of the lithotripter pulse and gas concentration in the coupling medium via pressure measurements at the focus and cavitation field characterization based on high-speed imaging. We introduce a method to remove cavitation nuclei from the propagation path between successive shockwave exposures using a jet flow. We further enhance the tensile strength of the coupling water by degassing. The cavitation nuclei lifetime is controlled by varying pulse repetition frequency (PRF), dissolved gas concentration, and the pumping flow rate, and their relationship can be described by a scaling law. At a fixed PRF (2 Hz), we found that if the gas concentration was above a critical value a bubble avalanche would result and proliferate within several lithotripter pulses, leading to significant attenuation of the lithotripter tensile pulse. For oxygen concentration <4 mg/L, the bubble cloud was found to remain sparse and the shock waves could be transmitted with negligible energy loss. For oxygen concentration >4 mg/L, the bubble cloud became progressively dense, leading to 75% reduction in the tensile duration of the lithotripter pulse. The peak tensile pressure delivered to the focus correlated with the bubble cloud density along the lithotripter beam path, and the corresponding stone comminution decreased sharply with increased gas concentration. One approach to dismiss the gaseous bubble remnants is to lower the PRF during SWL so that there is enough time for gas diffusion back into the liquid between successive pulses. Alternatively, a jet flow could be used to disperse residual cavitation nuclei formed along the shockwave propagation path. We have demonstrated that the lifetime of bubble nuclei in the acoustic beam can be reduced from ~7 s (without the jet) to ~0.3 s (with the jet) regardless of dissolved gases. Our results demonstrate the critical influence of cavitation bubbles in the water coupling medium in SWL. The results suggest that the tensile component of the lithotripter shock wave delivered to the stone would be better preserved in degassed water, especially when high PRFs (>1 Hz) are desired during SWL. Furthermore, it was demonstrated that if a jetting flow was used, cavitation-related attenuation can be eliminated at higher PRFs (>2 Hz), leading to improved stone comminution with reduced treatment time.
CONTINUUM-MICROSCOPIC 3D COMPUTATIONAL MODEL OF STONE COMMINUTION IN LITHOTRIPSY: THEORY AND EXPERIMENTAL COMPARISONS
Sorin Mitran 1, Daniel Fovargue 1, Pei Zhong 2, Georgy Sankin 2

A stochastic microscopic model of crack formation is combined with a continuum elasticity model of heterogeneous media to track the successive breakdown of stones in shock wave lithotripsy (SWL). A finite volume, adaptive mesh refinement procedure is used to define local stress states in a kidney stone simulant modeled as an elastic medium with heterogeneous properties. The stone is immersed in water, again modeled by linear elasticity equations. The stone is subject to passage of successive shocks, previously computed using a nonlinear Euler equation water model with Tait equations of state. A microscopic crack model based on stochastic crack formation and propagation leads initially to modification of local elasticity properties, and finally to breakdown of the stone. The breakdown process is tracked through multiple stages, under the successive action of tens of shocks. The model is used to predict comminution profiles. The first 4-8 fractures of a stone simulant can be captured at the current stage of the continuum-microscopic computational model. Various stone orientations and positions are considered to represent effect of respiratory motion. The comminution profile (resultant fragment size distribution) is compared with experimental results. A physically based computational model has been developed and shown to qualitatively capture the initial stages of the comminution process, allowing for more detailed study of lithotripsy processes than purely statistical models.
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ACOUSTIC FIELD OF A THERAPEUTIC TRANSDUCER FOR GENERATING BOILING HISTOTRIPSY LESIONS AT SIGNIFICANT DEPTHS IN TISSUE: COMBINED MEASUREMENT AND MODELING CHARACTERIZATION

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Boiling histotripsy (BH) is a new noninvasive ultrasound technology to produce mechanical fractionation of tissue inside the body using high intensity focused ultrasound (HIFU). The method relies on fast (millisecond) repetitive boiling bubbles generated by high-amplitude shocks. To perform such tissue treatment at deep targets in the body, the ultrasound transducer must provide sufficient power to generate a shocked acoustic wave at the transducer focus. A prototype transducer (Fig. 1, A) of 1 MHz operational frequency, 14.7-cm diameter and 14-cm focal length, assembled from 7 confocal elements, was built for generating histotripsy lesions in soft tissue through significant overlying tissue paths. The goal of this work was to characterize the nonlinear acoustic field of this transducer using a combination of numerical simulations and hydrophone measurements. In the experiment, waveforms at a fixed focal point were measured with a fiber-optic hydrophone for output levels up to 30% of the maximum (120 V of 400 V). Above this level, measurements could not be acquired because of cavitation. Experimental waveforms were analyzed to obtain peak positive and peak negative pressures and were compared with numerically simulated values. To set a realistic boundary condition (Fig. 1, B) to the 3D nonlinear Westervelt model, an acoustic hologram was measured in a prefocal plane at low voltage output of the transducer (pressure amplitude 0.01 MPa at the surface of the transducer). Nonlinear simulations were performed within operational power levels of the array ranging from 0 V up to 220 V. The hologram magnitude was scaled according to the relative input voltage to match the corresponding power levels. Measured and simulated focal waveforms for 90 V output, at which shock fronts have formed, are shown in Fig. 1, C. Experimental and theoretical waveforms agree very well. The peak positive and peak negative pressures are plotted in Fig. 1, D as functions of output voltage. Theoretical predictions agree very well with experimental data for voltages in the range from 2.5 to 100 V. However, from 100 V to 120 V experimental data are 5-10% greater than the theoretical curve, possibly due to increased noise and variability in measurements from cavitation. While measurements could not be obtained above 120 V, simulations were run up to 220 V. At such high amplitudes, peak pressure saturation is observed: a twofold increase in driving voltage (from 100 V to 200 V) resulted in only 10% increase in peak positive pressure (from 90 to 100 MPa). Theoretical and experimental results demonstrate that the numerical method based on the 3D Westervelt equation is a robust tool for predicting the acoustic field generated by high power HIFU devices. Simulations can be done at high power levels to determine the field within tissue for conditions in which hydrophone measurements are not possible. The strongest advantage of the numerical simulation method is that a full 3D field is obtained, which allows for calculation of maps of different parameters such as peak positive and negative pressures, intensity, and heating. Heat distributions in conjunction with the bioheat equation provide a way to quantify thermal effects on tissue and time to boil. Work supported by NIH T32 DK007779, 1R21EB016118-01A1 EB007643, CRDF, and by the grant of the President of Russian Federation MK-5895.2013.2. Numerical simulations were performed on “Lomonosov” cluster of the Moscow State University supercomputer center.

Photograph of the 7-element array transducer (A); reconstructed vibrational pattern of the transducer as an input to the model (B); comparison of measured and simulated waveforms at the focus for 90 V output voltage (C); comparison of measured and simulated peak positive and peak negative pressures as functions of the output voltage (D).
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GENERATION OF VOLUMETRIC BOILING HISTOTRIPSY LESIONS IN TISSUE USING A MULTI-ELEMENT ARRAY OF A CLINICAL HIFU SYSTEM
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In most high intensity focused ultrasound (HIFU) applications, tissue is thermally ablated due to heating caused by ultrasound energy absorption. Recently, a new method named boiling histotripsy was developed at the UW/MSU to mechanically fractionate tissue. The method applies MHz-frequency millisecond-long pulses with shocks to cause boiling in tissue by shock wave heating and interaction of shocks with the resulting vapor cavity. A typical treatment to generate a single lesion lasts around 30 s, requiring about 30 pulses with a pulse repetition frequency (PRF) of about 1 Hz. The dimensions of the resulting lesion are about 5 mm by 3 mm. Clinically relevant tissue volumes to be ablated may be up to several cubic centimeters; therefore, multiple lesions should be generated to cover the entire targeted region. The goal of this study was to test if a clinical HIFU system is capable of generating volumetric BH lesions and to develop exposure protocols for such treatments. A boiling histotripsy pulsing scheme was combined here with the electronic steering of a multi-element 1.2 MHz HIFU phased array (Sonalleve, Philips Healthcare, Vantaa, Finland) to generate large, mechanically fractionated lesions in polyacrylamide gel samples and in ex vivo bovine tissue. Sonications were performed at a tissue depth of 2 cm with 10 ms-long pulses, PRFs 1 – 10 Hz, and 250 W acoustic power, which corresponded to about 65 MPa in situ shock amplitude. Using electronic steering transverse to the axis of the transducer, two different spatial patterns of focal locations were tested: lines of single lesions separated by 2 mm and circles of single lesions with a similar spacing along each circular arc. Circles with radii of 2, 4, 6, and 8 mm were tested. Each single lesion in a pattern was generated with either a sequential treatment plan (by sending the required number of pulses to each location and then proceeding to the next location in a raster-like fashion), or a non-sequential treatment plan with consecutive HIFU pulses sent to different target locations. Strategies for non-sequential treatments included both raster-like scan patterns for consecutive pulses and patterns that maximized the distance between consecutive pulses to diminish heat accumulation and thermal effects. For all treatments, each point received 30 pulses. Final lesions were examined in a small MRI coil, then analyzed grossly and histologically. Sonications with a 1 Hz PRF produced purely mechanical lesions while increasing thermal effects were observed for sonications at repetition rates of 3 – 10 Hz. For purely mechanical lesions separated by 2 mm, adjacent lesions merged to produce uniform volumes of fractionated tissue. BH lesions produced with electronic steering up to 8 mm off axis were similar to those generated on-axis, even though full power compensation for off-axis sites was not used. Moreover, lesions appeared to be the same for both sequential and non-sequential treatment plans. Finally, it was observed in some lesions that larger vessels could be spared while surrounding liver tissue was effectively fractionated. It was shown that a clinical HIFU system is capable of producing volumetric lesions of mechanically fractionated tissue using a boiling histotripsy method in conjunction with electronic steering of the focal beam. Successful sonications performed at 2 cm depth in tissue required less than 25% of the maximum system power, thus permitting implementation of this approach under clinically relevant conditions with greater attenuation. Work supported by NIH EB7643, K01 EB 015745, T32 DK007779, and RFBR 13-02-00183.

Photographs of the experimental setup (A) and mechanically fractionated lesions arranged in either a line (B) or circles (C). In (B) there are 5 single lesions with 4 mm separation with (left) and without (right) fractionated content; in (C) a volumetric lesion formed by generating a central lesion and two circles of lesions separated by 2 mm radially with (top) and without (bottom) fractionated content.
USE OF MRI TO VISUALIZE MECHANICALLY FRACTIONATED LESIONS GENERATED BY BOILING HISTOTRIPSY IN TISSUE

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Boiling histotripsy (BH) is a novel high intensity focused ultrasound (HIFU) treatment method to generate mechanically fractionated lesions in target tissue. The method utilizes repetitive millisecond-long pulses with high amplitude shocks, rapid boiling in tissue within each pulse caused by shock-induced heating, and interaction of shocks with the resulting vapor cavity. Ultrasound (US) imaging methods have been used to target and visualize the BH treatment in real time based on scattering from boiling bubbles that form in the HIFU focus. However, it is still technically difficult to visualize the final lesion and to evaluate the mechanical bioeffect with US imaging. The objective of this study was to test the feasibility of using MR imaging methods to target, monitor, and characterize BH treatments with regard to lesion volumes and associated bioeffects. Samples of degassed ex vivo bovine liver (6x6x3 cm) were placed in deionized, degassed water and sonicated using a clinical MR-HIFU system (Sonalleve, Philips Healthcare, Vantaa, Finland). Volumetric lesions of various shapes and sizes were produced within the samples by electronic steering of the HIFU beam generated by a 256-element array transducer. Sonications were performed at a frequency of 1.2 MHz with 10 ms-long pulses, pulse repetition frequencies of 1–10 Hz, and an acoustic power of 250 W, which corresponded to an estimated in situ shock amplitude of about 65 MPa. Continuous exposures were used to generate thermal lesions for comparison with fractionated ones. A standard clinical MRI system (Achieva 3T, Philips Healthcare, Best, the Netherlands) was used for simultaneous real-time monitoring of lesion formation and temperature elevation using a fast-field-echo (FFE) -based MRI sequence and the proton resonance frequency shift (PRFS) -method for temperature mapping. In addition, MRI was used to visualize and characterize the final lesions using standard T2-weighted imaging and T2-mapping. In these post-treatment T2 maps, mean T2 values were 69 ms for mechanically fractionated BH lesions, 51 ms for thermal lesions, and 39 ms for normal tissue (Fig. B). In addition, temperature maps were acquired in real-time during a BH sonication with a 5% duty factor (Fig. C), demonstrating that MR can be used to monitor BH exposures and provide feedback on thermal effects both within the target location (Fig. D) as well as in the surrounding region. Lesions in ex vivo liver are visible and can be monitored by real-time MR-imaging during BH sonications; moreover, final lesions can also be imaged and characterized quantitatively in a similar way. MRI is sensitive to the fractionation of liver tissue into a liquid-like consistency, which is a goal of histotripsy treatments. Work supported by NIH EB007643, K01 EB 015745-01, T32 DK007779, and NSBRI SMST03402.

A) A real-time FFE magnitude image showing preferential signal enhancement in the BH targeted location at the end of a sonication. B) A T2 map showing higher T2 values for the purely mechanically fractionated BH lesion, as compared to thermal lesions and normal tissue. C) A temperature map (color scale) overlaid on the FFE magnitude image, showing the temperature distribution at the end of a BH sonication. D) Mean and maximum temperature within the BH target region over a 4860 s sonication, followed by a cool-down time.
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DUAL-BEAM HISTOTRIPSY: A LOW-FREQUENCY PUMP ENABLING A HIGH-FREQUENCY PROBE FOR PRECISE LESION FORMATION
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When histotripsy is applied with pulses shorter than 2 cycles, the generation of the dense bubble clouds only depends on where the peak negative pressure exceeds an intrinsic threshold of a medium (26 – 30 MPa in soft tissue with high water content). This paper investigates a strategic method for precise lesion generation in which a low-frequency pump pulse is applied to enable a sub-threshold high-frequency probe pulse to exceed the intrinsic threshold (“dual-beam histotripsy”). Since the low-frequency pump pulse is more immune to attenuation and aberrations, and the high-frequency probe pulse can provide precision in lesion formation, this dual-beam histotripsy approach would be very useful in situations where precise lesion formation is required through a highly attenuative and aberrative medium, such as transcranial therapy. This is particularly true if a smaller low-attenuation acoustic window is available for the high-frequency probe transducer. A custom hemispherical 20-element dual-frequency array transducer (500 kHz and 3 MHz elements confocally aligned) was used to generate dual-beam histotripsy pulses. The transducer was driven by a custom high voltage pulser, controlled by a field-programmable gate array (FPGA) development board. Fig. 1 shows representative focal acoustic waveforms in free-field. Red-blood-cell (RBC) tissue-mimicking phantoms and porcine hepatic tissues were exposed to the dual-beam histotripsy pulses at a pulse repetition frequency of 1 Hz with single-focal-spot exposures. Optical imaging was used to monitor and characterize bubble clouds and lesions generated in RBC phantoms. Ultrasound B-mode imaging was used to monitor the treatment in hepatic tissues and their resulting lesions were evaluated by both histological sections and ultrasound B-mode images. The results showed that, when sub-threshold pump (500 kHz) and probe (3 MHz) pulses were applied together, dense bubble clouds (and resulting lesions) were only generated when their peak negative pressures combined constructively to exceed the intrinsic threshold. The smallest reproducible lesion varied with the relative amplitude between the pump and probe pulses, and, with a higher proportion of the probe pulse, smaller lesions could be generated (Fig. 2). When the propagation direction of the probe pulse relative to the pump pulse was altered, the shape of the produced lesion changed based on the region that exceeded the intrinsic threshold. In this study, the capability of “dual-beam histotripsy” pulses for precise lesion formation is demonstrated both in RBC phantoms and ex vivo porcine tissues. In the future, we plan to study the feasibility of using diagnostic imaging transducers for probe pulse generation. This could provide not only the steering capability for the probe pulse during treatment, but also the image guidance and feedback if it is used in conjunction with an imaging system.
INVESTIGATION OF THE ROLE OF TISSUE STIFFNESS AND ULTRASOUND FREQUENCY IN HISTOTRIPSY-INDUCED CAVITATION

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Histotripsy generates a cavitation bubble cloud to fractionate soft tissue using short, high-pressure ultrasound pulses. The energetic expansion and collapse of cavitation bubbles is believed to cause tissue fractionation. Previous studies show that stiffer tissues such as cartilage or tendon (Young’s moduli >1MPa) are more resistant to histotripsy-induced damage than softer tissues such as fat or kidney (Young’s moduli ranging from 1-10kPa). We hypothesize that higher tissue stiffness suppresses bubble expansion during histotripsy, leading to the increased damage resistance. To investigate histotripsy parameters that are more effective for stiffer tissues, we test histotripsy with varying frequencies and hypothesize that lower frequencies facilitate greater bubble expansion and are more effective in fractionating stiffer tissues. Histotripsy-induced cavitation bubble expansion was tested using both simulations and experiments for a range of tissue stiffness and ultrasound frequencies. First, a numerical simulation based on a Rayleigh-Plesset model with Kelvin-Voigt viscoelasticity was developed, where an initial bubble of 0.1 µm in radius, mimicking pre-existing cavitation nuclei in tissue, was exposed to a histotripsy pulse in tissue with Young’s modulus ranging between 1kPa – 10MPa. Ultrasound pulses of 1-2 acoustic cycles long at 30MPa peak negative pressure measured from histotripsy transducers of varying frequencies (345kHz, 500kHz, 1.25MHz, and 3MHz) were used. Experimental validation of the simulated results were performed by applying the same histotripsy pulses at varying frequencies to agarose tissue phantoms with Young’s moduli tunable between 1kPa – 570kPa by changing agarose concentration. Bubble expansion and collapse was monitored using an ultra-fast digital camera (SIM 802, Optronis). The Radius-Time curve of individual bubbles produced by histotripsy was measured. A sample size of 8 was used for each agarose concentration and ultrasound frequency. Simulation and experimental results both supported the hypothesis that increases in Young’s modulus and ultrasound frequency cause a reduction in bubble expansion. For example, the simulation showed the maximum bubble radius produced by a 500kHz histotripsy pulse was observed to decrease from 450 µm to 50 µm as the Young’s modulus was increased from 1 kPa to 10 MPa (Fig.1A). Similarly, when the Young’s modulus of the agarose tissue phantom was increased from 21 kPa to 570 kPa, high speed images showed a >65% reduction in the maximum bubble radius produced by a 500kHz histotripsy pulse, decreasing from 177.7±30.7 µm to 61.6±14.9 µm (Fig.1B/C). For the agarose phantom with a 21 kPa Young’s modulus, the maximum bubble radius was reduced from 177.7±30.7 µm to 24.5±6.8 µm as the frequency was increased from 500kHz to 3MHz. This work demonstrates that histotripsy-induced cavitation bubble expansion is decreased when treating tissues with increased stiffness, which helps explain the higher resistance to histotripsy damage by these tissues. The findings also suggest that using lower frequency can facilitate bubble expansion to improve the fractionation of stiffer tissues. Overall, the results of this study support our hypothesis, improve our understanding of the effects of histotripsy in tissues with different mechanical properties, and provide a rational basis to tailor acoustic parameters for fractionation of specific tissues.
TREATMENT OF BREAST FIBROADENOMA WITH HIGH INTENSITY FOCUSED ULTRASOUND (HIFU): A FEASIBILITY STUDY

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The primary objective of the study is to evaluate the feasibility of High Intensity Focused Ultrasound (HIFU) delivered by the Echopulse device (Theraclion, Paris) for treatment of breast fibroadenomas using assessments of patient experience and tumor response to treatment. Secondary objectives include evaluation of the feasibility of HIFU for treatment of breast fibroadenomas using quantitative and qualitative assessments of device performance, assessment of general patient safety and cosmetic outcomes following HIFU treatment of breast fibroadenomas. Twenty female patients diagnosed with palpable, non-calcified breast fibroadenomas 1cm or larger will be enrolled in a single arm clinical trial and undergo treatment of their tumor utilizing a computer-driven, continuously cooled, extra-corporal HIFU probe mounted on an arm and moved by motors, and guided in real-time with an integrated ultrasound imaging scanner. The integrated probe is positioned by the operator and the lesion is imaged. Treatment planning is automated and presented for review and approval on an integrated computer screen. Optimal energy per sonication is determined by the minimal setting found to produce cavitation within the lesion in each patient as observed on real-time B-mode ultrasound monitoring. Patients will have tumors meeting the following criteria: Distance from the skin of ≤ 23 mm from the posterior border of the fibroadenoma, ≥ 5 mm from the anterior border of the fibroadenoma, and ≥ 11mm from the focal point of the HIFU treatment. The chest wall must be more than 1cm from the posterior margin of the tumor, and tumor volume must be between 2cc and 10cc. Subjects will be evaluated immediately after treatment and at 3, 6, and 12 months after therapy.

Primary endpoints assessed will include:
- Absence or presence of palpable lesion at 12 months following HIFU treatment session
- Patient-rated pain of the HIFU treatment assessed after completion of the treatment session
- Patient responses to Satisfaction Questionnaire at 3, 6 and 12 months following HIFU treatment session
- Change in volume of the fibroadenoma compared to baseline at 3, 6 and 12 months after the HIFU session as assessed by ultrasound

Secondary endpoints assessed will include:
- Absence or presence of palpable lesion at 3 and 6 months following HIFU treatment session
- Cosmetic evaluation at 3, 6 and 12 months following HIFU treatment session
- Investigator-rated evaluation of the device
- Incidence of local and/or general adverse events and other associated symptoms at 3, 6 and 12 months follow-up

-Treatment parameters including duration of the treatment session and device energy settings

The IDE application for this study has received conditional approval from the FDA and the trial is expected to begin accrual in March 2014. Previous studies conducted in the European Union have demonstrated safety, resulting in the device receiving approval for treatment of fibroadenomas. Preliminary data from these studies demonstrate efficacy in tumor volume reduction as measured by ultrasound, and subjective reduction in palpability, as reported by subjects. A study evaluating the device for the treatment of breast cancer is under development.
INVESTIGATION OF INTERSTITIAL ULTRASOUND ABLATION OF SPINAL AND PARASPINAL TUMORS: A PATIENT-SPECIFIC AND PARAMETRIC SIMULATION STUDY
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Preferential acoustic absorption and heating of bone can significantly impact interstitial ultrasound ablation of tumors within or bordering the spine. Furthermore, intervening cortical bone may provide acoustic and thermal insulation that can protect sensitive structures nearby, such as the spinal cord. The objectives of this study are firstly, to apply parametric and patient-specific models to theoretically assess the feasibility of interstitial ultrasound ablation of tumors within and near the spine, and secondly, to identify potential energy delivery strategies, safety criteria, advantages, and disadvantages of interstitial ultrasound in this setting. Transient biothermal models were employed using previously validated approximations for power deposition within bone from interstitial sources. Axisymmetric models were used to perform a parametric assessment of the impact of tumor dimensions, attenuation (dependent on residual bone content), perfusion, and maximum temperature thresholds on necessary treatment parameters and on treatment effectiveness. 3D patient-specific finite element models were generated based on segmented CT scans for nine representative patient cases selected to bracket a range of clinical interest, with tumors in or near the vertebrae, sacrum, and ilium. Tumors were 10-27 mm in diameter, 10-43 mm long, and 0-14 mm from the spinal canal. Paraspinal tumors, osteolytic vertebral tumors, and a mixed osteolytic/osteoblastic iliac bone tumor were considered. 7 MHz (1.5 mm OD) and 3.0 MHz (3.2 mm OD) applicators with an array of 1-4 tubular transducers (0.5 - 1.5 cm long, 150-360° sector angles) were applied in various implant configurations. Variable thicknesses of bone insulating critical anatomy from the tumor and insulation of the spinal cord with injected carbon dioxide were also investigated for definition of safety margins and possible protection of critical structures. 6-44 mm diameter osteolytic tumors surrounded by bone and blastic (high bone content) lesions up to 20 mm in diameter could be fully ablated by 7 MHz interstitial ultrasound using 120-5,900 J and treatment durations of 0.4-15 min. 100% of the volumes of five simulated tumors located 4.3-14 mm from the spinal canal and 94.6-99.9% of the volumes of four simulated tumors 0-4.5 mm from the spinal canal were ablated (>240 EM43°C) within 15 min without damaging (<6 EM43°C) critical nerves. Preferential ultrasound absorption and concomitant heating at bone surfaces allowed for faster, more effective ablations with less delivered energy. 3-5 mm of normal cortical bone was found to provide a safety margin and reduce temperature elevations in untargeted tissues. Critical anatomy less than 3–5 mm from a tumor encapsulated by bone could be preserved by reducing the acoustic energy aimed towards these structures and/or through injection of insulating CO2. Parametric and patient-specific studies demonstrated the feasibility of interstitial ultrasound ablation of paraspinal tumors and osteolytic tumors within the spine. Preferential absorption of ultrasound by bone may provide improved localization, faster treatment times, and larger treatment zones in highly osteolytic and soft tissue tumors in and near bone as compared to other heating modalities. (This work was supported by the NIH grant R44CA112852).

Left: Complete ablation of an osteolytic tumor invading the anterior portion of the L1 vertebral body, showing the FEM mesh on bone surface and the 240 EM43°C cloud. The thermal dose on the spinal canal did not surpass 0.1 EM43°C.

Right: Ablation by 2 directional transducers (gray) of an osteolytic tumor invading the left transverse process of L3, shown in an axial slice atop a temperature map (°C). Acoustic energy is successfully directed away from the spinal canal.
MODELING OF MOTION TRACKING AND FOCUSING STRATEGIES IN HIFU ABLATION OF HEPATIC TUMORS
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A major impediment of hepatic tumor HIFU ablation is the respiration-induced organ motion and displacement. If unaccounted for, the combination of this motion with the partial obstruction introduced by the thoracic cage and lung can lead to insufficient energy deposition in the targeted tissue, unsuccessful ablation, or collateral tissue damage. A dynamic anatomical model, deformed throughout a respiratory cycle based on 4D-MRI images, and the model of a randomized phased array transducer (RPAT) were used to perform acoustic and thermal simulations of hepatic ablation. The impact of motion tracking as well as intercostal targeting and compensation were investigated. In order to investigate hepatic ablation, a tumor was implanted in the right posterior hepatic lobe of an anatomical model, behind the 10th rib. The model was registered to 4D-MRI images of a respiratory cycle and warped to generate a transient model of 14 steps. The 4D-MRI images were processed to obtain separate displacement vector fields of the abdominal organs and of the chest wall, which were then combined through a Gaussian kernel at their interfaces. An RPAT with 256 circular elements was modeled and placed such that its geometric focus coincided with the center of the tumor in the nondeformed model. This setup was then employed to perform acoustic and thermal simulations of tumor ablation and ascertain the importance of motion-tracking as well as intercostal targeting approaches. Acoustic simulations were performed for each stage of the respiratory cycle with both analytical or simulation-based (time-reversal) steering and compensation. The deposited acoustic energy was then projected back onto the nondeformed model, and transient thermal simulations of gated and continuous ablation procedures with and without motion compensation and with triggering were performed. Employment of simulation-based time-reversal techniques offered significant diminution of the pericostal tissue exposure and acoustic shadowing effects induced by the thoracic cage when compared to their analytical counterparts. Furthermore, such approaches yielded a visible increase of the deposited acoustic energy in the targeted volume, improved targeting accuracy, augmented demarcation of the generated lesions, and higher temperature increases. With only distance-based corrections, the focus can shift out of the tumor and occasionally a second focus is observed near to the primary one. The focus strength decreases by a third. Transient simulations of the dynamic model without motion compensation showed an increased energy build up near the rib and lung (but below problematic levels), as well as a strongly exposed streak between the intercostal space and the tumor believed to be due to geometric constraints enhancing focus side-lobes. The main energy deposition is not evenly smeared along the liver movement magnitude. Instead, energy deposition is mostly observed in two region slightly bigger than the static focus size. This is due to slower liver motion at peak ex- and inhalation and to a lesser extent to reduced focusing quality in between. The peak temperature increase is reduced by a factor of three. Triggered sonication reduces the heating even further, but helps avoiding unwanted heating. Modeling of continuous motion compensation is ongoing. Modeling can be used to understand and optimize HIFU energy deposition for hepatic tumor ablation. Together with a population-based parametric liver motion and drift model that has been developed and can be used to assess deformation in real-time based on sparse MRI measurements, it will allow to overcome motion as well as focus distortion issues.

(Left) Peak exhalation and inhalation stages of the dynamic anatomical model. (Right) Temporal snapshot of the induced temperature increase.
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TRANSCOSTAL HIGH-INTENSITY FOCUSED ULTRASOUND: PLANNING TREATMENT DELIVERY FOR PHASED ARRAYS
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In this presentation we describe a comprehensive package of computation procedures developed for treatment planning and treatment delivery for transcostal high-intensity focused ultrasound using a phased-array. A number of robust computational routines designed to identify a target area, specify the position of the transducer, then perform parallelised ray-tracing from segmented CT data to ascertain the optimal position and angulation has been developed. The aim is to:
1. Minimize transmission losses through the skin/water interface arising from the angle of incidence between the field from each active element and the skin interface.
2. Minimize the propagation path in tissue.
3. Maximize the number of available elements which may be switched on if a isobaric beam corresponding to a given pressure value does not pass through the ribs.
4. Ensure that the transducer can be viewed by an optical tracking system, in order to register the position of the treatment head to the position defined by the treatment plan.
5. Ensure that an imaging probe located in the central aperture of the treatment head can image the target, for treatment monitoring.
6. Ensure that organs at risk such as lungs or bowel are not exposed to the field.

The location of an optical tracker placed on the transducer head is calculated, so that the location of the treatment head location compared to the treatment plan can be verified. For ease of identifying the location of ablated regions, surface lesions can be generated automatically. Centrelines of the ribs were extracted and electronic steering angles computed as well as losses in focal peak intensity due to steering for the transducer settings. Additionally, from the computed position image planes which can be compared with ultrasound images are computed.

The computation routines are written in python and fortran, with bindings performed with f2py, graphical user interface from wxpython and three-dimensional visualisation using mayavi. The numpy and mkl libraries are used extensively. Patient data can be provided as dicom images for target identification, while registered and segmented anatomical data can be provided as an stl or vtk dataset. Settings are outputted as xml data in html files for ease in a human readable format, as well as text files which can be passed directly to a phased-array drive system.

The appropriate phases can be calculated so that the acoustic intensity on the ribs is constrained using a boundary element method. A Rayleigh integral method, is used where the acoustic window is sufficiently large, or the tolerances of the ray-tracing algorithm sufficiently strict. For a given exposure duration, the amplitudes of each element required to give either a user-defined focal peak temperature rise or a volumetric dose as a function of the full-width half maximum are calculated. Thermal calculations are performed using a parallelised alternating-direction implicit method on a structured rectilinear grid derived from the unstructured polydata sets of the surface meshes of the skin, ribs and liver. Algorithms for motion compensation are introduced in order that motion can be exploited to enlarge the volume of the lesions treated, while still delivering a specified dose to the enlarged planning treatment volume. The system has been designed and implemented on an in-house high-performance computing facility, and is designed to be flexible for a variety of transducer designs. It has been validated on a rib phantom model and porcine models. Robust, deployable treatment planning software has been developed for transcostal high-intensity focused ultrasound for a general phased array system.
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Phase difference and directional backscattering from cells and particles: an indirect validation of intra-membrane cavitation
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Ultrasound is extensively used in medicine for imaging. In the last decades therapeutic ultrasound is becoming increasingly popular whereas many ultrasound manipulations of cells and tissues are being studied. We have provided two years ago a comprehensive explanation for the generation of sub-cellular-level forces by an ultrasound pressure wave. Using a physical model that incorporates molecular forces with bubble dynamics and gas diffusion, we predicted that ultrasound induces a pulsating bubble in the intra-membrane space between the two lipid leaflets; by periodically pulling the leaflets away from each other, while pockets of dissolved gas accumulate in the hydrophobic zone located between them. The described experiments were conducted under the assumption that cells in culture when exposed to ultrasound will behave as a cluster of micro- and nano-bubbles. Cell monolayers in a 12-well flask were placed at the focal point of a focused ultrasound (FUS) beam of 0.5MHz (CW) with pressure amplitude at the focus that varies in the range 0.1-2MPa. Hydrophobic polystyrene particles with 10-20µm in diameter were tested as well. To simulate the cell culture, the particles were confined to the bottom of the well. The backscattered beam on the FUS source surface was measured and analyzed. Field mapping was conducted in the close vicinity of the FUS source. We have found that the backscattered signal has a threshold; the signal that was measured on the FUS source was unnoticed below pressure at the focus that varied in the range 50 to 100kPa. The backscattered pressure amplitude on the FUS source increased with the focal pressure amplitude and accounted for about 10 to 20% of the broadcasted pressure. Much smaller pressure amplitudes, by at least one order of magnitude were measured on the side of the FUS source surface. Similar results were found for the polystyrene particles. The backscattered pressures on the FUS source in the control case (no cells or particles) were as low as the background noise (±3% of the broadcasted pressure). We found also a phase shift between the broadcasted and backscattered signals that vary with pressure amplitude in the range of about 0.05 to 0.3 radians on the FUS source in case of reflected signal from cells and particles placed in the focal point. Such a substantial reflected signal which is also highly directional and with a phase shift is not typical for passive reflectors and interfaces between substances of different impedance. A plausible explanation for these results is that pulsating microbubbles that were generated in the focal plane act as reflectors; these microbubbles were formed within the membranes of the cells or around the polystyrene particles. A directional reflection is also indicative of interference pattern of the integrated effect of a cluster of point sources, and microbubbles are such point sources broadcasting with a spherical symmetry. Theoretical simulations with a spherical cell that includes intra-membrane gas pockets (Sonophore) on the surface show a pressure threshold and a phase shift, qualitatively similar to the results above for cells and particles. We expect to obtain directional backscattering by calculating during a future work the integrated effect of a surface coated by microbubbles. The good agreement between experiments and theory provides a valuable support for the concept of intra-membrane cavitation and might have a potential impact on understanding the backscattering of a FUS beam from cells and tissues.
THEORETICAL DESIGN AND EVALUATION OF ENDOLUMINAL ULTRASOUND APPLICATORS FOR THERMAL THERAPY OF PANCREATIC CANCER UNDER IMAGE GUIDANCE

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To employ biothermal and acoustic simulations to evaluate the feasibility of targeted thermal therapy of pancreatic tumors using endoluminal ultrasound applicators within the duodenal lumen, and to determine favorable transducer configurations for various tumor sizes, locations, and geometries. Patient-specific 3D anatomical models were created based on axial CT scans of patients with tumors in the head of the pancreas. Relevant anatomical structures, such as the tumor, duodenum, pancreas, pancreatic duct, and sensitive vasculature, were segmented and finite element meshes were created (Mimics Innovation Suite) with each tissue having defined thermal/acoustic parameters. The applicator, surrounded by a water-cooled balloon, was positioned in the duodenal lumen. 3D acoustic pressure fields and power deposition distributions produced by 20x10 mm transducers were calculated in MATLAB using the rectangular radiator method for three transducer configurations: planar, weakly focused (curvilinear along 10 mm width), and strongly focused (curvilinear along 20 mm length). For each patient model and transducer configuration, transient 3D bioheat transfer FEM models of temperature and thermal-dose were solved using COMSOL Multiphysics, with integrated PI feedback control of the maximum temperature to simulate control under MRTI guidance. Parametric studies were performed using generalized and patient specific anatomical models to determine the effects of degree of focusing, frequency (2-5 MHz), and allowable maximum temperature on lesion size, penetration depth, and sparing of non-targeted tissues. The results of these studies were used in patient specific models to assess the feasibility of full tumor treatment, both via ablation (t43>240 min, T>51-52oC), performed with multiple applicator orientations over a 15-20 min treatment period, and hyperthermia (T>40oC), performed using either planar or tubular transducers. Segmented tumors were roughly spheroid (average diameter 20 mm), centered ~12-17.5 mm from the inner duodenal wall. Parametric studies showed that 2 MHz was preferable to higher frequencies for achieving penetration through a maximal tumor volume while sparing the duodenal wall and non-targeted tissues. Greatest penetration and highest specificity in targeted tissue ablation was achieved using strongly focused transducers at 2 MHz with a radius of curvature no less than the distance from the transducer to the tumor distal periphery. Weakly and strongly focused transducers demonstrated greater penetration (up to 31mm & 40mm, respectively, from inner duodenal wall) and duodenal sparing compared to planar transducers (max temperatures ~50C & ~20C lower), along with comparatively smaller lesion volumes. For patient-specific models of tumors with distal peripheries within 25mm of the duodenal wall, >90% of the tumor volume could be ablated (t43>240 min) in under 20 min without duodenal damage (t43>20 min) by rotating a weakly focused or planar 2 MHz applicator. For hyperthermia applications with a 1000 sectored tubular transducer, 90% of the tumor volume was 40-45oC at steady-state. For tumors extending ~30 mm from the duodenal wall, the translation and rotation of applicators with strongly focused 2MHz transducers could ablate >80% of the tumor volume in <20 min without damage to duodenum or nearby sensitive structures. Biothermal simulations illustrate the feasibility of thermal ablation and hyperthermia in ~20mm diameter tumors in the pancreatic head within 30-40 mm from the duodenal wall, using an endoluminal ultrasound applicator. (Supported by NIH P01 CA159992)
SIMULATING THERMAL EFFECTS OF HIGH-INTENSITY FOCUSED ULTRASOUND IN CORTICAL BONE AND ITS SURROUNDING TISSUE

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To help improve therapeutic results for treatment of bone tumors, high intensity focused ultrasound (HIFU) is being investigated as a non-invasive alternative to surgery and radiotherapy. Proper HIFU ablative treatment requires an imaging modality for guidance, and magnetic resonance (MR) is currently the strongest choice as it is able to provide temperature mapping throughout the treatment process. Unfortunately, the temperature feedback that is critical to ensuring optimal soft tissue ablation cannot be obtained in bone structures. As an alternative to obtaining feedback, this project is focused on developing a simulation algorithm that is capable of predicting the temperature distribution around and inside bone tissue during focused ultrasound therapy. Having such an algorithm would provide a better understanding of the thermal dosages incurred by the bone during HIFU treatment of tumors. The algorithm consists of two primary components: the acoustic field and the bio-heat transfer models. For the acoustic field, a modified solution to the Rayleigh integral was implemented to track the change in complex ultrasonic velocity potential (speed and attenuation) through solid and soft tissue, which have been assigned properties of human tissue. The velocity potentials at each voxel are then converted to form a volumetric heat distribution required by the bio-heat computational model. The bio-heat then computes a numerical solution to a heat transfer equation, creating a four dimensional temperature map capable of demonstration at specific time intervals throughout a therapeutic ultrasound procedure. The simulator has been tested with a virtual long bone, represented by an open cylinder 17mm in diameter. The acoustic parameters for the muscle have been assigned as: longitudinal speed of sound \( c = 1496 \text{m/s} \), attenuation coefficient \( \alpha = 21 \text{Np/m} \), and absorption factor \( \text{abs} = 0.85 \). For the cortical bone: \( c = 3000 \text{m/s} \), \( \alpha = 31 \text{Np/m} \), \( \text{abs} = 1 \), and the shear properties \( c_s = 1500 \text{m/s} \), \( \alpha_s = 62 \text{Np/m} \). For the marrow: \( c = 1580 \text{m/s} \), \( \alpha = 6.4 \text{Np/m} \), \( \text{abs} = 0.85 \). The transducer was implemented with a diameter of 0.13m, a focal length of 0.12m, and a frequency of 1.2MHz. Figure 1 demonstrates the final bio-heat model. The heat appears to accumulate mostly in the cortical layer, reaching 68.54°C at its peak cortical temperature. The peak marrow temperature produced was 52.2°C and the peak muscle 50.8°C. The acoustic simulation required between 18 and 22 seconds of computation time on a graphics processing unit and the bio-heat required between 6 and 9 seconds. Previous data from thermocouple probes in the bone marrow of a porcine femur yielded a maximum temperature of 56.0°C with a 40W treatment, while this simulation yielded a marrow maximum of 52.2°C. This is outside the desired accuracy, but differences in geometry and material properties are likely to account largely for the discrepancy. The next steps of this project will be to incorporate segmented bones from MRI images and to validate the temperature values against thermocouple data. With a fully validated prototype, this software tool will be able to start demonstrating the thermal effects of HIFU in various bone structures, and will help both physicians and scientists in understanding the full effects of this therapy for improved future HIFU procedures.

![Figure 1: Temperature map on one axis crossing through the middle planes of a virtual bone after 30 seconds of continuous HIFU (40W). The color maps are in degrees Celsius, and the maximum temperature reached is 68.54°C. Note that values below 40°C have been suppressed for a better view of the bone, the voxel size was chosen to be 1mm, the center of the bone was targeted, and that the inner circle represents marrow, the outer ring cortical bone, and all else muscle.](image-url)
MR-CT REGISTRATION FOR MR-GUIDED HIFU TREATMENT OF BONE METASTASES
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MR-guided HIFU for bone metastases is used as a palliative treatment for painful bone metastases: the nerves in the peristemeum are ablated to reduce the pain. Treatment planning is currently done on MR images [1,2], which is challenging because it is often hard to assess the presence of cortical bone in metastatic bone lesions on MRI. Incorrect assessment of the amount of cortical bone could create a dangerous situation, in particular when cortex is wrongfully expected to absorb a significant part of the ultrasound energy, while in fact this energy is absorbed elsewhere further along the HIFU beam, causing unwanted heating of healthy tissue. Using additional information from computer tomography (CT) scans would help to correctly assess the amount of cortical bone, in order to improve geometric beam planning and to support the decision for a specific sonication strategy. Therefore, we developed a registration algorithm that transforms the CT to the MRI coordinates. Data were obtained from nine patients with 18 bone lesions in total, referred for MR-HIFU treatment. Eight patients had lesions in the pelvis and one in the ribs. For each patient, a previously acquired CT scan covering the volume of interest was available (average voxel size 0.7x0.7x3.0 mm3). In addition, several pre-treatment MRI scans were acquired to assess the suitability for HIFU treatment. MRI scans differed per patient regarding scan sequence, voxel size, scan direction, field of view and depicted anatomy. However, a T1-weighted (T1w) turbo spin echo MRI (average voxel size 0.7x0.7x5.4 mm3) and at least four other MRI scans were available in all patients. The registration algorithm consisted of two steps. In the first step, in order to ensure satisfactory performance on all MRI scans, the CT image was simultaneously registered to all MR images, to obtain an initial rigid transformation. In the next step, the initial alignment was fine-tuned by separate registrations of the CT to each individual MR image. The registration was focused on bony structures, by a combined metric acting on intensities, gradient magnitude and a bone segmentation on CT. The images were subsequently registered with an affine and a non-rigid transformation. The T1w TSE scan was used for quantitative evaluation. Anatomical landmarks were placed in both the CT and MR images by two clinical experts for the pelvis patients, and by one expert for the rib patient. We calculated the target registration error (TRE), defined as:

\[ \text{TRE} = 1/L \sum_i ||L_{CT,i} - T(L_{MR,i})||, \]

where \( L_{CT,i} \) and \( L_{MR,i} \) are the landmarks placed in the CT and MR image, respectively, \( T \) defines the transformation from MR to CT and \( \| \cdot \| \) denotes Euclidean distance. Illustrations of the results are presented in Fig. 1. The average landmark errors per patient ranged from 3.1 to 6.2 mm, with a maximum error ranging from 5.9 to 13.8 mm. The total average error was 4.5 ± 2.7 mm. Our algorithm yielded registration errors of a few millimeters, which was comparable to the accuracy of the landmark annotations that can be expected given the slice thickness of the MRI scans. The feasibility of combining information from CT and MRI by non-rigid registration for HIFU treatment of bone metastases was demonstrated.

REFERENCES
Three-dimensional nonlinear pressure and temperature field simulation of 2D transducer arrays in heterogeneous media

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Advances in fabrication technologies and electronics have led to the advent of new transducer technologies with arbitrary geometries and electronic focusing. This calls for robust, efficient, and accurate numerical tools for the design and optimization purposes. We present three dimensional simulations of nonlinear pressure and temperature fields of multi-channel therapeutic 2D arrays in inhomogeneous tissue. A modified Westervelt equation is solved together with the Pennes bioheat transfer (BHT) equation using a Fourier collocation method. This gives an efficient and accurate computational tool to model the fields of different transducer designs. Our transducer design is a 2D array with 20 x 20 elements and 8 channels firing toward a layered water-tissue medium. The transducer performance is evaluated for both the linear and nonlinear pressure fields. For asymmetric ultrasound fields with large diffraction angles, the full-wave model (i.e., the Westervelt equation) must be solved. One limitation of this equation is that it provides a thermoviscous approximation to the absorption of the acoustic field. For the frequency regimes of ultrasound, however, the relaxation loss is the dominant mechanism of absorption. To address this, we use a modified Westervelt equation with a fractional-operator based absorption model. We use a Fourier collocation scheme to solve for the pressure field for both the linear and nonlinear cases. We use the BHT equation as the canonical model to estimate the temperature field, and thereby, the ablated region in inhomogeneous tissue. For integrating the BHT equation in time, an implicit time integration is preferred due to the tight requirements on the stability condition for explicit schemes. This impedes the application of the spectral methods to these problems as they lead to dense systems, and for implicit schemes the system needs to be solved at each time-step. We extend the k-space theory of the wave problems to the BHT equation, and use it along with the Fourier collocation method to solve for the temperature field. The k-space method enables having an explicit integration of the BHT equation by relaxing the stability requirement on the time-step, hence, allowing an efficient computation of the temperature field in heterogeneous media using the Fourier spectral method. We evaluate the pressure and temperature fields of a 1 MHz 20 mm x 20 mm 2D array with 20 x 20 elements grouped in 8 channels based on the phase delay from the array elements to the targeted focal point. The transducer is placed in water and the tissue interface is located 5 mm away from the transducer. Figure (1a) shows a three-dimensional view of the beam profile of the transducer focused at F_#=1 with 1 MPa peak surface pressure. Figure (1b) shows the ablated tissue volume after 5 sec for 3 sec of continuous sonication and 2 sec of cooling. The results show the design can achieve a gain of 11.7 and an ablated tissue volume of 0.35 cm^3. We present an efficient and accurate methodology for modeling the pressure and temperature fields of therapeutic transducers. This is used for evaluating different design criteria and also the field physics of 2D therapeutic arrays. This is particularly useful in the design analysis and optimization. This can lead to a considerable reduction of design iterations to achieve a desirable performance.
8:40 AM
COMBINING THERMOSENSITIVE LIPOSOMES WITH ULTRASOUND
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Dr. Milton Yatvin published the first report describing a thermosensitive liposome over two decades ago, which launched a flurry of activity seeking optimal drug formulations that could be used in combination with hyperthermia. The work was groundbreaking, but the original formulations were limited in clinical application because of short circulation half life and high temperature thresholds for drug release. Dr. David Needham published the first report of a novel thermally sensitive doxorubicin containing formulation in 2000, which exhibited novel drug release properties, including rapid drug release in a clinically relevant temperature range; the rapid release is essential for its performance in vivo, which can yield 25-30 fold increase in drug delivery to a heated tumor, compared with free doxorubicin with hyperthermia. The success of this formulation has been carried forward into human clinical trials, including a pivotal randomized phase III trial, in combination with thermal ablation for treatment of hepatocellular carcinoma. A variety of other drugs can be formulated into liposomes, but the critical question is what diseases can be targeted with such formulations. A number of criteria need to be satisfied for successful integration of what is in reality a drug-device combination. This lecture will review these principles, providing suggestions for future clinical applications with an emphasis on integration with focused ultrasound.
MRgHIFU AMIDST OTHER MINIMAL AND NON-INVASIVE TREATMENTS
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MRgHIFU is an emerging new technology that has to establish its place among other treatment options. Its focus is on tumour treatment although other options are being developed too. For all these indications, certainly for cancer treatments, complex therapies are already in place. In oncology this frequently consists of surgery, chemotherapy and radiotherapy that interacts in a complex way. All these established techniques are also in flux. Surgery is increasingly less invasive and is using imaging techniques like optical fluorescent imaging and Ultrasound to better localize and delineate tumours. Chemotherapy is increasingly used neoadjuvant and dependent on tumour make up. At last, radiotherapy, a completely non-invasive technique is becoming completely image guided. Besides these well-established treatment strategies MRgHIFU has to establish its place. Even more, there are also many new minimally invasive techniques such as Laser, RF ablation, plain- chemo- or radio- embolisation. Furthermore the HIFU technology is versatile too and can be used for ablation of the tumor, for hyperthermia in relation with radiotherapy or for improved drug delivery with heat sensitive liposomes. At last, the permeability of membranes such as the blood brain barrier can be improved by exploding micro bubbles inside the vessels of tumours. Besides all these technical considerations, patient selection, patient preferences, doctors convictions and believes and availability and reliability of the procedure are important. In the present days of evidence based medicine, scientifically proven value of treatment strategies has become very important too. Without such proof reimbursement is increasingly becoming problematic. In this lecture I will give two examples of the complex interaction of the different treatment options and the advantages and disadvantages of the different techniques in the treatment of breast cancer and uterine myomata.
OPTIMIZING MR IMAGING-GUIDED NAVIGATION FOR FOCUSED ULTRASOUND INTERVENTIONS IN THE BRAIN
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Intra-interventional MR imaging during transcranial MR imaging-guided Focused Ultrasound surgery (tcMRIgFUS) is challenging due to the complex ultrasound transducer setup and the water bolus used for acoustic coupling. Achievable image quality in the tcMRIgFUS setup using the standard body coil is therefore significantly inferior to diagnostic neuroradiologic standards. As a consequence, MR image guidance for precise navigation in functional neurosurgical interventions using tcMRIgFUS is basically limited to the acquisition of MR coordinates of salient landmarks such as the anterior and posterior commissure for aligning a stereotactic atlas. Here, we show how improved MR image quality provided by a dedicated MR coil and optimized MR imaging sequences can improve imaging-guided navigation for functional tcMRIgFUS neurosurgery by visualizing detailed anatomical structures that can be integrated into the navigation process to accommodate for patient specific anatomy. Functional tcMRIgFUS neurosurgery interventions were conducted using the 650kHz InSightec ExAblate Neuro system (InSightec Ltd., Tirat Carmel, Israel) integrated into a 3T GE 750 Discovery MR-Scanner (GE Healthcare, Milwaukee, USA). Intra-interventional MR images were acquired by a dedicated 8 channel phased array MR coil that is tightly integrated into the transducer setup (RAPID Biomedical, Rimpar, Germany). MR imaging sequences applied for intra-operative imaging-guided navigation included standard T2 weighted spin echo (SE) images, 3DT2 SE sequences, and an adapted inversion recovery 3DT1 gradient echo (GRE) sequence with prolonged echo time for additional T2 weighting. Under treatment conditions, the SNR of the 8 channel phased array MR coil is improved by a factor of 3.5 as compared to the standard body coil. In targeting the centro lateral nucleus of the thalamus for pain treatment atlas based navigation is achieved by aligning and scaling stereotactic atlas information according to the location of the anterior commissure, the posterior commissure, the thalamic border and some thalamic nuclei, which can be readily identified on intra-interventional MR images. For subthalamic targets, such as the cerebello-thalamic tract and the pallido-thalamic tract, used for treating movement disorders direct targeting can be achieved based on intra-operative MR-image information of the substantia nigra, the subthalamic nucleus, the internal capsule, the striatum, the pallidum, and the mamillo-thalamic tract. Compared to standard MR body coil imaging, dedicated MR imaging coils and optimized MR imaging protocols can significantly improve intra-interventional image guidance for functional tcMRIgFUS neurosurgery by providing more detailed anatomical information. Depending on the stereotactic targets to be applied such details can help to adapt mean atlases to patient specific geometry or to identify anatomical landmarks that can be used for direct targeting in the specific patient anatomy.
INTEGRATION OF AN INDUCTIVE DRIVEN MRI TRANSMIT-RECEIVE VOLUME COIL INTO A 
HEMISPHERICAL FOCUSED ULTRASOUND THERAPY SYSTEM FOR TREATMENT OF 
HUMAN BRAIN DISORDERS 
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The objective of this effort is to improve overall image quality of the MR imaging during 
treatment planning, thermometry during imaging treatment and post treatment imaging. 
Currently the whole body coil is used for imaging and suffers from RF non uniformity due to the 
interaction between the whole body MRI RF coil and the focused ultrasound transducer, which 
behaves as a shielded cavity. The whole body coil also suffers from reduced receive sensitivity 
relative to smaller local volume coils. A smaller local volume coils will also reduce the total 
patient absorbed RF power (SAR). A variation of a transmit/receive birdcage volume coil (3) has 
been designed that is split along the Z axis. (Figures1, 2, 3) This allows half of the coil assembly 
to be located inside the acoustic treatment volume inside the transducer and immersed in 
acoustic coupling medium (usually degassed water). The other half of the volume coil assembly 
is outside the transducer and direct connected to the MRI system with RF drive cables. The 
upper half of the coil is inductively driven by the lower half by way of inductive center rings. This 
allows the upper half to be electrically isolated through the water membrane and have no cable 
connections into the acoustic treatment region. The upper coil assembly has the conductors in 
planes radial to the acoustic field and on boundaries of the transducer sections to have minimal 
interaction with the ultrasound field. The coil is designed to be used with the InSightec Neuro 
treatment system used in conjunction with a GE Healthcare MR750 3 Tesla Magnetic 
Resonance Imaging system. As seen in Figure 4, interaction between the body coil and the 
transducer results in non uniform B1 in the middle of the treatment region. The body coil cannot 
make an adequate flip angle in this area and suffers from poor receive SNR. Figure 5 using the 
integrated volume coil shows significant improvement near the center of the phantom although 
some B1 non-uniformity remains. Over and above reducing the artifact from the body coil 
transducer interaction, the integrated split volume coil show a 300% improvement in SNR in the 
center of the phantom. This will significantly improve in the treatment planning phase as well as 
 improving temperature monitoring accuracy during ultrasound thermal therapy treatments. The 
integration of a unique variation of a birdcage volume coil into the MR Guided Focused 
Ultrasound System for human brain has been demonstrated to improve B1 transmit uniformity 
as well as improve RF receive sensitivity during during MRI imaging. By inductively separating 
the birdcage coil, one half can be placed inside the water filled acoustic treatment field inside 
the transducer and the other half direct connected to the MRI system without the use of 
conductive interconnections across the membrane into the water.
10:30 AM
QUANTITATIVE CHARACTERIZATION OF HIFU TRANSDUCERS USING INFRARED THERMOGRAPHY IN A GEL PHANTOM
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Infrared (IR) thermography is a potentially useful method for rapidly and noninvasively characterizing HIFU transducers. However, quantitative predictions of intensity fields based upon IR temperature data are complicated by axial and radial diffusion of heat, as well as by convection currents in the air layer residing between the propagation medium and the IR camera. The objective of this talk is to present a method for quantitative characterization of HIFU transducers using IR thermography in a gel phantom. Mathematical expressions are derived for use with IR temperature data acquired at times long enough that noise is a relatively small fraction of the temperature trace, but short enough that convection currents in the air volume between the phantom and the IR camera have not yet developed. Diffusion of heat in the axial and radial directions, over lengths comparable to the acoustic wavelength, is accounted for in the technique. Since diffusion is accounted for, it is not necessary to take IR measurements immediately after sonication. However, to minimize the influence of convection currents created in the air gap between the phantom and the camera, measurements should be made within about 2 seconds after the initiation of sonication. The IR technique was used to measure the intensity field of two 1.1 MHz HIFU transducers, one with a gain of 40 and one with a gain of 60. The acoustic absorption of the phantom was made high enough (1.9 dB/cm MHz) that reflection off of the air interface (between the phantom and the camera) back into the transducer was minimal. Agreement with hydrophone measurements was about 10% in the focal plane and a plane roughly 1 cm in front of the focus, for both transducers. In the comparisons, the intensity was kept less than 60 W/cm². In a plane about 1 cm beyond the focus, the accuracy of the IR technique was similar to the accuracy at the other axial locations for the lower gain transducer, but degraded to about 40% (relative to hydrophone measurements) for the higher-gain transducer. This decrease in accuracy beyond the focus for the higher-gain transducer was likely due to the breakdown of the "local plane wave" assumption made in the derivation of the relations between IR temperature measurements and acoustic intensity. The IR technique as presented shows considerable promise for rapid yet accurate transducer characterization at moderate intensities, where hydrophone damage is a potential problem but nonlinear propagation effects are not significant.
10:40 AM
HIGH-INTENSITY FOCUSED ULTRASOUND FIELD CHARACTERIZATION VIA INFRARED THERMOGRAPHY: INDUSTRIAL APPLICATION FOR OPHTHALMOLOGIC DEVICE
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Hydrophone scanning, the conventional method used for characterization of high intensity focused ultrasound (HIFU) fields, is slow for characterizing large numbers of probes in a production line situation. For multi-element systems, such as the HIFU device for the treatment of refractory glaucoma developed by Eyetechcare (Rillieux-la-Pape, France), the hydrophone method has prohibitively high costs in terms of time. An alternative modality for rapid qualitative assessment of the intensity distribution of a HIFU device is based on infra-red (IR) thermography. This modality has been used by other groups for characterizing spherical and phased array HIFU systems that operate in the frequency range of 1-5 MHz. Here, the method was used to characterize the beam profile of high frequency (19-21 MHz) line-focus US radiators and was further investigated as a method to be used during industrial production. The system investigated is a disposable ring-shaped probe, which contains six piezo-ceramic transducers operating at a frequency of 19-21 MHz. A high resolution IR camera (50 µm, 50 Hz, and 50 mK) was used to map the resultant temperature change induced in an acoustic absorber (0.6±0.1 mm thick) that was placed at the focal distance (10 mm) with an angle of 20° to the beam axis. Eight-five (85) different transducers were characterized. Short bursts of ultrasound (<1 s) were used to heat the absorber. The IR camera recorded radiometric images from the air-interfaced side of the absorber at a distance of 80 mm. At the time of maximum observed temperature in the defined region of interest, the corresponding frame was extracted for post-processing. The pressure profiles at -3, -6, and -12 dB (obtained by hydrophone scanning prior to thermal measurements) were then compared to the corresponding relative width of the temperature profiles. For the 85 transducers tested, the averaged widths (mm) of the pressure profile along the focal line were 1.23±0.24 at -3 dB, 1.67±0.16 at -6dB, and 2.44±0.17 at -12dB. The corresponding relative values from the temperature profiles were 1.19±0.14, 1.65±0.13, and 2.39±0.98 mm respectively. The difference of one-to-one comparison for each ceramic was estimated on average to be 13.9, 7.5, and 7.3% respectively. The estimated time for field mapping of 6 ceramics was 45 min via hydrophone vs. less than 2 min via the IR method. It was shown that this method provided good agreement with conventional hydrophone measurements and could be potentially applied for field characterization at high frequencies. The significant reduction in time necessary for characterizing HIFU devices makes this method a promising alternative to hydrophone measurements for industrial applications.
SKIN TEMPERATURE INCREASE MEDIATED BY WEARABLE LONG DURATION LITUS THERAPY
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One of the safety concerns with the delivery of therapeutic ultrasound is overheating of the transducer-skin interface due to poor or improper coupling. The objective of this research was to define a model that could be used to calculate the heating in the skin as a result of a novel, wearable long-duration ultrasound device. This model was used to demonstrate that theoretically, the maximum heating in the skin remained below the threshold necessary to cause thermal injury over multiple hours of use. In addition to this model data, human subjects’ data was taken using wire thermocouples on the skin surface to measure heating characteristics during actual treatment. For the modeling, a heat transfer model for the tissue was defined, considering the unique thermal properties of the dermis and sub-dermal strata. The heat output of the ultrasound device was two-fold. The energy lost in the conversion of electrical energy to acoustic energy within the transducer itself converted to heat, as well as acoustic energy from the device that is being absorbed by the body. To dissipate that heat, conduction and convection/perfusion effects were considered in the model. For experimental observations under institutional review board (IRB) approval and informed consent, 44 human subjects either underweight (22, 16 females, 6 males) or overweight (22, 8 females, 14 males) according to the BMI classification, wore the device on their arm or their leg. The two respective locations where further stratified into bony, tendon or muscle locations on each subject to obtain thermal regulatory information around the use of the device. Thermocouples were attached to the skin under the treatment locations, and monitored the temperature at the transducer-skin surface over the course of a four hour treatment. For the model, the bioheat equation was solved for steady state, given that steady state represents the maximum temperature in the tissue. Parametric analysis of the model determined that the maximum temperature increase is at the surface of the skin ranged from 40-43° C when perfusion was taken into account. The experimental data agreed well with the model predictions. The average steady state temperature observed across all 60 subjects was 40°C. The maximal temperature was observed when the device was placed over bony protrusions in the forearms of underweight subjects. From the results, it is observed that the average temperature of the skin was 40° C during the course of treatment across 60 subjects. Maximum temperature rise in worst-case use scenarios stayed below 44° C, which is clinically safe for over 5 hours of human skin contact. The resultant clinical temperature data paired well with the model data suggesting the model can be used for future transducer and ultrasound system design simulation. As a result, the device was considered to be designed for safe operation and use.
ULTRASONIC THERAPY ON A SUB-WAVELENGTH SCALE USING A SPHERICAL CAVITY TRANSDUCER WITH OPEN ENDS
Dong Zhang 1, Juan Tu 1, Xiasheng Guo 1, Zhibiao Wang 2, Faqi Li 2
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High intensity focused ultrasound (HIFU) is a noninvasive method of tissue thermal therapy, which has drawn much attention in the field of medical therapy for decades. Generally, ultrasonic focusing is achieved by lens, spherically curved transducer, or multi-element phased array. Restricted by sound diffraction, the dimension of focal zone is usually at the order of wavelength. The focusing dimension at this level cannot meet the requirement of ultrasonic treatment with high accuracy. The aim of this study is to develop an ultrasonic focusing modality by using a spherical cavity transducer with open ends. A spherical cavity transducer with open ends was designed to provide HIFU focusing, and corresponding HIFU-induced lesions were investigated for porcine liver tissues. Numerical simulations based on nonlinear acoustic equation and bio-heat equation were also applied to simulate the acoustic field and tissue lesion creation, and then compared with measured results. The measured length/width ratios of the lesion are estimated to be 2.4±0.1 mm/2.4±0.1 mm in the longitudinal section and 2.1±0.1 mm/2.4±0.1 mm in the transverse section, respectively, which indicates the measured lesion sizes are shorter than the wavelength of the source transducer. In addition, the simulated length/width ratios of the lesion cross-section along and perpendicular to the Z-axis are estimated to be 2.7 mm/2.7 mm and 2.2 mm/2.7 mm, respectively. The numerical simulations agree well with the experimental ones. Numerical simulations and experimental results both show that the acoustic field inside a spherical cavity transducer is intensively compressed to a sub-wavelength level while the intensity of sound pressure in the focal region significantly increases. If this new form of transducer could be applied in HIFU treatment in the future, the focusing precision would be enhanced a lot and the sub-wavelength therapy could be achieve to improve the treatment effects. This work is partially supported by the National Natural Science Foundation of China (Grant no’s. 81127901, 81227004, 11374155, 11174141, 11104140 and 11161120324), the National Basic Research Program 973 (Grant no’s 2011CB707900), the National High Technology Research and Development Program 863 (Grant no. 2012AA022700).
11:10 AM
ALGEBRAIC RECONSTRUCTION TECHNIQUE CONSIDERING CURVED RAY FOR SOUND-SPEED TOMOGRAPHY WITH RING-ARRAY TRANSUDER TO INTEGRATE HIFU THERAPEUTIC SYSTEM
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Our objective is to develop an ultrasound treatment and diagnosis integrated system for breast cancer. Ultrasound Computed Tomography (UCT) in imaging and High Intensity Focused Ultrasound (HIFU) in therapy was integrated to achieve ideal treatment system. Profiles of sound speed and attenuation obtained by UCT has informative parameters to correct deformation of HIFU beam dose amount in its treatment area. For development the system, we studied about UCT imaging system, particularly the sound-speed reconstruction technique in this paper. We try to develop an imaging system using a ring-array transducer with 1024-elements, multiplexer connecting 1024 to 256 and Verasonics programable imaging system with 256 channels. Firstly, to develop a reconstruction algorism, an iterative Simultaneous Algebraic Reconstruction Technique (SART) reconstruction methods was calculated and size errors were evaluated in the simulation study. In this simulation study, SART was applied to projection data calculated by a FEM simulator treating actual curved ray caused by tissue inhomogeneity. In the reconstruction process, curved ray was estimated based on a local gradient of refractive index caused by tissue inhomogenous. Secondly, the prototype ring array transducer above mentioned was constructed as shown in Fig1a. A urethane gel phantom with a diameter of 40 mm and an average sound speed of 1470m/s is used as an imaging target in water with a sound speed of 1485 m/s. The maximum estimated size error based on an assumption of straight ray was 50 % when the difference of sound speed was 100 m/s. This error increased when its sound speed difference increased. On the other hand, that error based on the refraction model was less than 20 %. And this error did not increased if its sound speed difference increased. These results indicated that consideration of bending ray is relatively important in the case of large sound speed difference. We applied this ray-trace integrated method to experimental data, and a reconstructed image was obtained as shown in Fig. 1b. Since estimated sound-speed of urethane gel is 1470 m/s in this figure, the reconstruction method is suggested to be accurate in case of sound-speed difference is relatively small. The algebraic reconstruction technique considering curved-ray was developed for an implementation to UCT imaging system. The results from our numerical simulation study suggest that size error depending on sound-speed can be reduced by reconstruction considering curved-ray. We fabricated the UCT imaging system based on the ring-array transducer, and sound-speed reconstruction from experimental data was performed with sufficient accuracy in the sound speed estimation.
HIGH FREQUENCY ANNULAR ARRAY IMAGING SYSTEM FOR HIFU APPLICATIONS BASED ON PIEZOCERAMIC THICK FILMS
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When using HIFU/HITU in therapeutic applications it is often beneficial to include a real time imaging capability. This can be accomplished in many ways, but one of the simplest and most cost effective ways is to include an ultrasonic imaging element in the therapeutic device. Most of available high frequency scanners use mechanical wobbling sector probe with fixed focus. This imposes a severe limitation on the lateral image resolution outside of the focal region. Also, the potential gain related to the encoded (Golay, chirp) transmission and post-receiving matched filter compression is partially lost due to divergent beam below the focus. New types of thick-film transducers (20 to 35 MHz), with integrated highly attenuating ceramic backing formed of porous PZT material and shaped to the required ROC, were developed. The deposition method used to manufacture the active film was pad printing. This method has been developed to manufacture high frequency transducers for medical imaging and it lends itself to high volume, low cost production. In the present solution, transducer with a diameter of 4.2 mm was fabricated, deposited on the carefully designed electrodes ring pattern on the ceramic backing. Six rings and center disk were designed to have the same active area each. The outer ring radius was equal to 2.1 mm and the gaps between the rings were close to 20 micrometers. The optimization software was developed to model and control the pressure field generated by the annular array to keep the uniform beam intensity in the range from 10 to 15 mm. The general description of the dedicated electronics driving the annular probe will be also presented. The images obtained using the thick film annular arrays will be presented. The thick film technology for piezoelectric elements supported by adapted and modified modelling offers improved quality of imaging.
10:10 AM
TRANSCRANIAL ULTRASOUND FIELD IN A PORCINE INTRACEREBRAL HEMORRHAGE MODEL
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The aims of this study were to characterize the transcranial 120-kHz ultrasound field in an established porcine intracerebral hemorrhage (ICH) model (Wagner et al., Stroke, 1996, 27:490-497), and to assess potential adverse effects caused by the pulsed ultrasound exposure. Experiments were conducted on 20 kg pigs, according to a protocol approved by the University of Cincinnati Animal Care and Use Committee. A hematoma was created in the frontal cerebral white matter by infusing 5 ml autologous blood using a catheter placed stereotactically through the parietal bone. After three hours, a 0.3 ml solution of recombinant tissue plasminogen activator (rtPA) or saline was infused through the same catheter. A 120-kHz ultrasound transducer was aligned with the hematoma which was exposed to ultrasound (80% duty cycle, 1667 Hz, peak to peak free-field acoustic pressure 600 kPa) for 30-min (Fig 1). Brains were frozen and sliced into 5-mm coronal sections for gross pathology examination. Standard neuropathological and immunocytochemical techniques were also used to assess deleterious bioeffects. Three intact pig heads with the brain removed were used for in vitro acoustic field characterization in a water tank. The transcranial acoustic pressure was measured with a hydrophone (TC4038, Reson) inserted through the foramen magnum. A thermocouple was used to measure the parietal bone temperature increase caused by the insonification. In order to assess acoustic pressure and temperature fields in the entire head, simulations based on computed tomographic scans (Bouchoux et al., Phys Med Biol, 2012, 57:8005-22) were performed for the 3 pig heads. The acoustic pressure measured in vitro at the central position of the hematoma was 503±50 kPa peak to peak (versus 600 kPa in the free field). Local acoustic pressure maxima up to 640 kPa were measured distally, and constructive interference proximal to the contralateral bone was consistently predicted by simulation (Fig 1). A parietal bone temperature increase of 2.28±0.41°C was measured in vitro. Simulations were in good agreement with measurements (2.15±0.34°C) and predicted that the peak temperature was located in the proximal bone. Visual examination of frozen brain sections from in vivo experiments did not reveal major secondary hemorrhages. The cortical gray matter cytoarchitecture of the gyri on hematoxylin and eosin and Nissl staining from the ultrasound exposed and unexposed groups were comparable. In ICH animals, the addition of ultrasound exposure with or without rtPA did not exacerbate injury in adjacent or in ipsilateral non-adjacent gyri. The hematoma was insonified reproducibly and homogeneously through the parietal bone. The in situ acoustic pressure was consistently in a range where sustained stable cavitation and enhanced thrombolysis have been observed in vitro (Datta et al., Ultrasound in Med Biol, 2006, 32:1257–67). Local maxima due to acoustic reflections in the cranial cavity were measured and simulated. Such local maxima have been observed in humans, and are a potential cause of adverse effects. However, gross pathology and histologic examination did not reveal any significant adverse effect in our acute porcine ICH model. Predicted and simulated temperatures were not likely to cause adverse effects, as confirmed by histologic examinations. This work was supported by a grant from the National Institutes of Health (R01 NS047603).

![Fig 1: Coronal frozen section of a pig brain with hematoma (a); 120-kHz ultrasound transducer placement (b); simulated ultrasound field (c and d).](image-url)
10:20 AM
ENDOTHELIAL CELL BIOEFFECTS DURING ACOUSTIC DROPLET VAPORIZATION
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This work is motivated by a developmental gas embolotherapy technique that involves injecting superheated liquid droplets that are small enough to pass through capillaries and subsequently vaporizing the droplets with ultrasound to selectively form vascular microbubbles. The vaporization of a superheated perfluoropentane (C5F12) droplet is a rapid process and results in a gas bubble that is approximately 125 to 150 times the volume of the liquid droplet from which it originated. Our objective is to examine the endothelial cell bioeffects arising from acoustic droplet vaporization, including the effects of proximity of the droplet to the cells.

HUVECs were cultured in OptiCell™ chambers until reaching confluence. Dodecafluoropentane microdroplets were added, attaining a 10:1 droplet to cell ratio. A single ultrasound pulse (7.5 MHz) consisting of 16 cycles (~2 µs ) and a 5 MPa peak rarefactual pressure was used to produce ADV while varying the vaporization distance from the endothelial layer by varying the height of the OptiCell™ chamber (2mm, 0.3mm, 0.1mm). Cell attachment and viability was significantly different if the distance was 0 µm (at the endothelial layer). Confinement of the droplet within the OptiCell™ was found to significantly increase bioeffects. Predicted pressure and shear stress fields from our previous computational models of acoustic droplet vaporization correlated with the observed damage. Increased bioeffects also coincide with unique bubble dynamics observed in our previous ultra-high-speed camera ADV experiments. Droplet concentration and flow conditions inside blood vessels may play an important role. During acoustic droplet vaporization, direct contact of droplets with cells results in localized damage, and confinement of the droplet leads to amplified damage. This work was supported by NIH grant R01EB006476.
Stroke is the fourth leading cause of death in the United States of America. Recombinant tissue-type plasminogen activator (rt-PA), an FDA approved thrombolytic therapy, is administered in only 1.5% of cases due to strict contraindication criteria. Ultrasound-enhanced thrombolysis (UET) is an adjuvant therapy that lowers the dose of rt-PA and increases its efficacy. The potential of UET has been demonstrated in vitro (Datta et al., Ultrasound Med Biol, 2008, 34, 1421-1433), ex vivo (Hitchcock et al., Ultrasound Med Biol, 2011, 37, 1240-1251), and in clinical trials (Alexandrov et al., N Engl J Med, 2004, 351, 2170-2178), but specific mechanisms explaining the enhancement have yet to be elucidated. The objective of this study is to use an in vitro model for visual observation of UET, to highlight the effects of stable cavitation and radiation force, and to correlate the action of these mechanisms with the lytic rate. An in vitro flow model was developed to observe the interaction of ultrasound with human whole blood clots exposed to rt-PA and microbubbles. Human whole blood was used to manufacture clots around a silk suture. Clots were immersed in a perfusate of flowing human fresh-frozen plasma, rt-PA, and the ultrasound contrast agent Definity®. Intermittent, continuous-wave, submegahertz-frequency ultrasound (120 kHz, 0.44 MPa peak-to-peak pressure) was used to insonify the perfusate. Ultraharmonic (UH) emissions, a key acoustic signature of stable cavitation, were monitored with a passive cavitation detector (PCD). The clot was observed with an inverted microscope. Images of the clot were recorded with a charge-coupled device (CCD) camera at a rate of 2.3 Hz for the 30-minute treatment duration. Images were post processed to determine the time-dependent clot width and root-mean-square velocity of the clot position. Definity® microbubbles were observed to coalesce during ultrasound exposure, resulting in resonant-sized bubbles (53 μm ± 19 μm). Clot lysis occurred preferentially surrounding these large bubbles undergoing sustained, stable oscillations when rt-PA was present. The instantaneous energy of UH emissions from stable cavitation was found to correlate with the lytic rate. Clots were observed to translate synchronously with the initiation and cessation of the ultrasound exposure. The root-mean-square velocity of the clot was found to correlate with the lytic rate when rt-PA and Definity® were present. The visual observations presented here suggest that the process of clot lysis during submegahertz-frequency UET is complex, with a combination of mechanisms contributing to this beneficial bioeffect. The diversity of effects during UET suggests that thrombolytic enhancement may be quite robust, and can be sustained over periods much greater than the acoustic period. However, this insonation scheme only enhanced thrombolysis in the presence of rt-PA. This work was supported by a grant from the National Institutes of Health (number R01 NS047603).
Exposure of blood clots to ultrasound and microbubbles has been previously shown to accelerate thrombus break-up [1], with applications in the treatment of ischaemic stroke and myocardial infarction. Delivery of microbubbles through the blood stream to an area of reduced flow is however a major challenge in terms of its clinical implementation. Magnetic targeting is a potential means of improving delivery by providing a local increase in the concentration of microbubbles in a blood vessel [2]. The aim of this in vitro study was to investigate the efficacy of magnetically targeted microbubbles in ultrasound-mediated thrombolysis. Porcine whole blood clots were placed in a flow phantom under a continuous infusion of magnetic microbubbles, in the presence and in the absence of a magnetic field. The clots were exposed to 0.5 MHz pulsed, focused ultrasound with peak rarefational pressures in the range 0.3-1 MPa, with a duty cycle of 4% and a pulse repetition frequency of 4 Hz. Clot diameter changes were monitored throughout the 15 minutes of treatment. Simultaneously, acoustic emissions at the clot site were recorded using a passive cavitation detection system. The results confirm that both targeted and non-targeted microbubbles considerably enhance lytic efficacy during ultrasound exposure. Significant reductions in clot diameter were observed only in samples treated with microbubbles; this was achieved even in the absence of any fibrinolytic drugs. Moreover, magnetically targeted microbubbles demonstrated significant potential to improve clot lysis over non-targeted microbubbles. Exposure to microbubbles was also associated with an increase in the energy of acoustic emissions at the clot site, both in the ultraharmonic and in the broadband frequency range. The present work suggests that magnetically targeted microbubbles are a promising method to accelerate sonothrombolysis, even in the absence of fibrinolytic drugs.

Numerous targeting strategies for ultrasound contrast agents have been developed. Targeted microbubbles with moieties attached to the surface have been designed to image inflammation, angiogenesis and to both detect and treat thrombus and tumours. Despite promising in vitro results, however, clinical translation has been limited especially for therapeutic applications and efficient targeting of microbubbles in vivo is still a considerable challenge. One factor, which is likely to have an effect on targeting, relates to the characteristics of blood. Blood is a particulate suspension, containing ~40% volume of particles mainly consisting of deformable red blood cells or erythrocytes. As such it is significantly different to water or saline – the fluids typically used in in vitro testing. Remarkably few studies however test targeted microbubbles in flowing blood prior to conducting experiments in vivo. The aim of this study was to investigate the effect of blood on two different targeting strategies: biochemical and magnetic. A 200 micrometre internal diameter capillary tube was suspended in a water tank attached to a high precision syringe pump and imaged using a 40 x water immersion microscope. The tube could be coated with avidin or a magnetic field could be brought in close proximity. The capillary was perfused with either magnetic microbubbles or biotin-coated microbubbles in water and the number of bubbles retained at a given flow rate was observed and quantified. Blood was then substituted for water and the difference in targeting examined. Each set of experiments was repeated three times. The results showed that blood has a significant impact on targeting efficiency. A 90% decrease in targeting occurred for biochemically-targeted microbubbles and a 70% decrease for magnetically targeted microbubbles. It seems likely that collision with erythrocytes is an important factor in the reduction in targeting seen in this study. The presence of cells in the suspension will both impede bubble motion, reducing the number of bubbles that can accumulate in a given time period; and potentially shield target sites in the case of biotinylated bubbles preventing adhesion. Collisions could also potentially detach adherent bubbles. No aggregation of bubbles and erythrocytes was observed in the experiments but this is another factor to consider which has shown to be important with certain types of nanoparticle. Further experimentation is required to find what elements of blood have the greatest impact and to develop strategies to overcome them; but the fact that these two very different methods of targeting suffered substantial reductions in efficiency in the presence of blood demonstrates the importance of utilising appropriate models when developing targeting strategies. It also supports the hypothesis that blood contributes significantly to the drop in targeting efficiency reported between in vitro and in vivo studies.

Figure 1, Optical microscope images (40 x magnification) of capillary tubes (200 μm ID), under the influence of a magnetic field, showing the number of magnetic microbubbles targeted in A) PBS and B) blood under the same flow conditions. Use of blood causes a decrease in the number of successfully targeted magnetic microbubbles.
Hypertrophic cardiomyopathy (HCM) occurring in 1 of 500 people can lead to sudden death in adults without prior indication. Echocardiography can be used to diagnose hypertrophic cardiomyopathy and current treatment involves invasive procedures such as surgery or catheter-based ablation, both resulting in major scaring. A novel technique using contrast echocardiography at higher than diagnostic pressure amplitudes, named Myocardial Contrast Enabled Therapy (MCET), is hypothesized to induce sparse microlesions (dead cells), which in turn thin the diseased heart muscle without scaring. An automatic characterization scheme of macrolesions, i.e. effective treated volume, induced by MCET has been implemented in order to optimize ultrasound pulse parameters, exposure duration and contrast agent dose. A total of 21 rats have been treated by MCET with Definity® (Lantheus Medical Imaging, Inc., N. Billerica, MA) injection at 5 μl/kg/min of agent infusion, 1.5 MHz ultrasound burst of 5 cycle pulses at 4 MPa from a 37.5 mm diameter single element transducer, 4.0 kHz pulse repetition frequency along with Evans blue staining indicating lethal injury of cardiomyocytes. After freezing in compound (Tissue-Tek, Sakura Finetek USA Inc. Torrance CA USA) on dry ice, each heart was sectioned to provide samples covering the entire exposed myocardial volume. Twenty-five 10 µm thick sections for each heart were cut every 200 µm into the sample to cover about 5 mm from the exposed central portion of the heart. Both brightfield (BF) and fluorescence (FL) images were taken for each tissue-section (4096x4096, 16-bit, RGB). Tissue detection and microlesion detection were first done based on 2D images to form microlesion masks, which contain the information of the outline of the heart and the dead cell regions. Image registration was then performed on microlesion masks to reconstruct a volume-based model according to the morphology of the heart. The therapeutic beam was estimated from the 3D stacked microlesions, and finally a macrolesion was characterized along the therapeutic beam.

A radially symmetric macrolesion was characterized via stepping disks of various radius determined by local distribution of microlesions. Treated groups show significant macrolesions with approximately 100 μL volume with an average of 2.5 mm radius, 6 mm length and 13% lesion density compared to zero radius, length and lesion density for the sham group. The in vivo point spread function (PSF) of the therapeutic beam was characterized first axially and then laterally. A decreasing trend of the lesion density was observed along the axial direction, possibly due to acoustic attenuation caused by contrast agents. The lateral PSF profile was obtained at the maximum of the axial response, which was regarded as the volume of interest of the therapy. The lateral full width half maximum of the therapy volume corresponds favorably with the acoustic PSF of the single element transducer. A three-dimensional evaluation scheme has been developed to characterize macrolesions, i.e. lesion size (including volume radius and length) and lesion density, for MCET to treat HCM, based on BF and FL imaging. This methodology reduces visual scoring ambiguity and provides a volume-oriented, quantity sensitive therapy evaluation. Future implementations of MCET involve formulating a set of optimized treatment parameters to create a desired total ablation based on lesion density within the target volume.
11:10 AM
EFFECT OF MICROBUBBLE-ENHANCED ULTRASOUND ON ETHANOL ABLATION OF WALKER-256 TUMOR IN RAT
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Percutaneous ethanol ablation (PEA) is a common and effective method for treating small liver cancer in clinical. Due to the quick washout of ethanol by tumor circulation, the ablative ability of PEA is limited to small tumor under 3 cm in diameter. Previously, we had found that microbubble-enhanced ultrasound (MEUS) could disrupt the tumor microvasculature and consequently block the tumor blood perfusion. This effect is supposed to prevent ethanol washout and therefore enhance PEA ablation. This study was aimed to investigate the joint ablative ability of combining MEUS and ethanol injection (EI) in Walker 256 tumor of rat. Twenty-eight SD rats bearing subcutaneous Walker-256 tumor ranging from 10-15 mm were included. The therapeutic ultrasound (TUS) transducer was comprised of an air-backed, spherically 25 mm concave disk with a 160 mm radius of curvature. The TUS was operated at the frequency of 831 KHz with the peak negative pressure of 4.3 MPa and the duty factor of 0.22%. A lipid-coated microbubbles with a bubble concentration of 9 × 10^10/mL was used for inducing acoustic cavitation at 0.1 ml/kg. We performed 5 min MEUS treatment on ten tumors followed by a 0.3 ml EI into the central tumor. The other eighteen tumors treated by the same MEUS only or the same EI only served as the controls. Contrast enhanced ultrasound (CEUS) were performed to estimate tumor perfusion before and 24h after treatment. The tumors were finally harvested for inspection of tumor necrosis rate under microscopy. The tumor necrosis rate was determined by calculating the mean necrotic percentages in three separated slices (Fig. 1e-f). CEUS showed that the tumor blood perfusion vanished or remarkably declined in all animals 24h after treatment (Fig. 1a-d). The mean CEUS peak intensity of tumor dropped 84.9% in the MEUS+EI treated tumors when compared to 30.9% in the MEUS treated tumors and 46.7% (p<0.05) in the EI treated tumors 24h after treatment. The tumor necrosis rate of the MEUS+EI treatment was 97.5%, significantly higher than that of the MEUS (66.2%) and the EI (81.0%) treated tumors. Disruption of tumor circulation induced by MEUS can greatly promote the tumor ablation ability of EI.

a-d: CEUS images of tumor from the MEUS+EI group. (a) The baseline tumor perfusion (white arrow). (b) Non-enhanced tumor (white arrow) right after MEUS treatment. (c) Ethanol injection. (d) Non-enhanced tumor after 24h. (e) Tracing (black arrow) of the whole tumor (e) and the surviving tumor (f) in the one section.
HIGH-SPEED IMAGING OF ULTRASOUND-MEDIATED BACTERIAL BIOFILM REMOVAL
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Bacterial biofilm infections on medical implants tend to have invasive treatment options with increasing recurrence rate, complications and costs with each treatment [1]. Ultrasound has been shown to be effective in bacterial biofilm disruption or enhancing the efficacy of antimicrobial agents against bacterial biofilm [2-4]. However, the mechanisms behind this behaviour are not fully understood. One of the objectives of this project is to study and report the cavitation activity or microbubbles interactions with bacterial biofilm during high frequency ultrasound exposure. We use a focused ultrasound transducer (250 kHz or 1.0 MHz) with a 50 cycles burst submerged in a water tank with de-ionized water. E. coli or P. putida biofilms are cultivated on glass coverslips for 24 hours in 1 x LB at 30 degC. Biofilm-attached coverslips are placed either horizontally or vertically in the ultrasound chamber which gives us orthogonal views to the disruption process. SonoVue® ultrasound contrast agent microbubbles are added to the ultrasound chamber filled with de-ionized water. Using a holographic laser optical trapping setup we are able to trap and position a microbubble at varying distances away from a boundary of interest. The images are taken at up to 3 Million frames per second (Mfps) by a high-speed imaging setup. Our setup is similar to that used by Prentice, P. et al. (2005) [5]. We are able to capture high-speed image sequences of one or more oscillating microbubbles in proximity to an bacterial biofilm-attached surface. The effect of ultrasound frequency, intensity and the initial stand-off distance of a microbubble to the biofilm-attached coverslip on the biofilm disruption efficacy is reported. The mechanics of ultrasound-mediated removal of bacterial biofilm has been investigated with our high-speed imaging setup using a holographic optical trapping method. Future work includes computational simulations to evaluate on this phenomenon.

REFERENCES
POSTER NUMBER: 200
SONOTHROMBOLYSIS USING MRI-GUIDED FOCUSED ULTRASOUND IN COMBINATION WITH THROMBOLYTIC DRUGS IN THE RABBIT CAROTID.
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The potential of MRI-guided focused ultrasound (MRgFUS) combined with the thrombolytic drug recombinant tissue plasminogen activator (rt-PA), to dissolve clots in the carotid of a New Zealand rabbit in vivo is evaluated. A spherically-focused transducers of 5 cm diameter; focusing at 10 cm and operating at 1 MHz was used. A pulsed ultrasound protocol was used that maintains a tissue temperature increase of less than 1 C in the clot (called safe temperature). MRgFUS has the potentials to dissolve clots that are injected in the carotid of rabbits in vivo. It was found that the time needed for opening the carotid artery using ultrasound and rt-PA was decreased compared to just using rt-PA. The time needed for opening the artery decreases with increasing acoustic intensity. With an intensity of 20 W/cm2 (SATA) which is not causing artery heating the time needed to completely open the artery was 70 mins. The proposed protocol was monitored using Magnetic Resonance Angiography (MRA) every 1 min. The proposed system has the potentials to dissolved clots using focused ultrasound and thrombolytic drugs. The next step is to apply the proposed protocols in humans.
POSTER NUMBER: 201
MRI GUIDED FOCUSED ULTRASOUND SURGERY (MRGFUS) SKULL PHANTOM
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Develop an MRI guided focused ultrasound surgery (MRgFUS) skull phantom with similar acoustic attenuation of humans. Images from an adult brain CT scan were used to segment the skull bone from adjacent cerebral tissue. The segmented model was exported in stereolithography format (STL) and was then reconstructed in ABS plastic on a rapid prototyping machine (Stratasys, USA). The cerebral tissue was mimicked by an agar-silica gel (2%-1.75% w/v) which was molded inside the skull model. The measured attenuation of the ABS skull was 16 dB/cm-MHz. The measured attenuation of the agar/silica mixture implementing brain tissue was 0.5 dB/cm-MHz. The measured agar-silica gel’s T1 and T2 relaxation times at 1.5 Tesla were 615 ms and 96 ms respectively. Due to growing interest for transcranial MRgFUS (cancer treatment and sonothrombolysis) the proposed head phantom can serve as a very useful tool for evaluating ultrasonic protocols, thus minimizing the need for animal models and cadavers.
Magnetic resonance guided focused ultrasound (MRgFUS) has shown promising results in the treatment of essential tremor. However, although the centre of the ventral intermediate nucleus (VIM) can be precisely targeted based on MR measurement, oblique lesion volumes angled to the main acoustic axes were observed in our initial patients. In this study, we reproduced the oblique focus in a skull phantom, and demonstrated solutions for correcting the obliqueness. Six patients with medication-refractory essential tremor have been treated with a MRgFUS brain system (ExAblate 4000, 650kHz central frequency, Insightec, Tirat Carmel, Israel). To reproduce the oblique focus observed in the patient treatment, a skull was filled with milk-agar based phantom and positioned similarly as in the patient treatment. MR thermometry was applied in three orthogonal dimensions separately to visualize the obliqueness of the focal volume. By default, the acoustic power from each transducer element was calculated by the ‘Uniform Intensity on the Skull Surface’ (UIS) algorithm. This power distribution was intended to evenly distribute acoustic power over the skull surface, thereby minimizing local skull heating. Then the acoustic power from each element was assigned by customized algorithms investigating different power contribution and the corresponding focal obliqueness. The algorithms include uniform intensity on transducers, and various degrees of inversion of the default UIS algorithm. The oblique focal volume was reproduced in the skull phantom in the coronal plane (Fig.1a). Since the VIM target was positioned close to the geometric focus of the FUS array, the head was off-centre in the left-right dimension relative to the array. Therefore, the obliqueness was in the left-right dimension and always angled towards the side closer to the skull. The equal distribution of power on transducers (Fig.1b) did reduce the obliqueness, but did not completely remove it. We suspect this was caused by higher reflection of acoustic power by the skull at the side further from the focus due to higher incident angles. With 50% inversion (Fig.1c) and 100% inversion (Fig.1d) of the UIS algorithm, the obliqueness was further reduced. However, this inversion may cause higher skull heating at the skull closer to the focus. The magnitude of skull heating will be investigated through phantom studies and computer simulations. In the patient treatment, we expect that there will be a practical tradeoff between the obliqueness of the focus and the feeling of pain by the patient due to the skull heating. Therefore, MR thermometry images, especially at the coronal plane, are important to visualize the focal volume at low to medium power levels. These sonications below the thermal damage threshold can then be used to adjust the power distribution to achieve a desired focal spot orientation.

Figure 1 MR thermometry images showing the focal volume in the skull phantom with a) the UIS algorithm; b) uniform intensity on transducers; c) 50% inversion of the UIS; d) 100% inversion of the UIS.
POSTER NUMBER: 203
UNFOCUSED TRANSCRANIAL INSONIFICATION OF THE MIDDLE CEREBRAL ARTERY: A SIMULATION STUDY
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Ultrasound has been shown to enhance recombinant tissue plasminogen activator (rtPA) thrombolysis efficacy. Efficient acoustic transmission through the temporal bone has been achieved at sub-megahertz frequencies (Ammi et al., Ultrasound Med Biol, 2008, 34, 1578-89) and ultrasound-enhanced thrombolysis has been demonstrated at 120 kHz (Datta et al., Ultrasound Med Biol, 2008, 34, 1421-33). The aim of this study was to evaluate simulated 120-kHz transcranial ultrasound fields in ischemic stroke patients. A transducer alignment technique based on external landmark was developed. Computed tomographic (CT) scans of 20 ischemic stroke patients were retrospectively collected with approval from the University of Cincinnati Institutional Review Board. The M1 segment of the middle cerebral artery (MCA, a common site of thrombus) was outlined on the CT images. The 120-kHz transducer was aligned with the M1 segment using an optimization scheme based on the CT data. An alternative alignment scheme was also established using external landmarks. The optimized position of the transducer was averaged over all patients relative to the canthomeatal line, which is easily assessed visually. The intracranial acoustic field and temperature maps were simulated for each patient using previously validated models based on CT data (Bouchoux et al., Phys Med Biol, 2012, 57, 8005-22). The spatial homogeneity of the insonification of the M1 segment was evaluated by the root mean square (RMS) of the variation of the simulated pressure. RMS variations of 21.5±4.3% and 23.44±5.1% were obtained for the optimized and the landmark-based positioning techniques, respectively. The relative standard deviation of the simulated pressure amplitude in the M1 segment, indicating the inter-patient variability, was 18.0% for the optimized alignment and 21.3% for the landmark-based positioning. A targeted 1 W/cm2 insonification of the M1 segment of the MCA caused a simulated temperature increase in the bone of 3.8±2.2°C for the optimized placement and 6.1±2.2°C for the landmark-based alignment. Local maxima due to reflections from the contralateral bone with amplitude up to 1.1 times the targeted zone pressure amplitude were predicted. Our results suggest that homogeneous and reproducible transcranial insonification of the thrombus in acute ischemic stroke patients can be achieved at 120-kHz. The landmark-based positioning technique is relevant in the emergency context of the management of ischemic stroke patients, and it performed similarly to the optimized transducer transtemporal placement based on CT data. This work was supported by a grant from the National Institutes of Health (R01 NS047603).

Simulated 120-kHz ultrasound field in an acute ischemic stroke subject.
POSTER NUMBER: 205
QUANTIFYING DISPLACEMENT: MR-ARFI IN THE RAT MODEL
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Transcranial focused ultrasound (FUS) in a mouse model at low frequencies (< 1MHz) has previously ignored the effect of the skull [King et al., 2013]. However, quantitative neurostimulation or BBB studies in larger animal models with smaller focal spots, such as the rat model with a focused 2.3 MHz ultrasound beam, may not be able to ignore the effect of the skull on the focal spot characteristics. The purpose is to use MR-Acoustic Radiation Force Imaging (MR-ARFI) for quantifying the focal spot characteristics as a 2.3 MHz focused beam is steered to various locations in the brain. Two rats were sonicated transcranially and electronically steered to five different locations laterally. Ultrasound was generated using the MR-compatible ExAblate 2100 2.3 MHz system (Insightec, Haifa, Israel) containing a 2D phased array originally designed for prostate treatment. The experimental setup was placed inside the bore of a 3T MR system (GE, Waukesha, WI). A 2DFT MR-ARFI sequence was used to acquire images encoded with the radiation force displacement after 5.5 ms of sonication [Chen et al., 2010]. A custom rectangular surface coil was built to optimize image quality and avoid interference with the ultrasound beam path. The coil was placed on top of the rat head below the transducer. Other imaging parameters included 8 cm FOV and 3 mm slice thickness. Figure 1 shows MR-ARFI of sonications electronically steered to five left/right (L/R) locations spaced by 1 mm. Figure 2 shows the L/R displacement profiles through the voxel of maximum displacement. Coronal MR-ARFI were performed on a second rat electronically steered to the same five L/R locations as Figure 1 as well as one axial sonication at the center location. Figure 3 shows an average displacement profile over the focal region for the five coronal and one axial images. Average maximum displacement agrees to 8% between the coronal and axial plane. Up to 40% variation in average max displacement is observed across the coronal images. The displacements in the more caudal region in Figure 3 are 2.5-3.5 um, while the displacements in the motor cortex are 0.5-1.2 um. Focal spot intensity and size vary greatly with small changes in steering in both the axial and coronal plane. Shifting the target spot laterally significantly changes the focal intensity and shape, most likely due to the varying bone thickness and curvature across the skull. We confirmed that max displacement in the axial plane corresponds well with max displacement in the coronal plane, further validating the MR-ARFI technique. We also observe that the lateral location of peak tissue displacement does not correspond exactly to the input electronic steering, suggesting that accurate targeting requires an iterative process. The maximum displacement at a particular acoustic power is not constant over different regions of the skull. MR guidance of transcranial FUS using MR-ARFI allows for precise targeting of specific brain regions and visualization of the focal region. The target location itself can strongly affect focal intensity and size; assuming constant intensity and spot size can result in ultrasound dose error. MR-ARFI enables more accurate quantification of ultrasound physical effects for ultrasound neuromodulation and other transcranial FUS applications. During neuromodulation studies, small adjustments in the subject’s position can significantly alter the focal spot location and intensity. Repeated imaging can correct or account for the shift in position and regulate ultrasound dose.
POSTER NUMBER: 206

ULTRASOUND NEUROMODULATION FREQUENCY DEPENDENCE IS NOT FULLY EXPLAINED BY CHANGING SONICATION DURATION

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Ultrasound neuromodulation is effective at generating neural responses but response efficacy is highly dependent upon sonication parameters. Previous work has shown a strong dependence on the carrier frequency, where lower frequency sonication requires significantly reduced intensities to achieve the same success rate for eliciting a motor response [King et al., 2013]. Because the source of this frequency dependence remains poorly understood, we performed experiments to examine whether controlling for sonication duration could account for this effect. Understanding the causes for frequency dependence could help elucidate the underlying mechanisms behind ultrasound neuromodulation. Six mice were sonicated with ultrasound transcranially at four carrier frequencies (300, 400, 500, 600 kHz) at seven intensity levels, while keeping the number of cycles constant (40,000 cycles) and again while keeping sonication duration constant (80 ms). The transducer and coupling column was the same as those used by King et al. 2013. Mice were lightly anesthetized at a constant level of 0.335% isoflurane at 1 liter per minute O2 throughout the experiment. Electromyograms (EMG) were measured in the forelimbs and processed to calculate the success rate for eliciting muscle contractions, defined by the EMG signal exceeding three times the noise threshold within 200 ms of the sonication. Intensities were estimated using hydrophone measurements in an open water tank. We observed a frequency dependence where lower frequencies require reduced intensities with both constant cycles and constant duration sonications (Figure 1). The frequency dependence is most evident at lower success rate thresholds (Figure 2). Maintaining constant duration sonications as opposed to constant cycles accounts for 53% and 26% of the frequency dependence for 25% and 33% success rate thresholds, as measured by the slope of the linear fit of intensity against frequency. Success rates were greater with longer duration sonications at 300 kHz, and success rates were lower with shorter duration sonications at 600 kHz (p = 0.03, one-tailed Wilcoxon signed rank test, Figure 3). Our results from attempting to replicate and extend past experiments show a frequency dependence similar to previously reported results. By directly comparing constant cycles and constant duration sonications on the same mice, we show that keeping sonication duration constant only partially explains the observed frequency dependence. Future work examining unresolved frequency-dependent factors such as standing waves and focal spot size will be necessary to fully explain the frequency dependence of ultrasound neuromodulation.
POSTER NUMBER: 207
MR-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND FOR THE TREATMENT OF TREMOR-DOMINANT PARKINSON’S DISEASE – FIRST EXPERIENCE
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MR-guided high intensity focused ultrasound (MRgFUS) is a novel, noninvasive technique for the treatment of functional brain disorders through the intact human skull at millimeter precision. The ExAblate 4000 transcranial MRgFUS system (InSightec, Haifa, Israel) uses a 1024-element phased array transducer, which is attached to the patient’s head via a standard stereotactic frame situated inside a 3T MRI scanner. It is CE certified for neurological interventions in the thalamus, hypothalamus and pallidum. Recently MRgFUS was successfully used as an alternative method to standard DBS for the treatment of a patient (m, 45), with severe tremor-dominant idiopathic Parkinson’s disease, who showed contraindication to DBS due to a bipolar disorder. During interventions the bilateral target was visually focused by MR-image guidance. In a first step, the correct focal location was verified with low, non-ablative energy, and targeted in the pallido-thalamic tract (fasciculus thalamicus). Continuous sonications lasting 15 to 25 seconds each were delivered with stepwise increased acoustic energy up to 13200 J to create thermocoagulations under real-time MR-thermometry. The sonications resulted in heating to 60°C at the focal point producing a thermal lesion. Circulating de-gassed water between the helmet shaped transducer and the patient’s head provided acoustic coupling and head cooling. After each sonication the patient was interviewed and neurologically tested. The size of the lesion was closely monitored by MR-imaging during and immediately after treatment, and again after 48 hours, at one and at three months. Clinically, MRgFUS resulted in a prompt and nearly complete suppression of tremor both at rest and under provocation, which remains to date. Rigidity and posturing did respond to treatment. The patient showed a fortification of bipolar disorder as transient side effect in relation to dynamic of surrounding oedema. MRgFUS is a novel technique for the treatment of neurological disorders that is non-invasive and does not use ionizing or radioactive radiation. The technique has been proven successful worldwide for neuropathic pain and essential tremor treatment in over 130 treated patients so far. First experience with MRgFUS suggests it to be potentially effective alternative to standard DBS implantation for the treatment of tremor-dominant Parkinson’s disease.
POSTER NUMBER: 208
HIFU OF THE BREAST CANCER STRAINS TO BE ONE OF THE STANDARD LOCAL TREATMENTS
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When the cases are strictly selected, MR guided Focused Ultrasound Surgery (MRgFUS) for the small breast cancer as the local treatment has been proved to be useful in our clinical study. It has a potential to instead of the usual breast conserving surgery. However there remains several problems to be one of the standard local treatments of breast cancer in the future. Especially in the point of treatment duration, there is a question that the using acoustic energy is too much to kill the cancer cells. The objective is to investigate of the clue to solve the problem of the treatment duration. Retrospective comparing the data of the excisionless clinical study with the usual surgical wide excision. Eighty patients were enrolled in the excisionless study and sixty seven lesions were treated. The median age was 57 years old (29 - 79). The average tumor size was 11.0mm (5 - 15). The average treatment duration was 126 minutes (41 - 246). The median follow-up period was 53 months (2 - 84). Twenty seven cases have been followed up for more than 60 months. There were no severe adverse events, local and distant recurrence cases. Five-year local recurrence rate was 0% in MRgFUS and 0.95% in the usual surgery. Five-year disease free survival was 100% in MRgFUS and 97.2% in usual surgery with a selection bias. On the other hand, the average treatment duration was 63 minutes (26 - 209) in 419 usual wide excision cases. Approximate 1,600J of the acoustic energy (40w acoustic power x 40 seconds sonications duration) was usually used per spot. Moreover it took 80 seconds to cool the breast skin. The cooling duration which is double of the sonication duration was the time determining factor of this treatment. The treatment duration should be made be a half of the present one to make MRgFUS instead of the usual surgery. Does need such as long cooling duration and much acoustic energy? Rising of temperature at the target tumor may be good enough with 1,000J to make the tumor be in complete thermal coagulation in the verification spot. Is thermal coagulation needed to kill the cancer cells immediately? Isn’t enough to lead gradually the cancer cell into lytic necrosis? Is adequate the extent of spots overlapping? We must make several efforts to shorten the treatment duration after closing of the present study.
POSTER NUMBER: 209
ABLATION OF LIVER METASTASES USING A TOROIDAL TRANSDUCER CAN BE RELIABLY MONITORED WITH ULTRASOUND IMAGING
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Evaluate speckle changes in sonograms when ultrasound-guided High Intensity Focused Ultrasound (HIFU) is applied in the liver using a toroidal-shaped transducer for treating liver metastases. The therapeutic transducer is a piezocomposite material operating at a frequency of 3 MHz. The transducer has a toroidal shape of 70 mm in diameter. The radius of curvature was 70 mm. An ultrasound-imaging probe was placed in a central circular opening of 26 mm in diameter. The HIFU transducer was divided into 32 rings of 78 mm2 each. Using a 32 channels amplifier with a phase resolution of 1.4 degrees, it was possible to change the location and dimensions of the focus to maximize the dimensions of ablations. Patients with liver metastases, who had been scheduled for elective surgical resection of their tumors, were recruited to a non-randomized Phase I-II study. The response to HIFU was assessed just after ablation using conventional ultrasound images and compared directly with histological analysis. Eighteen patients were treated. Six patients were included in Phase I and 13 patients were included in Phase II. It has been demonstrated that the demarcation between ablated and non-ablated tissue was clearly apparent in sonograms and histology. The dimensions measured on sonograms were correlated (r=0.88) with dimensions measured during histological analysis. The treatment of liver metastases of up to 2 cm in diameter was performed in 130 seconds. There were no major complications. Sonograms predicted complete ablation in all cases and this was confirmed by histological analysis. In sonograms, a cloud of ebullition appears momentarily (approximately during 1 min) at the location of the lesion just after the end of each HIFU exposure. Approximately five minutes after the end of HIFU exposures, the lesion appears on sonogram as a hyperechoic zone at its center and a hypoechoic zone at its boundaries. These changes were correlated to the thermal dose deposited in tissues. If the thermal dose is close to the threshold for creating an ablation (14400 seconds) it appears hypoechoic in sonograms. Conversely, when the thermal dose is more than 1000 times the threshold for creating an ablation it appears hyperechoic in sonograms. There was a high contrast (on average 14 dB) and a sharp demarcation between the hypoechoic zone, which was always located at the boundaries of the lesion, and the untreated liver (about 200 µm from histological findings). This high contrast allows delimitating precisely the contours of the HIFU lesion. The contrast between hyperechoic zones and untreated liver was on average 2 dB. The predominant histological characteristic of HIFU lesions in hypoechoic zones was the contraction of the nucleus in hepatocytes (caryopycnosis) as well as a homogenization of the cytoplasm. Histological characteristics of HIFU lesions in hyperechoic zones were the presence of several cavities, always located in the centrilobular veins. These cavities were due to high pressures of acoustic waves as well as boiling. This toroidal HIFU transducer can achieve fast (130 seconds for ablating a tumor of 2 cm in diameter), selective, safe and well-tolerated liver ablations. Due to the specific geometry of the transducer, ablations were visible with high contrast in sonograms. Ultrasound guidance of the treatment makes it possible to obtain an excellent therapeutic efficacy due to objective evaluation of the actual treated region. This HIFU treatment may have a role in treating unresectable colorectal liver metastases and may also be used in conjunction with resection to extend its limits.
POSTER NUMBER: 210
WAKEFULNESS HIFU THERAPY FOR HCC WITH NO ANESTHESIA
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We have done wakefulness HIFU therapy for HCC with no anesthesia about five years. To find out the factor of HIFU therapy was effective or not, we did statistical analyze about patients. HIFU therapy was done from 1 to 3 times within a week. 59 patients received HIFU therapy. (Male:35 Female:24 Age:70.8±8.3) And we selected 52 patients who were not abandoned HIFU therapy. (Male:29 Female:23 Age:70.5±9.1) 7 patients were abandoned HIFU therapy because of pain during therapy or could not stop breath or difficult to visualization the target. After therapy we did contrast enhanced ultra sonography (CEUS) and patients were divided into three groups.

Group A: Completely treated patients. 22 patients (Male:7 Female:15 Age:71.8±6.6)
Group B: Effective but not completely treated patients. 14 patients (Male:12 Female:2 Age: 69.1±11.4)
Group C: Not effective patients. 16 patients (Male:10 Female:6 Age:73.3±5.7)

We did analysis among three groups about age, sex, tumor location, size of tumor, depth, thickness of subcutaneous fat, liver function, session number, treatment route(from intercostals or not).

Depth(p<0.01), thickness of subcutaneous fat(p<0.01), session number(p=0.02), treatment route(p=0.02) were significant difference among three groups.

We suggested that their factors depend upon the effectiveness of HIFU therapy for HCC.
CLINICAL USEFULNESS OF HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) THERAPY FOR PANCREATIC CANCER
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High-intensity focused ultrasound (HIFU) as new advances in therapy for unresectable pancreatic cancer (PC) are expected. HIFU therapy with chemotherapy is being promoted as new method to control local advance by cauterizing tumor and achieve relief of pain caused by PC. We evaluated the therapeutic effect of HIFU in locally advanced pancreatic cancer and metastatic cancer, and the possibility of usefulness of HIFU therapy for PC. We treated PC patients using HIFU therapy as optional local therapy as well as systemic chemo / chemo-radiotherapy, with whom an agreement was obtained in adequate IC, from the end of 2008 in our hospital. This study took approval of member of ethic society of our hospital. HIFU device used is FEP-BY02 (Yuande Bio-Medical Engineering. Beijing, China). The subjects were 30 PC patients, i.e. 16 cases in stage III, 14 cases in stage IV. All pancreatic masses were visualized by HIFU ultrasound monitor system. Treatment data in Stage III and IV were followed; mean tumor size was 31.8 vs 30.1 mm, mean treatment sessions: 2.6 vs 2.7 times, mean total treatment time: 2.7 vs 2.2 hours, mean total number of irradiation: 2801 vs 1769, respectively. There was no significant difference in treatment data between two groups. The effects of HIFU therapy in Stage III and IV were the following; the rate of complete tumor ablation was 87.5 vs 71.4%, the rate of symptom relief effect was 80 vs 56%, the effectiveness of primary lesion was CR:0, PR:2, SD:13, PD:1 vs CR:0, PR:2, SD:10, PD:2, primary disease control rate (DCR) more than SD was 93.8% vs 78.6%. Mean survival time (MST) after HIFU therapy was 14.1 vs 7.2 month, respectively (p<0.01, p=0.0009). Combination therapy of HIFU with chemotherapy in Stage III was better result than common GEM single agent chemotherapy (MST: 5.7month). This study suggested that HIFU therapy has the potential of new method of combination therapy for non-metastatic PC.
MAGNETIC RESONANCE GUIDED FOCUSED ULTRASOUND SURGERY (MRGFUS) OF BONE METASTASES: FROM PRIMARY PAIN PALLIATION TO LOCAL TUMOUR CONTROL

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To evaluate the clinical performance of MRgFUS in primary pain palliation of painful bone metastases and in local tumour control. We enrolled 26 consecutive patients (female/male 12/14; age: 64.7±7.5yrs) with painful bone metastases. Before and 3 months after MRgFUS treatment pain severity and pain interference scores were assessed according to Brief Pain Inventory-Quality of Life (BPI-QoL) criteria and patients underwent both CT and MRI. Local tumour control was evaluated according to lesion size, density and perfusion at CT, dynamic contrast enhancement at MRI (Discovery 750HD, GE; Gd-Bopota, Bracco) and metabolic activity at PET or scintigraphy. Patients were classified as responders or non-responders. No treatment-related adverse events were recorded during the study. As statistically significant difference between baseline and follow-up values for both pain severity and pain interference scores was observed (p<0.05). Increased bone density was observed in 9/26 (34.6%) patients. Non-Perfused Volume values ranged between 20% and 92%. There was no difference in NPV values between responders and non-responders (46.7±24.2% [25 – 90 %] vs. 45±24.9% [20 – 93 %]; p=0.7). In 6 patients (5 prostate and 1 breast primary cancer) there was nearly absence of metabolic activity after treatment (mean SUV=1.2). MRgFUS can be safely and effectively used as the primary treatment for pain palliation in patients with painful bone metastases; moreover our experience demonstrated also a potential role for the MRgFUS in local tumour control.
POSTER NUMBER: 213
MRI TEMPERATURE MAP RECONSTRUCTION DIRECTLY FROM K-SPACE WITH COMPENSATION FOR HEATING-INDUCED GEOMETRIC DISTORTIONS
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Proton resonance frequency (PRF) change is used to measure tissue heating, but also distorts the image and causes geometric distortions in temperature estimates in the same manner as other chemical shift distortions if left uncompensated. We propose an algorithm that produces PRF temperature maps free of these distortions by fitting a signal model directly to acquired k-space data that accounts for PRF-induced phase both up to and during the readout. We hypothesize that compensating for chemical shift distortions will improve the accuracy of temperature change and thermal dose measurements. k-Space data of a simulated phantom with a Gaussian-shaped phase shift corresponding to a 33°C temperature rise were generated for a spiral trajectory with 16 interleave with 16 ms readout, 200 x 200 image matrix, 20 cm FOV, and 8 receive coils. Frequency shifts from the temperature rise were used as off-resonance field maps in synthesizing the k-space data. EPI and spiral data of a heated gel phantom were acquired at 3T (Philips Achieva, Philips Healthcare, Best, Netherlands) with 5 receive coils and EPI/spiral TR 24 ms/32 ms, TE 16 ms, FOV 20 cm, EPI/spiral matrix size 200 x 196/200 x 200, slice thickness 7 mm, EPI factor 7, and 16 spiral interleave with 16 ms acquisition readout. The phantom was heated for 41 s using a Philips Sonalleve HIFU system with a 4 mm treatment cell size, 110 W power, and 1.2 MHz frequency. EPI temperature maps were computed by conventional complex phase difference. Temperature maps from spiral data were reconstructed directly from k-space with and without compensating for chemical shift. Temperature maps used for thermal dose calculations were reconstructed at a 96 x 96 matrix size for both EPI and spiral data. Thermal dose maps were computed from the mean temperature change in each pixel. Without chemical shift compensation, the 33°C true peak of the simulated hotspot is estimated as 36°C; this overestimation is corrected using the proposed algorithm, which accurately estimates the peak as 33°C. The peak temperatures reconstructed from the phantom heating experiment with the same spiral acquisition trajectory without and with chemical shift compensation were 37°C and 33°C, respectively. Maximum thermal dose estimated from the spiral temperature maps without chemical shift compensation is 2.5 times higher than the spiral estimate with compensation and 2 times higher than the EPI estimate. The maximum dose estimated from the (higher pixel bandwidth) EPI images is a factor of 1.25 times higher than the chemical-shift compensated spiral estimate. However, the EPI data have not been compensated for heating-induced distortions. We presented a reconstruction algorithm that compensates for distortions resulting directly from heating. Accounting for this off-resonance effect reduces error in simulated and phantom heating estimates. Small errors in temperature more than double thermal dose estimates. Therefore, compensating for these errors can have a positive impact on clinical outcomes due to more accurate dosimetry.

Figure. A) Temperature maps and profiles across hotspot for simulation (top) and phantom heating data (bottom). True temperature (simulation only) and temperature reconstructed without and with chemical shift (CS) compensation are shown. B) Thermal dose maps calculated from temperature curves from EPI (left), and spiral without (middle) and with CS compensation (right) in cumulative equivalent minutes (CEM).
POSTER NUMBER: 214
CAVITATION DYNAMICS OF MAGNETIC MICROBUBBLES USING PASSIVE ACOUSTIC MAPPING
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Magnetic targeting of specially-formulated microbubbles has been demonstrated successfully for drug delivery and gene therapy applications both in vitro and in vivo. The ability to manipulate the location and concentration of microbubbles using an externally-applied magnetic field has numerous advantages which lend themselves to these and further applications such as sonothrombolysis, including more targeted initiation of cavitation activity, higher local concentration of a drug (which may be encapsulated or attached to the shell of a bubble), and more consistent supply of cavitation nuclei, reducing the effects of flow. However, before such techniques may enter clinical practice improved understanding of the effect of magnetic confinement on microbubble dynamics is required, in addition to the refinement of clinically-applicable treatment monitoring methods. In the present work, Passive Acoustic Mapping (PAM) was used to investigate the response of magnetic microbubbles to high intensity ultrasound, and the effects of magnetically confining the microbubbles on the type, sustainability, intensity and spatial distribution of cavitation activity. Magnetic microbubbles were produced from a phospholipid (DSPC) and a hydrocarbon suspension of superparamagnetic iron oxide nanoparticles, which were dispersed in water using an ultrasonic cell disruptor. The probe of the disruptor was then placed at the air-liquid interface as to entrain gas, producing magnetic microbubbles with mean diameter of 2µm and concentration on the order of 10^7 MBs/mL. Samples of the magnetic microbubble solution were placed in a channel formed in a polyacrylamide tissue phantom, beside which either a 1.5T neodymium magnet or non-magnetic stainless steel bar was placed in an acoustic absorber cast from polyurethane (Aptflex). The microbubble-containing channel was aligned with the focus of a 500kHz HIFU transducer featuring a rectangular cutout through which a linear array imaging probe was aligned. The HIFU transducer was used to excite the microbubbles at a range of peak negative focal pressures (0.1-1.0MPa), and pulse lengths (1-100,000 cycles), while the imaging array passively recorded 64 channels of acoustic emissions (1-1,800Hz frame rate). The acoustic emissions captured in each frame were mapped using the PAM algorithm and subsequently analysed in space, time and frequency. Spatial analysis of passive maps confirmed that static samples of acoustically active magnetic microbubbles could be successfully retained against buoyancy by application of a magnet, manifesting as a shift in the location of maximum cavitation energy in the maps. Overall intensity of cavitation (defined as average voxel energy value for a given area and time period) was consistently higher when the magnet was applied, suggesting that a greater number density of microbubbles were also retained in the focal region (from elsewhere in the channel) during or after sample injection. Future work will evaluate any impact on the sustainability and frequency spectra of cavitation activity, as well as incorporating the effects of flow. Passive Acoustic Mapping was applied to a new form of magnetically-targetable microbubble in an in vitro model. Application of a magnet under HIFU excitation showed clear changes in the spatial distribution and intensity of cavitation activity in the maps, suggesting that cavitation activity may be successfully targeted and a greater number density of microbubbles achieved using this technique. Potential applications for the method include targeted cavitation-enhanced therapies and drug delivery, with PAM forming the basis of a clinical treatment-monitoring system.
ENDOGENOUS MRI BIOMARKERS FOR THE EVALUATION OF HIFU TUMOR TREATMENT
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The clinical application of MR-guided HIFU for the ablation of malignant tumors requires accurate treatment evaluation to determine the extent of HIFU-induced tissue damage. We have previously assessed different MR methods for this purpose. These methods were all based on endogenous MR contrast, since the use of contrast-enhanced MRI may be unfavorable if re-treatment needs to be performed directly after treatment evaluation. It has been reported that HIFU treatment could induce entrapment of Gd3+ in the tumor tissue and that the presence of MR contrast agent during treatment introduces errors in the MR thermometry 1. The first method for HIFU evaluation based on endogenous contrast consists of multiparametric cluster analysis based on the conventional MR parameters T1, T2 and Apparent Diffusion Coefficient (ADC) 2. Secondly, we have studied the more advanced MRI parameters amide proton transfer (APT) imaging and T1ρ mapping for their sensitivity to HIFU-induced tissue necrosis. The aim of the current study was to quantitatively evaluate HIFU-induced changes in all assessed contrast parameters to determine which parameters are most suitable for evaluation of HIFU treatment and therefore might be considered for clinical translation. All MRI experiments were performed at 7 Tesla in CT26 tumor-bearing Balb/c mice (n=42 in total). In each of the studies, MRI was performed before (n=13-15/study), directly after (n=13-15/study) and at 3 days after (n=7-8/study) HIFU. Partial tumor treatment was performed outside the MR system with an 8-element therapeutic ultrasound transducer (TIPS, Philips). Ablation settings were: power 12 W, frequency 1.4 MHz, duty cycle 50 %. To assess the sensitivity of each parameter to HIFU-induced changes, average tumor parameter values were determined at each time point. The change in average parameter values after HIFU treatment was tested for significance with a paired t-test. Representative results of each evaluation method are displayed in Fig A. Distinct regions of HIFU-treated tumor tissue were defined by the cluster analysis that corresponded to non-viable tumor tissue in histology. The correlation between histology-derived non-viable tumor fractions and HIFU-treated tumor fractions derived from the multiparametric analysis based on T1, T2 and ADC was higher at 3 days after HIFU (r=0.80) than directly after HIFU (r=0.62). At both time points after HIFU, a shift toward lower APT-weighted signals and T1ρ values in the tumor tissue was observed. Average parameter values in whole tumor ROI’s at the different time points are displayed in Fig B. Directly after HIFU, the only significant change was observed for the APT-weighted signal. At 3 days after HIFU, both the APT-weighted signal and the T1 were significantly decreased. The sensitivity of the multiparametric cluster analysis to HIFU-induced necrosis was highest at 3 days after treatment. Although only partial tumor ablation was performed, global analysis of the average parameter values in the whole tumor already showed a significant difference between T1 and the APT-weighted signal before and after HIFU. The analysis of parameter changes after HIFU indicate that inclusion of APT imaging to the multiparametric analysis might provide enhanced sensitivity to HIFU-induced changes directly after HIFU treatment. Therefore, in the near future, we will investigate the efficacy of treatment evaluation with the use of a time-effective MRI protocol consisting of T1, T2, ADC, APT and T1ρ imaging.

A) Top: Representative results of the multiparametric MR analysis based on T1, T2 and ADC, showing distinct regions of MR-defined HIFU-treated tumor tissue, which corresponded to non-viable tissue in histology.
B) Average parameter values in the tumor tissue at all time points. The P-values result from paired t-tests between before and after HIFU.

1 Hijnen et al, Focused Ultrasound 2012
2 Hectors et al. MRM 2013
3 Hectors et al. ISMRM 2012

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POSTER NUMBER: 216
T2-BASED TEMPERATURE MONITORING IN ABDOMINAL FAT DURING MRgHIFU TREATMENT OF PATIENTS WITH UTERINE FIBROIDS
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Near-field heating is a serious problem in the treatment of uterine fibroids (UF) with MRgHIFU and may cause burns and necrosis of healthy tissue. Proton Resonance Frequency (PRF) shift thermometry is commonly used to monitor the heating during treatment. While effective in water-based tissues, PRF thermometry cannot detect temperature change in the subcutaneous abdominal fat. Previously, Baron et al. (Proc 21st ISMRM, 2013: 230) described the use of T2 mapping to measure near-field heating and demonstrated its application in a Philips HIFU system. The goal of this study was to investigate near-field heating in patients treated with the InSightec fibroid system. Accurate measurement of near-field heating in adipose tissue could lead to shorter treatments by eliminating unnecessary cooling time between sonications while preventing injury in healthy tissues. Fat temperature mapping was performed during three UF treatments using the ExAblate 2100 system (InSightec, Israel) with sonication energy up to 5000 J and duration of 20 s per sonication (86, 98 and 149 sonications total). T2-maps of abdominal fat were acquired between sonications (14, 13 and 11 images per patient, single coronal oblique slice (fig. a), double echo Fast Spin Echo, water suppression, TR=1500ms, TE=35/181 ms, 15 sec acquisition time). Maps of temperature change were generated from Gaussian-filtered T2 maps, assuming a T2 change of 5.17 ms per °C (Baron et al.) We observed a measurable change in T2 of fat tissue in the path of the ultrasound beam (fig. b,c). The areas of the increased temperature after a number of sonications matched the intersection of the US beam with the slice (fig. d). Fig. e shows the total change in temperature for the same time points. We observed temperature increase up to 18°C and sustained heating of more than 10°C for the duration of the treatment (fig. f). Our preliminary results demonstrate the feasibility and importance of monitoring near-field heating in fatty tissues using T2 mapping. During treatment with the ExAblate system, near-field heating can reach high temperatures and cumulative thermal dose that may cause necrosis of adipose tissues (Dewey, W. C., Int. J. of Hyperthermia, 1994; Diederich, C. J., Int. J. of Hyperthermia, 2005). The limitations of the current study include relying on previously reported calibration data and lack of absolute temperature measurement. The baseline temperature of the subcutaneous fat may be significantly lower than the core body temperature due to limited blood perfusion and cooling from the transducer oil bath (cooled to 14°C). More frequent measurements will allow better quantification of the cumulative thermal dose and the rate of cooling after the sonication.

(a) placement of the T2 mapping slice; (b) baseline fat T2 map; (c) T2 map during the treatment; (d) temperature change between subsequent measurements and (e) from baseline. Intersections of the beam axes and the slice are shown as circles; (f) measured temperature change from baseline (blue bars) for the location marked with a cross in (d,e) and energy of sonications (red bars) over the course of the treatment
MR-guided high-intensity focused ultrasound (HIFU) is a noninvasive technique for the treatment of painful bone metastases. Recent studies have shown that aggressive treatment (increased temperature and duration) is promising for local tumor control (Napoli, Invest Radiol 2013, 48(6):351-8). Proton resonant frequency shift (PRF) thermometry is commonly used for temperature monitoring in water-based tissues, but fails to detect temperature changes in tissues with high lipid content, such as bone marrow. Current clinical protocols rely on measurement of temperature change of adjacent muscle to estimate the temperature of the bone. This can lead to poor temperature accuracy in the treated area and sub-optimal ablation. Heijman (FUS Symposium 2012, p. 164) demonstrated the feasibility of T2-based MR thermometry in extracted samples of trabecular bone and yellow bone marrow. In this study, we investigated if T2-based temperature mapping could be used to determine the temperature within ex vivo trabecular bone during HIFU ablation. We also examined if T2-changes caused by the ablation were reversible and measured the patterns of heating and tissue damage in the trabecular bone. Two ex vivo experiments were performed on epiphysis segments of bovine femur with the birdcage head coil on a 3T scanner. Three fiberoptic sensors were placed into drilled holes within the trabecular bone (fig. a). The femur segments were sonicated with the ExAblate 2100 conformal bone system (InSightec, acoustic power = 17.6 W, sonication time = 60 secs repeated 8 times). Bone marrow T2 was quantified by using a double-echo fast spin-echo sequence with water suppression (TE = 35/181 ms, TR = 723 ms, ETL = 40, FOV = 24 cm, 10mm slice thickness, acquisition time = 8 s.) Images were acquired during heating and cooling, and after the sample reached room temperature. Fig. (b-d) show the T2 change during heating and cooling. Fig. (e,f) show the T2-change of another bone segment during heating and after it returned to room temperature. The profiles through the heated region (g,h) show residual elevated T2 of about 35 ms in the ablated area. Plotting the measured T2-change over the fiberoptic measurements (fig. i, red), showed a linear relationship (5.7 ms per °C) during the heating stage of the experiment. The T2-change during cooling (fig. i, blue) showed a reduction with temperature, but did not follow the same linearity as during heating. We have shown that T2-based ablation monitoring in the red marrow in trabecular bone is feasible. The linear relationship between T2-change and temperature could be used to quantify the temperature during heating in this range. Our results are consistent with previously published data in marrow and subcutaneous fat. The calibrated thermometry data showed propagation of thermal energy within the trabecular bone. The area of residual T2 elevation after cool-down matched the area of the heating. Elevated T2 values in the areas of thermal damage could allow for evaluation of treatment effects during bone MRgHIFU therapy.

(a) the bone sample with embedded fiber-optic sensors;  
T2 maps of sample 1 (b) before heating, (c) during heating, and (d) during cool-down;  
T2 maps of sample 2 (e) during heating, and (f) after reaching room temperature;  
(g) thermal profile of the sample along the line, shown on (e);  
(h) T2 profile after reaching room temperature;  
(i) temperature change measured by 3 probes and T2 change at corresponding locations during heating (red) and cooling (blue).
POSTER NUMBER: 218
QUANTITATIVE EVALUATION OF STONE FRAGMENTS IN EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY USING A TIME REVERSAL OPERATOR
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Extracorporeal shock wave lithotripsy (ESWL) has been a popular modality to noninvasively break kidney stones for thirty years. The fine fragments less than 2 mm in size can be discharged by urination, which determines the success of ESWL. Although ultrasonic and fluorescent imaging is used to localize the calculi, it’s challenging to monitor the stone comminution progress, especially at the late stage of ESWL when fragments spread out as a cloud. The lack of real-time and quantitative evaluation makes the procedure semi-blind and results in either under- (remaining stones for re-sessions) or over-treatment (more renal injury) after the legal number of pulses required by FDA. The decomposition of the time reversal operator (DORT) method [C. Prada, S. Manneville, D. Spoliansky, and M. Fink, J. Acoust. Soc. Am. 99 (4), 2067-2076 (1996)] provides the ability to detect point-like scatterers, and the number of non-zero eigenvalues of the time reversal operator is equal to that of the scatterers. Echoes from fragment(s) with varied diameter of 2-12 mm and positions and then picked up by an array of hydrophones were simulated using k-space method. Only one non-zero eigenvalue for a single stone showed the stability of DORT method. Even with the presence of two stones in different sizes our algorithm can also figure them out as shown in Figure 1. In addition, there is a good correlation between the amplitude of eigenvalues and detectable target size. It suggests that DORT method is effective in identifying the fragments in a stone cluster in real-time since computation is not time consuming. Further development of a detection system and evaluation of its performance both in vitro and in vivo during ESWL is necessary for application.

![Figure 1. Eigenvalues of three types of stone clusters.](image)
POSTER NUMBER: 219
SUITABILITY OF THE ECHO-TIME-SHIFT METHOD AS LABORATORY STANDARD FOR THERMAL ULTRASOUND DOSIMETRY
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Ultrasound therapy is a promising, non-invasive medical application already being used e.g. for physiotherapeutical applications, or lithotripsy (the destruction of kidney stones). More recent applications for surgery and therapy like treatment of cancer, bone repair and treatment of stroke show the great potential of high intensity focused ultrasound (HIFU). To ensure a save clinical application and repeatability of treatment measurable and traceable quantities are necessary, which leads to the requirement of a reliable laboratory dosimetry standard. We evaluated the suitability of the echo-time shift method for laboratory dosimetry and quality control, especially its general suitability, uncertainties and limitations at both laboratories. One of the most promising methods is measuring temperature rise caused by the therapeutical ultrasound device with diagnostic ultrasound in a phantom located in a water bath for laboratory dosimetry. A change of temperature causes a change in the speed of sound as well as a thermal expansion and therefore a time-shift in the measured backscattered RF-signal. Hence, the time-shift can be used to calculate the difference to a baseline temperature when the conversion factor k is known. The method however has its limitations. Too high temperature changes lead to a nonlinear change in speed of sound with temperature and too small temperature change between two diagnostic ultrasound frames are not detectable. One of the main contributions to the uncertainty budget of this method is the uncertainty of the conversion factor k. This factor is critically dependent on the linearity of speed of sound as a function of temperature. Further contributions are composition and age of the phantom material and temperature gradients within the phantom during measurements. Since the speed of sound does not change linearly with temperature the conversion factor can only be considered to be constant with a ten percent uncertainty up to approximately 45 °C. During measurements with HIFU other uncertainties like the accuracy of positioning the field of the diagnostic ultrasound probe within the focal region of the therapeutic ultrasound transducer and uncertainties of thermocouples when comparing temperature differences have to be added. An overall accuracy of 85 % can be reached when taking all uncertainties into account. The echo-time-shift method is a fast, cheap and comparatively accurate method for thermal ultrasound dosimetry. With small variances in the experimental setup the echo-time shift method hence in general is suitable to be used for laboratory dosimetry as well as for clinical quality control for HIFU devices.
POSTER NUMBER: 220
INITIAL EXPERIENCES WITH MR THERMOMETRY DURING PALLIATIVE TREATMENT OF BONE METASTASES WITH MR-HIFU
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Magnetic resonance guided high intensity focused ultrasound (MR-HIFU) is a non-invasive thermal therapy modality monitored by MR thermometry (MRT). MR-HIFU is used for palliative treatment of painful bone metastases by ablating periosteal nerves. The MRT method exploits the temperature-dependent water proton resonance frequency shift (PRFS) to calculate temperature changes from signal phase differences between subsequent images. The application in bone metastases is challenging since it involves various anatomies and highly variable MRT conditions in terms of spatiotemporal field heterogeneity. Moreover, cortical bone suffers from lack of MR signal and monitoring with PRFS is limited to the adjacent aqueous soft tissue. The objective of this study was to investigate the performance of PRFS MRT during MR-HIFU of bone metastases in patients. MRT datasets were used from 8 MR-HIFU (Sonalleve, Philips, Vantaa, Finland) treatment sessions in 7 patients who were referred to our hospital for palliative treatment. The patients provided written informed consent with the use of the acquired data for scientific purposes. The lesions were located in the pelvis (n=5) and thorax (n=2), one patient (pelvis) was treated twice. Two treatments were performed under conscious sedation, 6 under deep sedation. A total of 148 volumetric sonications were performed with (median, range) treatment cell size of (4,2-8)mm, power of (100,10-160)W and sonication time of (16,7-20) s. The MRT scans were multi-slice (2cor, 1sag, 1tra) 2D gradient-echo EPI water-selective scans (voxel size=2.5x2.5x7mm3, dynamic scan duration=2.3s). During the last 2 treatments a higher resolution scan was used for a total of 40 treatment cells (voxel size=1.5x1.5x5.8mm3, dynamic scan duration=5.7s). The MRT images of all sonication were scored for the occurrence of artifacts. The most prominent artifact observed was caused by respiratory motion (80%), even in the pelvis. During respiration the whole abdominal area moves, inducing periodical phase changes that cause time-varying artifacts in MRT images. These artifacts were observed to be less prominent in patients under deep sedation and were not observed in 1 treatment where the lesion was low in the pelvis. Arterial ghosting (57%) was observed in both pelvis (iliac arteries) and thorax (aorta). In pelvic treatments performed in supine position the ghosting hampered the visualization of the heat build-up at the focal spot in the transverse plane. Time-varying field heterogeneities (49%) were observed around tissue-air (bowels, rectum, lungs) and tissue-bone interfaces. Lastly, artifacts due to either gross patient motion or muscle contraction due to sonications were observed (38%), also in patients under deep sedation. The most prominent source of artifacts in PRFS MRT during MR-HIFU of bone metastases is respiratory motion. This problem may be tackled by using multi-baseline1 or referenceless MRT2. Deep sedation resulted in more regular and slower respiratory motion, but did not eliminate muscle contractions due to sonications. Arterial ghosting is location dependent and can possibly be eliminated by saturating the signal locally. Field heterogeneities near air cavities and cortical bone in combination with motion may lead to artifacts that can be interpreted as temperature changes at tissue interfaces. When interpreting temperature maps clinicians should be aware of this. Reliable thermal doses are difficult to determine when these artifacts have occurred in the MRT.

This research was supported by the Center for Translational Molecular Medicine (HIFU-CHEM)
1 Vigén et al. MRM, 2003, 50:1003-1010
2 Rieke et al. MRM, 2004, 51:1223-1231

Overview of artifact occurrences per patient in percentages of the number of sonications.
* = same patient; † = conscious sedation, others were under deep sedation.
POSTER NUMBER: 221
EFFECT OF MRI GUIDED HIFU ON THE T2 RELAXATION OF FAT
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MRI-guided high intensity focused ultrasound (MR-HIFU) allows non-invasive ablation of deep tissues without heating surrounding areas. MR-HIFU uses MRI to precisely target the HIFU beam and to monitor the temperature of the target and the surrounding regions. A novel application of MR-HIFU is ablating fat tissue to reduce the metabolic activity of fat deposits and reverse the development of obesity, diabetes and metabolic syndrome. Visceral fat may play a central role in fatty liver disease because of its proximity to the hepatic portal vein, allowing liver cells to be directly exposed to the metabolites and signaling molecules from visceral adipocytes. Animal studies have shown that surgical reduction of visceral fat volume can reduce liver fat accumulation and improve glucose tolerance. Unfortunately, accurate monitoring of HIFU-induced temperature changes in fat is difficult with the Proton Resonance Frequency Shift (PRFS) method used for most MR-HIFU procedures. To overcome this limitation, we used T2 mapping to evaluate the effects of HIFU on fat while using PRFS to monitor the temperature of surrounding tissues in real time. MR-HIFU was performed on a 1.5 Tesla whole body scanner (Philips IngeniaTM) equipped with a Philips SonalleveTM HIFU system. The 256-element HIFU transducer is integrated into the MRI table and can be translated and rotated to aim the HIFU beam at specific targets within the body. MR-HIFU was used to ablate perinephric visceral fat under MRI guidance in two obese male Sprague-Dawley rats weighing 650 and 510 g. One animal was treated with 70 watts of acoustic power applied for 16 seconds and focused onto a target area measuring 2 by 2 by 10 mm. The other rat was treated with 40 watts of acoustic power applied for 16 seconds and focused onto a target area measuring 4 by 4 by 10 mm. Real time MRI thermometry (2.5 second temporal resolution) via PRFS was used during the HIFU ablation to monitor temperature in nearby tissues, such as in the kidneys, muscle, skin, etc. Thermometry was performed in two orthogonal planes, one along the HIFU beam path and the other perpendicular to the beam. Fat tissue does not display an adequate PRFS dependency on temperature, so heating in the fat was assessed by measuring the T2 before and after HIFU ablation. T2 maps were acquired with a multi-echo sequence (scan time of 1 minute and 22 seconds) with 8 echo times ranging from 21 to 266 ms. At 1.5 T, the T2 of fat was 126.9 ms before ablation. During the HIFU ablation, some heating of the surrounding tissue was observed, reaching a maximum temperature of approximately 55o C. As expected, no temperature change was detected in the fat with the PRFS-based sequence. After ablation with 70 watts of power, the T2 of the targeted fat increased by 31% to 165.0 ms (FIGURE 1). Decreasing the ablation power to 40 watts and increasing the diameter of the treatment area to 4 mm led to an 18% increase in the T2 of fat, to 151.1 ms (FIGURE 1). Other areas of fat outside the target region showed no change in T2 after ablation. We have demonstrated that T2 mapping can be used to monitor the ablation of fat tissue after the application of focused acoustic energy. The approach can be used together with PRFS methods to monitor temperature changes in surrounding tissue to ensure procedure safety. These methods will be further developed to correlate the fat T2 values to the in-vivo temperature, and assess the therapeutic effect of visceral fat ablation in animal models of obesity and diabetes.

Figure 1: Change in T2 value (color) overlaid onto T2-w images (grayscale) after application of MR-HIFU to fat (red arrows). Areas of fat not treated with HIFU showed no change in the T2 value. Ablation with 70 watts of power over an area 2 mm in diameter increased the T2 of fat by 39 ms (left). Ablation with 40 watts of power over an area 4 mm in diameter increased the T2 of fat by 23 ms (right).
POSTER NUMBER: 222
REAL-TIME MONITORING SYSTEM FOR COAGULATED AREA USING LOCALIZED MOTION IMAGING

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A real-time ultrasound (US) coagulation monitoring system based on acoustic radiation force is described in this paper. US imaging to facilitate HIFU has advantages with respect to portability, cost effectiveness and spatiotemporal resolution. Localized motion imaging (LMI) is one of the techniques based on US to detect a change of tissue mechanical properties caused by its thermal coagulation. In our previous study, estimated coagulation sizes using a prototype off-line LMI system corresponded with coagulation sizes visually extracted from the optical cross section images. In this paper, our purpose is the development of a real-time monitoring system for coagulated area using LMI. LMI is an acoustic radiation based method. In this method, acoustic radiation force generated by a transducer is used as a mechanical input to deform tissue at the focus. The acoustic radiation force is modulated by changing the US intensity. The size of localized oscillation area can be controlled by amplitude modulation frequency. An imaging probe placed at the center of the transducer sends and receives echo signals from the oscillating tissue. The amplitude of the oscillating tissue can be measured by a cross-correlation between echo signals in consecutive frames. The stiffness of after coagulation is more than 10 times before coagulation. After coagulation, the tissue stiffness changes are detected as changes of tissue oscillation. A coagulated area is estimated from decrease ratios of the amplitude before and after coagulation. A prototype real-time one-dimensional LMI monitoring system using a ring buffer memory was constructed. The signal and image processing for LMI was implemented with Matlab code on a windows PC. Because we choose 1 s as a sampling period of the LMI monitoring to meet a practical requirement and the acquisition duration of oscillation data was 40ms, the LMI estimation should be computed within about 960 ms. AM frequencies, HIFU frequency and exposure period were 67 Hz, 2 MHz, 30 s, respectively. The target porcine liver tissue was embedded in polyacrylamide gel. Figure shows a M-mode image of LMI oscillation (in the upper) and that of normalized LMI oscillation (in the lower). The horizontal and vertical axis are time-axis and the distance from the surface of target sample in depth direction, respectively. A growing of coagulated area is visualized in this image. In this condition, on-line LMI images were updated before the start of next data acquisition. The average and maximum computation time including data transfer and displaying LMI were 600 and 800 ms, respectively. The detection of beginning of coagulation is expected to be useful for a dose control of HIFU, and the real-time estimation of coagulation length in the US propagation direction is expected to be practically useful for a lesion control of HIFU. We have developed an US monitoring system using LMI. A prototype real-time monitoring system has been fabricated and a coagulation area can be estimated by this system every second. This temporal resolution is expected to be sufficient to realize a feedback control system for coagulation size control.

M-mode image of LMI oscillation (in the upper) and that of normalized LMI oscillation (in the lower) at the AM frequency of 67 Hz.
POSTER NUMBER: 223
CLUSTER ANALYSIS OF DCE-MRI-DERIVED PHARMACOKINETIC PARAMETERS TO ASSESS VASCULAR EFFECTS OF TUMOR ABLATION WITH HIFU
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Dynamic contrast enhanced MRI (DCE-MRI) has shown to be a valuable tool in the evaluation of HIFU treatment of malignant tumors and the non-perfused volume is regarded an important readout parameter 1. However, the vascular status of the tissue around the non-perfused volume has not been extensively investigated. In this study, a cluster analysis was performed on the pharmacokinetic parameters around the non-perfused volume to identify subregions with different vascular characteristics after HIFU. MRI (6.3T) of CT26 tumor-bearing Balb/c mice was performed 1 day before (n=12), directly after (n=12) and 3 days after (n=6) HIFU. For DCE-MRI, a dual gradient-echo planar imaging sequence (scan time: 5 sec) was used to determine the dynamic contrast agent (Dotarem) concentration. Partial tumor ablation was performed outside the MR system with an 8-element therapeutic ultrasound transducer (TIPS, Philips). Ablation settings were: power 12 W, frequency 1.4 MHz, duty cycle 50 %. A literature-based arterial input function 2 combined with the standard Tofts model was used to determine the transfer constant Ktrans and the extravascular extracellular volume fraction ve. Non-perfused pixels were defined based on the extent of contrast enhancement (median [Gd3+]<5*std pre-contrast). The non-perfused fractions were quantitatively compared to non-viable tumor fractions derived from histology performed directly after and at 3 days after HIFU using NADH-diaphorase staining. K-means clustering with 6 clusters was performed on the combined Ktrans and ve data of the perfused pixels of all time points. Representative Ktrans and ve maps before and after HIFU are shown in Fig A. At both time points after HIFU, a large region of decreased Ktrans and generally decreased ve was observed. Directly after HIFU, the non-perfused tumor fraction was significantly higher (0.58±0.18) than before HIFU (0.19±0.18). At 3 days after HIFU, the non-perfused fraction was significantly lower (0.32±0.14) than directly after HIFU. A higher one-to-one correspondence between histology-derived non-viable and MRI-derived non-perfused tumor fractions was observed at 3 days after HIFU (R2 to line of identity=0.91) than directly after HIFU (R2 to line of identity=0.78). The non-perfused fraction directly after HIFU was higher than the histology-derived non-viable fraction, while at three days after HIFU a better agreement was observed (not shown). Fig B shows the results of cluster analysis on the perfused pixels. The fraction of pixels in three clusters (cluster 1, 3 and 4) was significantly increased after HIFU. The average parameter values in the different clusters are displayed in Fig C. The Ktrans values in the treatment-associated clusters were lower than in the other clusters. Both decreased and increased ve values were observed in the treatment-associated clusters. In addition to an analysis of the non-perfused tumor fraction after HIFU, cluster analysis on the pharmacokinetic parameters in the perfused areas can give additional insight in HIFU-induced vascular changes. The treatment-associated cluster with low Ktrans and low ve might represent regions of vascular destruction with minor contrast enhancement. In regions belonging to the other treatment-associated clusters with low Ktrans and higher ve the flow could be hampered due to vascular congestion and hemorrhage and the leakage space could be increased due to disruption of barriers 3.

This research was supported by the Center for Translational Molecular Medicine (VOLTA).

Figure A) Pharmacokinetic parameter maps (Ktrans and ve) in the tumor tissue before, directly after and at 3 days after HIFU treatment. B) Mean±SD fractions of pixels in the six clusters before, directly after and at 3 days after HIFU treatment. * and ** indicate a significantly increased fraction of pixels after HIFU compared to before HIFU with p<0.05 and p<0.001, respectively (one-sided paired t-test). C) Mean±SD parameter values in the six clusters.

1 Zhou. World J Clin Oncol (2011)
POSTER NUMBER: 224

ECHO DECORRELATION IMAGING OF EX VIVO FOCUSED AND BULK ULTRASOUND ABLATION USING IMAGE-TREAT ARRAYS

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Thermal ablation, including minimally invasive radiofrequency ablation (RFA) and noninvasive high-intensity focused ultrasound (HIFU), is an important treatment option for liver cancer and other soft tissue tumors. Safety and efficacy of these ablation modalities would be improved by a suitable ultrasound imaging method for real-time monitoring of treatment progress. Echo decorrelation imaging, which maps millisecond-scale, heat-induced changes in pulse-echo ultrasound signals, has potential for real-time ablation guidance and control. In this study, the ability of ultrasound echo decorrelation imaging to map and predict heat-induced cell death was tested using bulk thermal ablation, HIFU ablation, and pulse-echo imaging of liver tissue. All ablation and imaging was performed using the same image-treat ultrasound array, enabling precise comparison of images with tissue histology. Ablation and imaging were performed on fresh ex vivo bovine liver tissue using a custom 64 element, 5×24 mm² linear array with >40% pulse-echo bandwidth for imaging and >40 W available acoustic power for therapy. Tissue was sonicated at 5.0 MHz for 30-120 s using either pulses of unfocused ultrasound (7.5 s, 60-120 W/cm² in situ spatial-peak, temporal-peak intensity) for bulk thermal ablation or focused ultrasound (1 s, 200-1200 W/cm² SPTP intensity) for HIFU ablation. Echo decorrelation images were formed from pulse-echo signals recorded at 118 frames per second during 3-5 s rest periods following each sonication pulse, both for the ablation trials and for matching sham trials. Treated tissue samples were frozen at −80 °C, sectioned, and scanned with 21 micron resolution after TTC vital staining. Scanned sections were then segmented based on local TTC uptake for comparison with echo decorrelation images. Monitoring performance of echo decorrelation imaging was assessed by construction of receiver operating characteristic (ROC) curves for prediction of local ablation. Areas under the receiver operating characteristic curves (AUROC) were statistically significant for prediction of both bulk thermal ablation and HIFU ablation by echo decorrelation imaging. The mean cumulative echo decorrelation in the segmented ablated region was significantly greater after ablation than after corresponding sham treatments, and also significantly greater than the mean decorrelation in the non-ablated region. Echo decorrelation magnitude was found to correspond qualitatively with severity of the ablation treatment. Echo decorrelation imaging is a successful positive predictor of local tissue ablation. Real-time monitoring by echo decorrelation imaging is a promising approach for real-time prediction of heat-induced cell death during clinical thermal ablation treatments, including RFA and HIFU.
POSTER NUMBER: 225
INITIAL FEASIBILITY OF HARMONIC MOTION IMAGING FOR HIGH-INTENSITY FOCUSED ULTRASOUND ABLATION OF MOUSE PANCREATIC TUMORS
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High-intensity focused ultrasound (HIFU) is a therapeutic modality that permits noninvasive treatment of various solid tumors, including pancreatic tumors. The purpose of this study was to demonstrate the feasibility of a fully integrated technique-harmonic motion imaging for focused ultrasound (HMIFU)-for simultaneous HIFU ablation and monitoring of mouse pancreatic tumors. A transgenic pancreatic mouse model (KrasLSL.G12D/+; p53R172H/+; PdxCretg/+ (or KPC)) that represents many aspects of the human pancreatic tumors was used. Tumor ablation was performed sing a 93-element phase array HIFU transducer (f= 4.5 MHz, diameter = 10 mm and focal depth = 70 mm) with all elements synchronously excited by a continuous amplitude-modulated (AM) excitation signal at 25 Hz. The AM modulated-HIFU beam also produced a 50 Hz stable harmonic radiation force. Tissue displacements induced by the radiation force were monitored by a 64-element diagnostic imaging probe, which was confocally aligned with the HIFU transducer. The center frequency of the imaging probe was 2.5 MHz and the imaging frame rate was 1000 frame per second. The acquired RF data were reconstructed using a GPU-based sparse matrix technique, filtered to remove interference due to the HIFU beam, and processed by 1D cross correlation for estimating tissue displacements. The peak-to-peak displacements of the targeted tumor region before, during and after HIFU ablation were quantified. After sonication, mice were sacrificed and tumors were processed for H&E staining. At the end of HIFU ablation, tissue displacements decreased by 10-40% of the pre-ablation displacements, indicating tissue stiffening. The lesion locations and sizes were estimated based on the 2D HMIFU displacement images, which were confirmed by H&E histological assessment. The HMIFU technique was therefore demonstrated feasible for monitoring HIFU treatment of pancreatic tumors.
The main problem, which is common to HIFU systems, is that there is no compensation for movements of an affected area in an organ, which are caused by respiration, heartbeat, etc. We herein propose an non-invasive ultrasound theragnostic system (NIUTS) that compensates for movements by tracking and following the area to be treated by stereo ultrasound imaging while irradiating the affected area with HIFU. We aim to enhance the tracking and following performances based on our original medical support system construction methodology, which is called "technologizing and digitalizing medical professional skills (TDMPS)," and our accumulated unique core-technologies. In this section, we discuss the problems and their solution approaches to track and follow body targets by ultrasound images. The ultrasound images incorporate various types of noise factors, mainly due to their measurement principles, as follows: (NF1) speckle noises (random bright spots), (NF2) organ transformation, (NF3) artifacts such as acoustic shadows by rib bones, etc., (NF4) out-of-plane organ motion, (NF5) confusing surrounding tissues/bubbles, as generated by HIFU itself, (NF6) oscillation of mechanical system, etc. Servoing errors cause the ultrasound images to change due to the change of the viewpoints of the ultrasound probes, which in turn increases the servoing error. This negative spiral causes the servoing performance to become increasingly worse. However, if the servoing performance can be improved by some method that results in a positive spiral, the possibility of dramatically enhancing the servoing performance is increased. We take two approaches to solve the above-mentioned problems: (Approach 1) Minimize the servoing error by also minimizing the servoing error so as to reduce the changes of the viewpoint. (Approach 2) Reduce the effect of servoing error.

With respect to the first approach, we developed two solutions to enhance not only the servoing performance to realize efficient therapy but also the safety of the patient. One solution is a robust detection method of the target kidney stone position based on information in the ultrasound image. The second solution is a controller that compensates for the periodic respiratory motion of the affected area. With respect to the second approach, we are now developing two solutions. One solution is HIFU irradiation control in accordance with the servoing error based on the identified HIFU irradiation pattern. Second solution is the recovering algorithm to tracking status automatically by utilizing the robust template matching method and 3D positioning sensor data. We conducted an servoing experiment for human kidney to confirm the performance of the constructed NIUTS. A tracking performance of 1.7 mm in average, 2.0 mm in standard deviation has been achieved for a real human kidney with our constructed NIUTS. In this paper, we clarified problems during extracting, tracking, and monitoring the affected area on ultrasound images. To cope with the above-mentioned problems, we proposed two solution approaches and 4 solutions based on "TDMPS". Finally, we confirm that the system can track and follow a real human kidney with the precision of 1.7 mm, properly by using the constructed NIUTS based on TDMPS.

Overview of NIUTS (a). Mechanism of XYZ stage in watertank. Robot has spherical piezoelectric transducer and two ultrasound probes (c) Two ultrasound image planes are shown in (d).
POSTER NUMBER: 227
THERMAL DOSE VOLUME VS. NON-PERFUSED VOLUME: A PRIOR BASELINE THERMOMETRY APPROACH FOR IMPROVED THERMAL DOSE PREDICTION IN MRGIFU OF PATIENTS WITH SOFT TISSUE TUMORS
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MR guided High Intensity Focused Ultrasound of (MR-HIFU) uterine fibroids have shown that conventional PRF thermometry thermal dose volume under-predicted treatment when compared with non perfused volume (NPV) of MRI contrast enhanced (CE) images (Fig 1c (left and right)). The purpose of this work was to investigate how much under prediction of thermal dose volume was due to errors in thermometry due to an assumption of the return to baseline temperature in patients with soft tissue tumors. We propose the use of a prior baseline method of PRF thermometry to better predict treatment dose volume during a MR-FUS treatment. We developed a prior baseline method to predict thermal dose and applied it in retrospective study of MRgIFU treatments of patients with soft tissue tumors of the extremities. The prior baseline method searches the previously acquired sonication baseline images for a match. Criteria for prior baseline similarity match include: 1. 2D normalized cross correlation of magnitude images to check for motion, 2. Magnitude weighted mean of the phase difference images between prior and immediate baselines to check for large phase difference errors. If no appropriate prior baseline is found, the immediate baseline image is used. Thermal dose area was calculated using the 43°C or 240 CEM criteria, and multiplying by the slice thickness for dose volume per image slice. Dose contours overlays (Fig 1 c, left and center, indicated in red) indicate only those pixels that met or exceeded the lethal threshold. Four patients with soft tissue tumors located in the extremities and right buttock were treated with MR-HIFU ablation. The treatments were performed in a GE 3T scanner using the InSightec ExAblate 2000 system. For each sonication the ultrasound parameters were, 1.1 MHz, 20s, 500 J– 1300J. The thermometry sequence was a 2DFT SPGR (TE/TR =12ms/25ms, SlTk=5mm), acquired every 3 seconds. CE images were acquired immediately following the treatment using a 3D GRE with fat suppression (LAVA, GE, TE/TR=1.7ms/5.4ms, SlTk=3mm). In all patients, we found that the thermal dose volume was less than the post-treatment non-perfused volume using the standard, immediate baseline method. Baseline images of the same slice location taken over the time course of the treatment show a lack of return to 37°C baseline temperature, and heat accumulation in the region of treatment (Figure 1a,b). The prior baseline method estimated a larger treatment volume than was calculated using immediate baselines (Fig 1c). The fraction of thermal dose volume to non-pefused volume was calculated using the prior baseline and immediate baseline methods for each patient. All patients showed some increase in fractional thermal to NPV dose volume using this method (Fig 1d). Prior baseline thermometry can account for errors in baseline temperature assumption of the traditional pre-sonication thermometry approach, and calculates thermal dose volumes that better match post treatment CE non-perfused volume. The method does not account for the entire NPV, however, acquiring a pre-treatment library of all possible baselines so that all images acquired during treatment have a prior baseline could further improve thermometry dose prediction.

Figure 1. A. Temperature maps of immediate baseline images of the same slice location over the course of a patient treatment. The pre-treatment image/prior baseline on the far left used as the reference. B. Mean immediate baseline temperatures in the region of treatment (black circle) as a function of sonication number (treatment time). Prior baseline processing shows subsequent immediate pre-sonication baselines do not actually return to 37C. C. Magnitude image with immediate baseline thermal dose overlay. Gray overlay is region of treatment. Red is lethal dose contour (left). Magnitude image with prior baseline dose (middle). Post treatment contrast enhanced image of similar slice showing non-perfused volume (purple dotted line)(right). D. Estimated treatment volumes of all patients using immediate and prior baseline methods as a fraction of NPV. Fraction of 1 is 100% agreement between thermal dose volume and NPV.
Focused ultrasound (FUS) in combination with microbubbles is a technique for noninvasive, transient, localized and reversible blood-brain barrier (BBB) opening in order to aid the drug delivery to the brain. Various molecules have been shown to cross the BBB under this technique and exhibit therapeutic effects. However, safety, and real-time monitoring thereof, remains one of the key elements before clinical translation of this technique. The objective of this study is to investigate if acoustic cavitation can be potentially used to assess the reversibility and permeability of the induced BBB opening. This study links the microbubble dynamics, represented by the cavitation dose, as monitored during BBB opening to the reversibility of BBB opening. The dependence of acoustic emissions on the reversibility, including the closing timelines of the BBB opening volume and its permeability, was investigated under three different clinically relevant acoustic pressures (0.30, 0.45 and 0.60 MPa) and microbubble sizes (of diameters of 1 - 2, 4 - 5, or 6 - 8 μm). A 10-MHz, single-element, pulse-echo ultrasound transducer served as a passive cavitation detector was used to acquire the cavitation signals generated during sonication that targeted the mouse right hippocampus (n=49). The stable cavitation dose (SCD) and inertial cavitation dose (ICD) were monitored during sonication. Contrast-enhanced dynamic and T1-weighted MR scans were performed immediately after sonication on Day 0 and every 24h up to 6 days thereafter. Volumes and diffusion rates of the contrast agent (Gd-DTPA-BMA) were quantified as indicators for the induced amount of BBB opening. Cavitation response was found to be well correlated with (1) the duration for the induced BBB to close (r² = 0.80 for SCD and r² = 0.27 for ICD); (2) the permeability of the induced BBB opening (r² = 0.82 for SCD and r² = 0.72 for ICD) and (3) the likelihood of safe opening (p < 0.05: compared the SCD of safe opening cases to the cases with mild damage). Stable cavitation was found to be more reliable at predicting the BBB opening than inertial cavitation. In summary, we have shown that monitoring of cavitation behavior during FUS has the potential to reliably predict the duration of opening, the permeability of the induced BBB opening and the likelihood of safe opening. The stable cavitation dose may therefore provide a real-time predictor of the properties of the induced reversible disruption. Finally, the dependence of the BBB reversibility on the bubble diameter and FUS pressure allows us to control the safety profile of this technique.
DETECTION AND TREATMENT MONITORING OF EX VIVO HUMAN BREAST TUMORS USING HARMONIC MOTION IMAGING
Yang Han 1, Shutao Wang 1, Elisa Konofagou 1, 2

Breast cancer is the second leading cause of cancer death in women and is the most common cancer among women. High-Intensity Focused Ultrasound (HIFU) techniques are slowly emerging as less invasive, but equally effective, in the treatment of early-stage breast cancer and benign tumor. To facilitate its translation to the clinic, there is a need for a simple, cost-efficient device that can reliably monitor HIFU treatment. We have developed the radiation-force technique of Harmonic Motion Imaging (HMI) that can be used seamlessly in conjunction with HIFU for tumor ablation monitoring, namely HMI for Focused Ultrasound (HMIFU). Specimen collection and handling of post-surgical breast tissues were approved by the Institutional Review Board (IRB) board of Columbia University and informed consent was obtained from all enrolled patients. HMIFU was performed in 4 normal, 1 fibroadenoma specimen and 1 invasive ductal carcinoma (IDC). To mimic the in vivo environment, the specimens were securely embedded in a tissue-mimicking agar phantom and merged in degassed PBS. The HMIFU setup consists of a 4.75-MHz HIFU transducer using an amplitude-modulated HIFU beam for tissue probing, and a confocal 7.5-MHz single-element, pulse-echo transducer used for simultaneous RF acquisition. 2D raster scan with HMI with performed before and after thermal ablation using 0.6 s duration and 2800 W/cm2 in situ acoustic intensity at each point. For ablation, same intensity was applied but the duration was prolonged to 120 s to cause the lesion. After 2D raster scan, the 3D HMI displacement maps could be reconstructed representing the stiffness of the tissue. The average peak-to-peak displacement in the ROI of normal breast tissue, fibroadenoma and IDC were found to be 39.17±8.48 μm, 8.81±2.01 μm and 2.42 ±0.92 μm respectively. There are also significant differences between before and after HMIFU ablation in both normal and tumor specimen. HMIFU for focused ultrasound (HMIFU) has been experimentally shown to be capable of mapping and differentiate stiffness in normal and abnormal breast tissues. HMIFU can also successfully generate thermal lesions on normal and abnormal breast tissues. The clinical objective of this technique is to develop an all ultrasound-based system for real-time thermal ablation generation and monitoring and test in phantom and post-surgical breast specimens.
POSTER NUMBER: 230
COSTUCTION OF KIDNEY PHANTOM MODEL WITH ACOUSTIC SHADOW BY RIB BONES AND RESPIRATORY ORGAN MOTION
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It is possible using high-intensity focused ultrasound (HIFU) to treat an affected area in focal volume without damaging surrounding or overlying healthy tissues. HIFU, as a noninvasive technique, is an attractive alternative to current open and endoscopic surgery. We propose a noninvasive ultrasound theragnostic system (NIUTS) that compensates for movement by tracking and following the area to be treated by using stereo ultrasound imaging. We set the goal of motion compensation accuracy 2.5 mm RMS, expecting to generate 5 mm lesions by HIFU thermal ablation for respiratory-moving Renal Cell Carcinoma (RCC).

In the present study, the visual servoing accuracy is 1.7 mm (RMS) for the moving kidney phantom model, but 4 mm (RMS) for the human kidney. The main noise factor of this result is acoustic shadows generated by high-acoustic-impedance tissues such as the ribs.

To cope with this noise factor, we propose making a new system able to robustly track even with the presence of ribs. Therefore, we need to make a phantom model to evaluate the new NIUTS with the presence of ribs. First, we clarify the problem of tracking by using stereo ultrasound imaging under the presence of ribs. Next, we construct a phantom model aiming at evaluating NIUTS for kidney tumours / stones under the presence of ribs. This phantom model has craniocaudal motion generator which is able to simulate human kidney’s respiratory motion.

Finally, we compare the human kidney and phantom model concerning ultrasound imaging and show the effectiveness of the proposed phantom model. There are ribs between the surface of the body and the kidney. Because the acoustic impedance of the ribs is much larger than that of the surrounding tissues, its surface reflects most of the ultrasound (about 60%), and the acoustic shadow is formed on the rear of ribs as an artifact. Therefore, the ultrasound imaging pattern of the kidney changes greatly, causing a decrease in tracking accuracy. Moreover, an obstacle, which interrupts the target monitoring during treatments by acoustic shadow, decreases the safety of the patient. The kidney moves due to respiration, but the ribs are stationary. Due to this, to distinguish the lower floor containing the rib phantoms from the upper floor containing a kidney phantom, only the upper floor is made to be able to move by linear motor. This phantom model can imitate the acoustic shadow of ribs. To verify the validity of the constructed phantom model, we conducted a comparison experiments between the human and phantom model. Fig.1 shows the result. From Fig(b1), (b2), we confirmed that the formation of the acoustic shadow, which is caused by rib bones in the phantom model, and also the human on the ultrasound image. First, we have clarified the problem of tracking using stereo ultrasound imaging with the presence of ribs. Second, we have constructed a phantom model in order to evaluate NIUTS for kidney under the presence of ribs. This phantom model has a craniocaudal motion generator which is able to simulate the human kidney’s respiratory motion. Finally, we compared the human kidney with the phantom model under ultrasound imaging and showed the effectiveness of the constructed phantom model.

Fig. 1. Comparison between human and phantom kidney model.
POSTER NUMBER: 231
MONITORING OF THERMAL COAGULATION AREA USING LOCALIZED MOTION IMAGING DURING HIFU EXPOSURE
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In High Intensity Focused Ultrasound (HIFU) treatment, real-time monitoring technique is important for detecting the coagulation area caused HIFU exposure. Localized Motion Imaging (LMI) treatment is one of the monitoring methods based on ultrasound (US) to detect a localized mechanical response that is dependent on changes in tissue stiffness caused by thermal coagulation. In our previous study, estimated coagulation sizes using LMI corresponded with coagulation sizes visually extracted from the optical cross section images. The aim of this study is to evaluate the accuracy of estimated coagulation sizes using LMI in different HIFU exposure conditions. LMI is an acoustic radiation force based method that induces oscillation at the HIFU focal area for the detection of changes in localized stiffness. In LMI, an amplitude-modulated (AM) HIFU is used to generate localized tissue oscillation. An imaging probe placed at the center of the HIFU transducer transmits and receives back scattered echo signals from the oscillating tissues at the focal area. The amplitude of the oscillating tissues can be measured by a cross-correlation between echo signals in consecutive frames. The stiffness of after coagulation is more than 10 times that of before coagulation. After thermal coagulation, the tissue stiffness changes are detected as changes of tissue oscillation. A coagulated size was estimated from decrease ratios of the amplitude before and after coagulation. In this study, HIFU frequency and intensity were 2.2 MHz and 1.2 kW/cm², respectively. AM frequencies were 67 Hz and 168 Hz. HIFU exposure durations were 15 s, 20 s, and 30 s. The target was degassed porcine liver tissue embedded in polyacrylamide gel. The HIFU focal point in the propagation direction is located at depth of 20 mm from the liver surface. After HIFU exposure, the coagulation regions in the liver were removed and measured their long axis length with a scale. Using LMI, the localized tissue oscillating area were 19.4±2.7 mm at low AM frequency (67 Hz) and 10.0±1.7 mm at high AM frequency (168 Hz), respectively. The estimated coagulation sizes using LMI were compared with the actual coagulation sizes measured with a scale as shown in Figure (left side: the results of 67 Hz, right side: those of 167 Hz). The estimated coagulation sizes by LMI were 0.8±1.1 mm (15 s), 2.6±2.2 mm (20 s), 10.6±4.1 mm (30 s) at 67 Hz and 3.5±2.8 mm (15 s), 5.4±3.0 mm (20 s), 9.0±1.7 mm (30 s) at 168 Hz, respectively. In contrast, the actual coagulation sizes were 6.2±1.0 mm (15 s), 8.2±1.0mm (20 s), 10.8±1.1mm (30 s). In the results of most of 67Hz (30s) and 168Hz (20s and 30s), the errors of estimated sizes and measured sizes were within 2 mm. Additionally, the coagulations were able to be detected mostly using LMI at 168 Hz compared with the results of 67 Hz in case of the 15 s HIFU exposure. The results indicate that low AM frequency is suitable for the size estimation of large coagulation due to large oscillation area using LMI. In contrast, high AM frequency is suitable for the detection of a small coagulation area or initial coagulation. We have developed an US monitoring system for thermally induced coagulation using LMI. To evaluate the accuracy of estimated coagulation sizes using LMI, we performed the experiment using the porcine liver as tissue sample. As a result, the estimated coagulation sizes were roughly same as actual coagulation sizes at 67 Hz under 30 s HIFU exposure and 168 Hz under 20 s and 30 s its exposure, respectively.
POSTER NUMBER: 232

FABRICATION & EVALUATION OF TISSUE-MIMICKING GELATIN PHANTOMS FOR USE WITH MR-ARFI AND MRgFUS

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It is important to have a tissue-mimicking phantom that accurately represents human tissue properties both for safety testing and for validating new imaging techniques such as MR acoustic radiation force imaging (MR-ARFI). To achieve a variety of desired human tissue properties, we have fabricated and tested several variations of gelatin phantoms. These phantoms have been customized for mimicking acoustic tissue properties important for quality assurance testing as well as MR-ARFI validation, specifically the speed of sound, attenuation, and Young’s modulus values. Gelatin-based phantoms were fabricated from raw powder (Vyse Gelatin Co. and Sigma-Aldrich Corp.) with three different nominal bloom values, 125, 175, and 250 bloom, where a higher bloom value equates to increased stiffness. The speed of sound and attenuation of each phantom were measured using the through-transmission technique. To achieve a speed of sound and attenuation similar to human tissue, the gelatin mixtures were made with a concentration of 50% evaporated milk and 50% water. The Young’s modulus for each type of phantom was measured using an Instron 5944 single column testing system (Norwood, MA) at a strain rate of 0.5 s⁻¹. All phantoms were fabricated 3 to 18 hours prior to MR-ARFI experimental measurements, acoustic measurements, and Young’s modulus testing; and all testing was done at room temperature. The Young’s modulus and attenuation values found for the three types of bloom gelatin-based phantoms with 50% evaporated milk are reported in Table 1. The reported values for Young’s modulus were derived by taking the mean of six samples per batch, then averaging the means from three separate batches. The Young’s modulus intra-batch variation was typically 0.4 Standard Error Mean (SEM). The average attenuation values reported were calculated from four different phantom batches for each gelatin bloom value. All values for each bloom came from phantoms fabricated out of the same lot of raw gelatin powder. The 125-bloom phantom is similar in elastic properties to brain tissue in humans; Soza et al. 2005 reported the Young’s modulus of brain in the range of 8.1 to 10.2 kPa. Krouskop et al. 1998 reported 19 ± 7 kPa for human fat and 33 ± 11 kPa for glandular tissue, similar to the 175- and 250-bloom values recorded in Table 1. We can achieve reliable tissue-mimicking phantoms with various representative speeds of sound, attenuations, and Young’s modulus values for quality assurance testing and validation of experimental techniques.

References:

<table>
<thead>
<tr>
<th>Gelatin Phantom w/ 50% Milk</th>
<th>Ave. Young’s Modulus ± Std. Dev. (kPa)</th>
<th>Ave. Speed of Sound ± Std. Dev. (m/s)</th>
<th>Ave. Attenuation ± Std. Dev. (dB/cm/MHz)</th>
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</thead>
<tbody>
<tr>
<td>125 Bloom</td>
<td>9.5 ± 1.8</td>
<td>1553 ± 26</td>
<td>0.31 ± 0.05</td>
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<tr>
<td>175 Bloom</td>
<td>18.8 ± 2.7</td>
<td>1549 ± 18</td>
<td>0.31 ± 0.08</td>
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<tr>
<td>250 Bloom</td>
<td>29.4 ± 4.7</td>
<td>1553 ± 12</td>
<td>0.36 ± 0.05</td>
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</table>

Table 1: Summary of Properties for Various Bloom Gelatin-Based Phantoms
POSTER NUMBER: 233

ASSESSMENT OF A QA PHANTOM AFTER REMOLDING

Alexis I Farrer 1, 3, Allison Payne 2, 3, Douglas A. Christensen 1, 4
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The ATS Laboratories daily quality assurance (DQA) hydrogel phantom is commonly used with MR-guided focused ultrasound (MRgFUS) systems. One benefit of the ATS DQA phantom is its ability to be heated up to a liquid state and poured into a custom mold. The same volume of ATS DQA phantom can be liquefied and molded multiple times, increasing its versatility. This study investigates whether the acoustic properties and MR signal are altered after multiple reheatings, and whether any observed changes are reversible. A cylindrical control sample was extracted from the original ATS DQA phantom. The remaining volume of ATS was heated in a microwave until it was in a uniform liquid state between 45°C and 50°C, measured with a thermometer. After each heating, a portion was poured into a labeled cylindrical tube indicating the number of heatings the material had undergone, and the remaining volume was allowed to re-solidify between each phase change. A total of five heating cycles were performed, resulting in five sample tubes plus the control tube. To assess whether any potential water loss caused by the multiple heating cycles could be reversed, 2 mL of water was mixed in with the ATS phantom in liquid form during the fifth cycle. Each tube was identical and contained an equal volume of phantom material. The control, the remolded tubes, and original volume of ATS were kept refrigerated and in a moist environment between heatings. The through-transmission technique was used to measure the speeds of sound and attenuation values for all six samples. A 2-D GRE, high-resolution, proton density weighted sequence was used with a 3T Siemens MRI to measure the signal intensity for all six tubes. Table 1 provides a summary of the acoustic properties and the MR signal measured for all six tubes. The standard deviation, measured sequentially six times for a sample that had been through four heatings, was less than 1 m/s for speed of sound and less than 0.01 dB/cm/MHz for attenuation. The standard deviation across all six samples was found to be 5 m/s for the speed of sound and 0.041 dB/cm/MHz for the attenuation. After five reheatings, only minor differences in the acoustic properties or MR signal intensity were observed in the ATS DQA phantom.

<table>
<thead>
<tr>
<th>No. of Heatings</th>
<th>Speed of Sound (m/s)</th>
<th>Attenuation (dB/cm/MHz)</th>
<th>MR Signal Mean ± Std. Dev.*</th>
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</thead>
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<tr>
<td>0 (control)</td>
<td>1588</td>
<td>0.719</td>
<td>589 ± 22</td>
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<tr>
<td>1</td>
<td>1575</td>
<td>0.631</td>
<td>531 ± 34</td>
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<tr>
<td>2</td>
<td>1588</td>
<td>0.721</td>
<td>491 ± 35</td>
</tr>
<tr>
<td>3</td>
<td>1586</td>
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<td>4</td>
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<td>0.642</td>
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<td>5</td>
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<td>0.637</td>
<td>522 ± 22</td>
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</table>

*A spatial average over the same circular region of interest was performed for all six samples.

Table 1: Summary of Acoustic and MR Properties for the ATS DQA Phantom with Multiple Heatings
ENERGY EFFICIENCY OF VOLUMETRIC MR-HIFU ABLATION IN VIVO: RESULTS FROM ANIMAL PIG MUSCLE AND HUMAN UTERINE FIBROIDS
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MR-HIFU has become a major non-surgical therapeutic modality for ablation of tumor tissue such as uterine fibroid [1-2]. Studies have shown that volumetric ablation by electronic steering of the HIFU beam can result in dose efficient ablations [3-4]. Several groups have correlated the treatment cell size with energy efficiency [5]. In this work, we sought to assess the relationship between dose efficiency and thermal ablation volume (> 240 EM at 43 degC) in pig thigh muscle in vivo, and uterine fibroid in vivo. MR-HIFU procedure: All experiments were done on a Philips 1.5T MR scanner (Achieva) with a modified table-top that had a 256 channel spherical shell HIFU transducer with five degrees of freedom, and an integrated surface coil suitable for real time temperature imaging. The ultrasound frequency ranged from 1.2 to 1.4 MHz. The temperature evolution of total volumetric sonication (n = 187 for uterine fibroid, n = 51 for pig thigh muscle) was recorded in real-time using a multi-shot echo planar imaging technique [3]. Three slices (perpendicular to HIFU beam) bisected the focal ellipsoid coronally, and one sagittal (parallel to HIFU beam) slice was positioned to visualize the long axis of the ellipsoid.
Animal Subjects: The study was approved by the Institutional Animal Care and Use Committee (IACUC). Thermal lesions were created in the thigh muscle of six pigs (50-65 kg) using the volumetric MR-HIFU procedure. The animals were under sedation throughout the procedure and were sacrificed immediately after the procedure under Institutional guidelines. Human Subjects: 9 women who fulfilled the inclusion/exclusion criteria of the pilot/pivotal phase of MR-HIFU trial (SOFIA trial, Philips Healthcare) from two institutions (clinical trials.gov identifiers: NCT00837161/ NCT01504308) were included in this study. All subjects provided written informed consent. A total of 10 fibroids were treated from these 9 subjects, and the pivotal phase of the study is ongoing. Data Analysis: The energy efficiency of each sonication was defined as the ratio of the volume of lethal thermal dose (defined as 240EM at 43degC), divided by the product of applied acoustic power and heating duration. Treatment cell diameters of sonications used in all human, animal and phantom studies were ranged from 4 mm to 16 mm. All treatment cells that had at least 1 pixel with thermal dose greater than 240 EM at 43 degC were included in the analysis (n= 238 sonications). There were a total of 51 sonications in pig thigh muscle, and 187 in uterine fibroids. In all three cases, energy efficiency improved as lesion volume increased (Figure 1). (1) The lesion sizes in volumetric ablation can vary from theoretically predicted lesion volumes depending on local tissue thermal properties; (2) Larger ablations are significantly more dose efficient than smaller ablations for both skeletal muscle and uterine fibroid in vivo.

Acknowledgements:

Figure 1: Semi-log-plot of thermal energy efficiency vs the volume of 240 EM lethal thermal dose at 43 degC in uterine fibroid (dot) in vivo, pig thigh muscle (downward-pointing triangle) in vivo. The inserted table shows that mean and standard deviation of the energy efficiency at various ablated lesion volume ranges.
POSTER NUMBER: 235
FEASIBILITY OF MRI MONITORING OF HISTOTRIPSY THERAPY
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Due to its superior soft tissue contrast, magnetic resonance imaging (MRI) is used extensively to guide therapeutic ultrasound procedures. In this study, we explore the feasibility of extending MR imaging techniques to monitor histotripsy therapy. Histotripsy uses highly focused, pulsed ultrasound to induce controlled cavitation within a focal volume, mechanically fragmenting tissue structures. Since this mechanism does not require a sustained change in tissue temperature, traditional MRgHIFU techniques, such as thermometry, may exhibit inconsistent therapy-based contrast. However, the localized, intense, chaotic flow induced during histotripsy cavitation may be able to produce consistent and robust contrast on diffusion weighted MR (DW-MR) images. In the following, we investigate the feasibility of using DW-MRI to monitor histotripsy therapy in water, agar gel, and excised porcine liver. Tap water, porcine liver, and 1% agar gel samples were respectively placed in a water bath and coupled with an MR safe, 1 MHz, circularly focused transducer array (4.5 cm focal length, 8.5 cm aperture) capable of emitting 5 us long pulses with peak negative pressures of 27.5 MPa. The whole setup was then placed in a 7T MR (Agilent Technologies, Walnut Creek, CA) scanner and subjected to 3000 histotripsy pulses. After completion of therapy, a gradient-echo sequence was used to scan a plane transecting the transducer focus. This sequence was made sensitive to diffusive motion by inserting a balanced, bi-polar gradient between the slice-select-rewind and phase-encode gradients and directed along the slice-select direction. This sequence had a b-value of 0.36 s/mm² and required diffusivities of over 12 mm²s⁻¹ to induce at least 1% signal attenuation. During imaging, the histotripsy transducer was timed to fire a single acoustic pulse immediately after the first lobe of the DW gradient. Control images were obtained by repeating the experiment with the transducer amplifiers turned off. The MR parameters are: DW gradients amplitude = 3.5 G/cm⁻¹, duration = 1 ms, separation time = 3.5 ms, TE/TR = 10/2500 ms, FOV = 30x30x1 mm, Matrix = 128x128x1, Bandwidth = 50 kHz, flip angle = 90°, NEX = 1. Control images of the water, liver, and agar phantoms, taken with the transducer amplifiers turned off, are shown in column (1) of Fig. (1). Images taken with the amplifiers turned on are shown in column (2). Subtractions between the two are shown in column (3). Contrast induced by cavitation can be observed directly in the MR images as well as in the subtraction images (arrows). The hyper-intense region in the liver sample corresponds to the increased T2* relaxation rate of homogenized liver tissue. Disrupted agar gel does not demonstrate visible T2* contrast in these scans. Contrast (σ) between the attenuated region and the control image is also reported. During histotripsy, cavitation occurs on too brief a time scale for MRI to directly image the bubble void. Further, the bubbles which persist after cavitation collapse are too small and far too sparse to generate appreciable susceptibility contrast. However, the bubble cloud’s expansion and collapse is sufficiently violent to incoherently change the positions of the surrounding water molecules, resulting in signal attenuation on an MR image. This mechanism is able to capture MR contrast specific to a single cavitation event in a variety of media.

Figure 1: DW-MR images of water (A-C), porcine liver (D-F), and agar gel samples (G-I) that have been subjected to 3000 pulses of histotripsy therapy. While scanning, a single histotripsy pulse is timed to fire between the diffusion encoding gradient lobes. In column (1), control images are acquired with the transducer amplifiers turned off. In column (2), the images are acquired with the transducer amplifiers turned on. Column (3) displays a subtraction between the images in columns (1) and (2). Signal attenuation induced by cavitation is visible (arrows) in all three samples, though its size and amplitude varies with sample type. Contrast between the attenuated region and the control image are reported as σ.
POSTER NUMBER: 236
NOVEL MR METHODS FOR ACOUSTIC RADIATION FORCE AND SHEAR WAVE IMAGING
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Magnetic resonance-guided focused ultrasound (MRgFUS) provides non-invasive guidance for interventions that can alter the stiffness of biological tissue. MR-Acoustic Radiation Force Imaging (ARFI) facilitates visualization and quantification of changes in tissue stiffness. Here, we combined a high field 7 T MR scanner and 3 MHz Focused Ultrasound (FUS) system to obtain a high resolution MRI image, narrow ultrasound focus and reduced ultrasound depth of focus. MR-ARFI was performed in in vitro and in vivo studies and the tissue stiffness pre and post the ablation were determined. Furthermore, we propose a rapid MR-ARFI and shear wave velocity estimation protocol that can be employed in interventional radiology procedures in the future. MRgFUS was performed on a 7T MR scanner (Biospec 70/30 USR, Bruker Biospin, Germany) using a FUS system consists of a 16-element annular array transducer (IMASONIC SAS, France, 3 MHz central frequency, 300 kHz bandwidth, 120 W peak acoustic power, 48 mm diameter, 35 mm radius of curvature, adjustable focus depth, 1 × 1 × 2 mm3 focal spot volume at -6 dB) and an embedded MR compatible 2-dimensional positioning system. Eight and 10% gelatin phantoms and a Silken tofu (firm) phantom were studied to determine the shear wave speed and develop an ARFI protocol for in vivo studies (TR/TE/FA = 200ms/23.5ms/180°, 29.44 watts acoustic power, 7ms duration and 3.5% duty cycle). Three female FVB mice implanted with murine NDL mammary carcinomas were studied before and after tumor ablation. The location of the ARFI measurements was then ablated (7 s, >70 °C at the focus) and a second ARFI measurement was acquired 48 hours later. In order to estimate the shear wave speed, a delay was programmed into the ARFI sequence before and after the 180 degree pulse and between the two motion encoding gradients (MEGs). Phase images were acquired at delays of 0, 1, 2 and 4 ms. Visualization of shear waves was validated in vitro, where the diameter of the expanding wave increases with increasing delay. The shear wave velocity in the 8% and 10% gelatin phantoms was estimated as 1.78 m/s and 2.22 m/s, respectively, demonstrating the effective increase in shear wave velocity with stiffness. The estimated shear wave speed in the silken tofu phantom was 4.027 m/s. We found that the expanding shear wave could not be visualized within 5 mm mouse tumors. ARFI-induced displacement was observed in the in vivo studies, with a displacement of 5.98 ± 0.27 and 2.85 ± 0.7 μm of pre and post ablation, respectively. MR-ARFI and ARFI-induced displacement estimation are feasible with a high field MRgFUS system. Focal displacement and stiffness properties can both be obtained with the same MR-ARFI sequence. Shear waves can be visualized in vitro and the velocity estimated rapidly by changing the delay parameter in the MR-ARFI sequence. Rapid and efficient visualization and quantitation of displacement and shear wave velocity is feasible with high field MRI.
POSTER NUMBER: 237

NONINVASIVE TISSUE TEMPERATURE ESTIMATION USING NONLINEAR ULTRASOUND
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One of the major limitations of thermal therapies (hyperthermia and HIFU) is the lack of a reliable non-invasive and real-time tissue temperature monitoring technique to control the treatment. Monitoring and controlling the temperature distribution during thermal therapy will help to maintain the target temperature in the region of interest and improve efficacy and safety. In this study, a non-invasive thermometry technique has been developed based on the measurement of harmonic amplitudes generated by nonlinear ultrasound propagation in tissue. Analysis of the ratios of the harmonic amplitudes as a function of temperature can provide information on the temperature distribution. The fundamental frequency (f0), the second (fH2) and the third (fH3) harmonics were obtained from the frequency spectra of the backscattered radiofrequency (RF) signals from tissue-mimicking gel phantoms and ex vivo bovine muscle tissues. A high-frequency ultrasound imaging scanner (Vevo® 770, Visualsonics Inc., Toronto, ON, Canada) with a 25-MHz center frequency wide-band single-element transducer (RMV-710B, f-number 2.1, 15 mm focal length) was used to generate and detect acoustic harmonics. Higher harmonics were generated using a 13-MHz 30-cycle excitation pulse that resulted in a focal peak pressure of approximately 3.9 MPa in water. Both the tissue sample and the transducer were immersed in a temperature controlled circulating water bath (Haake DC10, Thermo Electron Corp., Newington, NH) with an accuracy of ±0.1°C in order to produce a homogeneous heat distribution throughout the sample. The temperature was increased from 26°C to 46°C in increments of 2°C. In order to reach the steady state, the sample was kept 30 minutes at each temperature before making the measurement. The experiments on tissue-mimicking gel phantoms and ex vivo tissue samples were each repeated for 5 times. At each temperature, 50 consecutive backscattered RF frames were captured for averaging. Each frame consisted of 100 RF backscattered echo lines covering a region of interest of 16 × 16 mm2 within the sample. The sampling frequency was 420 MHz and the window size for taking Fourier transformation was 10×Λ (~0.7 μs) to obtain the f0, fH2 and fH3 of the echo signal. The frequency spectrum of each window along the signal was first averaged over the 50 frames and then averaged with the same window along all the 100 RF lines. The harmonic amplitudes and their ratios (fH2/f0, fH3, fH2/f0 and fH3/f0) were obtained for each window axially, and their maximum values were plotted. The average and standard deviation of the maxima of the harmonic amplitudes and their ratios were measured. For a temperature increase from 26°C to 46°C the average of the maximum values of the harmonics fH3 and fH2 increased by 113% and 47% for the gel phantoms and 169% and 50% for the tissue samples, respectively. The ratios fH3/f0 and fH2/f0 increased by 80% and 30% for the gel phantoms and 109% and 13% for the tissue samples, respectively. All experiments demonstrated the same trend as a function of temperature. In this study, the temperature dependence of the harmonic amplitudes and their ratios were obtained in gel tissue phantoms and ex vivo tissue samples in pulse echo mode with a commercial high-frequency ultrasound imaging scanner. The harmonic amplitudes and their ratios show high sensitivity to temperature compared to other acoustic parameters such as speed of sound and the attenuation coefficient. The results indicate that the harmonic amplitudes, fH2 and fH3, and their ratios to the fundamental frequency could potentially be used for non-invasive temperature monitoring in tissue.
PALLIATIVE TREATMENT OF PAINFUL BONE METASTASES WITH MAGNETIC RESONANCE GUIDED FOCUSED ULTRASOUND

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Bone pain is the primary factor negatively influencing quality of life for any patients with disseminated cancer. Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS) is an innovative technology combining noninvasive deposition of high intensity focused ultrasound energy into a specified target inside the body, with high resolution Magnetic Resonance Imaging (MRI) guidance and real-time thermal feedback. The ExAblate system is a noninvasive thermal ablation device that has been used for the ablation of tissue. This system combines a focused ultrasound surgery delivery system and a conventional diagnostic 1.5 T MRI scanner (MRgFUS/MR guided focused ultrasound surgery). Treatment 35 patients with painful bone metastases was performed using the ExAblate™ MRgFUS system (InSightec, Tirat Carmel, Israel) at N.N.Petrov Research Institute of Oncology, St. Petersburg, Russian Federation. Immediately after procedure patients were examined for any adverse events and after a brief recovery discharged. Patients were followed up on 1 and 3 days, 1 and 2 weeks, 1, 2 and 3 months post treatment. During each visit, treatment safety was evaluated by recording and assessment of device or procedure related adverse events. Effectiveness of palliation was evaluated using the standard pain scale (0-no pain/10-worst pain imaginable) and by monitoring changes in the intake of pain-relieving medications. A reduction of 2 points or more on pain scale was considered a significant response to treatment. Male were 7 patients and 28 female. Mean age was 57 years old (19-79). The primary cancers were: 24 breast, 2 rectums, 2 bronchus, 2 bladders, 5 other. Targeted lesions were 8 osteolytic 27 mixed. 21 were pelvis metastases, 4 were located in the femoral bone, 3 were located in the upper extremity bones and 7 were located in the ribs. No significant device or procedure related adverse events were recorded. 3 patients died during the follow-up period due to disease progression, thus 3 months follow-up data includes only results of 32 patients. All 32 patients were reported significant improvement in pain with no change in their medication intake. Mean worst pain score at baseline, 1 day, 3 days, 1 week, 2 weeks, 1, 2 and 3 months post-treatment was 6.8, 6.2, 5.2, 3.6, 2.7, 1.9, 1.3 and 1.1 accordingly. Palliative treatment patients with painful bone metastases performed using the noninvasive ExAblate™ MRgFUS system can provide effective and safe result. The ability to achieve rapid pain relief after only one treatment session, combined with the high safety profile of the procedure implies that MRgFUS has a significant potential for patients suffering from painful bone metastases.
CAVITATION-ENHANCED HEATING IN A LARGE REGION WITH HIGH-SPEED ULTRASONIC IMAGING

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HIFU thermal treatment has a problem of long treatment time because cooling time is needed between two consecutive shots of focused ultrasound exposure to avoid near-field heating owing to heat accumulation. It is known that acoustic cavitation generated in the focal region of HIFU enhances tissue heating. The objective of this study is to develop a method to accelerate HIFU thermal treatment by using cavitation bubbles in a large region. Cavitation bubbles were generated at six positions in the direction perpendicular to ultrasound propagation. High-speed ultrasound imaging was used for the cavitation monitoring to detect small cavitation bubbles which dissolve within an order of or less than ms. A 128-ch transducer was placed in a water tank. The transducer had outer and inner diameters of 120 and 40 mm, respectively, and a curvature radius of 120 mm. An ultrasound imaging probe was placed in the hole of the HIFU transducer. High-intensity pulses at a maximum intensity of 30 – 35 kW/cm² were focused into six points sequentially to generate cavitation. Immediately after that, lower-intensity ultrasound at a maximum intensity of 1.7 – 2.7 kW/cm² was exposed. The sequence consisting of the high-intensity pulses and lower-intensity ultrasound was repeated for 11 s at a frequency of 8 – 16 Hz with an interval time of 2 ms. The driving frequency of the transducer was 1 MHz. Within an interval time of 2ms, cavitation bubbles were monitored by ultrasound imaging at a center frequency of 7.5 – 9 MHz, in which plane waves were transmitted for the high-speed monitoring. HIFU with or without the high-intensity pulses was exposed to an excised chicken breast muscle tissue or rabbit thigh muscle. The coagulation volume of chicken breast with and without the high-intensity pulses was compared. The high-intensity pulses at an intensity of 35 kW/cm² was repeated at 16 Hz. The spatial-peak temporal-average intensity, ISPTA was 1.9 and 1.6 kW/cm² with and without the high-intensity pulses, respectively. The coagulation volume was 1700 and 450 mm³ by HIFU exposure with and without the high-intensity pulses, respectively. Figures show the ultrasound images during and just after the HIFU exposure with the high-intensity pulses to the rabbit thigh muscle and a picture of cut rabbit thigh muscle. The high-intensity pulses at an intensity of 30 kW/cm² was repeated at 8 Hz. The intensity, ISPTA was 2.4 kW/cm² with and without the high-intensity pulses because the duration time of the high-intensity pulses was so short. The ultrasound images show a hyperechoic region, indicating the residual cavitation bubbles in the interval time. In the picture of the rabbit thigh, a large coagulated region is seen. Some red regions were also observed, which was probably caused by hemorrhage induced by oscillating cavitation bubbles. The coagulated region was not observed without the high-intensity pulses. The results of in vivo and in vitro experiments show the higher efficiency of the proposed HIFU exposure sequence using cavitation bubbles in a large region. The rapid focus scan and combination of the high-intensity pulses and lower-intensity ultrasound were used for cavitation-enhanced heating in a large region. Residual cavitation bubbles were observed by high-speed ultrasound imaging within a HIFU interval time of 2 ms. The results show the high efficiency of the proposed HIFU exposure sequence for HIFU thermal treatment.
COMPARISON STUDIES ON EFFICIENCY ENHANCEMENT OF HIFU TREATMENT BY ENCAPSULATED MICROBUBBLES AND MESOPOROUS SILICA NANOCAPSULES FILLED WITH PERFLUOROCARBON DROPLETS USING AN EGG WHITE PHANTOM

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To increase the efficiency of HIFU treatment has been considered a primary goal in the HIFU research community. Ultrasound contrast agents are commonly used to achieve this goal. In this study, the effects of encapsulated microbubbles (SonoVue) is compared with two types of our home-made mesoporous silica nanocapsules (MSNC) filled with perfluoropentane (PFP) droplets and perfluorohexane (PFH) droplets, the boiling points of PFP and PFH are 29 °C and 57 °C respectively. The same amount of 0.3 ml of SonoVue, MSNC-PFP, MSNC-PFH were uniformly mixed into three 100 ml egg white phantoms separately, The temperature in each phantom was controlled lower than 20 °C during preparation stage. Then the phantoms of Control group and experimental groups (SonoVue group, MSNC-PFP group, MSNC-PFH group) were sonicated using US guided HIFU with acoustic power 160 W, exposure time 10 s and focal depth14mm. The target area of the experimental groups and the control group in the B-mode ultrasound imaging became hypoechoic immediately after HIFU, the hypoechoic intensity and the volume of lesion for MSNC-PFP group were the largest, and those for control group were the smallest. The hypoechoic range and the volume of lesion for MSNC-PFH and SonoVue groups were not statistical difference, and between those of MSNC-PFP group and control group. The results suggest that the mesoporous silica nanocapsules filled with low boiling point fluorocarbon droplets can relatively easier to be vaporized under HIFU treatment and the set-free-vapor bubbles can effectively improve the efficiency of HIFU treatment.

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A SOFTWARE TOOL FOR ADVANCED MRGFUS PROSTATE THERAPY PLANNING AND FOLLOW-UP

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For almost 20 years, diagnostic ultrasound (US) guided high intensity focused ultrasound (HIFU) ablation of prostate cancer is in clinical use. In the last years, there are also first clinical trials of MR (magnetic resonance) guided FUS (focused ultrasound surgery) for prostate cancer therapy. MR imaging has the advantage to be the best suited imaging modality for the precise diagnosis and localization of prostatic tumors. However, multi-parametric MRI examination of the prostate is a time consuming procedure and not practicable within an MRgFUS therapy session. The aim of our ongoing work is to develop software to support therapy planning and post-therapy follow-up for MRgFUS on localized prostate cancer, based on multi-parametric MR protocols. In order to customize the software to the special needs of prostate MRgFUS therapy, the clinical workflow of diagnosis, therapy and follow-up of MR guided FUS on prostate cancer was deeply analyzed. Based on this, the image processing workflow was designed and all necessary components, e.g. GUI, viewer, registration tools etc. were defined. The software bases on MeVisLab (Medical image processing and visualization tool, MeVis Medical Solutions, Bremen) with several implemented C++ modules for the image processing tasks. A typical scenario for the software looks as follows. All images (T1w, T2w, DWI and Perfusion etc.) and other related data, e.g. ADC- or perfusion maps, acquired in the diagnostic MRI session will be automatically registered. Manual refinement of the registration is available. Images are visualized and a cursor shows the synchronized position in all images based on the registration. With this maximum of diagnostic information the therapist can segment the tumor, the target region and the organs at risk. Final therapy planning will be performed based on these segmentation data. For this purpose, fast morphological MR scans acquired at the beginning of the therapy session will be registered to the image and segmentation data of the diagnostic session by the software. In addition, the developed software should help to evaluate the therapy success, by synchronization and display of pre-therapeutic, therapy and follow-up image data including the therapy plan and thermal dose information.

In this ongoing project, the first stand-alone prototype of the software was completed and will be evaluated in a retrospective study, e.g. the precision of image registration. The use of MeVisLab with its advanced image processing modules gives our software a high flexibility for the implementation of additional features, e.g. the incorporation of transrectal US images to improve US guided HIFU procedures. Finally our software should be integrated in a new MRgFUS setup for prostate therapy and we hope to achieve MRgFUS therapy planning with a very high local precision.
To develop a method of dehydration of typical uterine fibroids with edema to improve the results of MRgFUS treatment. 12 patients with hypointense on T2 weighted image coarsely layered uterine fibroids structure were conducted dehydration (histology - a typical uterine fibroids with a diffuse edema of stroma). Exclusion criteria: defined lactate peak during 1H-MRS with the absence of the resonance peaks of other metabolites. For the first time, for the non-invasive dehydration the mechanical lymphatic drainage was used. The results of dehydration were assessed on the basis of MRgFUS data of myoma node volume before and after dehydration, MR signal intensity, MRgFUS treatment parameters (energy of FUS is used to achieve the destruction of uterine tissue). As a result of dehydration in 83.3% (10) cases was a decrease in volume of fibroids nodes and restore in it’s MRgFUS-structure. In 75% (9) cases there was a uniform energy absorption of FUS, the duration of treatment in the majority of cases (11 (91.6%)) from 1.5 to 3 hours. As a result the MRgFUS therapy 58.3% (7) a NPV was obtained more than 80%. At 1, 3, 6 and 12 months after MRgFUS the decrease in the intensity of uterine bleeding was noted, according to the tables of PBAC, sustained pain relief and improved quality of life according to the results of the questionnaire. Therefore, we have developed a non-invasive method of dehydration, which is effective for the reduction of edema in the nodes of fibroids and can be used to improve the results of the MRgFUS procedure.
Ultrasonic cavitation bubbles can not only enhance the thermal bioeffect of HIFU treatment but also produce sonochemical bioeffect in combination with a sonoseisitizer. Such sonochemical bioeffect is induced through activating the sonosensitizer by the collapse of cavitation bubbles and generating active oxygen which can induce irreversible changes to the tissue. Sonodynamic treatment utilizes such sonochemical bioeffect and has been expected to expand the application of therapeutic ultrasound. Rose Bengal (RB) is such a sonosensitizer, which has also been found to reduce cavitation threshold. For realizing effective as well as safe sonodynamic treatment in combination with RB, the effect of RB on the inception and lifetime of cavitation bubbles were investigated by using high-speed camera observation in this study. A focused ultrasound array transducer and a gel phantom were placed in a PMMA water tank. The phantom consisted of a polyacrylamide (PAA) gel containing either 0, 0.1, 1, 10 mg/L of RB. The focus was located in the gel, and a high-speed camera was set to observe the behavior of cavitation bubbles generated in the vicinity of the focus. An exposure sequence, consisting of an extremely high-intensity short pulse for cavitation cloud inception, called as a trigger pulse, immediately followed by a modulate intensity long burst for sustaining them by volume oscillation, called as the sustaining burst, was employed. The intensity and exposure duration of the trigger pulse and the sustaining burst both at 1.2 MHz were 40 kW/cm² for 60 µs, and 300 W/cm² for 100 ms, respectively. The cavitation cloud being incepted by the trigger pulse and the bubbles being sustained by the sustaining burst were observed, and their amounts and spatial distributions were calculated from the high-speed camera pictures. Fig.1 shows the high-speed camera pictures of cavitation cloud at 30 and 60 µs, and Fig.2 shows sustained cavitation bubbles calculated by the high-speed camera pictures after 1 and 100 ms after a trigger pulse at each RB concentration. Clear concentration dependence was observed in both of the incepted cloud and the sustained bubbles. Both total areas of the incepted cloud and sustained bubbles became larger as the RB concentration increased. The former area significantly depended on the concentration of RB. This result indicates that the intensity threshold for cavitation cloud inception can be significantly reduced by RB. In this study, the effects of RB on cavitation cloud inception and sustained cavitation bubbles were investigated. As a result, RB increased the amounts of both cavitation cloud and the sustained cavitation bubbles. These observed effects by RB may be useful for utilizing sonochemical as well as thermal effect of ultrasound for therapeutic applications.
POSTER NUMBER: 244
HIGH-INTENSITY INTERSTITIAL ULTRASOUND FOR THERMAL ABLATION OF FOCAL CANCER TARGETS IN PROSTATE
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To investigate strategies for thermal ablation of focal prostate cancer using multiple interstitial ultrasound applicators through patient specific numerical modeling and simulations. Recent advances in image based techniques such as multi-parametric MRI (MP-MRI) can provide precise targeting of focal disease in the prostate. Thermal ablation of such cancer targets while avoiding rectum, urethra, neurovascular bundles (NVB) and sphincter is clinically challenging. Endorectal ultrasound ablation probes can deliver thermal energy to such prostate cancer targets with selectivity and precision. However they are limited by long treatment times and in their ability to treat anterior gland targets. The approach described here employs multi-element ultrasound linear arrays designed for transperineal placement within prostate. They consist of independently powered sectored tubular transducers (6.5 – 8.0 MHz) that provide spatial control of energy deposition in angle and length. Feasibility and practicability of image-guided ablation of prostate with such devices has been demonstrated previously through in vivo canine studies.

Volumetric ablation strategies were investigated through patient-specific biothermal models based on Pennes bioheat transfer equation. The acoustic and heat transfer models used here have been validated in several previous simulation and experimental studies. Focal disease sites in prostate were identified through multi-parametric MR images of representative patient cases (n=5). Focal cancer lesions and critical anatomy (prostate, urethra, rectum, bladder, seminal vesicles) were manually segmented (Mimics, Materialise) and converted to 3D finite element meshes (3-Matic, Materialise). The chosen patient cases consisted of unifocal targets in a single quadrant in posterior prostate, bilateral targets in posterior prostate, hemi-gland targets, “hockey-stick” targets (lesions in three quadrants), and targets in anterior gland. Ultrasound applicator placement was determined such that devices were positioned along the prostate periphery while avoiding surrounding anatomy. Transducer sector angles were chosen based on applicator location within limits of fabrication practicability. Tissue and temperature dependent variations in physical and physiological properties were included. Thermal models were numerically solved using finite element methods (FEM) in COMSOL Multiphysics. Temperature and thermal dose distributions were calculated to determine treatment volumes (> 240 CEM43C, >50 oC) and safety profiles (<6 CEM43C, <45 oC) for nerve, rectal and urethral sparing. Modeling studies indicated that focal targets could be ablated (>240 CEM43C, >50 oC contours) with single or multiple interstitial applicators placed along the prostate periphery. In the representative cases explored during this study, thermal targets could be ablated with acoustic intensity values between 20 – 25 W/cm2 within 5 – 10 min of sonication time. Unifocal ablation could be performed by a single directional applicator (210o sectors). Bilateral and hemi-gland (Fig. 1) targets were ablated by two directional applicators (210o sectors). Hockey-stick ablations were performed using 3 directional applicators (2 - 210o and 1 - 150o) The estimated maximum temperatures were ~67 oC in the target volume and ~42 oC in the rectum. Interstitial ultrasound may be used to provide directional and spatially controlled thermal ablation of focal prostate cancer. Single or multiple devices can be used for volumetric ablation of focal targets in under 15 minutes while avoiding surrounding critical anatomy.

3D patient specific modeling applied to percutaneous transperineal ablation of a focal prostate tumor showing resulting destructive thermal dose and safety margin contours for single NVB sparing dual applicator hemi-gland ablation.
POSTER NUMBER: 245
UPDATE ON EUS-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND
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High-intensity focused ultrasound (HIFU) is a promising technology for non-invasive and minimally invasive ablation of benign and malignant tumors. However, extracorporeal targeting of pancreatic and liver tumors is problematic due to lack of an acoustic window through overlying bowel gas, respiratory motion, and absence of monitoring. An EUS-guided HIFU transducer provides many advantages, including improved targeting, decreased energy requirements, and decreased potential for injury to intervening structures. We previously described the development of such a device. We set out to correlate the application of specific EUS-guided HIFU parameters with resultant hepatic/pancreatic lesions in gel phantom, ex vivo, and in vivo models. The EUS-guided HIFU transducer includes a spherically curved PZT element (radius of curvature = 35 mm, focal area = 15 mm x 2 mm) that serves as the therapeutic element, and an Olympus B-mode imaging probe (freq = 10MHz) that provides image guidance. A fixed metal housing is fitted with a degassed-water-filled balloon and plastic cover. Preliminary gel phantom, ex vivo and in vivo studies were performed to assess the ergonomics of the transducer design and demonstrate the feasibility of targeting and creating lesions in the porcine pancreas and liver. Both 2.66MHz and 3.73MHz operating frequencies were used to compare their bioeffects. Treated tissue was sectioned and stained with H&E and NADH-diaphorase as an indicator for thermal damage. The EUS-guided HIFU transducer successfully created lesions in gel phantoms, ex vivo bovine livers, and in vivo porcine liver and pancreas and preliminary data was gathered for optimization of pulse protocols. Hyperechoic foci visualized via EUS during and after HIFU ablations were found to correlate well with both gross specimens and histology. Figure 1A demonstrates hyperechoic focus during treatment overlying a target area in the pancreas during an in vivo porcine study. This correlated with gross specimen of the pancreas harvested after (1B), as well as subsequent histologic analysis showing absence of color in an NADH-d stain of the ablated region (1C). A generally successful pulse protocol in ex vivo bovine liver included settings of P=5.5MPa, Duty Cycle = 50% (pulse duration=0.2s, interval=0.4s), Duration= 5s. A generally successful pulse protocol in in vivo porcine pancreas included settings of P=8.5MPa, Duty Cycle = 50% (pulse duration=0.2s, interval=0.4s), Duration= 30s. An EUS-guided HIFU transducer successfully created lesions in gel phantoms, ex vivo bovine livers, and in vivo porcine liver and pancreas. Further development of this technology will allow endoscopists to perform therapeutic ablation of peri-luminal lesions. Potential applications include ablation of tumors in the liver, pancreas and bile duct. In addition, EUS-guided HIFU can be used to perform ablation of the celiac plexus for palliation of pain.

Figure 1 - "A" demonstrates hyperechoic focus during treatment overlying a target area in the pancreas during an in vivo porcine study. "B" shows the gross specimen of the pancreas harvested after ablation with correlative lesion. "C" shows an NADPH-d stain showing absence of color in the ablated region.
Patients with high-risk prostate cancer undergoing radical prostatectomy, external beam radiation therapy (EBRT) combined with androgen deprivation therapy (ADT) or ADT alone. The widely accepted definition of high-risk prostate was first proposed by D'Amico based on a pretreatment Gleason score of \( \geq 8 \), clinical stage T2-T3, PSA level \( \geq 20 \) ng/mL. There is no trial that compares traditional methods of treatment of such patients with robotic HIFU therapy. Here we explored the effectiveness of the robotic HIFU for patients with high risk prostate cancer. 701 patients with high risk prostate cancer were treated in our center between September 2007 and December 2013. Gleason score were 8-10, stage T3N0M0, age 69 (58-86) years, mean PSA before treatment 43.3 (22.1-92.9) ng/ml, mean prostate volume - 59.3 (38-123) cc. 248 patients were treated by HIFU. We compare this group of patients with patients who undertook EBRT: number 196, and ADT: number 257. Mean follow-up time 43 months (3-72). After HIFU in 203 patients (82%) at six months after treatment the median PSA was 0.4 (0-3.2) ng / mL, in 60 months - 0.9 (0.4-7.5) ng / mL and no data for progression. In general, the 6-year follow-up showed that the survival rates in patients after HIFU were 82 %, after EBRT – 70 % and after ADT – 14 %. Our experience shows that HIFU therapy for patients with high risk prostate cancer were more successful method of treatment with much better survival rate than after EBRT and ADT.
POSTER NUMBER: 247
SPATIAL ACCURACY OF VOLUMETRIC ABLATION OF SYMPTOMATIC UTERINE FIBROIDS USING MAGNETIC RESONANCE IMAGING GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (MR-HIFU)
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MR-HIFU has become a major non-surgical therapeutic modality for ablation of tumor tissue such as uterine fibroid [1-2]. It has been shown that volumetric ablation of tissue coupled with real-time monitoring of temperature can improve thermal dose efficiency and save treatment time [3-4]. Here, we report on the spatial accuracy of thermal dose delivery using volumetric ablation of uterine fibroid in vivo. Subjects: 9 women who fulfilled the inclusion/exclusion criteria of the pilot/pivotal phase of MR-HIFU trial from two institutions (clinical trials.gov identifiers: NCT00837161/NCT01504308) were included in this study. All subjects provided written informed consent. A total of 10 fibroids were treated from these 9 subjects, and the pivotal phase of the study is ongoing. MR-HIFU procedure: All experiments were done on a Philips 1.5T MR scanner (Achieva) with a modified table-top that had a 256 channel spherical shell HIFU transducer with five degrees of freedom, and an integrated surface coil suitable for real time temperature imaging. The ultrasound frequency ranged from 1.2 to 1.4 MHz. The temperature evolution of volumetric sonication (n = 187) was recorded in real-time using a multi-shot echo planar imaging technique [3]. Three slices (perpendicular to HIFU beam) bisected the focal ellipsoid coronally, and one sagittal (parallel to HIFU beam) slice was positioned to visualize the long axis of the ellipsoid. Data Analysis: Using custom-built software, the spatial location of the centroid of the thermal dose for each cell was compared against the intended location of the lesion to yield the dose offset. 96% of the volumetric sonications (187/195) resulted in tissue necrosis as measured from thermal dose maps (> 240 EM at 43degC). Treatment cell diameters of sonications ranged from 4 mm to 16 mm (4mm (n = 5), 8mm (n = 91), 12mm (n = 61), 16mm (n = 30)). Sonications were aborted if the near-field temperature exceeded either pre-defined temperature limits, or if the expert observer concluded that near-field heating was high from monitoring temperature images. Technical errors caused treatment aborts in 7/195 sonications, and patients terminated treatments in 9/195 cases. A representative thermal dose map at the planes for coronal and sagittal following treatment of 16 mm cell is shown in Figure 1A and 1B respectively. The offset between the actual caused lesion region and the intended location at the planes for coronal and sagittal are shown in Figure 1C and 1D respectively. 97.9% and 80.7% sonications fell within two pixels (2.5 mm/pixel) away from the intended location at the plane perpendicular and parallel to HIFU beam direction respectively. The preliminary results suggest that the spatial accuracy of volumetric ablation is very high, and volumetric HIFU lesion centers in vivo are within 5 mm of the prescribed spatial locations. Acknowledgements:
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Figure: Thermal dose maps following MR-HIFU ablation using a 16 mm cell in the coronal(1A) and sagittal(1B) plane. Thermal dose > 240 EM at 43degC is shown in red. Note the sharp boundary between the treated (ellipsoid) and untreated areas. Dose offset in the planes perpendicular(1C) and parallel(1D) to the HIFU beam.
POSTER NUMBER: 248
HIGH ACCURACY POSITION CONTROL OF HIFU TRANSNUCER FOR BREAST CANCER TREATMENT USING 5 DOF PARALLEL-LINK ROBOT
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A prototype robotic system for position control of HIFU (High Intensity Focused Ultrasound) transducer to treat breast cancer is described. In several difficulties of current HIFU systems, reduction of total treatment time is one of important clinical issues. This long treatment time is mainly caused by the requirement to reduce a risk of skin burn explained by following. When tumor is larger than a HIFU focal area, multiple exposures are needed. If multiple foci are exposed in a sequence from a fixed position of the HIFU transducer, heat accumulation at the skin, which was exposed in every HIFU shot, will increase the risk of skin burn. In order to prevent skin burn, it needs sufficient intervals to cool an entrance surface of HIFU beam. As a result, treatment time is long. Because our prototype system uses an ultrasound imaging method as a guide method, working area for the HIFU transducer motion is not restricted, unlike in the case of a MRI (Magnetic Resonance Imaging) guide HIFU. In addition, various approaching paths accessing to breast cancer can be defined. In this study, precise robotic control system to realize multidirectional exposures was constructed and evaluated. An ultrasound probe was fixed in the center of the HIFU transducer. 3D ultrasound image data relating with geometrical information about tumor can be acquired by the robotic motion. In addition, ultrasound probe receives echo signals generated through scattering of the HIFU beam to visualize the HIFU beam shape. To avoid heat accumulation at the skin, a pivot motion is used. In the case of the focal area is set on the fixed point of pivot motion, heat is accumulated within focal area and entrance surface is expanded and the skin heating is suppressed. In addition, if the focal area is set apart from the fixed point of pivot motion with a few millimeter, the treat area was expanded. In previous work, a 4 DOF serial-link robot was constructed in order to operate the HIFU transducer and ultrasound imaging probe. However, its accuracy and degree of freedom is insufficient. Therefore, sonication with the HIFU transducer rotation can only treat tumor which is on the robot’s axis of rotation. In this study, parallel-link robot which has 5 DOF is developed. Parallel-link robot is more accurate and stiffer than serial-link. In addition, its 5 DOF enable sonication with the HIFU transducer rotation to treat tumor which is not on the robot’s axis of rotation. The position accuracy of the fabricated prototype was evaluated by an optical measurement with Polaris Spectra with accuracy of 0.25 mm. An optical marker was set at near the focus. After a round-trip motion of one input axis of serial-link robot, its maximum error was 10 mm. On the other hand, when focus of the parallel-link robot moved along a round-trip path with distance of 15 mm in x axis by 1 mm unit, there was hysteresis in its path and the z-axis error with size of 0.6 mm were occurred at the turning point. However, average of step except turning points and its standard deviation were 1.00 mm and 0.12mm, respectively. Similarly, average of step in y axis and its SD were 1.01mm and 0.02mm, respectively. When focus moved along a round-trip path with distance of 75 mm in z axis by 5 mm unit at theta axis = 90, 100, 110 and 120 degrees, averages of step were, respectively, 5.08, 5.11, 5.13 and 5.20 mm. Their SD were respectively 0.04, 0.06, 0.75 and 0.69 mm. This error sizes were sufficiently less than typical HIFU lesion size. Therefore, new robot had sufficient accuracy for HIFU treatment.

This study improves robot’s accuracy and realizes HIFU treatment with high flexibility.
POSTER NUMBER: 249

PROSTATE TISSUE ABLATION WITH MRI GUIDED TRANSURETHRAL THERAPEUTIC ULTRASOUND AND INTRAOPERATIVE ASSESSMENT OF THE INTEGRITY OF THE NEUROVASCULAR BUNDLE

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Evaluation of the precision of prostate tissue ablation with MRI guided therapeutic ultrasound by intraoperative objective assessment of the neurovascular bundle in canines in-vivo. In this ongoing IACUC approved study, eight male canines were scanned in a clinical 3T Achieva MRI scanner (Philips) before, during, and after ultrasound therapy with a prototype MR-guided ultrasound therapy system (Philips). The system includes a therapy console to plan treatment, to calculate real-time temperature maps, and to control ultrasound exposures with temperature feedback. A transurethral ultrasound applicator with eight transducer elements was used to ablate canine prostate tissue in-vivo. Ablated prostate tissue volumes were compared to the prescribed target volumes to evaluate technical effectiveness. The ablated volumes determined by MRI (T1, T2, diffusion, dynamic contrast enhanced and 240 CEM43 thermal dose maps) were compared to H&E stained histological slides after prostatectomy. Potential nerve damage of the neurovascular bundle was objectively assessed intra-operatively during prostatectomy with a CaverMap Surgical Aid nerve stimulator (Blue Torch Medical Technologies). Transurethral MRI -guided ultrasound therapy can effectively ablate canine prostate tissue in-vivo. Coronal MR-imaging confirmed the correct placement of the HIFU transducer. MRI temperature maps were acquired during HIFU treatment, and subsequently used for calculating thermal dose. Prescribed target volumes corresponded to the 240 CEM43 thermal dose maps during HIFU treatment in all canines. Ablated volumes on high resolution anatomical, diffusion weighted, and contrast enhanced MR images matched corresponding histological slides after prostatectomy. MRI guidance with realtime temperature monitoring showed no damage to surrounding tissues, especially to the neurovascular bundle (assessed intra-operatively with a nerve stimulator) or to the rectum wall. Our study demonstrates the effectiveness and precision of transurethral ultrasound ablation of prostatic tissue in canines with MRI monitoring and guidance. The canine prostate is an excellent model for the human prostate with similar anatomical characteristics and diseases. MRI guidance with real-time, intraoperative temperature monitoring reduces the risk of damaging critical surrounding anatomical structures in ultrasound therapy of the prostate.

Temperature maps during MRI guided transurethral ultrasound treatment of the prostate.
POSTER NUMBER: 250
FEASIBILITY OF LARGE VOLUME TUMOR ABLATION USING MULTIPLE-MODE STRATEGY WITH FAST SCANNING METHOD: A NUMERICAL STUDY
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When using HIFU to ablate a tumor with large volume, numerous sonications are necessary to cover the whole treatment area in the traditional scanning method with single focus, because the focal size of ultrasound is relatively small compared with that of tumor. In the consideration of safety and efficiency, the treatment parameters including foci arrangement, sonication sequence, duration of each sonication, the intersonication cooling time, need to be effectively determined, which leads to a complex problem of planning. The present paper proposed a multiple-mode strategy to ease the complexity for the HIFU treatment of large tumor, in which fast scanning method was used to generate the basic element of treatment. In the fast scanning method, a single focus was moved rapidly along the predetermined scanning paths with 10 Hz of switching focus frequency, indicating that each sonication on one location was conducted for 0.1 s before the ultrasound focus was immediately steered to the next focus location. The effect of scanning path to the size of lesion and treatment time was negligible, making it suitable for generating treatment element instead of single focus. Three different focus pattern was applied in the fast scanning method and regarded as basic element to respectively ablate target area with the size of 16, 36 and 64 mm^2 in the focal plane. The treatments using multiple modes were investigated by calculating the bio-heat transfer equation, and compared to those using traditional scanning method. The target areas were all fully ablated by using multiple-mode strategy, and the total treatment time were respective 154, 262 and 431 s. Compared to the results of traditional method, the treatment time was significantly reduced. Because the size of basic element formed by fast scanning method in the new strategy was larger than the single focus, the number of required elements for ablation was less. Hence total cooling time between consecutive treatment elements was shorter in the multiple-mode strategy. Based on the simulation results, multiple-mode strategy with fast scanning method is able to fully ablate large tumor, and more efficient than the single focus scanning method. Using different focus patterns in fast scanning method can result in different size of treatment element, which provides more flexibility in applying this new strategy.
TREATMENT TIME REDUCTION THROUGH OPTIMIZATION OF FOCAL POINT TRAJECTORY

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Treatment time reduction is a key point to generalize the use of high intensity focused ultrasound (HIFU) surgery, especially for benign pathologies. Several strategies have been reported to achieve this goal, based on MRI monitoring, optimization of pulse arrangement or multiple focusing with phased array. These strategies aim to maximize thermal build-up while maintaining pre-focal heating at an acceptable level and avoiding overtreatment.

This study aims at quantitatively assessing the potential reduction of the treatment time, arising from using long pulses (~20s) and moving the focal point during the pulses. In this context, the optimization of the focal point trajectory is crucial to achieve a uniform thermal dose repartition and avoid boiling.

At first, a numerical study gave us insights on the relevant trajectories and pulse durations. Then, ex vivo experiments allowed us for comparing the performance of the resulting strategies. We conducted a numerical study to optimize the trajectory of the focal point during a single pulse. Thermal conduction was simulated in 3D with a finite difference code and damages to the tissue were modeled using the thermal dose formula. Given an initial trajectory, the thermal dose field is first computed, then, based on Pontryagin's maximum principle, the trajectory is refined using a gradient method. Several cost functions were implemented and the impact of the modeling assumptions was analyzed. Several initial trajectories and pulse durations were tested.

Then, we quantitatively assessed the resulting optimized strategies by an ex vivo study: single pulses were performed at 3MHz on fresh veal liver samples with an Echopulse. The samples were formerly degased and maintained at an initial temperature of 37°C in a salted water bath. The experiment was monitored with an ultrasound imaging probe. The transducer and the imaging probe were both held by a robotic arm which allowed for a precise control of the motion. The size of each unitary lesion was assessed by cutting each sample along three orthogonal planes and measuring the dimension of the whitened area based on photographs. We estimated the cooling time based on a power level corresponding to a representative clinical situation. Finally, we computed the damage volumetric rate as the volume of the unitary lesion divided by the sum of the pulse duration and the cooling time, which allowed for a relevant comparison of the different strategies. The numerical optimization algorithm was shown to provide a reliable insight on trajectories improving treatment strategies. The use of long pulses appears promising as it allows for a greater thermal build-up compared to short pulses. In ex vivo experiments, the volumetric damage rate was increased by a factor 2 or more on unitary pulses compared to Theraclion current procedure. We proposed a promising approach to significantly shorten HIFU treatment time. An in vivo study needs to be conducted in order to validate the skin safety conditions for long pulses and the reproducibility of lesion size. In order to define a treatment procedure, an algorithm must also be defined to arrange the unitary pulses in order to cover a target in compliance with clinical requirements.
Pancreatic cancer is one of the leading causes of cancer related deaths in the United States with 45,220 new diagnosis in 2013 (cancer.org). Of these patients, only approximately 9000 are expected to survive more than five years. The aggressiveness of this tumor is often associated with the difficulty to resect them and their tendency to metastasize. Treating these tumors with extracorporeal ultrasound transducers is often difficult due to the lack of a good acoustic window. To overcome this limitation we propose an endoluminal treatment that can couple with the pancreas following anchoring at the duodenum or stomach. The objective of this work is to develop and evaluate components of a treatment delivery monitoring platform interface that incorporates MR-guided placement of the transducer (through active tracking coil localization) and treatment monitoring using MR-thermometry proton resonant frequency measurements. A custom interface originally designed for real-time MRgHIFU treatment of canine prostate was modified to incorporate pulse sequences for imaging the pancreas. Two pulse sequences, a scout sequence (minTE=2.26 ms, minTR=3.18ms, minFOV=30cm 128x128) and a thermometry sequence (minTE=7.7 ms, minTR=25 ms, minFOV=30cm 128x128) were designed using HeartVista's Spinbench platform. The Spinbench platform helps generate pulses that are optimized to scanner parameters such as maximum gradient strength and slew rate. These sequences where then uploaded and manipulated using RTHawk to modify sequence parameters such as flip angle and FOV in realtime. A Hadarmard encoding tracking sequence (minTE=2 ms , minTR= 4 ms, minFOV=30cm, samples=512) (Dumoulin et al. MRM 93) was used to help localize the active coils attached to the transducer. Dithering along six orthogonal directions was incorporated to reduce bulk noise (Dumoulin et al. MRM 2010).

An endoluminal ultrasonic applicator (Fig 1A) with active tracking coils was used to perform feasibility test in phantom and ex vivo. Feasibility tests for updating slice location based on tracking coil data were performed on phantom and thermometry sequence was tested in an ex vivo porcine carcass. The two coil locations were used to generate an oblique saggital slice. To visualize the slice that was selected the device was inserted into an agar phantom and axial slices were interleaved along with the slice that was automatically prescribed. A saturation band corresponding to the prescribed slice then became visible. Hadamard encoding tracking coil localization is working and has been incorporated for automatic slice selection demonstrated in phantom since the prescribed slice agreed with the insertion of the device in the middle slot of the agar phantom (Fig. 1B). Thermometry sequence implemented with multislice in cadaveric ex vivo porcine carcass was also successful (Fig. 1C). Evaluations within phantom and carcass indicate interface is ready for implementation in in vivo porcine model. In vivo tests will combine automatic slice selection based on the tracking coil data for treatment planning and MR thermometry for treatment monitoring. Supported by NIH P01 CA159992, and the NSF Graduate Fellowship.
POSTER NUMBER: 253
MICE MELANOMA TREATMENT WITH REALTIME MR IMAGE GUIDED HIFU AT 7 TESLA, FEASIBILITY STUDY
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There are many different High intensity focused ultrasound (HIFU) ablation techniques for the treatment of tumors such as hyperthermia, thermal or mechanical ablation. However the pathologic and immunologic effects of these techniques are often uncertain. Large mice studies to evaluate these effects could help to investigate the response of these treatment techniques. High field (7T) MR guided HIFU gives the opportunity for real time visualization and follow up with high resolution. There for in this study 7T MR guided HIFU to treat mice melanoma is created and evaluated for accuracy and safety. C57Bl/6n wild type mice are subcutaneously injected with B16OVA tumor cells at the right femur. After 10-12 days a tumor size of >7x7mm is reached. Hair at the tumor area was removed with hair removal gel. A 3MHz, 48W acoustic output power HIFU system is placed in a 7T wide bore animal MR scanner. An in-house made gel pad is placed at the membrane of the HIFU system in line with the transducer. The mouse is carefully positioned in the cavity (+/-3.5x3.5x1cm) of the gel pad, which is filled with degassed water for acoustic coupling. An 2x2 array receive surface coil is positioned on top of the mouse. A small phantom cube is positioned next to the mouse. The core temperature of the mouse was measured using a rectal thermometer and maintained using a heated air flow device.
Coronal and axial T1 weighted MR images are acquired to localize the transducer and to check the US beam path. Axial T2 weighted (T2W) images are made before and after treatment for therapy planning. These images are sent to the HIFU trajectory planner software to align the HIFU system with the MR and treatment planning. A test pulse is created within the phantom cube to check the accuracy of the focus spot. After trajectory planning, the ablation is started. The ablation process is visualized using real time MR guided thermometry (single slice GRE-EPI sequence, proton resonance frequency shift method) with a temporal resolution of 1.9s/dynamic. A total of 6 mice were treated with continuous wave HIFU ablation of 4 seconds per focus spot. 3 focus spots were positioned within the tumor. The mice were sacrificed 1 and 3 days after treatment (3mice per group). The tumor was removed for pathologic evaluation, using Hematoxylin and eosin-staining (HE). With the use of the gel pad the mouse could easily be positioned with good acoustic coupling between the transducer and the mouse. The core temperature of the mouse remained between 34-37°C. No skin burns were noted directly after treatment, however 2 mice showed a necrotic point at the skin 1 day after treatment. One mouse had difficulties using the leg 1 day after treatment. The standard deviation from the baseline temperature (after phase drift correction) was 0.35°C, measured over 3minutes. The heated focus spots were accurately correlated with the preset focus spot. The maximum temperature within the focus spots varied between 57 and 70°C. In 4 of the mice a high intensity spot was shown at the preset focus spot on the T2W images after treatment. HE stained sections showed large necrotic areas within the tumor which correlated with the temperature rise shown at the MR thermometry maps, although separate focus spots as shown at the T2W images could not be distinguished.
A stable and safe set up is created to treat mice melanoma using real time temperature measurement at a 7T animal MR scanner. The focus can remotely positioned within the tumor. Further research is now possible for optimization of the treatment settings and follow up MR imaging after HIFU treatment.
MOTION COMPENSATION FOR HYPERTHERMIA TREATMENT IN THE HEAD AND NECK REGION USING MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND: AN IN VIVO FEASIBILITY STUDY

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Tumours in head and neck represent a challenge in oncology because the important presence of critical organs in that area. Hyperthermia with Magnetic Resonance-guided High Intensity Focused Ultrasound (MRgHIFU) is an attractive alternative that can be combined with radio therapy to improve clinical outcome. Breathing motion is often reduced by using immobilizing methods such as fixation masks or molds. However, literature reports indicate that motion remains in the order of few millimetres in the caudal-cranial direction (Br J Radiol. 2006, 79:158). This motion represents a source of noise for thermometry methods based on water-proton resonance frequency shift (PRFS).

This paper presents a method and preliminary results showing the feasibility of performing motion-compensation for hyperthermia treatments in the neck area with MRgHIFU. The omohyoid muscle at the middle section of a pig neck area was targeted for the treatment. Experiments were done using a Sonalleve MR-HIFU system and a 3T Achieva scanner (Philips Healthcare). Animal was under anesthesia and breathing rate was set to 20 bpm with a volume of 200 mL. Baseline temperature was measured with an optic fibre inserted in the neck area close to the targeted region. The neck was immobilized using a mold built with a foaming agent (AC 250, Alpha Craddle) and treatment was performed on the right side of the neck. Motion compensation was achieved by using a modification to a technique based on a look-up table (LUT) (Mag Res Med, 2009, 61:1494). This technique uses displacement information from pencil-beam navigator data to classify the motion based on the breathing phase (inhalation, motionless or exhalation). A zero-phase low-pass filter combined with an ARB-filter predictor was used to classify each displacement value. Images were stored in the LUT and classified according to the navigator-based displacement estimate and the breathing phase. To calculate a new thermal map, the position of the latest image was matched with the closest entry in the LUT. This entry was used for the phase difference step in the PRFS technique. To avoid artifacts introduced by "old" images due to gradual changes, only images captured during the last 200s were kept in the LUT. Control of the Sonalleve system and real-time thermometry was performed using using MatMRI and MatHIFU software toolboxes (J Therap Ultrasound, 2013, 1:7). Imaging was performed with four (4) images per dynamic: three coronal and one transverse. One coronal and transverse image were located at focus. Ultrasound frequency was set to 1.2 MHz. Navigator beam was located the closest as possible to the upper diaphragm. Acquisition was performed during 40 minutes. Thermometry maps calculated with the motion-compensation technique were compared to maps calculated with the standard PRFS technique using only the immediate image before. Motion was observed especially in the regions close to the diaphragm that translated in a noisy estimation of the thermometry. Measured motion was in the order of 1mm. The peak-to-peak temperature variation in the non-heated area was 1.0°C when motion compensation was used. Without motion compensation, this variation was 2.6°C. Results indicated that it is feasible to compensate motion artifacts in the neck area using a PRFS technique based in a look-up table in the context of hyperthermia treatments using MRgHIFU.

A and B: Temperature at focal region (A) and in proximity to the diaphragm (B) on the coronal plane calculated without (red) and with (green) motion-compensation. C: Navigator position and classification of motion. After filtering, the navigator displacement is classified accordingly to the breath phase: motion-less (yellow), inhalation (green) and exhalation (purple). Navigator positions of imaging slides are also shown.
Patients with locally recurrent rectal cancer have severe morbidity and poor quality of life associated with pain, bleeding and obstructive symptoms. Most are ineligible for surgery, while combined re-irradiation and chemotherapy provides limited symptom palliation and tumor control (Mohiuddin et al, Cancer 2002). Clinical data suggests that adding hyperthermia to radiation for inoperable, recurrent rectal cancer improves tumor response (Gonzalez, Thermoradiotherapy & Thermochemotherapy, 1996). However, these studies were flawed by the lack of image guidance, and use of poorly-tolerated and insufficiently-sampled invasive thermal dosimetry, which limited the ability to achieve precise spatial and temporal temperature control. The objective of this work was to evaluate in pigs the feasibility of using MR-guided focused ultrasound to achieve mild hyperthermia in normal tissue targets that correspond to typical locations for local recurrences of rectal carcinoma in the pelvic sidewall. In vivo hyperthermia sonifications were performed with the Sonalleve MR-HIFU platform utilizing modified research software designed for large-volume, long-duration mild heating under MR temperature control (Tillander et al, MRgFUS Symposium 2013). Real-time feedback was based on MR thermometry in five coronal slices perpendicular to the ultrasound beam, and one slice along the beam axis. To mimic treatment of lateral rectal cancer recurrences, the pig was placed in a tilted decubitus position to allow for sonication between the sacrum and ischium towards the rectum. An enema catheter with inflatable cuff was used to fill the rectum with a mixture of degassed water and diluted ultrasound gel, to minimize the presence of air bubbles and acoustic reflection at the rectal wall. Hyperthermia treatment cells of 18 mm diameter were set at a depth of 40 mm from the skin, adjacent to the rectum. Target temperatures of 42-42.5°C were tested with maximum temperature thresholds of 43 and 45°C, using 1.0 MHz sonifications at 120 to 160 W, ranging in duration from 10 to 60 minutes. Contrast-enhanced T1-weighted MRI and gross histology were used to identify unintended thermal damage. Sonication with a target temperature of 42.5°C and maximum temperature threshold of 45°C achieved mean temperatures in the target plane of 42.5 to 42.6°C. The temperatures that 10% and 90% of pixels exceeded (T10 and T90), used to indicate the spatial uniformity of heating within the 18 mm diameter target region on the central image slice, were 43.4-43.7°C and 41.2-41.3°C, respectively. The maximum temperature threshold of 45°C allowed T10 temperatures in near field images to reach a time-average of 43.6 to 45.0°C. For sonication durations of 30 to 60 minutes, this resulted in thermal damage confirmed by a non-perfused region on contrast-enhanced images and coagulated tissue observed upon dissection. Sonication with a target temperature of 42°C and maximum temperature threshold of 43°C achieved mean temperatures in the target plane of 41.9 to 42.0°C with T10 and T90 temperatures of 42.6-42.7°C and 41.1-41.2°C (Figure 1). Near field T10 temperatures averaged only as high as 42.8°C. No thermal damage was observed. MR-guided focused ultrasound was used to achieve mild hyperthermia in anatomical locations of normal pigs that correspond with lateral recurrences of rectal carcinoma in humans. Mild hyperthermia over long sonication durations can be achieved safely through the use of real-time multi-planar temperature control with strict upper temperature bounds.
EVALUATION OF THE PAIN AND LOCAL TENDERNESS IN BONE METASTASIS TREATED WITH MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND SURGERY (MRGFUS)

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It has been reported that MRgFUS has pain palliative effects on the local pain in patients with bone metastasis. However patients often have multiple bone metastases and expansive pain around the lesions, there are not a few cases that focal pain evaluation seemed to be difficult. And so far, pain evaluation were only subjective method with NRS and VAS, we think it is desirable to add objective methods. On the other hand, most of the patients have complained local tenderness on painful bone metastasis, and we noticed a decrease of the local tenderness after MRgFUS treatment. Therefore, we thought that local tenderness evaluated by pain algometer may be useful for evaluate clinical outcome and determine target lesion. The aim of this study is to investigate the change of local tenderness and pain of painful bone metastasis after MRgFUS treatment. We have conducted MRgFUS for pain palliation of bone metastasis using ExAblate® 2100 system (InSightec Ltd, Haifa, Israel). So far, 8 patients had evaluated the local tenderness quantitatively. The mean patients age was 65.6 years [41-81]. The primary cancers differ in each case, except for each two cases of prostate cancer and myeloma. Targeted lesion types were, osteolytic (n=5), osteoblastic (n=2), and mixed(n=1). We evaluated the change of the subjective local pain using the Numerical rating scale (NRS) and the local tenderness using Pressure Pain Threshold (PPT). We measured PPT at the most painful tender point on the bone metastasis and another point where contralateral normal area as control using an electronic pressure algometer (Algomed system, Medoc Ltd.). The NRS score shows a significant decrease (p<0.05) from 6.0 [4-8] at the baseline to 1 [0-3] at 3 months after treatment. The PPTs at metastasis side shows a significant increase (p<0.05) from 10.7 [4.0-43.2] at the baseline to 27.1 [9.4-53.4] at 3 months after treatment. Before the treatment, PPT were 11.5 N[4.0-43.2] at metastasis side and 34.5 N[20.6-66.7] at normal control side, which showed significant difference(p<0.05). The mechanism of pain palliation is most likely local denervation caused by the heat denaturation of the heated area. The result of our study that PPT significantly increased after treatment, seems to support the above mentioned mechanism. And we think that focal tenderness can be used as objective scale for evaluate the palliation of pain, and the palliation of pain can be obtained when we treat the lesion that has low PPT.
POSTER NUMBER: 257
HIGH INTENSITY FOCUSED ULTRASOUND FOR THE TREATMENT OF DEGENERATED INTERVERTEBRAL BOVINE DISCS: THERMAL RESPONSE OF BOVINE DISCS
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High Intensity Focused Ultrasound (HIFU) can be used for the non-invasive removal of degenerated nucleus pulposus (NP) in the intervertebral disc (IVD), potentially enabling its replacement using injectable hydrogels. The key underlying mechanism is cavitation, but due to high absorption and non-linearity within the NP, thermal effects are also possible. In this study, the thermal responses of cells and collagen within the IVD were investigated to identify the maximum temperature rise that can be safely induced without disc damage. Two HIFU transducers (0.5 MHz), one with a co-axial imaging array and the other with a co-axial single element passive cavitation detector, were confocally aligned onto a thermocouple embedded in the centre of a bovine IVD, which was immersed in a degassed water tank kept at 37°C. Using a range of duty cycles, the HIFU-induced temperature elevation was kept constant at different values ranging from 43°C to 70°C for 10 minutes. Cell survival and collagen structural changes were assessed histologically. Cell death was found to occur for temperatures around 50°C for 10 minutes, whilst collagen denaturation required significantly higher temperatures. During cavitation-inducing HIFU exposures of the IVD, temperature elevations as large as 10°C can thus be tolerated without direct thermal damage.
POSTER NUMBER: 258
THERAPEUTIC EFFECT OF ULTRASOUND-MICROBUBBLES WITH GOLD NANOROD LASER THERMAL THERAPY
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Gold nanorod laser thermal therapy (AuNR+L) is a non-invasive method of increasing the temperature of a target tissue using near infrared light. In this study, the effect of treatment order of ultrasound and microbubbles (USMB) in combination with AuNR+L were investigated in an in vitro cell model. MDA-MB-231 cells in suspension were treated with combinations of (1) USMB at 500 kHz frequency, 16 cycles, 1 kHz pulse repetition frequency and Pneg of 0.6 or 1.0 MPa for one minute in the presence of Definity microbubbles (1.7% v/v) , (2) laser (L) at 810 nm and 1.9 W/cm² for three minutes, and (3) mPEG coated AuNR with a peak absorption wavelength of 813 nm at a concentration of 3x10¹¹ np/mL. Cells were treated with combinations of AuNR, laser and USMB with 3 different treatment orders: 1) AuNR and USMB followed by L, 2) AuNR +L followed by USMB, and 3) USMB followed by AuNR+L. Cells were analyzed using propidium iodide as a cell viability stain with flow cytometry (VPI) and colony assays (VCA). Sample temperature was monitored with a thermal camera during laser treatment. Cell viabilities were compared using student t-test to the values predicted by the Bliss Independence Model. USMB improved cell death when combined with AuNR+L. VPI of 17±2% (Pneg = 0.6 MPa) and 11±4% (Pneg = 1.0 MPa) were observed with combined treatment of AuNR and USMB followed by L compared to VPI of 22±3% with AuNR+L. VPI of 60±2% with USMB at 0.6 MPa and 42±3% with USMB at 1.0 MPa alone. The effect of AuNR+L and USMB combined treatment was additive regardless of treatment order. Combining AuNR+L and USMB resulted in predicted viability of 13±2% at 0.6 MPa and 9±2% at 1.0 MPa. However, cell viability varied with treatment order. The most significant therapeutic effect occurred when AuNR+L was performed prior to USMB at 1.0 MPa which decreased VPI to 5±3%. VCA results agreed with the additive effect caused by combining AuNR+L and USMB for all treatment orders. In addition, cell viability correlated with the average sample temperature. In the absence of AuNR, samples exposed to laser prior to ultrasound treatment at 0.6 MPa increased cell viability by 13% (p<0.05) showing a protective effect which is consistent with previous biomodulation studies that show a protective effect from NIR light on cells. The combined effect of AuNR+L and USMB increased cell death compared to either treatment alone. In addition, cells exposed to low intensity NIR light appear to be protected against ultrasound and microbubble exposure.
POSTER NUMBER: 259
ULTRASOUND ABLATION VERSUS REGIONAL HYPERTHERMIA INDUCE DIFFERING IMMUNE CELL PROFILES IN A MURINE BREAST CANCER MODEL
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Hyperthermia is a well-documented tumor-treatment modality that has long been used as an adjunct to chemotherapy, radiotherapy and other cancer treatments. Its use in clinical practice is based on the observation that direct cytotoxicity and sensitivity to chemotherapeutics and radiotherapies are enhanced when temperatures above 41-42°C are applied to the tumor as a function of time. Additionally it is now thought that the anti-cancer effects of hyperthermia may be due to a synergy between direct cytotoxicity and upregulation of anti-tumor immunological responses. To investigate whether traditional mild hyperthermia (41–45°C) or high-temperature ablation therapy (>55°C) achieves enhanced anti-tumor immunity, we compared the therapeutic effects of two hyperthermia temperatures, 42 and 60°C, in terms of alterations in immune cell profiles in a mouse metastatic breast cancer model. Ten female FVB mice bearing bilateral NDL tumors in the mammary fat pad were separated into three treatment groups (No-Treatment Control, n = 3; Hyperthermia, n = 3; Ablation, n = 4). Tumors (one tumor per mouse) were ablated with MR-guided High Intensity Focused Ultrasound (Image Guided Therapy, France) for 7 seconds with 5.75 W acoustic power at 3 MHz and reached a maximum temperature of 60°C. Mild hyperthermia was achieved using a modified Siemens Antares ultrasound scanner, a custom dual-mode linear array transducer, and a temperature feedback system. One tumor per mouse was heated to 42°C for a total of seven minutes with approximately one minute temperature rise time (from 37°C), using a mechanical index of 1.9, acoustic pressure of 2.4 MPa and total acoustic power of 4.7 W. To investigate the hyperthermia-induced immunological response, one week after treatment, tumors and spleens were extracted and enzymatically digested. To label CD4+ and CD8+ T cells, regulatory T cells, macrophages, dendritic cells and natural killer cells, single cell suspensions from each tissue were incubated with Fc block (BD Biosciences) followed by staining with anti–mouse antibodies, including CD3, CD4, CD8, CD45, F4/80, CD11b, MHCII, CD11c, CD25, FOxp3 and CD122. FCS data files were collected using a Fortessa cell analyzer with FACSDiva software (BD). All datasets were analyzed using FlowJo software.

Ablation versus mild hyperthermia heating result in different immune cell profiles within treated tumors. Application of regional hyperthermia at the ablation temperature of 60°C induced significant increases in immune cell recruitment to the treated tumor site whereas conventional mild hyperthermia (42°C) reduced infiltration of the same immune cell populations. The numbers of macrophages, dendritic cells, natural killer cells and CD8+ T cells in ablation-treated tumors were all significantly increased with respect to the no-treatment control (p < 0.05) and hyperthermia-treated tumors (p < 0.01). Within hyperthermia-treated tumors, a trend toward a reduction in these same cell populations was observed, with CD4+, CD8+ and regulatory T cell numbers being significantly lower than those in control tumors (p < 0.05). Contralateral tumors not receiving treatment displayed immune cell profiles similar to those of control tumors, and all animals exhibited comparable splenocyte immune profiles. The significant increase in immune cell number within the tumor may play a role in the underlying anti-tumor mechanisms of a localized ablation treatment strategy.

Macrophage, dendritic cell, natural killer cell and T cell numbers in hyperthermia- and ablation-treated tumors compared to control tumors. * p < 0.05, ** p < 0.01.
Breast cancer is the commonest cancer in women in the UK, accounting for 30% of all new cancers in women, with an estimated 49,500 new cases in 2010(1). With the widespread negative publicity around over-diagnosis and over-treatment of low risk breast cancers, interest in the application of non-invasive treatments such as magnetic resonance imaging (MRI) guided high intensity focused ultrasound (HIFU) has increased. Development has begun of novel US transducers and platforms specifically designed for use with breast lesions, so as to improve the range of breast lesions that can be safely treated. However, before such transducers can be evaluated in patients in clinical trials, there is a need to establish their efficacy. A particular issue is the accuracy of temperature monitoring of FUS with MRI in the breast, since the presence of large amounts of surrounding fat can hinder temperature measurement. An appropriate anatomical model that imposes similar physical constraints to the breast and that responds to FUS in the same way would be extremely advantageous. The aim of this feasibility study is to explore the use of Thiel embalmed cadaveric tissue for these purposes. We report here the early results of laboratory-based experiments sonicating dissected breast samples from a Thiel embalmed human cadaver with a high body mass index (BMI). A specially developed MRI Compatible chamber and sample holder was developed to secure the sample and ensure reproducible sonications at the transducer focus. A HIFU transducer of frequency of 1.08 MHz and focal length of 69mm was used for sonications. An MRI compatible thermocouple was used to measure the temperature rise induced in the chosen tissues by sonication. A rectangular block of breast tissue was carefully dissected from the breast sample without damaging the skin. The efficacy of sonication was first studied with chicken breast and porcine tissue. The experiments were then repeated with the dissected fatty breast tissue samples from the soft-embalmed human cadavers. Sonications of chicken breast and porcine tissue yielded visible lesions over 2cm in size, indicating that sonications were accurate (Sonication parameters: Power-60W, Sonication time- 3 min). The thermocouple recorded temperatures up to 95 degrees Celsius. However, sonication of Thiel breast tissue failed to produce a discrete lesion. The sonicated Thiel breast tissue (which was largely fatty as shown by mammography (Fig 1) of the specimen) was examined histopathologically, which confirmed the absence of any discrete lesion. To investigate further, fresh chicken breast tissue was embalmed and the embalmed tissue was sonicated with the same parameters. The results confirmed the inability to produce a discrete lesion in the Thiel embalmed samples. Initial experiments sonicating fatty Thiel breast tissue & Thiel chicken have not produced visible thermo ablated zones. We suspect that this is a result of the denaturation of tissues produced by the salt solution used for Thiel embalming. It may also reflect the fact that the sonicated tissues were initially at room temperature rather than body temperature. The preliminary results shows that the best model for pre-clinical HIFU trails will be the fresh breast tissue. However, more experiments will be needed before driving further conclusions.


Fig 1. Mammogram of the fatty Thiel breast tissue.
Polyethylenimine (PEI), a cationic polymer, has been shown to aggregate plasmid DNA and facilitate its internalization. It has also been shown that combining ultrasound (US) with PEI could enhance and prolong in vitro and in vivo transgene expression. However, the role US in the enhancement of PEI uptake is poorly understood. This study investigates the impact of US on PEI-mediated gene transfection. Specific endocytosis pathway siRNA, including clathrin HC siRNA, caveolin-1 siRNA and PKC-δ siRNA, are used to block the corresponding endocytosis pathways prior to the transfection of luciferase DNA/PEI polyplexes to cultured cells by 1-MHz pulsed US. Transgene expression was found to not be enhanced by US treatment in the presence of the PKC-δ siRNA. We further demonstrated that PKC-δ protein could be enhanced at 6 hr after US exposure. Moreover, intracellular calcium levels were found to be significantly increased at 3 hr after US exposure, while transgene expressions were significantly reduced in the presence of calcium channel blockers both in vitro and in vivo. Our results suggest that US enhanced PEI-mediated gene transfection specifically by increasing PKC-δ related fluid phase endocytosis, which was induced by increasing the intracellular calcium levels.
POSTER NUMBER: 262
COMBINED BEVACIZUMAB AND FOCUSED-ULTRASOUND INDUCED BLOOD-BRAIN BARRIER OPENING FOR GLIOMA TREATMENT: PRECLINICAL EVIDENCE IN MICE
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Bevacizumab (BEV) is an antiangiogenic drug approved for glioblastoma (GBM) treatment. However, it does not increase survival and is associated with glioma invasion. One factor contributing to this poor clinical performance of brain cancer is limited access to tumor across the blood-brain barrier (BBB). Microbubble-facilitated focused ultrasound (FUS) has been shown to be able to locally and reversibly open the BBB and brings opportunity to deliver therapeutic agents to the target brain for CNS disease treatment. The purpose of this study is to use an intracranial human glioma model (U87) in nude mice and evaluate the usefulness of combining FUS-BBB opening and BEV delivery to enhance antiangiogenic effect and tumor progression control. 18 male nude mice were obtained and injected stereotactically with $3 \times 10^5$ human glioma (U87) cells for brain tumor model establishment. 7-10 days after tumor implantation, mice received 50 microliters BEV (Avastin®) intravenously and FUS exposure weekly totally for 5 weeks. We performed histopathological analysis of tumors treated with FUS or BEV alone or in combination, followed tumor progression response via magnetic resonance imaging (MRI). Animal survival was also monitored. Our results showed that the IV administered Bevacizumab combined FUS treatment can successfully restrain the brain tumor growth from 3,602% to 843% within 5 weeks and increase the survival from 5 weeks to over 10 weeks. Longitudinal MR monitoring also showed the tumor-necrosis region occurred earlier than the control group. Inhibition of vascular endothelial growth factor (VEGF) expression were also confirmed with immunohistochemical (IHC) examinations, demonstrating the effectiveness of the enhanced delivery of Bevacizumab improve antiangiogenic effect as well as glioma treatment efficacy. This study provides useful information that using FUS-BBB opening indeed provides benefits on enhancing Bevacizumab delivery for glioma treatment, and may provide alternative to improve current clinical brain tumor therapy.
Inertial cavitation is the primary mechanism for ultrasound-assisted transdermal drug delivery. The violent collapse of bubbles and associated microjets are believed to be responsible for increased skin permeability, whilst existing studies have incorporated chemical permeability enhancers acting synergistically with ultrasound to improve transdermal diffusion of a liquid drug (Mitragotri et al., 2000). However, deposition of liquid droplets on the skin surface is impractical and no mechanisms have been proposed to date for the active transport of a therapeutic from a dosage form such as ultrasound coupling gel. Work by the authors has shown that inertial-cavitation-induced microstreaming can enable active convection of drug molecules embedded within an ultrasound matching gel, overcoming the increased viscosity that may hinder delivery (Bhatnagar et al., In submission). In the present study, a novel gel formulation that includes a fluorescently labelled model drug (bovine serum albumin) and artificial cavitation nuclei is used in conjunction with exposure parameters known to maximize inertial cavitation activity to investigate whether ultrasound can be used to actively deliver a therapeutic from the gel into skin. BSA labelled with FITC dye and cavitation nuclei (talc) were added to a commercially approved ultrasound coupling gel at concentrations of 1.3mg/ml, and 0.25% w/v respectively. Electrical conductivity of the skin pre and post- ultrasound exposure was measured via electrodes placed in PBS in the donor and receiver compartments separated by skin in a Franz diffusion cell (Mitragotri et al., 2001). 3ml of loaded gel were placed into donor compartment of height 15mm, positioned below a therapeutic ultrasound transducer (Sonic Concepts H117D, active diameter 64mm, 60mm focus) with a water-filled applicator cone designed to ensure that the focus lies 1mm above the skin. Ultrasound parameters (265kHz frequency, 1.4MPa PRFP, 10ms pulse duration, 10Hz pulse repetition frequency, 90s exposure duration) were selected on the basis of previous work to maximize acoustic emissions associated with inertial cavitation. Acoustic emissions were recorded throughout exposure using a 5MHz passive cavitation detector confocally and coaxially aligned with the therapeutic transducer, as previously described (Hockham et al., 2010). Post exposure, depth and spread of delivery in sections of skin (300x300x50µm) was visualised in 3D using confocal microscopy. 3D confocal microscopy showed a 3-fold increase in the amount of labelled BSA that was able to penetrate up to 50µm into the skin in the presence of cavitation nuclei. Analysis of acoustic emissions showed a 6-fold increase in inertial cavitation activity over the exposure period with cavitation nuclei in the gel, resulting in a doubling in skin conductivity. This study has shown that the addition of cavitation nuclei enhances the delivery of a protein from a gel into the skin, presenting a possible alternative to the use of chemical penetration enhancers for ultrasound-assisted transdermal delivery. Acoustic emission data confirmed the increased presence of inertial cavitation when cavitation nuclei were present, yielding enhanced transport into the skin. Recorded increases in inertial cavitation activity were found to correlate with a corresponding increase in skin permeability as measured by changes in conductivity. It is thus hypothesized that nuclei-promoted inertial cavitation within the donor layer presents a dual benefit, both enhancing skin permeability and enabling active transport from the donor layer into skin by virtue of cavitation-induced microstreaming.
POSTER NUMBER: 264
SONOSENSITIVE NANOLIPOSOMES RELEASABLE EXCLUSIVELY BY SONOVUE-
NUCLEATED INERTIAL CAVITATION
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To develop inertial-cavitation-sensitive liposomes for triggered drug release at acoustic
intensities comparable to those achieved by diagnostic ultrasound (US) scanners in the
presence of SonoVue® microbubbles (SV). Liposomes made of HSPC, cholesterol and DSPE-
PEG 2000 were prepared using thin film hydration and size-reduced to 120-150 nm by
membrane extrusion. Doxorubicin or luciferin was remotely loaded into the liposomes by citrate
buffering. Liposomes were insonated using a 0.5 MHz spherically focused ultrasound
transducer (FUS) driven with a pulse length of 100 ms at a 5% duty cycle for 30s, at peak
rarefractional pressures (PRP) of 0.14, 0.5, 0.8, 1.2 and 1.5 MPa, in the presence or absence of
SV. Acoustic emissions were measured using a 7.5 MHz passive cavitation detector coaxially
and confocally aligned with the FUS transducer. Doxorubicin release was measured by
fluorimetry whilst efficacy was assessed using an in vitro B16F10-luciferase cell viability assay.
In vivo studies were carried out by intravenously injecting luciferin loaded liposomes and SV in
C57Bl6 mice bearing B16F10-luciferase tumors and exposing to US as described above at 1.2
MPa PRFP. Imaging of luciferin release was performed using an IVIS 100 system. In vitro and in
vivo analysis of stability at 37°C for 30 min demonstrated that DSPE liposomes showed leakage
of payload that was minimal (5%) and equivalent (p>0.05) to that seen with HSPC liposomes.
However, cavitation-triggered drug release was highly dependent on lipid composition with
DSPE liposomes demonstrating a 30% increase in luciferin release compared to 0% with HSPC
liposomes. Notably, in vitro studies showed no luciferin release from DSPE liposomes in
absence of SV, and therefore cavitation, over the 0.14 -1.5 MPa PRFP range, demonstrating the
requirement for co-administrating cavitation nuclei. Similarly no release was observed in the
presence of SV at pressures of 0.14, 0.5 or 0.8, despite the instigation of stable cavitation, as
evidenced by the detection of harmonic emissions. In contrast, the presence of SV did trigger
luciferin release from the liposomes when 1.2 or 1.5 MPa US was applied and high levels of
inertial cavitation, as evidenced by the detection of broadband emissions, were detected. When
doxorubicin was used as the payload instead of luciferin, the same results were observed. In
vivo studies showed a 16-fold increase (p<0.001) in photons/sec/cm2 in tumors of liposome+SV
+US treated mice compared to non-US liposome+SV treated mice, suggesting significant
enhancement of delivery of luciferin to the luciferase expressing cancer cells. Liposomal
composition plays a crucial role in determining sensitivity to cavitation- triggered drug release.
Drug release can be reproducibly triggered from DSPE liposomes using modest acoustic
intensities in the presence of SV, whilst passive cavitation detection provides a low-cost method
for non-invasive monitoring of drug delivery in real time.
POSTER NUMBER: 265
CHARACTERIZING THE PRESSURE FIELD IN A MODIFIED FLOW CYTOMETER QUARTZ FLOW CELL: A COMBINED MEASUREMENT AND MODEL APPROACH TO VALIDATE THE INTERNAL PRESSURE.
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Flow cytometry has been adapted to characterize ultrasound contrast (thin-shelled) microbubbles with high throughput. An ultrasound transducer is affixed to a flow cell to activate the microbubbles as they pass through the interrogation zone of the cytometer. Without ultrasound activation, the population distribution of the microbubbles is obtained. With ultrasound, the dynamical response is fitted to a bubble dynamics model to extract the shell viscosity and elasticity modulus. The objective of this study was to develop a calibration method for the pressure field. A 3-D finite element method (FEM) model was developed to predict the pressure within the 200-µm flow channel. Because the channel is too small to accommodate a hydrophone, the pressure field propagating through the flow cell and into water was measured and compared to the model results. In order to measure the pressure field, the flow cell was placed against a water surface so that the acoustic waves passing through the cell could be measured with a hydrophone (Fig. 1). Short and long (simulating continuous wave) sinusoidal tone-bursts were applied at 0.5MHz, 1MHz, and 2MHz (near the resonance frequency). A 3D-positioning stage with 10 µm precision was used to scan along the long and short axes of the flow cell and record acoustic pressures at different points with a minimum step size of 500 µm. The voltage measured at the PZT was also recorded. A finite element multiphysics model in Comsol was used to simulate the experimental conditions for comparison to our experimental measurements. Both 2D and 3D simulations were performed using COMSOL’s acoustic-piezoelectric interaction physics module for time dependent and frequency domain models. The mesh resolution was defined in each material based on the material sound speed to yield 7 elements per wavelength using 2nd order tetrahedral elements. We utilized two 3D simulation paradigms; the first being a time dependent simulation and the second a frequency domain study. The time dependent simulation is driven by an input voltage across the PZT electrodes which goes on to develop structural displacements which are then propagated as an acoustic simulation through the quarts and into the water. The pressure waves predicted by the simulation were directly compared to the hydrophone measurements from our experimental setup. The frequency domain study allowed us to look at field metrics and trends in a less computationally expensive forum. Scans along the x- and y-axis (along the long and short axes of the flow cell) compared favorably with the model predictions at 1.0 MHz. At 2.0 MHz, there are significant differences between the predicted pressure and the measured time trace. We hypothesize that near resonance, the vibrations are much more complex, leading to larger discrepancies. When applying the same electrical input voltage in the model as the measured voltage experimentally, the model accurately predicted the pressure as measured by a calibrated hydrophone. The model further captures the change of individual pulse shapes. We developed a measurement-model approach to validate the pressure field in the flow channel using hydrophone measurements outside the channel in a water bath. The favorable fit with the data suggests that the model accurately models the pressure field in the flow cell at our working frequency of 1 MHz.

Figure 1. Schematic of the experimental setup. The centerpoint x0,y0,z0" is defined as being 1 mm below the quartz flow cell, centered below the PZT.
Recently, many researches about the application of ultrasound and microbubbles (MBs) to the medical field have been conducted. Should MBs be manipulated contactlessly, it will contribute to the mechanism investigation on the drug delivery system (DDS) using MBs as drug carrier or the gene transfer. It is expected that the technique allows MBs accumulate selectively on target cells and allow the positional relation between cells and MBs to be investigated quantitatively. In previous works, using primary Bjerknes force, MBs flowing in a microchannel were pushed or driven one-dimensionally to create high concentrations or to select the flow direction at a junction. However no technique has yet to be established that can trap MBs at any desired position, manipulate them in any desired direction, and along any desired path with precise two-dimensional control. Accordingly in this research, we investigated whether it was possible to trap MBs at desired position, manipulate them in desired direction, and along desired paths through experiments aimed at the development of MB manipulation tools that utilize ultrasound. Moreover, we will propose to verify the validity as the tool by evaluating the accuracy of MB manipulation. Bubbles in the ultrasound wave field are subjected to the primary Bjerknes force which is an acoustic radiation force represented by product of MBs volume and gradient of pressure. In a standing wave field, this force drives bubbles to certain direction that is to the antinode if bubbles are smaller than the resonant radius and that is to the node if bubbles are larger. Our method aimed that MBs are trapped at the antinode or the node and manipulated with moving the position of the antinode or node. We fabricated two devices. The one has a 30mm diameter ring shaped transducer divided into six elements, and another has a concave transducer which radiates focused ultrasound and its focal length is 40mm. Frequency is 1.0MHz and 2.0MHz, respectively. We used sonazoid™ as MBs and they were trapped at the focal point with the incident ultrasound. The ring-transducer changes frequency per element to move its focal point and the concave transducer moves its own position to manipulate MBs. In an experiment with the ring-transducer, MBs were trapped concentrically as shown in Fig. 1 and we could manipulate MBs along an aimed path which is a hexagonal 200μm length of one side with phase control which. In an experiment with the concave transducer, MBs were trapped at the focal point and manipulate along a rectangle of about 0.5×0.5 mm by moving the concave transducer itself. In these results, a bubble-cloud contains about 100 MBs was trapped and manipulated. Fig. 2 shows the path of the concave transducer and trapped MBs. From these results it is implied that MBs can be manipulated along any desired path. To verify the validity of the method, we will evaluate performance such as trapping force and manipulation accuracy. Fig. 1 shows MBs trapped concentrically. Fig. 2 shows paths of the concave transducer and trapped MBs.
Sonodynamic therapy (SDT) of cancer is based on preferential uptake and/or retention of a sonosensitizing drug in tumor tissues and subsequent activation of the drug by ultrasound irradiation. Ultrasound can penetrate deeply into tissues and can be focused into a small region of a tumor to activate a sonosensitizer. Here, we evaluated immediate antitumor effects of short pulsed HIFU (high-intensity focused ultrasound) combined with Titania-silica aqueous solution on an oral squamous cell carcinoma cell line (HSC-2) in vitro. Oral squamous cell carcinoma cells were maintained in a MEM medium (Wako, Osaka, Japan) with 10% Fetal Bovine Serum 37.0 degree C in humidified air with 5% CO2. Cell viability before treatment was always over 95%. Suspended oral squamous cell carcinoma cells (2×10^6 cells/ml) were irradiated in 24-well film bottom plates with HIFU (frequency, 3.5 MHz; burst rate, 100 Hz; duty cycle, 50%) in the presence and/or absence of “RINKOH”. Cell viability of the cells exposed to different US intensities of 60, 100, 160, and 210 W/cm^2 was measured immediately after HIFU irradiation for 0, 0.1, 1, or 3 seconds. Cytotoxic effect of RINKOH with HIFU in vitro was greater than that of RINKOH or HIFU alone. Cell viability had direct correlation with the intensity and duration of HIFU exposure, as well as concentration of RINKOH in the suspension. The effect of cell killing in vitro was more enhanced by the combination of RINKOH and HIFU than each of them alone. The effect had direct correlation with the applied mechanical energy (intensity and duration of HIFU exposures) and concentration of the RIKOH in the medium. High intensity ultrasound was able to intensify TiO2/SiO2 transfection into cytoplasm of the tumor cells, which normally are tightly guarded by the cell membrane, preventing introduction of any extracellular molecules. Mechanism of toxicity and increased transfection involved at least mechanical cavitation, since the results represent the findings immediately after the interaction with HIFU. Our findings provide a rational basis for the development of an effective HIFU based sonodynamic activation method.
POSTER NUMBER: 268
LOCALIZED DELIVERY AND BIOEFFECTS OF THE NEURTURIN NEUROTROPHIC FACTOR THROUGH THE FOCUSED ULTRASOUND MEDIATED BLOOD-BRAIN BARRIER OPENING IN WILD TYPE AND PARKINSON'S DISEASE ANIMAL MODEL
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The blood-brain barrier (BBB) constitutes a major obstacle in drug delivery to the brain. Focused Ultrasound (FUS) in conjunction with microbubbles has been shown to open the BBB non-invasively, locally and transiently to allow the delivery of molecules to the tissue parenchyma. Neurturin (NTN), a member of the glial cell-line derived neurotrophic factor family, has been demonstrated to have neuroprotective and regenerative effects on dopaminergic neurons, suggesting its therapeutic potential for Parkinson's disease (PD). The ascending nigrostriatal pathway, i.e., neurons in the substantia nigra (SN) projecting to the caudate putamen (CP), is the most severely damaged brain system in PD and was therefore selected as the target area in this study, aiming to delivery NTN to those area and investigate the bioeffects first in wild-type mice and then in MPTP-lesioned PD mouse-model. First, using FUS (center frequency: 1.5 MHz, PRF: 10 Hz, peak negative acoustic pressure: 0.45 MPa) in conjunction with systemically administered polydisperse lipid-coated microbubbles (mean diameter: 1.3 μm), the acoustic parameters and sonication locations were optimized in CB57/bl wild type mice (n=20) for efficient and safe drug delivery in both CP and SN. Fluorescence microscopy and Magnetic Resonance Imaging (MRI) were used to quantify and assess the BBB opening characteristics after the injection of fluorescently-tagged dextrans and gadolinium, and safety was assessed upon histological examination of H&E stained brain sections. For the second part of this study, NTN (20 mg/ kg, Invitrogen, CA, USA) diluted in saline was injected intravenously to wild type mice after BBB opening. The diffusion and the downstream signaling bioactivity were detected using immunostaining for NTN, as well as for its downstream signaling molecules: phosphorylated RET, ERK1/2 and CREB. Finally, for the third part of the study, NTN effects in PD disease MPTP-model mice were studied. The volume of opening after FUS could cover the entire CP with an average volume of opening 39.4 ± 4.1 mm3 when two non-overlapping sonication locations were targeted. A single sonication location target could cover the SN with an opening volume of 18.6 ± 4.7 mm3, while BBB-openings were monitored longitudinally and their closing, i.e. reversibility, timeline was found to 4-5 days for both the CP and SN. No damage was detected upon histological examination of the brain tissue. Microscopy of brain horizontal sections revealed NTN's bioavailability, i.e. diffusion in the brain tissue, in the entire area of CP (9.1 mm2 ± 1.1 mm2) and SN (4.6 ± 0.7 mm2). No downstream signaling activation was detected due to FUS alone. Quantification showed a 175% relative difference between the FUS-treated and the control side. The bioavailability of the protein after FUS was also compared to the bioavailability after the conventional method of direct injection (D.I.) of NTN to the CP and SN formations independently, which were found to be limited to an average area of 0.23 ± 0.04 μm2 around the injection site. Preliminary results showed neuro-preservation in the FUS+NTN group compared to the control groups. These findings confirm the effective delivery of NTN to the murine brain parenchyma which could also serve as a good therapeutic candidate for reversing the PD phenotype in animal models.
ENHANCED ANTICANCER IMMUNE MODULATION OF COMBINED IL-12 ADMINISTRATION WITH FOCUSED-ULTRASOUND BLOOD-BRAIN BARRIER OPENING IN GLIOMA ANIMALS
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Focused ultrasound (FUS) can be applied to temporally and locally open the blood-brain barrier (BBB), and has been applied for CNS anticancer therapeutic molecule delivery for glioma treatment. BBB-opening can induce substance exchange between CNS parenchyma and vascular circulation, therefore immunological response may be triggered or modulated. The purpose of this study is to elucidate the possibility of concurrent FUS-BBB opening with enhanced delivery of anticancer immune-triggering chemokine (IL-12) for glioma treatment. Cultured C6 glioma cells implanted in Sprague-Dawley rats were used as the tumor model. IL-12 was administered intraperitoneally for enhance systemic immune response. A 500-kHz burst tone focused ultrasound energy combined with microbubble administration was delivered to transcranially open the blood-brain barrier (BBB). The anticancer immune-triggering chemokine, IL-12, was delivered concurrently during the treatment phase to evaluate the immunological response modulation to tumor progression. Animals with FUS exposure conducted flow cytometry analysis to verify consequent immune cell population change of tumor-infiltrating cells (TILs) groups including regulatory T lymphocytes, cytotoxic T lymphocytes, as well as macrophages. Brain sections of sacrificed animals were also used to perform histological and immunohistochemical (IHC) analysis. For glioma-bearing animal group, tumor progression and survival was analyzed, which tumor progression was followed in vivo via T2-weighted magnetic resonance (MR) imaging. We demonstrated that with the pressure capable of inducing BBB-opening, no significant change of the immune cells were found in spleen and abdominal lymph node, indicating no hazardous systemic immune response was induced. However, the immune cells including significant TILs and macrophage population change locally in brain tumor region. Focused ultrasound exposure alone can successfully trigger cytotoxic-T lymphocytes and helper-T cells, and FUS-BBB opening can effectively modulate the permeability of the tumor-infiltrating lymphocytes, but the concurrent IL-12 administration can significantly enhanced immunological response. We also found that combined IL-12 administration and FUS-BBB opening provide the most significant tumor progression suppression as well as animal survival improvement. This study provide evidence to confirm FUS-BBB opening combined with immune-modulating agent may benefit anticancer immune response for cancer treatment.
POSTER NUMBER: 270
CONTROL AND MONITORING OF FOCUSED ULTRASOUND INDUCED BLOOD-BRAIN BARRIER OPENING USING DUAL-CONFOCAL ULTRASOUND TRANSDUCER
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Burst-mode focused ultrasound (FUS) exposure combined with the presence of micro-bubbles has been proved to induce local and reversible blood-brain barrier (BBB) opening effect. However, the current FUS-BBB opening effect is post-operatively observed and validated with the use of contrast-enhanced magnetic resonance imaging, and cannot be monitored intra-operatively. This thesis aims to explore the use of confocal concentric-ring type focused ultrasound transducer to perform the FUS-BBB opening and simultaneously record the echo signal at the focal positions to explore the possibility of real-time BBB opening observation. The signals, received by focused ultrasound transducer, were analyzed by energy spectral density, and the analysis characterized and quantified sub-harmonic oscillations that occur when the BBB is disrupted. And then, we used this characteristic to design a feedback control system to control the time of treatment. We found that increasing the exposure level until a sub-harmonic emission signal was observed was an effective means to ensure BBB disruption. We had the sensitivity of 92% in feedback control system and the specificity of 92.3%. In this study, we have demonstrated that the use of confocally arranged double ring FUS transducer with subharmonic-based passive acoustic emission detection can successfully monitor FUS-induced BBB opening. We reported the sensitivity and specificity can reach 92 and 92.3%. This study may provide useful and valuable information when designing a feedback control system.
OPTIMAL CONDITION FOR ULTRASOUND FOR MICROBUBBLE-NANOLIPOSOME COMPLEX MEDIATED DELIVERY

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The purpose of this study is to set up the optimal condition for ultrasound and microbubble (MB) + Nanoliposome Complex mediated gene and drug delivery and to evaluate the uptake ratio. MB-FITC complex including SF6 gas and FITC was synthesized using various phospholipids including DPPC and DSPE-PEG-SPDP. Lipid film was made of the mixture of DPPC, DSPE-PEG-SPDP, and FITC and then transferred to hermetic vial and filled by SF6 gas. MB containing FITC was prepared.

Nanoliposome containing Texas red is composed of DPPC and Texas red. As the same method with MB-FITC synthesis process, lipid film was prepared. Texas red in H2O was poured onto lipid film and then lipid film was sonicated by a bath-type sonicator. Nanoliposome-Texas red complex was added into MB-FITC complex and stirred.

In order to target SkBr3 that is a breast cancer cell overexpressing HER2 receptor, trastuzumab (Herceptin®) that interferes with the HER2/neu receptor was used. MB-FITC+Nanoliposome-Texas red stirred with trastuzumab in overnight. Finally, MB-FITC+Nanoliposome-Texas red + Her2Ab complex was prepared.

To induce delivery by ultrasound, SkBr3 was treated by ultrasound. The ultrasound device (SONIDEL SP 100, MA, Sonoporator) equipped the 1 MHz probe was used. Several parameters including intensity (w/cm²), time (minutes), duty cycle (%) were changed; 1 w/cm², 1 min, 20 %; 1 w/cm², 1 min, 60 %; 1 w/cm², 2 min, 20 %; 2 w/cm², 1 min, 20 %; 1 w/cm², 2 min, 60 %; 2 w/cm², 1 min, 60 %; 2 w/cm², 2 min, 20 %; 2 w/cm², 2 min, 60 %. Confocal laser scanning microscopy (CLSM) was used to confirm the delivery of MLC into SkBr3 cells after ultrasound insonication. The MB-FITC+Liposome-Texas red+Her2Ab complex including fluorescent dyes and trastuzumab was synthesized successfully. By treating the complex to SkBr3, the targeting effect of trastuzumab of the complex was confirmed by CLSM. The membranes of SkBr3 showed green (FITC) and red (Texas red) fluorescence but the case of MB-FITC+Liposome-Texas red without Her2Ab did not show any fluorescence. The optimal conditions for ultrasound mediated delivery were 1 w/cm², 2 min, 60 % (uptake ratio; 95%) and 2 w/cm², 2 min, 60 % (uptake ratio; 95.6%). We could synthesize the functional microbubble complex including fluorescent dyes and trastuzumab. On the basis of CLSM results, we confirmed cancer targeting effect by antibody of the complex. The optimal condition for could be found by modifying energy intensity, duration, and duty cycle. In our results, the highest uptake ratio by tumor cell was 95.6% under the condition of 2 w/cm², 2 min, 60 %. Ultrasound mediated gene and drug delivery have a lot of potential for image guided therapy.
POSTER NUMBER: 272
SYNERGISTIC ENHANCEMENT OF BREAST CANCER CELL DEATH USING ULTRASOUND-MICROBUBBLES IN COMBINATION WITH CISPLATIN
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Cisplatin (CDDP), an anti-cancer agent, can effectively treat several cancerous tumours such as testicular, bladder, and ovarian cancers. CDDP binds to specific DNA bases causing 1,2-intrastrand cross-links, single strand and double strand breaks inducing apoptosis. However, the effectiveness of CDDP is limited in tumours such as breast cancer due to drug resistance. In this study, the application of ultrasound-microbubble (USMB) in improving the therapeutic effect of CDDP in breast cancer cell line is investigated. Human breast cancer (MDA-MB-231) cells in suspension (2x10^6 cells/mL concentration and 0.6 mL volume) were treated with CDDP (30 μM and 300 μM) and USMB at 0.5 MHz pulse centered frequency, 60 s insonation time, 16 μs pulse duration, 1 kHz pulse repetition frequency, and 1.7% v/v (volume concentration) of Definity agent. Following USMB treatment, cells were plated in 96-well plates for 48-hour incubation, after which cell viability was measured using MTT assay (VMTT). Cell viability decreased significantly with the combined treatment of CDDP and USMB compared to CDDP alone (p<0.001). VMTT of 49±1% and 42±1% with the combined treatment compared to 97±4% and 80±3% with CDDP alone at 30 μM and 300 μM, respectively. The results are shown in the figure below. The combined treatment was synergistic at lower concentrations (30 μM, p=0.0173) and additive at higher concentrations (300 μM, p=0.0783) based on Bliss Independence model. The combination of ultrasound-microbubble and cisplatin synergistically enhances chemotherapeutic effectiveness in breast cancer cells. However, this enhanced effectiveness, in breast cancer cells, is dependent on incubation time, cisplatin concentration and ultrasound-microbubble exposure conditions.

Figure 1: Percent cell viability of breast cancer cells for both CDDP alone and combinational treatment with USMB, all values are normalized to no treatment controls, measured using MTT assay after 48 hour incubation.
REVERSIBLE AND IRREVERSIBLE VASCULAR BIOEFFECTS INDUCED BY ULTRASOUND AND MICROBUBBLES IN CHORIOALLANTOIC MEMBRANE MODEL

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The application of ultrasound and microbubbles at therapeutic conditions has been shown to improve delivery of molecules, cause vasoconstriction, modulate blood flow and induce a vascular shut down in in vivo cancerous tissues. The underlying mechanism has been associated with the interaction of ultrasonically-induced microbubble oscillation and cavitation with the blood vessel wall. In this study, the effect of ultrasound and microbubbles on blood flow and vascular architecture was studied in a fertilized chicken egg CAM (chorioallantoic membrane) model. CAM at day 12 of incubation (Hamburger-Hamilton stage 38-40) were exposed to ultrasound at varying acoustic pressures (160, 240 and 320 kPa peak negative pressure) in the presence of Definity microbubbles and 70 kDa FITC dextran fluorescent molecules. A volume of 50 µL Definity microbubbles were injected into a large anterior vein of the CAM prior to ultrasound exposure. The ultrasound treatment sequence consisted of 5 s exposure at 500 kHz frequency, 8 cycles and 1 kHz pulse repetition frequency with 5 s off for a total exposure of 2 minutes. Fluorescence videos and images of the CAM vasculature following intravascular injection of FITC dextran were acquired using intravital microscopy prior, during and following the ultrasound exposure. Perfusion was quantified by measuring the length of perfused capillaries in a region of interest using Adobe Illustrator. The vascular bioeffects induced by USMB increased with acoustic peak negative pressure. At 160 kPa, no visible differences in capillary length were observed compared to the control. At 240 kPa, a transient decrease in functional capillary density with subsequent recovery within 13 minutes was observed, whereas at 320 kPa, the fluorescent images showed an irreversible vascular damage. The study indicates that a potential mechanism for the transient decrease in capillary perfusion may be related to blood coagulation (Fig. 1). Ultrasound and microbubbles can induce reversible and irreversible vascular changes depending on the ultrasound exposure pressure.

Fig 1. Fluorescent micrographs through time of CAM vessels during ultrasound exposure at 240 kPa. Arrows point to vascular blockage which is visible after 10 seconds of ultrasound exposure. White scale bar represents 100 µm.
POSTER NUMBER: 274
TRANSIENT PERMEABILITY/PERFUSION CHANGE DURING MICROBUBBLE-FACILITATED FOCUSED ULTRASOUND BLOOD-BRAIN BARRIER OPENING: A SMALL-ANIMAL OBSERVATION
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Focused ultrasound (FUS) with the presence of microbubbles can temporarily open the blood-brain barrier (BBB) and open up new windows for noninvasive and targeted CNS drug delivery. Dynamic contrast-enhanced MRI (DCE-MRI) has been employed to provide evaluation to identify BBB-opened region, and blood-brain permeability can be estimated. However, no reports so far elicit whether FUS-BBB opening would cause corresponding cerebral blood flow or volume change. The purpose of this study is to evaluate perfusion change caused by FUS-BBB opening, and evaluate the correlation with the permeability change. Six SD Rats were used in this study. Before FUS exposure, DCE MRI by 7T MR was performed before and after sonication for two times. After the first DCE MRI scan finished, animal underwent microbubble administration with the followed burst-tone (400 kHz or 1 MHz) 0.4-MPa FUS exposure, following with a second DCE MRI acquisition. Permeability (Ktrans and Ve) and perfusion (CBV and CBF) information was calculated from MRI post-processing. ROIs of permeability/perfusion map obtained from before and after experimental brains were selected for statistical analysis. BBB-opening both induce apparent Ktrans change and CBV change, which implies that both vessel permeability and volume were altered simultaneously. Furthermore, CBV increase ratio is much higher than CBF that implies the CBV change is more significant than CBF change when BBB-opening was induced by FUS. A good correlation was observed between Ktrans and CBV, which implies vessel permeability and volume increase after sonication are highly dependence. The permeability increase after BBB opening highly correlates with the cerebral blood volume increase, and independent of the cerebral blood flow. This information provides useful insights in understanding the pharmacodynamic behavior when intending to apply this approach to deliver drugs into the brain.
POSTER NUMBER: 275
MICRO/NANOBUBBLE-BASED CONTRAST-ENHANCED ULTRASOUND FOR EVALUATING AND ENHANCING THE EFFICACY OF CHEMOTHERAPEUTICS
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During the past decade, microbubble-based ultrasound imaging technique has evolved from an investigational tool to a standard diagnostic procedure. Microbubbles show their capabilities in visualizing bloodstream which provides physicians to evaluate the blood perfusion of organs. However, there are seldom studies focusing on the evaluation of microcirculation of tumors because of the lack of a reliable bubble agent capable to defuse to higher interstitial fluid pressure areas. In this study, a micro/nanobubble agent was used to overcome the plight and investigate the usefulness of contrast-enhanced ultrasound in osteosarcoma treatment. The micro/nanobubble agent was obtained by cooperating with Trust Biosonics, Inc. (Hsinchu, Taiwan). The fabricated micro/nanobubbles have a mean size of 500 nm and the concentration of $3 \times 10^{10}$ bubbles/mL. The drug-loaded micro/nanobubble was further prepared by mixing doxorubicin (DOX) with a specific lipid formulation in a concentration of 2 mg/mL under 60°C for 30 min before being activated to bubble solution. Cultured MG63 human osteosarcoma cells implanted into Nude mice in tibia site were used as the tumor model. The 3-MHz ultrasound insonations combined with DOX-loaded micro/nanobubble (DOX-MB) administration was delivered to locally release the drugs and facilitate the drug permeability of tumor. The tumor perfusion before and after the treatment was evaluated by three-dimensional power Doppler and contrast harmonic imaging techniques (CHI) (Aplio500, Toshiba, Japan) using a live 4D transducer (14-MHz). The color flow, contrast flow and volume of tumor were analyzed. Three experimental groups including control, DOX-MB without, and with ultrasound-triggered release were comprised for the comparisons (N=6, each). Firstly, we demonstrated that the bubble agent is capable to enhance the Doppler power of tumor vessels. The administration of micro/nanobubbles clearly performed the trend of tumor angiogenesis and perfusion. However, microcirculation or small vessels were hard to be detected under Doppler mode due to the effect of bubble destruction (MI=0.4). Through the use of ultra-low MI CHI mode (MI=0.07), the perfusion information could be further evaluated. With the administration of DOX-MB, ultrasound insonations enhanced the DOX molecules release. The tumor volume suppression was 2.82-fold increase compared with the group without ultrasound insonations. The introduction of DOX-MB and ultrasound insonations led to the substantial necrosis of osteosarcoma tumor in day 5 after the treatment. The mean contrast flow dropped to 24.6% compared with the flow before the treatment. The results revealed that the micro/nanobubbles can be applied as a multi-functional agent for cancer diagnosis and therapy, and the use of 4D CHI technique provided a convenient tool to evaluate the tumor therapeutic outcome and might help for tumor treatment planning and new drug discovering.
POSTER NUMBER: 276
ULTRASOUND-MEDIATED NANOPARTICLE DELIVERY ACROSS THE BLOOD-BRAIN BARRIER
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The intact blood-brain barrier (BBB) presents a major obstacle for drug delivery to the brain, as it prevents the vast majority of therapeutics from entering brain tissue, limiting treatment options for CNS disorders ranging from glioblastoma to Parkinson’s. Focused ultrasound (FUS) in conjunction with microbubbles (MB) has been shown to cause reversible, localized disruption of the BBB. This technique is noninvasive and causes minimal damage. Incorporating MR guidance with FUS offers the ability to exquisitely target BBB opening to specific regions of the brain, thereby permitting drug delivery in a highly localized manner. This work examines the ability of MR guided FUS to deliver highly specialized brain-penetrating nanoparticles (NP) across the BBB in a compartment-specific manner in both healthy and tumor-bearing rats. NPs were 60 nm in diameter and covered with an exceptionally dense PEG coating to permit excellent diffusion through brain tissue. For tumor-bearing studies, intracranial inoculation of 160-170 g rats was performed approximately 2 weeks prior to FUS treatment. The heads of anesthetized 200g rats were depilated and positioned in a degassed water bath coupled to the FUS system. Rats received an intravenous co-injection of fluorescent NPs and MBs 30 seconds before sonication. All sonications were performed using a 1.14 MHz single element focused transducer operating at a 0.5% duty cycle for 2 minutes. Peak negative pressure was either 0.4 MPa or 0.6 MPa. High resolution MR images were utilized to place sonication focal points with high accuracy. Four locations were sonicated in healthy animals, while animals bearing tumors received up to 9 sonications along the tumor periphery. Immediately following sonication, MRI contrast agent was delivered intravenously and T1-weighted contrast enhanced MRI images were captured to verify BBB disruption. Animals were then removed from the MRI table and placed on a heating pad at 37°C for one hour to allow increased NP uptake. Following euthanasia, brains were perfused with 2% heparinized saline, desiccated and cryosectioned. Mounted sections were stained with BS-I lectin to reveal endothelial cells (ECs) and imaged with fluorescent microscopy. Images were thresholded and the EC signal was subtracted from the NP signal to isolate NPs delivered to the brain parenchyma (NP “clouds”). In healthy animals, treatment with US pressures of 0.4 MPa and 0.6 MPa did not produce significant differences in total NP delivery (not shown). However, treatment with 0.6 MPa greatly increased the area of NP coverage within the brain parenchyma, both qualitatively (Figure 1A) and quantitatively (Figure 1B). The average NP cloud size was nearly doubled at higher FUS pressure, and the occurrence of large NP clouds (>100 µm²) was significantly increased as well. Furthermore, treatment with higher FUS pressure shifted the delivery of NPs to the brain parenchyma rather than to the endothelial cells lining the vasculature (Figure 1C). Control regions showed no NP delivery. These results indicate that we may be able to tune NP delivery for specific applications by judicious alterations in US parameters. * indicates p<0.05, n=4. Noninvasive localized disruption of the BBB using MR guided FUS offers a platform for drug- and/or gene-bearing NP delivery to the brain. Our results indicate that varying US pressure can divert NP delivery between the endothelium and brain parenchyma. We are currently analyzing the changes in NP delivery and dispersion in the tumor microenvironment.

Figure 1: Transcranial MR-guided FUS delivers large 60 nm NPs across the BBB in a pressure-dependent manner. Higher FUS pressure produces significantly larger NP “clouds” extending into the brain parenchyma (A,B) while also shifting NP delivery away from the endothelial cells lining the vessels (C).
POSTER NUMBER: 277
EXTENSION OF THE K-SPACE METHOD TO THE CONVECTIVE BIOHEAT TRANSFER EQUATION IN HETEROGENEOUS ANISOTROPIC TISSUE
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The emerging ultrasound imaging/therapeutic techniques require more sophisticated multi-physics simulation tools for accurate and reliable predictions. Biological tissues often behave quite differently in response to different physics and at multiple scales. Many of these processes, such as bioheat transfer and drug delivery, can be treated as diffusion-transport-reaction phenomena, which are examples of parabolic problems. We present the theory of the k-space method extended to parabolic problems in one, two, and three dimensions, and its direct application to the Pennes bioheat transfer (BHT) equation, which is widely used to predict the temperature field induced by a high intensity ultrasound beam in tissue. This leads to an efficient and accurate numerical scheme which is explicit in time and allows choices of time-steps in the order of those of the implicit schemes such as the Crank-Nicolson model. This makes it feasible to apply the Fourier spectral methods for fast evaluation of the spatial derivatives at each time-step, and hence, fast advancement of the solution in time. We consider the scalar diffusion-convection-reaction problem with inhomogeneous, an anisotropic and non-quiescent material behavior, in which case the corresponding coefficients of the governing partial differential equations may have explicit temporal/spatial dependence. The diffusion and convection terms are treated linearly but we allow nonlinear behavior of the reaction terms. We construct the k-space operator by solving the model problem in homogeneous media based on a priori known integration scheme. The solution is used to define the k-space operator and construct the k-space explicit time-integration scheme. This is then applied to integrate the equations in heterogeneous media. Next, the equations are discretized using a Fourier collocation method to achieve a fully discrete scheme. This gives a fast and accurate calculation of the spatial derivatives using the fast Fourier transform algorithm. We present the technical implementation of the fully discrete scheme for the BHT equation with explanations of the staggered grid, source incorporation, and boundary conditions. The k-space scheme is validated through a set of numerical tests. The accuracy and efficiency are compared with some well-established numerical schemes, such as the Crank-Nicolson method, for model problems for which the analytical solutions are known. The results of more sophisticated ultrasound systems are presented as the applications of the proposed method. We present an efficient and accurate numerical method for modeling bioheat transfer (or similar diffusion-convection-reaction phenomena) in tissue. The method is explicit in time and uses the fast Fourier transform routine to compute the spatial derivatives. Hence, the time advancement can be done in order of $N \log(N)$ operations, where $N$ is the number of unknowns. This is, therefore, well-suited for large-scale computations in tissues with anisotropic, heterogeneous, and non-quiescent material behaviors.
POSTER NUMBER: 278
SHORT- AND LONGTIME STABILITY OF THERAPEUTIC ULTRASOUND REFERENCE SOURCES FOR DOSIMETRY AND EXPOSIMETRY PURPOSES
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The objective of this work was to create highly stable therapeutic ultrasound fields with well-known exposimetry and dosimetry parameters that are reproducible and hence predictable with well-known uncertainties. Such well-known and reproducible fields would allow validation and secondary calibrations of different measuring capabilities, which is a widely accepted strategy for diagnostic fields already. A reference setup has been accomplished that comprises two therapeutic ultrasound sources (one HITU source and one physiotherapy-like source), standard rf electronics for signal creation and a computer-controlled feedback to stabilize the input voltage. Within this talk, the setup and the voltage feedback will be presented, as well as the short- and longtime stability of the acoustical output. For the former, measurements over typical laboratory measurement time periods (i.e. some seconds or minutes) of the input voltage stability with and without feedback control will be shown as well as a correlation with acoustical parameters. For the latter, the results of measurements of typical acoustical exposimetry parameters will be presented that have been performed every second month over one year. The measurement results show that the short- and the longtime stability of the reference setup is very good and that it is especially significantly improved in comparison to a setup without any feedback control. The presented setup is suitable to create highly stable therapeutic ultrasound fields with well-known and reproducible exposimetry and dosimetry parameters. Thus, the setup might be used for validation and secondary calibrations of different measuring capabilities. For this purpose, in addition to the stability characterizations, an overall uncertainty budget for the prediction of the relevant parameters will be estimated.
POSTER NUMBER: 279
DISRUPTION OF ACTIN CYTOSKELETON NETWORK BY SONOPORATION ON A SINGLE-SITE BASIS
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Targeted microbubbles have created new opportunities in the drug delivery field as they can play a pivotal role in realizing sonoporation with spatiotemporal control. Although the design principles of targeted microbubbles have matured in recent years, their biological impact on living cells is perhaps less known and has yet to be properly characterized. Of particular interest is that, since targeted microbubbles bind to cell membrane and are thus in close proximity from the cell, their resulting cavitation activities generated upon ultrasound pulsing may excessively puncture the membrane and in turn lead to deleterious effects. We hypothesize that under such circumstances, sonoporation is not solely a membrane integrity disruption process in that the actin cytoskeleton would be concomitantly disrupted since this network of subcellular filaments is physically interconnected with the plasma membrane. Confocal fluorescence imaging was performed to track single-site sonoporation episodes induced by ultrasound-triggered collapse of a single targeted microbubble. This was done using an acoustically coupled microscopy platform (ultrasound frequency: 1 MHz; in-situ calibrated peak negative pressure: 0.45 MPa; single pulse with 30-cycle duration). For the cells under observation (ZR-75-30 breast carcinoma), their actin contents were labeled using the transfection-based CellLight Actin-GFP dye. Also, propidium iodide (PI) was used as a sonoporation tracer to identify the correspondence between exogeneous marker influx and pre-exposure microbubble position (tracked with bright-field imaging). The targeted microbubbles were fabricated in house (1-4 um in diameter), and their binding preference was tagged to VEGF receptors on the membrane of the cells. The dye-loaded and microbubble-bound cells were observed live at a single-cell level. sonoporation dynamics were observed in-situ before and after instigation of sonoporation that was initiated by single-shot ultrasound pulsing. To quantify the extent of actin cytoskeleton changes in response to sonoporation, structure tensor analysis was carried out on the acquired actin fluorescence images using the ImageJ software. Disruption of the actin cytoskeleton was generally observed upon the onset of microbubble-mediated sonoporation at a single site. Also, following the initial F-actin rupturing in response to sonoporation, further disassembly of the actin cytoskeleton was apparent over a 60 min timeframe. This corresponded well with a significant decrease in the actin fluorescence images’ tensor coherency, which corresponds to the loss of dominant directional orientation at various parts of the actin cytoskeleton. Moreover, upon analyzing different cells with a single sonoporation site, a more substantial impact on actin disruption can be observed in those with stronger intracellular fluorescence of PI. Our results demonstrate that sonoporation is not solely a membrane-level phenomenon: organization of the actin cytoskeleton is concomitantly perturbed. Noting the pivotal role that actin plays in regulating cytomechanical behavior, these findings serve explain why various morphological changes have been observed in sonoporated cells downstream from the onset of sonoporation.
POSTER NUMBER: 280
ULTRASONIC ATOMIZATION: A MECHANISM OF TISSUE FRACTIONATION IN BOILING HISTOTRIPSY
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Ultrasonic atomization, or the emission of droplets from an acoustically excited thin liquid film, is a well-known phenomenon that was first observed by Wood and Loomis (1927). Since then, several hypotheses have emerged to explain the mechanism of atomization, with the most accepted theory, the cavitation-wave hypothesis, describing atomization as a combination of capillary waves and cavitation bubble collapses. More recently, high intensity focused ultrasound (HIFU) has been shown to mechanically fractionate tissue in either pulsed-cavitation or millisecond boiling histotripsy therapies. In boiling histotripsy, shock wave heating causes a millimeter-diameter boiling bubble to explosively expand at the transducer focus; however it is unclear how this millimeter-size boiling bubble fractionates tissue into its submicron components. In this work, we show experimental evidence that acoustic fountain formation and atomization may explain tissue fractionation in boiling histotripsy in vivo and ex vivo. A 2-MHz HIFU transducer operating at in situ pressures of 56 MPa positive and 12.5 MPa negative (linear intensity = 14 kW/cm²) was focused at flat and curved, bubble-like tissue-air interfaces. In the ex vivo experiments, bovine and porcine liver sections with thicknesses up to 1.5 cm were partially submerged in a water tank for coupling to the HIFU transducer while maintaining the tissue-air interface. For the in vivo exposures in porcine liver, a water-filled cone and ultrasound gel coupled the transducer to the lower liver surface and atomization was attempted both when the liver capsule was intact and when it was cut. All experiments were backlit, and high-speed photography was used to monitor atomization. At the end of the 10-ms HIFU pulses repeated at 1 Hz pulse repetition frequency, surface erosion was evaluated and tissue samples were analyzed histologically. Atomization and tissue erosion was observed in the millimeter-diameter, bubble-like hole in ex vivo bovine liver. Histology of the emitted droplets showed only partial tissue fractionation; however when the fountain projectiles were re-circulated as would be expected in bulk tissue, only submicron tissue fragments remained. Atomization and tissue erosion also occurred similarly in porcine liver in vivo and ex vivo both when the liver capsule was cut and when it was left intact. In fact, when the liver capsule was cut, atomization appeared more efficient in vivo (fig. 1B) than ex vivo (fig. 1A), perhaps due to bleeding from the cut in the capsule; however when the liver capsule remained intact, atomization was not successful in vivo or ex vivo (fig. 1C). If we consider that blood surface wetting enhances atomization, it is possible that the dryness of the liver capsule prevented atomization from being successful. This hypothesis was tested in vivo by wetting the intact liver capsule with a surfactant, where it was found that atomization became successful and caused a breach the liver capsule (fig. 1D). From these results, we can conclude that atomization explains a mechanism of tissue fractionation in boiling histotripsy. We also found that surface wetting appears to enhance atomization perhaps by forming capillary waves on the surface and refocusing the inverted acoustic wave at or near the tissue surface. More research is needed to determine how surface wetting enhances atomization before it can be used to improve bulk boiling histotripsy. [Work supported by NIH R01 EB007643, P01 DK043881, and NSBRI through NASA NCC 9-58.]

Select frames from high speed videos of atomization when the liver capsule was removed in A) ex vivo porcine liver, B) in vivo porcine liver. Atomization appears more dramatic in in vivo porcine liver, perhaps because of the blood wetting the surface. High speed video frames from atomization of the intact liver capsule in vivo are shown when the capsule surface is C) dry and D) surfactant-wetted. Atomization and erosion does not occur when the liver capsule surface is dry; however, when the surface is wetted with a surfactant, atomization becomes successful and the liver capsule is breached.
The Khokhlov-Zabolotskaya-Kuznetsov model has shown remarkable utility in therapeutic ultrasound. It is limited, however, in accurately modeling strongly focused beams, with F/1 (aperture equal to focal depth) being the minimum. To model shallower focal depths typical of modern single-element focused transducers, the full Westervelt equation is usually employed, at the expense of greater implementation and computational effort. The objective here is to obtain a more accurate parabolic model which is no more complicated or computationally intensive than the standard parabolic approximation used to obtain the KZK equation. Using a higher-order Pade approximation of the diffraction term in the one-way Westervelt equation results in simple Crank-Nicolson-type numerical schemes, one of which has the “stiff decay” property which is necessary for solution stability in the oscillatory boundary layer near the transducer. The perfectly matched layer absorbing boundary condition is straightforwardly incorporated into the schemes. This model produces stable and accurate solutions at F-numbers far lower than the traditional parabolic approximation with no additional computational overhead or implementation complexity. A perfectly matched layer thickness of only 1.5 wavelengths is sufficient for preventing boundary artifacts in the solution. A wide-angle parabolic equation is presented which offers greater versatility than the KZK-type model without the additional overhead associated with using the full Westervelt equation, particularly for axisymmetric ultrasound beams.
POSTER NUMBER: 282
ACOUSTIC CHARACTERIZATION OF HIGH INTENSITY FOCUSED ULTRASOUND FIELD GENERATED FROM A TRANSMITTER WITH LARGE APERTURE
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This study aims at acoustic characterization of HIFU field generated from the focused transmitter with a large aperture. In this work, a combined experiment and simulation approach is applied to determine the HIFU field distribution. The spheroidal beam equation (SBE) is utilized to describe the nonlinear sound propagation. The curve of the source pressure amplitude versus electronic excitation can be determined by fitting the ratio of the second harmonic to the fundamental component of the focal waveform measured by the fiber optic hydrophone to the simulation result; then the acoustic pressure field from the strong focused HIFU transmitter can be predicted by using the SBE model. A commercial fiber optic hydrophone is utilized to measure the acoustic pressure field generated from a 1.1 MHz HIFU transmitter with both aperture and focal length of 10 cm. The maximum measured peak-to-peak pressure is up to 72 MPa. For low excitations, this method is not valid since the second harmonic is too low to identify. When the shock wave generated, although the measured focal waveform does not confirm with the simulation, the normalized harmonic amplitudes confirms well with the frequency range of 50 MHz. It is shown that the combined approach can be used to predict the nonlinear acoustic distribution.
POSTER NUMBER: 283
A COMPARATIVE EVALUATION OF FOUR HYDROPHONES IN HIGH INTENSITY FOCUSED ULTRASOUND FIELD MEASUREMENTS
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A reliable characterization of the acoustic field distribution is important for both patient safety and treatment efficacy during clinical high intensity focused ultrasound (HIFU) applications. Even though acoustic hydrophones are used extensively in ultrasound exposimetry for pressure measurements, technical challenges still exist due to the highly focused, intense, and nonlinear HIFU acoustic field.

In this work, four different acoustic hydrophones were compared for pressure measurement: a piezoceramic needle hydrophone designed for HIFU, a PVDF capsule hydrophone with small sensing element and two fiber-optic acoustic hydrophones. The focal pressure waveform and field characteristics of a single element HIFU transducer were measured at several acoustical power levels from 1.0 W up to 55 W.

Complex deconvolution between the hydrophone output signal and the hydrophone frequency-dependent complex sensitivity was performed to obtain the focal pressure waveform. With increasing acoustic power outputs, the deconvolved focal waveform, compressional pressure, rarefactive pressure, spatial-peak temporal-average intensities and lateral focal beam profile are compared and possible reasons for differences are evaluated. In particular, the effect of hydrophone spatial averaging was compared and discussed between the different hydrophone sensors.

This study aimed to compare measurement accuracy using different acoustic hydrophones and assess the measurement variation due to sensor selection and analysis method during HIFU field characterization.
POSTER NUMBER: 284
EFFICIENT IMPLEMENTATION OF ACOUSTIC HOLOGRAPHY FOR CHARACTERIZING PULSED ULTRASOUND SOURCES
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Acoustic holography is a method of reproducing a 3D pressure field from a 2D distribution of pressures measured with a hydrophone along some surface transverse to the wave propagation. Such a distribution of measurements thus can be described as a hologram that comprises at each location either the pressure magnitude and phase in the continuous-wave regime or the entire waveform for the general transient case. A measured hologram can be numerically backward-propagated towards the source to provide a boundary condition for the wave equation, and as such is an important characteristic of any ultrasound source. In therapeutic applications of intense ultrasound such as histotripsy, the acoustic field is typically transient in the form of short, quasi-sinusoidal pulses. Similarly, diagnostic sources emit tone bursts. The goal of the present work is to modify the previously developed transient version of acoustic holography into a more efficient form that is particularly applicable to the characterization of fields generated by pulsed sources in medical ultrasound. In our previous work we have implemented various holographic approaches for medical ultrasound sources, including transient and nonlinear versions. The backward-propagation numerical algorithm of the transient version is based on the Rayleigh-type integral. Here we modify this integral by taking into account the narrow-band feature of the tone bursts emitted by piezoelectric ultrasound sources used both in therapy and imaging. Such pressure signals are characterized by a slowly varying complex amplitude (or real magnitude and phase), which can be represented by a smaller number of frequency components than an arbitrary transient signal. A modified Rayleigh-type integral is derived and then used to build a numerical modeler for forward and backward propagation. In experiments, a broadband hydrophone (GL-0150, SEA) is raster-scanned by a computer-controlled positioning system (Velmex Inc.) to record holograms by saving a pressure waveform at each measurement location. From these waveforms, transient source characteristics are calculated using the developed modeler. The method was applied to several typical ultrasound sources. Two sources were 1 MHz piezoelectric elements with a round 10 cm aperture. One of these sources was flat and the other was curved with 10 cm radius of curvature. In addition, the transient field of a commercial imaging probe with a convex shape (HDI C5-2) was studied. It was shown experimentally and numerically that the method has high accuracy with spatial resolution on the order of a wavelength. Simulations and experiments demonstrate that the acoustic field in transient tone-burst regimes can be accurately reconstructed using a limited number of spectral components around the center frequency of the transducer, enabling calculations to be performed relatively quickly. This approach can be used as an effective metrological tool capable of characterizing modern therapeutic and diagnostic sources. Work supported by NIH 1R21EB016118-01A1, EB007643, RFBR, and CRDF.

![Fig.1. Instantaneous patterns of normalized surface displacements for transducers undergoing transient excitation. Left image corresponds to a 1 MHz source of 10 cm aperture; right image shows the HDI C5-2 diagnostic probe with elements excited at different times to generate a focused beam.](image)
POSTER NUMBER: 285
THE RESEARCH ON IMAGE DENOISING IN SOUND FIELD MEASUREMENT BASED ON INFRARED IMAGING
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The background of the research is to explore the distribution of focused ultrasound field. Making use of the heat property of focused ultrasound, we can measure the distribution of heat sources to calculate the distribution of focused ultrasound field. During the exploration, we found that the temperature rise rate have a linear relation to sound intensity, so the distribution of temperature rise rate is directly related to the distribution of focused ultrasound field. After the experiments, we can get the infrared charts with noise. In order to obtain an accurate distribution of focused ultrasound field, it’s necessary to find out a solution to get rid of the noise in infrared charts. The traditional method to explore the distribution of focused ultrasound field is measuring it directly by hydrophone, but it can’t be used in the nonlinear area. So the present investigation was focused on the experimental validation of a filter which is most suitable for image process of infrared chart, as a consequence, most noise is removed and the distribution of temperature rise rate is not changed. The purpose of the analysis is to compare the effects of different common filtering techniques. After processing the raw data, we compared the distribution of the temperature rise rate, the measurement index is -6dB width of temperature rise charts. By comparing the distribution of temperature rise rate, we can tell which kind of filter is better in keeping the distribution of focused ultrasound field in steady. All simulations, semi-simulations and experiments use six kind filters to deal with the raw data to obtain related information, and the related information of noise and noise-free temperature rise charts can be obtained from the raw data processed and unprocessed. From the experiment results of simulation, semi-simulation and experiment, we can draw a conclusion that gauss filter is superior to the others filter, it has a better ability to keep the distribution of focused ultrasound field in steady.
CHARACTERIZATION OF THE ACOUSTIC PROPERTIES OF A PEDIATRIC SKULL USING A CLINICAL MR-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND SYSTEM
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This paper presents a method for characterizing the insertion loss and time-of-flight of biomaterials by combining a hydrophone acquisition system with a magnetic resonance imaging (MRI) guided high intensity focused ultrasound (HIFU) therapy device. Results are shown for a calvarium from an 8-yr old pediatric skull. Skull characterization was achieved by calculating the insertion loss and change in time-of-flight introduced between the geometric focus and the 256 elements of a Philips Sonalleve phased array HIFU transducer. The transducer has a diameter of 13 cm, a focal length of 12 cm (F#0.9) and was operated at a transmit frequency of 1.2 MHz. To do this, a hydrophone was positioned at the geometric focus of the transducer by triangulating the time-of-flight between each element and a time-of-flight of an arbitrary reference channel. Once aligned, and baseline measurements of amplitude and time-of-flight were made, a degassed skull cap from an 8 year old cadaveric sample was positioned in the near field sonication path in one of five orientations (Fig. 1). The software toolkit MatHIFU (Journal of Therapeutic Ultrasound 2013, 1:7) was used for the programming and control of the Philips Sonalleve system. Ultrasound exposures were done on a per element basis. The pressure was measured using a 0.2-mm PVDF needle acoustic hydrophone system (Precision Acoustics, Dorchester, United Kingdom). Each element of the transducer was driven one after another using a pulsed driving signal with 40 cycles at 1.2 MHz and with a repetition rate of 40 Hz. The average of 64 signals was calculated using an oscilloscope (MDO4054-3, Tektronix, Beaverton, OR, USA). Querying the status of the MR-HIFU system was used to determine when the ultrasound exposure was finished, after which the average reading of the 64 acquisitions was transferred through an Ethernet link to the external computer running MathIFU. The total time required to capture a measurement data for all 256 transducer elements was < 10 min. Measurements were taken with the skull at 0°, +/-15°, and +/-30°. The 0° position defined where the axis of symmetry of the transducer was coincident with the transverse axis of the skull. Positive degrees corresponded to rotating the skull to sonicate through the frontal bone, and negative degrees corresponded to sonicating through the parietal bone. The delay per channel between the reference and skull measurements was calculated using a cross-correlation technique. The insertion loss per channel was calculated by the change in the root mean square of the hydrophone signal after the cadaveric skull was positioned in the beam path. The average time-of-flight delay in microseconds (+/- s.d.) for the 256 transducer elements introduced by the 8 year-old cadaveric skull sample for the orientation at 0°, 15°, -15°, 30° and -30° was found, respectively, -0.7 (+/- 0.35), -0.57 (+/- 0.5), -0.68 (+/- 0.37 us), -0.65 (+/- 0.43) and -0.6 (+/- 0.5 us). In the same order of orientation, the average of insertion losses in decibels (+/- s.d.) was, respectively, 7.5 (+/- 4.7), 9 (+/- 7.6), 6.6 (+/- 4.3), 9.1 (+/- 8) and 8 (+/- 6.3) db. This indicates that as we move away from the top of the skull where the coronal and sagittal sutures are located, the skull gets thicker at the frontal and parietal bones, increasing insertion losses. This study shows that it is feasible to use an existing device designed for therapy, for the characterization of biomaterials such as the skull. The use of an existing device for therapy to perform the measurements allows performing characterization studies in a setting close to clinical conditions.

Figure 1: Computer model of the acquisition setup. The position of the focus of the acoustic field is aligned to a hydrophone. A series of measurements were done in water-only conditions and in the presence of the skull.
POSTER NUMBER: 287
DOSE FOR ULTRASOUND THERAPY - WHAT DOES IT MEAN TO YOU?
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Dosimetry for Ultrasound Therapy (www.duty-project.eu) is a large international project which aims to develop the metrological infrastructure for the determination of ultrasound exposure and dose to tissue. Part of the project (Work Package 1: Quantities and definitions) is to review dose and in situ exposure quantities that have been suggested or used previously and to seek the views of the wider therapy ultrasound community. The project is led by NPL, involves eight other partner institutes and is partly funded by the European Metrology Research Programme.

To collect community input, we have created a web-based questionnaire << www.surveymonkey.com/s/DUTy-dose >> with a range of questions covering the type of ultrasound equipment that is used and the range of applications for which it has been developed. In 2006, an earlier questionnaire specifically for field and equipment measurements related to HIFU provided important input leading eventually to the publication of three International Standards for HIFU last year. This new questionnaire covers all therapeutic ultrasound applications (including physiotherapy, lithotripsy, drug delivery etc…) and also asks specific questions about quantifying in situ exposure and dose: especially with a view to eventual treatment planning, standardisation and/or regulation. As well as informing the progress of the DUTy project, the answers to this questionnaire will be made available online and will be important in formulating future International Standards. This poster will discuss some of the issues around defining quantities for ultrasound dose and in situ exposure, and will summarize answers submitted up to the end of March 2014.

The questionnaire will remain open until at least the end of June 2014 and we encourage further submissions to build up the fullest possible picture of the development and use of therapeutic ultrasound.

DUTy: Dosimetry for Ultrasound Therapy
www.duty-project.eu
POSTER NUMBER: 288
3D NAVIGATION OF HIFU TRANSDUCER USING MOTION SENSOR
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In the existed HIFU systems, a phased array HIFU transducer is generally used for the volumetric treatment. However, due to the restriction in the electrical steering range of the focus, several movements of the transducer are required to treat the large volume. When the HIFU transducer is transferred manually from previous treated volume to the next volume, the transducer position should be provided to user. We measured the transducer positions using three-dimensional infrared cameras with high spatio-temporal resolution and small reflection markers attached to the transducer housing. And the 2D images of the markers are captured by the cameras and the images are delivered to the data acquisition hub. The 3D coordinates are extracted from the 2D images. In order to extract 6 DOFs motion of the transducer, local coordinates of the transducer are required. To get the local coordinates, it is necessary to distinguish each marker to be tracked during motion. The generation algorithm of the local coordinates is developed. And the 6 DOFs motions of the transducer are calculated from the local coordinates using kinematics. Finally, the location of the geo-metrical focus is estimated in real-time. In this system the high spatio-temporal resolutions for roll, pitch, and yaw motions were obtained below 5% errors. The system showed sub-millimeter performance of 3Dmesional x, y, z positions with high frame rate. Thus the information for the geometrical focus and the US radiation direction of the transducer was obtained with high accuracy in real-time. In this paper, it was confirmed that the accurate positions of the transducer be obtained in real-time using the infra-red cameras and small reflective markers. It is expected that the developed camera system could be helpful to user with the accurate positioning of the transducer toward the planned treatment volume.
POSTER NUMBER: 289

CORRELATION OF P63 IMMUNOHISTOCHEMISTRY WITH HISTOLOGY AND CONTRAST ENHANCED MRI IN CHARACTERISTIC LESIONS INDUCED BY MINIMALLY INVASIVE THERMAL TREATMENTS IN A DOG PROSTATE MODEL

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The biomarker p63 gene is highly expressed in basal cells of various epithelial tissues, and is thought to play a role in prostate gland development and repair. Our lab works with MRI-guided thermal ablations (High intensity focused ultrasound – HIFU, and cryoaulation) in a dog prostate model in order to optimize device development and improve minimally invasive treatments for prostate cancer and benign prostatic hyperplasia. Our ultimate goal is to provide radiologists with a better understanding of the visible differences between dead and sub lethally damaged tissue (i.e. areas that should be re-treated) on contrast enhanced (CE) MR real-time images obtained post treatment (pt). In order to better understand the histopathology of lesions created during prostate ablations, we performed IHC for p63 to determine if staining with this marker would help differentiate between viable, sub lethally damaged and normal glands in a more informative way than routine hematoxylin and eosin (H&E) staining. Prostates were harvested within 2 hrs/pt (acute), 4 days pt (subacute), or 35- 53 days pt (chronic), fixed in 10% formalin, processed for histology and IHC with p63 (Biocare Medical, 4A4, mouse mAb) following standard protocols. Corresponding H&E and p63 stained slides were digitized and analyzed (Sedeen Viewer software) with respect to regions of interest (ROI) that include: cryo lesions – central coagulation necrosis (CZ), surrounded by fragmented glands in fragmented zone (FZ); HIFU lesions – central heat-fixed zone (HF), surrounded by FZ. In addition, other ROIs include areas of gland regeneration, (GR) and normal, untreated prostate (UT). Scoring for the intensity of p63 staining is represented as -, none, +, scattered, ++, less than normal, ++++, normal and +++++, increased. Results of p63 IHC from a total of 6 prostate gland ablations (3 cryo, 3 HIFU) are presented in the table and representative images of MRI, H&E stained and p63 stained sections for acute and chronic duration prostates only are depicted in Figure 1. In the acute duration prostates treated with cryotherapy, p63 IHC was negative in the CZ (ROI subjected to the coldest temperatures), while in HIFU treated prostates, the central HF zone (ROI subjected to the hottest temperatures) still displayed + p63 staining, suggesting either inadequate heat to destroy basal cells, or heat-fixation of the p63 antigen and false positive staining with the antibody. The subacute/chronic duration cryo-treated prostate glands displayed extensive gland regeneration and had robust p63 staining most prevalent in areas that corresponded to the outer edge of the FZ. In subacute/chronic duration HIFU treated prostates, the formerly HF zone appears as a large area of hemorrhage or a hole surrounded by gland regeneration with robust p63 staining. This study demonstrates the persistence of prostate basal cells within various ROIs of ablated prostate glands treated with HIFU or cryoaulation. Our results suggest that with cryoaulation, the non-enhancing region viewed with MRI (deemed the CZ histologically) exhibits complete loss of p63 staining and therefore confirms basal cell death in this area. However, because the HF zone in acute duration prostates still displays some p63 staining, this additional staining method is not beneficial in determining if basal cells in the HF zone are dead or still viable. Additional IHC cell markers are currently being evaluated to identify a better method of identifying dead tissue in HIFU-treated prostate glands.

Figure 1. H&E and IHC stained sections of cryo and HIFU-treated prostates. A – J) acute duration prostates; A) CE MRI of cryo- treated prostate, B,G) H&E stained prostate sections showing ROIs, C,H) anti-p63-stained prostates, D) CZ and FZ IHC, E, J) UT prostate IHC, F) CE MRI of HIFU- treated prostate, I) HF and FZ IHC. K - T chronic duration prostates; K) CE MRI of cryo- treated prostate 53 days pt, L,Q) H&E stained prostate sections showing ROIs, M,R) p63 IHC, N,S) GR p63 increased staining O,T) UT p63 normal staining and P) CE MRI of HIFU treated prostate 35 days pt.
ENHANCEMENT OF CARDIOMYOGENESIS IN STEM CELLS BY LOW INTENSITY PULSED ULTRASOUND

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Low intensity pulsed ultrasound (LIPUS) has been shown to enhance bone and cartilage regeneration from stem cells. Gene expression of angiotensin II type 1 (AT1) receptor can be increased in LIPUS-treated osteoblasts. The AT1 receptor is a known mechanoreceptor in cardiomyocytes. It suggests that LIPUS may enhance cardiomyogenesis via mechanotransduction by increasing AT1 expression. Murine embryonic stem cells (ESCs) were treated daily by 10-min 1MHz LIPUS at spatial-average temporal-peak acoustic intensities of 30 mW/cm^2 and 300 mW/cm^2 in both continuous exposure and 20% duty cycle for 10 days. Polymerase chain reaction (PCR), immunocytochemistry, and beating rate were used to evaluate the cardiac viability quantitatively. After the treatment of LIPUS, beating rate of contractile areas and cardiac gene expression, such as α- and β-myosin heavy chain, were improved. Furthermore, endodermal differentiation was also reduced upon LIPUS stimulation. LIPUS stimulation has the capacity of enhancing cardiomyogenesis from embryonic stem cells and increasing its selectivity towards cardiomyocytes by reducing the spontaneous differentiation. With the benefit and the ease in incorporating LIPUS into various culture platforms, LIPUS has the potential to produce cardiomyocytes for clinical use in the future.
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MRI COMPATIBLE POSITIONING DEVICE FOR FOCUSED ULTRASOUND PROSTATE CANCER TREATMENT.
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A prototype magnetic resonance imaging (MRI)-compatible positioning device that navigates a focused ultrasound (FUS) transducer is presented. The positioning device has 2 user-controlled degrees of freedom (linear and angular) and one manual (Z-axis). The intention is to treat prostate cancer in humans in the future. The positioning device was designed and fabricated using construction materials selected for compatibility with high magnetic fields and fast switching magnetic field gradients encountered inside MRI scanners. The positioning device incorporates only MRI compatible materials such as piezoelectric motors, and ABS plastic. The FUS/MRI system includes a) Focused ultrasound system, b) MR imaging, c) Positioning device (robot) and associate drivers, and d) Software written in C. The system includes MRI compatible optical encoders for feedback controlled movement. The MRI compatibility of the system was successfully demonstrated in a clinical high-field MRI scanner. The robot has the ability to accurately move the transducer thus creating discrete and overlapping lesions in biological tissue was tested successfully in turkey tissue in vitro. The maximum error of the positioning device is 20 micro meters. A simple, cost effective, portable positioning device has been developed which can be used in virtually any clinical MRI scanner since it can be placed on the scanner’s table. The proposed system can be used in the future for clinical trials for prostate cancer treatment using HIFU.
By adding HIFU to Radiotherapy (RT), a totally new weapon (FUS/RT) against cancer can be realized. This new therapy retakes the benefits of the two methods, but is more than a simple addition of the two. In fact the hyperthermia field and cavitational effects (sonoporation), generated by FUS are a potent enhancers of the radiation effects, and allow a relevant dose reduction and a totally different spatial distribution. In fact HIFU ablation can be reserved to a reduced part of the tumor, in principle to just the hypoxic region, which is nearly insensitive to X-Ray radiation and is generally located in the most internal part of the tumor. It's well known that the survival of hypoxic cell is the main cause of local recurrence and treatment failure. Having destroyed with HIFU this region, we can administer X-Ray radiation only to the highly oxygenate, annular shaped volume, surrounding the central tumor region, where pathological cells infiltrate healthy tissue. The lower dose level and the reduced irradiation volume drastically reduce the side effects (sequeleae) of the radiation treatment. In addition, the FUS opens the door to facilitate mediated drug delivery, eventually, in conjunction with radiation. This combination of therapies, that can be administered to the patient in a short time period, may open a new horizon in patient's tailored, Medical Oncology [1]. We will use an MRgFUS ExAblate 2000 and 2100 CBS with GE Signa 1.5 T with “cradle” for animal support, high resolution 8 channel animal MR coil, biological Laboratory with histology and cell culture capabilities. OEC 9900 C Arm for radiological Imaging, that will be used also as the animal irradiation system, and Siemens Acuson wireless Ultrasound for tumor size control. The animal model will be severe combined immune deficient (SCID) mice for human tumors and rats in which Dunning R3327-AT prostate tumor, tumor size between 500 and 2500 mm^3. Preliminary: testing animal and tumor grow to different sizes, imaging improvements, optimized HIFU/FUS protocols, animal handling, RT levels and related aspect of the experiment. 1st phase: Safety study: About 1000 mm^3 size tumors, TEST of sham, RT (0.5, 1 and 2 Gy)-one session, MRgFUS one session, RT+HIFU. In the last 3 cases irradiation/ablation of the whole tumor. While the experimental phase is now in progress, we provide a detailed simulation of the whole treatment, starting with a complete modeling of the thermal field and the effect of radiation sensitization, based on current knowledge. The study arms will allow to compare the efficacy of micro-bubble [2] induced versus hyperthermia enhanced radio-sensitivity and to see how combining the effects could be more effective. If the animal study is successful FUS/RT can be considered as a neo adjuvant way to administer and support RT. This would expand enormously the application of FUS, whose adoption will be potentially extended to the thousands of RT Centre all over the world. In fact, FUS/RT could represent a realistic future for RT, providing a more powerful and cheaper treatment than gigantic, extraordinary expensive and elitist protons or heavy ions radiation therapies. Some proposal for adding HIFU facility to existing accelerators are presented and discussed.

We developed compact and high power multi-element amplifier module for therapeutic ultrasound transducer. We adopted a direct drive amplifier system for the multi-element transducer. This system has an advantage of reduce the energy loss at the connecting cable between the transducer element and the amplifier. So, we could assemble the very compact multi-element transducer system combined with multi-element amplifier. High-intensity focused ultrasound (HIFU) is widely used for therapeutic applications because it is an attractive and non-invasive tool by which to provide thermal therapy. Although HIFU treatment has been applied to limited regions. It is difficult to treat targets that lie behind bone (e.g., brain tumors) or that lie deep inside the body (e.g., liver tumors), because the ultrasound beam is reflected, refracted, and attenuated by the intervening tissue and/or bone. In order to resolve this problem, focus position control of HIFU by multi-elements phase control is very popular in clinical application. However, multi-elements driving amplifier is very large size like a large refrigerator. Our motivation of the study is to develop the handheld mobile phased array HIFU system. So, in this study we tried to make very small amplifier system module. In this study, we evaluated the specification and system design of the first prototype module transducer with numerical simulation and output power measurement of the amplifier module. In the numerical simulation, we use four parameters, Element pitch, Element size, focal distance from the transducer surface and focus sift value. This module connected to array amplifier modules directly. One amplifier module has 16ch driving circuit. This amplifier module size was 70mm height, 20mm width and 5mm thickness. Four amplifier modules were set on the backside of array elements with direct connection. We measured the driving performance of the single amplifier. As a result we decided the requirement of the specification as follows. Number of the transducer elements are 64 (8 x 8). Transducer Pitch is 2 mm. The module amplifier capacity is 0.1 Watt per element during the ON time. We measured the performance of the amplifier module. The graph showed input voltage versus output wattage through the single amplifier. We measured single element transducer drive performance and quad elements transducer drive performance with single amplifier on the module. One of the amplifier on the module can drive 2 x 2 mm^2 single transducer element. This result shows that this amplifier has an enough capacity to drive 4 x 4 mm^2 four elements. This graph showed an electrical power consumption of this module was very low. So, this module may be drive with a mobile battery. In this study, we developed first prototype of the compact and high power multi-element amplifier module for therapeutic ultrasound transducer. Various types of therapeutic ultrasound array transducer design can be realized easily by this module system.

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Acoustic cavitation in biological tissues has potential for therapeutic applications. In this scope, the present work studies the properties of a device composed of two focused transducers with beams crossing at their focal point. Simulations are used to compare this device with a single focused transducer. The first advantage of the confocal configuration is a reduction of the nonlinear effects. This allows an increase of the depression at the focal point increasing cavitation induction. The reduction of nonlinear effects is investigated numerically in the first part. The crossing of the beams for the confocal case creates an interference pattern. This pattern is shown to induce more inertial cavitation in the focal zone compared to the single transducer in the second part of this study. A simulator based on the Westervelt equation was used for the single transducer and the confocal device. This simulator takes into account diffraction, absorption, and nonlinear propagation. The positive and negative pressures at the focal point when varying input power, the focal volume, and the signal frequency content are compared for the two configurations. The single transducer has a diameter and a radius of curvature of 50 mm. In the confocal device two of these transducers are placed with 66.6° separation. Their beams cross at 50 mm. The frequency used is 1 MHz. To evaluate the impact of the interference pattern on inertial cavitation, an unbalance is created to the input power delivered to each transducer while the negative peak pressure was kept constant. This reduces the symmetry of the focal spot. For each repartition of power a chemical dosimeter (terephthalic acid) is used to quantify the activity of inertial cavitation. The total input electrical power is 300 W when the applied power is equal on both transducers. The emitted signal is a 60 second-long sequence of sinusoidal bursts transmitted at 250 Hz repetition frequency with 1% duty cycle. The ratio of the power applied to each transducer varies from 1 to 49, corresponding approximately to the single transducer case. The numerical study shows a greater depression for the confocal case, which is beneficial to cavitation induction. In the case of the single transducer, the nonlinear distortion is greater. The estimated focal volume is 22.8 mm³ in the case of the single transducer and 4 mm³ for the confocal setup. In the experiments, when varying the power ratio applied to each transducer, the estimated cavitation activity remains constant for ratios below 3, and sharply decreases for larger ratios. This study shows that there is a reduction of nonlinear distortion in the case of the confocal setup. The measurements show that the interference pattern created by the confocal device enhances the inertial cavitation activity. Moreover, this activity is not sensitive to slight changes in the symmetry of the interference pattern, which is important for in vivo applications. Finally, the confocal configuration seems more adapted to applications involving cavitation whereas the greater absorption due to nonlinearity makes the single transducer more appropriate to thermal applications.

![Normalized fluorescence of the exposed samples according to the power repartition between the two transducers.](image-url)
The purpose of this study was to investigate low frequency Magnetic Resonance guided Focused Ultrasound (MRgFUS) lesioning obtained with either pure thermal effect (no cavitation) or in presence of cavitation. It was additionally aimed to characterize the lesions on MRI and histology and correlate the findings with passive cavitation detection. Ten pigs which had a craniectomy underwent an MRgFUS procedure with an ExAblate4000 Neuro (InSightec, Haifa, Israel). Consistently, a thermal lesion was aimed on the right thalamus, while a cavitation (mechanical) lesion was aimed on the contralateral side. For thermal lesioning, a low power (50 acoustical Watts) 40s duration sonication was first performed and the corresponding MR temperature elevation was measured. The power was then prorated to target a 58°C peak temperature at the target with a 40s duration sonication. For mechanical lesioning, 20s duration sonications were performed and power a 300 to 700 acoustical Watts range was explored. Signals collected by two passive cavitation detectors (custom made by Insightec) were stored in memory during each sonication and cavitation activity was integrated over the 50-182kHz range. The bandwidth of the detectors ranges from 50kHz to 250kHz. 2D MR thermometry was performed during treatment, and post-sonication MRI protocols included T1-weighted pre- and post-Gadolinium contrast-enhanced, T2-weighted, T2*-weighted, gradient echo and FLAIR. Pigs were euthanized immediately after the last series of MR imaging. Pig brains were harvested and fixed in the formalin solution. Histology was performed to identify two parenchymal lesions. Passive cavitation signals exhibited three main types of signal interpreted as follows: no cavitation (Figure 1a), stable cavitation (Figure 1b) and inertial cavitation (Figure 1c). Pure thermal lesions, as assessed by histology, could be generated with low frequency ultrasound. Figure 1d shows a typical example of the MR post treatment image of such a thermal lesion, as opposed to typical hemorrhagic mechanical lesion (Figure 1e). The size of the hemorrhages measured on gross histology correlated with cavitation activity (R²=0.74) and a threshold for cavitation activity of 0.09V.Hz (given the sensitivity of the Insightec cavitation detector or the frequency range) was found to divide the experiments into two separate groups: with and without hemorrhage. This work demonstrates that low frequency ultrasound can induce thermal lesions in the brain of living swines without hemorrhage. This work paves the way towards passive-cavitation-based automatic shutdown of low frequency ultrasound for safe ablation.

Typical cavitation signal corresponding to (a) no cavitation (b) stable cavitation and (c) inertial cavitation. Typical post treatment MR image for (d) a thermal lesion (e) a mechanical lesion.
A concern for MR-guided focused ultrasound hemisphere transducers that use a conducting surface is that they become a RF resonant cavity during MRI imaging. High sensitivity near the conducting surface is accompanied by lower sensitivity around a half wavelength from the transducer surface. The result is poor image quality due to non uniform spin excitation as well as poor receive sensitivity. The purpose of this work was to investigate the ability to RF shim with pads of a high permittivity material. Simulations and experiments were performed for pads of barium titanate placed outside the water bath. Electromagnetic simulations were performed using xFDTD (Remcom, State College, PA) using the “Hugo” whole body model. Compared to the situation without filling of the water bath, Figure 1 shows that with the water bath filled, B1+ is enhanced in the top part of the brain, with signal loss in the central and lower part of the brain. These effects are due to the large displacement currents induced in the water. The inhomogeneous nature of the B1+ field is reduced by introducing the even higher permittivity (εr=290) barium titanate pads, where the additional displacement currents “pull” the magnetic field towards the bottom of the brain. For Experimental Validation: Barium titanate power was mixed with water and sealed into plastic bags. These were then used to shim the RF field in the InSightec ExAblate 4000 Brain System in a GE 3T MRI scanner. A volunteer was positioned with the head resting on a plexiglas platform attached to a stereotactic head frame, in order to hold the head in the water bath. A rubber membrane was placed around the head and attached to the transducer. The water bath was filled and the patient table advanced into the MR. The subject was imaged with a 3-plane localizer fast GRE sequence with the following parameters: TE/TR = 1.4/4.9, FOV=42 cm, 256x128 image matrix, 7 mm slice, nominal flip angle = 30. Two conditions were studied: a) without the barium titanate bags, b) with a bag placed to the right of the subject (arrow in Figure 2b), and an additional smaller bag placed above the subject. The bags were touching the rubber membrane. As compared to the condition without the barium titanate bags, improvements in signal and homogeneity were seen across the head with the pads in place. Coronal and axial images demonstrating the improvement in SNR are shown in Figure 2. In the area of the biggest signal dropout (ROI indicated in Figure 2b), the signal demonstrated a 12-fold improvement in SNR. In conclusion, pads of barium titanate placed appropriately around the subject can reduce significant signal dropouts in a resonant cavity transducer. Further Image quality improvements can be realized with the design of a custom local volume coil integrated into the ultrasound transducer.
POSTER NUMBER: 297
MODEL-BASED FEASIBILITY ASSESSMENT AND EVALUATION OF PROSTATE HYPERTHERMIA WITH A COMMERCIAL MR-GUIDED ENDORECTAL HIFU ABLATION ARRAY
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To assess the feasibility of targeted prostate hyperthermia with a commercial MR-guided endorectal ultrasound phased array (ExAblate 2100, InSightec Ltd) through numerical modeling and experiments in tissue-mimicking phantoms. This high-intensity focused ultrasound phased array is already in clinical trials for prostate ablation, and can be potentially fast-tracked for clinical hyperthermia treatments. However the phased array design has been optimized to perform high-temperature, short duration sonications required for HIFU ablation. Here operational modifications to this system which will enable protracted mild (40 – 45 oC) hyperthermia delivery to large contiguous target volumes in the prostate were investigated. Numerical simulations consisted of patient-specific biothermal modeling based on Pennes bioheat transfer equation, and acoustic field calculations for the ExAblate prostate array (2.3 MHz, 2.3×4.0 cm2, ~1000 channels) using the rectangular radiator method. Thermal solutions were computed using 3D finite element methods (FEM) implemented in COMSOL Multiphysics (Comsol Inc). The patient-specific geometries were created through manual segmentation of anatomical structures from representative patient MRIs and 3D rendering (Mimics, Materialise). Finite element meshes were generated using 3-Matic (Materialise). Array beamforming was employed and acoustic fields were synthesized (Matlab, MathWorks) to deliver protracted continuous wave hyperthermia to focal prostate cancer targets identified in the patient-specific models. Constraints on power densities, sonication durations and switching speeds imposed by the ExAblate hardware and software were incorporated in these models. Sonication strategies explored during modeling were implemented on the ExAblate prostate array and preliminary experiments were conducted in tissue mimicking phantoms under MR temperature monitoring at 3 T (GE Discovery MR750W). Therapeutic temperatures (40 - 45 oC) could be established conformably in focal cancer targets in a single prostate quadrant using focused heating patterns (simultaneous multi-focus as shown in figures 1 and 2, or curvilinear focusing) and hemi-gland heating was possible using diffused heating patterns (iso-phase or diverging). T>41 oC was calculated in 13–23 cm3 volumes for sonications with planar or diverging beam patterns at 0.9–1.2 W/cm2, in 1.5-4 cm3 volumes for simultaneous multi-point focus beam patterns at 2 – 3.4 W/cm2, and in ~6.0 cm3 for curvilinear (cylindrical) beam patterns at 0.75 W/cm2. Patient-specific models also revealed that treatable volume sizes may be limited from pubic bone heating, especially if the pubic bone is within 15 mm from the prostate. Parametric studies also showed that therapeutic heating was possible within power constraints of the phased array for a range of perfusion values (0.5 – 8 kg/m3/s), rectal cooling (22 – 35 oC) and sonication duty cycles (80% - 90%). Focused (simultaneous 6-point, simultaneous 4-point, cylindrical) and diffused (iso-phase, cylindrically diverging) phasing patterns investigated during modeling were successfully implemented on the ExAblate prostate array. They produced 4-12 oC temperature rises during protracted heating of tissue-mimicking phantoms (~0.86 W/cm2, 15 min). The ExAblate 2100 prostate array, designed specifically for thermal ablation, can be controlled for delivering continuous targeted hyperthermia to large contiguous volume while working within operational constraints (NIH R01CA122276, Focused Ultrasound Foundation).

Conformable hyperthermia to a small focal region in the right quadrant of the prostate containing cancerous tissue. Multi-focal pattern (six simultaneous foci) employed in hyperthermia delivery (plotted SAR contour = 300 W/kg) is overlaid upon 3D anatomical geometry along with temperature on tumor surface.

Temperature distribution obtained from patient specific model is plotted in an oblique sagittal plane through target center (I = 3.4 W/cm2, Tmax = 44.9 oC) for 6-point focusing.
EVALUATION OF THE SAFETY AND ACCURACY OF A PORTABLE HIGH-INTENSITY FOCUSED ULTRASOUND SYSTEM WITH 3D ELECTRONIC STEERING, REAL-TIME CAVITATION MONITORING, AND 3D IMAGE RECONSTRUCTION ALGORITHMS: A PRECLINICAL STUDY IN PIGS

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This study was designed to evaluate the safety and accuracy of a new portable ultrasound-guided high-intensity focused ultrasound (USg-HIFU) system. The device consists of a 3D electronic steering transducer with simultaneous ablation and imaging module, real-time cavitation monitoring, and 3D image reconstruction algorithms. In order to address the accuracy of the transducer, hydrophones in a water chamber assessed the generation of sonic field. Animal studies were performed in five pigs. Targets in the thigh were ablated in vivo either by single point sonication (n=10) or volume sonication (n=10). The kidneys were also ablated ex vivo by single point sonication (n=10). At the end of the animal studies, histologic and statistical analyses were followed. Consequently, the peak-pressure near the sonication targets were detected by a hydrophone within 1.0 mm distances from the targets on the y- and z-axes, and within 2.0 mm spans in the x-axis. Twenty-nine of 30 HIFU sessions successfully created ablations at the targets. The in vivo porcine thigh study showed only small discrepancy (0.5-1.1 mm in width, 3.0 mm in depth) between the planning US images and pathologic specimens. No inordinate thermal damage was observed in the adjacent tissues and sonic pathway in both in vivo thigh and ex vivo kidney studies. Based on the results, our study suggests that this new USg-HIFU system is able to safely and accurately ablate soft tissues and encapsulated organs.
INTERLEAVED DUAL FREQUENCY SONICATION FOR TRANSURETHRAL PROSTATE THERMAL THERAPY

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To induce heating with a transurethral ultrasound transducer using both the first and third harmonics in order to provide accurate control of ablation depth during prostate treatment. A transurethral transducer (Sunnybrook Health Sciences Centre, Toronto, Canada) composed of 8 piezo elements, each having dimensions 5x4 mm2 and operating at 4.6 MHz and 14.4MHz, was attached to a rotational piezoelectric motor and inserted in a tissue-mimicking gel phantom. Tests were conducted inside a Philips Achieva 3T MRI, with the acquisition of 3 contiguous thermal maps aligned with each element for which target contours were defined. Sonication at low and high frequency were interleaved within each second with variable ratio to modulate the temperature decay along the beam axis. This interleaving ratio was adjusted as function of the target radius targeted radius ranging from 11 to 28 mm. A binary temperature controller was used to regulate the power so as to maintain a temperature rise of 15°C along the target contours. While performing multiples heating of 2 min without rotation, the length L of the heating at 15°C appears to be proportional to the interleaving ratio according to relation L = 33mm - Fx1.5mm/MHz (r2=0.98) with F representing the average frequency in MHz. The exponential decay D of the temperature along the beam axis is also proportional to the average frequency: D = 13.66mm - Fx0.77mm/MHz (r2=0.99). During rotational heating the binary temperature controller, combined to the interleaved frequency function of the targeted radius, allows adjustment of the temperature at 15°C along the target contour with 0.65 mm accuracy. The use of interleaved frequency sonication adds the ability to control precisely the temperature decay along the beam axis despite the fact that the piezo materials can operate only at the first and third harmonics. Binary temperature control of the power combined with interleaved frequency method is an effective way to control the temperature precisely along multiple slice targeted contours.
Sonoporation is an attractive method for inducing cell permeability for large-molecule delivery. In vitro studies employing sonoporation are often done using custom sonoporation hardware set-ups. Replicating the physical conditions between experiments and research groups is important for repeatability and verification. The objective of this study is to develop a prototype platform for in vitro sonoporation that not only reduces the technical expertise required to perform sonoporation experiments but also provides consistent physical conditions between experiments and groups. The OptiCell™ (Nunc) cell culture system was chosen in order to perform adherent cell culture. These cell culture chambers grow cells on a thin plastic film and are fully submersible, avoiding reflection of the wave and allowing positioning of an acoustic absorber behind the chamber to prevent standing waves. Six flat transducers (DelPiezo) with 20 mm in diameter were arranged in a 3×2 grid to expose a large area in the cell culture. The ultrasound frequency was fixed to 1 MHz from previous validated studies [1]. The transducer housings and mountings were designed and printed using a 3D printer and ABS filament (Replicator, Makerbot Industries). The transducers were mounted, electrically verified, and waterproofed. A matching network was built and tuned for each transducer to 50 Ω at 1 MHz to maximize power transfer using L-networks. The acoustic field for each transducer was measured using a hydrophone (#1426 / 0.2mm, Precision Acoustics) and a micro-positioning system. Slices of 10.4×10.4 mm were obtained perpendicular to the beam path at half-wavelength resolution (0.7 mm). These slices were taken every 0.1 mm along the beam path, between 1 and 2 cm from the surface of the transducer. The slice which had the highest homogeneity was chosen to be the optimal treatment distance and it was where the OptiCell™ chamber was positioned. The transducers were fixed beneath an OptiCell™ holder at their optimal treatment distances using echo measurements. At this optimal treatment distance, a point that was approximately 90% of the maximum pressure of the slice was then chosen to calibrate the electrical power required to produce the desired pressure. The excitation signal was generated by a function generator (33522, Agilent) and then amplified (A150, ENI). The device was tested by performing sonoporation efficacy measurements on CaSki cells seeded and cultured overnight. Plasmid DNA expressing green fluorescent protein (GFP, 250 μg) and ultrasound contrast agent (Definity®, 0.33% v/v) were added to the chamber and it was then exposed to either pulsed ultrasound (1 MPa, 4.8% duty cycle, 1.6 kHz pulse repetition frequency and 30 s total duration [1]) or sham control (no ultrasound, same exposure time). GFP expression was used to evaluate transfection efficiency on fixed cells 24 hours after exposure. [1] Togtema et al. 2012 PLOS ONE 7(11):e50730
Six ultrasound transducers were built, successfully waterproofed, matched and characterized. The average treatment distance was 15.9±0.688 mm. The average continuous electrical power required to reach 1 MPa was 101±12.1 W. Sonoporation was verified by a GFP expression significantly higher for the ultrasound exposure group compared to the control group (5.4±0.9% and 0.5±0.2% respectively; p < 0.001; n=3). A prototype for in vitro sonoporation platform that aims to reduce the level of expertise required to perform sonoporation experiments as well as provide consistent physical conditions between experiments and groups was developed. Future work will include the design of a dedicated generation and amplification system to produce a stand-alone sonoporation device.

3D renderings showing the spatial relationship between the 3×2 transducer array (ø2cm) and the OptiCell™ cell culture system.
POSTER NUMBER: 301
AN IMPROVED MRI GUIDED ULTRASOUND SYSTEM FOR SUPERFICIAL TUMOR HYPERTHERMIA
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Ultrasound hyperthermia is one of the most important methods in tumor treatment and characterized by high safety and non-invasiveness. Magnetic resonance temperature imaging (MRTI) is non-invasive and is widely applied in the field of tissue temperature monitoring. The proton resonance frequency (PRF) method is relatively advanced among various MRTI methods, which is near-independence of tissue composition and is able to provide accurate temperature information. This research is conducted on an MRI guided ultrasound superficial tumor hyperthermia instrument based on PRF method. Based on the feedback of temperature, the system calculates the proper output power of the amplifier and the flow rate of circulating cooling water using strategically advanced PID algorithm, adjusts the overall treatment time and by the excited transducer, submits ultrasound wave, which goes through water, the coupling agent layer and skin to the lesions and keeps the temperature of the targeted area at 42-43 degrees C while skin surface not scalded. The transition of the signals mentioned above is completed by the upper controller and the lower control chip. The former sets controlling parameters of ultrasound output amplifier and by RS232 communication interface sends them to the latter, which executes the instructions. The temperature measurement module consists of an MR scanner and a module, located in the control system, receives specific images from the scanner and deduces the temperature change of skin and the targeted area from the phase difference of between reference data and data acquired during heating. This precise temperature information then is transmitted to the upper controller, guiding tumor hyperthermia. Some essential components are used for the sake of electromagnetic leakage or interference between the MR scanner and the rest part of the system. Up to now this system is on the research with animal experiment, during which its performance has reached our first-level expectations. Ultrasound can be used to heat lesions non-invasively and MR scanning is harmless to human body and helpful in accurate positioning and non-invasive temperature measurement. In conclusion, this system can heat the targeted tumor area safely and effectively, achieving non-invasive and secure hyperthermia.
POSTER NUMBER: 302
A NEW FPGA-DRIVEN P-HIFU SYSTEM WITH HARMONIC CANCELLATION TECHNIQUE
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An ultrasound transducer excited by a waveform with harmonic cancellation can produce a sound field with low grating lobes and has high electroacoustic efficiency. This study introduces a FPGA-driven ultrasound amplifier system with low harmonic distortion, which needs no additional filtering circuitry at the amplifier output. Without additional filtering circuitry, the amplifier can work in a wide bandwidth. And a FPGA phase signal generator can generate square waveform with high frequency and high phase precision, especially for large number of elements. Two channels of square waveform signal from FPGA phase signal generator drive one amplifier, which have a phase difference of π/3. Each channel is divided into two channels, passing through an inverter and a compensator respectively. All the four channels are added together in two centre-tapped transformers. A voltage-changeable DC power supply is added to the transformers. The secondary voltage of the transformer is the amplified signal, driving the ultrasound transducer after an electronic matching circuit. So, when we need a phased array with 65 elements, an FPGA chip is chosen which has more than 130 general outputs and meet the requirement of timing constrain. The output waveform of the amplifier with harmonic cancellation had fewer harmonic components and higher electroacoustic efficiency than the amplifier without harmonic cancellation. The study demonstrates that the amplifier driven by an FPGA signal generator meets the requirements of high frequency and high phase precision.
POSTER NUMBER: 303
DEVELOPMENT OF A NOVEL HIGH INTENSITY FOCUSED ULTRASOUND LAPAROSCOPIC PROBE FOR RENAL CANCER ABLATION
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Intra-cavity and Extracorporeal HIFU applicators for the treatment of certain deep seated organs have restricted applications due to HIFU beam aberration by the intervening tissue paths and body motion. This study validated, Sonatherm device with a novel 12 mm laparoscopic HIFU probe. The probe has an integrated confocal imaging and water coupling that can safely and efficaciously treat multiplicity of organs by providing direct acoustic coupling to diseased organs by avoiding beam aberration and tissue motion issues. In this animal study, we developed and optimized a protocol for a 12 mm HIFU probe for the treatment of small renal masses (<3 cm in diameter) in a porcine model. The objectives of the protocol were to demonstrate efficacy of the probe in ablation of renal tissue and to demonstrate safety of the probe and procedure in live surgery. This study was conducted at Indiana University after receiving approval of the protocol by the local animal research committee. The laparoscopic dissection exposed each of the 16 individual kidneys in 8 animals. The HIFU probe was fixed to a surgical cart and sterilized probe tip was introduced in the body cavity using a 12 mm trocar under optical guidance. The probe tip was placed in direct tissue contact using adjustable water coupling sheath and surgical gel. The bi-plane B-mode images were used to localize and plan the treatment. The planned treatment extended from the focal zone to the surface of the organ. The tissue ablation was carried out in a robotic mode at two planned locations within each kidney. After four days of survival, kidneys were retrieved and pathologic analysis of the lesions was carried out. Twelve (12) volumetric lesions were subjected to blind quantitative histology analysis by precisely slicing the fixed tissue and measuring extent of cellular tissue necrosis and boundary of cell damage. The analysis provided correlation between histologically found necrotic tissue volume (NV) to planned treatment tissue volume (PV) and defined the treatment accuracy. In addition, histology provided information on cell viability in the areas of highly perfused tissue. Pre-operative and post-operative blood was collected from all animals for serum analysis. A series of optimizations were carried out as the experiment progressed. An interim data analysis was used to optimize ultrasound energy dosage by adjusting beam spacing and steering speed of continuous HIFU application. During kidney removal, all planned volumetric lesions (30/30) were observed as dark coagulative sharply demarcated lesions reaching to the surface of the kidney where the HIFU treatment was planned. Histology analysis demonstrated necrotic zones (NV) with similar volumes to targeted zones (PV). The quantitative analysis of NV/PV (in 10/12 lesions) was near optimal at a value of 1.02 (SD=0.33). There were no skipping or viable cells in 10/12 treated tissue lesions and lesions were contiguous. All animals survived the surgeries and no complications were identified during the study. No acute renal failure was identified in serum analysis in these animals. We successfully employed a novel 12mm laparoscopic HIFU probe to consistently ablate porcine renal tissue. A value of NV/PV near the ideal ratio of 1.02 was achieved with optimized energy delivery format. The rate of tissue ablation was @1 cc / minute. The safety profile of the Sonatherm probe was found to be excellent with no complications identified. Further studies are warranted to characterize the probe’s efficacy in ablation of small renal masses in humans and in other organs.
POSTER NUMBER: 304
A 2-D CIRCULAR SPARSE ARRAY FOR HIFU TRANSDUCER
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It has been known that the half wavelength element spacing requirement must be satisfied to be free of high grating lobes (GLs). The half wavelength criterion can be met easily for imaging transducers (e.g., phased array), which is, however, an unrealistic condition for HIFU transducers because it needs at least thousands of elements due to the large aperture size. Therefore a random sparse array (RSA) is widely used as a HIFU transducer. Although RSAs have shown good performance in GL suppression, it has limitations in element size and inter-element separation due to random distribution of elements. In this paper, we proposed a 2D circular sparse array (CSA) of which the geometry was illustrated in Fig. 1(a). In CSA, elements are distributed on the center of a circular aperture and concentric circles with radii which equally divide the radius of an aperture into equal distances. On each circle, the first element is placed randomly and other elements are distributed around the center of a circular aperture in concentric circles with radii which divide the radius of aperture with equal distance. The sidelobe and grating lobe of beams produced with CSA can be separately controlled to have desired levels by adjusting the radial and circular element spacings (i.e., RES and CES). For the performance evaluation, three kinds of 2D transducers (i.e., uniform array, RSA and CSA) with same number of elements (566) and aperture size (40 mm diameter) were designed and then their field patterns and resultant temperature distributions were compared through computer simulation. In simulation, One-way field responses and temperature profiles were calculated by using Field II software and bio-heat transfer equation. Figure 1(b) shows the calculated temperature distributions for the three HIFU transducers designed for this study. 5 MPa of the peak pressure was induced for 5 seconds to heat the target which is indicated by arrow. As shown in Fig. 1(b), undesirable heating by GLs are observed when UA is used. These GLs were generated because the element spacing of UA is larger than half-wavelength. On the contrary in CSA as well as RSA, only target area was heated over 60°C since GLs were effectively suppressed. From simulation results, it was shown that GL suppression of CSA was comparable to RSA. It should be noted that CSA has some advantages over RSA. CSA can be easily designed to meet any required specifications on sidelobe and grating lobe levels because the former is controlled by RES and the later by CES. Moreover, element size and inter-element distance of CSA can be controlled more freely than those of RSA, leading to an optimized beam profile. It may also have to be pointed out that CSA can be fabricated more easily than RSA because its elements are regularly distributed on the transducer surface.

Figure 1. (a) Geometry for a 2D circular sparse array and (b) simulated temperature distributions of 2D uniform array, random sparse array and circular sparse array.
Boiling histotripsy is an experimental therapy that produces noninvasive mechanical tissue ablation by high-intensity focused ultrasound (HIFU). Under this modality, millisecond-long pulses containing shock waves cause rapid, localized heating, leading to boiling at the focus and disruption of the tissue structure without significant thermal injury. As boiling histotripsy is dependent on the formation of high-amplitude shocks at the focus, the transducer must generate sufficient power to overcome attenuation losses in tissue and by bones and deliver high pressures to the focus in situ. This presentation describes the design approach and realization of boiling histotripsy systems capable of transcostal therapy and treatment through significant overlying tissue paths. We have developed two transducers for boiling histotripsy. The first device is a 1-MHz, 7-element array with circular elements. The transducer is driven with a custom amplifier system that can generate high-power pulses for up to 10 ms duration. The second transducer is a 1.5-MHz 12-element sector array designed for use with the same amplifier, as well as a Verasonics HIFU research platform. Both are designed based on nonlinear acoustic simulations used to estimate the shock amplitudes for different driving conditions, and fabricated using a rapid prototyping method. The transducer elements are designed in such a way to minimize mechanical stress and potential failure during operation. Because of the large focal pressures produced, the field cannot be directly measured in water over their entire power range. Instead, the transducers are characterized by a combination of acoustic holography and nonlinear modeling using the Westervelt equation. These results are compared with focal pressure measurements using a fiber optic hydrophone at lower pressures. The devices are tested by generating lesions in ex vivo liver and kidney through porcine body wall and rib sections, for total tissue paths up to 6 cm. At maximum electrical output, the transducers produced up to an estimated 11.5 kW pulse-average acoustic power at 1% duty cycle without measurable damage or degradation of the elements. Simulations of the pressure field have been performed up to the maximum output, and give good agreement with the measured waveforms at lower output. Histotripsy lesions could be generated without overlying tissue in liver and kidney at as low as 360 W acoustic power, corresponding to in situ shock amplitudes of approximately 70 MPa. Lesion generation at different depths in liver up to 6 cm indicated that the threshold for boiling can be predicted by derating the acoustic output based on an attenuation coefficient of approximately 0.6 dB/cm/MHz. With the 1 MHz system, we have been able to generate boiling histotripsy lesions in liver through body wall sections containing ribs using 4.4-11.5 kW power. We have developed transducer systems capable of performing boiling histotripsy through clinically-relevant tissue paths. The design process provides estimates for the required shock amplitudes needed to generate lesions and flexibility in producing necessary power to compensate for losses from tissue and bone. The combined approach of measurements and modeling provides a valuable process for treatment planning and accurate characterization of transducers over their entire output range. Work supported by NIH 2T32DK007779-11A1 and 2R01EB007643-05 and NSBRI through NASA NCC 9-58.
POSTER NUMBER: 306
APOPTOSIS INDUCED BY LOW-INTENSITY ULTRASOUND IN VITRO: ALTERATION OF PROTEIN PROFILE AND POTENTIAL MOLECULAR MECHANISM
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Low intensity ultrasound induced apoptosis of several carcinoma cells has been regarded as potential assistant cancer therapeutic regimen. It has been proved mitochondrion was involved in the process. However, detailed mechanism has not been elucidated. The purpose of this study was to evaluate the potential molecular mechanism of low-intensity ultrasound-induced apoptosis by analyzing protein profile alteration in response to ultrasound exposure. Human hepatocarcinoma SMMC-7721 cells were irradiated by low intensity US in this study. Cell viability was measured by a trypan blue dye exclusion test. Morphologic changes were examined by light microscopy. Apoptosis was assessed by flow cytometry with double staining of FITC-labelled Annexin-V/PI and DNA fragmentation. Protein profile alteration was analyzed by comparative proteomics based on 2-dimensional polyacrylamide gel electrophoresis (2DE) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). Low-intensity ultrasound (3.0 W/cm2, 1 minute, cells incubated for 6 hours after ultrasound exposure) induced early apoptosis (mean ± SD, 26.5% ± 6.2%) significantly (P < .05) with minimal lysis in human hepatocarcinoma cells in vitro. Morphological characteristics of apoptosis cells, such as condensation of nucleus, chromatin margination and formation of apoptosis bodies, were found in US irradiated cells, however few in control cells. The fluorescent photos of apoptosis cells (only with green excluding red fluorescence) also proved it. Several proteins, such as cellular tumor antigen protein 53, BH3-interacting domain death agonist, apoptosis regulator Bcl-2, and heme oxygenase 1 were identified as responding to ultrasound irradiation, suggesting that mitochondrial dysfunction and oxidative stresses were involved in ultrasound induced apoptosis. Especially, the different expression characteristics of VDAC and its chaperone protein BID and BAX assumed that a mitofilin-regulated crista remodeling may be a potential channel of mitochondrial membrane permeabilization pore formation involved in low-intensity ultrasound-induced apoptosis. This study suggests that 2 potential molecular signaling pathways are involved in ultrasound-induced mitochondria-dependent apoptosis. It is a first step toward low-intensity ultrasound-induced apoptotic cancer therapy via understanding its relevant molecular signaling and key proteins. Regulating VDAC channel could act as the target for the cancer therapy.
EFFECT OF PIG BODY WALL TISSUES ON HIGH-AMPLITUDE ACOUSTIC WAVES
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In therapeutic ultrasound, high amplitude acoustic waves generated either by a shock wave (SW) lithotripter or a high intensity focused ultrasound (HIFU) transducer pass through various layers of body wall tissues of considerable thickness to reach the treatment site. Knowledge of the pressure field at the treatment site is desired for understanding the working mechanisms of these strong acoustic waves. Numerical simulations or in vitro tests with tissue mimicking phantoms often cannot adequately represent the morphologically and physiologically complex nature of tissue. We sought to determine how body wall tissues interact with the transmission of acoustic waves, especially non-linear SWs. To overcome the technical challenges and often uncontrollable test conditions encountered during in vivo measurements, we took an ex vivo approach. Pig body wall specimens were harvested immediately after pigs were sacrificed and transported in saline solution to the lithotripsy laboratory. The tissues were secured in the blast path of a clinical Dornier Compact S electromagnetic lithotripter. A fiber-optic probe hydrophone was used to conduct acoustic pressure measurements, determine shock rise times and map the acoustic field at the focal zone. In these measurements we assessed peak pressures, the -6 dB focal width of the acoustic field at the focus, and shock rise time. Passage through the body wall attenuated the shock pulse, reducing the peak positive pressure (P+) by approximately 6% per centimeter. Large-scale tissue irregularities affected the symmetry of the acoustic field, shifting the maximum P+ laterally by as much as ~2mm from the geometric focus. Mapping of the field showed negligible effects of the body wall on focal width, regardless of thickness of the body wall. Measures of rise time of SWs upon exiting the tissue were in the range of ~17-21 ns, indicating the formation of a shock within tissue. Unfortunately, the actual effect of body wall tissue on shock rise time could not be fully assessed due to the limited time resolution of the hydrophone (7-15 ns limited by electronics). The characteristics of lithotripter SWs are minimally affected by passage through the body wall. Other than reducing pulse amplitude and potentially affecting the symmetry of the focused wave, the body wall has minimal influence on the acoustic field. Because single-pulse SWs generated by a lithotripter and multiple-pulse acoustic waves in HIFU or histotripsy share similar characteristic features of nonlinear acoustic signals, the findings in this study may be applicable to other fields such as HIFU and histotripsy.

(NIHDK43881)
Type 2 diabetes mellitus is a complex metabolic disease that has reached epidemic proportions in the United States and around the world. Controlling type 2 diabetes is often difficult. Many patients are poorly compliant with lifestyle change recommendations, and pharmacological management routinely requires complex therapy with multiple medications, and loses its effectiveness over time. Thus, new modes of therapy are needed that will target directly the underlying causes of abnormal glucose metabolism. The objective of this study is to explore a novel, non-pharmacological approach that utilizes the application of ultrasound energy to augment insulin release from pancreatic beta cells. Our experiments focus on determination of effectiveness and safety of ultrasound application in stimulation of insulin release from pancreatic beta cells. ELISA insulin release assay was used to determine and quantify the effects of ultrasound on basal and glucose-evoked insulin release in cultured pancreatic beta cells. Effects of ultrasound on cell viability were assessed by employing MTT, Caspase-3, LDH release and Annexin-apoptotic cytotoxic assays. Ultrasound exposure was generated using a commercial ultrasound device (Sonicator 740, Mettler Electronics) and a planar ultrasound transducer with center frequency of 1 MHz and intensity of 0.8 W/cm² was used to treat the cells for 5 minutes. Insulin has been shown to be released in a calcium-dependent manner in response to changes in blood sugar levels. Therefore, our study also looked to evaluate extracellular calcium influx as a potential mechanism for enhanced ultrasound induced insulin release. Thus, calcium transients were measured and quantified by ratiometric calcium-imaging assay. Our preliminary data indicated that application of therapeutic ultrasound may lead to increase of insulin secretion from beta cells in a calcium dependent manner while maintaining cell viability. ELISA results showed a 25% increase in insulin release from beta cells after ultrasound exposure for 5 minutes. Cell viability was not significantly affected during and for up to one hour after treatment. Insulin release and cell viability results will be correlated as a function of temperature increase and cavitation activity to demonstrate the potential mechanical and thermal effects of ultrasound on pancreatic beta cells. If shown successful our approach may eventually lead to new methods in the treatment of diabetes and other secretory diseases. Our future studies will focus on application of ultrasound to the pancreas in an in vivo animal model to determine whether it would be possible to stimulate beta cells without stimulating other endocrine and exocrine cells of the pancreas.
POSTER NUMBER: 309
A FEASIBILITY STUDY OF HISTOTRIPSY THERAPY FOR TRANSCRANIAL TISSUE ABLATION
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The main objectives of this study were to investigate the feasibility of using histotripsy therapy as a potential technique for transcranial tissue ablation and evaluate the degree of treatment precision that could be achieved through an intact human skull. To increase ablation precision, short histotripsy pulses were applied to achieve a small cavitation bubble cloud at the focus. This was done in contrast to previous studies using longer pulses, which were observed to increase the size of the bubble cloud by creating additional cavitation due to the scattering and inversion of positive shock fronts from subsequent cycles on the existing microbubbles. A focused 32-element hemispherical array operating at a center frequency of 500 kHz was designed in our laboratory, allowing high instantaneous peak negative pressures to be generated at the focus using extremely short pulse driving regimes (< 2 full cycles). An ex vivo human skull cap sample was used to provide realistic acoustic attenuation and aberration patterns. Prior to treatment, phase correction was performed using a hydrophone placed at the focus of the array. Histotripsy lesion profiles were created in tissue phantoms and ex-vivo liver samples by the application of 500 pulses using repetition frequencies (PRF) of 1, 10 and 100 Hz. The skull cap significantly attenuated the focal pressure value to approximately 14% of free-field conditions, which was improved to 28% after phase correction was performed on the 32-elements of the array. This allowed cavitation bubble clouds to be generated at the focus at a p-pressure level of approximately 29-30 MPa. Well defined focal lesions as small as 0.8 x 1.9 mm in the agarose phantoms and 0.5 x 1.2 mm in the tissue samples were generated through the intact skull, representing a range significantly smaller than the full width half maximum of the focal pressure main beam (1.8 x 3.9 mm). Treatments at lower PRF were observed to result in more confined lesions with sharper ablation boundaries, with reduced collateral damage outside the focal region. Histotripsy therapy produced consistent and uniform bubble clouds and generated precise, sub-wavelength lesion profiles through the skull. The capability of achieving a high degree of ablation precision using this short-pulse sonication strategy could be potentially useful for non-invasive brain therapy applications.

Figure 1. Transcranial histotripsy lesions generated in red blood cell (RBC) tissue phantoms at different pulse repetition frequencies. Cavitation damage appears as the bright translucent area surrounded by the opaque RBC layer. Ultrasound propagation: top to bottom.
POSTER NUMBER: 310
MECHANICAL DECELLULARIZATION OF TISSUE WHILE SPARING VASCULAR STRUCTURES USING BOILING HISTOTRIPSY
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HIFU is rapidly advancing as an alternative therapy for noninvasively treating specific cancers and other pathological tissues mainly through thermal ablation. Recently, new types of HIFU therapy aiming at mechanical fractionation of tissue into subcellular fragments has shown great promise, namely cavitation-cloud histotripsy and boiling histotripsy (BH). BH uses millisecond-long bursts of HIFU waves containing shock fronts to induce repetitive boiling at the focus; then the interaction of incident HIFU waves with the boiling bubble fractionates tissue. It has been shown that the degree of mechanical tissue damage induced by both types of histotripsy depends on the tissue type; in general, the more fibrous structures such as vasculature tend to resist mechanical disruption while cells are more easily damaged. This attribute holds clinical promise since many applications require the sparing of critical tissues such as vessels and ducts adjacent to, or within, the treatment site. In this study we have demonstrated that BH can be used to decellularize large tissue volumes while sparing extracellular matrix, blood vessels and similar structures. Degassed ex vivo bovine liver samples were sonicated using a clinical MR-HIFU system (Sonalleve, Philips Healthcare, Vantaa, Finland). The BH lesions were produced by the 256-element array operating at the frequency of 1.2 MHz with 10-ms long pulses and pulse repetition frequencies (PRFs) of 1-10 Hz to cover a range of effects from pure mechanical fractionation to thermal ablation. The peak acoustic power was 250 W, corresponding to the estimated in situ shock front amplitude of 65 MPa. The HIFU focus was targeted at an axial depth of 20 mm in tissue and electronically steered over an 8-16 mm range transverse to the axis of the transducer. Neighboring focal positions were separated by 2 mm in the transverse direction, and each treatment site received 30 HIFU pulses. Large cylindrical lesions of 10-20 mm diameter and 10 mm length were obtained. After treatment, the lesions contained in the samples were either processed for histological analysis or cut open for gross analysis and careful retrieval of the contents for protein analysis. The treatments performed with PRFs of 1, 3, 5, and 10 Hz resulted in fractionated lesions with increasing amounts of thermal damage to the tissue, as evident in the protein analysis and NADH-diaphorase staining. Tissue fractionation in the volumetric lesions was less complete with increasing PRFs. These results were similar to those previously found for single lesions. On histological evaluation, larger caliber blood vessels and supporting extracellular matrix were spared in lesions formed with 1, 3, and 5 Hz PRF, with the remaining blood vessels surrounded by homogenized tissue debris. These vessels could be observed macroscopically in samples bisected and washed after BH (Figure 1). However, smaller caliber vessels were more sensitive to BH at the higher PRFs. At 10 Hz, a dense thermal paste with vaporized cavities was formed inside the volumetric lesion. This study demonstrates that large volumes of liver tissue can be decellularized by BH in a clinical HIFU system while leaving certain 3-D tissue structures like vessels intact without any thermal damage. With further tailoring of the pulsing scheme parameters, this treatment modality could potentially be utilized for multiple applications where selective disruption of tissue is desirable, such as in tumor ablation and the decellularization of organs for tissue engineering applications. Work supported by NIH EB007643, K01 EB 015745-01, T32 DK007779, and NSBRI through NASA NCC 9-58

Figure 1: Photo of cross-sectional view of volumetric lesion (dotted line) with homogenized tissue washed out. Large vascular structures (arrow) could be seen as well as smaller vessels (arrow head). Scale bar=5 mm
POSTER NUMBER: 311
PRECLINICAL SAFETY AND EFFECTIVENESS STUDIES OF ULTRASONIC PROPULSION OF KIDNEY STONES
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The incidence of nephrolithiasis is increasing, and the costs represent a $5 billion burden annually. Current treatment options are effective, but commonly leave behind residual stones. Our research group has developed ultrasonic propulsion to transcutaneously reposition kidney stones to facilitate passage. We report the final preclinical safety and effectiveness studies in pigs which formed the basis for regulatory approval to conduct human clinical trials. The system is a diagnostic ultrasound platform programmed with a longer, slightly higher amplitude transient ultrasound burst for pushing stones. Our second generation system consisted of a 1000 ms burst, which was reduced to 50 ms in our third generation system. This 50 ms burst contains 450-µs, 2-MHz pulses interlaced with 165 µs of quiet time. The reduction in push duration was achieved by increasing the duty cycle from 3.3% (Gen-2) to 73% (Gen-3).

Reduction in pulse duration and increase in duty cycle allowed more efficient energy delivery to our target. Pressure amplitude, and therefore intensity of each pulse, was unchanged (ISPPA.3=63 W/cm2). In effectiveness study 1, focused ultrasound was used to expel 2-5 mm human calcium oxalate monohydrate (COM) stones placed ureteroscopically in the right kidneys of five 50-60 kg domestic female pigs. Stone displacement was graded on a scale of 0-4: 0 = no movement, 1 = stone vibration, 2 = movement and rollback, 3 = translation < 4 mm, and 4 = translation > 4 mm. In effectiveness study 2, de novo stones were imaged and repositioned in a porcine model. Acute safety studies were performed on two kidneys (3 sites per kidney) and three pancreases. Each kidney site was exposed to maximum continuous B-mode output with a maximum output push burst delivered every 30 seconds for a total of 40 bursts. Each pancreas was exposed similar conditions every 30 seconds for a total of 120 bursts (60 min). Survival studies followed 10 animals for 1 week after simulated treatment. Animals received up to 40 pushes at maximum output over multiple sites within the kidney. Serum and urine analyses pre- and post- treatment were performed. Tissues were evaluated histologically for all safety studies. All ureteroscopically implanted stones were repositioned from the lower pole into the uretero-pelvic junction (4) or ureter (2) with a mean treatment of 14 ± 5 bursts over 14 ± 8 min. On average, only 4 pulses (per kidney) resulted in stone movement more than 4 mm, and collectively accounted for the majority of relocation. Two 2-3 mm de-novo stones were detected in 200 kg stone forming animals with both stones successfully repositioned into the collecting system. Average treatment was 10 ± 8 bursts over 20 ± 13 minutes. No injury was detected in the acute or survival studies in comparison to untreated control tissue samples. In the survival studies, no animals displayed adverse clinical signs and all blood and urine values were within control limits. The use of ultrasound to reposition renal calculi is safe and effective in the porcine model. All stones were expelled from the lower pole in an average of 14 minutes. No adverse effects were identified with the acute studies directly targeting kidney or pancreas tissue, or during the survival studies, indicating no evidence of delayed tissue injury. In addition to facilitating the passage of residual fragments, potential application of this technology includes treating sub clinical de-novo stones, relieving obstructing calculi, and repositioning pre-surgical stones for improved outcomes. Work supported by NIH P01 DK043881, R01 DK092197, and NSBRI through NASA NCC 9-58.

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0 = no movement; 1 = wobble; 2 = movement with rollback; 3= movement < 4mm; 4 = movement > 4mm
Ultrasound Non-thermal Therapies

POSTER NUMBER: 312
PILOT EVALUATION OF BOILING HISTOTRIPSY OF THE KIDNEY: ASSESSMENT IN HUMAN EX VIVO KIDNEYS AND VALIDATION OF THE PORCINE MODEL
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Histotripsy is a non-thermal high intensity focused ultrasound (HIFU) technology that mechanically homogenizes targeted tissue. Recently, a new histotripsy method, termed boiling histotripsy (BH), has been developed at the University of Washington. The method utilizes milliseconds-length HIFU bursts containing shock fronts to create boiling bubbles at the focus. Interaction of shocks with the ensuing vapor cavity homogenizes tissue with negligible thermal effect. As a noninvasive, non-thermal based approach, BH may have several advantages over existing clinically available thermal techniques for ablation of renal masses. The aim of this study was to evaluate the feasibility of BH renal ablation in fresh human kidneys. In addition, the results obtained in human tissue were compared to fresh porcine kidneys in order to validate the porcine model for future preclinical studies. Fresh human kidneys and benign renal tissue were obtained via an IRB approved institutional rapid autopsy and tissue procurement program. Fresh porcine kidneys were obtained from a local abattoir. All specimens were acquired within 4 hours from death/nephrectomy. Tissue samples were degassed for ≥30 min in phosphate buffered saline (PBS) and then treated ex vivo in a bath of degassed PBS with ultrasound guided BH using a 1-MHz 7-element HIFU transducer. The pulsing scheme parameters were: repetitive 10 ms-long pulses with 98 MPa shock amplitude, 17 MPa peak negative pressure, and 1% duty factor. Single focal volumes within the cortex, medulla, or collecting system were treated at various doses (30-180 pulses). Treated kidneys were evaluated grossly or formalin-fixed for histologic assessment with hematoxylin and eosin staining. Treatment with BH in both human and porcine ex vivo kidneys producing localized hyperechoic bubbles at the focus that dissipated between the pulses. Grossly, BH resulted in liquid-filled lesions within the targeted volumes of tissue in a dose dependent fashion with minimal observable thermal effects (see figure). In both human and porcine kidneys there was histologic evidence of targeted tissue homogenization within the cortex at doses as low as 30 pulses. However, homogenization was incomplete at low doses with relative sparing of the glomeruli compared to other cortical structures; homogenization trended toward completion as doses approached 150-180 pulses/lesion. The medulla was more resistant to BH than cortical tissue, requiring 60 pulses to produce apparent tissue effect. There was no definitive tissue effect observed within the collecting system up to the maximum delivered dose of 180 pulses. BH of human kidney appears feasible, yielding anticipated tissue disintegration. The increased resistance of the medulla and collecting system may provide a margin of safety when developing BH clinically for ablation of renal tumors. The observed similarities between porcine and human renal tissue in response to BH support the development of the porcine model for further preclinical studies. Work supported by NIH 2T32DK007779-11A1, R01EB007643, 2P01DK043881-15, 1R01DK092197-02, and NSBRI through NASA NCC 9-58.
POSTER NUMBER: 313
ACTIVE REMOVAL OF RESIDUAL BUBBLE NUCLEI FOLLOWING A CAVITATION EVENT: A PARAMETRIC INVESTIGATION
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Upon their collapse, the primary cavitation bubbles generated by a high intensity acoustic pulse can fragment to yield a large population of microscopic residual bubble nuclei. The lifetime of these residuals can be on the order of a second, and if subsequent acoustic pulses are applied prior to their dissolution, they can seed additional cavitation events. This behavior can limit the efficacy of cavitation-based ultrasound therapies such as shockwave lithotripsy and histotripsy. Our previous work has identified a strategy for mitigating these effects, as we have demonstrated that low amplitude acoustic pulses can actively remove residual bubble nuclei from the field by stimulating their aggregation and subsequent coalescence. The present study further explores this bubble removal process with an investigation of the acoustic parameter space for optimal nuclei coalescence. All experiments were conducted in degassed water and monitored using high speed photography at 20 kfps. The following general pulse scheme was used: (A) Cavitation Initiation Burst: Primary cavitation bubbles were initiated by a 2 MHz histotripsy transducer using a burst of five very short intense pulses (P- > 30 MPa) at 1 kHz PRF. (B) Bubble Removal (BR) Pulse: Residual bubble nuclei were sonicated using a 500 µs pulse from a separate transducer to stimulate coalescence. BR transducers with center frequencies of 0.5, 1, and 2 MHz were tested; at each frequency, pulse amplitudes ranging from 0 to approximately 1.5 MPa were applied. (C) Interrogation Pulse: The presence of residual nuclei following the BR pulse was probed using an additional 10 cycle pulse generated by the BR transducer. When this interrogation pulse propagated through the field it experienced attenuation commensurate with the extent of residual nuclei remaining, measured by a needle hydrophone distal to the bubble population. Five trials were performed for each parameter combination. Interrogation pulse transmission data is presented in the figure. The received P- of the interrogation pulse is normalized to the control case (cavitation initiation pulse amplitude set to 0—i.e., no cavitation bubbles generated prior to interrogation), and plotted as a function of the mechanical index of the BR pulse. Three distinct regimes of behavior are apparent: (1) MI < .4: Interrogation pulse transmission does not deviate significantly from the baseline case in which no BR was applied (t-test, P > .08); correspondingly, minimal nuclei coalescence was observed on high speed imaging. (2) .4 < MI < 1: Interrogation pulse transmission increases as the BR pulse amplitude is increased; enhanced nuclei coalescence was observed with increasing BR pulse amplitude on high speed images. (3) MI > 1: Interrogation pulse transmission decreases as BR pulse amplitude is increased; rather than coalescence, high speed imaging showed that residual nuclei seed violent cavitation at these amplitudes, with their expansion and subsequent collapse producing additional remnant bubbles. The 2 MHz BR transducer was not capable of producing sufficient amplitude to investigate this third regime. Results indicate that there is a narrow amplitude band in which BR pulses produce optimal bubble coalescence and alleviate the attenuative effect of residual nuclei on subsequent acoustic pulses. Placing these bounds on the process will allow us to further optimize the coalescence phenomenon within a simplified parameter space, and we anticipate that the resulting BR sequences will drastically enhance the efficacy of ultrasound therapies that suffer from the effects of residual bubble nuclei.

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THE EFFECT OF STONE SIZE ON COMMINUTION EFFICIENCY IN SHOCK WAVE LITHOTRIPSY
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We aim to investigate the effect of stone size on comminution efficiency during shock wave lithotripsy (SWL). A Siemens experimental electromagnetic shock wave source was operated at an output voltage of 13.8 kV with 1 Hz pulse repetition frequency. The acoustic field of the shock wave source was characterized by a FOPH, from which the average peak positive pressure, $p^+(\text{avg})$, inside a 14-mm stone holder was determined at six different field positions where stone comminution tests were conducted. For comminution experiments, cylindrical hard BegoStone phantoms with three different sizes, i.e., 4, 7, and 10 mm, were prepared. To maintain comparable total mass during each test, either one 10-mm stone (~1.5 g) or three 7-mm stones (~1.3 g) or fourteen 4-mm stones (~1.5 g) were placed inside the stone holder. A total of 1000 shocks were administered to the stone holder, which was filled with either water or 1,3-Butanediol (which has similar acoustic impedance as water but suppresses cavitation). After the treatment, all residual fragments were collected from the holder, rinsed, dried overnight, and sequentially sieved to separate fragments of different sizes. The efficiency of stone comminution (SC) was determined by the weight percentage of fragments less than 2 mm. A strong correlation was observed between SC and $p^+(\text{avg})$ both in water and 1,3-Butanediol. For each size group, two correlation lines (in water and 1,3-Butanediol) intercept at a similar $p^+(\text{avg})$ threshold for the initiation of fragmentation. The $p^+(\text{avg})$ threshold was found to increase from 6.0 to 7.5 to 12.9 MPa for 10, 7, and 4 mm stones, respectively. In addition, the scope of the correlation line in water decreases with increasing stone size, while the opposite trend was observed for stones treated in 1,3-Butanediol. Our study demonstrates that stone size can significantly influence the comminution efficiency in SWL. The contrasting difference in stone comminution rate in water vs. in 1,3-Butanediol further indicate the varying contribution of stress waves vs. cavitation in stone fragmentation during SWL. Our results also suggest that optimization of treatment strategy may improve the treatment efficacy for stones of different sizes.
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4th International Symposium
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