



19th International Symposium of ISTU
5th European Symposium of EUFUS
Barcelona 2019 | 13th - 15th June

ABSTRACT BOOK



Scientific Organizing Committee

Robin Cleveland, *Co-Chair*

Vera Khokhlova, *Co-Chair*

Local Organizing Committee

Joan Vidal-Jové, *Chair*

EUFUS Organizing Committee

Andreas Melzer, *Co-Chair*

Wladyslaw Gedroyc

Alessandro Napoli

Matthias Matzko

Lisa Landgraf

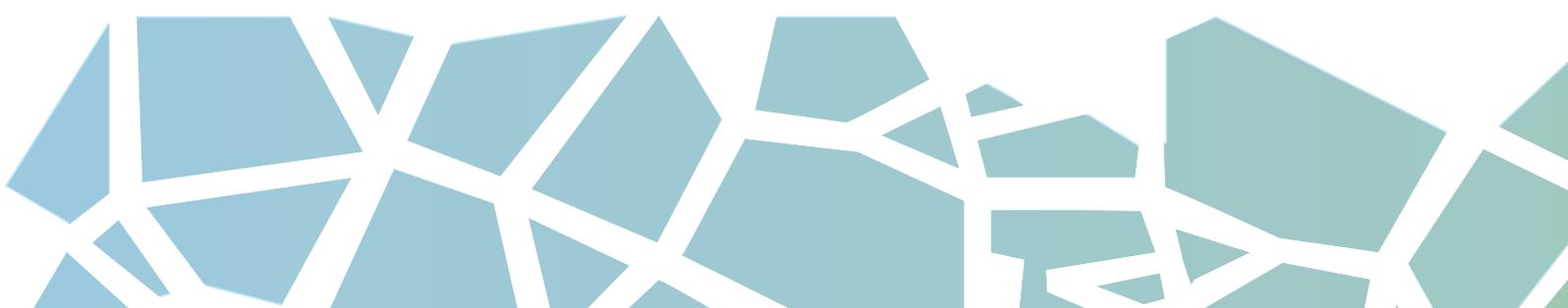
ISTU

Joo Ha Hwang, *President*

Kim Butts Pauly, *Secretary General*

Jean-François Aubry

Gail ter Haar



Thursday, June 13th 2019		Friday, June 14th 2019		Saturday, June 15th 2019	
Education: Neurological Disease		Education: Immunology		Education: Getting Medical Devices to Market	
<i>Raúl Martínez</i>		<i>Elizabeth Repasky</i>		<i>Nicolas Guillen</i>	
Welcome		Education: Bioeffects of US		Education: Hyperthermia Technologies	
<i>Joo Ha Hwang, Joan Vidal-Jové, Andreas Melzer</i>		<i>Diane Dalecki</i>		<i>Holger Gruell</i>	
Fry / Lizzi / Pioneer Award Session		Horizon / Jolesz Lectures		Organ Panel: Brain	
Invited speakers: <i>Chrit Moonen Kevin Haworth W. Apoutou N'Djin Leonid Gavrilov</i>	Chairs: <i>Lawrence Crum Jean-François Aubry Joo Ha Hwang</i>	Invited speakers: <i>Morry Blumenfeld Neal F. Kassell</i>	Chairs: <i>Alessandro Napoli Wladyslaw Gedroyc</i>	Invited speakers: <i>Jin Woo Chang Cesare Gagliardo Roland Beisteiner Henning Lohse-Busch</i>	Chairs: <i>Wladyslaw Gedroyc Marine Sánchez</i>
Physics and Modelling		Drug Delivery		Organ Panel: Uterus	
Invited speakers: <i>Jean-François Aubry Robert Staruch</i>	Chairs: <i>Bradley Treeby Aki Pulkkinen</i>	Invited speakers: <i>Karun Sharma Juan Tu</i>	Chairs: <i>Holger Grull Michael Gray</i>	Invited speakers: <i>Suzanne LeBlang Jaron Rabinovici</i>	Chairs: <i>Matthias Matzko Nikolaos Bailis</i>
Break		Break		Break	
Hardware		Immunotherapy		Organ Panel: Prostate and Kidney	
Invited speakers: <i>Gil Dubernard Adam Maxwell</i>	Chairs: <i>Amanda Beserra Cyril Lafon</i>	Invited speakers: <i>Elizabeth Repasky Chandan Guha</i>	Chairs: <i>Natasha Sheybani Tatiana Khokhlova</i>	Invited speakers: <i>Jens Rassweiler Mark Emberton</i>	Chairs: <i>Andreas Melzer George Schade</i>
Industry Pitch					
Lunch & Posters session		Lunch & Posters session		Lunch break	
Monitoring and feedback		Therapy ultrasound plus		Industry Pitch Presentations	
Invited speakers: <i>Henrik Odeen Sunao Shoji</i>	Chairs: <i>Elodie Cao Shin-ichiro Umemura</i>	Invited speakers: <i>Sarah Brüningk Edwin Heijman</i>	Chairs: <i>Gail ter Haar Lisa Landgraf</i>		
Nonthermal mechanisms		Neuromodulation		Organ Panel: Musculoskeletal	
Invited speakers: <i>Tatiana Khokhlova Zhen Xu</i>	Chairs: <i>Ki Joo Pahk Oleg Sapozhnikov</i>	Invited speakers: <i>Elisa Konofagou Jan Kubanek</i>	Chairs: <i>Lennart Verhagen Wynn Legon</i>	Invited speakers: <i>Francisco Aparisi Pejman Ghanouni Francesco Arrigoni</i>	Chairs: <i>Markus Duex Alessandro Napoli Alberto Bazzocchi</i>
Break		Break		Break	
Drug delivery design/engineering		Brain – preclinical		Organ Panel: Liver and Pancreas	
Invited speakers: <i>John Callan Michel Versluis</i>	Chairs: <i>Dario Carugo Eleanor Stride</i>	Invited speakers: <i>Richard Price Nathan McDannold</i>	Chairs: <i>Elisa Konofagou Muna Aryal</i>	Invited speakers: <i>Joo Ha Hwang Xavier Serres</i>	Chairs: <i>Joan Vidal-Jové Milka Marinova</i>
ISTU General Assembly		Debate – Micron-sized contrast agents have a great future in clinical HIFU		Other clinical HIFU applications	
		Invited speakers: <i>Constantin Coussios Mike Averkiou</i>	Chairs: <i>Gail ter Haar Joo Ha Hwang</i>	<i>Andreas Melzer Joan Vidal-Jové</i>	
USgHIFU Meeting: Clinical Application (sponsored session)		EUFUS General Assembly		Closing	
Welcome Reception		Gala Dinner		<i>Joo Ha Hwang, Joan Vidal-Jové, Andreas Melzer</i>	



EDUCATION

Neurological Diseases



MRgFUS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS: A CLINICAL UPDATE

Raul Martinez Fernandez, Centro Integral en Neurociencias A.C. (HM CINAC), Madrid
e-mail: rmartinez.hmcinac@hmhospitales.com

Since the first studies using MRgFUS for the treatment of essential tremor came out in 2013, its applications for neurological diseases have progressively increased. Today, MRgFUS thalamotomy is a FDA-approved treatment for both essential and parkinsonian tremors and some evidence suggests that it can also be useful for tremors of other origins. Furthermore, ablation of other targets such as the subthalamic nucleus and the internal globus pallidus has preliminary shown to safely provide benefit on all Parkinson's disease motor features and complications. MRgFUS has also been applied, with initial but promising results, in dystonia or obsessive-compulsive disorder, and has started to experimentally be considered in other neurological conditions like refractory epilepsy or stroke. While the main objective of the mentioned applications is the symptomatic relief, the ability of FUS to transiently and focally open the Blood-Brain Barrier through a physical mechanism, have paved the way to impact on the neurodegenerative process and achieve a disease modifying effect. Accordingly, experimental trials for Parkinson's disease, Alzheimer dementia and amyotrophic lateral sclerosis are ongoing.

This talk will present an overview of the current evidence with focused ultrasound in Neurology, with special attention in movement disorders, the most investigated field so far.



AWARDS SESSION

FRY / LIZZI / PIONEER

FRY AWARD, INVITED TALK:

Towards an increased clinical impact of focused ultrasound - *Chrit Moonen*

LIZZI AWARD, INVITED TALKS:

Exploding droplets and singing bubbles in therapeutic ultrasound - *Kevin Haworth*

A healthy future for focal conformal therapeutic ultrasound - *W. Apoutou N'Djin*

PIONEER AWARD: Presentation of the ISTU/EUFUS Pioneer Award winner, Leonid Gavrilov



TOWARDS AN INCREASED CLINICAL IMPACT OF FOCUSED ULTRASOUND

Chrit Moonen

Imaging Division, University Medical Center, The Netherlands

E-mail C.Moonen@umcutrecht.nl

HIFU is a disruptive, minimally invasive, therapeutic technology in medicine, and its history follows the nature cycle from the inventive stage, technical developments, preclinical and clinical applications. Following early promise by the Fry brothers, the advent of image guidance and many technical refinements, clinical applications started with prostate cancer, and have since broadened considerably to other tumors, and include not only tissue ablation but also drug delivery and immune system stimulation. The current status and progress is well described by the FUSFoundation annual reports. Although HIFU fits well in current strategies of personalized and precision medicine, of patient Quality-of-Life, clinical adoption of HIFU is slow, and adequate reimbursement is often lacking. Here, the hurdles for further progress are analyzed. A comparison is made between HIFU and recent developments in RadioTherapy. Clinical workflow for HIFU and RadioTherapy are similar, and image guidance has become a major issue for both therapeutic technologies. The importance of moving beyond feasibility studies of HIFU towards randomized, multi-site, clinical trials is highlighted. Financial issues play an important role since the business model for companies working in HIFU is very different from that in Pharma, and Radio Therapy, and it is hard to find financial support for such Phase 3 trials. For hospitals, HIFU equipment is an additional investment, not replacing other modalities. Sufficient patient numbers have to be treated to guarantee a return on investment. In addition, since HIFU is a disruptive technology, FDA approval based on 510k clearance, is not possible and hence, regulatory issues are more difficult for HIFU than for RadioTherapy. Nevertheless, recent highlights in the treatment of essential tremor, its increasing share in prostate cancer therapy and in uterine fibroid treatment, show that it is possible to increase the clinical impact of HIFU. As patient awareness of HIFU is increasing, HIFU is finding its way into the clinic.

EXPLODING DROPLETS AND SINGING BUBBLES IN THERAPEUTIC ULTRASOUND

K. J. Haworth^{1,2}

¹ Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA

² Department of Biomedical Engineering, University of Cincinnati, Cincinnati, Ohio, USA

e-mail: hawortkn@ucmail.uc.edu

Though widely used clinically for diagnostic imaging, microbubbles also provide a rich opportunity for inducing bioeffects, both intended and unintended. Phase-change agents that take advantage of acoustic droplet vaporization are particularly interesting for therapeutic applications due to their in situ ultrasound-mediated production of microbubbles. The first half of this presentation will provide a review of these applications (with a focus on the author's humble contributions to the field), including a new subfield of localized dissolved gas scavenging. In addition to the direct mediation of therapies, the microbubbles can also be used to improve both therapeutic insonation focusing and image-guidance. Using microbubble scattering and emissions for guiding therapy will be reviewed in the second half of this presentation. In particular, passive cavitation imaging will be reviewed, including methods, applications, limitations, and future directions.

A HEALTHY FUTURE FOR FOCAL CONFORMAL THERAPEUTIC ULTRASOUND

W.A. N'Djin¹

¹ LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, Lyon, France

e-mail: apoutou.ndjin@inserm.fr

Therapeutic ultrasound is in constant evolution. Focal/conformal strategies are now often sought after to improve the patient care, but their development remains challenging and requires bringing together new solutions.

In open surgery, we proposed an unconventional toroidal focusing strategy for USgHIFU therapy of liver metastases. This solution allowed optimizing the energy distribution, to generate and juxtapose manually large ablations, little affected by vascularization and organ motions. A clinical study ran in France validated the concept of complementary tool to surgery.

In interventional radiology, the use of single-/dual- frequency exposures for interstitial MRgHIFU allowed 3D control of the energy deposition for conformal ablations. In Canada, a clinical study validated this approach for transurethral prostate ablation (extensions: United States, Europe).

Our contributions to conformal/focal approaches also involved emerging MEMS technologies (CMUT transducers) and image guidance methods (3D US navigation, real-time HIFU beam visualization). The first *in-vivo* study for MRgHIFU brain ablation with a CMUT catheter was initiated, as the development of an endocavitary prototype for USgHIFU prostate ablation. CMUTs exhibited groundbreaking characteristics (miniaturization, frequency modulation) which appeared interesting beyond ablative applications (e.g. neurostimulation).

However, ultrasound innovations are not always sufficient to advance our knowledge on new therapeutic strategies. For studying ultrasound neurostimulation, we considered advanced electrophysiological techniques from neurosciences. Our recent observations confirmed focal ultrasound-induced electrical activities in several neural models and suggested a preponderant role of the radiation force.

Future directions will reinforce openness towards emerging technologies and other disciplines for developing new generations of focal/conformal therapeutic ultrasound, especially in neurosciences.

CONTRIBUTION TO THERAPEUTIC ULTRASOUND. BRIEF OVERVIEW

L.R. Gavrilov

Acoustics Institute, Moscow, Russia,

e-mail: lrgavrilov@gmail.com

Below is a short list of contributions to therapeutic ultrasound made with my participation.

- 1971. Research on the use of HIFU for local ablation of deep brain structures was initiated in the Soviet Union. (Together with the Brain Institute, Academy of Medical Sciences of the USSR).
- 1972-1973. The possibility of ablating deep brain structures through an intact human skull by focused ultrasound was demonstrated for the first time using the Schlieren method.
- 1973-1974. First quantitative measurements of cavitation thresholds in living brain tissues of animals were performed. Ultrasound doses that corresponded to purely thermal and purely cavitation mechanisms of tissue ablation were determined. (With the Brain Institute, Moscow).
- 1972-1973 and further. A novel method of stimulating neural structures of humans and animals by focused ultrasound was proposed. It was shown for the first time that single stimuli with short duration and relatively high intensity focused ultrasound, directed at the human skin, cause various types of sensations: tactile, thermal (heat or cold), various types of pain, etc. (With the Institute of Evolutionary Physiology and Biochemistry, Leningrad - IEPHB).
- 1973-1975. It was shown that irradiation of transplantable tumors in mice with low-intensity ultrasound at a certain time before gamma-irradiation noticeably increased the sensitivity of tumor cells to the action of ionizing radiation. (With the All-Union Oncological Scientific Center).
- 1977. Localised ablation of deep brain structures through an intact skull was shown in experiments on human cadavers. (With the 1-st Moscow Sechenov Medical Institute).
- 1982. A method of diagnosing neurological and hearing diseases was developed and tested in clinics. (With IEPHB and the Leningrad Research Institute of Ear, Throat, and Nose).
- 1985. The use of focused ultrasonic receivers for remote measurements of temperature rise in biological tissues, cavitation thresholds, and acoustic field distributions was shown.
- 1996-1997. A novel miniature optical fiber probe for measurements of the intensity of MH-frequency ultrasound, and increments of temperature was designed and tested. (With the University of Kent and Imperial College, London, UK).
- 1996-1997. Intracavitary linear phased array for transrectal prostate surgery was designed and fabricated. (With the Hammersmith Hospital, Imperial College, London).
- 2000 and further. A new design of multi-element 2-D therapeutic arrays with random distribution of their elements was proposed and fabricated. (With the Imperial College, London).
- 2010. HIFU-ablation of liver by sonication through the rib cage using a 2-D therapeutic random phased array was demonstrated. (With the Department of Acoustics, Moscow State University (MSU), Russia).
- 2011-2013. Method of measuring the intensity of acoustic fields using a digital infrared camera was proposed and tested. (With NPL, Teddington, UK and MSU).
- 2016-2017. Possibility of reaching high-amplitude shocks at the focus of an ultrasound beam when irradiating through the skull in brain tissue was demonstrated in simulations. (With Laboratory of Industrial and Medical Ultrasound (LIMU) at MSU).
- 2014-2019. Methods for designing high-density and fully populated random 2D ultrasound phased arrays were developed. (With LIMU-MSU).

ACKNOWLEDGEMENTS

Supported by RFBR, RSF, NIH, ISTU, and EUFUS.



PHYSICS AND MODELLING

INVITED TALKS:

What can physics and modelling do for neurosurgeons and neurologists? -*Jean François Aubry*

MRI-Guided transurethral ultrasound ablation of prostate tissue: clinical impact of intensified treatment parameters - *Robert Staruch*

ORAL PRESENTATIONS:

Design and simulation of a phased array for ultrasound therapy in the spinal cord - *Rui Xu*

New design of a fully populated random array for treating deep-seated tumors - *Pavel Rosnitskiy*

Exploring the role of laser and ultrasound on gold-loaded droplet vaporization - *Yanye Yang*

Experimental validation of models of ultrasound propagation - *Elly Martin*

OptimUS: A fast multi-domain full wave solver for therapeutic ultrasound treatment planning - *Pierre Gelat*

Computational modeling of tissue-selective liver ablation in histotripsy -*Lauren Mancia*

Scattering from microbubble clouds: A fast multipole model with experimental validation - *Gregory Clement*

Improved numerical method for the design of 3D printed acoustic lenses for the correction of transcranial focused ultrasound aberrations - *Marcelino Ferri Garcia*



WHAT CAN PHYSICS AND MODELLING DO FOR NEUROSURGEONS AND NEUROLOGISTS?

J.-F. Aubry¹

¹Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Paris, France
e-mail: jean-francois.aubry@espci.fr

OBJECTIVES

This talk will give an overview of the underlying physics and modelling for transcranial brain therapy.

METHODS

Due to the increased defocusing effect of the human skull with increasing frequency, transcranial focusing techniques divide into two groups: (i) the use of very low frequencies (ii) the use of adaptive techniques based on Computed Tomography (CT) or Magnetic Resonance (MR) Imaging of the patient head. These approaches will be explained and reviewed

RESULTS

Beyond current techniques under clinical use, novel developments are on their way to meet the clinician's needs for safer, more precise, and faster treatments. They will be reviewed in this talk.

CONCLUSIONS

Physics and modelling already plays a crucial role in MR guided transcranial ultrasonic brain therapy by estimating the phase delays used during treatments. But it will expand soon to patient selection guidance, automatic power adjustment and faster treatment time.

ACKNOWLEDGEMENTS

Supported by the Bettencourt Schueller Foundation and the "Agence Nationale de la Recherche" under the program "Future Investments" with the reference ANR-10-EQPX-15.

MRI-GUIDED TRANSURETHRAL ULTRASOUND ABLATION OF PROSTATE TISSUE: CLINICAL IMPACT OF INTENSIFIED TREATMENT PARAMETERS

R.M. Staruch¹, J. Bishop¹, M. Allard¹, M. Burtnyk¹

¹Profound Medical, Mississauga, Ontario, Canada

e-mail: rstaruch@profoundmedical.com

MRI-guided transurethral ultrasound ablation of prostate tissue (TULSA) uses real-time MRI thermometry, directional ultrasound, and closed-loop feedback control for customizable incision-free ablation of targeted prostate tissue. TULSA treatment parameters are based on histological studies of ablation thresholds and validated numerical simulations of MRI-controlled ultrasound heating.

An initial 30-patient Phase I study of the safety and feasibility of TULSA in men with predominantly low-risk prostate cancer applied conservative whole-gland ablation with treatment margins that intentionally spared 10% of the viable prostate tissue. This enabled MR thermometry measurement of the spatial treatment precision and the extent of delayed cell kill within the prostate, while accepting a high risk of residual disease.

The recently-completed TULSA-PRO Ablation Clinical Trial (TACT) pivotal study assessed treatment efficacy and safety in 115 men with predominantly intermediate-risk prostate cancer across 13 institutions in the United States, Europe, and Canada. In the pivotal study, feedback control parameters were intensified for complete prostate ablation, by aiming to achieve higher temperatures closer to the capsule and reducing the minimum speed of rotation. Simulations of acoustic field propagation, heat transfer, and MRI thermometry feedback predicted that these changes would deliver irreversible cell kill to 99% of the targeted prostate volume. The clinical results of the TACT study demonstrated increased ablation volumes as measured by MRI thermometry, increased prostate volume reduction at 12-month MRI, and improved biochemical and histological disease control, with minimal changes in adverse events and functional quality of life outcomes.

DESIGN AND SIMULATION OF A PHASED ARRAY FOR ULTRASOUND THERAPY IN THE SPINAL CORD

R. Xu^{1,2}, M. A. O'Reilly^{1,2}

¹Department of Medical Biophysics, University of Toronto, Toronto, Canada

²Physical Sciences, Sunnybrook Research Institute, Toronto, Canada

e-mail: rxu@sri.utoronto.ca, moreilly@sri.utoronto.ca

OBJECTIVES

To design and simulate the performance of a phased array for producing controlled foci within the human vertebral canal.

METHODS

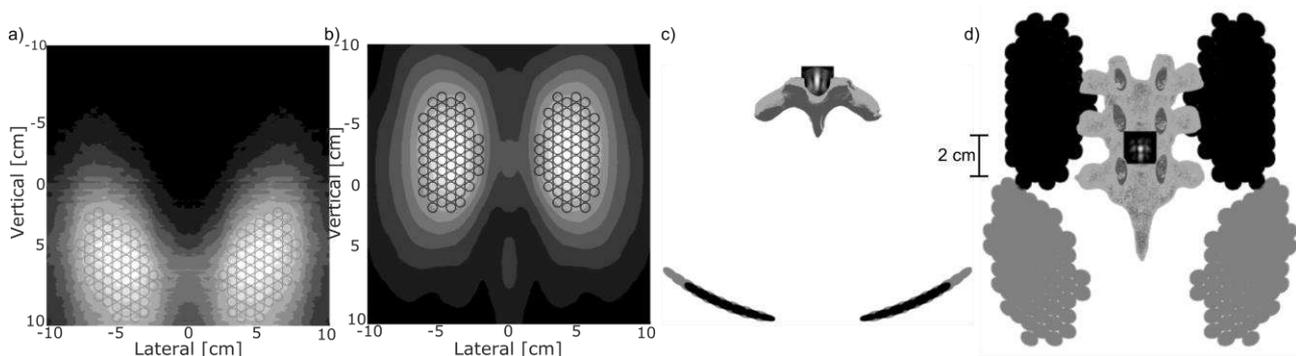
A simulation system was generated using CT scans of *ex vivo* human thoracic vertebrae, semi-automatic segmentation, and binary mask-based mesh generation. 300 simulated sources were placed within the vertebral canal. Ray acoustics was used to simulate acoustic propagation from each source via paravertebral and transvertebral paths to a corresponding measurement surface. The mean sound fields were used to place 256 elements (7.5mm diameter, 500kHz), maximizing ultrasound reception and transmission for targets spanning the thoracic spinal cord. Array efficiency (canal focal pressure/water focal pressure) and focal dimensions were evaluated for 300 targets.

RESULTS

The mean paravertebral (Fig.a) and transvertebral (Fig.b) sound fields were spatially distinct, and were used to design a spine-specific 4-component phased array (Fig.c,d). All elements were placed in locations with >60% normalized sound pressure to maximize array sound reception and transmission efficiency. Mean array efficiency was $29\pm 13\%$, and mean focal dimensions were $10.8\pm 2.7\text{mm}$ (axial), $4.2\pm 2.7\text{mm}$ (lateral), and $5.9\pm 2.1\text{mm}$ (vertical). Target-specific reconfiguration of the array through relative motion of the four components increased efficiency to $36\pm 8\%$. Further gains in efficiency may be possible through amplitude correction.

CONCLUSIONS

A phased array capable of focusing to the human vertebral canal has been design. Future work will include fabrication and preclinical testing, advancing clinical-scale methods for therapy in the spinal cord.



CAPTION: Mean a) paravertebral, and b) transvertebral propagation maps (elements overlaid). Transspine focusing example: c) superior and d) anterior views.

NEW DESIGN OF A FULLY POPULATED RANDOM ARRAY FOR TREATING DEEP-SEATED TUMORS

P.B. Rosnitskiy¹, O.A. Sapozhnikov^{1,2}, H. Gröll³, V.A. Khokhlova^{1,2}

¹Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Dept. of Radiology, University Hospital of Cologne, Cologne, Germany

e-mails: pavrosni@yandex.ru; oleg@acs366.phys.msu.ru; holger.gruell@uk-koeln.de;

vera@acs366.phys.msu.ru

OBJECTIVES

First exploratory US-guided clinical studies on HIFU ablation of pancreatic cancer have shown promising results. The deep location of this cancer means that only a subset of patients can be treated with HIFU systems such as MR-guided Sonalleve[®] V2 (Profound Medical Inc.) with its beam focused up to 9 cm deep in tissue (Fig. (a, b)). New array designs for sonications at most clinically relevant depths could expand the patient population for HIFU therapy.

METHODS

A new algorithm for designing fully populated arrays with the elements of equal area and aperiodic arrangement was used [Rosnitskiy *et al.*, IEEE UFFC, 2018].

RESULTS

A 256-element 1.2-MHz array with $D=160$ mm aperture, $F=180$ mm focal length, 0.3 mm inter-element spacing, and 94% filling factor was proposed (Fig. (c)). The array field simulated in water using the Rayleigh integral was compared to that of the V2 array ($F=D=140$ mm). For the same intensity at the elements, the proposed array provided 1.7 times higher focal pressure (Fig. (d)) while maintaining a spatial range of the safe and efficient electronic steering.

CONCLUSIONS

The proposed array can provide significant increase in the total power, focal pressure, and thus irradiation depth for destructing deep-seated pancreatic tumors.

ACKNOWLEDGEMENTS

NIH R01EB7643 and student stipends from “Basis” Foundation and the President of Russia SP-2644.2018.4.

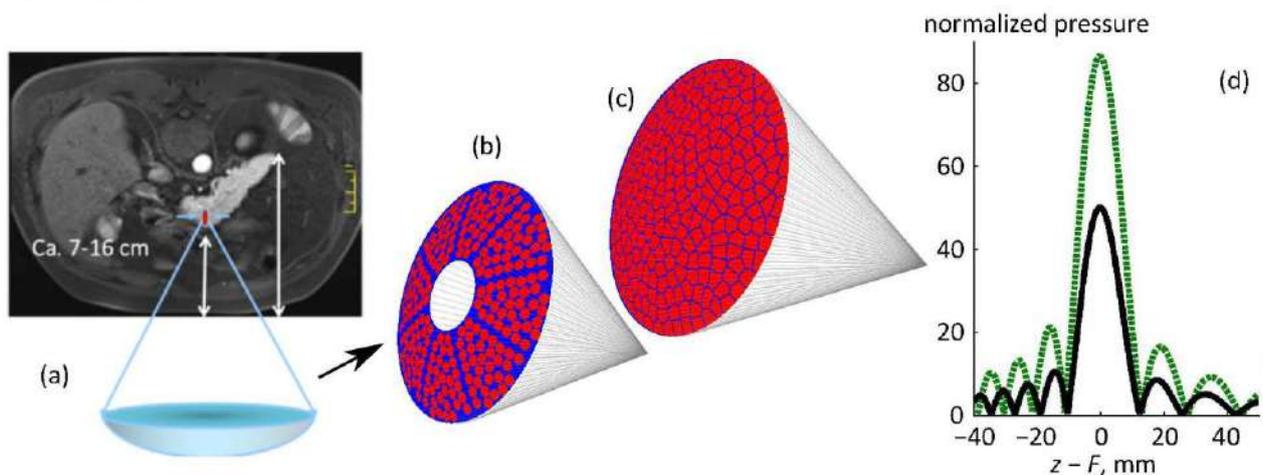


Figure Caption: (a) Geometry of ultrasound beam focused into the pancreas. (b,c) Diagrams and (d) axial pressure distributions normalized to the pressure amplitude at the array elements for the V2 (solid curve) and the proposed (dashed curve) arrays.

EXPLORING THE ROLE OF LASER AND ULTRASOUND ON GOLD-LOADED DROPLET VAPORIZATION

Yanye Yang¹, Dongxin Yang¹, Juan Tu¹, Xiasheng Guo¹, Dong Zhang^{1,2}

¹ Key Laboratory of Modern Acoustics (MOE), Department of Physics, Collaborative Innovation Center of Advanced Microstructure, Nanjing University, Nanjing, China

² The State Key Laboratory of Acoustics, Chinese Academy of Science, Beijing, China

e-mail: camusaga@hotmail.com

OBJECTIVES

It is widely accepted that the combination of ultrasound and laser can downshift the vaporization threshold of gold-loaded droplets. However, the exact downshift mechanism is still worthy of exploring. The objective of this work is to study the roles of ultrasound and laser in different vaporization stages of gold nanoparticle-loaded droplets.

METHODS

A kind of gold nanoparticle-loaded nanodroplet was fabricated and its ultrasound enhancement under laser and ultrasound irradiation was experimentally recorded. To explore the roles of laser and ultrasound during the whole vaporization process, a theoretical model was established. In this model, the vaporization process of a droplet loaded with a single gold nanosphere was divided into four parts: heating, nucleating, vaporizing and oscillating. The dynamics of vaporization in different stages were explored and further compared with experiment results.

RESULTS

From the theoretical model, it was witnessed that the laser energy dominated heating and nucleating process, while the ultrasound pressure played the leading role in vaporizing and oscillating stage. In the experiment, the 44mJ (output energy) laser pulse can assist droplet vaporization at relatively low ultrasound pressures. When the laser energy further increases to 60mJ, a jump in contrast enhancement arose, indicating that smaller droplets may be vaporized due to the augmented laser energy.

CONCLUSIONS

In order to achieve higher ultrasound enhancement, it is vital for laser energy to first create a thin layer of gas around the gold nanoparticle. After the gas layer is formed, ultrasound pressure takes control of the vaporization process.

EXPERIMENTAL VALIDATION OF MODELS OF ULTRASOUND PROPAGATION

Elly Martin¹, Jiri Jaros², James Robertson¹, Bradley Treeby¹

¹Medical Physics and Biomedical Engineering, University College London, London, UK

²Faculty of Information Technology, Brno University of Technology, Brno, Czech Republic

e-mail: elly.martin@ucl.ac.uk

OBJECTIVES

Numerical models of ultrasound propagation have applications across many fields including medical ultrasound. When used for treatment planning or computational dosimetry, their accuracy is particularly important in ensuring patient safety. Careful validation of the models is therefore required.

METHODS

Model validation can include comparison with analytical solutions, other models, and measurements of ultrasound fields. For validation against measurements, it is necessary to establish the expected uncertainties arising both during the measurement of acoustic pressure, and in the simulations, e.g. from the definition of medium properties and geometry, in order to determine the level of agreement between measurements and simulations

Here we describe a program of experimental validation of the open source k-Wave Matlab toolbox, which includes comparison of measurements and simulations of ultrasound fields in water and heterogeneous fluid and elastic absorbing media, with a discussion of the associated uncertainties.

RESULTS

Both in water and with glycerol filled phantoms or bone-mimicking phantoms, there was close agreement in the size and position of the measured and simulated focal regions. The measured and simulated spatial peak pressure amplitudes agreed to within 6%, which is within the expected uncertainty in the measured pressure.

CONCLUSIONS

When the medium properties and geometry are well characterized, close agreement is obtained between measurement and simulation, demonstrating the validity of k-Wave under these conditions. To help enable future validation of other codes, the measurement data generated is to be made available in an open access database hosted by UCL.

OPTIMUS: A FAST MULTI-DOMAIN FULL WAVE SOLVER FOR THERAPEUTIC ULTRASOUND TREATMENT PLANNING

S.R. Haqshenas^{1,2}, P. G elat², E. van 't Wout³, T. Betcke¹ and N. Saffari²

¹Department of Mathematics, University College London, London, UK.

²UCL Mechanical Engineering, Ultrasonics Group, University College London, London, UK.

³School of Engineering, Pontificia Universidad Cat olica de Chile, Santiago, Chile.

e-mail: s.haqshenas@ucl.ac.uk

OBJECTIVES

Ultrasound therapies are currently hindered by an inadequate capacity for treatment planning based on numerical models. For realistic clinical scenarios, all simulation methods which employ volumetric meshes require several hours/days to run on a computer cluster. The wider clinical adoption and translation of therapeutic ultrasound will be greatly facilitated by the ability to produce fast and accurate full wave patient specific simulations, with minimal computational overheads.

METHODS

We use the open source Bempp library to implement a multi-domain boundary element formulation with hybrid CPU/GPU architecture. By discretizing only the contours of the different tissue types, computational overheads are substantially reduced. Compounding this with efficient preconditioners and matrix compression techniques, the interactions of the incident ultrasonic field with multiple tissue domains may be accurately computed within a realistic clinical timeframe, and with no staircasing or numerical dispersion effects.

RESULTS

Figure 1 shows the interaction of a 1MHz plane wave field with (a) a right adult kidney surrounded by perinephric fat and (b) two ribs and an abdominal fat layer. Solving the system of equations associated with these problems required 15 and 5 minutes, respectively, on a single workstation.

CONCLUSIONS

A multi-domain boundary element formulation with hybrid CPU/GPU architecture has been implemented and tested on clinically relevant scenarios. OptimUS represents a disruptive innovation in fast and accurate patient specific therapeutic ultrasound treatment planning.

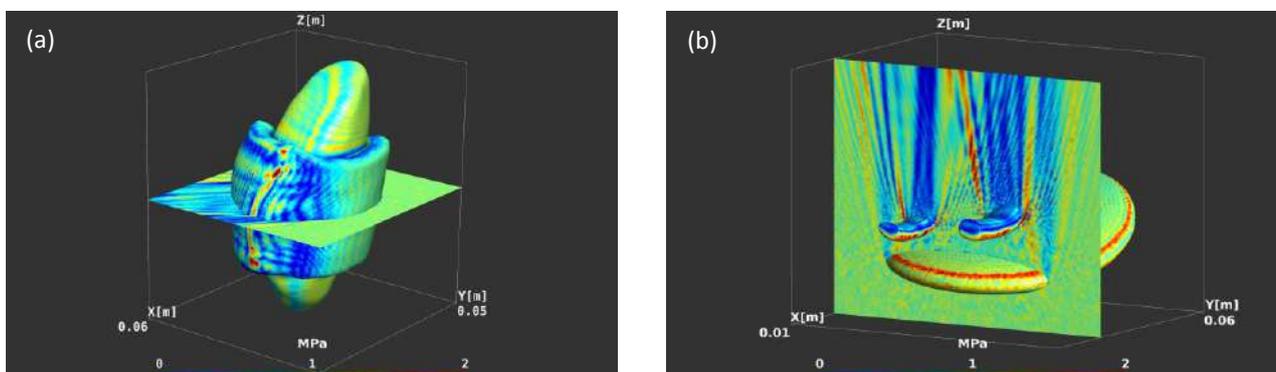


FIGURE 1: Pressure field magnitude for (a) a right kidney and perinephric fat layer with a 1 MHz plane wave propagating along the direction specified by the vector $[1,-1,0]$ and (b) two ribs and an abdominal fat layer, with a 1 MHz plane wave propagating along the positive z-axis.

COMPUTATIONAL MODELING OF TISSUE-SELECTIVE LIVER ABLATION IN HISTOTRIPSY

Lauren Mancia^{1,2}, Eli Vlasisavljevich³, Nyousha Yousefi², Zhen Xu⁴, Eric Johnsen¹

¹Department of Mechanical Engineering, University of Michigan, Ann Arbor, USA

²University of Michigan Medical School, Ann Arbor, USA

³Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, USA

⁴Department of Biomedical Engineering, University of Michigan, Ann Arbor, USA

e-mail: lamancha@umich.edu; eliv@vt.edu; ejohnsen@umich.edu

OBJECTIVES

Histotripsy is a non-thermal focused ultrasound procedure that uses targeted groups of microscopic bubbles to homogenize soft tissue into acellular debris. Experimental studies have shown that tissues with higher Ultimate Tensile Stress (UTS) are more resistant to cavitation damage and that higher pulse frequency produces smaller lesions. These observations support mechanical stress as a contributor to damage and suggest that tissue and waveform characteristics can be used to design liver tumor treatments that spare critical structures. However, stresses developed within microns of cavitation bubbles are too localized and transient to measure. A computational approach is used to quantify stresses produced by cavitation in liver tumors and adjacent tissues.

METHODS

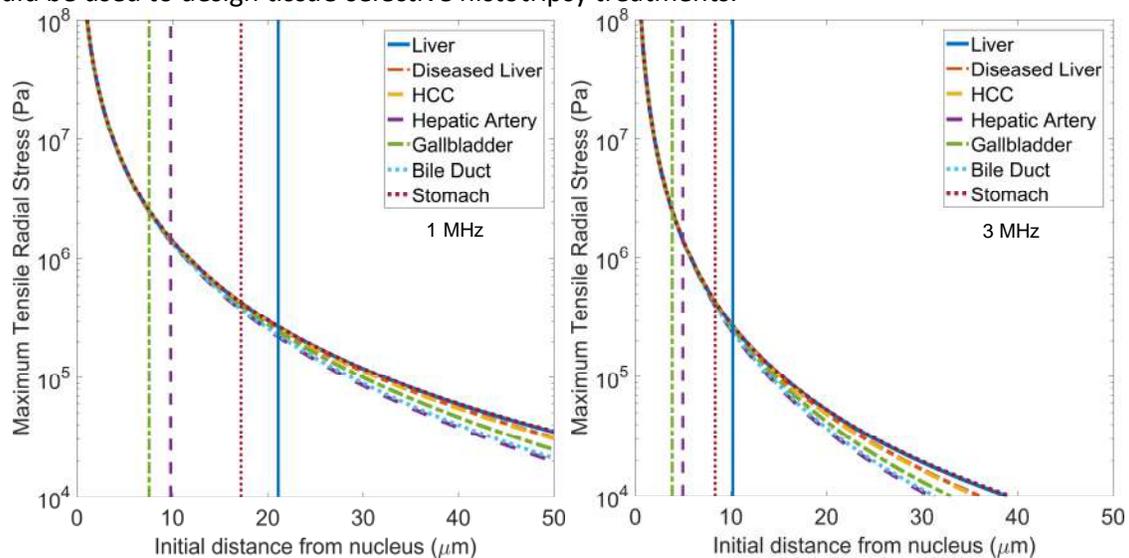
We model bubble dynamics in response to histotripsy waveforms of variable frequency in viscoelastic media representative of each tissue. Calculated stresses are then compared to the UTS of different tissues to estimate the spatial extent of stresses large enough to rupture cells.

RESULTS

Stresses capable of tissue rupture ($>$ UTS) achieved a greater spatial extent in liver tissue than in stomach, artery, and gallbladder. Higher waveform frequencies are associated with smaller predicted damage radii.

CONCLUSIONS

Simulation results support the hypothesis that differences in tissue and waveform characteristics could be used to design tissue-selective histotripsy treatments.



Stress-induced damage radius from bubble at 1 MHz (left) and 3 MHz (right) pulse frequencies. Vertical lines intersect at UTS of respective tissues, indicating predicted damage radii measured from nucleation site (e.g. damage radius in liver at 1 MHz is 21.1 μm and at 3 MHz is 10.2 μm).

Scattering from microbubble clouds: A fast multipole model with experimental validation

G.T. Clement, Y. Liu

Office of Science and Engineering Laboratories, Center for Devices and Radiological Health,
US Food and Drug Administration, Silver Spring, MD, USA

e-mail: gregory.clement@fda.hhs.gov

OBJECTIVES

Microbubbles originally developed as contrast agents have shown substantial potential in therapy. Ultrasound-driven encapsulated bubbles increase thermal effects, enhance vascular gene delivery, and cause transient opening of the blood-brain-barrier. However, the scattering response of multiple spatially-separated and size-variant bubbles can be complex and difficult to interpret, even at low driving pressures (< 50 kPa). We compare the scattering response of bubble clouds over a range of bubble diameters and concentrations to a multi-bubble model that incorporates a modified Rayleigh-Plesset equation and a utilizes the fast multipole method (FMM). Both the active emission of sound as well as the passive scattering contribution are considered.

METHODS

Sulfur hexafluoride bubbles encapsulated in lipid bilayer shells were separated into size groups ($1 \mu\text{m} - 2 \mu\text{m}$, $2 \mu\text{m} - 6 \mu\text{m}$, and $> 6 \mu\text{m}$,) and *volume* concentrations ($10^9 \mu\text{m}^3/\text{mL}$, $10^{10} \mu\text{m}^3/\text{mL}$, $10^{11} \mu\text{m}^3/\text{mL}$). Scattering measurements were obtained as a function scattering angle at 0.5-3 MHz for low (~ 10 kPa), medium (~ 100 kPa), and high (~ 1 MPa) amplitude pulses. Corresponding parameters were also simulated using FMM with- and without- the inclusion of Rayleigh-Plesset to determine signal contribution from passive scattering.

RESULTS

Attenuation and backscattering coefficients indicated an expected frequency dependence on bubble volume. Angular-dependent spectra compared to FMM simulations found passive scattering is a significant source of scattering signal at lower amplitudes.

CONCLUSIONS

Simulations predict backscattering spectra that correlates with experiments over microbubble size and concentration, and could have utility in interpreting signals for passive acoustic mapping of bubbles and others.

IMPROVED NUMERICAL METHOD FOR THE DESIGN OF 3D PRINTED ACOUSTIC LENSES FOR THE CORRECTION OF TRANSCRANIAL FOCUSED ULTRASOUND ABERRATIONS

M. Ferri¹, J.M. Bravo¹, J. Redondo², J.V. Sánchez-Pérez¹,

¹Centro de Tecnologías Físicas. Universitat Politècnica de València, Valencia, Spain

²Instituto para la Gestión Integrada de las zonas Costeras. Universitat Politècnica de València, Gandia, Spain.

e-mail: mferri@fis.upv.es; jusanc@upv.es

ABSTRACT

Numerous medical treatments can be enhanced by applying non-invasive transcranial focused ultrasounds. In recent years, the emission through multi-element phased arrays has been the most widely accepted method to correct skull induced aberrations and improve focusing. However a new disruptive technology, based on 3D printed acoustic lenses, has recently been proposed. State of art 3D printers achieve a spatial resolution that surpasses the spatial limitations of phased arrays, and being 3D printing a booming sector, this trend will continue in the near future. With 3D printed lenses, the bottleneck of the whole aberration correction process is no longer in the quality of the electronics of the phase array but in the numerical method applied to define the lens shape. In this study we present and evaluate two improvements in the numerical model which consist, first, in allowing the propagation of shear waves in the skull by means of its simulation as an isotropic solid and, second, in the introduction of the absorption in the set of equations that describes the dynamics of the wave in both fluid and solid media. The results obtained in the numerical simulations evidence that the inclusion of both s-waves and absorption significantly improves focusing.



HARDWARE

INVITED TALKS:

Transrectal High-Intensity Focused Ultrasound as local therapy of posterior deep invasive endometriosis - *Gil Dubernard*

Design and fabrication of therapy transducers to produce mechanical bioeffects - *Adam Maxwell*

ORAL PRESENTATIONS:

A new therapeutic device for transthoracic treatment of calcified aortic stenosis - *Wojciech Kwiecinski*

Multichannel system for translational research in high intensity focused ultrasound - *Steffen Tretbar*

Preliminary investigations of a deployable concentric ring ultrasound applicator for endoluminal and laparoscopic intervention - *Mathew Adams*

A prototype system for boiling histotripsy in abdominal targets comprising a 256-element spiral array combined with a power-enhanced Verasonics engine - *Vera Khokhlova*

CMUT prototype for endocavitary ultrasound-guided HIFU therapy - *W. Apoutou N'Djin*

A device for treating chronic total occlusions with catheter-based ultrasound and collagenase - *David Goertz* Improving image quality in transcranial magnetic resonance guided focused ultrasound using a copper screen - *Rock Hadley*

Preclinical X-Ray/PET-guided focused ultrasound system for neuro and abdominal applications - *Amanda Beserra*



Transrectal High-Intensity Focused Ultrasound as focal therapy of posterior deep invasive endometriosis

G. Dubernard , Cyril Lafon, M. Dairien, N. Guillen, A. Gellet, H. Tonoli , F. Chavier, C-A. Philip

Introduction :

Posterior deep invasive endometriosis (DIE) includes lesions of the utero-sacral ligaments, *torus uterinum* and the rectosigmoid. The rectal lesions are associated with painful symptoms that can alter quality of life. High Intensive Focused Ultrasound (HIFU) can induce tissue devitalization using acoustic cavitation and thermal ablation. FocalOne is a transrectal HIFU device, which is validated to treat prostatic cancer. The aim of the study was to assess the feasibility, the safety and the efficacy of the FocalOne in patients presenting posterior DIE with rectal involvement.

Methods:

We conducted a Phase I, non-controlled, prospective monocentric clinical study. The inclusion criteria were patient older than 25 years old, without project of pregnancy in the next 3 months, who presented a single lesion of posterior DIE with a rectal invasion and after failure of hormonal therapy. All lesions were preoperatively assessed using a rectal water contrast transvaginal sonography (rectosonography and pelvic MRI). Patients filled questionnaires about gynecologic and digestive symptoms and quality of life (MOS-SF36) before treatment and at 1, 3 and 6 months after treatment. The probe was introduced into the rectum or the lower part of the sigmoid colon. Real-time guided ultrasonography was used to determine the location and the volume of the endometriotic nodule. Then, a succession of HIFU exposure was used to treat the maximum volume of the lesion, excluding a security margin of 3 mm with the digestive mucosae to prevent the risk of fistulae.

Results: Twenty three patients were included between september 2015 and October 2020. For the last 12 patients, we included only patients with rectal endometriosis. All the lesions were visualized with FOCALOne sonographic probe. Only 20 of them satisfied security condition to be treated. Thus, the “feasibility rate” was 86.9%. For 13 patients we were able to treat the entire lesion. For the remaining 7 patients, we treated approximately 50% of the lesion. The median duration of the procedure was 5 minutes and was performed under rachianesthesia.

We observed a significant improvement ($p < 0.05$) in visual analogic scales at one and 6 months for pelvic pain, diarrhea, dyschesia, posterior irradiation pain, Constipation, tenesmus, false urge to defecate, dysmenorrhea, dyspareunia and asthenia. There was also a significant improvement ($p < 0.05$) of the MOS-SF36 with an improvement of both Physical Composite Score and Mental Composite Score at 1, 3 and 6 months. No complications occurred during and after the procedure. All the patients left hospital the day after the procedure.

Conclusion: HIFU therapy for posterior DIE can be considered as feasible and safe. It could be an interesting alternative to surgery for the treatment of posterior DIE. Further studies are required to confirm these preliminary results.

Design and fabrication of therapy transducers to produce mechanical bioeffects

Adam Maxwell^{1,2}, Tatiana Khokhlova^{2,3}, Timothy Hall⁴, Brian MacConaghy², Michael Bailey², Vera Khokhlova²

¹Department of Urology, University of Washington School of Medicine, Seattle, USA

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Department of Gastroenterology, University of Washington School of Medicine, Seattle, USA

⁴Department of Biomedical Engineering, University of Michigan, Ann Arbor, USA

e-mail: amax38@uw.edu

OBJECTIVES

As the capabilities of therapeutic transducers increase, so do the variety of therapeutic modalities such as soft tissue ablation, kidney stone disintegration, and drug delivery. This presentation will cover aspects of focused transducer design and fabrication with emphasis on mechanical therapies.

METHODS

Electroacoustic modeling of transducer elements is performed by 1-dimensional analytical models or finite-element methods to estimate their surface vibration amplitude and bandwidth in connection to driving electronics. The geometry of the radiating surface is designed based on linear and nonlinear propagation numerical simulations to accurately assess focal waveforms and beam field (**Figure**). These transducers can be fabricated using rapid prototyping to create large multi-element configurations with highly focused fields for different applications.

RESULTS

Techniques to design transducer elements for different outputs will be discussed, including appropriate materials and strategies to avoid thermal and mechanical limitations. The effects of frequency, transducer aperture, and F -number are specified to control nonlinear waveform amplitudes and beam geometry. The interplay between these parameters, resulting nonlinear waveforms, and different bioeffects will also be described, along with example designs from preclinical and clinical studies. These transducers, when interfaced with low-impedance amplifiers, can produce pulses with up to 10 kW acoustic power generating shock waves >100 MPa amplitude.

CONCLUSIONS

Transducers can achieve high-pressure output with controllable nonlinear waveforms that enable several modalities of focused ultrasound therapy.

ACKNOWLEDGEMENTS

Supported by NIDDK through K01 DK104854 and P01 DK043881 and NIBIB through R01 EB007643.

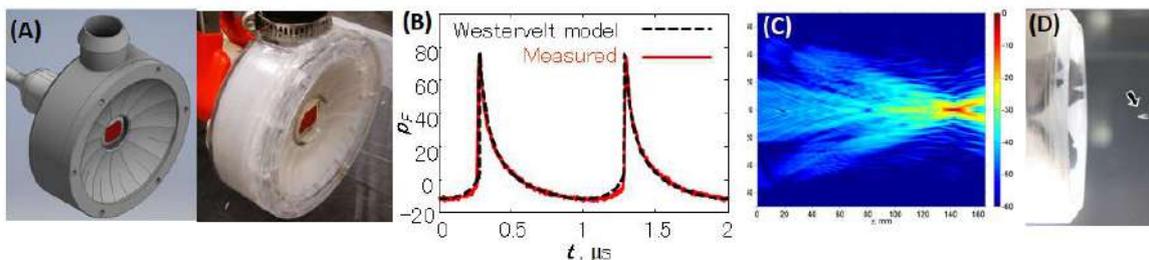


Figure: (A) CAD model and physical rapid-prototype histotripsy transducer. (B) Example focal pressure waveform and (C) peak-positive pressure field (dB) from nonlinear simulation using the Westervelt equation. (D) Localized cavitation generated at a transducer focus for tissue ablation.

A new therapeutic device for transthoracic treatment of calcified aortic stenosis

M. Pernot¹, Mathieu C. Rémond², Robin Penot², Delphine Ladarré², Philippe Mateo¹, Nathalie Ialy-Radio¹, D. Suarez^{1,2}, Guillaume Goudot³, Wojciech Kwiecinski², Michael Vion², Fabienne Betting², Aurélien Corbel², Ana Fouquier², Sergio Cammarata², Eric Noël², Zahir Larabi², M. Tanter¹, E. Messas³

¹Institute Physics for Medicine Paris, Inserm U1273, ESPCI Paris, CNRS FRE 2031, PSL University, 17 rue Moreau, 75012 Paris, France

² Cardiawave SA, 29 rue du Faubourg Saint Jacques, 75014, Paris, France

³ Hopital Européen Georges Pompidou, Paris, France

E-mail : mathieu.pernot@espci.fr

OBJECTIVES

Non-invasive therapy of calcified valve stenosis remains a major goal in cardiology. To date, no drug has demonstrated therapeutic efficacy on calcified valves. Valve replacement by surgery or minimally invasive techniques remains the only solutions available, despite the high risks and comorbidity. We recently proposed a novel non-invasive therapeutic approach based on the use of pulsed cavitation ultrasound (PCU) to soften the calcified valve tissues and improve the valvular function [1]. Our objective is to develop an extracorporeal clinical device guided by real-time echocardiography for the treatment of calcified aortic stenosis on human patients.

METHODS

A PCU system (Valvosoft, Cardiawave, Paris, France) was designed for transthoracic cardiac focusing. The system was composed of a high-power multi-element transducer with a bandwidth of [700kHz-1.25MHz] and driven by high-power electronics. Pulsed ultrasound emissions were delivered at a pulse repetition frequency (PRF) between 100 and 300Hz. Electronic steering was used to move the focus point at different depth [70-120mm]. Focal pressure was calibrated in a water tank using a hydrophone at low intensity (<10MPa). A 2D Echocardiographic probe at 2.5MHz was embedded in the center of the therapeutic transducer to guide and monitor the treatment. The device was evaluated in vitro on ex vivo samples including ribs and in vivo on the aortic valve of pigs (N=16).

RESULTS

A maximal amplitude of 70 MPa and -19 MPa respectively for positive and negative peak pressure was found at the focus by linear extrapolation of low intensity measurements. In vitro, the propagation through the ribs was found to induce an average loss of 59% ± 9 %. In vivo experiments demonstrated that the device can accurately target the valve cusps. Cavitation activity was monitored in real-time by echocardiography embedded in the device. Feasibility and safety were demonstrated in all animals with no serious adverse event. Survival at 30 days was 100% and no significant histopathology damage was found.

CONCLUSIONS

We have developed the first device, to our knowledge, for non-invasive calcified aortic stenosis therapy and demonstrated in vivo the feasibility and safety of transthoracic PCU

targeting aortic valve. This novel ultrasound therapy could become a non-invasive therapeutic strategy in cardiology.

[1] Villemain O, Robin J, Bel A, Kwiecinski W, Bruneval P, Arnal B, Rémond M, Tanter M, Messas E, Pernot M. Pulsed Cavitation Ultrasound Softening: a new non-invasive therapeutic approach of calcified bioprosthetic valve stenosis. *JACC Basic Transl Sci.* 2017 Aug;2(4):372-383

Multichannel system for translational research in high intensity focused ultrasound

S. Tretbar¹, M. Fournelle¹, C. Risser¹, H. Hewener¹, A. Melzer²

¹Ultrasound Department, Fraunhofer IBMT, Sankt Ingbert, Germany

²Innovation Center Computer Assisted Surgery, Leipzig, Germany

e-mail: steffen.tretbar@ibmt.fraunhofer.de

OBJECTIVES

In research on different HIFU-applications (neuromodulation, hyperthermia, immunotherapy), fundamental processes are first investigated on cell models and stepwise translated to small animal models and humans. For this reason, we developed a translational ultrasound system for application in different settings from in-vitro to clinical.

METHODS

This new modular research platform consists of a mainboard accommodating 16 frontboards (16 RX/TX channels each), a PC (connected to the mainboard via PCIe), a power board and a connector board for integration of different ultrasound applicators.

The system is upgradable with 1-2 boosters (128 channels) for high-power applications. It works as a stand-alone system with touch screen based UI and provides open software interfaces to MATLAB, C++, C# or an API. In addition, the system is MR-compatible.

RESULTS

The 256 transmission channels provide up to +/-100V (adjustable) in the frequency range 0.1-20 MHz. The tri-state pulsers allow the transmission of square wave burst signals with programmable frequency, number of periods and delays for each channel, however the duty cycle (DC) is limited to < 10%.

In combination with a 128-channel booster, it allows free pulse coding ($f = 0.1-5$ MHz), an output power of up to 16 W/channel @50 Ω and a DC up to 100% for max. 100s.

In addition, the 256 receive channels are available for therapy control/imaging.

CONCLUSIONS

A new open MR-compatible US research platform has been developed and characterized. The capability to drive different transducers (96-well-applicator, matrix-arrays for small animal/clinical settings) has been demonstrated and enables translational research for many HIFU applications.



CAPTION: Research-System DiPhAS-Therapy

PRELIMINARY INVESTIGATIONS OF A DEPLOYABLE CONCENTRIC RING ULTRASOUND APPLICATOR FOR ENDOLUMINAL AND LAPAROSCOPIC INTERVENTION

M.S. Adams¹, C.J. Diederich^{1,2}

¹Thermal Therapy Research Group, University of California San Francisco, San Francisco, USA

²University of California, Berkeley – University of California, San Francisco Graduate Program in Bioengineering, CA, USA.

e-mail: matt.adams@ucsf.edu; chris.diederich@ucsf.edu

OBJECTIVES

To investigate a novel design for a deployable forward-firing catheter-based ultrasound applicator consisting of a 1D cylindrical phased array centered in an expandable conical or paraboloid balloon-based reflector.

METHODS

Parametric analyses were performed using 3D acoustic and biothermal simulations to characterize on-axis electronic steering and focusing capabilities as a function of array dimensions, subdivision, and reflector geometry. A proof-of-concept applicator assembly (1.6 MHz, 9 mm OD x 20 mm length array, 8 elements) in combination with 3D printed reflector fixtures (as balloon surrogates) were fabricated and characterized using hydrophone and force balance measurements.

RESULTS

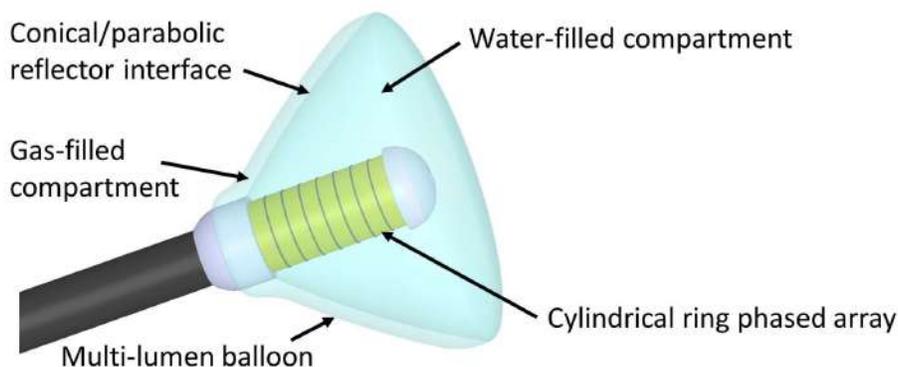
Simulation results indicate that practical transducer arrays (1.5 MHz, 10 mm OD x 20 mm length, 8/16 elements), balloon sizes (43-57 mm expanded diameter) and sonication durations (30s) can produce spatially-localized focal intensity patterns and ablative thermal lesions (width: 2.8-4.8 mm; length: 5.3-40.1 mm) in generalized soft tissue across a 5-100 mm depth range. Acoustic measurements of the prototype applicator assembly demonstrate electronic focal depth steering between 8-92 mm, with focal gain, dimensions, and steering range modulated by reflector geometry. Smaller focal dimensions and higher peak amplitudes were achieved using paraboloid reflectors, and larger foci and extended steering ranges attained using conical reflectors.

CONCLUSIONS

Development of a novel ultrasound applicator design that can be collapsed for compact endoluminal or laparoscopic delivery and then deployed *in situ* to emulate a larger diameter concentric ring array with tight focusing, deep penetration, and electronic steering capabilities is underway.

ACKNOWLEDGEMENTS

Supported by NIH grants R21CA230120 and R01EB025990.



CAPTION: Schematic of deployable concentric-ring ultrasound applicator.

A PROTOTYPE SYSTEM FOR BOILING HISTOTRIPSY IN ABDOMINAL TARGETS COMPRISING A 256-ELEMENT SPIRAL ARRAY COMBINED WITH A POWER-ENHANCED VERASONICS ENGINE

V.A. Khokhlova^{1,2}, B.W. Cunitz¹, M.A. Ghanem¹, W. Kreider¹, C. Hunter¹, C.R. Bawiec³, A.D. Maxwell⁴, G.R. Schade⁴, O.A. Sapozhnikov^{1,2}, T.D. Khokhlova³

¹Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

²Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

³Division of Gastroenterology, University of Washington School of Medicine, Seattle, USA

⁴Department of Urology, University of Washington, Seattle, USA

e-mails: verak2@uw.edu; bwc@uw.edu; mghanem@uw.edu; wkreider@uw.edu; tdk7@uw.edu

OBJECTIVES

Boiling histotripsy (BH) uses millisecond-long ultrasound bursts with high amplitude shocks to mechanically fractionate tissue. For pre-clinical BH studies of abdominal organs in large animals with aberration correction for body wall inhomogeneities, a high-power multi-element phased array system is needed.

METHODS

A BH system was built comprising a custom 256-element 1.5 MHz phased array (Imasonic, Besanson, France) with a central opening to mount a P6-3 probe for real-time ultrasound imaging (a, b). The array was electronically matched (c) to the Verasonics V1 engine with a 1.2 kW external power source, and driving electronics were supplemented by an extra capacitor bank (d). System performance was characterized by hydrophone measurements in water. Volumetric lesions were generated in *ex vivo* bovine liver with 1 mm spacing, 10 ms pulse length, 5 pulses/focus, and 1 % duty cycle (e, f). Doppler sequences were used to monitor tissue liquefaction.

RESULTS

The maximum pulse average acoustic power of the system was 3.5 kW sustained for 10 ms. Fully developed shocks of 100 MPa amplitude formed at the focus at 275 W acoustic power. The -3 dB steering range was 19 mm laterally and 38 mm axially. As measured on Doppler imaging, bubble velocities within lesions increased during lesion formation.

CONCLUSIONS

A BH prototype system was constructed and successfully implemented to produce volumetric mechanical lesions in *ex vivo* tissue using electronic steering. Lesion formation was confirmed in real time by evaluating the degree of tissue fractionation using Doppler US imaging.

ACKNOWLEDGEMENTS

Work supported by NIH R01EB7643, R01GM122859, and R01EB25187.

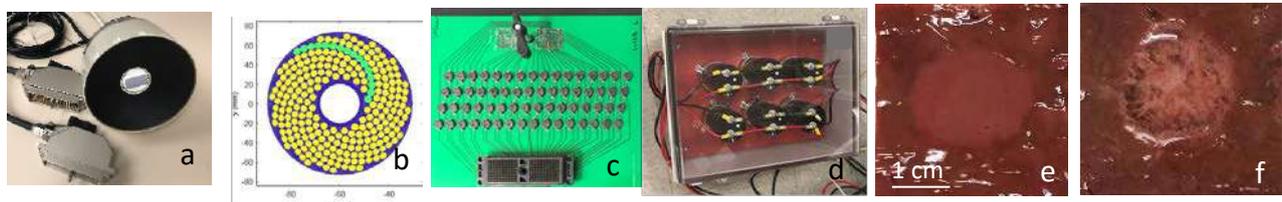


Figure Caption: (a) Photo and (b) sketch of a 256-element 16-arm spiral array. (c) Custom-designed matching network and (d) extra bank of capacitors. Bisected volumetric BH lesions generated *in ex vivo* bovine liver with (e) and without (f) content.

CMUT PROTOTYPE FOR ENDOCAVITARY ULTRASOUND-GUIDED HIFU THERAPY

W.A. N'Djin¹, C. Bawiec¹, A. Ganeau¹, A. Nguyen¹, L. Daunizeau¹, N. Guillen², N. S n gond³, J.Y. Chapelon¹

¹ LabTAU, INSERM, Centre L on B rard, Universit  Lyon 1, Univ Lyon, F-69003, Lyon, France

² EDAP TMS, Vaulx-en-Velin, 69120, France

³ Vermon, Tours, 37038, France

e-mail: apoutou.ndjin@inserm.fr

OBJECTIVES

Focal HIFU therapies have brought additional challenges for spatial-temporal control of energy delivery. Endocavitary approaches are particularly concerned with the need for miniaturization and coupled modalities. Capacitive Micro-machined Ultrasound Transducers (CMUTs) may play a role in the future development of HIFU devices, as they show some advantages over piezotechnologies (miniaturization, thermal robustness, broadband frequency). Presented here is an USgHIFU CMUT device developed in the context of endocavitary prostate ablation.

METHODS

The developed CMUT prototype was compatible with a dual-mode ultrasound platform (Vantage, Verasonics) for piloting HIFU and imaging modalities. A planar HIFU CMUT annular array (64-element, $f = 3$ MHz) had a central space containing a 256-element linear imaging array ($f = 7$ MHz). The prototype included electronics (pre-amplifying, mixing, matching circuits) and water circulation circuit for acoustic coupling with target tissues. The potential of this CMUT design for dynamic HIFU and guidance has been studied.

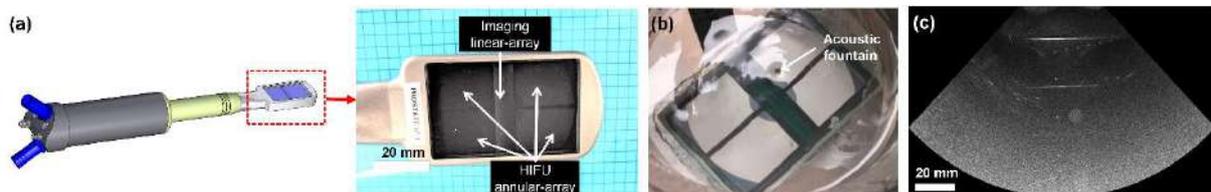


Figure 1: (a) USgHIFU CMUT prototype; (b) HIFU-induced acoustic fountain; (c) US imaging guidance

RESULTS

The planar HIFU CMUTs could focus dynamically over distances ranging from 3-7 cm, similarly to the piezo-based geometrically focused Focal One[®] system used in clinic for prostate therapy. The array produced over $6\text{W}/\text{cm}^2$ surface acoustic intensity, compatible with thermal ablation. The imaging CMUT allowed forming extended images with resolutions ranging 0.3-0.7 mm.

CONCLUSIONS

CMUTs were successfully used to develop an endocavitary USgHIFU system. The full potential of this technology both for imaging and therapy, is under investigations.

ACKNOWLEDGEMENTS

Project supports: BPI (FUI, 2013), Labex DEVweCAN, Whitaker Foundation (2015), ANR (RHU, 2018).

A DEVICE FOR TREATING CHRONIC TOTAL OCCULSIONS WITH CATHETER-BASED ULTRASOUND AND COLLAGENASE

Alex Wright¹, Bradley Strauss¹, Kullervo Hynynen¹, David Goertz¹

¹Sunnybrook Research Institute, Toronto, ON, Canada

e-mail: alex.wright@sri.utoronto.ca; goertz@sri.utoronto.ca

OBJECTIVES

Chronic total occlusions (CTO) are thrombotic obstructions that can develop collagen rich proximal fibrous caps (PFC). Minimally invasive percutaneous (PCI) CTO revascularization is frequently unsuccessful. The injection of collagenase softens CTO/PFC, and has shown favorable clinical trial results. The addition of ultrasound stimulated microbubbles (MBs) has also shown improved performance in animals. A catheter-based transducer allowing for the delivery of collagenase, MBs and forward-looking therapeutic ultrasound has potential to improve patient outcomes.

METHODS

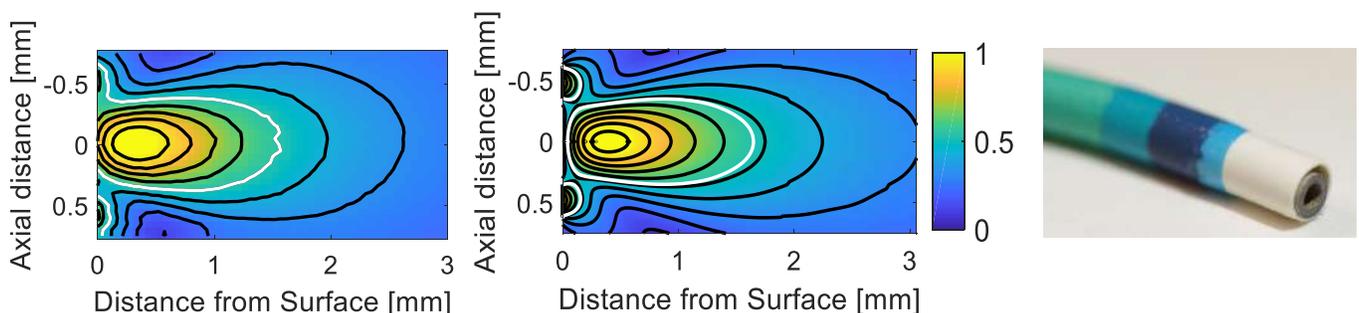
A radially polarized PZT transducer (1.2/0.8 mm outer/inner diameter, 3 mm length) is situated at the catheter tip. A thin-walled metal tube connects the inner electrode. Stimulation at length or radial-mode frequencies directs sub-MHz to MHz pressure in a forward-looking direction. The inner hole accommodates a guide wire to situate the tip adjacent to the PFC, and the lumen allows enzyme and MB delivery. PZFlex™ simulations assessed the effects of transducer geometry and materials on resulting acoustic fields. Prototype transducers with matching circuits were characterized with hydrophone scans. Initial evaluation within anthropomorphic CTO phantoms assessed MB injection and cavitation using high speed microscopy.

RESULTS

Hydrophone measured pressures closely matched simulations. Peak pressures over 2.5 MPa were attainable 0.5mm from the face. Lower frequency modes showed internal cavitation behavior limiting pressure output. Higher frequency radial modes projected high pressures. Phantom experiments demonstrated significant microbubble displacement and cavitation from acoustic radiation force.

CONCLUSIONS

The forward-looking catheter transducer produces high pressures in the MHz range and permits fluid injection through its lumen.



CAPTION: Hydrophone and simulated pressure maps, and transducer within guiding catheter.

Improving Image Quality in Transcranial Magnetic Resonance Guided Focused Ultrasound Using a Copper Screen

J.R. Hadley¹, H. Odeen¹, R. Merrill¹, R.C. Haag-Roeger², V. Rieke¹, A. Payne¹, D.L. Parker¹

¹Radiology and Imaging Sciences Faculty, University of Utah, Salt Lake City, USA

²Biomedical Engineering Student, University of Utah, Salt Lake City, USA

e-mail: rock.hadley@utah.edu

OBJECTIVES

To find solutions to the Radio Frequency (RF) signal banding artifacts that can occur with Magnetic Resonance Imaging (MRI) of the head inside an Insightec Transcranial Transducer (ITT).

METHODS

A human skull filled with gelatin was imaged in the ITT (650kHz) with a 2D Gradient Echo pulse sequence using a Skyra MRI with body coil (Siemens Medical Solutions). Imaging was done with and without a copper screen (0.25mm diameter wire, ~1.6mm squares) positioned over the top of the head as shown. The screen was held in position with string and foam ear plugs separated the screen from the skull.

RESULTS

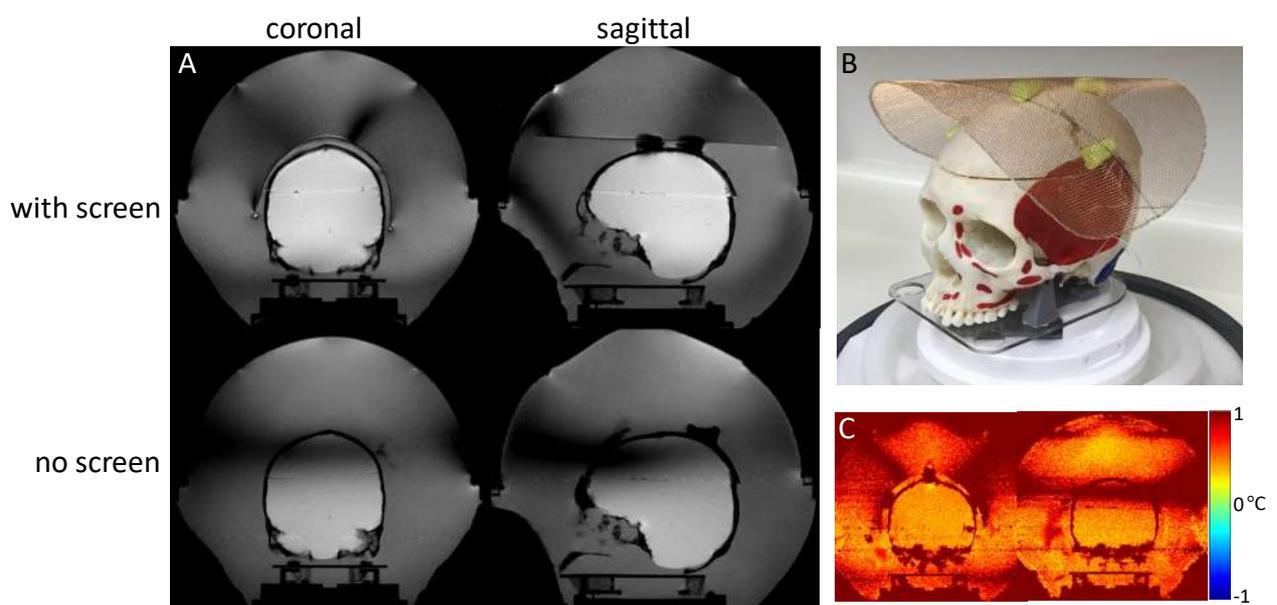
The screen caused negligible pressure attenuation (0.25% and 0.35%, when tilted at 0° and 45°, respectively) compared to a no-screen hydrophone study performed with a 950kHz transducer. Imaging results show improved signal homogeneity in the brain region. The Signal-to-Noise Ratio (SNR) was improved by a factor of 2-3 and temperature accuracy was improved and more homogeneous throughout the brain when using the screen.

CONCLUSIONS

Copper screen positioned around the head greatly improved imaging transmit/receive homogeneity through the region of the brain and improved the SNR by 2-3 compared to imaging without the screen. We hypothesize that the copper screen reduced the dielectric resonance effects of the water bath and disrupted the waveguide nature of the transducer ground plane.

ACKNOWLEDGEMENTS

The Mark H. Huntsman endowed Chair.



CAPTION: A) Imaging results, with and without the copper screen. B) Human skull with ultrasound transparent copper screen positioned around the top of the head. C) Temperature accuracy maps.

Preclinical X-Ray/PET-Guided Focused Ultrasound System for Neuro and Abdominal Applications

Amanda Beserra¹, Samuel Pichardo¹, Laura Curiel¹

¹University of Calgary, 2500 University Drive NW, Calgary, AB, T2N1N4

e-mail: amanda.beserra@ucalgary.ca, samuel.pichardo@ucalgary.ca, laura.curiel@ucalgary.ca

OBJECTIVES

The objective of this study is to design a focused ultrasound system for mice that uses X-Rays for guidance, and Positron emission tomography (PET) to track molecular events (FUS-X-Ray/PET-Guided). PET provides information about the metabolic response and neuronal function [1]. Hence, this system provides anatomical and functional information combining two modalities.

METHODS

This system was designed to work with the G4 PET scan (Sofie Biosciences) [2]. A user-centred design (UCD) methodology was applied to enhance the user experience by taking into consideration their needs, behaviour and preferences to achieve high levels of usability [3]. An X-Ray is used to select one out of 30 targets in a 24-mm² area (1-mm steps). The device keeps the mice under anesthesia and warm during the procedure.

RESULTS

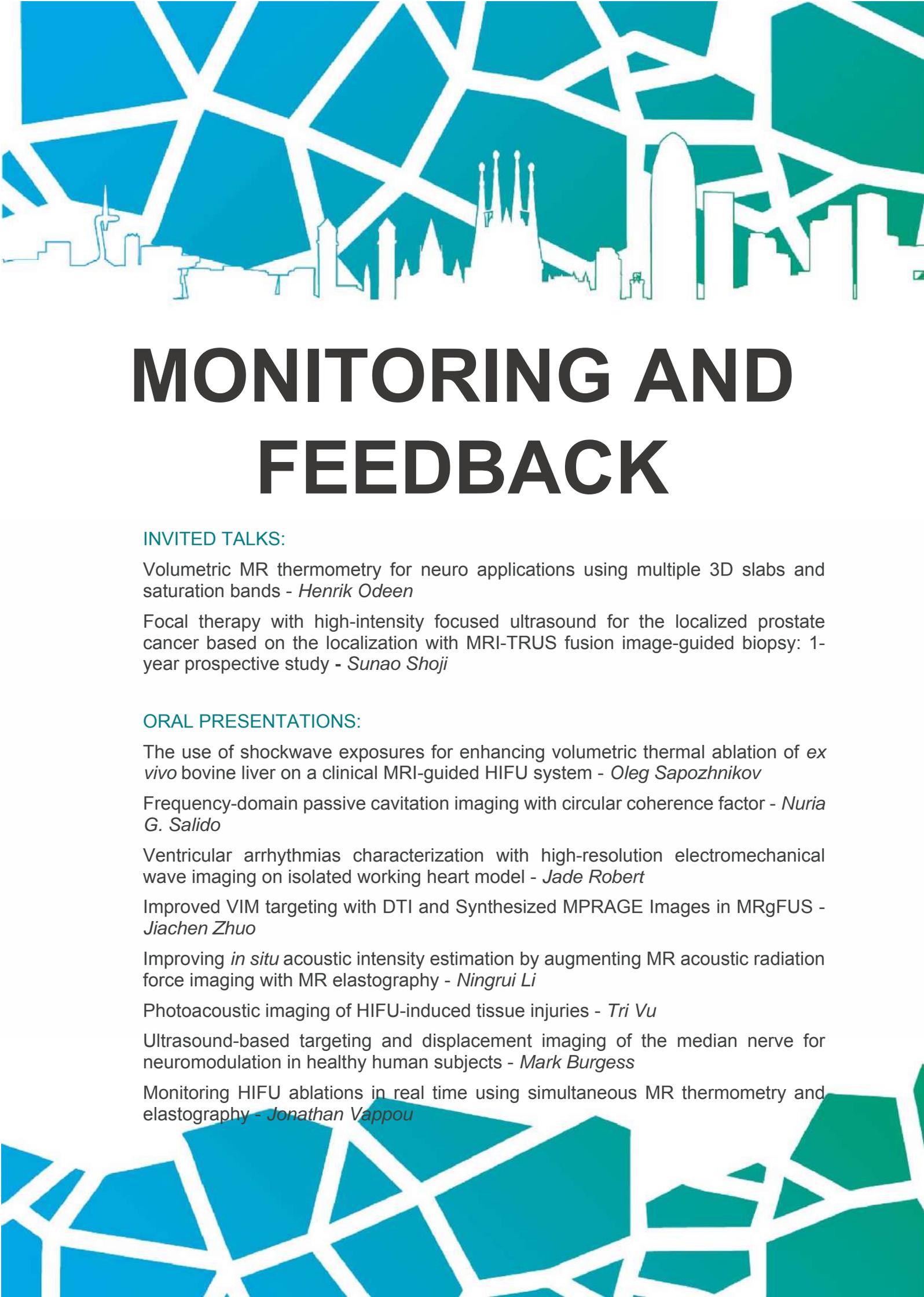
The first UCD interaction showed features on the G4 system that disrupted the workflow because of layout, language, and level of automation. All those features were integrated into actions for design. The system was built and the target positions were validated through an in-house Python interface. Also, a watershed segmentation algorithm was implemented as a safety feature to ensure no motion between the targeting X-Ray and therapy. The system allows for abdominal or neuro targets and operates at 1 MHz with a diameter of 13.5 mm and a focus of 15 mm.

CONCLUSIONS

This proposed FUS-X-Ray/PET-Guided platform allows users to target focused ultrasound, keeping track of the planned location. The designed platform will allow to use X-rays to initially target and finally overlay PET images to evaluate the procedure.

REFERENCES

- [1] Voges, J. , Reszka, R., Gossmann, A. , Dittmar, C. , Richter, R. , Garlip, G. , Kracht, L. , Coenen, H. H., Sturm, V. , Wienhard, K. , Heiss, W. and Jacobs, A. H. (2003), Imaging-guided convection-enhanced delivery and gene therapy of glioblastoma. *Ann Neurol.*, 54: 479-487. doi:10.1002/ana.10688
- [2] Sofie. (n.d.). G4 PET / X-Ray. Retrieved January 25, 2019, from <https://sofie.com/imaging/>
- [3] R. Wever, J. van Kuijk, and C. Boks, "User-centred design for sustainable behaviour," *Int. J. Sustain. Eng.*, vol. 1, no. 1, pp. 9–20, 2008.



MONITORING AND FEEDBACK

INVITED TALKS:

Volumetric MR thermometry for neuro applications using multiple 3D slabs and saturation bands - *Henrik Odeen*

Focal therapy with high-intensity focused ultrasound for the localized prostate cancer based on the localization with MRI-TRUS fusion image-guided biopsy: 1-year prospective study - *Sunao Shoji*

ORAL PRESENTATIONS:

The use of shockwave exposures for enhancing volumetric thermal ablation of *ex vivo* bovine liver on a clinical MRI-guided HIFU system - *Oleg Sapozhnikov*

Frequency-domain passive cavitation imaging with circular coherence factor - *Nuria G. Salido*

Ventricular arrhythmias characterization with high-resolution electromechanical wave imaging on isolated working heart model - *Jade Robert*

Improved VIM targeting with DTI and Synthesized MPRAGE Images in MRgFUS - *Jiachen Zhuo*

Improving *in situ* acoustic intensity estimation by augmenting MR acoustic radiation force imaging with MR elastography - *Ningrui Li*

Photoacoustic imaging of HIFU-induced tissue injuries - *Tri Vu*

Ultrasound-based targeting and displacement imaging of the median nerve for neuromodulation in healthy human subjects - *Mark Burgess*

Monitoring HIFU ablations in real time using simultaneous MR thermometry and elastography - *Jonathan Vappou*

Volumetric MR thermometry for neuro applications using multiple 3D slabs and saturation bands

Henrik Odéen^a, Viola Rieke^a, Sunil Patil^b, Brad Bolster^b, Himanshu Bhat^b, and Dennis L Parker^a

^aDepartment of Radiology and Imaging Sciences, University of Utah, Salt Lake City, UT, USA

^bSiemens Healthineers, USA

e-mail: henrik.odeen@hsc.utah.edu, viola.riek@hsc.utah.edu, dennis.parker@hsc.utah.edu

OBJECTIVES

MRgFUS neuro applications are monitored by single-slice 2D MR thermometry (MRT). Volumetric 3D MRT is desirable to provide more complete monitoring/feedback. We developed and evaluated volumetric MRT using multiple 3D slabs and satbands.

METHODS

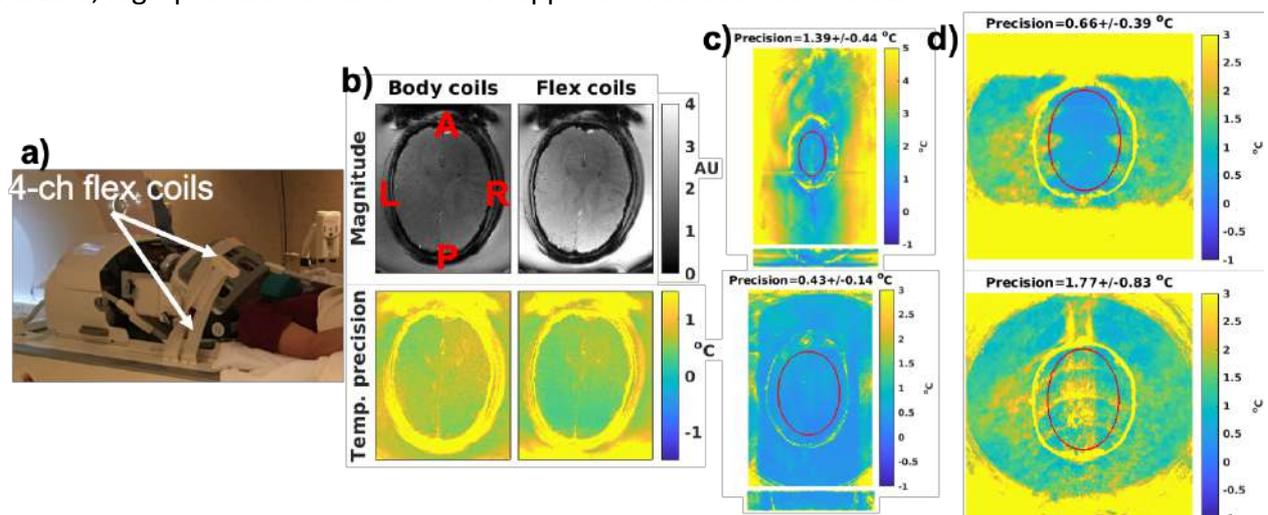
A 3D segmented echo planar imaging pulse sequence was implemented on a 3T MRI scanner (Skyra, Siemens). Two four-channel flex-coils, previously shown to improve MRT precision by 35-70% in volunteers, were used for signal detection. Two experiments were performed in a gelatin-filled ex-vivo human skull; **[1]** Applying satbands to kill water signal and reduce phase-encoding field-of-view to reduce acquisition time, and **[2]** using satbands to kill water signal with water-circulation ON, which is potentially useful for improved skull cooling. All scans used 2x3D slabs, echo-train-length=17, resolution=1.1x2.2x3.0mm, field-of-view varied from 280x175 to 280x36mm in **[1]**, and was 280x280x36mm in **[2]**, t_{acq} =4.8 **[1]** and 7.7 **[2]** s, respectively.

RESULTS

For **[1]** high MRT precision (0.43°C) is seen in a lower slab, while lower precision (1.39°C) is observed in a slab over the skull cap due to the low signal band resulting from the known dielectric-effect, with scan time-reduction of $\sim 10\%$ compared to full field-of-view. For **[2]**, using satbands (placed head/foot) significantly improves precision when water flow is ON (0.66 vs. 1.77°C).

CONCLUSIONS

A flexible, high-precision volumetric MRT approach has been described.



CAPTION: a) Setup using 2x4-channel flex-coils (shown on volunteer) and b) improved MRT precision. MRT precision for c) Experiment **[1]** with 2 orthogonal views of 2x3D slabs (satbands right-left) and d) Experiment **[2]** water-flow ON with satbands (top) and no satbands (bottom).

Focal therapy with high-intensity focused ultrasound for the localized prostate cancer based on the localization with MRI-TRUS fusion image-guided biopsy: 1-year prospective study

Sunao Shoji¹, Shinichiro Hiraiwa², Izumi Hanada¹, Masahiro Nitta¹, Kazunobu Hashida³, Terumitsu Hasebe³, Takuma Tajiri², Akira Miyajima¹, ¹Department of Urology, Tokai University School of Medicine, Kanagawa, Japan, Departments of Pathology², and Radiology³, Tokai University Hachioji Hospital, Hachioji, Tokyo, Japan

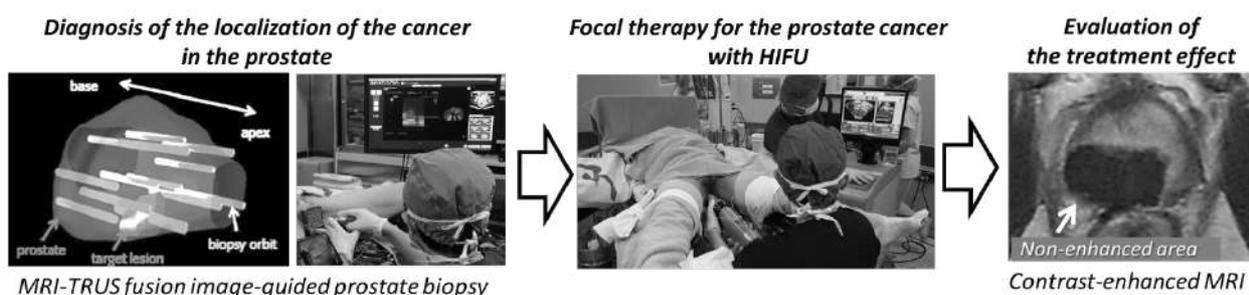
Objectives: To evaluate outcomes of intra-prostatic partitioned-region therapy with high-intensity focused ultrasound (HIFU) for multiparametric (mp) magnetic resonance imaging (MRI)-visible localized prostate cancer (PCa), based on MRI–transrectal ultrasound (TRUS) elastic fusion image-guided transperineal prostate biopsy

Methods: We prospectively recruited patients with low- and intermediate-risk PCa, located their significant tumors using MRI-TRUS elastic fusion image-guided transperineal prostate biopsies with BioJet system (D&K Technologies GmbH, Barum, Germany), and focally treated these tumors and adjacent tissues, using HIFU (Sonablate[®] 500, SonaCare Medical, Indianapolis, IN, USA). Patients' functional and oncological outcomes were analyzed prospectively.

Results: We treated 62 men (median age: 71 years; median serum Prostate Specific Antigen (PSA) level: 6.64 ng/ml; median operative time: 29 minutes). Catheterization was performed within 24 hours after the treatment in all patients. Blood flow was completely disappeared in all treated area in contrast-enhanced MRI. At 6 months after the treatment, 8.1% of the patients were positive for significant cancer in follow-up prostate biopsy. At 1 year after the treatment, serum PSA level decreased to 1.47ng/ml, and the biochemically disease-free rate was 92%. Urinary functions, including International Prostate Symptom Score (IPSS) ($p<0.0001$), maximum urinary flow rate (ml/sec) ($p<0.0001$), residual urine (ml) ($p<0.0001$), and International Index of Erectile Function (IIEF)-5 sexual function scores ($p=0.049$) had significantly deteriorated at 1 month after treatment, but improved to preoperative levels at 3 months. Among complications, 3 patient (4.8%) suffered a Grade 3 urinary tract infection and 2 patients (3.2%) suffered Grade 3 urethral strictures. No patients suffered acute urinary retention, incontinence, or recto-urethral fistula. Among the 38 patients who had erectile function without phosphodiesterase-5 inhibitor (PDE-5 inhibitor) before treatment, erectile dysfunction rate without PDE-5 inhibitor was 20% ($n=8$), and ejaculation was preserved in 64% ($n=18$) at 12 months post-treatment.

Conclusions: The present treatment is accurate for targeted mpMRI-visible significant PCa, with little negative impact on urinary and sexual function, and QOL at 1 year.

Process of the focal therapy for the localized prostate cancer



THE USE OF SHOCKWAVE EXPOSURES FOR ENHANCING VOLUMETRIC THERMAL ABLATION OF *EX VIVO* BOVINE LIVER ON A CLINICAL MRI-GUIDED HIFU SYSTEM

O.A. Sapozhnikov^{1,2}, T.D. Khokhlova³, W. Kreider¹, A. Partanen⁴, Y.-N. Wang¹, M.M. Karzova², and V.A. Khokhlova^{1,2}

¹Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

²Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

³Division of Gastroenterology, School of Medicine, University of Washington, Seattle, WA

⁴Clinical Science, Profound Medical Inc., Mississauga, ON, Canada

e-mail: olegs2@uw.edu, verak2@uw.edu

OBJECTIVES

Clinical sonication protocols for volumetric lesion formation are based on heat deposition due to linear absorption of ultrasound waves in multiple foci and heat diffusion, which limits the accuracy of predicted lesion dimensions. This study characterizes the use of shockwave-assisted, ultrafast heating for predictable lesion formation.

METHODS

Volumetric thermal lesions (8-mm diameter) were generated in *ex vivo* bovine liver by concentric rings of focal target sites (c) using a clinical MR-HIFU system (Sonalleve V2, Profound Medical Inc). MRI was used for real-time guidance and post-sonication evaluation (a, b). Lesions obtained with the clinical protocol (CP) were compared to a shockwave protocol (SWP) with the same time-average but higher peak power. SWP sonications were designed based on ultrasound and thermal simulations (d). Lesions were analyzed grossly (e, f), by MRI (b), and histology for thermal denaturation (g, h).

RESULTS

CP lesions exhibited a diameter-to-length ratio of 1:2.5, with fuzzy margins (e, g). SWP lesions had narrow margins with shapes that correspond to predicted heat deposition patterns (f, h). Formation of volumetric SWP lesions required a denser distribution of focal sites (0.5 mm spacing *versus* 2 mm in CP); however, only a single 5-ms exposure was needed at each site (SWP: 5-ms pulse at 1 kW peak power followed by a 20-ms pause; CP: multiple 50 ms-pulses at 200 W).

CONCLUSIONS

A novel sonication protocol with shockwave heating allows delivery of precise thermal lesions with sharp borders between normal and thermally denatured tissue.

ACKNOWLEDGEMENTS

Work supported by FUSF and NIH R01EB025187 and R01EB007643.

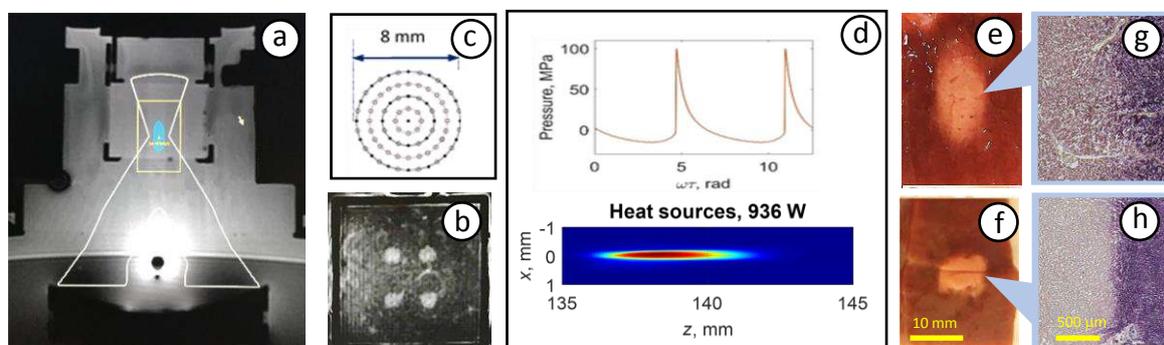


FIGURE CAPTION: a) MR image of the experiment set-up; b) transverse MR image of four SWP lesions; c) representative treatment foci pattern; d) focal pressure profile and calculated heat-source pattern in SWP; e) CP lesion; f) SWP lesion; g, h) NADH-diaphorase stained lesion borders showing viable tissue in purple and thermally denatured tissue in white.

FREQUENCY-DOMAIN PASSIVE CAVITATION IMAGING WITH CIRCULAR COHERENCE FACTOR

N. G. Salido¹, K. J. Haworth^{1,2}, M. Lafond¹, C. Genstler³, C.K. Holland^{1,2}

¹ Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA

² Department of Biomedical Engineering, University of Cincinnati, Cincinnati, Ohio, USA

³ EKOS Corporation, Bothell, Washington, USA

e-mail: salidona@ucmail.uc.edu

OBJECTIVES

Circular coherence factor (CCF) weighting has been used to improve B-mode image quality. The objective of this study was to determine if CCF weighting applied to passive cavitation images (PCIs) could reduce the point spread function without substantially increasing the imaging frame rate relative to frequency-domain delay-sum-and-integrate (F-DSI) beamforming.

METHODS

A modified F-DSI beamforming algorithm was developed by applying a pixel-based CCF weighting to the PCIs (F-CCFDSI). The pixel-based weights, which scale between 0 and 1, were computed as a function of the phase dispersion of pre-steered signals. The weighting was computed independently for each frequency. The algorithm was easily parallelizable for implementation on a graphics processing unit (GPU). Performance of the F-CCFDSI algorithm was analyzed using passively acquired cavitation emissions induced by an EkoSonic[®] catheter inserted into an arterial flow phantom with Definity[®]. The F-CCFDSI image quality was compared to F-DSI and a narrow-band frequency-domain robust capon beamformer (F-RCB) applied to harmonic, ultraharmonic, and inharmonic frequency bands by calculating the artifactual PCI area (cavitation activity mapped outside the tube lumen).

RESULTS

Figure 1 shows duplex B-mode (grayscale) and PCI (colormap) images averaged over 100 frames. F-DSI, F-CCFDSI, and F-RCB frame rates were 10 Hz, 10 Hz, and 0.004 Hz, respectively. The artifactual PCI area for harmonic, ultraharmonic and inharmonic emissions was greater than 5 mm² for F-DSI, and less than 0.3 mm² for F-CCFDSI, and F-RCB.

CONCLUSIONS

The F-CCFDSI algorithm takes advantage of F-DSI beamforming to provide an accurate location of multiple cavitation events in real time.

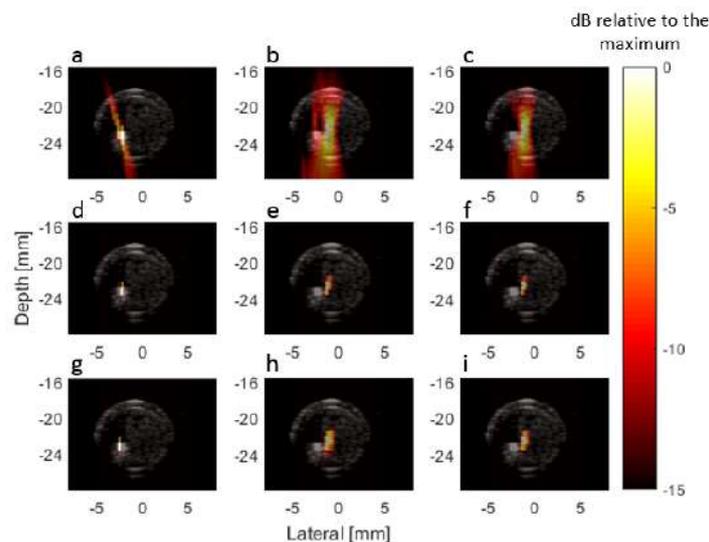


Figure 1: Duplex Bmode-PCI using F-DSI (a,b,c), F-CCFDSI (d,e,f) and F-RCB (g,h,i) using either harmonic (a,d,g), ultraharmonic (b,e,h), or inharmonic (c,f,i) frequency bands.

VENTRICULAR ARRHYTHMIAS CHARACTERIZATION WITH HIGH-RESOLUTION ELECTROMECHANICAL WAVE IMAGING ON ISOLATED WORKING HEART MODEL

J. Robert¹, F. Bessière^{1,2}, E. Cao¹, A. Zorgani¹, L. Daunizeau¹, S. Catheline¹, F. Vaillant³, B. Quesson³, C. Lafon¹

¹LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, LYON, France

²Hôpital cardiologique Louis Pradel, Hospices Civils de Lyon, 69677 Lyon, France

³Institut Liryc, Université Bordeaux, 33604 Pessac, France

E-mail: jade.robert@inserm.fr; cyril.lafon@inserm.fr

OBJECTIVES

Electromechanical Wave Imaging (EWI) is an imaging method providing global mapping of mechanical activation into the myocardium during sinus and stimulated rhythms. This study aims at demonstrating EWI's ability to differentiate epicardial from endocardial arrhythmia activation and from sinus rhythm at high temporal and spatial resolution.

METHODS

ECG-gated ultrafast acquisitions (4000 fps) with a 15MHz ultrasound probe were performed on an isolated swine heart in recirculating mode. Three acquisitions were consecutively performed at three pacing sites during sinus rhythm, endocardial or epicardial pacing. Transient displacement maps were reconstructed at each time point using a phase-based motion tracking algorithm on RF data, without prior knowledge of the pacing protocol. Electromechanical wave front propagation was then tracked to predict whether the heart was paced and if so, determine the surface of pacing.

RESULTS

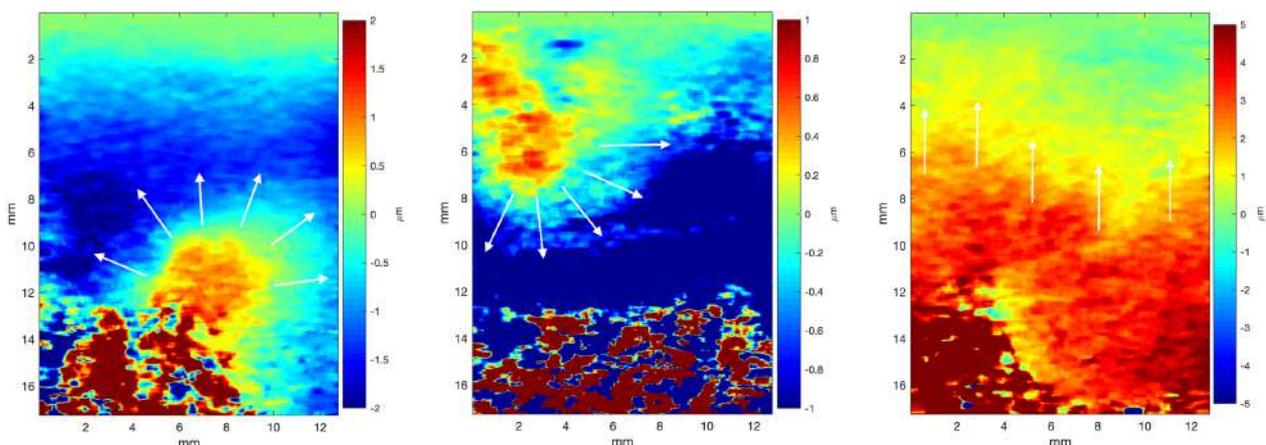
In a preliminary analysis, the pacing protocol was accurately retrieved in 59% of the cases. Focal origin of the electromechanical wave front allowed to identify stimulated rhythms, whereas global mechanical activation was characteristic of sinus rhythms. Propagation direction of the wave front and depth of first activation then helped discriminating epicardial from endocardial pacing.

CONCLUSIONS

Propagation patterns depicted by EWI at high resolution allows to precisely identify and localize arrhythmogenic foci and could improve ventricular arrhythmia treatment planning.

ACKNOWLEDGEMENTS

This work was supported by the French National Research Agency (ANR17-CE19-0017) and France Life Imaging WP3 Interventional Imaging.



CAPTION: EWI of stimulated rhythms (left/middle) depict focal activation and propagation towards the opposite layer of the myocardium whereas activation wave front is spread during sinus rhythm (right).

Improved VIM targeting with DTI and Synthesized MPRAGE Images in MRgFUS treatment of Essential Tremor

Jiachen Zhuo¹, Steven Roys¹, John Hebel¹, Sijia Guo¹, Erma Owen¹, Timothy Miller¹, Dheeraj Gandhi¹, Rao Gullapalli¹
¹Department of Diagnostic Radiology, University of Maryland School of Medicine, Baltimore, MD, USA
Email: jzhuo@umm.edu

OBJECTIVES

The ventral intermediate nucleus(VIM) of the thalamus is an important target for treating medication refractory essential tremor(ET) in both DBS and MRgFUS. Both DTI and synthetic MPRAGE(SynMPRAGE) techniques are promising methods in identifying VIM. Objective of this study is to analyze the efficacy of using DTI and SynMPRAGE for VIM targeting, as oppose to the traditional stereotactic method.

METHODS

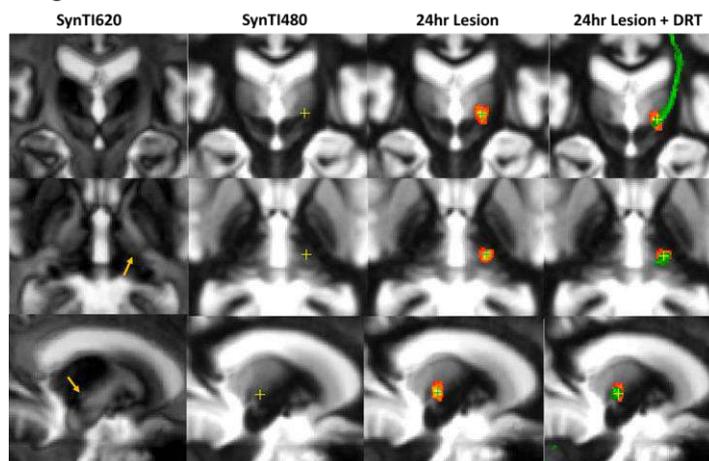
MRI was performed before and 24hr after the MRgFUS treatment on 17 patients on Siemens TimTrio 3T scanner. Imaging included DTI(45 directions, $b=1000,2500$ s/mm², isotropic resolution 2.7mm) and 3D-T2-SPACE. 6 patients also had 3D-T1MPRAGE and 3D-FGATIR(MPRAGE sequences with TI's of 1500 & 406ms, TR=4000ms, isotropic resolution 1mm). Synthetic MPRAGE(SynTI) images at arbitrary TI's were generated by estimating the S0(proton density) and T1-maps from the T1MPRAGE and FGATIR images. DTI-based VIM target(VIM_{DTI}) was identified by dento-rubro-thalamic tract(DRT). SynMPRAGE-based VIM target(VIM_{Syn}) was identified by anatomical landmark as compared to atlas. The treated VIM location(VIM_{treat}) was defined as the zone2 lesion center on T2-SPACE images post-treatment. These targets were compared to the commonly used stereotactic targeting VIM_{stereo}, with targeting success defined as within 2mm to VIM_{treat}.

RESULTS

VIM_{Syn}(yellow cross) as identified on the group-averaged SynTI images based on anatomical landmarks showed good agreement with the summed DRT mask(green) and 24hr lesion mask(hot color) from individual patients(Figure). Group analysis reviewed a targeting success rate of 71% for VIM_{DTI}, 83% for VIM_{Syn} and 53% for VIM_{stereo}.

CONCLUSIONS

Including both DTI and SynMPRAGE for identifying VIM target can greatly improve the workflow for MRgFUS of ET.



IMPROVING *IN SITU* ACOUSTIC INTENSITY ESTIMATION BY AUGMENTING MR ACOUSTIC RADIATION FORCE IMAGING WITH MR ELASTOGRAPHY

N. Li¹, P. Gaur², K. Butts Pauly²

¹Department of Electrical Engineering, Stanford University, Stanford, CA

²Department of Radiology, Stanford University, Stanford, CA

e-mail: ningrui.li@stanford.edu

OBJECTIVES

MR acoustic radiation force imaging (MR-ARFI) has the potential to estimate *in situ* acoustic intensity, since the applied ARF is proportional to the acoustic intensity at the focus. However, tissue mechanical properties vary across patients, brain regions, and disease states, which confounds the relationship between MR-ARFI displacements and acoustic intensity. The objective of this study is to investigate whether stiffness information from MR elastography (MRE) can improve MR-ARFI-based estimates of *in situ* acoustic intensity.

METHODS

An elastography phantom (Fig. 1a), containing a stiff lesion embedded within a softer background region, was sonicated at 550 kHz with varying power levels (ExAblate-2100, Insightec Ltd.). MR-ARFI data were acquired at 3T using a 2DFT spin-echo sequence with repeated bipolar gradients (Signa Excite, GE Healthcare). MRE was performed by inducing 60 Hz shear waves in the phantom using a passive driver, and stiffness maps were reconstructed using 3D direct-inversion.

RESULTS

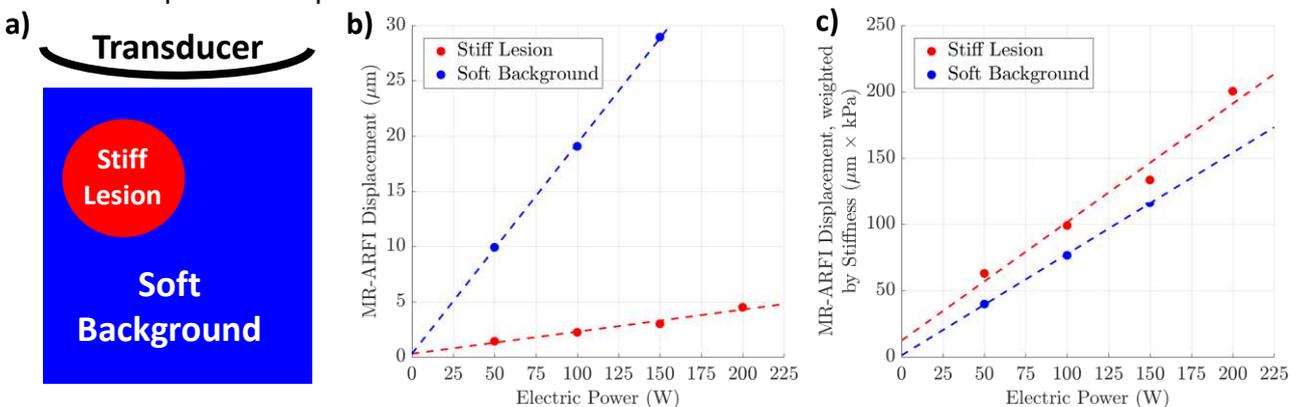
The same applied power produced substantially different MR-ARFI displacements between the two regions (Fig. 1b). MRE revealed that the average shear modulus within the stiff lesion (44.71 ± 2.83 kPa) was greater than the soft background (4.02 ± 0.25 kPa). Weighting the ARFI-induced displacements by MRE-derived stiffness values led to superior agreement between the estimated intensity within the two regions (Fig. 1c).

CONCLUSIONS

Our results demonstrate the potential for MR-ARFI to provide both focal spot localization and estimated acoustic intensity in combination with MRE, which would be beneficial for enhancing the safety and efficacy of non-ablative focused ultrasound therapies.

ACKNOWLEDGEMENTS

This work was supported by NIH T32 CA009695, T32 EB009653, and NSF DGE 1656518. The authors would like to acknowledge Richard L. Ehman and Kevin Glaser from the Mayo Clinic for providing the MRE sequence and passive actuator.



CAPTION: a) Experimental setup showing the phantom with a stiff lesion embedded in a softer background region. b) MR-ARFI intensity estimates differed between the two regions at similar applied powers, but c) better agreement was achieved using MRE-derived stiffness corrections.

PHOTOACOUSTIC IMAGING OF HIFU-INDUCED TISSUE INJURIES

Tri Vu¹, Junjie Yao¹, and Pei Zhong^{1,2}

¹Department of Biomedical Engineering, Duke University, North Carolina, USA

²Department of Mechanical Engineering and Materials Science, Duke University, North Carolina, USA

e-mail: junjie.yao@duke.edu; pzhong@duke.edu

OBJECTIVES

Develop an integrated photoacoustic imaging (PAI) system with high-intensity focused ultrasound (HIFU) to monitor HIFU-induced thermal ablation and vascular injury in small animal models.

METHODS

HIFU is a promising non-invasive and cost-effective cancer treatment modality, compared to chemotherapy and radiotherapy. Currently, there is a pressing need for real-time monitoring of HIFU treatment to maximize efficacy while minimizing adverse effects. PAI is a hybrid imaging modality with unique optical absorption contrast, balanced penetration and resolution, and high sensitivity to vasculature, temperature and molecular information. In this study, we aim to develop an integrated HIFU-PAI system to monitor HIFU-induced thermal ablation and mechanically-induced destruction of tumor vasculature. The integrated HIFU-PAI system consists of a high-power pulsed laser for PA excitation at 1064 nm, a half-ring ultrasound transducer array (128 elements) for PA signal detection, a single-element HIFU transducer for tumor treatment, and a Verasonics system for imaging and PAI data acquisition. The half-ring transducer is co-axially aligned with the HIFU focus, and the laser emission, HIFU trigger, and PA data acquisition can be precisely synchronized.

RESULTS

We have constructed the integrated system (Fig. 1), and are performing proof-of-concept studies on phantoms and small animals to determine the key imaging parameters, and to demonstrate the feasibility of real-time PAI monitoring of HIFU-induced thermal ablation and vascular injury.

CONCLUSIONS

We have developed an integrated HIFU-PAI system capable of simultaneous HIFU therapy and real-time PA monitoring, which may offer valuable feedback to HIFU therapy.

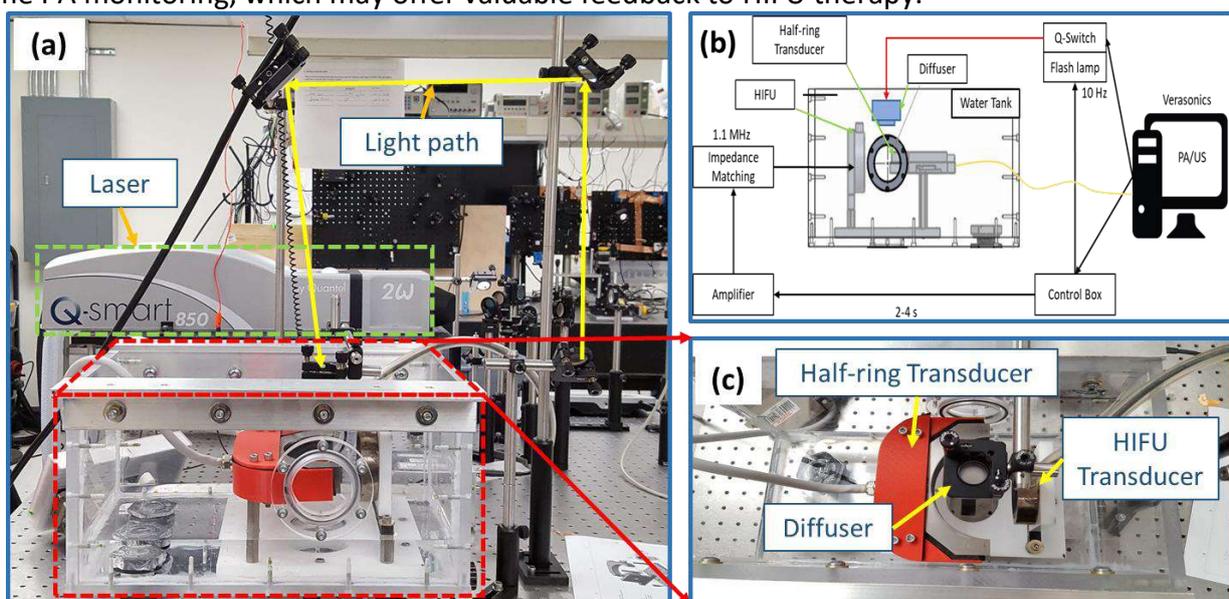


Figure 1. Integrated HIFU-PAI system. (a) Constructed system showing the Q-switched laser, optical path and water tank containing the transducers. (b) Schematics of the HIFU-PAI system. (c) A closer look at the transducer-diffuser setup from the top view.

ULTRASOUND-BASED TARGETING AND DISPLACEMENT IMAGING OF THE MEDIAN NERVE FOR NEUROMODULATION IN HEALTHY HUMAN SUBJECTS

S.A. Lee¹, H.A.S. Kamimura¹, E.E. Konofagou^{1,2}

¹Department of Biomedical Engineering, Columbia University, New York, NY, USA

²Department of Radiology, Columbia University, New York, NY, USA

OBJECTIVES

Focused ultrasound (FUS) neuromodulation provides an important noninvasive technique for treating peripheral neuropathies. However, targeting relies upon magnetic resonance imaging (MRI) or neuronavigational systems, which require bulky equipment. The objective of this study was thus to investigate the feasibility of using a single system for FUS neuromodulation and monitoring for clinical translation.

METHODS

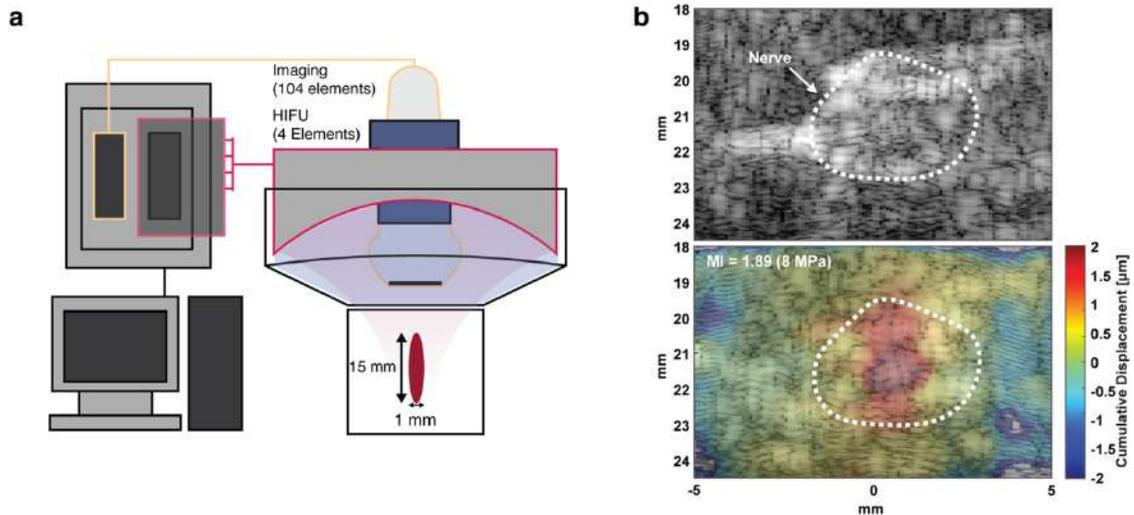
We used a confocally aligned imaging (7.8 MHz, 104-element array) and therapeutic (1.1 MHz, 1-element) transducer for real-time targeting of the human median nerve. We have produced an imaging sequence for a single 256 FUS Vantage research platform for increased portability and mobility, that can modulate nerve activity and image tissue displacement simultaneously. The same transducer setup was previously reported to produce sensations in human volunteers (n = 14) after FUS modulation of the median nerve. The imaging technique was validated *in silico*, in *ex vivo* liver and chicken breast. Human displacement imaging was also validated with another transducer setup (16 MHz imaging, 4 MHz FUS).

RESULTS

This imaging sequence successfully produced displacement maps corresponding to the region of the nerve within the ultrasound focus during application of FUS sequences used for neuromodulation.

CONCLUSION

The imaging technique described herein can be used to target the human nerve and monitor modulation *in vivo*. This technique may prove essential in the reproducibility and safety of human peripheral neuromodulation.



CAPTION: Imaging system developed to generate displacement images for neuromodulation targeting and monitoring. a) Single 256-channel FUS displacement imaging for simultaneous imaging and modulation. b) Displacement images during FUS modulation.

MONITORING HIFU ABLATIONS IN REAL TIME USING SIMULTANEOUS MR THERMOMETRY AND ELASTOGRAPHY

J.Vappou¹, K. Kim¹, P. Cabras¹, E. Breton¹

¹ICUBE Laboratory, CNRS, University of Strasbourg, France

e-mail: jvappou@unistra.fr

OBJECTIVES

Tissue elasticity is a promising biomarker for monitoring HIFU ablations. Magnetic Resonance Elastography (MRE) protocols are not optimal for ablation monitoring due to poor temporal resolution and requirement of bulky excitation hardware. A new all-in-one protocol is proposed that uses electronic steering of the HIFU transducer to generate quasi-planar supersonic shear waves through multiple acoustic radiation pushes while simultaneously generating a thermal lesion.

METHODS

The proposed method relies on (1) Generating quasi-planar supersonic shear waves, (2) Encoding shear waves using an ultrafast MRE-like sequence, (3) Interleaving pushes and HIFU ablation within each MR TR, (4) Estimating Shear Wave Velocity (SWV) and (5) temperature changes (Proton Resonance Frequency shift). Experiments were performed at 1.5T in a gelatin phantom using a 128-element 1MHz transducer. Ablation was performed during 120s. Shear waves were generated at the central axis of the transducer whereas HIFU ablation was performed 1cm lateral of the central axis. A dual Thermometry/MRE single-shot EPI acquisition provided elasticity and temperature measurements every 2 seconds.

RESULTS

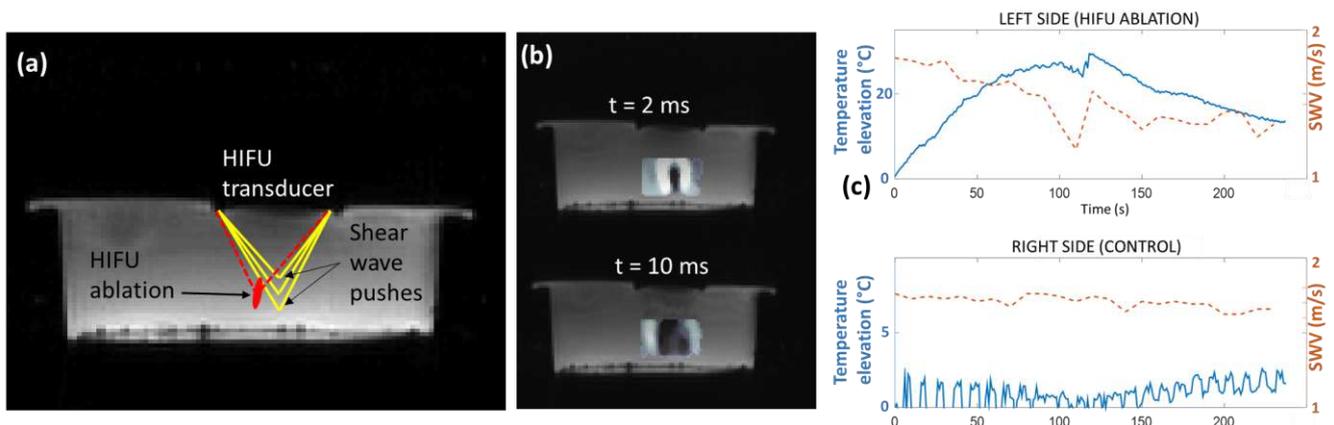
Supersonic shear waves were clearly seen propagating from the central axis. Heating of the gelatin, confirmed by MR Thermometry, was correlated to significant decrease of SWV, suggesting softening of the gel undergoing HIFU ablation.

CONCLUSIONS

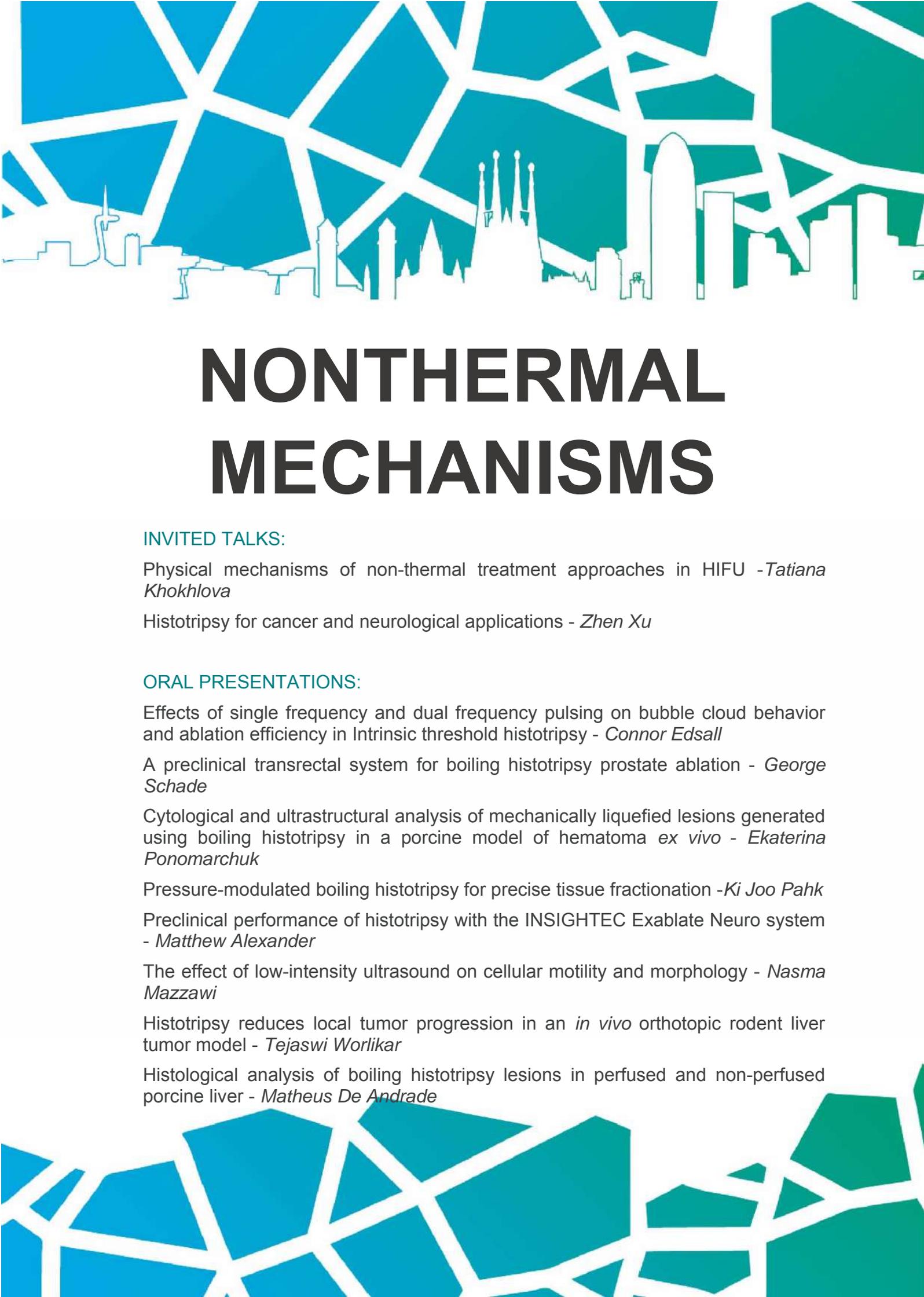
The proposed all-in-one MR-guided protocol allows for simultaneous ablation and monitoring of both temperature and elasticity at high frame rate, without the need for MRE-dedicated hardware.

ACKNOWLEDGEMENTS

This project is funded by “Fond Unique Interministeriel” (UFOGUIDE 2017-2020).



CAPTION: Generation of shear waves and HIFU ablation using electronic steering(a); Supersonic shear waves(b); Temperature variation and elasticity (SWV), showing that temperature elevation correlates to gel softening(c).



NONTHERMAL MECHANISMS

INVITED TALKS:

Physical mechanisms of non-thermal treatment approaches in HIFU - *Tatiana Khokhlova*

Histotripsy for cancer and neurological applications - *Zhen Xu*

ORAL PRESENTATIONS:

Effects of single frequency and dual frequency pulsing on bubble cloud behavior and ablation efficiency in Intrinsic threshold histotripsy - *Connor Edsall*

A preclinical transrectal system for boiling histotripsy prostate ablation - *George Schade*

Cytological and ultrastructural analysis of mechanically liquefied lesions generated using boiling histotripsy in a porcine model of hematoma *ex vivo* - *Ekaterina Ponomarchuk*

Pressure-modulated boiling histotripsy for precise tissue fractionation - *Ki Joo Park*

Preclinical performance of histotripsy with the INSIGHTEC Exablate Neuro system - *Matthew Alexander*

The effect of low-intensity ultrasound on cellular motility and morphology - *Nasma Mazzawi*

Histotripsy reduces local tumor progression in an *in vivo* orthotopic rodent liver tumor model - *Tejaswi Worlikar*

Histological analysis of boiling histotripsy lesions in perfused and non-perfused porcine liver - *Matheus De Andrade*

Physical mechanisms of non-thermal treatment approaches in HIFU

Tanya Khokhlova

Division of Gastroenterology, University of Washington School of Medicine, Seattle, USA

e-mail: tdk7@uw.edu

OBJECTIVES

Tissue effects of HIFU can be broadly divided into thermal and mechanical, the latter being primarily mediated by cavitation and ranging from complete tissue disintegration down to subcellular debris (histotripsy) to micro-scale tissue disruption, depending on the specifics of HIFU treatment protocol. This talk will review the physical mechanisms underlying different cavitation-based HIFU treatments, instrumentation considerations and clinical applications.

METHODS

In cavitation-based HIFU treatments, short (microseconds to milliseconds) bursts of high amplitude HIFU waves are delivered at low duty cycle to induce gas and/or vapor bubble activity at the transducer focus which mechanically disrupts or disintegrates tissue. Achieving a specific type of bubble activity requires the knowledge of high-amplitude HIFU focal waveform that can be either measured by robust, wideband hydrophones or modelled. Direct observation of bubble activity in transparent tissue-mimicking phantoms using high-speed photography has been an invaluable tool in elucidating the mechanisms of tissue disruption and designing optimal pulsing protocols. Characterization of cavitation activity in tissue has most commonly been performed using ultrasound imaging and passive cavitation detection.

RESULTS

Multiple histotripsy approaches have been proposed and implemented over the years, including shock-scattering histotripsy, boiling histotripsy, and microtripsy. The approaches differ in the specific physical mechanisms that lead to the generation of bubbles, and imply different pulsing protocols, HIFU pressure levels and requirements to transducers and instrumentation. Less dramatic inertial cavitation activity that facilitates micro-scale tissue disruption requires lower HIFU pressure levels and has been proposed for use in drug delivery and inducing inflammatory changes in tissues.

CONCLUSIONS

Through the choice of HIFU output levels and pulsing protocols it is possible to generate and control specific types of bubble activity leading to a range of tissue effects.

Histotripsy for Cancer and Neurological Applications

Zhen Xu, Department of Biomedical Engineering, University of Michigan

Histotripsy is a non-thermal ultrasound ablation technique based on acoustic cavitation. Using microsecond-length, high-pressure ($p > 20\text{MPa}$) focused ultrasound pulses, cavitation microbubbles are generated from endogenous gas nuclei in the target tissue. The rapid growth and collapse of the microbubbles produces high strain to disrupt cells within the targeted volume into a liquid-appearing acellular homogenate. This talk will cover the latest results on development of histotripsy for cancer and neurological applications.

For cancer applications, histotripsy has been investigated for treatment of liver, renal, and pancreatic cancer in large and small animal models. Multiple *in vivo* porcine studies have shown complete and precise ablation in the liver, kidney, and pancreas through the intact chest while preserving large blood vessels and bile ducts within the ablation zone, without damaging the chest wall. Recent data in rodent cancer models show that histotripsy significantly reduced local tumor progression, lengthened survival, and reduced metastases. Further, preliminary evidence of increased immunogenicity of tumors after histotripsy was also observed, far superior to that seen with radiation and thermal ablation.

Histotripsy has also been investigated to treat brain tumors and hemorrhagic stroke. Recent results show that histotripsy applied through excised human skulls was used to ablate a wide range of locations and brain volumes inside the skull, while keeping the temperature increase in the skull under 4°C , which may allow histotripsy to treat brain tumors. Histotripsy can also liquefy a large clot volume ($>30\text{mL}$) through the skull within 20 minutes, facilitating rapid clot drainage for treatment of hemorrhagic stroke.

Effects of Single Frequency and Dual Frequency Pulsing on Bubble Cloud Behavior and Ablation Efficiency in Intrinsic Threshold Histotripsy

Connor Edsall¹, Emerson Ham¹, Hal Holmes¹, Tim Hall², Eli Vlaisavljevich¹

¹Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, VA, USA

²Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

E-mail: eliv@vt.edu;

OBJECTIVES

Histotripsy bubble clouds can be formed by a single pulse when the negative pressure exceeds an intrinsic threshold of ~25-30 MPa, with the ablation efficiency dependent upon the size and density of bubbles within the cloud. This work investigates the effects of single and dual frequency pulsing on the bubble cloud behavior and ablation efficiency in intrinsic threshold histotripsy.

METHODS

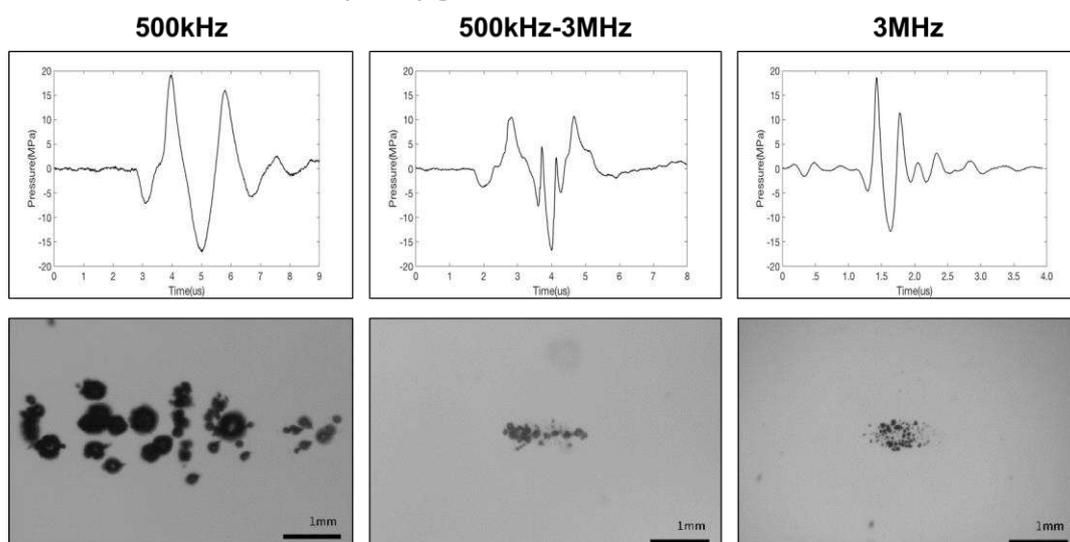
Single cycle pulses using 500kHz, 3MHz, or dual-frequency (1:1 ratio) were applied to agarose phantoms using a modular histotripsy transducer. Cavitation activity was characterized by high-speed photography (Fig.1). Optical images were analyzed to determine the cavitation threshold, bubble cloud dimensions, “bubble density” within the cloud, and individual bubble size. The effects of frequency on ablation efficiency was also investigated by applying histotripsy to red blood cell phantoms, with results visualized using optical imaging.

RESULTS

The intrinsic threshold did not significantly change with frequency. Cloud size closely matched theoretical predictions, with the largest clouds observed at 500kHz. The “bubble density” was shown to increase at 3 MHz compared to 500 kHz. For dual-frequency pulsing, cloud size, individual bubble size, and cloud density were measured to be at an intermediate level, matching our hypothesis. Finally, ablation experiments showed a significant increase in treatment efficiency for 500kHz compared to 3MHz, with the dual-frequency pulses showing an intermediate efficiency.

CONCLUSIONS

Results demonstrate the effects of single and dual-frequency pulses on histotripsy bubble cloud behavior and show that lower frequency generates more efficient tissue ablation.



A PRECLINICAL TRANSRECTAL SYSTEM FOR BOILING HISTOTRIPSY PROSTATE ABLATION

G.R. Schade¹, T.D. Khokhlova², C. Hunter³, W. Kreider³, P.B. Rosnitskiy⁴, P.V. Yuldashev⁴, O.A. Sapozhnikov^{3,4}, V.A. Khokhlova^{3,4}

¹Department of Urology, ²Department of Medicine, ³Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

⁴Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

e-mail: grschade@uw.edu; chunter6@uw.edu; wkreider@uw.edu; tdk7@uw.edu; olegs2@uw.edu; verak2@uw.edu

OBJECTIVES

Boiling histotripsy (BH) is a focused ultrasound (FUS) method that produces precise mechanical tissue ablation using milliseconds duration FUS pulses containing shocks. BH's non-thermal mechanism and real-time treatment monitoring may improve on outcomes of contemporary thermal FUS prostate ablation.

METHODS

We built a preclinical transrectal BH system comprising a 2 MHz FUS transducer (5.0 x 3.5 cm, focus 4.0 cm) with inline B-mode imaging (Figure A), 1000 W amplifier, function generator and clinical imaging system. Acoustic output of the system was characterized in water. The ability to produce BH was assessed in polyacrylamide gel (PAC) and agar-embedded chicken breast (CB). BH thresholds were established for 1-10 ms pulses. BH lesions were generated in PAC (1-10 ms pulses) and CB (10 ms pulses) by administering 30 pulses at 1% duty factor.

RESULTS

The system outputs are presented in Figure B and produced peak+ and peak- pressures of 115 MPa and -21 MPa at 413 W acoustic power. Observed BH thresholds required shock amplitudes of 76, 76, 86, and 112 MPa for 10, 5, 2, and 1 ms pulses in PAC and 112 MPa for 10 ms pulses in CB. For all pulse durations, sharply demarcated lesions consistent with BH mechanical ablation were observed in both PAC (Figure C) and CB.

CONCLUSIONS

A custom-built transrectal BH system was acoustically characterized and demonstrated the ability to produce BH lesions *ex vivo*. Future experiments will evaluate *ex vivo* and *in vivo* prostate ablation.

ACKNOWLEDGEMENTS

Work supported by NIH R01EB007643, R01EB025187, R21CA219793 and RFBR 17-54-33034.

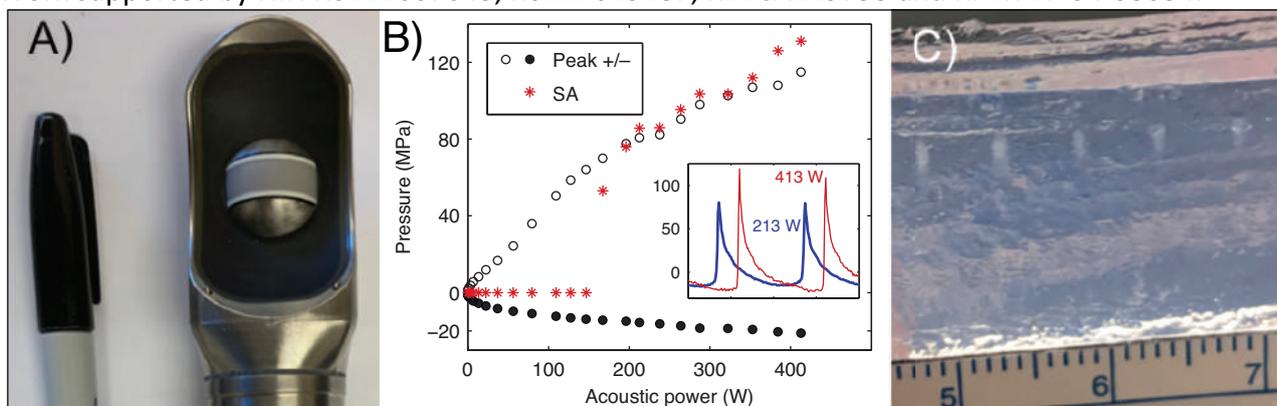


FIGURE: A) Transrectal FUS transducer, B) Plot of peak pressure values and shock amplitudes (SA), with inset showing waveforms at 130 W and 251 W, and C) appearance of lesions in PAC gel.

CYTOLOGICAL AND ULTRASTRUCTURAL ANALYSIS OF MECHANICALLY LIQUEFIED LESIONS GENERATED USING BOILING HISTOTRIPSY IN A PORCINE MODEL OF HEMATOMA *EX VIVO*

E.M. Ponomarchuk¹, S.V. Buravkov², P.B. Rosnitskiy¹, S.A. Tsysar¹, M.M. Karzova¹, A.V. Kunturova¹, K.D. Topchu¹, O.A. Sapozhnikov^{1,3}, and V.A. Khokhlova^{1,3}

¹Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

²Faculty of Fundamental Medicine, M.V. Lomonosov Moscow State University, Moscow, Russia

³Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

e-mails: msu.ekaterina.ponomarchuk@gmail.com; sergey@wolf.ru; verak2@uw.edu

OBJECTIVES

The goal of this study was to evaluate the degree of mechanical disintegration of coagulated porcine blood volumes using boiling histotripsy (BH) method.

METHODS

Coagulated porcine blood representing a model of a large hematoma was enclosed into an agar gel and exposed to BH in a degassed water under B-mode imaging (Figure a). A volumetric liquefied lesion (1.5x1.5x1.1 cm) was generated using a 1.5 MHz transducer of 8 cm aperture and 6 cm focal length operating at 215 V (b). The exposure parameters were: 2.5 ms pulse length, 1% duty cycle, three layers of 4x4 points each with 4 mm spacing, 15 pulses per focus. Cytological and submicroscopic examination of the lesion and control sample was performed using light microscopy and scanning electron microscopy (SEM).

RESULTS

The content of untreated coagulated porcine blood (Figure c, e) appeared as densely populated red blood cells (echinocytes) covering fibrin fibers. After BH exposure, most of the blood cells in the lesion were lysed (d, f), only few of them were present in blood smears and appeared as nonviable (d). SEM images showed multiple fused layers of fibrin network debris.

CONCLUSIONS

Both cytological and ultrastructural analysis using light microscopy and SEM have revealed complete destruction of red blood cells in the liquefied BH lesion.

ACKNOWLEDGEMENTS

Supported by the FUSF student Global Internship Program, NIH EB007643 and GM122859.

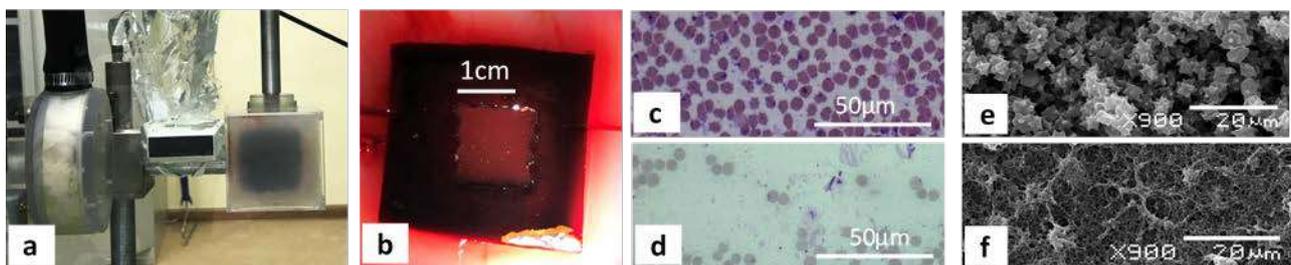


FIGURE: (a) BH transducer, US imaging array, and hematoma sample in agar gel. (b) Transverse section of the liquefied lesion. (c,d) Blood smears with Wright-Giemsa staining for intact (c) and liquefied (d) hematoma. (e,f) SEM images of (e) untreated sample and (f) lesion content.

PRESSURE-MODULATED BOILING HISTOTRIPSY FOR PRECISE TISSUE FRACTIONATION

K.J. Pakh¹, B.C. Lee², M.J. Choi³, N. Saffari⁴, H. Kim¹

¹Center for Bionics, Biomedical Research Institute, Korea Institute of Science and Technology (KIST), Seoul, Republic of Korea; ²Center for BioMicrosystems, Brain Science Institute, KIST, Seoul, Republic of Korea; ³Dept. of Medicine, Jeju National University, Jeju, Republic of Korea; ⁴Dept. of Mechanical Engineering, University College London, London, UK.

e-mail: kipahk@kist.re.kr

OBJECTIVES

In boiling histotripsy (BH), shockwave heating enables a boiling vapour bubble to be induced at the HIFU focus in soft tissue. Further interaction of incoming shockwaves with this bubble then leads to the generation of cavitation clouds which appear between the HIFU source and the bubble. Because of this cavitation cluster, it is difficult to predict the size of a BH lesion as well as to control the degree of mechanical damage produced at a given BH exposure condition. Herein, we propose and demonstrate a novel approach to minimise the formation of cavitation clouds during BH exposure.

METHODS

A 10 ms-long pressure-modulated BH pulse (4 ms with $P_+ = 92$ MPa and $P_- = -14$ MPa; 6 ms with $P_+ = 30$ MPa and $P_- = -9.4$ MPa at focus) with a driving frequency of 2 MHz was used to create a boiling bubble and induce mechanical damage whilst minimising the shock scattering effects. A high speed camera and a passive cavitation detection system were used to observe bubble dynamics induced in liver tissue phantoms at the frame rate of 0.11 Mfps.

RESULTS

High-speed images captured over 10 ms plotted in Figure 1 show the formation and dynamic behaviour of a vapour bubble at the HIFU focus in the absence of the shock scattering effect-induced cavitation clouds. This boiling bubble eventually resulted in mechanical fractionation.

CONCLUSIONS

Pressure-modulated boiling histotripsy was proposed and demonstrated. Results show that our proposed method could potentially be used for precise tissue fractionation and cell therapy such as tissue decellularisation.

ACKNOWLEDGEMENTS

Supported by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIT) (No. CAP-18-01-KIST) and a grant of National Research Foundation of Korea (NRF) (Grant No. 2017R1A2B3007907) funded by the Korean government.

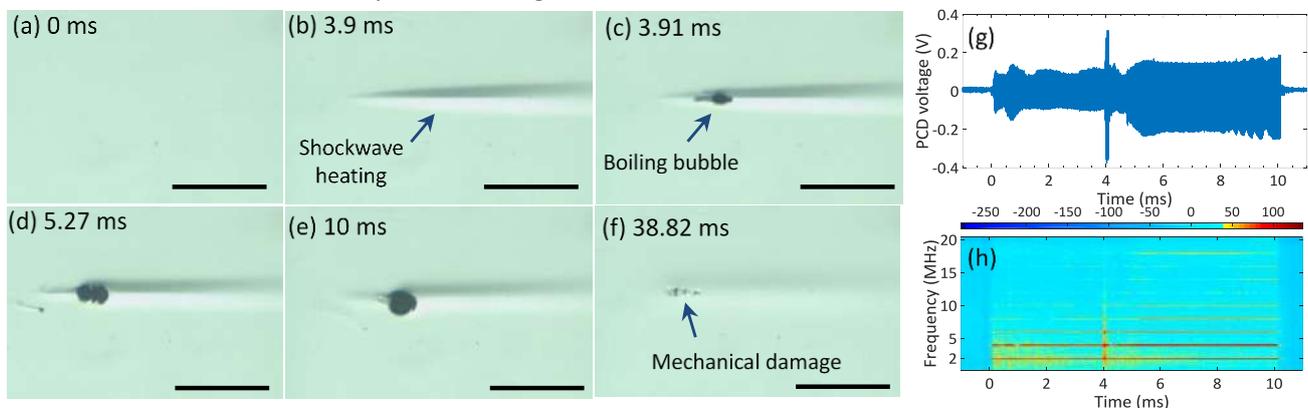


Figure 1. (a) to (f) show a series of high-speed camera images of bubble dynamics induced in an optically transparent liver tissue phantom. A 10 ms long pressure-modulated boiling histotripsy pulse was used (4 ms with $P_+ = 92$ MPa and $P_- = -14$ MPa; 6 ms with $P_+ = 30$ MPa and $P_- = -9.4$ MPa at focus). (g) and (h) are the corresponding PCD voltage results and the spectrogram respectively. The time at 0 ms corresponds to the start of the HIFU exposure. The HIFU beam propagates from left to right. A scale bar represents 1 mm.

PRECLINICAL PERFORMANCE OF HISTOTRIPSY WITH THE INSIGHTEC EXABLATE NEURO SYSTEM

V. Rieke¹, H. Odéen¹, D. Parker¹, K. Albertine², L. Hofstetter¹, J. Rolston³, A. Payne¹, M. Alexander^{1,3}
Departments of ¹Radiology and Imaging Sciences, ²Pediatrics, and ³Neurosurgery, University of Utah, Salt Lake City, Utah, USA
e-mail: matthew.alexander@hsc.utah.edu

OBJECTIVES

Clinically available MR-guided focused ultrasound treatments ablate tissue through heating. Histotripsy is an alternative technique that cavitates tissue via mechanical effects. Prior reports of histotripsy in preclinical models utilized MRgFUS systems not clinically available for brain applications. Additionally, histotripsy performed in the brain has required a preoperative craniectomy.

METHODS

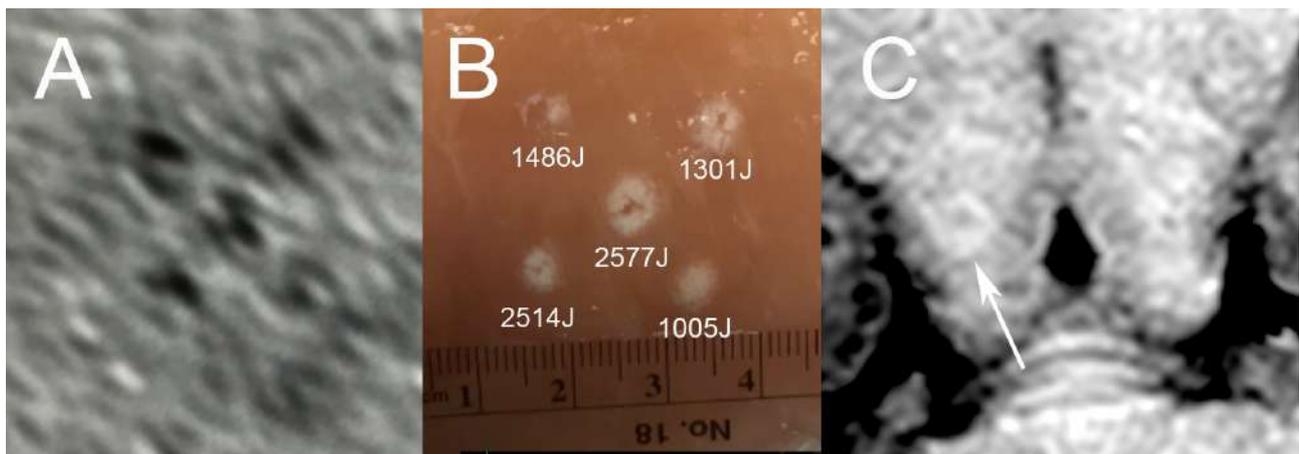
Histotripsy was performed in chicken breast and neonatal lamb brain. Chicken breast was placed in the InSightec Exablate Neuro (IEN) quality assurance phantom and submerged in degassed deionized water. Histotripsy was performed at five locations for a total of 180s or 360s (20ms duration, 0.5Hz repetition, 1500 electric watts). A neonatal lamb was euthanized. Its head was shorn and depilated. After CT registration, histotripsy was performed in the thalamus on the IEN system.

RESULTS

MR thermometry measured 20-35 °C rise in chicken breast temperature. Cavitation was noted at all locations except one, which received the lowest deposited energy. Post-ablation MRI of the lamb brain demonstrated a focal lesion at the targeted thalamus. Pathology results are pending for the lamb brain.

CONCLUSIONS

The IEN system can be used to perform histotripsy. Further validation in living lambs is underway.



CAPTION: A) Pre-post subtraction of magnitude temperature measurement images of chicken breast specimen following histotripsy demonstrates focal changes at five targeted sites. B) Cut-edge gross photograph of the same chicken breast specimen demonstrates cavitation at all but the lowest energy. Delivered energy for each site is noted. C) Coronal T1-weighted MR image after histotripsy demonstrates a focal lesion at the targeted site in the right thalamus (arrow).

The Effect of Low-Intensity Ultrasound on Cellular Motility and Morphology

Nasma Mazzawi¹, Eitan Kimmel¹, Ilan Tsarfaty²

¹Faculty of Biomedical Engineering, Technion - IIT, Haifa, Israel

²Department of Clinical Microbiology and Immunology, Sackler School of Medicine, Tel Aviv

E-mail: snasmamz@campus.technion.ac.il; nasma.mazzawi@gmail.com

Low-intensity ultrasound (LIUS) was shown to have a great potential in cancer therapy applications. The ongoing research for such applications show highly promising results while understanding the mechanism of ultrasound-cell interaction is still far from being complete. In 2011, the bilayer sonophore (BLS) model suggested that cell intramembrane cavitation is the underlying mechanism for ultrasound-induced bioeffects [1]. For cancer cells, the activation of MET, a biochemical cellular signaling pathway, contributes to tumor progression, invasion and metastasis [2]. MET activation induces cell motility via membrane alterations. Here we present the crosstalk between LIUS (external force) and MET (inner cellular process) and their effect on cell membranes [3].

OBJECTIVES

Membrane dynamics and morpho-kinetic behavior of cells under LIUS and MET activation were studied. The combined effect of LIUS and DOXIL (anti-cancer chemotherapy drug) on cell membranes was studied as well.

METHODS

A ring-shaped transducer, with a resonance frequency at 960 KHz, was placed inside a cell-cultured dish and mounted on a microscope stage [3]. Acoustic pressure of 200 kPa was applied on membrane-labeled cells. Live cell imaging and single cell time-lapse analysis was performed.

RESULTS

The application of LIUS was shown to inhibit the motility of MET-activated cells and to modulate their morphology (Fig.1). LIUS magnified the effect of DOXIL by formation of bubble-like dynamic circular shapes within the cell membranes.

CONCLUSIONS

Cell membranes are the intersection between inner cellular processes and external forces. Characterizing membrane modifications under LIUS can improve the performance of existing LIUS-based cancer treatment modalities, including chemotherapy, and help develop new ones.

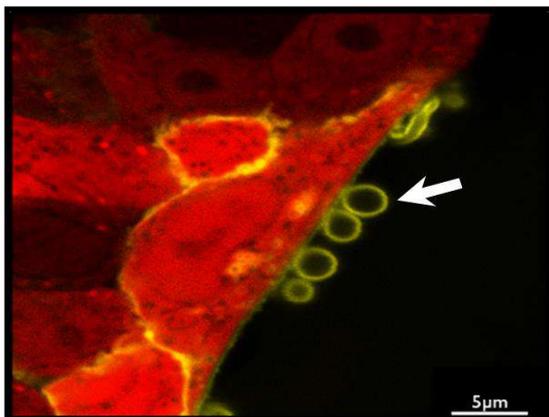


Fig.1: Formation of circular shapes from fragmented regions of cell membranes during LIUS exposure on pEYFP-mem & pmCherry MDCK cells [3].

REFERENCES

- [1] Krasovitski B, Frenkel V, Shoham S, Kimmel E. Intramembrane cavitation as a unifying mechanism for ultrasound-induced bioeffects. *Proceedings of the National Academy of Sciences*. 2011 Feb 3;201015771.
- [2] Laser-Azogui A, Diamant-Levi T, Israeli S, Roytman Y, Tsarfaty I. Met-induced membrane blebbing leads to amoeboid cell motility and invasion. *Oncogene*. 2014 Apr; 33(14):1788.
- [3] Mazzawi N, Kimmel E, Tsarfaty I. The effect of low-intensity ultrasound and met signaling on cellular motility and morphology. *Applied Acoustics*. 2019 Jan 1; 143:1-6.

HISTOTRIPSY REDUCES LOCAL TUMOR PROGRESSION IN AN *IN VIVO* ORTHOTOPIC RODENT LIVER TUMOR MODEL

Tejaswi Worlikar¹, Mishal Mendiratta-Lala¹, Ryan Hubbard¹, Eli Vlaisavljevich², Jonathan Lundt¹, Timothy Hall¹, Joan Greve¹, Clifford Cho¹, Fred Lee³, Zhen Xu¹

¹University of Michigan, Ann Arbor, USA

²Virginia Polytechnic Institute and State University, Blacksburg, USA

³University of Wisconsin, Madison, USA

email: wtejaswi@umich.edu, zhenx@umich.edu

OBJECTIVES:

Histotripsy mechanically ablates tissue through precisely controlled, noninvasive acoustic cavitation. This study evaluates the ability of histotripsy to reduce local tumor progression in an *in vivo* orthotopic, immunocompetent rat hepatocellular carcinoma (HCC) model.

METHODS:

HCC tumors were generated by injecting 2-4 million rat-derived N1-S1 cells into the livers of n=21 immunocompetent Sprague-Dawley rats (n=6, control and n=15, treatment). Real-time ultrasound-guided histotripsy was applied to ablate either 50-75% tumor volume (n=6, partial treatment) or 100% tumor volume + 2 mm margin (n=9, complete treatment) by delivering 1-2 cycle histotripsy pulses at 100 Hz PRF ($P > 30$ MPa) using a custom 1 MHz transducer. Animals were monitored weekly using T2-weighted MRI for 3 months or until tumors reached ~2.5cm.

RESULTS:

MRI revealed effective post-histotripsy reduction of tumor burden with near-complete resorption of the ablated tumor in 14/15 (93.3%) animals for both complete and partial treatment groups. Gross morphology showed shrunken, non-tumoral, fibrous tissue at treatment site. 3/6 control and 1/15 treatment animals were euthanized early at 3 weeks due to increased tumor burden. In other controls, gross evaluation revealed residual tumor not detected on MRI. There was no evidence of histotripsy-induced adjacent tissue injury.

CONCLUSIONS:

Complete and partial histotripsy ablation enabled tumor removal, with no evidence of local tumor progression or recurrence in orthotopic rat liver tumor model.

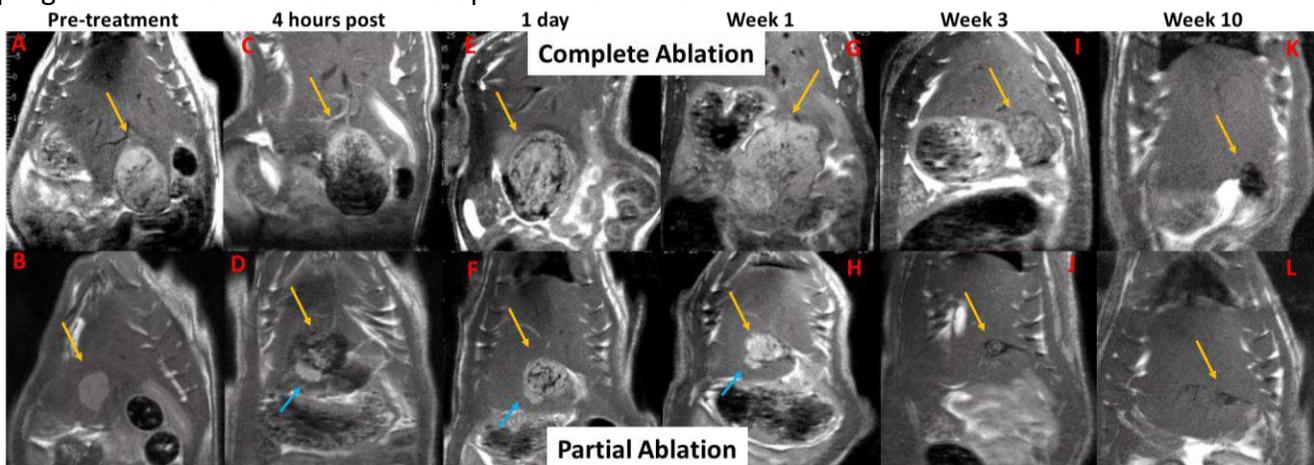


Figure 1. MRI demonstrated local tumor regression in complete and partial histotripsy (*non-targeted tumor, blue arrow*) cases without radiographic evidence of tumor by week 10. At week 10, T2-hypointense tissue at treatment site corresponded to gross non-tumoral, fibrous tissue.

HISTOLOGICAL ANALYSIS OF BOILING HISTOTRIPSY LESIONS IN PERFUSED AND NON-PERFUSED PORCINE LIVER

M. O. de Andrade¹, S. Froghi², B. Davidson², P. Sibbons², B. Fuller², N. Saffari¹

¹UCL Mechanical Engineering, University College London, London, UK

²UCL Division of Surgery and Interventional Science, University College London, London, UK

e-mail: matheus.andrade.15@ucl.ac.uk

OBJECTIVES

This work aims to compare the effects of perfusion in the patterns of mechanical and thermal lesioning in boiling histotripsy.

METHODS

Lesions were created with a single-element, 2 MHz bowl-shaped transducer (Sonic Concepts H106) driven at 150 W input electrical power, 1 Hz PRF and 1% duty cycle. The porcine liver samples were excised on the same day, flushed at the abattoir and taken to the laboratory where two lobes were perfused at 375 ml/h and one lobe was kept non-perfused as an internal control. The contents of the lesions were extracted for cell culture and then cubes of 1 cm³ around the lesion were extracted for H&E and Sirius Red staining.

RESULTS

Although no gross thermal damage was visible in any of the lesions at excision, Sirius Red staining showed significant thermal degradation of connective tissue in all non-perfused specimens. In perfused specimens, connective tissue displayed a distinct pattern of mechanical damage. H&E staining showed the extent of cell disintegration pointing out “islands” of intact cells in both groups. Culture of these cells showed them to be viable for as long as 7 days post experiment. Finally, histology has also shown significant damage to the vasculature within the HIFU focus.

CONCLUSIONS

Perfusion plays an important role in the patterns of disturbance to adjacent connective tissue in boiling histotripsy. The observation of living cells inside of the lesions combined with vascular damage suggest more caution is needed in applications of histotripsy to the mechanical ablation of malignant tumours.



DRUG DELIVERY DESIGN / ENGINEERING

INVITED TALKS:

Ultrasound targeted microbubble destruction for the targeted chemo-sonodynamic therapy of pancreatic cancer - *John Callan*

Nanoparticle-loaded microbubbles for US-triggered drug delivery: sonoprinting and the multiscale parameter - *Michel Versluis*

ORAL PRESENTATIONS:

A one-pot process for the preparation of ultrasound-responsive microbubbles loaded with paclitaxel and gemcitabine for the treatment of pancreatic cancer - *Keiran Logan*

Intra-pulse monitoring of microbubble destabilization during ultrasound-induced blood-brain barrier opening - *Anthony Novell*

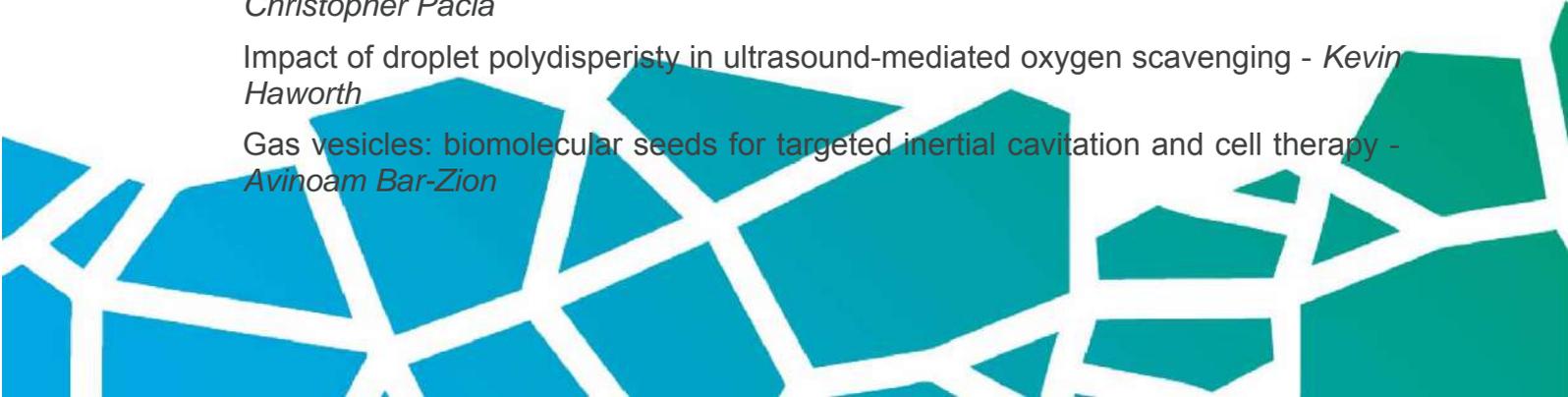
Optimising the composition of microbubbles to improve the delivery of model drugs *in vitro* and *in vivo* - *Oliver Vince*

The extracellular matrix rigidity alters sonoporation dynamics at cellular level - *Ning Rong*

Developing a magnetic resonance-focused ultrasound system for focused ultrasound-enabled brain tumor liquid biopsy (FUS-LBx) in a porcine model - *Christopher Pacia*

Impact of droplet polydispersity in ultrasound-mediated oxygen scavenging - *Kevin Haworth*

Gas vesicles: biomolecular seeds for targeted inertial cavitation and cell therapy - *Avinoam Bar-Zion*



Ultrasound Targeted Microbubble Destruction for the targeted Chemo-Sonodynamic Therapy of Pancreatic Cancer.

K. A Logan¹, H. Nesbitt¹, S. Kamila¹, E Stride², A.P. McHale¹, J. F Callan¹

1. School of Pharmacy and Pharmaceutical Sciences, Ulster University, Northern Ireland, UK.

2. Institute of Biomedical Engineering, University of Oxford, Oxford, UK, OX3 7DQ

email: j.callan@ulster.ac.uk

Abstract: Pancreatic cancer has the lowest survival rate among the 21 most common forms of cancer with only 5% of patients surviving 5 years following diagnosis. Surgery remains the only cure for pancreatic cancer but surgery with curative intent is only possible in approximately 20% of patients. The remaining 80% of patients present with either metastatic disease (40%) or locally advanced / borderline resectable disease (LAPC / BRPC) (40%). In recent years, significant effort has focussed on treating LAPC / BRPC patients with neo-adjuvant chemo- or chemo/radio therapy in an attempt to downstage their tumours and increase the proportion of patients eligible for surgery. Unfortunately, the chemotherapy used in these treatment regimens is extremely toxic and results in significant off-target side effects. We have developed a microbubble based platform capable of carrying drug payloads on their surface and oxygen gas in their core. We have demonstrated the ability to target delivery of the oxygen gas and drug payloads to murine pancreatic cancer tumours using externally applied ultrasound to disrupt (burst) the microbubbles in the tumour vasculature. We have also demonstrated that combining conventional cancer chemotherapeutics with sonodynamic therapy (SDT) produces a significantly improved tumour response compared to chemotherapy alone. In this talk, we present our pre-clinical results to date and outline the next steps toward translation of this technology to the clinic.

NANOPARTICLE-LOADED MICROBUBBLES FOR US-TRIGGERED DRUG DELIVERY: SONOPRINTING AND THE MULTISCALE PARAMETER

M. Versluis¹

¹Physics of Fluids group, Technical Medical (TechMed) Centre, MESA+ Research Institute for Nanotechnology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands
e-mail: m.versluis@utwente.nl

OBJECTIVES

Several studies have shown the potential of nanoparticle-loaded microbubbles to effectively enhance the delivery of therapeutic agents to target tissue. Nanoparticle-carrying microbubbles can deposit nanoparticles onto cell membranes in localized patches, a process termed 'sonoprinting'. The biophysical mechanisms underlying sonoprinting are not entirely clear. In addition, the question remains how the ultrasound parameters, such as acoustic pressure and pulse duration, relate to the sonoprinting efficacy.

METHODS

The behavior of nanoparticle-loaded microbubbles under ultrasound exposure is studied using three advanced optical imaging techniques with frame rates ranging from 5 frames per second to 10 million frames per second, while capturing the biophysical cell-bubble interactions that occur on a multitude of timescales.

RESULTS

Details of the observations include US-mediated microstreaming, and translation of the microbubbles, due to acoustic radiation forces. Quantitative flow analysis showed that sonoprinting resulted in the delivery of large amounts of nanoparticles to cells when ultrasound pressures of 300 kPa and ultrasound pulse lengths of more than 100 cycles are applied.

CONCLUSIONS

By combining this information obtained with three imaging techniques, each operating at a different timescale, the microbubble-cell interactions involved in drug delivery with nanoparticle-loaded microbubbles was elucidated in an in vitro setting. The recordings revealed that microstreaming transported the released nanoparticles away from the cells. In contrast, when using higher acoustic pressures and longer ultrasound pulses, the released nanoparticles were dragged along with the translating microbubble gas core and were eventually deposited in patches onto the cell membranes, thereby giving full insight in the sonoprinting mechanisms.

ACKNOWLEDGEMENTS

The sonoprinting project was joint work between the Physics of Fluids group of the University of Twente and the Research Group on Nanomedicine of Ghent University. This work is funded by the Special Research Fund in Flanders Belgium (BOF-Vlaanderen), and NanoCOMIT, an SBO project granted by the Institute for the Promotion of Innovation through Science and Technology in Flanders, Belgium (IWT-Vlaanderen, projectnumber 140061). This work is also supported by NanoNextNL, a micro- and nanotechnology consortium of the Government of the Netherlands and 130 partners.

A One-Pot Process for the Preparation of Ultrasound-Responsive Microbubbles loaded with Paclitaxel and Gemcitabine for the treatment of Pancreatic Cancer.

K. A Logan¹, H. Nesbitt¹, S. Kamila¹, A.P. McHale, J. F Callan¹

¹School of Pharmacy and Pharmaceutical Sciences, Ulster University, Northern Ireland, UK.
email: Logan-K9@ulster.ac.uk

OBJECTIVES

To prepare a novel gemcitabine functionalised phospholipid (LipidGem) and determine the ability of the GemLipid to form microbubbles (LipidGem MB). LipidGem MB, loaded with paclitaxel in the MB shell were also prepared (PTX-LipidGem MB). The efficacy of these MBs upon ultrasound activation was determined in a mouse model of pancreatic cancer.

METHODS

A novel phospholipid conjugate of gemcitabine (LipidGem) was synthesized using a transphosphatidyl reaction (Fig 1a) and characterized by Mass Spectrometry and ¹H NMR spectroscopy. The purified lipid was used to form stable microbubbles with a mean diameter of $2.27 \pm 1.67 \mu\text{m}$ (Fig 1b). PTX-LipidGem MBs were also successfully prepared. The *in vivo* effectiveness of the MB conjugate following ultrasound activation was determined in BxPC-3 tumour bearing mice following IV administration of the MB suspension. Untreated animals, animals treated with MBs containing LipidGem only and animals treated with free Gem (i.e. not MB bound) were used for comparative purposes.

RESULTS

The results reveal significant control of tumour growth for mice treated with LipidGem \pm PTX MBs when compared to mice treated with a clinical dose of Gem ($p < 0.05$) (Fig 1c). In addition, no significant decrease in body weight was observed for mice treated with the MB conjugates indicating that the treatments were well tolerated.

CONCLUSIONS

A facile method for the preparation of a single MB formulation carrying two drug payloads was successfully developed. When stimulated using ultrasound, the MB proved effective at controlling tumour growth in a murine model of pancreatic cancer

ACKNOWLEDGEMENTS

K. Logan thanks Department for the Economy in Northern Ireland for PhD studentship.

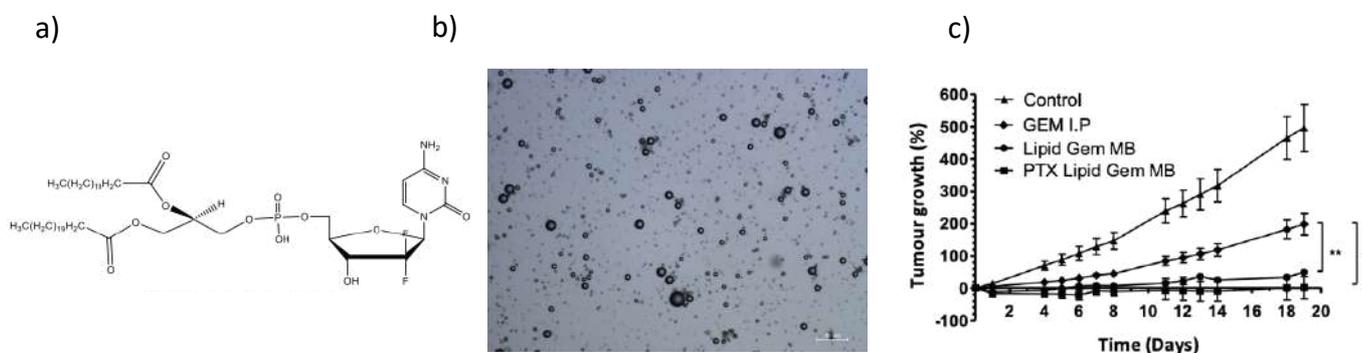


Figure 1. a). Structure of LipidGem b). Microscope image of PTX LipidGem MBs c). BxPC-3 tumour growth plot for mice treated with LipidGem MB \pm PTX and free Gem.

INTRA-PULSE MONITORING OF MICROBUBBLE DESTABILIZATION DURING ULTRASOUND-INDUCED BLOOD-BRAIN BARRIER OPENING

A. Novell¹, H.A.S. Kamimura^{1,2}, A. Cafarelli³, M. Gerstenmayer¹, J. Flament², J. Valette², P. Agou¹, E. Selingue¹, A. Conti¹, R. Aron Badin², P. Hantraye² and B. Larrat¹

¹Neurospin, Institut des Sciences du Vivant Frédéric Joliot, Commissariat à l'Énergie Atomique et aux Énergies Alternatives (CEA), Gif-sur-Yvette, France

²Molecular Imaging Research Center (MIRCent), Institut de Biologie François Jacob, Commissariat à l'Énergie Atomique et aux Énergies Alternatives (CEA), Fontenay-aux-Roses, France

³The BioRobotics Institute, Scuola Superiore Sant'Anna, Pontedera, Italy
e-mail: anthony.novell@u-psud.fr

OBJECTIVES

Ultrasound-induced blood-brain barrier (BBB) opening is a promising technique for local delivery of therapeutic molecules into the brain. While inertial cavitation regime revealed through passive cavitation detection has been associated with potential damage, there is still no consensus in the presence and exploitation of specific nonlinear frequency components such as ultra-harmonics (UH). We propose an intra-pulse monitoring of UH evolution during BBB opening procedure. We hypothesize that the destabilization of microbubbles exposed to ultrasound (US) results in the generation of UH content.

METHODS

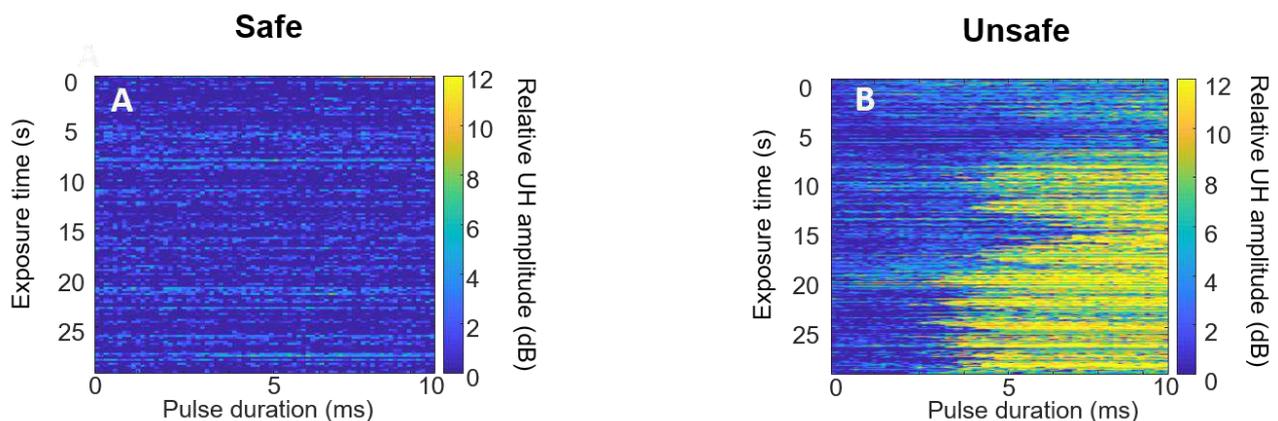
The approach was validated *in vivo* for BBB opening in rats and non-human primates (NHP). US bursts (0.50-0.65 MHz, 10 ms) were applied every 100 ms for 30 s. For each burst, the backscattered signal from microbubbles was divided into 75 consecutive windows of 128 μ s. The 1st window was used as a reference to estimate the evolution of UH amplitude through the burst duration.

RESULTS

Our results demonstrated that the generation of UH was an instantaneous phenomenon that occurred after few milliseconds of US excitation (typically > 3 ms for NHP). A substantial intra-pulse change of UH level (+ 8dB) was related to the occurrence of unwanted side effects such as hemorrhage and edema on both rats and NHP, as revealed by MRI and brain gross pathology.

CONCLUSIONS

We developed a new and very sensitive safety parameter based on intra-pulse monitoring of UH that can be used to tune closed-loop systems avoiding potential harmful US conditions.



CAPTION: Intra-pulse signatures of safe (A) and hemorrhagic (B) BBB opening in NHP

OPTIMISING THE COMPOSITION OF MICROBUBBLES TO IMPROVE THE DELIVERY OF MODEL DRUGS *IN VITRO* AND *IN VIVO*

Oliver Vince¹, Sarah Peeters², Miles Aron¹, Vanessa Johanssen², Michael Gray¹, Nicola Sibson², Eleanor Stride¹

¹BUBBL, Institute of Biomedical Engineering, University of Oxford, UK

²Cancer Research UK and Medical Research Council Institute for Radiation Oncology, Department of Oncology, University of Oxford, UK

Email: oliver.vince@eng.ox.ac.uk

OBJECTIVES

This study investigates the effect of microbubbles containing lysolipids (lyso-MBs) on cell-cell tight junction opening and cell membrane permeabilisation *in vitro*, then takes these findings forward to investigate the effect of lyso-MBs on ultrasound mediated blood-brain barrier disruption (US-BBBD).

METHODS

Quantitative fluorescence microscopy techniques were used to quantify changes in the molecular packing, viscosity and permeability to model drugs of cancer cells under mild ultrasound exposure *in vitro*. MBs were size and concentration matched before all experiments and no significant difference in acoustic emissions was observed.

To assess US-BBBD *in vivo* (500kHz, 200-600kPa, 1% DC, 3 mins exposure), pre/post T1-weighted MRI was used to assess Gadolinium extravasation; histological analysis was used to assess Evans Blue and IgG extravasation.

RESULTS

Lyso-MBs were found to give a ~6 fold increase in sonoporation *in vitro* ($p < 0.0001$), whilst exhibiting similarly low toxicity and enhanced stability. Lysolipid was also found to transiently reduce the TEER of a cell monolayer, indicating temporary cell-cell tight junction opening.

Lyso-MBs significantly increased the volume of US-BBBD *in vivo* at 600kPa when compared to MBs containing no lysolipid, and caused equal US-BBBD at lower pressures.

CONCLUSIONS

The composition of the microbubble shell plays an important role in both cell membrane fluidity and sonoporation *in vitro*, along with US-BBBD *in vivo*. This study demonstrates the potential therapeutic benefit that can be achieved by optimising the chemical composition of the microbubbles themselves and takes steps towards exploiting these effects *in vitro* and *in vivo*.

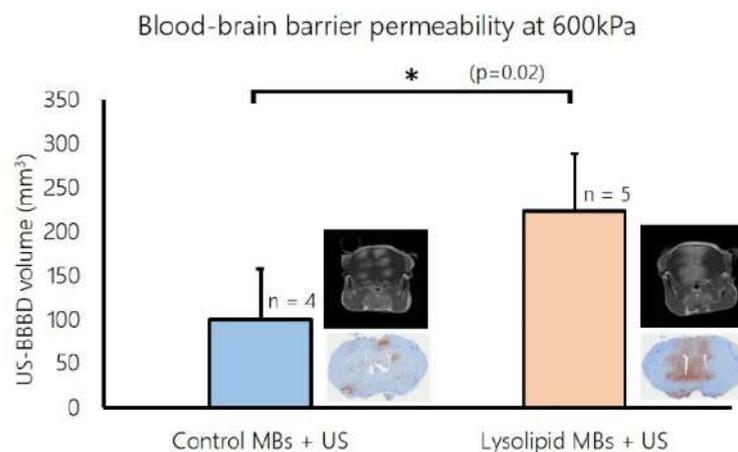


Figure 1: The effect of microbubbles containing lysolipid on US-BBBD at 600kPa

THE EXTRACELLULAR MATRIX RIGIDITY ALTERS SONOPORATION DYNAMICS AT CELLULAR LEVEL

Ning Rong¹, Yan Wang¹, Zhenzhen Fan^{1*}

¹Department of Biomedical Engineering, Tianjin University, Tianjin, China

*e-mail: zhenzhen.fan@tju.edu.cn

OBJECTIVES

The physical properties of the microenvironment in vivo have profound influence on cell morphology, gene expression profile and fate. However, it has not been appreciated in the application of sonoporation, a technique uniquely suitable for targeted drug delivery clinically. This study aims to reveal how the delivery outcomes and dynamics of sonoporation is altered by different extracellular matrix (ECM) rigidity on single cell level.

METHODS

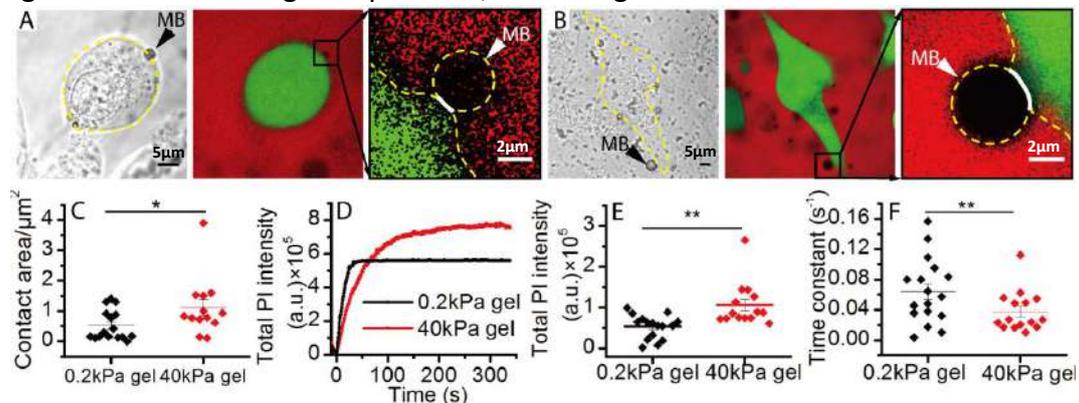
Polyacrylamide hydrogel with rigidity of 0.2kPa and 40kPa was produced. Uniform sized targeted microbubble conjugated with RGD was attached to NIH 3T3 cell. A single ultrasound pulse with 0.45MPa, 10 μ s was applied to stimulate microbubbles, while high cell viability and good sonoporation efficiency was achieved. Real time fluorescent microscopy of propidium iodide (PI) was employed to track the membrane perforation process.

RESULTS

Fluorescence confocal microscopic images unveiled that targeted microbubbles attached to cells on 0.2kPa gel have an average contact area of $0.51 \pm 0.16 \mu\text{m}^2$ (Fig.A), which is 41.4% smaller than that (0.88 ± 0.14) on 40kPa gel (Fig.B-C). Driven by the same ultrasound condition, PI uptake dynamics, which reflects the pore opening and resealing dynamics on the cell membrane, show distinctive characteristics for the cells cultured on different gels (Fig.D). The total PI uptake intensity ($5.25 \pm 0.73 \times 10^5 \text{a.u.}$) for cells on 0.2kPa gel is much less than that ($9.10 \pm 0.68 \times 10^5 \text{a.u.}$) on 40kPa gel (Fig.E). Moreover, it took significantly shorter time for the transient pore resealed for cells on 0.2kPa gel, compared with cells on 40kPa gel, indicated by the 72.9% larger recovery time constant ($0.064 \pm 0.010 \text{ s}^{-1}$) on 0.2kPa than that ($0.037 \pm 0.006 \text{ s}^{-1}$) on 40kPa gel (Fig.F).

CONCLUSIONS

Our results unambiguously show that the physical properties of microenvironment, specifically, the ECM rigidity, can substantially vary the delivery outcomes and dynamic procedures of sonoporation. By integrating in vivo relevant ECM rigidity, our study provides new insight of the underlying mechanisms during sonoporation, advancing the clinic translation of this technique.



CAPTION: Bubble localization on cell membrane (A) 0.2kPa gel, (B) 40kPa gel. (C) Bubble-cell contact area. (D) PI intensity fitting curve. (E) Total PI intensity inside cell. (F) Cell membrane pore resealing time constant.

DEVELOPING A MAGNETIC RESONANCE-FOCUSED ULTRASOUND SYSTEM FOR FOCUSED ULTRASOUND-ENABLED BRAIN TUMOR LIQUID BIOPSY (FUS-LBx) IN A PORCINE MODEL

Christopher Pham Pacia¹, Lifei Zhu¹, Yimei Yue², Yaoheng Yang¹, H. Michael Gach^{1,2,3}, Hong Chen^{1,2}

¹Department of Biomedical Engineering, Washington University in St. Louis, Saint Louis, USA.

²Department of Radiation Oncology, Washington University School of Medicine, Saint Louis, USA.

³Department of Radiology, Washington University School of Medicine, Saint Louis, USA.

Email: cpacia@wustl.edu; hongchen@wustl.edu

OBJECTIVES

Although blood-based liquid biopsy is a promising non-invasive method to detect biomarkers from various cancers, limited progress has been made for brain tumors, at least partly due to hindrance of tumor biomarker release into the peripheral circulation by the blood-brain barrier (BBB). In our previous study, we demonstrated the feasibility for focused ultrasound-enabled brain tumor liquid biopsy (FUS-LBx) in mouse models. The objective of this study was to develop a FUS system for FUS-LBx application in a large animal model.

METHODS

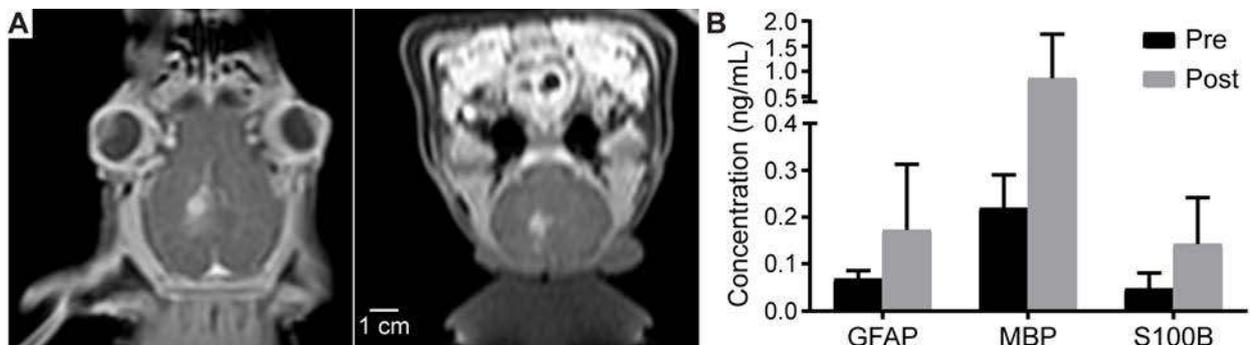
A stereotactic frame was designed to stabilize the head of anesthetized piglets. A magnetic resonance (MR)-compatible FUS transducer was used for FUS treatment. Software was developed to target a specific brain location with MR guidance. FUS sonication was performed after intravenous injection of microbubbles. After treatment, contrast-enhanced MR images were acquired to evaluate BBB permeability. Blood was collected and brain-specific biomarkers were analyzed using enzyme-linked immunosorbent assay.

RESULTS

Contrast-enhanced T1-weighted MR images confirmed BBB opening (Fig. A). The concentration of brain-specific biomarkers, GFAP, MBP, and S100B, increased respectively by a factor of 2.5, 4, and 3 after FUS treatment compared with before (Fig. B).

CONCLUSIONS

This integrated system allowed precise BBB disruption to enhance brain-specific biomarker release into the bloodstream. This study established a tool for FUS-LBx in large animals, which can be translated to the clinic for diagnosing various brain cancers.



CAPTION: A) Contrast-enhanced T1-weighted MR images verified successful BBB opening in a porcine model. B) FUS-LBx enhanced the release of brain-specific biomarkers (GFAP, MBP, S100B) from the brain to the blood.

IMPACT OF DROPLET POLYDISPERISITY IN ULTRASOUND-MEDIATED OXYGEN SCAVENGING

H. Su¹, R. Benton², R. Srivastava³, K.P. Mercado-Shekhar¹, B. Zhang⁴, Kevin Haworth^{1,3}

¹Department of Internal Medicine, University of Cincinnati, Cincinnati, USA

²Neuroscience Baccalaureate Program, University of Cincinnati, Cincinnati, USA

³Medical Sciences Baccalaureate Program, University of Cincinnati, Cincinnati, USA

⁴Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital, Cincinnati, USA

e-mail: hawortkn@ucmail.uc.edu

OBJECTIVES

Microbubbles produced by acoustic droplet vaporization (ADV) can reduce the oxygen partial pressure (PO_2) in a fluid. Size isolation of polydisperse microdroplets for ADV can eliminate large droplets that may embolize within the microvasculature and small droplets that have a lower transition efficiency. The objective of this study was to determine if size isolation affects the droplet transition efficiency and oxygen scavenging.

METHODS

Differential centrifugation was used to size-isolate a 1 to 18 μm polydisperse droplet distribution to a 2 to 6 μm distribution. Droplets were infused at different concentrations through a flow phantom and exposed to ultrasound (5 MHz frequency, 40 cycles, 0.8% duty cycle). The PO_2 was measured before and during ADV, as well as the ADV droplet transition efficiency. A predicted PO_2 was calculated using the average measured transition efficiency.

RESULTS

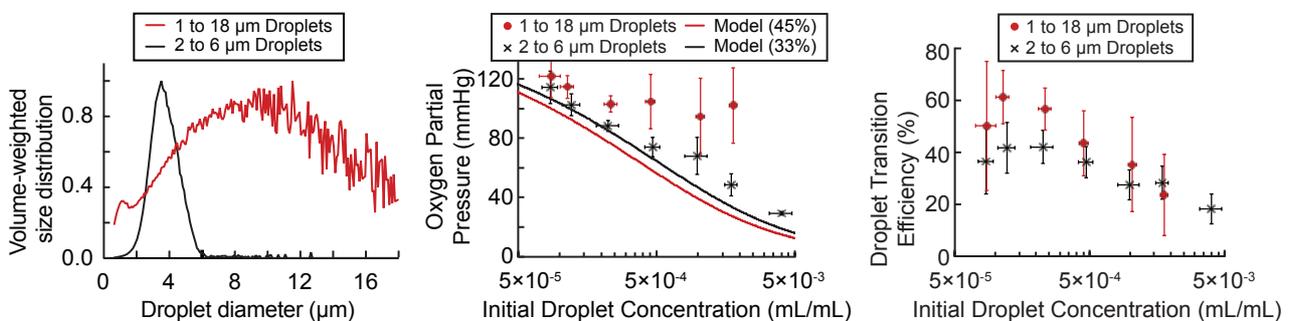
As the droplet concentration increased, less PO_2 reduction was observed with polydisperse droplets compared to size-isolated droplets despite an equal or greater transition efficiency. Better agreement between measured and predicted PO_2 was observed for size-isolated droplets. The variance of the measured PO_2 and ADV transition efficiency were larger for polydisperse droplet populations.

CONCLUSIONS

Size-isolated droplets produced more consistent and a larger magnitude of ultrasound-mediated oxygen scavenging.

ACKNOWLEDGEMENTS

This work was supported in part by USA National Institutes of Health grant K25HL133452.



CAPTION: (Left) Polydisperse (red) and size-isolated (black) droplet distributions. (Center) Measured (data points) and modeled (lines) PO_2 as a function of droplet concentration. (Right) The average ADV transition efficiency is used to compute the modeled PO_2 .

GAS VESICLES: BIOMOLECULAR SEEDS FOR TARGETED INERTIAL CAVITATION AND CELL THERAPY

Avinoam Bar-Zion¹, Atousa Nourmahnad¹, David Mittelstein², Sangjin Yoo¹, Dina Malounda¹, Mohamad Abedi³, Audrey Lee-Gosselin¹, David Maresca¹ and Mikhail G. Shapiro¹

¹ Division of Chemistry and Chemical Engineering, Caltech, Pasadena, CA, USA.

² Division of Engineering and Applied Science, Caltech, Pasadena, CA, USA.

³ Division of Biology and Biological Engineering, Caltech, Pasadena, CA, USA.

e-mails: barz@caltech.edu; mikhail@caltech.edu

OBJECTIVES

Ultrasound-enhanced drug delivery has shown great potential to improve the efficiency of anti-cancer therapeutics. However, it is currently limited by traditional cavitation nuclei, that are mostly intravascular and have short circulation times. To overcome these limitations, we proposed using gas vesicles (GVs), a unique class of stable gas-filled protein nanostructures derived from buoyant microbes, as cavitation nuclei. GV are genetically encoded and can be expressed by engineered cells that home to sites of disease inside the body.

METHODS

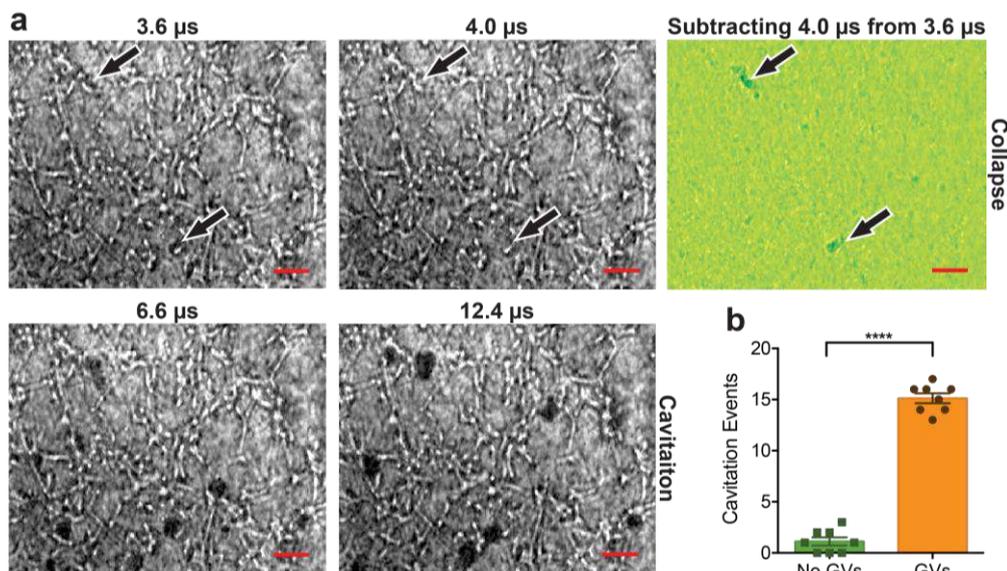
First, we identified ultrasound parameters that lead to GV cavitation using passive cavitation detection and ultrafast optical microscopy. Then, we quantified cavitation-induced lysis of GV-expressing bacteria, and measured ultrasound-triggered luminescent protein release from these cells. Finally, we demonstrated *in vivo* cavitation of purified GV inside hind-limb MC26 tumors.

RESULTS

Inertial cavitation of purified GV was detected at pressure levels higher than 0.2MPa. High frame rate microscopy supported a collapse-induced model for GV cavitation (Fig. 1). Exposing GV expressing cells to HIFU resulted in significant cell lysis (42%, $p=0.001$) and release of Nanoluc into the surrounding medium ($p = 0.001$). Finally, inertial cavitation of GV inside tumors produced significant wideband emissions compared to saline control ($n=4$, $P<0.01$).

CONCLUSIONS

Here, we showed that biomolecules and engineered cells could seed inertial cavitation, opening a range of new possibilities for therapeutic ultrasound and potential combinations with emerging technologies such as cell therapy and immunotherapy.



CAPTION: a. GV attached to u87 tumor cells showing collapse and subsequent cavitation under HIFU exposure. b. Number of cavitation events.



EDUCATION

IMMUNOLOGY:

How did immuno-oncology move from humble origins to become the dominant force in cancer therapy? An overview of progress in cancer immunology - *Elizabeth Repasky*

BIOEFFECTS OF US:

Ultrasound Bioeffects: mechanisms and implications for therapy and safety - *Diane Dalecki*



HOW DID IMMUNO-ONCOLOGY MOVE FROM HUMBLE ORIGINS TO BECOME THE DOMINANT FORCE IN CANCER THERAPY? AN OVERVIEW OF PROGRESS IN CANCER IMMUNOLOGY.

Elizabeth A. Repasky, PhD
Professor of Oncology
Department of Immunology
Program Leader: Cell Stress and Biophysical Therapies Program
Roswell Park Comprehensive Cancer Center
Buffalo, NY 14263 USA
elizabeth.repasky@roswellpark.org

When the first version of the famous “Hallmarks of Cancer” was published, (Hanahan and Weinberg, Cell, 2000) there was no discussion of the ability of tumors to evade immune responses. Nor was there any mention of the importance of the “immune contexture” of the tumor microenvironment in predicting success of immune- and other therapies, for patients with cancer. How things have changed! Today, the ability of immunotherapies to improve outcomes for thousands of patients each year provides great hope to the cancer research community. At the same time, many more patients still do not benefit from this “revolution” in cancer therapy development, providing great stimulus for new therapeutic strategies.

This presentation will provide a succinct set of information defining many of the immune cells that are now known to play critical roles in the development of effective anti-tumor immunity. These include: CD8⁺ and CD4⁺ T cells and their activation, antigen presenting cells and natural killer (NK) cells, as well as cells which are known to suppress the anti-tumor immune response such as myeloid derived suppressor cells (MDSCs). I will also highlight anatomical features, such as the importance of draining lymph nodes which collect material shed from tumors, and the various histological features of the tumor microenvironment which can provide barriers to immune cells. I will also summarize features which define the success of the “checkpoint inhibitor” immunotherapies.

This brief overview will also include selected publications which dramatically increased recognition of a major role for anti-tumor immunity in achieving improved responses to radiation and chemotherapy. Now we are witnessing combinations with ultrasound which suggest that therapeutic ultrasound could be a very useful combination with immunotherapy. This presentation will conclude with identifying some major gaps in the field which should be addressed to optimize combinations of immunotherapy with ultrasound and other biophysical therapies.

ULTRASOUND BIOEFFECTS: MECHANISMS AND IMPLICATIONS FOR THERAPY AND SAFETY

Diane Dalecki, Ph.D.

Department of Biomedical Engineering, University of Rochester, Rochester, NY 14627

e-mail: dalecki@bme.rochester.edu

Ultrasound provides unique avenues for a wide range of biomedical therapies. Many therapeutic applications rely on the ability of ultrasound to focus within tissues and produce a biological effect noninvasively and site specifically. Ultrasound fields can interact with biological tissues and systems through thermal and/or mechanical mechanisms. This presentation will provide an overview of the fundamentals of key acoustic mechanisms for the interaction of ultrasound with biological tissues. These acoustic mechanisms include ultrasound-induced heating, acoustic cavitation, and acoustic radiation force. Creative design of safe, new therapeutic applications of ultrasound relies on harnessing these acoustic mechanisms to produce desired therapeutic effects in tissues. Thermal and mechanical mechanisms can act in combination, and the effects may be either synergistic or confounding. Several categories of biological effects will be reviewed to provide insight on the range of ultrasound bioeffects, underlying acoustic mechanisms, and the relevance to therapeutic ultrasound and safety.



HORIZON / JOLESZ LECTURES

INVITED TALKS:

The Journey of MRI Guided Interventions and FUS - *Morry Blumenfeld*



The Journey of MRI Guided Interventions and FUS Morry Blumenfeld

The history of MRI Guided Interventions and the collaboration between Morry Blumenfeld at GE Medical Systems and Ferenc Jolesz at the Brigham and Women's Hospital began in the late 1980's. Professor Jolesz, who initially trained in Biomedical Engineering and Computer Sciences and then as a Neurosurgeon in Budapest and was the Director of the Division of Magnetic Resonance Imaging at The Brigham and Women's Hospital, was increasingly frustrated at the lack of use of image guidance to direct surgery. At the same time, Morry Blumenfeld was asked, after 8 years in developing MRI, to look for the "next big thing". It was clear to both of them that the key was to use MR imaging to plan, guide, monitor and control therapy, because MR provides superior image guidance for surgical interventions as well as being able to monitor what you are doing while you are doing it. This led to the development of an open MR system, the "Double Donut" and then to the use of MR guided focused ultrasound as the interventional technology. This talk is dedicated to the memory of Professor Ferenc Jolesz.



DRUG DELIVERY

INVITED TALKS:

Mechanisms underlying sonoporation: How do microbubbles interact with cells? - *Juan Tu*

MR-HIFU and drug delivery - *Brad Wood*

ORAL PRESENTATIONS:

Clinical translation of ultrasound-guided cavitation-enhanced drug delivery: challenges and results in large animal models with a novel handheld array and gas-stabilizing nanoparticles - *Calum Crake*

Enhancement of drug delivery to tumor tissue by the combination of new lipid bubbles and ultrasound - *Kazuo Maruyama*

Focused Ultrasound mediated Blood-Spinal Cord Barrier Opening (BSCO) using short burst, phase keying exposures - *Stecia-Marie Fletcher*

Inertial cavitation activity induced by nonlinear HIFU waves: implications for drug delivery - *Tatiana Khokhlova*

Localized drug delivery by MR-guided focused ultrasound with low temperature sensitive liposomes - *Chulyong Kim*

Targeted chemo-sonodynamic therapy of breast cancer using ultrasound responsive microbubbles as delivery vehicle - *Dean Nicholas*

Microbubble-mediated intracellular drug delivery for recurrent urine infections - *Eleanor Stride*



Mechanisms underlying sonoporation: How do microbubbles interact with cells?

J. Tu¹

¹Key Laboratory of Modern Acoustics (MOE), School of Physics, Nanjing University, Nanjing 210093, China

E-mail: juantu@nju.edu.cn

OBJECTIVES

The past several decades have witness great progress in “smart drug delivery”, an advance technology that can delivery gene or drugs into specific locations of patients’ body with enhanced delivery efficiency. Ultrasound-activated mechanical force induced by the interactions between microbubbles and cells, which can stimulate so-called “sonoporation” process, has been regarded as one of the most promising candidates to realize spatiotemporal-controllable drug delivery to selected regions.

METHODS

Both experimental and numerical studies were performed to get in-depth understanding on how the microbubbles interact with cells during sonoporation processes, under different impact parameters.

RESULTS

At low acoustic pressures, microbubbles undergo symmetrical linear oscillations. At slightly higher ultrasound pressures, repeated small-amplitude asymmetric oscillations can be observed for stable cavitation microbubbles, which can stimulate cellular massage to disturb the membrane integrity. Violent microbubble collapse and fragmentation (inertial cavitation), are excited by ultrasound exposures at even higher driving pressures (e.g., greater than several hundred kPa). If inertial cavitation microbubble sits close to the cell membrane, strong shock wave and/or liquid jet can be formed towards nearby surface due to the asymmetrical microbubble implosion, which can puncture the cell surface to cause membrane perforation and cytoskeleton rupture, and even disrupt the endothelial membrane of blood vessels.

CONCLUSIONS

Sonoporation outcomes could be significantly affected by acoustic driving parameters, microbubble-to-cell relative parameters, as well as cellular structures (e.g., cytoskeleton).

ACKNOWLEDGEMENTS

Supported by the Ministry of Science and Technology Key Research and Development Plan of China (No. 2018YFC0115900) and the National Natural Science Foundation of China (No.11774168).

CLINICAL TRANSLATION OF ULTRASOUND-GUIDED CAVITATION-ENHANCED DRUG DELIVERY: CHALLENGES AND RESULTS IN LARGE ANIMAL MODELS WITH A NOVEL HANDHELD ARRAY AND GAS-STABILIZING NANOPARTICLES

C. Crake¹, F. Monnier¹, M. Jackson¹, C. Rowe¹, R. Carlisle^{1,2}, C.C. Coussios^{1,2}, C.M. Coviello¹

¹OxSonics Therapeutics, The Magdalen Centre, Robert Robinson Avenue, Oxford, OX4 4GA, UK

²University of Oxford, Oxford, UK

e-mail: calum.crake@oxsonics.com

OBJECTIVES

Ultrasound-mediated cavitation has been shown to improve delivery of a range of therapeutics including drugs, viruses and immunotherapeutics which could enhance efficacy and reduce toxicity for cancer treatment. However, the majority of pre-clinical studies have used either laboratory equipment such as single-element transducers in water baths or expensive immobile systems such as MRI, which precludes widespread clinical adoption. Our aim is to develop an ultrasound-guided platform to enhance drug delivery with the ease of use of conventional sonography, to facilitate routine treatment of organs such as liver and pancreas in an outpatient clinical setting.

METHODS

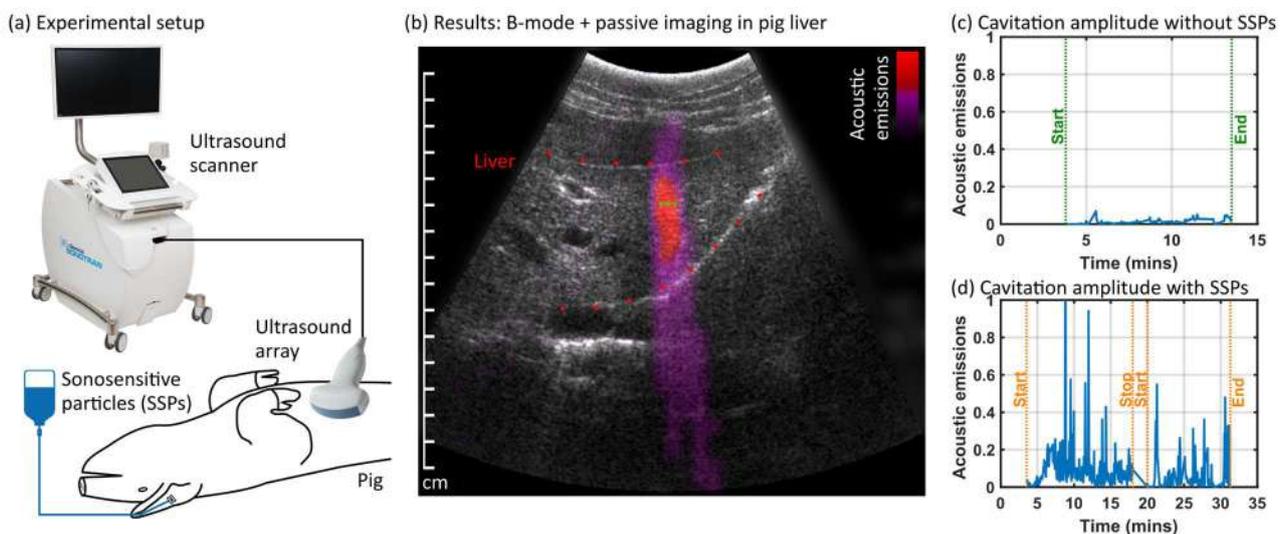
A novel array incorporating low-frequency therapy and high-frequency imaging functionality into a standard handheld form-factor was developed. Multi-channel signal-processing hardware was produced to allow therapy delivery and passive acoustic mapping (PAM) alongside conventional b-mode. Imaging was evaluated using QA phantoms (CIRS); therapeutic excitation and mapping were tested with hydrophones (Onda), agar phantoms and flow models. *In vivo* functionality was assessed in porcine liver. Pigs (n=3, 55-65 kg) were anaesthetized and treatment regions selected under b-mode. Therapeutic excitation was delivered alongside b-mode and PAM with and without infusion of gas-stabilizing sonosensitive particles (SSPs) to induce cavitation.

RESULTS

Cavitation could be induced and mapped in real-time in porcine liver, and increased by an order of magnitude using SSPs. Signal processing was optimized to improve mapping quality *in vivo*.

CONCLUSIONS

An ultrasound-guided platform for cavitation-enhanced delivery was demonstrated in a large animal model. Future work will investigate delivery in a transgenic porcine model.



CAPTION: Experimental setup; images showing cavitation in pig liver

ENHANCEMENT OF DRUG DELIVERY TO TUMOR TISSUE BY THE COMBINATION OF NEW LIPID BUBBLES AND ULTRASOUND

K. Maruyama¹, D. Omata¹, T. Osaki², R. Suzuki¹

¹Faculty of Pharma-Sciences, Teikyo University, Tokyo, Japan

²Faculty of Agriculture, Tottori University, Tottori, Japan

e-mail: maruyama@pharm.teikyo-u.ac.jp

OBJECTIVES

We have developed a new lipid bubble (LB) suitable for sonoporation. For good storage stability and ease of handling, lipid bubbles were made into freeze-dried formulations. Here we investigate neovascular imaging and enhancement of drug delivery by combination of LB and ultrasound and describe a new drug delivery technology.

METHODS

New Lipid Bubble: Lipid-stabilized bubbles were prepared by homogenization of a lipid dispersion in the presence of perfluoropropane (PFP) gas. Different phospholipid compositions were tested and evaluated. Lyophilized preparation of LB in the presence of sucrose was examined.

Animal experiments: DOXIL[®] (liposomal DOX, 100 nm in size) and LB were co-administered to thyroid cancer dog and ultrasound treatment (power, 2W/cm²; frequency, 1 MHz) was done four times.

RESULTS

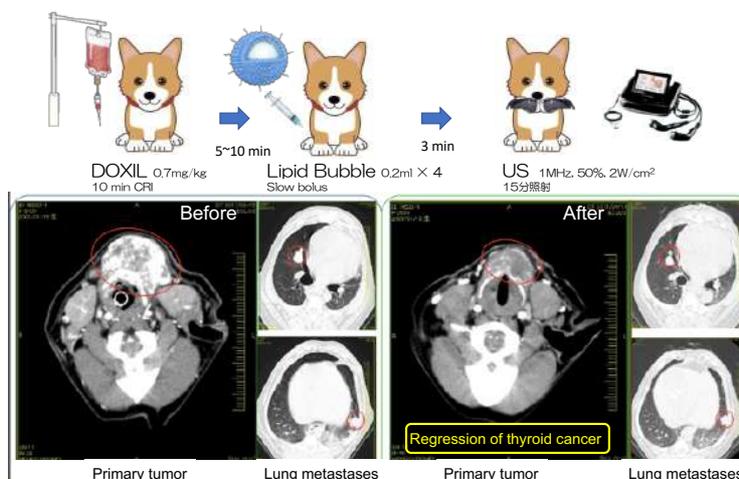
New LB could effectively be preserved by freeze-drying and then re-constituted by addition of water. Average bubble sizes were around 2 μm for all bubbles after re-constitution. The US theranostics capabilities of LB for the solid tumor were studied in osteosarcoma-bearing mice. LB was injected to mice via tail vein and linear imaging US was exposed to solid tumor site transdermally. The flow of LB in blood was observed and neovasculature of tumor tissue was imaged clearly.

A thyroid cancer dog was administered DOXIL[®] and LB and ultrasonic treatment was performed four times. This cancer is a good experiment for proof of concept because it is close to human cancer from the viewpoint of spontaneous onset. From the CT image,

the primary tumor volume was clearly reduced. In contrast, because lung metastases were not irradiated with ultrasound, no reduction was observed. From these results, it was considered that DOXIL[®] was efficiently delivered to the tumor tissue from the blood circulation by LB and ultrasound.

CONCLUSIONS

New LB with 1-3μm in size was stable *in vivo* for long time. New LB was freeze-dried and then kept in PFP atmosphere until use. Oscillation and cavitation of LB induced by therapeutic US exposure showed transiently open the neovasculature of tumor tissue and allowing DOXIL[®] co-injected with LB was delivered into deep area in the tumor tissue. This new approach by the combination of LB and US could delivery medicines and gene into tumor tissue and work better.



Antitumor effect of DOXIL+LB+UDS in thyroid cancer dog

There is no reduction in cancers in lungs not irradiated with therapeutic ultrasound

FOCUSED ULTRASOUND MEDIATED BLOOD-SPINAL CORD BARRIER OPENING (BSCBO) USING SHORT BURST, PHASE KEYING EXPOSURES

S.P. Fletcher^{1,2}, M.A. O'Reilly^{1,2}

¹Physical Sciences Platform, Sunnybrook Research Institute, Toronto, Ontario, Canada

²Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

e-mail: steciamarie.fletcher@mail.utoronto.ca, moreilly@sri.utoronto.ca

OBJECTIVES

We previously developed short burst, phase keying (SBPK) focused ultrasound (FUS) to mitigate standing waves in the human vertebral canal. Here we investigate microbubble (MB) emissions under SBPK FUS and test these exposures for BSCBO in rats.

METHODS

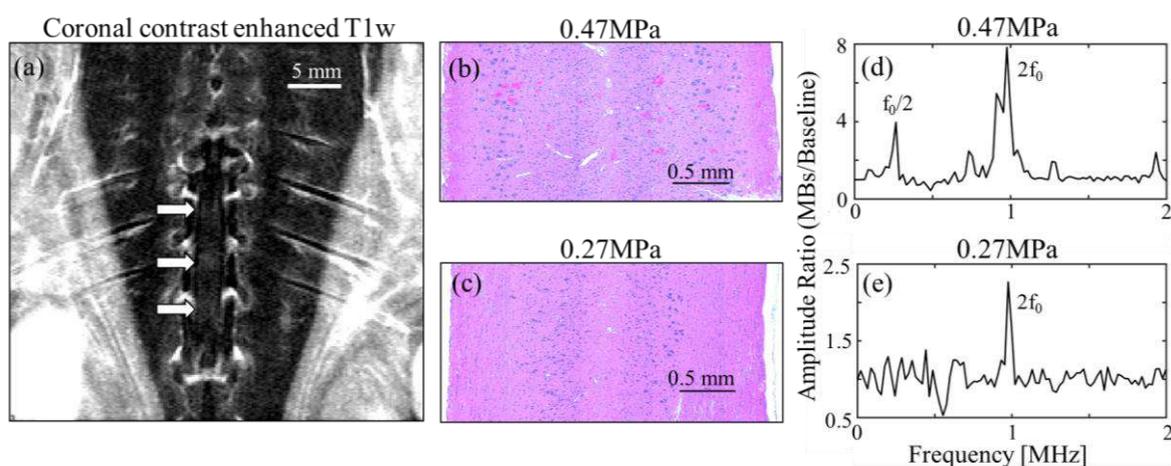
On the bench, circulating MBs were sonicated through *ex vivo* human vertebrae (60kPa-1MPa) using SBPK pulse trains from confocal transducers ($f_0=514\text{kHz}$; aperture=5cm; FN=1.2). Frequency spectra of received signals (250kHz receiver) were calculated using the maximum projection of short time windows. Pulse inversion (PI) was leveraged to improve detection of transvertebral emissions. In rats ($n=7$), SBPK FUS+MBs (0.02ml/kg Definity; 10ms pulse trains; 1Hz PRF; 2min duration) was applied to 3 locations/spinal cord at fixed pressures ($\sim 0.27\text{-}0.47\text{MPa}$ *in situ*). MRI and histology were used to assess BSCBO and tissue damage.

RESULTS

PI suppressed f_0 , and increased $f_0/2$ and $2f_0$ sensitivity up to 360%. *In vivo*, BSCBO was achieved at 19/21 locations, with mean enhancement $51\pm 45\%$ (15%-182%). Using PI, $f_0/2$ was detected at 12/19 BSCBO locations. At the highest pressures ($f_0/2$ present) histology showed widespread red blood cell (RBC) extravasation throughout the focus. At the lowest pressures, BSCBO was achieved without RBC extravasation.

CONCLUSIONS

SBPK exposures successfully modified the BSCB. $2f_0$ MB emission indicated successful opening, while $f_0/2$ emission indicated widespread bleeding, consistent with existing reports using longer bursts. Further *in vivo* studies investigating a broader set of parameters, are needed to optimize SBPK exposures for BSCBO.



CAPTION: (a) MRI image showing BSCBO (arrows). Representative histology (H&E) images showing widespread (b) and no (c) RBC extravasation. (d)-(e) Corresponding frequency spectra.

INERTIAL CAVITATION ACTIVITY INDUCED BY NONLINEAR HIFU WAVES: IMPLICATIONS FOR DRUG DELIVERY

T.D. Khokhlova¹, C.R. Bawiec¹, C. Hunter², W. Kreider², A.D. Maxwell³, V.A. Khokhlova², and O.A Sapozhnikov²

¹Division of Gastroenterology, University of Washington School of Medicine, Seattle, USA

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Department of Urology, University of Washington School of Medicine, Seattle, USA

e-mail: tdk7@uw.edu

OBJECTIVE

Inertial cavitation induced by pulsed HIFU in tumors has been shown to successfully permeabilize tumor tissue and enhance chemotherapeutic drug uptake. In addition to HIFU frequency and peak rarefactional pressure (p^-), the threshold for cavitation-induced bioeffects has recently been correlated with the formation of shocks at the focus. Here, the sensitivity of inertial cavitation behaviors to shock formation was investigated in transparent gel phantoms.

METHODS

Multiple transducers were characterized and used to generate a range of HIFU exposures in agarose gel phantoms using 1 ms pulses delivered every second with p^- from 1-15 MPa. Transducers had the same aperture but different F -numbers (0.77, 1.02, and 1.52) and frequencies (1, 1.5, and 1.9 MHz); a 280 kHz transducer (F -number=1) was also utilized. Coaxial passive cavitation detection (PCD) and high-speed photography were used to characterize bubble activity.

RESULTS

Four distinct behaviors were observed on high-speed photography as the acoustic power increased: isolated, stationary bubbles (a); isolated, slowly moving bubbles (b); sparse bubble clouds that grow slowly towards the transducer (c); and dense bubble clouds (d). Notably, the bubble clouds were only observed under shock-forming conditions regardless of frequency. Different behaviors corresponded to specific spectral characteristics of the PCD signals.

CONCLUSIONS

These studies provide direct evidence that inertial cavitation behaviors are qualitatively different when highly nonlinear or shocked HIFU waves are used. The formation of sparse bubble clouds is consistent with previously observed tissue permeabilization in pulsed HIFU exposures for drug delivery. Work supported by NIH R01EB023910, K01DK104854, and R01EB007643.

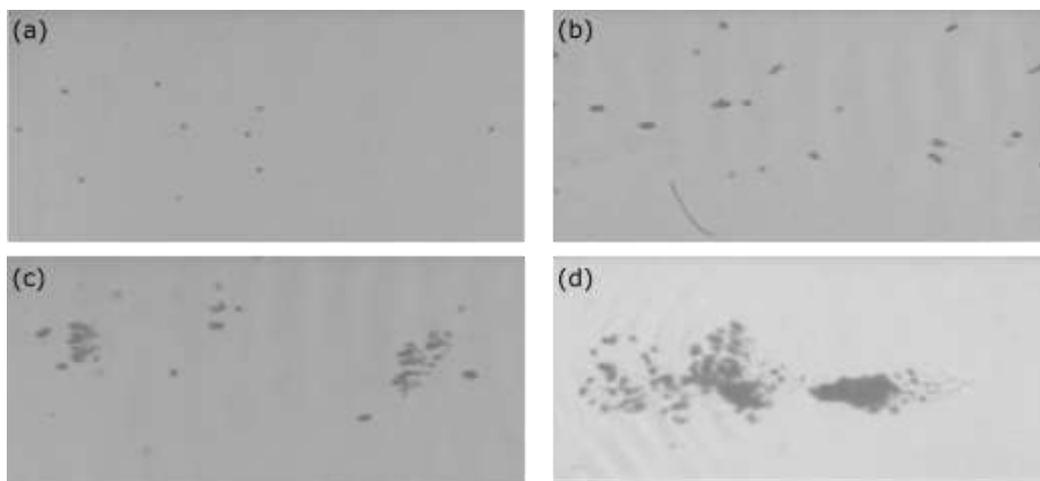


FIGURE: Representative high-speed photographs of the four types of inertial cavitation behavior.

LOCALIZED DRUG DELIVERY BY MR-GUIDED FOCUSED ULTRASOUND WITH LOW TEMPERATURE-SENSITIVE LIPOSOMES

Chulyong Kim¹, Anastasia Velalopoulou¹, Johannes Leisen³, Anjan Motamarry⁴, Dieter Haemmerich⁴, and Costas D. Arvanitis^{1,2}

¹Department of Mechanical Engineering, Georgia Institute of Technology, Atlanta, Georgia, USA

²Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia, USA

³Department of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia, USA

⁴Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina, USA

e-mail: costas.arvanitis@gatech.edu; ck379@gatech.edu

OBJECTIVES

Recent clinical studies have demonstrated the potential for chemotherapy to increase survival in patients with glioblastomas (GBM), suggesting that strategies that can effectively deliver drugs to GBMs and reduce the systemic dose can be beneficial. In this study, we examine the abilities of MR-guided focused ultrasound (MRgFUS) to perform controlled release of doxorubicin encapsulated by low temperature-sensitive liposomes (LTSL-Dox) in glioblastoma mouse brain tumors.

METHODS

We injected GL261 glioma cells in C57BL/6 mice brains. After 14 days we assigned the animals to the following groups (n=4/group): 1)Control(no-drug), 2)TSL-Dox, 3)LTSL-Dox+FUS@41.5°C, 4)LTSL-Dox+FUS@42.5°C. Using an MR Thermometry based closed-loop controller ("on-off" controller), we performed transcranial hyperthermia treatments for 10 min (41.5 or 42.5°C) with concurrent intravenous administration of 150 µg of LTSL-Dox. 45 mins post treatment we sacrificed the animals, sectioned their brain, and examined it under fluorescent microscopy. Prior to the experiments, we optimized the FUS system (1.74-MHz, f-number 0.75) for maximum focal heat deposition using mathematical modeling.

RESULTS

The experimentally determined controller temperature profiles were in agreement with numerical simulations and for the two treatment groups were (Mean±StDev) 41.5±0.3°C (group 3) and 42.2±0.3°C (group 4). Fluorescence microscopy of the extracted tissue samples showed significantly larger doxorubicin uptake in LTSL-Dox+FUS groups (group 1 vs 3: p=0.001, 2 vs 3: p=0.1919, 1 vs 4: p<0.0001, 2 vs 4: p=0.0074).

CONCLUSIONS

Our results demonstrate that localized MR guided FUS-induced hyperthermia applied transcranially can trigger the release of doxorubicin from LTSL-Dox in mice brain tumors. Further investigations assessing the therapeutic efficacy of the treatment are warranted.

TARGETED CHEMO-SONODYNAMIC THERAPY OF BREAST CANCER USING ULTRASOUND RESPONSIVE MICROBUBBLES AS DELIVERY VEHICLE.

H. Nesbitt¹, K. Logan¹, S. Kamila¹, M. Rea¹, F. Foglietta¹, A.P. McHale and J.F. Callan¹

¹School of Pharmacy and Pharmaceutical Sciences, Ulster University, Northern Ireland, UK.

e-mail: h.nesbitt@ulster.ac.uk

OBJECTIVES

Our technology involves ultrasound-responsive drug-loaded microbubbles (MB) for targeted chemotherapy delivery to the tumour and reduced off-target side effects.

METHODS

Phospholipid stabilised oxygen carrying MBs were prepared and loaded with paclitaxel (PTX) in the hydrophobic region of the shell and either Doxorubicin (Dox) or the sonosensitiser Rose Bengal (RB) attached to the surface (Figure 1a-b). The efficacy (O₂MB-PTX-DOX and O₂MB-PTX-RB) was determined in MCF-7 tumour bearing mice following IV administration of the mixed MB suspension in the absence and presence of low-intensity ultrasound positioned at the tumour.

RESULTS

Figure 1c reveals a 11% reduction in tumour volume for animals treated with O₂MB-PTX-DOX / O₂MB-PTX-RB +US at 25 days compared to pre-treatment size. The combined treatment was significantly better than the free drugs (Free PTX/Dox).

CONCLUSIONS

Chemo-sonodynamic therapy using oxygen carrying MBs to deliver the drug payloads has significant potential as an efficacious and targeted treatment for breast cancer.

ACKNOWLEDGEMENTS

JFC thanks Norbrook Laboratories Ltd for an endowed chair.

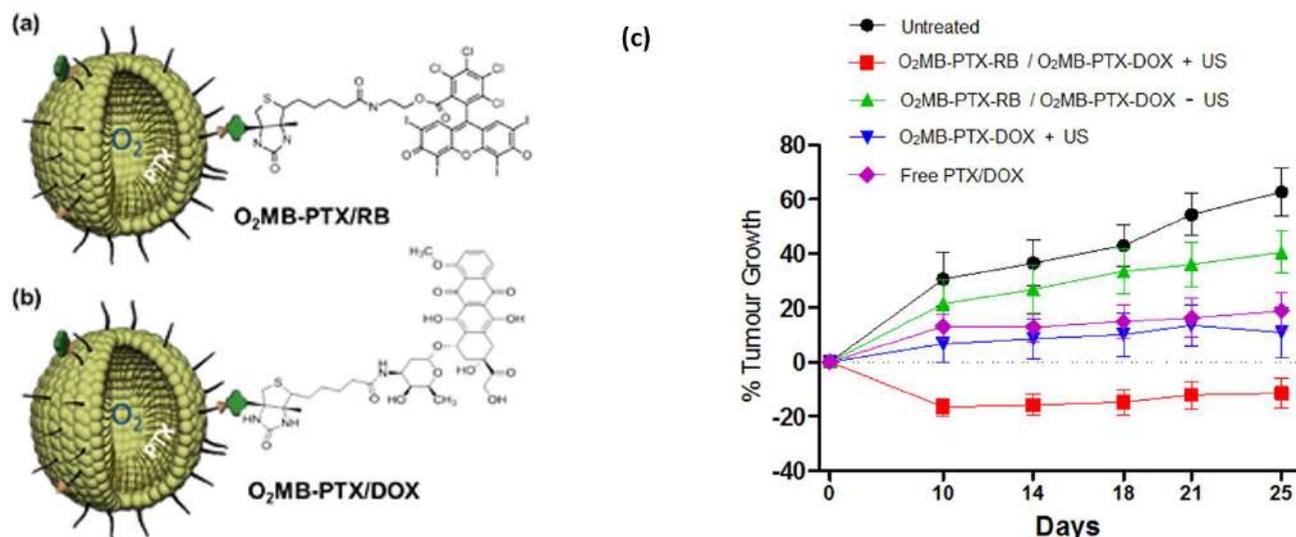


FIGURE 1: (a) O₂MB-PTX/RB and (b) O₂MB-PTX/DOX. (c) Tumour growth delay plot in a MCF-7 Xenograft model following (i) no treatment (ii) a mixed suspension of O₂MB-PTX/RB and O₂MB-PTX/DOX + US (iii) as for (ii) but -US treatment (iv) O₂MB-PTX/DOX +US and (v) free PTX and DOX.

MICROBUBBLE-MEDIATED INTRACELLULAR DRUG DELIVERY FOR RECURRENT URINE INFECTIONS

H. Horsley¹, J. Owen², D. Carugo³, J. Malone-Lee¹, E. Stride², J.L. Rohn¹

¹ Department of Renal Medicine, Division of Medicine, University College London, UK

² Institute of Biomedical Engineering, University of Oxford, UK

³ Faculty of Engineering and Physical Sciences, University of Southampton, UK

email:eleanor.stride@eng.ox.ac.uk; j.rohn@ucl.ac.uk

OBJECTIVES

To determine whether ultrasound-driven microbubbles could increase the intracellular concentration of an antibiotic in infected apical cells and hence be used to treat recurrent urinary tract infections caused by cell-internalised bacteria.

METHODS

Human urothelial organoids were infected with patient-isolated *Enterococcus faecalis* before being treated with the cell impermeant antibiotic gentamicin in one of 3 forms: solution of free drug, encapsulated in liposomes, or in liposomes bound to the surface of phospholipid microbubbles. The organoids were exposed to ultrasound (1.1 MHz, 2.5 MPa, 5,500 cycles at 5 Hz pulse repetition frequency) or sham treatment in an optically and acoustically transparent chamber for 20 seconds. Intracellular drug concentrations were measured using confocal microscopy. Bacterial load was determined by direct counting from the confocal images and by lysing the urothelial cells to release intracellular bacteria, which were then cultured on agar and the number of colony-forming units counted at 24h.

RESULTS

The combination of microbubbles and ultrasound produced significantly higher intracellular concentrations of gentamicin than either free drug or drug-loaded liposomes. This was mirrored by a significant reduction in the number of bacteria per cell (Figure 1). No cell damage was observed.

CONCLUSIONS

The results indicate that microbubbles can safely deliver high concentrations of antibiotics into apical cells under non-ablative ultrasound exposure conditions. This approach could be exploited for the treatment of recurrent infections, such as those of the urinary tract.

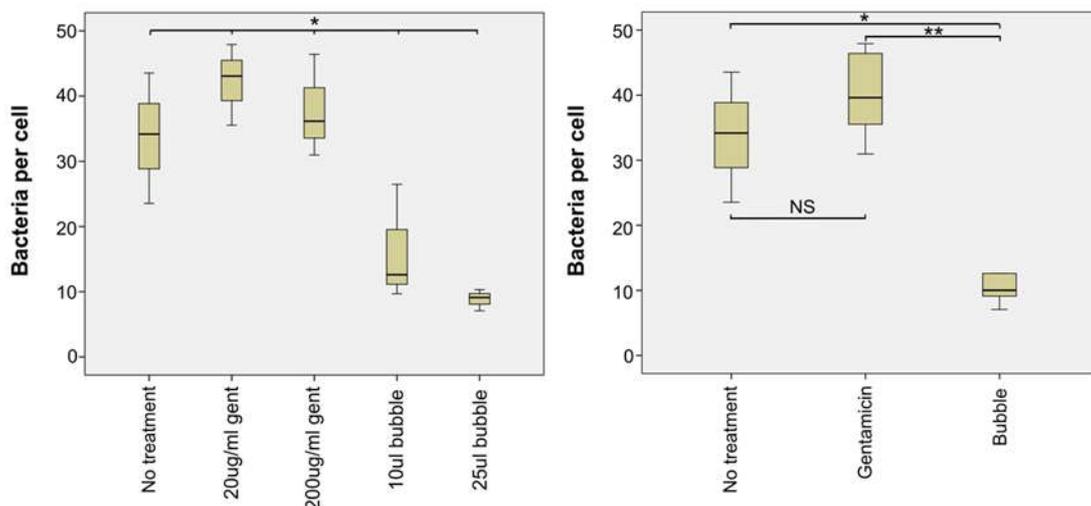


FIGURE 1: Antibiotic-loaded microbubbles were found to be more effective than free drug or drug-loaded liposomes at eliminating intracellular bacteria



IMMUNOTHERAPY

INVITED TALKS:

Why therapeutic ultrasound could be an outstanding choice for combination with immunotherapy: what are the barriers to success? - *Elizabeth Repasky*

In situ tumor vaccines - *Chandan Guha*

ORAL PRESENTATIONS:

A preclinical study of the combined effects of pulsed focused ultrasound and immune checkpoint inhibitors in pancreatic cancer - *Petros Mouratidis*

Can focused ultrasound modulate and repolarized myeloid cells in metastatic breast cancer? - *Natasha Sheybani*

Immune cell modulation of pulsed focused ultrasound in murine melanoma and breast cancer models - *Joseph Frank*

Transcriptomic profiling of thermally ablated b16f10 tumors reveals temporal variability in immunogenicity - *Alexander Mathew*

Blood brain/tumor barrier disruption with MR image-guided FUS elicits marked shifts in tumor-immune profile in murine glioblastoma - *Natasha Sheybani*

Histotripsy induced immunomodulation - *Ryan Hubbard*

Investigation of the local and systemic immune response to histotripsy ablation of breast cancer in a mouse model - *Alissa Hendricks*



**Why therapeutic ultrasound could be an outstanding choice for combination with immunotherapy:
what are the barriers to success?**

E. A. Repasky, Department of Immunology, Roswell Park Comprehensive Cancer Center
Elm/Carlton Sts., Buffalo NY, 14221 USA. e-mail: elizabeth.repasky@roswellpark.org

Several aspects of therapeutic ultrasound technology and its effects on tissues strongly suggest that it could be successfully combined with immunotherapy to enhance local and systemic anti-tumor immunity. This short presentation will highlight the problematic aspects of the “cancer-immunity cycle” that must be solved in order to achieve improved baseline anti-tumor immunity and more successful outcomes from immunotherapy. Excitingly, there is evidence from recent literature in the field of therapeutic ultrasound that it could help overcome these barriers, and improve anti-tumor immunity at both at the local and systemic levels. Several of these publications will be highlighted as an INTRODUCTION to this session.

IN SITU TUMOR VACCINES

C. Guha¹

¹Departments of Radiation Oncology, Pathology and Urology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY-10461, USA

e-mail: CGUHA@montefiore.org

The goal of our research is to combine adaptive, energy-based, focal therapies, such as, radiation therapy (RT) and therapeutic ultrasound, with targeted agents and immunotherapeutics for engineering tumor microenvironment to drive systemic anti-cancer immunity. Evidence from multiple groups suggesting that local application of RT in combination with immuno-therapeutics has the potential to produce sustained remission in murine and human models of solid tumors through the activation of the immune system. We will discuss the mechanism of action with respect to radiation-enhanced antigen presentation (REAP) and tumor microenvironment modulation. A rationale for generating *in situ* tumor vaccines using a combination of focal therapies and immunotherapy along with a roadmap for designing combination clinical trials will be discussed.

A PRECLINICAL STUDY OF THE COMBINED EFFECTS OF PULSED FOCUSED ULTRASOUND AND IMMUNE CHECKPOINT INHIBITORS IN PANCREATIC CANCER

Petros Mouratidis¹, Gail ter Haar¹

¹Joint Department of Physics, The Institute of Cancer Research: Royal Marsden Hospital, London, UK

Email: petros.mouratidis@icr.ac.uk

OBJECTIVES

No clinical benefit of immunotherapy has yet been realized in pancreatic cancer. Focused ultrasound (FUS) can be used in the treatment of solid tumours, either by inducing necrosis (using ablative temperatures), or by creating cavitation. Both of these processes may make the tumours more susceptible to immunotherapeutic treatments. In this study, pancreatic tumours have been exposed to pulsed FUS and co-treated with immune checkpoint inhibitors (ICI) to explore whether therapeutic benefit can be achieved.

METHODS

Orthotopic KPC pancreatic tumours were grown in immune-competent murine C57BL/6 subjects. Tumours were exposed to pulsed FUS using the small animal Alpinion VIFU 2000 platform. Pulsed FUS exposure parameters were designed to result in cavitation (monitored using a PCD) in the target tissue (power = 200 W, duty cycle = 1 %, pulse repetition frequency = 1 Hz, 25 repeats). A combination of anti-CTLA4 and anti-PD-1 antibodies were administered intraperitoneally 3 days before treatment, and every 3 days thereafter. Tumour growth was estimated using ultrasound imaging, and with calipers at the time of culling.

RESULTS

Pulsed FUS exposure of pancreatic tumours resulted in the induction of cavitation in all treated subjects. No skin damage was observed. Combination of a single pulsed FUS exposure with administration of ICIs extended the survival of subjects relative to non-treated animals. Additional results for the systemic and localised abundance of immune cells will be presented.

CONCLUSIONS

This study provides the first evidence that focused ultrasound has the potential to be combined with immunotherapy to provide therapeutic benefit in pancreatic cancer.

Can focused ultrasound modulate and repolarize myeloid cells in metastatic breast cancer?

Natasha Sheybani¹, Alexandra Witter², Cyril Lafon^{3,4,5}, Frederic Padilla^{3,4,5}, Richard Price¹, Timothy Bullock².

¹ University of Virginia School of Medicine Department of Biomedical Engineering

² University of Virginia School of Medicine Department of Pathology

³ LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ-Lyon, F-69003, LYON, France

⁴ Focused Ultrasound Foundation, Charlottesville, VA, USA

⁵ Department of Radiation Oncology, University of Virginia School of Medicine, Charlottesville, VA, USA

OBJECTIVES

Myeloid cells serve as key players in the effective mounting of immune response against tumors. We evaluate whether Focused Ultrasound (FUS) can impact the representation and polarization of myeloid cells in a murine model of metastatic breast cancer - 4T1 mammary carcinoma - characterized by a highly immunosuppressive microenvironment.

METHODS

Mice bearing subcutaneous 4T1 tumors were exposed to one of three different ultrasound exposure conditions targeting ~50% tumor volume: boiling histotripsy, thermal ablation, or microbubble destruction, and in a separate round of experiments to single fraction radiation therapy. Seven days following treatment, animals were sacrificed and tumors, secondary lymphoid organs, and blood were harvested for analysis by flow cytometry to quantify myeloid and T cell subsets.

RESULTS

Marked trends could be observed among all the conditions and tissues tested. Most notably, thermal ablation and radiation induced an increase in the proportion of MDSCs among the immune cells in tumors.

CONCLUSIONS

The data demonstrate a relatively weak impact of the FUS monotherapy on the myeloid compartment in 4T1 tumors, irrespective of regimen – with the exception of thermal ablation impacting MDSCs. While the activation status and function of these MDSCs remains to be investigated, the results suggest that FUS alone may not mitigate or reverse myeloid cell polarization, thereby limiting the efficacy of any combination of FUS with immunotherapy in tumor characterized by a strong imbalance in favor of immunosuppression over immune response. In such instances, additional targeted adjuvant therapies such as a chemotherapy, may be required to mitigate this immunosuppressive environment.

ACKNOWLEDGEMENTS

Supported by the Focused Ultrasound Foundation.

IMMUNE CELL MODULATION OF PULSED FOCUSED ULTRASOUND IN MURINE MELANOMA AND BREAST CANCER MODELS

P. Chandran, G. Cohen, R. Lorsung, S.R. Burks, J.A. Frank

Frank Laboratory, Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD 20892, United States

e-mail: jfrank@cc.nih.gov

OBJECTIVES

This study evaluated the temporal changes following non-ablative pulsed focused ultrasound (pFUS) on tumor microenvironment (TME) immune cell profiles in spleen (Sp), lymph nodes (LN), and tumors (B16 melanoma and 4T1 mammary carcinoma).

METHODS

Murine B16 and 4T1 cells were subcutaneously, bilaterally implanted into C57BL/6J and BALB/c mice (n=10 tumors/time-point), respectively. pFUS (1 MHz, PRF 10Hz, DC 10%, US Burst 10ms, PNP 6MPa) was administered to 5 mm tumors. At days 1, 3, and 5 post-sonication, Sp, LN and tumors were harvested, fixed and processed for flow cytometry (FACS) analysis of immune cell populations [cytotoxic (T_{cyt}), helper (T_{h}), and regulatory T-cells (T_{reg}), natural killer (NK), dendritic cells (DC), F4/80⁺ macrophages (M1 and M2), myeloid-derived suppressor cells (MDSC)].

RESULTS

B16 mice at days 1, 3 and 5 post-sonication revealed a 3-4 fold increase in T_{cyt} , T_{h} , NK and M1 macrophage activity in tumor, which peaked at day 3, and decreased by day 5, compared to control tumors. At day 5, a shift of cell populations toward LN, with increased T_{reg} , T_{cyt} , NK, F4/80, M1 and M2 activity was observed. 4T1 mice showed high levels of T_{cyt} in Sp on day 1, and NK cells on day 3 in LN. Interestingly, these cell populations decreased in Sp and LN by day 5, with 3-4 fold increase in 4T1 tumors, along with increasing macrophage and DC activity.

CONCLUSIONS

The results suggest that pFUS induced anti-tumor responses by activating both innate and adaptive immunity, shifting an anti-inflammatory, immunosuppressive TME towards a pro-inflammatory, anti-tumor TME.

TRANSCRIPTOMIC PROFILING OF THERMALLY ABLATED B16F10 TUMORS REVEALS TEMPORAL VARIABILITY IN IMMUNOGENICITY

A.S. Mathew¹, T.J. Bullock², R.J. Price¹

¹Department of Biomedical Engineering, University of Virginia, Charlottesville, USA

²Department of Pathology, University of Virginia, Charlottesville, USA

e-mail: asm6gy@virginia.edu

OBJECTIVE

To comprehensively delineate the enrichment of inflammatory pathways through time after FUS ablation using RNA sequencing.

METHODS

B16F10 murine flank tumors were treated with thermally ablative sparse-scan FUS (3.3 MHz; 12 W power; 10s sonications; 75°C focal temperature; 2 mm sonication spacing). RNA-sequencing was performed on sham and treated tumors 8, 24, 72, and 168 h post-treatment. Differential gene expression and pathway analysis were performed using DESeq2 and FGSEA respectively.

RESULTS

Tumor growth was transiently inhibited (Fig 1A). The strongest immune response was observed at 8h (Fig 1B) and involved substantial upregulation of heat shock proteins and transcripts associated with inflammasome-mediated cell death (Fig 1B). Net anti-inflammatory responses, including downregulation of interferon and complement cascades, were observed at the later time points, possibly implicating wound healing mechanisms (Fig 1C-D).

CONCLUSIONS

Sparse-scan thermally ablative FUS is acutely (8h) immunogenic, yet chronically (>24h) immunosuppressive in B16F10 tumors. Going forward, these results will inform the selection of adjunct immunotherapies that optimally synergize with thermally ablative FUS.

ACKNOWLEDGEMENTS Supported by NIH R01CA197111 and R01EB020147.

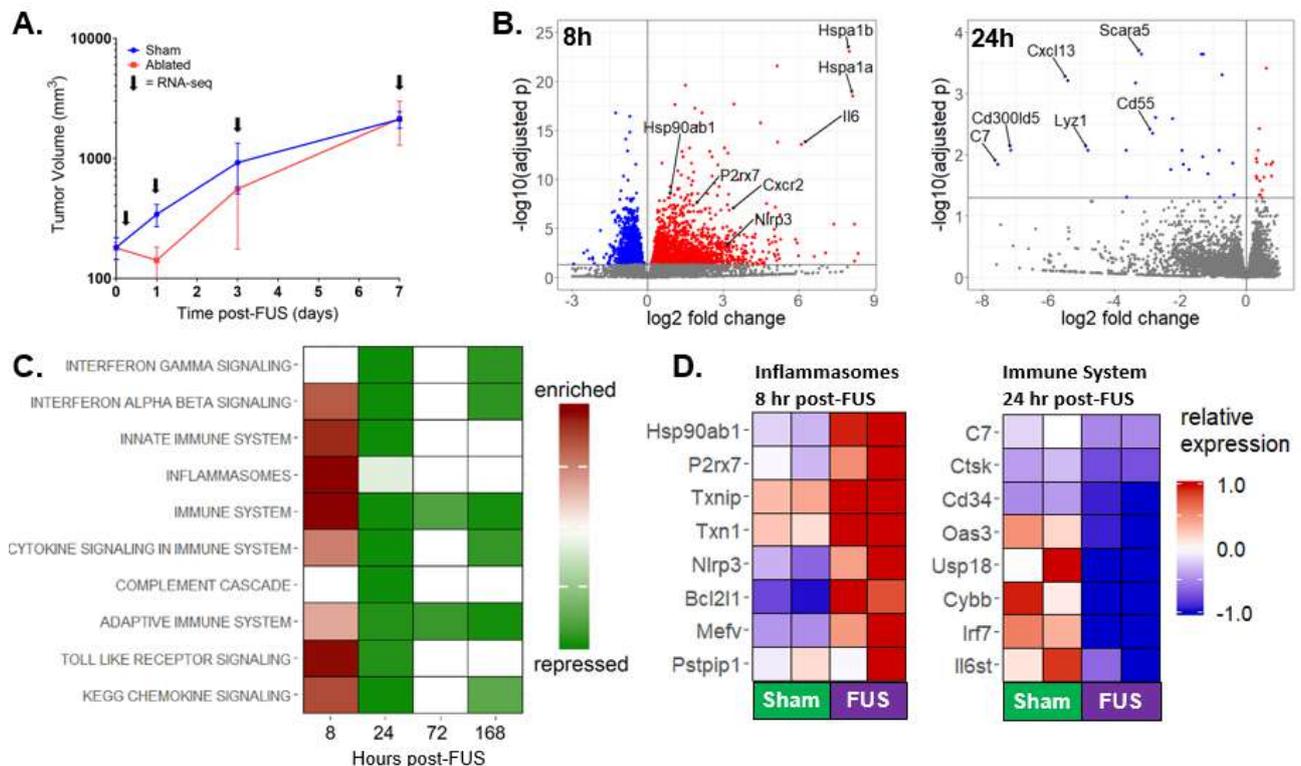


FIGURE 1: A. B16F10 tumor growth curves. **B.** Volcano plots with labeling of pro-inflammatory transcripts. **C.** Gene set enrichment analysis suggests acute induction of pyroptosis, followed by broad repression of adaptive immunity. **D.** Leading edge analysis at 8 hr and 24 hr reveals transcripts driving immune response variability.

BLOOD BRAIN/TUMOR BARRIER DISRUPTION WITH MR IMAGE-GUIDED FUS ELICITS MARKED SHIFTS IN TUMOR-IMMUNE PROFILE IN MURINE GLIOBLASTOMA

N.D. Sheybani¹, A.R. Witter², W.J. Garrison¹, G.W. Miller^{1,3}, T.N.J. Bullock², R.J. Price¹

¹Department of Biomedical Engineering, ²Department of Pathology, ³Department of Radiology and Medical Imaging; University of Virginia, Charlottesville, VA 22908

E-mail: nds3sa@virginia.edu; rprice@virginia.edu

OBJECTIVES: To understand the impact of focused ultrasound (FUS)-mediated blood brain/tumor barrier disruption (BBB/BTB-D) on immune sequelae in glioblastoma (GB).

METHODS: FUS BBB/BTB-D was applied to MR-visible GL261-luc2 murine gliomas using a 4-spot sonication grid (0.4-0.6 MPa, 0.5% duty cycle, 120s period) and i.v. microbubbles (MBs) (Fig.1A-B). Two weeks later, brains and peripheral lymphoid organs were examined by flow cytometry.

RESULTS: The percentage of CD8 T cells expressing CD44 and Granzyme-B in superficial cervical lymph nodes (SLN) increased significantly (Fig.1C-D). However, dendritic cells (DC) in the draining lymph nodes and non-immune cells (i.e. tumor and stroma) within targeted tumor exhibited upregulated checkpoint ligand expression (i.e. PD-L1, CD155) (Fig.1E-F).

CONCLUSIONS: FUS-mediated BBB/BTB-D in gliomas leads to peripheral T cell activation, yet concurrent local and peripheral adaptive resistance mechanisms. Combining FUS-mediated BBB/BTB-D with adjunct drug and gene delivery strategies aimed at controlling adaptive resistance may improve therapeutic outcomes. The potential for low pressure FUS-mediated BBB/BTB-D to shift local and systemic immunological signatures may also be an important consideration for GB clinical trials.

ACKNOWLEDGEMENTS: Supported by NIH R01CA197111, FUS Foundation, NCI F99/K00 (F99CA234954), NSF GRFP & Wagner Fellowship.

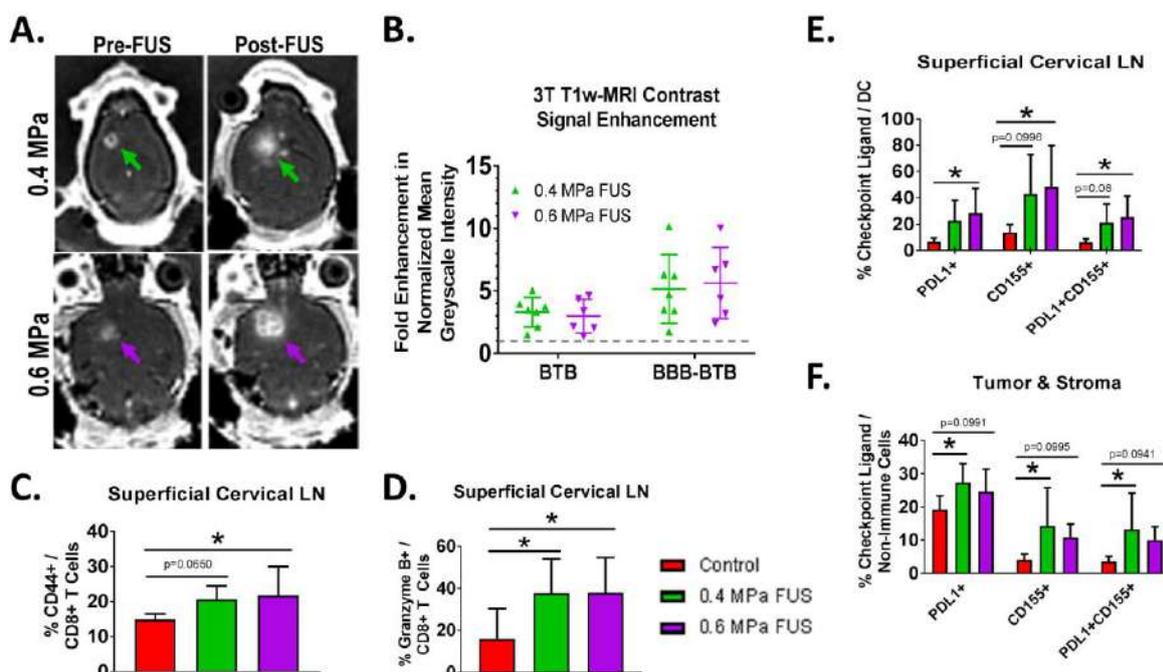


FIGURE 1: (A-B) Representative T1-weighted contrast-enhanced MR images and quantification of FUS-mediated BBB/BTB disruption in GL261-luc2 tumors. (C-D) Percentage of CD8+ T cells in SLN expressing CD44 or Granzyme B two weeks post-FUS. (E-F) Percentage of DC and non-immune cells expressing checkpoint ligands in SLN and in the tumor/stromal compartment, respectively, two weeks post-FUS.

HISTOTRIPSY INDUCED IMMUNOMODULATION

R.J. Hubbard¹, T. Worlikar¹, A. Felsted², S. Qu², A. Ganguly², A. Pepple², A. Kevelin², M. Toma³, C.S. Cho², Z. Xu¹

¹ Department of Biomedical Engineering, University of Michigan, Ann Arbor, Michigan

² Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan

³ Surgical Service, VA Ann Arbor Healthcare System

e-mail: ryanhub@umich.edu

OBJECTIVES

Histotripsy uses cavitation to mechanically fractionate tissue via high pressure, microsecond-length ultrasound pulses. The objectives of this study are to 1) quantify the histotripsy induced immune response and 2) Investigate the potential of histotripsy to enhance checkpoint inhibition immunotherapy.

METHODS

C57BL/6 mice received bilateral subcutaneous melanoma inoculations. The first group of mice received either histotripsy, no therapy (control), tumor irradiation (XRT), or radiofrequency ablation (RFA) 7 days after inoculation. Subtotal, unilateral histotripsy was performed using 1-cycle pulses from a 1 MHz focused transducer at 100 PRF with an estimated p- of 30 MPa. The immune response in the untreated contralateral tumor, tumor draining lymph nodes (TDLN), and spleen was quantified via flow cytometric (FACS) analysis on day 20. The second group of mice received either histotripsy, checkpoint inhibition (200 μ g anti-CTLA-4 mAb intraperitoneal injections), a combination of both, or no therapy (control).

RESULTS

In the first group, histotripsy generated a significant increase in activated, tumor-specific CD8⁺ TIL within the contralateral tumor, TDLN and spleen compared to XRT, RFA, and control (Fig 1A). In the second group, the combination of histotripsy and CI produced the greatest reduction of the tumor volume growth compared to the others (Fig 1B).

CONCLUSIONS

Histotripsy not only produces significant local and systemic immunostimulatory effects but also shows the potential to enhance checkpoint immunotherapy.

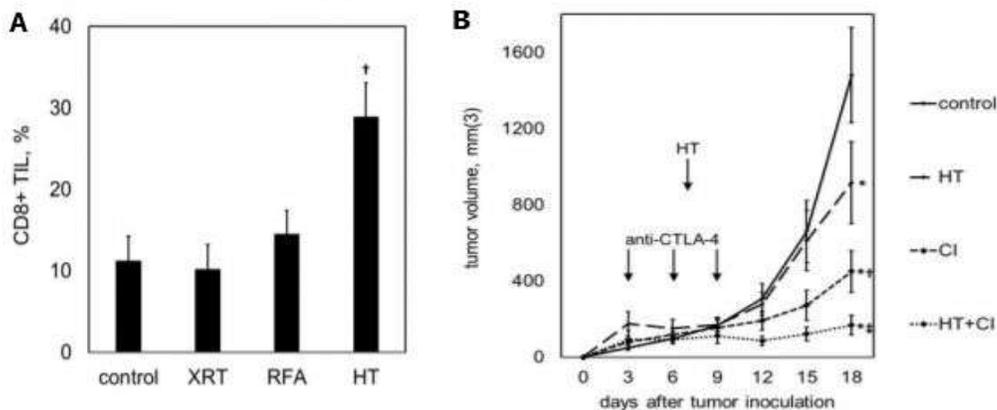


Figure: A) Histotripsy induced marked increase in CD8⁺ tumor-infiltrating T-cells compared to XRT and RFA. B) Serial measurements of contralateral tumor following no treatment, histotripsy (HT), checkpoint inhibition (CI), or both.

Investigation of the Local and Systemic Immune Response to Histotripsy Ablation of Breast Cancer in a Mouse Model

Alissa D Hendricks^{1,2,3}, Rebecca Schmieley¹, Justin Howell¹, Alex Simon¹, Sheryl L Coutermarsh-Ott², Irving C Allen², and Eli Vlaisavljevich¹

¹Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, VA, USA

²Department of Biomedical Sciences and Pathobiology, Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA, USA

³Graduate Program in Translational Biology, Medicine and Health, Virginia Tech, Roanoke, VA, USA

E-mail: eliv@vt.edu

OBJECTIVES

Histotripsy is a non-thermal and non-invasive ultrasound ablation strategy that uses cavitation to liquify targeted-tissues with millimeter precision. In this study, we investigated the treatment of breast cancer using the murine 4T1 model to evaluate the effectiveness of histotripsy ablation, including the reduction of disease burden and immune response.

METHODS

4T1 cells were injected into BALB/C abdominal mammary glands. Tumors, ~0.5cm, were treated with a custom-built 1MHz therapy-system guided with real-time ultrasound imaging (Fig1.A). Animals were treated using an automated treatment strategy to cover the entire tumor volume plus margin, with 50–250 pulses applied per focal location. Mice were euthanized immediately for histopathological analysis of ablation and 24-48 hours or 2-3 weeks after treatment to evaluate immune responses and morbidity.

RESULTS

Histotripsy resulted in complete ablation of tumor regions targeted (Fig.1B). Analysis of early response showed increased necrosis (40-80%), innate immune cell infiltration, and expression of pro-inflammatory cytokines (IL-6 and IL-1 β) with decreased TSLP, all correlating with an anti-tumor microenvironment. Additionally, serum IL-6 and TNF level remained unremarkable, indicating no systemic inflammation. After 2-3 weeks, histotripsy diminished overall disease burden as quantified by a 15% decreased tumor size and reduction in metastatic colonies up to 3000-fold compared to untreated mice.

CONCLUSIONS

Together, these results demonstrate histotripsy can both stimulate an anti-tumor microenvironment in treated areas as quickly as one day after treatment and significantly impact overall disease morbidity.

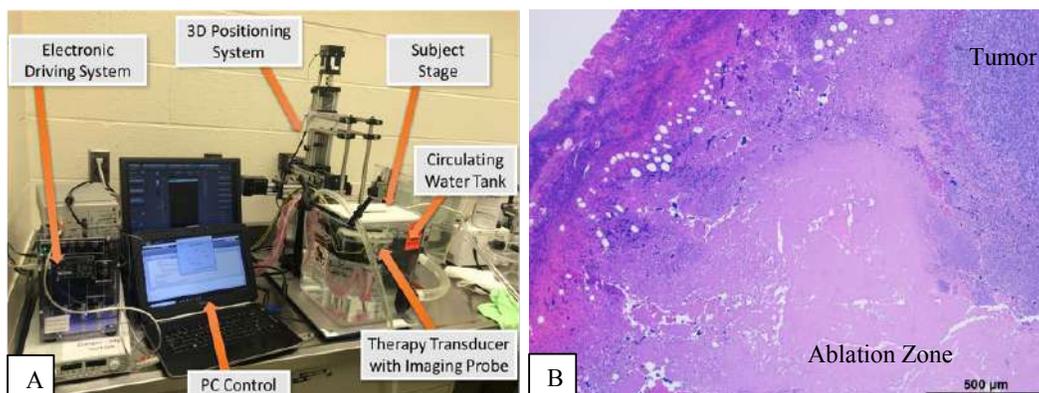


Figure 1. (A) Treatment set up, with user-controlled positioning, therapy, and imaging. (B) Example histopathology immediately after partial ablation.



THERAPY ULTRASOUND PLUS

INVITED TALKS:

Analysis, quantification and modelling of biological effects induced by combination treatments of radiation and hyperthermia at cell (population) level - *Sarah Brüningk*

How to sell “MR-HIFU induced hyperthermia” as an adjuvant treatment - *Edwin Heijman*

ORAL PRESENTATIONS:

HIFU thermotherapy enhancement in *ex-vivo* pig kidneys using a new class of endovascular sono-sensitizers - *Orane Lorton*

Randomized Phase II Multicenter Clinical trial of ultrasound hyperthermia combined with chemotherapy in oral cancer - *Wei Guo*

Controlled bubble-enhanced heating with added microbubbles - *Mike Averkiou*

The enhanced HIFU-induced thermal effect via magnetic ultrasound contrast agent microbubbles - *Dongxin Yang*



Analysis, quantification and modelling of biological effects induced by combination treatments of radiation and hyperthermia at cell (population) level

Sarah C. Brueningk, Ian Rivens, Uwe Oelfke, Gail ter Haar

OBJECTIVES Heat-induced radiosensitization delivered locally to a tumour using focused ultrasound is a promising approach for the treatment of radioresistant tumours where dose escalation is limited due to normal tissue toxicities. Understanding and quantifying the synergistic action of these treatments is key to establishing a biologically weighted equivalent dose (BEQD) concept that provides the basis for treatment planning and response prediction.

METHODS This presentation gives an introduction to biological response modelling starting from individual cells towards response prediction *in vivo*. The biological effects induced by radiation and hyperthermia at a cellular level are reviewed and an overview of recent advances in the field of modelling BEQD based on clonogenic cell survival data is given. Experimental data from 3D tumour spheroids from two human cancer cell lines will be presented to point out the advantages and limitations of these models. An outlook into *in vivo* combination treatments of partial tumour ablations and RT concludes the presentation.

RESULTS Whereas the induction of DNA (double) strand breaks has been identified as the major reason for radiation-induced cell killing, heating affects a multitude of different cellular components including cell membranes, and both structural and functional proteins such as those involved in DNA repair. The linear quadratic, the Arrhenius and the AlphaR cell survival models are presented and a description of model parameters as a function of heating temperature and duration is provided for two human cancer cell lines for BEQD calculation. Clonogenic survival does not, however, account for differences in the dynamics of the cell death mechanisms induced by radiation or heating that significantly affect spheroid growth response. Heated spheroids shed dead cells within days and display faster growth post-exposure than samples that received radiation or no treatment. Irradiated spheroids maintained a dense structure and exhibited a longer growth delay than spheroids receiving hyperthermia or combination treatment at biologically equivalent dose levels, calculated based on clonogenic cell survival.

CONCLUSIONS Although clonogenic cell survival modelling provides valuable information on the intrinsic treatment sensitivity of cells, BEQD calculations based on this description alone may overestimate the efficacy of hyperthermia treatments relative to radiation since factors such as the cell death mechanism induced, cell proliferation and micro-environmental changes are not captured in this model.

How to sell “MR-HIFU induced hyperthermia” as an adjuvant treatment

E. Heijman^{1,2}

¹Oncology Solutions, Philips Research, Eindhoven, NL

²University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department of Diagnostic and Interventional Radiology, Cologne, DE

e-mail: edwin.heijman@uk-koeln.de

Introduction

For decades research has been done to elucidate on the different biological effects induced by hyperthermia from systemic to cellular level. The scientific literature shows that hyperthermia is not only capable of malignant cell killing at moderate hyperthermia levels (42-44°C), but also improves adaptive immunity and enables the sensitization of tissue for radiation and/or chemotherapies at mild temperature levels (39-42°C).

But can we justify an additional treatment within the context of value-based healthcare? MR-HIFU induced mild hyperthermia is not a therapy on its own, and hence, alliances should be made with other therapies and technologies to solve burning clinical needs improving quality of life and outcomes for patients.

Clinical evidence on hyperthermia

Although less cytotoxic, mild inductive and capacitive based hyperthermia shows the biggest clinical value based on the published clinical evidence from palliative to curative care nowadays. Clinical studies show an improved outcome when combined with established oncological therapies without adding toxicity. Here, a literature overview will be given including the intended biological effects.

The added value of MR-HIFU

MR-HIFU induced hyperthermia is a new kid on the block in the hyperthermic domain and has two advantages in comparison with the well-established inductive or capacitive hyperthermia: by design, MR-HIFU incorporates MR based temperature control and has the promise to heat tumor tissue conformally. Both are good selling points in further exploiting the fully therapeutic efficacy, due to the narrow temperature bandwidth of in vitro found benefits, and enables dose painting by creating a larger difference between health and tumor tissue. In addition, powerful combination is MR-HIFU mediated drug delivery. Several preclinical drug delivery studies show a 5-20 times increase of intratumoral drug concentration compared to standard of care. Preclinical data and the current status of MR-HIFU mediated drug delivery will be presented.

The start of clinical translation of MR-HIFU hyperthermia

Through promising robust clinical evidence is required for clinical translation. First steps in clinical translation of MR-HIFU induced hyperthermia has been made by starting a phase I clinical trial for the treatment of recurrent rectal cancer combined with chemoradiotherapy. Additionally, a single case treatment of a patient with a liposarcoma in a compassionate use setting will be presented. Preliminary results of these first-in-man studies will be discussed including future directions.

HIFU thermotherapy enhancement in ex-vivo pig kidneys using a new class of endovascular sono-sensitizers

Orane Lorton¹, Pauline Guillemin¹, Romain Breguet², Stéphane Desgranges³, Laura Gui¹, François Lazeyras², Antonio Nastasi⁴, Nicolas Taulier⁵, Christiane Contino-Pépin³, Rares Salomir²

¹Image Guided Interventions Laboratory, Faculty of Medicine, University of Geneva, Switzerland.

²Radiology Department, University Hospitals of Geneva, Geneva, Switzerland. ³University of

Avignon, CBSA-IBMM, (UMR5247), Avignon, France. ⁴Visceral and Transplantation Service,

University Hospitals, Geneva, Switzerland. ⁵Sorbonne Universités, UPMC Univ Paris 06, CNRS,

INSERM, Laboratoire d'Imagerie Biomédicale (LIB), F-75006, Paris, France

e-mail : orane.lorton@unige.ch

OBJECTIVES

We developed a new concept of endovascular micro-droplets, used as sono-sensitizers for the enhanced absorption of the HIFU beam and demonstrated the improvement of the HIFU thermal effect after adjunction of micro-droplets in the perfusion fluid of freshly excised viable pig kidneys.

METHODS

Pig kidneys were perfused with an MR-compatible perfusion system and received two doses of 50mL of a micro-droplet emulsion 1.8% v/v of PFOB at 30min interval. Two sonication protocols were conducted using an MR-compatible transducer to observe the effect of micro-droplet injections on temperature rise, either fixed focal point or iterated 4mm-diameter circle.

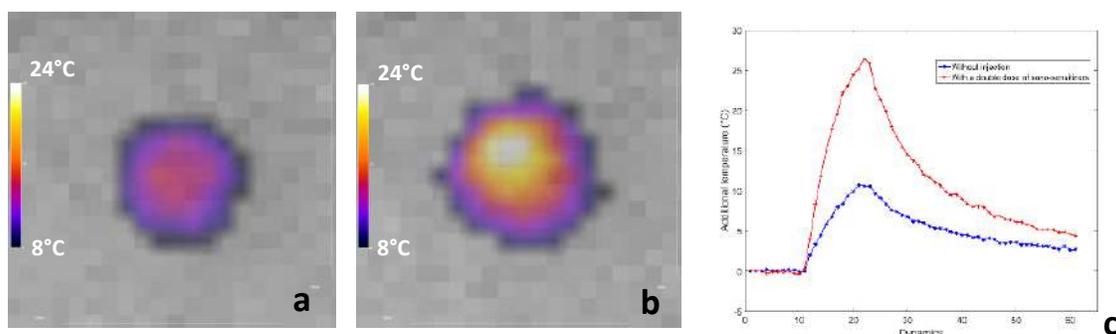
Experimental data were acquired in a whole-body 3T MRI scanner with a segmented GRE-EPI sequence using a 11cm-diameter receive loop coil.

RESULTS

The additional temperature elevation achieved after the second dose was 16.8°C at 60W and 16.6°C at 135W at the focal point and 16.1°C for the circular pattern. Adjunction of sono-sensitizer coupled to 30s sonication produced a boiling core beyond 100°C.

CONCLUSIONS

Injections of micro-droplets in the endovascular system did not modify the capilar permeability and demonstrated a dramatic enhancement in the heating efficiency of the MRgHIFU. The fluid circulation in the kidney allowed a renewal of fresh micro-droplets, which enabled an optimal efficiency of the method. Micro-droplets allowed reaching high temperature with less HIFU power, less technological constraints and less risk for near/far- field heating.



Temperature maps for the circular pattern a) before injection, b) after one dose of sono-sensitizers and c) additional temperature at the focal point before injection and with 100mL of sono-sensitizers.

Randomized Phase II Multicenter Clinical trial of Ultrasound Hyperthermia Combined with Chemotherapy in Oral cancer

Abstract

Wei GUO¹, Guoxin REN¹, Jian MENG², Guofeng SHEN³, Yunteng WU¹, Qianwei ZHUANG²

1.9th People's Hospital, School of Medicine, Shanghai Jiaotong University, P.R.China

2.Xuzhou Centre Hospital, 3. School of Biomedical Engineering

Objective: To evaluate the efficacy and the main side-effects during the clinical trial of this new ultrasound hyperthermia system combined with chemotherapy in oral cancer, meanwhile, to observe the preliminary clinical response of this combined therapeutic modality.

Methods: One hundred and twenty two cases of oral squamous cell carcinoma entered this clinical trial, 60 patients of them with advanced oral carcinoma were treated with new ultrasound hyperthermia system combined plus docetaxel–cisplatin–fluorouracil regimen (test group), 62 patients only received chemotherapy with docetaxel–cisplatin–fluorouracil regimen (control group). The thermo-index were detected during the course of hyperthermia, the chief-complain of the patients were also recorded. The systemic physiological, biochemical and immunological index were tested before and after the treatment respectively. The therapeutic response was assessed 1 month after 2cycles of the treatment. The follow-up period was 2 months to 36 months. The median follow-up period was 12 months.

Results: Sixty cases of oral squamous cell carcinoma enrolled the clinical trial of local ultrasound hyperthermia combined with chemotherapy. Ten times of ultrasound hyperthermia in total were performed for each patient. The ultrasound hyperthermia system operated smoothly, no malfunction was found. The main thermo-index were: the maximum heating temperature was 107.33 ± 32.43 °F, the average heating temperature was 106.07 ± 33.15 °F, the minimum heating temperature was 103.76 ± 33.02 °F, the fraction of heating time more than 107.6 °F was 0.46 ± 0.35 , the average treatment time was 37.74 ± 8.88 min. PR+CR was 64.4% (test group) and 42.4% (control group, $p<0.05$) respectively. The main local side-effects were low-grade pain (12 / 60). The incidence of adverse effects was similar between both study groups, no bone marrow suppression (over III).

Conclusions: The system combined with docetaxel–cisplatin–fluorouracil regimen is effective and safe in the treatment of advanced oral cancer. The main side-effects of local ultrasound hyperthermia combined with chemotherapy are low-grade pain or tolerable pain. There is no serious systemic complication observed. Local ultrasound hyperthermia enhances the immune function and obtains satisfying short-term response. Further observations are needed for long-term follow-up.

CONTROLLED BUBBLE-ENHANCED HEATING WITH ADDED MICROBUBBLES

Dingjie Suo, Alicia Clark, Sierra Bonilla, Sara Keller, Mike Averkiou
Department of Bioengineering, University of Washington, Seattle, USA
e-mail: dsuo@uw.edu, maverk@uw.edu

OBJECTIVES

High-intensity focused ultrasound (HIFU) is used for thermal ablation of tissues and cancers. HIFU can raise the temperature by 60 °C (or more) and induce necrosis at the focal area. However, there is a concern that the high acoustic energy may cause unwanted tissue damage, e.g. skin and skull burn during brain applications since most of the acoustic energy is either absorbed or reflected by the skull. Microbubbles (MBs) have been used widely as contrast agents and have been suggested as a method to considerably lower the required acoustic energy for a certain temperature elevation. The main objective of this work was to study and perform controlled bubble-enhanced heating (BEH) *in vitro* in glycerol mixture and in tissue mimicking phantoms. Results from both setups (fluid and tissue mimicking phantoms) suggest BEH leads to a more efficient temperature elevation either with inertial cavitation or with added MBs.

METHODS

Two transducers at 1 MHz (focused and unfocused) and custom MBs were used. The focused transducer produced larger spatially confined pressures in a small focal area (2x10 mm) to study BEH in the presence of inertial cavitation without microbubbles. The unfocused transducer was used to create a uniform pressure field extending almost in the whole phantom to study BEH in the presence of microbubbles. Temperature changes in the sample were measured by two 40-gauge thermocouples, one at the focus and one away from the focus to record the ambient temperature. Diagnostic ultrasound was used to align the thermocouple with the transducer focus and to monitor MB destruction during BEH. BEH was first explored in an enclosure containing glycerol mixture, and subsequently in a tissue-mimicking gel phantom. The peak negative pressure was varied from 0.2 MPa to 2.5 MPa. Continuous wave (CW) excitation for 30 seconds was used.

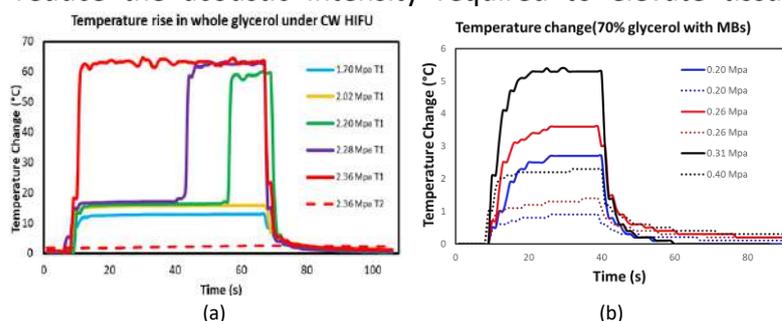
RESULTS

As the acoustic power increased, the temperature rise measured at the focus also increased linearly for both with and without MBs. For the focused transducer without MBs, the temperature rise was about 20 °C (Fig. a) at 2 MPa. At higher pressures, the temperature rise undergoes a sudden increase (reaching 60 °C), indicating the presence of cavitation. We were able to achieve controlled BEH by adding microbubbles (Fig. b) but the observed additional temperature rise was only a few degrees due to the low pressures used with an unfocused transducer. The same is observed in gel phantom.

CONCLUSIONS

Inertial cavitation was observed at pressures between 2 and 3 MPa and was found to dramatically increase the temperature (by about 40 °C) of glycerol without MBs. With lower pressures and by adding MBs, we were able to induce controlled BEH in a water-glycerol mixture and gel phantom. Controlled BEH is feasible and can reduce the acoustic intensity required to elevate tissue temperature during HIFU. The question whether inertial cavitation is a requirement for BEH in the presence of microbubbles remains unanswered.

Figure: (a) BEH with inertial cavitation in glycerol; (b) controlled BEH with MBs (solid line) and without MBs (dash line) at low pressures.



The enhanced HIFU-induced thermal effect via magnetic ultrasound contrast agent microbubbles

Dongxin Yang¹, Yanye Yang¹, Xiasheng Guo¹, Juan Tu¹, Dong Zhang^{1,2}

¹Key Laboratory of Modern Acoustics (MOE), Department of Physics, Collaborative Innovation Center of Advanced Microstructure, Nanjing University, Nanjing 210093, China

²The State Key Laboratory of Acoustics, Chinese Academy of Science, Beijing 10080, China
e-mail: juantu@nju.edu.cn, dzhang@nju.edu.cn

OBJECTIVES

Many studies have shown that adding contrast agent microbubbles (MBs) can improve the high intensity focused ultrasound (HIFU)-induced thermal effect. However, due to the shielding effect of MBs, uncontrollable injury might be induced when the concentration gets too high. Therefore, urgent demand still exists for the optimization of MBs that can enhance HIFU-induced thermal effect with higher efficiency.

METHODS

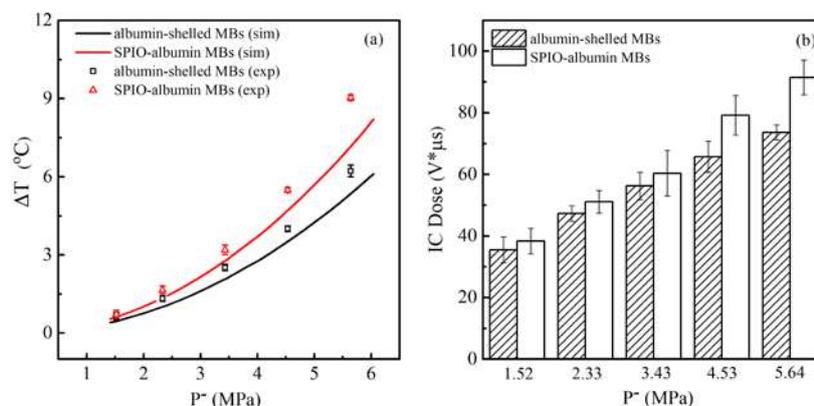
In the present study, dual modality magnetic ultrasound contrast agent MBs were synthesized by loading the super paramagnetic iron oxide nanoparticles (SPIOs) into the albumin-shelled MBs (referred as SPIO-albumin MBs). Then, both experimental measurements and numerical simulations were performed to evaluate the ability of SPIO-albumin MBs of enhancing HIFU-induced thermal effect.

RESULTS

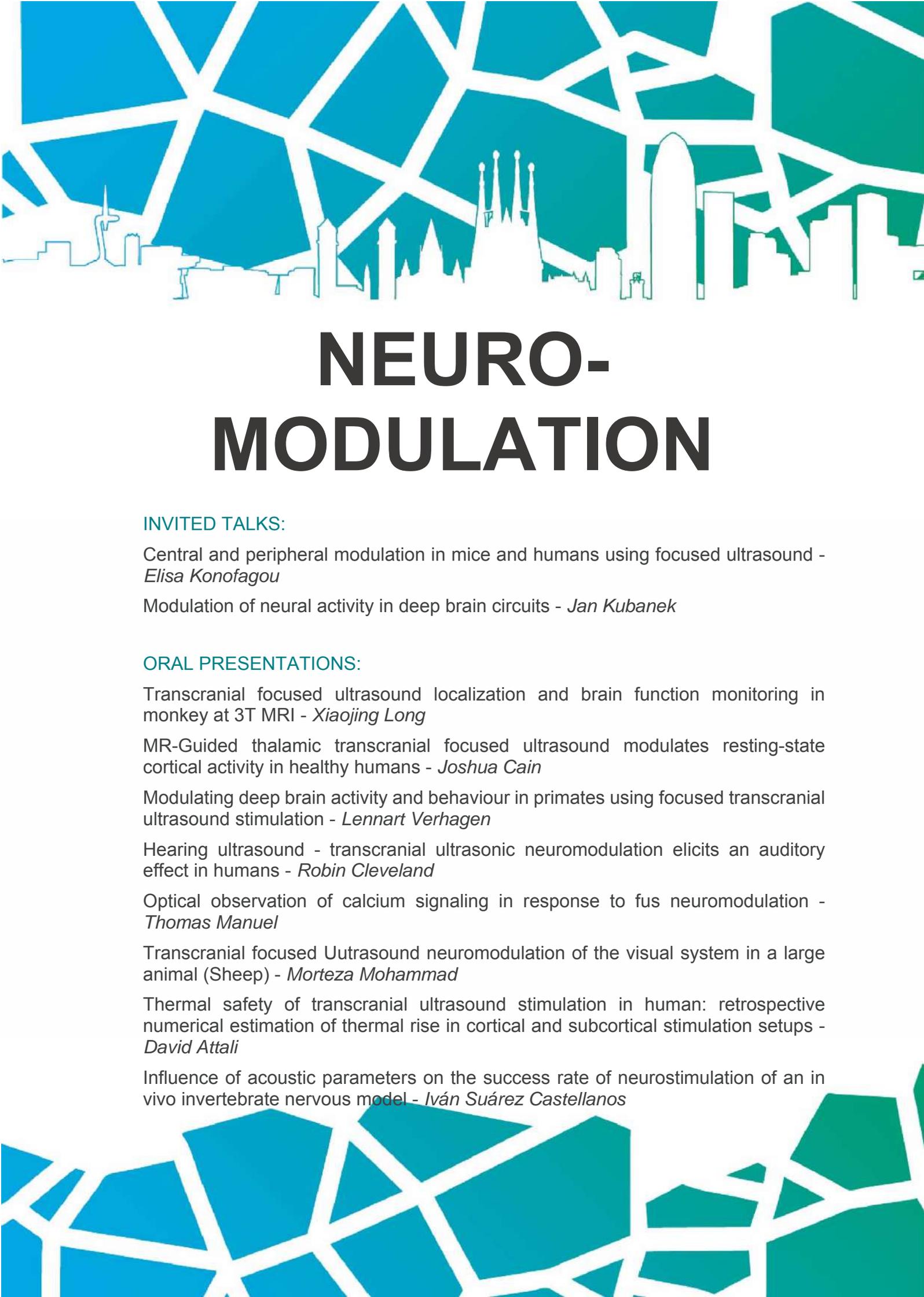
The results indicated that, comparing with regular albumin-shelled MBs, the SPIO-albumin MBs would lead to quicker temperature elevation rate and higher peak temperature. This phenomenon could be explained by the changes in MBs' physical and thermal properties induced by the integration of SPIOs into MB shell materials. In addition, more experimental results demonstrated that the enhancement effect could be further strengthened with more SPIOs combined with albumin-shell MBs. These observations suggested that more violent cavitation behaviors might be activated by ultrasound exposures with the presence of SPIOs, which in turn amplified ultrasound-stimulated thermal effect.

CONCLUSIONS

The results of the current work should be helpful for getting better understanding of the mechanisms underlying hybrid-MB-enhanced HIFU thermal effect.



CAPTION: The experimental and the simulation results of the peak temperature of albumin-shelled and SPIO-albumin MBs (a) and IC doses of these two kinds of MBs (b).



NEURO- MODULATION

INVITED TALKS:

Central and peripheral modulation in mice and humans using focused ultrasound - *Elisa Konofagou*

Modulation of neural activity in deep brain circuits - *Jan Kubanek*

ORAL PRESENTATIONS:

Transcranial focused ultrasound localization and brain function monitoring in monkey at 3T MRI - *Xiaojing Long*

MR-Guided thalamic transcranial focused ultrasound modulates resting-state cortical activity in healthy humans - *Joshua Cain*

Modulating deep brain activity and behaviour in primates using focused transcranial ultrasound stimulation - *Lennart Verhagen*

Hearing ultrasound - transcranial ultrasonic neuromodulation elicits an auditory effect in humans - *Robin Cleveland*

Optical observation of calcium signaling in response to fus neuromodulation - *Thomas Manuel*

Transcranial focused Ultrasound neuromodulation of the visual system in a large animal (Sheep) - *Morteza Mohammad*

Thermal safety of transcranial ultrasound stimulation in human: retrospective numerical estimation of thermal rise in cortical and subcortical stimulation setups - *David Attali*

Influence of acoustic parameters on the success rate of neurostimulation of an in vivo invertebrate nervous model - *Iván Suárez Castellanos*

CENTRAL AND PERIPHERAL MODULATION IN MICE AND HUMANS USING FOCUSED ULTRASOUND

Elisa E. Konofagou^{1,2}

¹Department of Biomedical Engineering, ²Department of Radiology, Columbia University, NY, USA. email: ek2191@columbia.edu

Stimulation of the brain has been a topic of curiosity of humans since the beginning of time. Being able to selectively stimulate the brain to enhance performance such as think deeper and remember faster remains, a formidable challenge. Ultrasound has been consistently reported for neuronal stimulation for several decades in both animals and humans including eliciting brain activity detected by functional MRI and electroencephalography. In addition, this knowledge can be used to understand the differences between normal and pathological brains to treat patients. In the peripheral nervous system, the leading technique to treat peripheral neurological disorders is implantation of electrodes along the peripheral nerve and stimulating the nerve with electrical current. A noninvasive alternative that could treat neuropathic pain and suppress nerve activity constitutes thus an important challenge in interventional neurology.

Our group has been studying the noninvasive stimulation or inhibition of both the central and peripheral nervous system in live animals. In the brain, we have shown that focused ultrasound is capable of noninvasively stimulating paw movement as well as sensory responses such as pupil dilation and eye movement when different brain regions are targeted, showing for the first time that ultrasound can tap into both the motor and sensory brain regions. In the periphery, when the ultrasound beam is focused on the sciatic nerve in a live, anesthetized animal, the thigh muscle becomes activated and muscle twitches can be induced at low ultrasonic intensities while the same twitches can be inhibited at higher intensities due to associated temperature rise that inhibits nerve firing. Cellular and fiber responses in excised tissue have confirmed the live animal responses. An overview of the aforementioned findings together with the most recent results will be presented.

MODULATION OF NEURAL ACTIVITY IN DEEP BRAIN CIRCUITS

Jan Kubanek

Department of Biomedical Engineering, University of Utah, Salt Lake City, UT, USA

e-mail: jan.kubanek@utah.edu

The ability to modulate neural activity noninvasively has had profound impact on our understanding of brain function and on the treatment of brain disorders. Current methods that rest on fields—electrical or magnetic—can be applied to modulate neural activity in cortical layers, but their ability to modulate deep brain structures is severely limited. Given this limitation, several researchers have begun to apply waves of sound of high frequencies (ultrasound) to noninvasively modulate brain activity in deep brain regions with sharp focus. I will provide a brief review of this literature, talk about the individual approaches, sketch the mechanisms of action, and provide directions for future research.

Transcranial focused ultrasound localization and brain function monitoring in Monkey at 3T MRI

Xiaojing Long¹, Yangzi Qiao¹, Chao Zou¹, Teng Ma¹, Weibao Qiu¹, Jo Lee¹, Changjun Tie¹, Lijuan Zhang¹, Xin Liu¹, Hairong Zheng¹

¹Paul C. Lauterbur Research Center for Biomedical Imaging, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences
e-mail: hr.zheng@siat.ac.cn

OBJECTIVES

Focused ultrasound (FUS) has been a fast developing technology for noninvasive neuromodulation. MRI-guided approach has facilitated the safety and accuracy of stimulation and simultaneously studying the brain effects induced by FUS. In this study, we investigated the MRI-based acoustic radiation force imaging (ARFI) in monkey at a 3T MRI system and obtained the functional MR images (fMRI), to validate the ultrasound focal location and the regional brain responses.

METHODS

A customer-designed 300 kHz single element focused ultrasound transducer was fixed above the top of the head on a Rhesus monkey. The input electrical power was set to 170W for the ARF generation. The duty cycle of the ultrasound pulse was 2.1%. As to the brain stimulation and fMRI, 4 cycles of stimulation was applied with each cycle be composed of 30-second stimulus and 30-second resting. An acoustic pressure of 800kPa was used for stimulation. The MR-ARFI data were acquired using a spin echo sequence and fMRI was achieved using the EPI sequence.

RESULTS

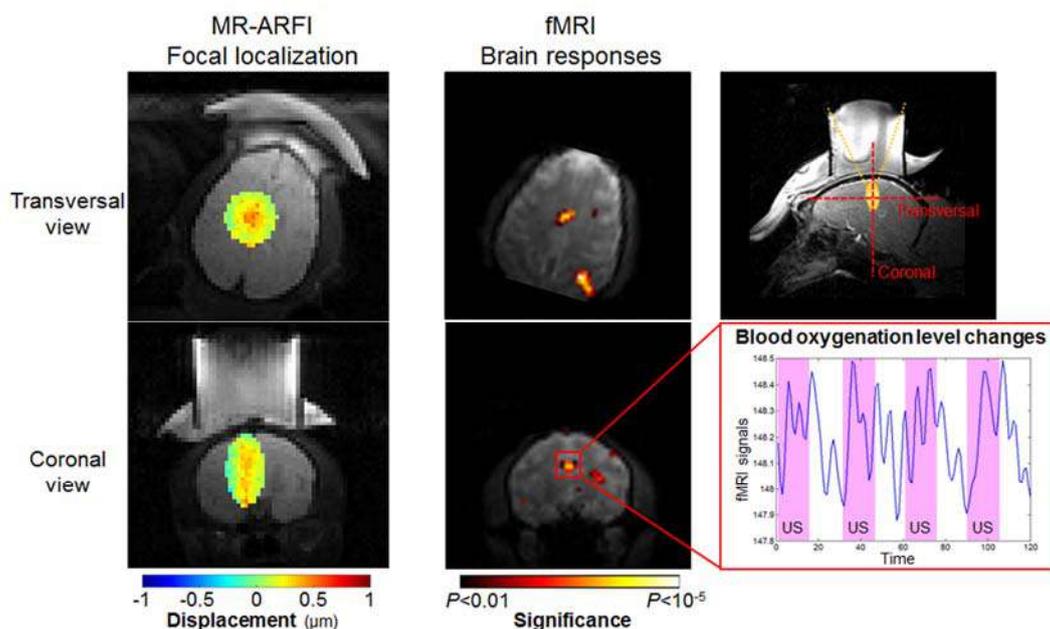
The ultrasound focus was localized with MR-ARFI and the regional blood oxygenation level was observed with significantly changes at the corresponding target area.

CONCLUSIONS

The transcranial ultrasound focal localization and monitoring of brain responses in monkey were successfully achieved at a clinical 3T system.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No.81527901).



CAPTION: Ultrasound focal localization and brain responses at target.

MR-Guided Thalamic Transcranial Focused Ultrasound Modulates Resting-State Cortical Activity in Healthy Humans

J.A.Cain¹, M.M.Monti^{1,2}

¹Department of Psychology, University of California, Los Angeles, USA

²Department of Neurosurgery, University of California, Los Angeles, USA

e-mail: joshcain@ucla.edu; monti@ucla.edu

OBJECTIVES

We aim to explore the impact of low intensity focused ultrasound pulsation (LIFUP) applied to higher-order thalamic nuclei on thalamocortical communication using MRI.

METHODS

We administered LIFUP to a region subsuming the left-central mediodorsal and left-central intralaminar thalamus concurrent with fMRI (n=16). In two discrete sessions, two 10-minute blocks of LIFUP (either both 100 Hz or 10 Hz Pulse Repetition Frequency (PRF); counterbalanced) were administered concurrent with BOLD, preceded and followed by arterial spin labeling (ASL), a measure of blood perfusion (before and after LIFUP 1; after LIFUP 2). LIFUP was administered in interleaved 30s blocks of LIFUP-on, 30s blocks of LIFUP-off during each 10-minute sonication.

RESULTS

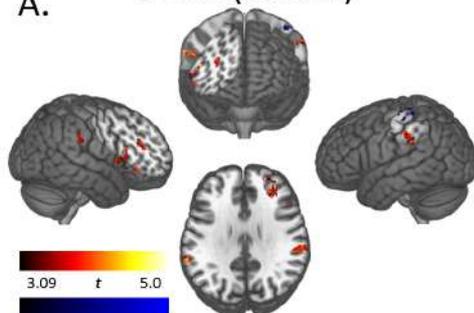
Heightened BOLD signal was observed during LIFUP (compared to LIFUP-off) in 5 cortical clusters and a decrease in one (see Figure 1a; PRF = 100Hz). Heightened blood perfusion was observed in regions generally subsuming the BOLD response observed during 100Hz in both 100Hz and 10 Hz PRF LIFUP (see Figure 1b). Reduced blood perfusion was observed throughout the left frontal and temporal lobes. We found inhibition of the target region (5mm kernel) as well as Ipsilateral Globus Pallidus (100Hz PRF only).

CONCLUSIONS

These results support the notion that central thalamic LIFUP results in ipsilateral inhibition with contralateral excitation, reflecting, perhaps, compensatory mechanisms.

Figure 1

A. BOLD (100Hz)



B. ASL (100Hz)

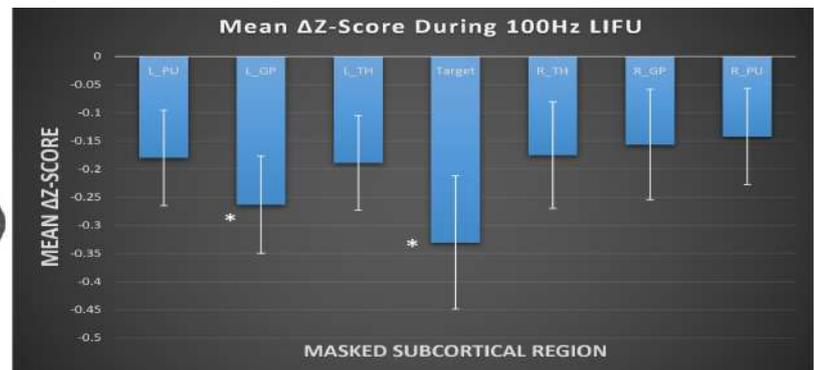
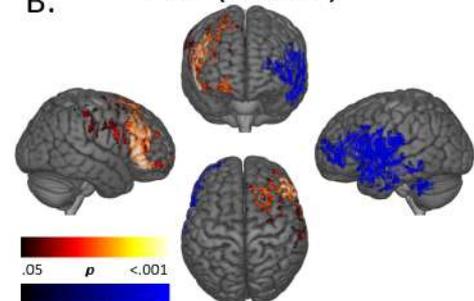
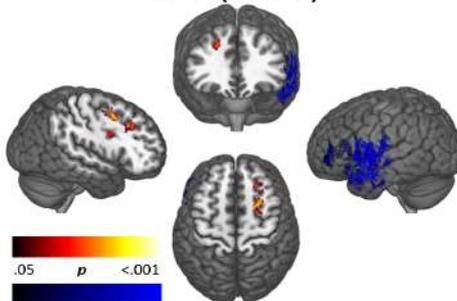


Figure 2

ASL (10Hz)



CAPTION: Figure 1a: BOLD response (increase = red/yellow) during 30s blocks of LIFUP 100Hz (no results from 10Hz). Figure 1b: modulation of blood perfusion after 100Hz and 10Hz sonication. Figure 2: significant inhibition of Left Pallidum and Thalamic Target ROI's during LIFUP (FDR correction).

MODULATING DEEP BRAIN ACTIVITY AND BEHAVIOUR IN PRIMATES USING FOCUSED TRANSCRANIAL ULTRASOUND STIMULATION

Lennart Verhagen^{1,2}, Davide Folloni^{1,2}, Cécile Gallea³, Charlotte Constans⁴, Elsa Fouragnan^{1,5}, Nima Khalighinejad^{1,2}, Alessandro Bongioanni^{1,2}, Pierre Pouget⁶, Jean-François Aubry⁷, Jérôme Sallet^{1,2}, Matthew FS Rushworth^{1,2}

¹ Wellcome Centre for Integrative Neuroimaging (WIN), Department of Experimental Psychology, University of Oxford, Oxford, United Kingdom

² Wellcome Centre for Integrative Neuroimaging (WIN), Centre for Functional MRI of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom

³ Institute du Cerveau et de la Moelle épinière (ICM), Centre for Neuroimaging Research (CENIR), Inserm U 1127, CNRS UMR 7225, Sorbonne Université, Paris, France

⁴ Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Université Paris Diderot, Sorbonne Paris Cité, Paris, France

⁵ School of Psychology, University of Plymouth, Plymouth PL4 8AA, United Kingdom

⁶ Institute du Cerveau et de la Moelle épinière (ICM), UMRS 975 INSERM, CNRS 7225, UMPC, Paris, France

⁷ Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Paris, France

e-mail: lennart.verhagen@psy.ox.ac.uk

OBJECTIVES

The causal role of an area within a neural network can be determined by interfering with its activity and measuring the impact. Many current reversible manipulation techniques have limitations preventing their application, particularly in deep areas of the primate brain. Focused transcranial ultrasound stimulation (TUS) has the potential to overcome these limitations.

METHODS

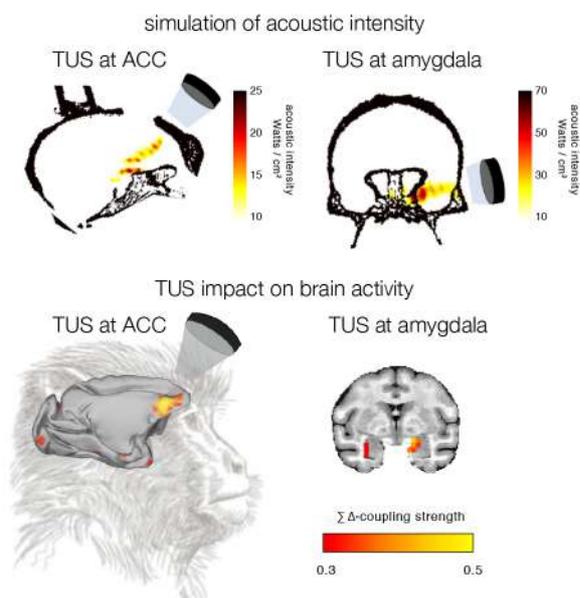
TUS neuromodulatory effects were measured by examining relationships between activity in each area and the rest of the brain using functional magnetic resonance imaging (fMRI). The impact of TUS on behavioural performance in learning and decision-making was also measured.

RESULTS

In control conditions without sonication, activity in a given area is related to activity in interconnected regions, but such relationships are reduced after sonication, specifically for the targeted areas. Dissociable and focal effects on neural activity could not be explained by auditory confounds. TUS' impact on behaviour was specific to the computations performed by the targeted areas.

CONCLUSIONS

We demonstrate that transcranial ultrasound stimulation can impact activity even in deep brain areas, with effects lasting up to two hours and modulating behaviour in a specific way.



CAPTION: Top panels: Estimation of the acoustic intensity based on a simulation of the ultrasound wave propagation, when targeted at the deep cortical anterior cingulate cortex (ACC, left panel), or the subcortical amygdala (right panel). Bottom panels: Spatial extent of the neuromodulatory impact of transcranial ultrasound on brain activity coupling as measured with fMRI, when targeted at ACC (left panel) or amygdala (bilateral, right panel).

HEARING ULTRASOUND - TRANSCRANIAL ULTRASONIC NEUROMODULATION ELICITS AN AUDITORY EFFECT IN HUMANS

R.O. Cleveland¹, J. Blackmore¹, V. Braun², C.R. Butler²

¹Institute of Biomedical Engineering, University of Oxford, UK

²Nuffield Department of Clinical Neurosciences, University of Oxford, UK

e-mail: robin.cleveland@eng.ox.ac.uk

OBJECTIVES

Transcranial ultrasonic neuromodulation (TUN) is an emerging method where low-intensity ultrasound is delivered through the skull to brain tissue with the goal of stimulating or modulating neural activity. Recent animal work suggests TUN can indirectly stimulate early auditory pathways which may confound interpretation of stimulation effects.

METHODS

We carried out an investigation in 18 healthy volunteers in which TUN was focused to visual brain areas using 500 kHz ultrasound modulated with a 1 kHz square wave.

RESULTS

We found that participants could hear sound during TUN and could distinguish between active and sham trials. EEG recordings of auditory evoked potentials confirmed the activation of auditory pathways when TUN was applied. Ex vivo skull experiments demonstrated that ultrasound was absorbed by the skull resulting in a 1 kHz flexural wave that propagated to the ear canals. This suggests that the TUN was not modulating auditory brain circuits but coupling into a mechanical wave that excites the cochlea. We were able to mask the effect by playing an audio waveform through earphones while TUN was applied. 15 of 18 participants were no longer able to detect the TUN when the audio mask was employed.

CONCLUSIONS

Our results show that TUN does result in auditory activation, via flexural waves that propagate to the cochlea, and that by playing an audio signal in the ear the effect can be masked.

ACKNOWLEDGEMENTS

This work was supported by the John Fell Fund of the University of Oxford.

OPTICAL OBSERVATION OF CALCIUM SIGNALING IN RESPONSE TO FUS NEUROMODULATION

Thomas J Manuel¹, Jiro Kusunose², Xiaoyan Zhan³, Arron Yang³, Hakmook Kang⁴, Zixiu Xiang³, Charles F Caskey^{1,5}

¹Biomedical Engineering, Vanderbilt University, Nashville, USA.

²Vanderbilt University Institute of Imaging Science, Nashville, USA.

³Department of Pharmacology, Vanderbilt University, Nashville, USA.

⁴Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, USA.

⁵Department of Radiology, Vanderbilt University, Nashville, USA.

email: thomas.j.manuel@vanderbilt.edu

OBJECTIVES

The neuroscience community is increasingly exploring focused ultrasound (FUS) as a tool to provide targeted reversible non-invasive neuromodulation with millimeter spatial resolution. In the present study, we targeted a genetically encoded calcium indicator to specific neuron populations in a mouse model and quantified changes in fluorescence signal in response to FUS neuromodulation pulses across a broad FUS parameter space known to elicit motor responses in intact animals.

METHODS

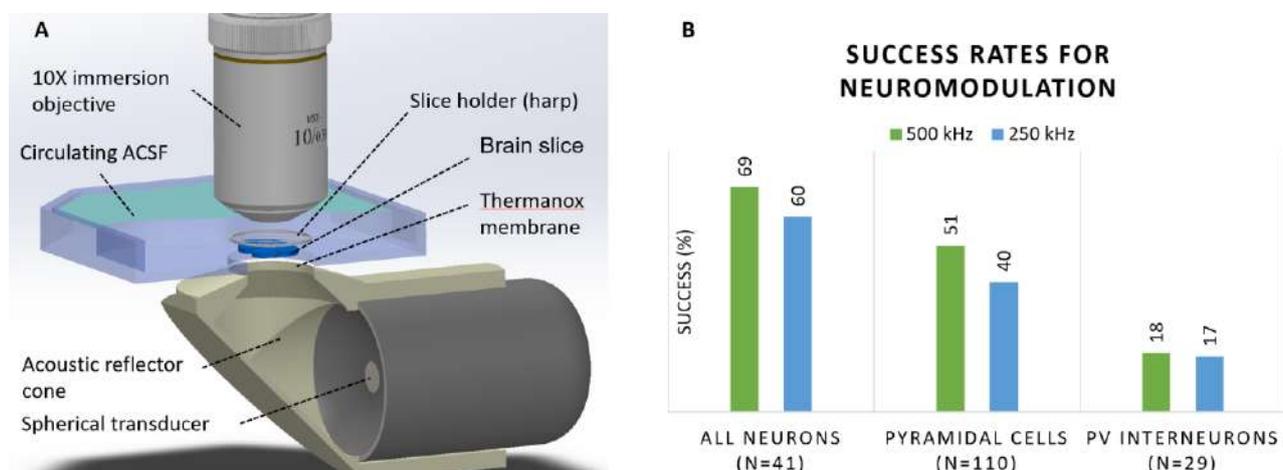
We developed an *ex vivo* mouse brain slice model with the calcium indicator (GCaMP-6s) targeted to three different cell groups: all neuronal cells (Syn), pyramidal cells only (CaMKII), and parvalbumin (PV) interneurons only. Slices were sonicated from beneath at spatial peak pulse averages ($I_{sp\text{ppa}}$) between 2 and 20 W/cm², 50 and 250 kilocycles, at 250 and 500 kHz frequencies while imaging with a fluorescent microscope (Fig 1A). Significant changes in fluorescence before and after sonication were quantified with a method inspired by fMRI cluster analysis. A successful trial required a clustered response greater than twice the standard deviation plus the mean of the group baseline.

RESULTS

We report success rates for this slice model for three neuron groups (Fig 1B). These results demonstrate effective neuromodulation at parameters consistent with *in vivo* behavioral studies reported by others.

CONCLUSIONS

FUS directly modulates calcium signaling in pyramidal cells and PV interneurons in mouse brain slices. This model will facilitate future investigations in targeting cell subpopulations.



CAPTION: A) The experimental setup. FUS stimulates the brain slice from below during fluorescent imaging. B) Aggregate success rates for neuromodulation in three cell populations with $I_{sp\text{ppa}}$ between 2 and 20 W/cm² and 50 to 250 kilocycles. Success was defined relative to baseline measurements.

Transcranial Focused Ultrasound Neuromodulation of the Visual System in a Large Animal (Sheep)

M. Mohammadjavadi¹, P. Gaur¹, J. Kubanek³, Y. Saenz¹, G. Popelka^{1,2}, K.B. Pauly¹

¹Department of Radiology, Stanford University, Stanford, CA, USA

²Department of Otolaryngology–Head and Neck Surgery, Stanford University, Stanford, CA, USA

³Department of Biomedical Engineering, The University of Utah, Salt Lake City, Utah, USA

e-mail: mmohammadjavadi@stanford.edu

OBJECTIVES

Fry showed a suppression of visual-evoked potentials (VEP) with ultrasound stimulation directly from visual cortex in craniotomized cat (Fry et al. 1958). We studied the long-term effect of transcranial focused ultrasound (tFUS) sonication of the lateral geniculate nucleus (LGN) on VEPs, but in a larger animal with intact skull and MR targeting.

METHODS

Twelve male sheep each were positioned in an MR head coil with an MR-compatible ultrasound transducer (ExAblate 2100, Insightec Ltd) affixed to the head coil. The anatomical position of LGN was determined with T2-weighted MRI. VEPs were elicited with 20 ms pulsed white light (binocular at 1 Hz) and recorded from subdermal EEG electrodes, up to 6 trials in each animal. tFUS neuromodulation pulses (PW 300 ms pulse duration, 50% duty cycle, 550kHz center frequency, at in situ estimated I_{SPTA} values between 1 and 51 W/cm²) were applied to LGN and in separate trials to control locations. Two control animals were studied under the identical conditions except with no ultrasound. The VEP peak-to-peak amplitude (N70 and P100) was calculated for each trial.

RESULTS

The tFUS reversibly suppressed the VEPs peak-to-peak amplitude by almost 50% over 1 hour compared to control conditions and gradually returning to baseline. (Figure 1).

CONCLUSIONS

These results suggest that tFUS can be non-invasively delivered to the deep structures in the brain to modulate visual neural activity.

ACKNOWLEDGEMENTS

Supported by NIH T32 CA009695, R01, MH111825, RF1 MH116977.

I would like to thank our MR technologists Karla and Kevin Epperson for all their help.

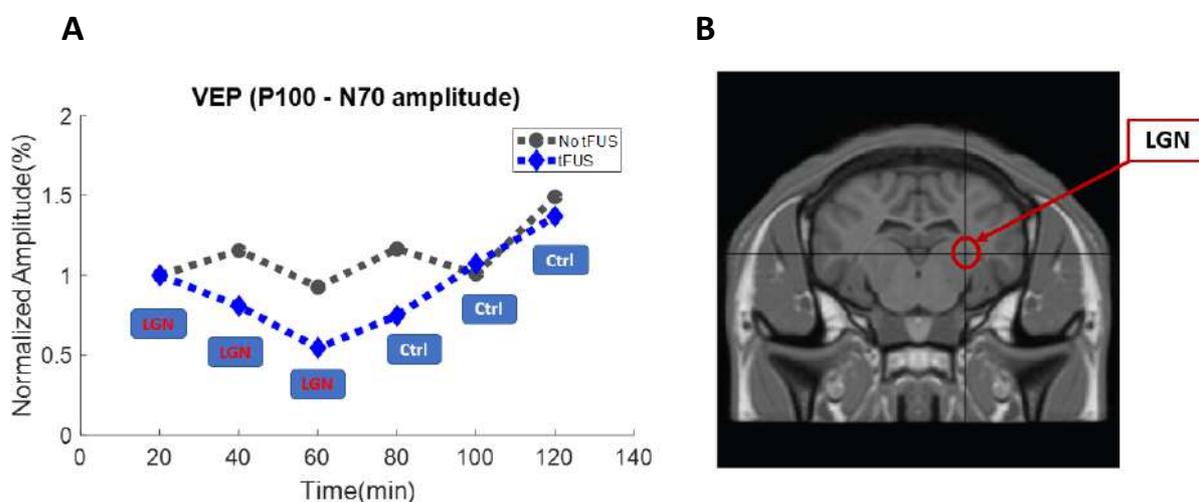


Figure 1. Mean amplitude of P100-N70, normalized to the non-tFUS condition (A). Coronal T2-weighted MR image showing the LGN target (B).

THERMAL SAFETY OF TRANSCRANIAL ULTRASOUND STIMULATION IN HUMAN: RETROSPECTIVE NUMERICAL ESTIMATION OF THERMAL RISE IN CORTICAL AND SUBCORTICAL STIMULATION SETUPS

D. Attali^{1,2}, A. Houdouin¹, M. Tanter¹, J.F. Aubry¹

¹Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Paris, France

²Department of Psychiatry, Service Hospitalo-Universitaire, Centre Hospitalier Sainte-Anne, Paris Descartes University, Paris, France

e-mail: d.attali@ghu-paris.fr; jean-francois.aubry@espci.fr

OBJECTIVES

The use of low intensity Transcranial Ultrasound Stimulation (TUS) is promising but its thermal safety profile must be assured. Here, we estimate the temperature rise for two previously published human setups: one targeting a cortical area (the primary visual cortex (PVC), Lee 2016) and one targeting a subcortical area (the thalamus, Legon 2018).

METHODS

Stimulation characteristics were extracted from both studies (brain target coordinates, transducer properties, acoustic intensities, sonication pattern). These data were first used to simulate the acoustic propagation of focused ultrasound through the human skull and the resulting pressure maps. Then, using a previously validated numerical model (Constans 2017), we estimated the temperature rises in the skull, the brain close to the skull and the brain at the focal spot area.

RESULTS

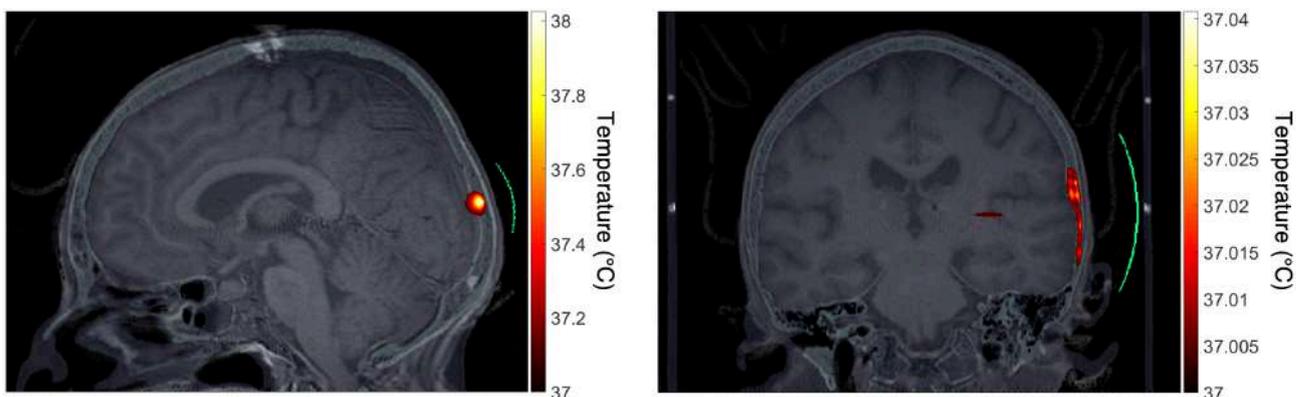
In the PVC stimulation, we estimated temperature rises of +0.046°C, +0.004°C and +0.005°C in the skull, the brain close to the skull and the focal spot area, respectively. In the thalamus stimulation, we estimated temperature rises of +1.081°C, +0.285°C and +0.042°C in the skull, the brain close to the skull and the focal spot area, respectively.

CONCLUSIONS

Our retrospective analysis shows that low intensity TUS setups produce minimal thermal elevation in brain, both when targeting cortical and subcortical areas. Maximum thermal rise occurs within the skull. These results support the thermal safety profile of TUS.

ACKNOWLEDGEMENTS

Supported by the Bettencourt Schueller Foundation and the Agence Nationale de la Recherche (ANR-10-EQPX-15).



CAPTION: Temperature in a cortical (PVC, left) and a subcortical (thalamus, right) TUS setup.

INFLUENCE OF ACOUSTIC PARAMETERS ON THE SUCCESS RATE OF NEUROSTIMULATION OF AN *IN VIVO* INVERTEBRATE NERVOUS MODEL

J. Vion-Bailly¹, W.A. N'Djin¹, I.M. Suarez-Castellanos¹, A. Carpentier², J.-Y. Chapelon¹

¹LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, Lyon, France

²Research Laboratory on Advanced Surgical Technologies (LRTCA), La Pitié-Salpêtrière Hospital, Paris 6 Sorbonne University Paris, France

e-mail: jeremy.vion@inserm.fr

OBJECTIVES

An *in vivo* invertebrate nervous model has previously been proposed to study the biomechanisms involved in the phenomenon of ultrasound (US) neurostimulation. The purpose of this study is to study the influence of different acoustic parameters on the neurostimulation success rate (NSR) associated with this nervous model, and gain mechanistic knowledge from the highlighted trends.

METHODS

The general method to evaluate the influence of an acoustic parameter on the success rate of ultrasound stimulation consisted in administrating US sequences compound of randomly mixed types of bursts, each type of burst varying from one another only by the value of the investigated parameter. The NSR associated with each type of subgroup of stimuli of the sequence was then calculated.

RESULTS

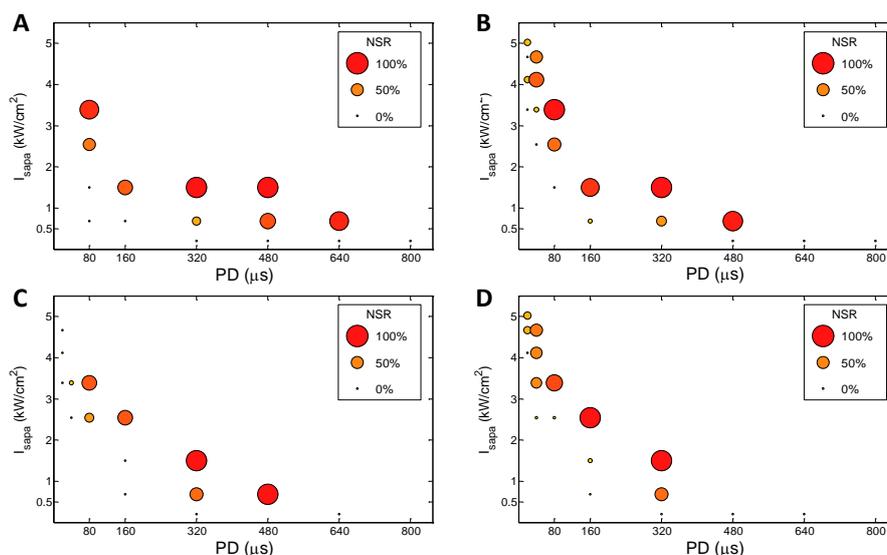
Amongst several clearly identified trends, the NSR was observed to be increasing with increasing values of US pulse intensity, duration and repetition frequency.

CONCLUSIONS

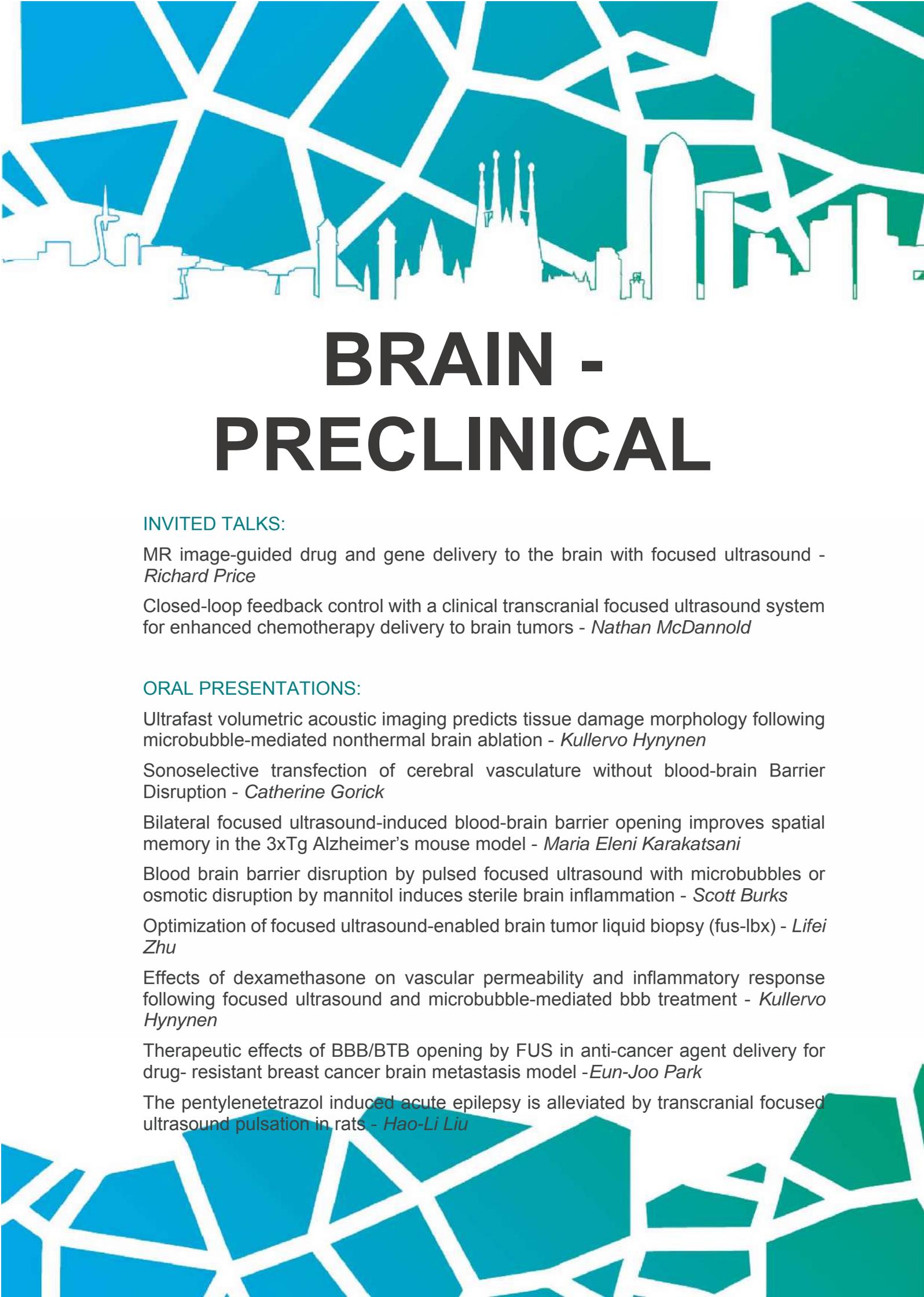
Results suggest afferent nerves are sensitive to the value of the 'mean radiation force' carried by the US stimulus, whatever combination of parameters leading to it.

ACKNOWLEDGEMENTS

This project was supported by the French National Research Agency (ANR 2016, N° ANR-16-TERC-0017) and the Laboratory of Excellence (LabEx) DevWeCan.



CAPTION: Illustration of the combined influence of pulse intensity (I_{sapa}) and pulse duration (PD) over the neurostimulation success rate. Each chart (A-D) presents the results associated with a single trial, performed on a single animal.



BRAIN - PRECLINICAL

INVITED TALKS:

MR image-guided drug and gene delivery to the brain with focused ultrasound - *Richard Price*

Closed-loop feedback control with a clinical transcranial focused ultrasound system for enhanced chemotherapy delivery to brain tumors - *Nathan McDannold*

ORAL PRESENTATIONS:

Ultrafast volumetric acoustic imaging predicts tissue damage morphology following microbubble-mediated nonthermal brain ablation - *Kullervo Hynynen*

Sonoselective transfection of cerebral vasculature without blood-brain Barrier Disruption - *Catherine Gorick*

Bilateral focused ultrasound-induced blood-brain barrier opening improves spatial memory in the 3xTg Alzheimer's mouse model - *Maria Eleni Karakatsani*

Blood brain barrier disruption by pulsed focused ultrasound with microbubbles or osmotic disruption by mannitol induces sterile brain inflammation - *Scott Burks*

Optimization of focused ultrasound-enabled brain tumor liquid biopsy (fus-lbx) - *Lifei Zhu*

Effects of dexamethasone on vascular permeability and inflammatory response following focused ultrasound and microbubble-mediated bbb treatment - *Kullervo Hynynen*

Therapeutic effects of BBB/BBB opening by FUS in anti-cancer agent delivery for drug-resistant breast cancer brain metastasis model - *Eun-Joo Park*

The pentylentetrazol induced acute epilepsy is alleviated by transcranial focused ultrasound pulsation in rats - *Hao-Li Liu*

MR IMAGE-GUIDED DRUG AND GENE DELIVERY TO THE BRAIN WITH FOCUSED ULTRASOUND

R.J. Price

Department of Biomedical Engineering, University of Virginia, Charlottesville, VA 22908

Email: rprice@virginia.edu

OBJECTIVES

Our primary research objective is to engineer MR image-guided focused ultrasound (FUS) approaches for drug and gene delivery to the brain. Indications include Parkinson's Disease (PD), brain tumors, and ischemic stroke.

METHODS

MR image-guided focused ultrasound drives the oscillation of microbubbles (MBs) flowing through cerebral microcirculation. This transiently opens the blood-brain (BBB) and/or blood-tumor (BTB) barriers to permit drug and gene bearing nanoparticle (NP) delivery. "Sono selective" transfection of cerebrovascular endothelium is achieved using low pressure levels and plasmid-coated MBs.

RESULTS

We have published on the use of MR image-guided FUS and MBs in combination with NPs to transfect neural tissue, reduce glioma invasiveness, and treat PD rats. More recent research indicates that (i) FUS enhances BPN transport via augmented convective fluid flow (Fig 1A), (ii) cerebrovascular endothelium may be selectively transfected without BBB opening (Fig 1b), and (iii) BBB/BTB opening of gliomas elicits complex immunological responses. These responses suggest opportunities for synergistic immunotherapy (Fig 1C); however, they also highlight the potential significance of confounding immunosuppressive counter-responses.

CONCLUSIONS

MR image-guided FUS represents a disruptive platform technology for drug and gene delivery to the central nervous system. As clinical BBB/BTB opening trials move forward, a continued emphasis on the parallel pre-clinical development of innovative new delivery strategies will be imperative.

ACKNOWLEDGEMENTS

Supported by NIH R01CA197111, R01EB020147, R21CA230088, and R21EB024323.

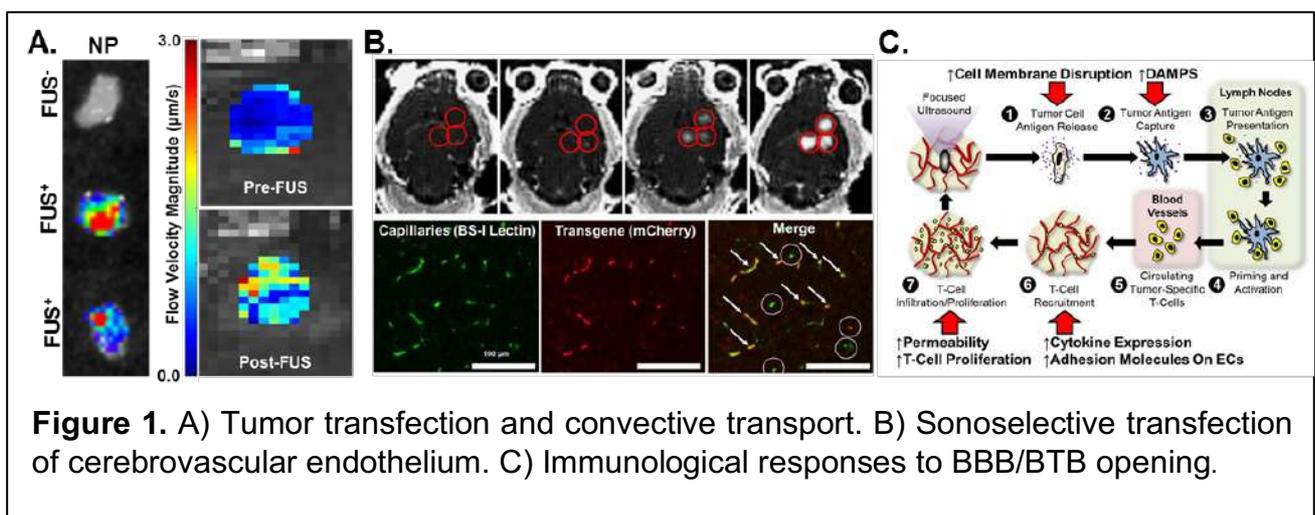


Figure 1. A) Tumor transfection and convective transport. B) Sono selective transfection of cerebrovascular endothelium. C) Immunological responses to BBB/BTB opening.

Acoustic feedback enables safe and reliable carboplatin delivery across the blood-brain barrier with a clinical focused ultrasound system and improves survival in a rat glioma model

The blood-brain barrier (BBB) restricts delivery of most chemotherapy agents to brain tumors. Here, we investigated a clinical focused ultrasound (FUS) device to disrupt the BBB in rats and enhance carboplatin delivery to the brain using the F98 glioma model. In each rat, 2-3 volumetric sonications (5 ms bursts at 1.1 Hz for 75s) targeted 18-27 locations in one hemisphere. Sonication was combined with Definity microbubbles (10 μ l/kg) and followed by intravenous carboplatin (50 mg/kg). Closed-loop feedback control was performed based on acoustic emissions analysis. Safety and reliability were established in healthy rats after three sessions with carboplatin; BBB disruption was induced in every target without significant damage evident in MRI or histology. In tumor-bearing rats, concentrations of MRI contrast agent (Gadavist) were 1.7 and 3.3 times higher in the tumor center and margin, respectively, than non-sonicated tumors ($P < 0.001$). Tissue-to-plasma ratios of intact carboplatin concentrations were increased by 7.3 and 2.9 times in brain and tumor respectively, at one hour after FUS and 4.2 and 2.4 times at four hours. Tumor volume doubling time in rats receiving FUS and carboplatin increased by 96% and 126% compared to rats that received carboplatin alone and non-sonicated controls, respectively ($P < 0.05$); corresponding increases in median survival were 48% and 66% ($P < 0.01$). Overall, this work demonstrates that actively-controlled BBB disruption with a clinical device can enhance carboplatin delivery without neurotoxicity at level that reduces tumor growth and improves survival in an aggressive and infiltrative rat glioma model.

ULTRAFAST VOLUMETRIC ACOUSTIC IMAGING PREDICTS TISSUE DAMAGE MORPHOLOGY FOLLOWING MICROBUBBLE-MEDIATED NONTHERMAL BRAIN ABLATION

R.M. Jones¹, D. McMahon^{1,2}, K. Hynynen^{1,2}

¹Physical Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada

²Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

e-mail: rmjones@sri.utoronto.ca

OBJECTIVES

Nonthermal ablation via focused ultrasound(FUS) and microbubbles(MBs) is under investigation for non-invasive brain surgery. Existing sources of variability can yield inconsistent treatment outcomes, warranting development of methods for online monitoring and control prior to clinical testing. Here we investigate ultrafast 3D MB imaging for predicting the spatial distribution of tissue damage following nonthermal brain ablation.

METHODS

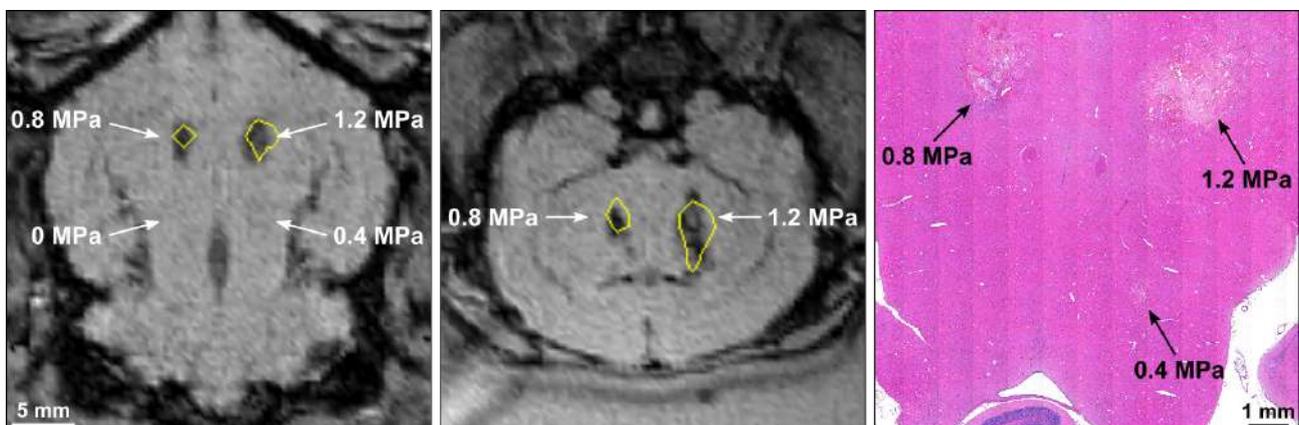
Experiments were performed on craniotomized rabbits using a clinical-scale prototype FUS brain system[Jones et al., 2018]. Pulsed FUS ($f_0=612$ kHz, pulse length=10 ms, PRF=1 Hz, duration=120 s) was electronically steered over a 2x2 point grid (side length=6 mm) starting concurrently with MB infusion (200 μ l/kg Definity™ over 90 s) via 3D subharmonic imaging-based feedback control ($f_0/2=306$ kHz). Exposures were carried out at 0/50/100/150% of the pressure required to detect subharmonic activity *in-vivo* (p_{sub}). Short-time analysis of the acoustic emissions data(non-overlapping 1 μ s beamforming windows) was performed offline. 3T MRI was carried out to assess the induced tissue effects. Animals were sacrificed 48 hr post-FUS for histological examination.

RESULTS

Multi-point exposure calibration via 3D subharmonic imaging was feasible *in-vivo* ($p_{sub}=0.67\pm 0.09$ MPa). T_2^*w MRI displayed signal hypointensities induced by exposures at $p\geq 100\%p_{sub}$. H&E sections associated T_2^*w hypointensities with red blood cell extravasations and tissue necrosis, the spatial extent of both increased with increasing exposure level. Ultrafast 3D MB imaging data correlated well with the spatial distribution of both T_2^*w hypointensities and tissue necrosis.

CONCLUSIONS

Volumetric imaging of contrast agent MBs *in-vivo* over microsecond timescales shows promise as a method for online monitoring and control of nonthermal brain ablation.



CAPTION: Axial (left) and coronal (middle) T_2^*w MRI immediately post-FUS demonstrates regions of signal hypointensity induced by the exposures at 0.8 MPa (100% p_{sub}) and 1.2 MPa (150% p_{sub}). -8 dB source field intensity contours from the corresponding anatomical plane are overlaid in yellow (1 MHz volume rate). Axial H&E stained tissue section 48 hr post-FUS (right) shows regions of red blood cell extravasations and tissue necrosis (arrows).

SONOSELECTIVE TRANSFECTION OF CEREBRAL VASCULATURE WITHOUT BLOOD-BRAIN BARRIER DISRUPTION

C.M. Gorick¹, A.S. Mathew¹, W.J. Garrison¹, J. Song¹, A.L. Klivanov¹, G.W. Miller¹, R.J. Price¹

¹University of Virginia, Charlottesville, USA

Email: cmg6ae@virginia.edu

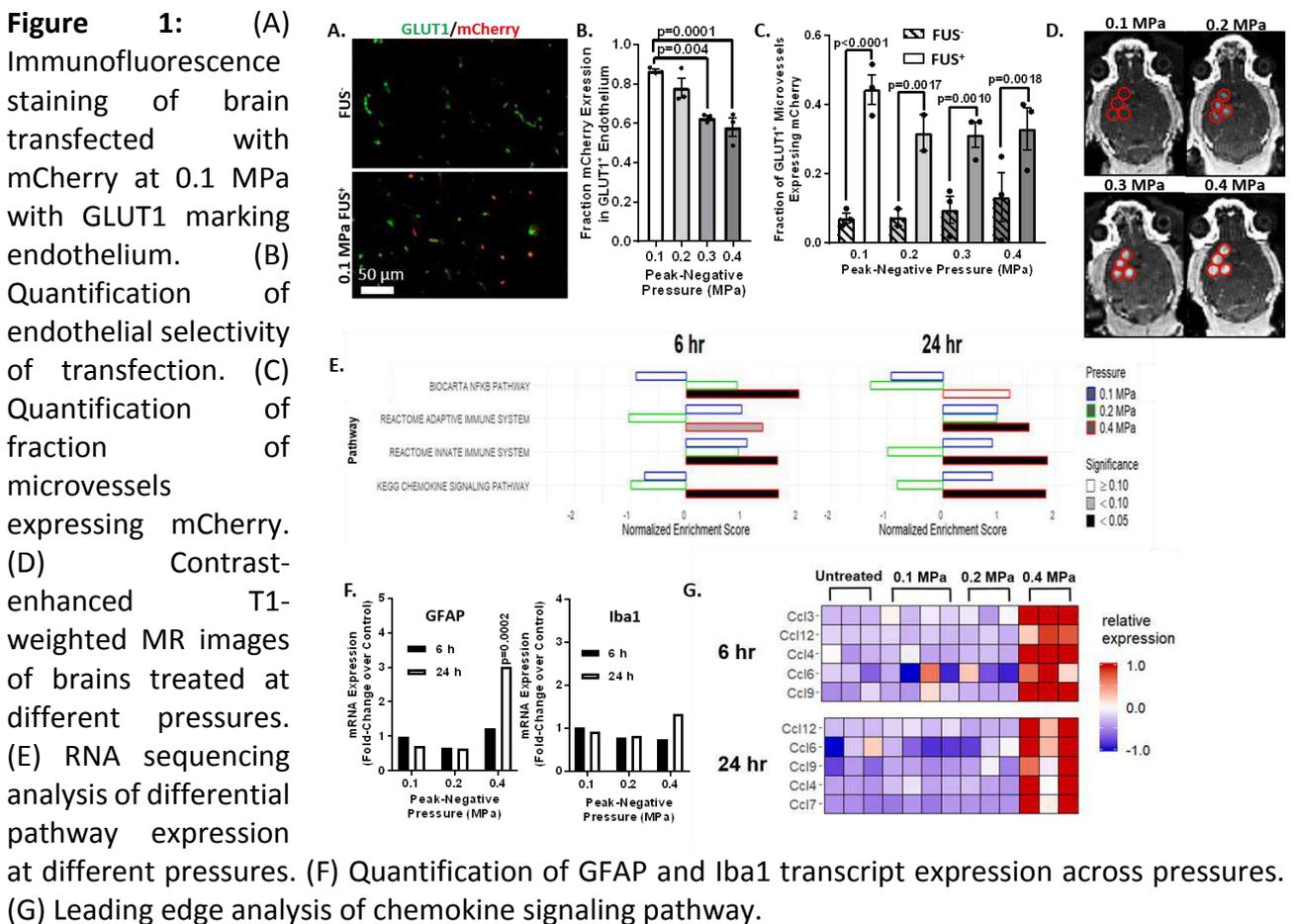
OBJECTIVE: To develop a novel gene therapy platform for focused ultrasound (FUS)-targeted endothelial-selective transfection in the brain independent of blood-brain barrier (BBB) opening.

METHODS: Cationic lipid microbubbles (i.v.) bearing mCherry plasmid were activated with pulsed FUS [peak-negative pressures (PNPs) = 0.1, 0.2, and 0.4 MPa] targeted to the striatum in C57BL/6 mice. Endothelial transfection was assessed (co-localization with GLUT1) at 24h. Bulk RNAseq was performed at 6 and 24h.

RESULTS: At 0.1 MPa, endothelial transfection selectivity (Fig. 1A) was maximal (Fig. 1B), with no decrease in transfected microvessels when compared to higher PNPs (Fig. 1C). Further, BBB disruption was not detectable (Fig. 1D), inflammation-associated pathways (RNAseq-GSEA) were not activated (Fig. 1E), and GFAP (astrogliosis), Iba1 (microgliosis), and multiple “leading edge” chemokines were unaffected (Fig. 1F and 1G).

CONCLUSIONS: Sonoselective transfection of cerebral endothelium, independent of BBB disruption and sterile inflammation, may be achieved with MB-plasmid constructs by tuning PNP. This provides a FUS-mediated gene therapy platform for applications wherein even transient BBB disruption may be contraindicated.

ACKNOWLEDGEMENTS: Supported by NIH R21EB024323, R01CA197111, and R01EB020147.



Bilateral focused ultrasound-induced blood-brain barrier opening improves spatial memory in the 3xTg Alzheimer's mouse model.

Maria Eleni Karakatsani¹, Maria Murillo¹, Robin Ji¹, Tara Kugelman¹, Karen Duff² and Elisa Konofagou^{1,3}

¹Department of Biomedical Engineering,

²Taub Institute for Research on Alzheimer's Disease and the Aging Brain

³Department of Radiology

OBJECTIVES

Focused ultrasound (FUS) has been proven to eliminate amyloid plaques and reduce the hyperphosphorylated tau protein from the hippocampal formation in different mouse models of Alzheimer's disease (AD), by opening the blood-brain barrier and triggering an immune response. Given the beneficial effects of FUS on isolated AD pathologies, it is essential to investigate its functional and morphological outcomes on brains bearing both pathologies simultaneously.

METHODS

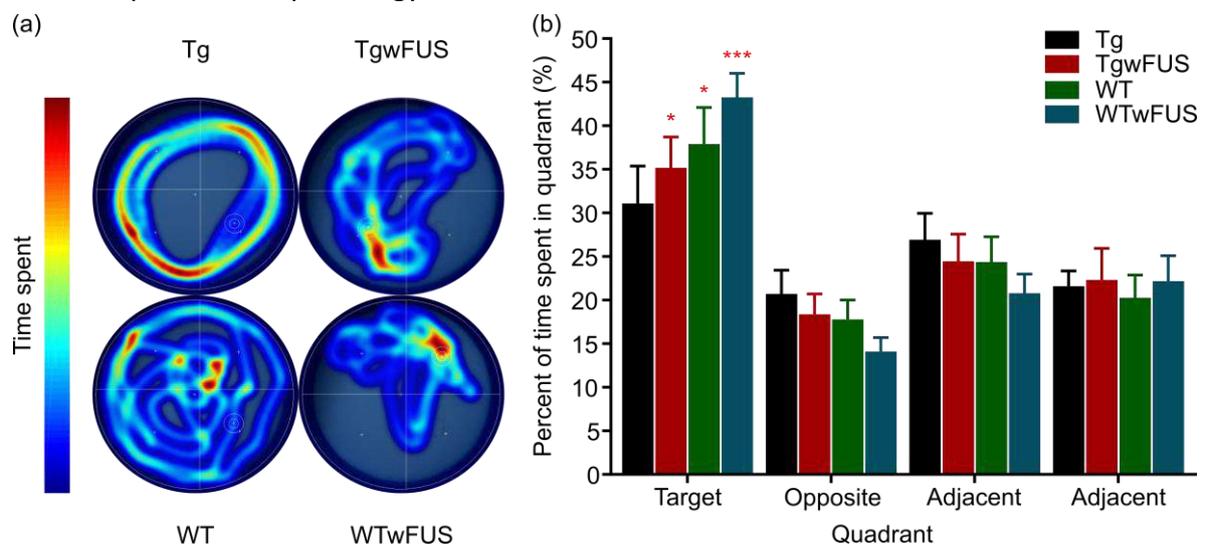
Eleven transgenic mice of the 3xTg line (14 months old) and eleven age-matched wild-type animals received bilateral sonications covering the hippocampus once per week for four consecutive weeks. The week following the last treatment, sonicated animals and control littermates underwent behavioral testing in the Morris water maze (MWM). All mice received a 5-day training familiarizing with reaching the escape-platform within 60 seconds. Following the training, the platform was removed and the amount of time spent in each MWM quadrant was quantified. The following week all animals were sacrificed and their brains processed for immunohistochemistry and biochemical analysis.

RESULTS

Animals that received FUS spent significantly more time in the quadrant where the platform was located on the order of 35.18% for the transgenic and 67% for the wild-type animals relative to the opposite sector.

CONCLUSIONS

Bilateral sonication significantly improved the spatial memory of the transgenic animals with complex AD pathology. FUS was shown to improve short-term memory performance both in the absence and presence of pathology.



CAPTION: a. Spatial distribution heatmaps of the time spent in the MWM. b. Percent time spent in each quadrant.

Blood brain barrier disruption by pulsed focused ultrasound with microbubbles or osmotic disruption by mannitol induces sterile brain inflammation

S.R. Burks¹, J.M. Colon¹, R.M. Lorsung¹, C.M. Kersch², M.A. Pagel², L. Muldoon², E.A. Neuwelt², J.A. Frank^{1,3}

¹Radiology and Imaging Sciences, NIH Clinical Center, Bethesda, USA

²Department of Neurology, Oregon Health & Science University, Portland, USA

³National Institute of Biomedical Imaging and Bioengineering, Bethesda, USA

e-mail: scott.burks@nih.gov

OBJECTIVES

To compare the proteomic and transcriptomic effects of blood brain barrier disruption (BBBD) by magnetic resonance (MR) image-guided pulsed focused ultrasound with microbubbles (pFUS+MB) to BBBD by intracranial infusion of mannitol.

METHODS

Sprague Dawley rats received MR-guided pFUS ultrasound using an LP100 (FUS Instruments, Toronto, Canada)(0.548MHz, 100 10-ms pulses, 9 cortical sonication spots). Peak rarefactional pressure for each pulse was increased by 0.008 MPa until ultraharmonic emissions (1.5f or 2.5f) recorded by hydrophone exceeded 3.5 fold above baseline. For pFUS, 20ul/kg Definity was intravenously infused at the start of the sonication. Other rats were given mannitol (25%, 0.5g/kg) infusions through the internal carotid artery. At various times post-BBBD-treatment, rats (n=5 per BBBD technique per time point) were euthanized for proteomics by multi-plexed ELISA or RNAseq using an Illumina6000.

RESULTS

Brains were harvested at 5 min, 30 min, 2, 6, 24 or 48 hr post-mannitol or 30 min, 2, 6, 12, 24, or 48 hr post pFUS+MB. KEGG pathway enrichment following RNAseq analyses for both BBBD techniques revealed pathway enrichment for nuclear-factor-kB (NFkB) activation, T-cell differentiation, and cytokines at early time points(<6 hr). Pathways enriched at later times are associated with autoimmune diseases, graft-versus-host disease, and apoptosis. Proteomics following either BBBD technique show increased expression of pro-inflammatory factors (e.g. TNFa, IL1a, IL1b, MIP1a). With pFUS+MB, many cytokines return to baseline levels by 24 hr, while elevations persist at 24hr with mannitol BBBD.

CONCLUSIONS

BBBD by either hyperosmotic mannitol or pFUS+MB induces sterile brain inflammation and immune activation profiles by proteomic and transcriptomic analyses.

OPTIMIZATION OF FOCUSED ULTRASOUND-ENABLED BRAIN TUMOR LIQUID BIOPSY (FUS-LBx)

Lifei Zhu¹, Arash Nazeri², Yimei Yue¹, Weijun Liu³, Xiaowei Wang³, Gavin P. Dunn^{4,5,6}, Allegra A. Petti⁷, Eric C. Leuthardt^{1,2,4,5,8}, Hong Chen^{1,3}

¹ Department of Biomedical Engineering, ² Mallinckrodt Institute of Radiology, ³ Department of Radiation Oncology, ⁴ Department of Neurosurgery, ⁵ Department of Neuroscience, ⁶ Andrew M. and Jane M. Bursky Center for Human Immunology and Immunotherapy Programs, ⁷ Department of Medicine, ⁸Center for Innovation in Neuroscience and Technology, Washington University, Saint Louis, USA

e-mail: hongchen@wustl.edu

OBJECTIVES

In our previous proof-of-concept study, we demonstrated the feasibility of focused ultrasound enabled brain tumor liquid biopsy (FUS-LBx) technique using mouse models of glioblastoma. The objective of this study was to investigate the effects of FUS acoustic pressure on tumor biomarker release efficiency and brain injury to optimize the FUS-LBx technique.

METHODS

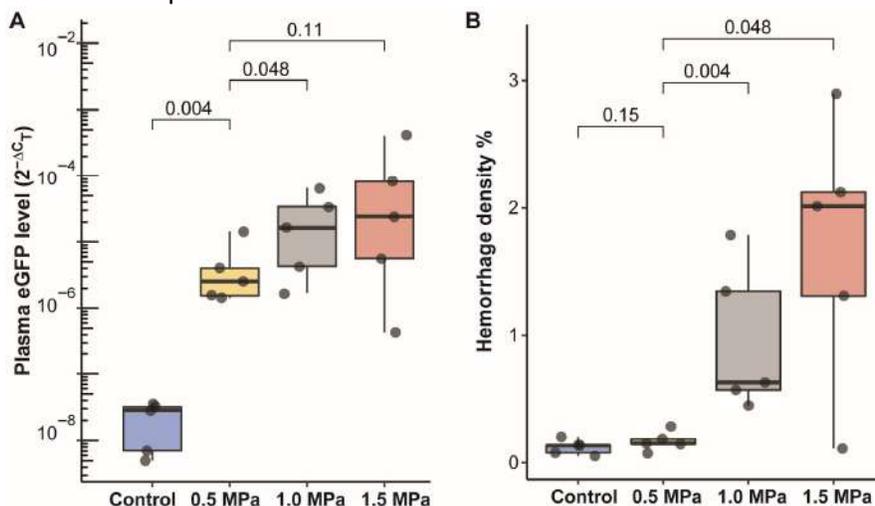
Mice with orthotopic implantation of enhanced green fluorescent protein (eGFP)-transfected glioblastoma cells were treated using magnetic resonance (MR)-guided FUS system in the presence of systemically-injected microbubbles at three different peak negative pressure levels (0.5 MPa, 1.0 MPa, and 1.5 MPa). Plasma eGFP mRNA levels were quantified using quantitative polymerase chain reaction (qPCR). Contrast-enhanced MR images were acquired before and after the FUS treatment.

RESULTS

FUS at 0.5 MPa demonstrated an increase in plasma eGFP mRNA level that was comparable to those at higher acoustic pressures (1.0 MPa and 1.5 MPa) (Fig. A). Hemorrhage associated with FUS at 0.5 MPa was significantly lower than that with higher acoustic pressures and not significantly different from the control group (Fig. B). MRI analysis revealed that post-sonication intratumoral and peritumoral hyperenhancement was linearly correlated with the level of FUS-induced biomarker release and the extent of hemorrhage.

CONCLUSIONS

This study suggests that FUS-LBx technique can be optimized to be a safe and effective image-guided biomarker release technique.



(A) Plasma levels of eGFP mRNA quantified using quantitative PCR and (B) Hemorrhage density in the control and FUS-treated mice.

EFFECTS OF DEXAMETHASONE ON VASCULAR PERMEABILITY AND INFLAMMATORY RESPONSE FOLLOWING FOCUSED ULTRASOUND AND MICROBUBBLE-MEDIATED BBB TREATMENT

Dallan McMahon^{1,2,*}, Wendy Oakden¹, and Kullervo Hynynen^{1,2,3}

¹ Physical Sciences, Sunnybrook Research Institute, Toronto, ON, Canada

² Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

³ Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada

* Corresponding author: dallan.mcmahon@mail.utoronto.ca

OBJECTIVES: Preclinical research has demonstrated the utility of focused ultrasound (FUS) and microbubbles (MBs) to transiently increase BBB permeability for therapeutic agent delivery; however, recent work has shown that some degree of inflammation accompanies this increase in BBB permeability. Dexamethasone (DEX), a synthetic glucocorticoid, has anti-inflammatory properties and is known to rapidly reduce BBB permeability in brain tumours. Work presented here explores the effects of post-sonication DEX administration on BBB permeability and inflammation.

METHODS: Male Sprague Dawley rats received unilateral hippocampal sonication; BBB permeability (K^{trans}) was assessed 15 minutes later by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). Following imaging, animals received either DEX (5 mg/kg; ip) or saline and were imaged two hrs post-FUS+MBs. Protein expression was assessed two days following sonication.

RESULTS: Hippocampal K^{trans} dropped by $60.8\% \pm 9.7\%$ and $74.2\% \pm 10.4\%$ between 15 minutes and two hrs following FUS+MBs in saline and DEX-treated animals, respectively ($p = 0.003$). DEX prevented FUS+MB-induced elevations in ICAM1, MCP1, VEGF, and GFAP expression two days post-sonication.

CONCLUSION: The expedited restoration of BBB integrity, combined with the anti-inflammatory properties of DEX, may lead to a reduction in the magnitude of the inflammatory response following FUS+MB treatment. This may provide greater clinical flexibility, allowing repeated treatments in short succession with reduced risk for deleterious effects to accumulate.

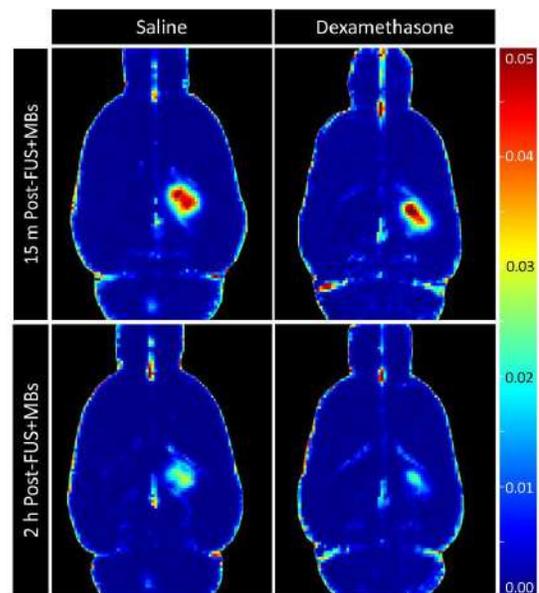


Figure 1: Impact of DEX on BBB permeability following FUS+MBs. Representative K^{trans} maps (min^{-1}) acquired at 15 min and two hrs post-FUS+MBs, demonstrating a reduction in dorsal hippocampal BBB permeability in DEX-treated animals compared to saline control.

Therapeutic effects of BBB/BTB opening by FUS in anti-cancer agent delivery for drug-resistant breast cancer brain metastasis model

Eun-Joo Park^{1,2*}, Yuri Cheon¹, Yundeok Ahn¹, Jae Young Lee^{1,3}

¹Department of Radiology, Seoul National University Hospital, Seoul, Korea

²Biomedical research institute, Seoul National University Hospital, Seoul, Korea

³Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

e-mail: ejpark@snuh.org, yr861117@gmail.com, duck512@gmail.com, lee4u@snu.ac.kr

OBJECTIVES

This study was designed to evaluate therapeutic effects of the combined treatment of anti-cancer agent with BBB/BTB opening induced by MRgFUS, especially for drug-resistant breast cancer brain metastasis model.

METHODS

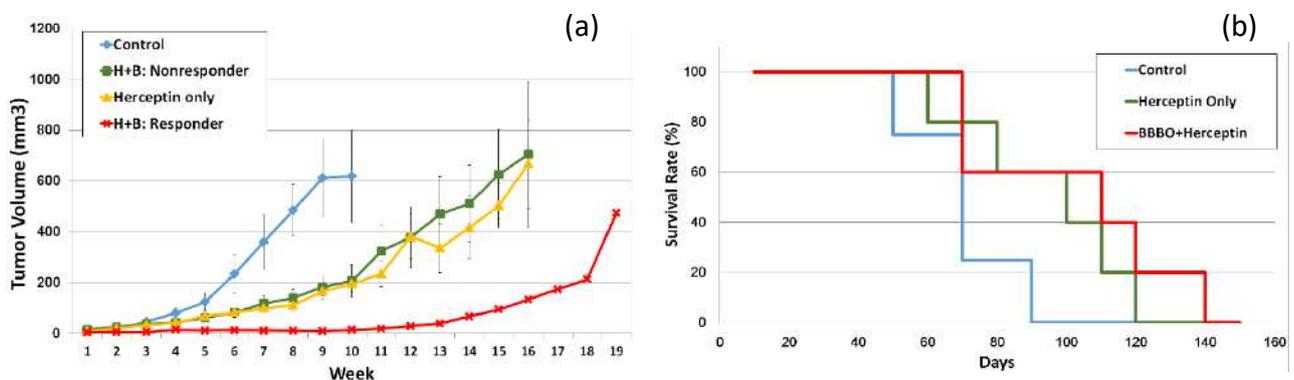
Human breast cancer cells (BT474) were pre-treated with paclitaxel and the drug-resistance of cells were evaluated by the expression level of FOX M1 which plays a key role in cell cycle progression. Tumor bearing animals were divided into three groups: control, anti-cancer agent treatment, and combined treatment of FUS and anti-cancer agent. Animals in the treatment groups received IV administration of trastuzumab with/without FUS treatment once a week for six times. Tumor growth and survival rates were monitored for additional 12 weeks after the treatments were done.

RESULTS

The mean tumor volumes of both treatment groups were significantly less than those of the control group. The tumor growth of the 'responder' in combined treatment group showed significant outcome of tumor growth control while the 'non-responder' showed similar tumor growth with the group treated with anti-cancer agent only.

CONCLUSIONS

In this study, drug-resistant breast cancer cells were used to mimic the breast cancer brain metastasis in patients and the study results showed the possibility of applying BBB/BTB opening induced by FUS in pre-treated, drug-resistant breast cancer brain metastases. However, the results also showed therapeutic limitations of passive drug delivery even with enhanced permeability. Therefore, an active drug delivery in combination with BBB/BTB opening by FUS is needed for more effective therapeutic outcomes.



Tumor volume measurements (a) and survival analysis (b) for each group.

The pentylenetetrazol induced acute epilepsy is alleviated by transcranial focused ultrasound pulsation in rats

Sin-Guang Chen^{1, 2}, Chih-Hung Tsai¹ and Hao-Li Liu^{1, 3}

¹Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan

²Department of Health Technology and Informatics, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hong Kong, China

³Department of Neurosurgery, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
e-mail: singuang.chen@gmail.com; chihung_tsai@hotmail.com; haoliliu@mail.cgu.edu.tw

OBJECTIVES

This study seeks to verify the use of FUS pulsations to suppress spikes in an acute epileptic small-animal model, and to investigate possible biological mechanisms by which FUS pulsations interfere with epileptic neuronal activity.

METHODS

The study used a total of 83 Sprague-Dawley rats. For the epilepsy model, rats were administered pentylenetetrazol (PTZ) to induce acute epileptic-like abnormal neuron discharges, followed by FUS exposure. Various ultrasound parameters were set to test the epilepsy-suppressing effect, while the electroencephalogram (EEG) was concurrently monitored and postoperatively analyzed. Animal behavior was monitored and histological examinations were conducted to evaluate the hazard of ultrasound exposure, and Western blotting was used to evaluate the correlation between FUS-induced epileptic suppression and the PI3K-mTOR signaling pathway.

RESULTS

We observed that FUS exposure contributes to epileptic activity suppression, and this suppression effect depends on the selection of ultrasound parameters. Increased exposure levels and pulse duty both contributed to improved suppression of PTZ-induced spikes. Testing exposure parameters did not cause tissue damage, inflammatory response, or behavioral abnormalities. We also found that the pulsed sonication disturbed the PTZ-activated mammalian target of the rapamycin (mTOR) and S6 kinase signaling pathways.

CONCLUSIONS

Our results suggest that pulsed FUS exposure effectively suppresses epileptic syndrome in an acute epilepsy animal model, and confirmed that ultrasound pulsation regulates the PI3K-Akt-mTOR pathway, which might be a potential mechanism for using ultrasound for epilepsy control.

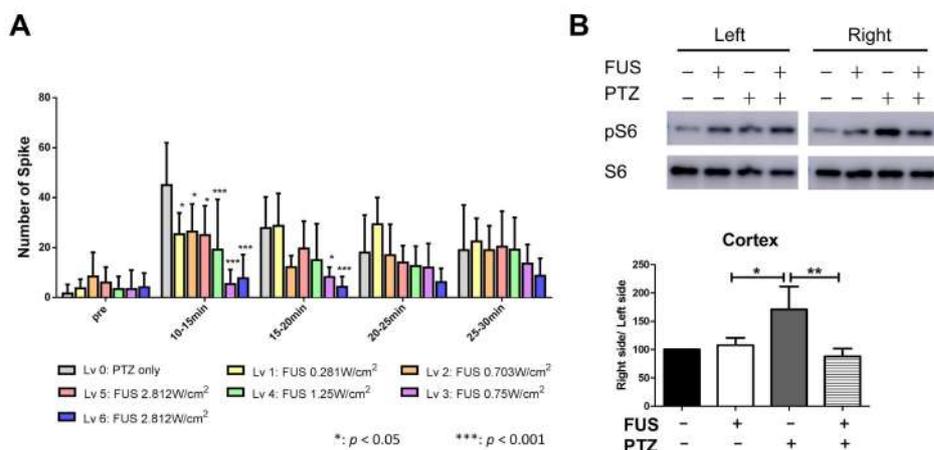


Figure 1. (A) Quantification of epileptic EEG signal bursts. The number of epileptic EEG spikes in different time frames was calculated from raw EEG peaks. The bar chart compares EEG bursts in PTZ-induced rats treated with or without FUS in different time frames. The results are means \pm SD of seven animal groups. * $p < 0.05$, *** $p < 0.001$, vs. PTZ-induced rats without FUS treatment. (B) FUS treatment suppressed the PTZ-induced hyperphosphorylation of S6 in the right cortex. The phosphorylated S6 and S6 were detected by western blotting. The quantified results are shown in the bar chart.



EDUCATION

GETTING INNOVATIVE MEDICAL DEVICES TO MARKET:

Getting innovative medical devices to market – *Nicolas Guillem*

HYPERTHERMIA TECHNOLOGIES:

Hyperthermia Technologies – *Holger Gruell*



Getting innovative medical devices to market

Nicolas Guillen, EDAP-TMS, Vaulx en Velin (France)

e-mail: nguillen@edap-tms.com

How do we move from a technological concept to a product launched on the market and used in daily routine for the benefit of patients?

Taking the Focal One[®] system used for prostate cancer therapy by HIFU as an example, this course will provide a detailed description of the major steps leading up to the market release of a medical device: from technological design to regulatory certification through the validation phases of its technical and clinical performance.

In addition, it will shed light on the complexity of the Innovation process leading to the introduction on the market of a medical device. This aspect will be addressed through the presentation of the roles of the main actors of the ecosystem:

- Developers, composed of members of academic research, manufacturers as well as bodies that structure and finance innovation.
- Requesters, who are mainly patients, caregivers and the medical corps.
- Regulators, represented by the State through its competent authorities and more generally by the European Union through its directives and standards.
- Broadcasters, whose role is to promote technologies in the health care system: health authorities, social insurance, health mutual and health care institutions.

HYPERTHERMIA TECHNOLOGIES

Prof. H. Gröll, PhD

Professor, chair “Experimental Imaging and Image-guided Therapy”

Department of Diagnostic and Interventional Radiology

University Hospital of Cologne, 50937 Cologne, Germany

e-mail: holger.Gruell@uk-koeln.de

Abstract

It has been long recognized that heating of malignant tumors to hyperthermic temperatures in the range of 41-43 °C enhances the efficacy of radio-, and chemotherapy in a synergistic fashion. In vitro and in vivo studies performed over the last decades showed that hyperthermia is a multitarget treatment acting on cellular as well as tissue level sensitizing malignant tissue for damage from radiation of cytostatic drugs. Furthermore, hyperthermia can act as a stimulus to trigger local drug delivery using drug loaded nanoparticles such as temperature sensitive liposomes (TSLs). As the temperature window is narrow and needs tight spatial and temporal control much research was devoted to devices that allow application of hyperthermia in a clinical setting.

This talk will explain first some basic aspects of hyperthermia and its biological mode of action. Next, an overview will be given on medical devices used in the past and present to induce hyperthermia, such as light, water bath, radiofrequency as well as focused ultrasound. The latter will be explained in detail including aspect of image guidance and in vivo temperature measurement and control. Also, the current strengths and weaknesses of HIFU for hyperthermia applications compared to current standard techniques will be explained and put into context of possible clinical applications such as combination of thermal therapies or drug delivery.



ORGAN PANEL: BRAIN

INVITED TALKS:

The future of focused ultrasound surgery: perspectives based on the recent clinical & basic researches - *Jin Woo Chang*

David vs. Goliath: the Italian results with a trans-cranial MRgFUS system integrated with a 1.5T scanner - *Cesare Gagliardo*

Cutting edge imaging-based ultrasound therapies for the brain - *Roland Beisteiner*

Focused low energy single pulse ultrasound therapy in neurological rehabilitation. An overview of actual trends - *Henning Lohse-Busch* Long-term results of MR Guided Focused Ultrasound Vimthalamotomy in Parkinson's patients with medication-refractory disabling tremor - *Ilana Schlesinger*

ORAL PRESENTATIONS:

MR guided focused ultrasound thalamotomy for tremor: Lessons learned from 120 cases - *Michael Schwartz*

Neuronavigation-Guided Focused Ultrasound (NaviFUS) for transcranial blood-brain barrier opening clinical trial in recurrent glioblastoma patients - *Ko-Ting Chen*

Alendronate might improve the skull density ratio of MRgFUS candidates with brain disorders - *Hisashi Ito*

Beyond the Thalamus-Unilateral MR guided focused ultrasound for the treatment of essential tremor targeting the ventral intermedius nucleus and the zone incerta - *Ayesha Jameel*

Does treatment efficiency change when performing bilateral treatments using tcMRgFUS thlamotomy? Study on 4 patients treated bilaterally for Neuropathic Pain - *Jiachen Zhuo*

Three-Year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor - *Pejman Ghanouni*

The world's initial experience of bilateral treatment of essential tremor using MR guided focused ultrasound - *Ayesha Jameel*



The future of focused ultrasound surgery: perspectives based on the recent clinical & basic researches

Jin Woo Chang, M.D., Ph.D.

Center for Innovative Functional Neurosurgery, Department of Neurosurgery, Brain Research Institute, Yonsei University College of Medicine, Seoul, Korea

Our knowledge of the nervous system in health and disease has, however, increased considerably during the last fifty years. Recently, neurosurgery reveals promising new stereotactic strategies such as neuromodulation by the thermal lesioning, deep brain stimulation, radiosurgery, and a laser ablation to deal with diseases of the central nervous system.

Most recently, the field of MRI guided high intensity focused ultrasound surgery (MRgFUS) is evolving and offers the new hope for the treatment of many brain disorders through both ablative mechanism and non-ablative mechanisms such as drug delivery, neuromodulation and blood brain barrier (BBB) opening. Currently we demonstrated the beneficial effect of MRgFUS by performing incisionless minimally invasive Vim thalamotomy as a treatment for essential tremor (ET). And, we also underwent the clinical studies for the evaluation of the role of MRgFUS in the management of Parkinson's disease (PD), obsessive compulsive disorders (OCD) and depression especially for those who are refractory for the medical managements. As well, we recently are undergoing the clinical trial of the feasibility study of glioblastoma (GBM). All MRgFUS was performed in a 3.0 T MRI

(Signa, GE, USA) using the Exablate 4000 device (Insightec, Israel), which features a 30 cm diameter hemispherical 1024 elements phased array transducer operating at 680 KHz or 220 KHz with immobilization of patient's head by fixation in an MRI compatible stereotactic frame (Radionics, USA). In our clinical trials, we found that MRgFUS was a safe and very effective almost non-invasive surgical method for the medically refractory functional neurological disorders. However, we also notice that there are several important issues and unsolved problems for MRgFUS. In this presentation, I will also demonstrate personal experiences, trouble shootings as well as laboratory works for MRgFUS.

David vs. Goliath: the Italian results with a trans-cranial MRgFUS system integrated with a 1.5T scanner

Dr Cesare Gagliardo – University of Palermo

Trans-cranial MRgFUS (tcMRgFUS) is taking place as a revolutionary treatment modality for several neurological disorders. MRI plays a central role in these treatments since it is necessary for optimal targeting, real-time thermal monitoring and to verify intra and post-treatment effects of the focused ultrasound beam in the targeted area. Results in patients with several neurological disorders (mostly essential tremor, tremor-dominant Parkinson and neuropathic pain) have been published with systems operating with 3T MR scanners.

In the past three years we have successfully used a tcMRgFUS system integrated for the first time with a 1.5T MRI scanner. The use of a dedicated surface coil allowed us to achieve a reliable thermal imaging and morphological sequences provided the expected signal-to-noise ratio for planning and monitoring the procedure. This high-quality intra-procedural imaging resulted in precise treatment planning and a good localization of the lesion during the ongoing treatment (thus before discharging the patient from the treating table).

Furthermore, thanks to the crucial support of state-of-the-art advanced neuroimaging techniques as thalamic nuclei parcellation for optimal target identification, 1.5T units are confirmed to be still completely adequate for most MRI examinations acquired for clinical diagnostic, research as well as interventional procedures.

Even if further insights and extended studies are required, the possibility of integrating a tcMRgFUS system with a 1.5T scanner may lead to a greater spread of this promising, emerging technology even in centres that are not equipped with 3T systems, resulting in increased patient accessibility to this promising treatment option.

Cutting edge imaging-based ultrasound therapies for the brain

In recent years, groundbreaking research has focused on imaging-based ultrasound techniques which allow new low-invasive or noninvasive therapies for brain diseases. Currently 3 approaches exist which open new avenues for innovative therapies. First, low-invasive and highly focal ablation of dysfunctional tissue, second low-invasive and exactly targeted opening of the blood brain barrier (BBB) and third, noninvasive focal and exactly targeted neuromodulation. All these methods depend on state of the art morphological and functional neuroimaging techniques for optimized targeting and therapeutic control. Major advances concern the possibility to target neuromodulation with unprecedented precision in pathological brains, to perform deep brain stimulation (DBS) for the first time with a non-invasive or low-invasive approach, and to offer add on brain therapy in extension to already running treatments. This talk will focus on the latest developments (like Transcranial Pulse Stimulation (TPS)) and their clinical benefits for Alzheimer's Disease (AD). fMRI data related to TPS will be shown.

**Focused low energy single pulse ultrasound therapy in neurological rehabilitation.
An overview of actual trends.**

H. Lohse-Busch, Rheintalklinik, 79189 Bad Krozingen, Germany

The overview will deal with the symptomatic improvement by low energy single pulse ultrasound therapy of spasticity, dystonia and muscular stiffness in children and adults, with casuistics of spinal cord injury and myelomeningocele, of unresponsive wakefulness syndrome, distally symmetric polyneuropathy and Parkinson's disease. The application was performed by the treatment of the periphereal muscles and/or with transcranial pulse stimulations (TPS) of the brain itself.

An open pilot study with 15 patients aiming on the general feasibility of TPS treatment for Alzheimer's disease will be presented. The patients received 6 sessions with TPS in 2 weeks. The outcome was assessed with the corrected CERAD-Plus test battery before and after the 2-week treatment series with an improvement of cognitive abilities of 8,9%. The results then were followed up after 1 month (+ 11.9 % against baseline) and 3 months (+12.8%) without any further TPS treatment. In the following 2 years 6 of these patients received regularly one session with TPS every 6 weeks. The result after 12 months was still good (+12.0%). After 2 years of the described 6-week interval TPS treatment the results had declined back to the baseline (+0.2). After another 2-week TPS treatment the cognitive abilities improved again partially. This feasibility study deals with only a small number of patients. But it gives encouraging hints to more investigations in this interesting field.

**LONG-TERM RESULTS OF MR GUIDED FOCUSED ULTRASOUND VIM-
THALAMOTOMY IN PARKINSON'S PATIENTS WITH MEDICATION-REFRACTORY
DISABLING TREMOR**

I. Schlesinger^{1,2}, A. Sinai³, A. Eran⁴, M. Nassar¹, M. Constantinescu³

¹Department of Neurology, Rambam Health Care Campus, Haifa, Israel

²Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

¹Department of Neurosurgery, Rambam Health Care Campus, Haifa, Israel

¹Department of Radiology Rambam Health Care Campus, Haifa, Israel

OBJECTIVES

Long term results of MR-guided focused ultrasound (MRgFUS) VIM-thalamotomy in Tremor-Dominant Parkinson's Disease (TDPD) patients are lacking. We report our single center 5-year experience with VIM MRgFUS thalamotomy.

METHODS

Between Feb-2014 and Mar-2019, thirty-four TDPD patients underwent unilateral MRgFUS VIM thalamotomy and were assessed by the motor part of the Unified PD rating scale (UPDRS) and the PDQ-39 quality of life questionnaire.

RESULTS

In all patients treatment resulted in immediate cessation of tremor in the treated hand. Twenty-seven were male, mean age was 63.4 ± 9.3 years, with a mean disease duration of 6.7 ± 4.6 years. UPDRS scores decreased from 25.6 ± 7.7 to 13.4 ± 8.6 (34 patients, $p < 0.001$) at 1 month, to 11.8 ± 8.2 (30 patients, $p = 0.0001$) at 6 month, to 10.6 ± 7.0 (19 patients, $p < 0.0001$) at 1 year, 8.6 ± 6.6 (11 patients, $p < 0.001$) at 2 years, 11.4 ± 7.9 (8 patients, $p = 0.0004$) at 3 years, 11.2 ± 9.0 (6 patients, $p = 0.02$) at 4 years and 7.0 ± 4.0 (2 patients) at 5 years due to decreased tremor and rigidity. PDQ-39 scores significantly improved from 42.8 ± 21.1 to 24.5 ± 18.4 at one year ($p = 0.002$) and remained lower than baseline over time. In 5 patients tremor returned to the same degree as before MRgFUS. Adverse events after the procedure were mild and resolved within 3 months in all patients.

CONCLUSIONS

MRgFUS thalamotomy for TDPD is an effective, durable and safe procedure that provides long-term tremor relief and in some cases reduced rigidity, with subsequent improvement in quality of life. Additional studies are needed to substantiate our favorable results.

MR GUIDED FOCUSED ULTRASOUND (MRgFUS) THALAMOTOMY FOR ESSENTIAL TREMOR: LESSONS LEARNED FROM 120 CASES

M.L. Schwartz^{1,2}, Y. Huang³, R.M. Jones³, R. Endre³, D. Riegert⁴, N. Lipsman^{1,2}, K. Hynynen^{3,5}

¹Division of Neurosurgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

²Department of Surgery, University of Toronto, Toronto, ON, Canada

³Physical Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada

⁴Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

⁵Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

e-mail: m.schwartz@utoronto.ca

OBJECTIVES

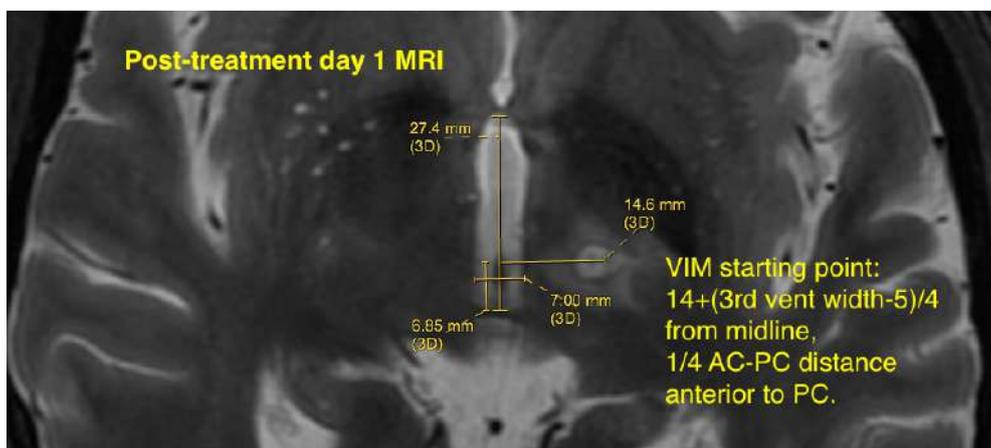
Since 2012, experience with >120 patients treated for essential tremor (ET) with MRgFUS thalamotomy has modified our practice.

METHODS/RESULTS

Our initial targeting of the VIM is illustrated in the figure below. Cognizant of the thalamic homunculus, we are cautious about moving laterally to stabilize the proximal arm due to internal capsule proximity. We readily adjust anteromedially when initial small volume lesioning produces only modest tremor abatement (Boutet, 2018). When writing is disproportionately affected and not mitigated by lesioning at the initial focus, we target VOP/VOA anteromedially (Meng, 2018). We do not correct for focal displacements superior to the AC-PC plane. Because sonications are progressively less efficient (Hughes, 2018), we increase the sonication energy as quickly as possible, provided there is no sensory reference. Sonication parameters may be set such that the controlling software predicts temperatures >60°C, with sonications halted manually at the desired temperature. Bone thickness is as important as skull density ratio (SDR). A practical lower limit for SDR is 0.32, but we have failed with thick skulls and have succeeded with lower SDRs. Large round heads are favorable. Repeated sonications with temperatures of 50° can accumulate sufficient dose to produce lesions with good effect (Huang, 2018). When repeated high-energy sonications are required, remifentanyl, administered immediately pre-sonication by the anesthetist, is effective analgesia. It is metabolized rapidly, permits examination of the patient immediately post-sonication, and does not accumulate because of the long cooling times between sonications.

CONCLUSIONS

These refinements in technique contribute to greater efficacy of MRgFUS for ET.



Neuronavigation-Guided Focused Ultrasound (NaviFUS) for Transcranial Blood-Brain Barrier Opening Clinical Trial in Recurrent Glioblastoma Patients

Ko-Ting Chen^{1,2}, Pin-Yuan Chen³, Ya-Jui Lin¹, Wen-Yen Chai⁴, Hao-Li Liu^{1,5}, Kuo-Chen Wei¹

¹Department of Neurosurgery, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

²Ph.D. Program in Biomedical Engineering, Chang Gung University, Taoyuan, Taiwan,

³Department of Neurosurgery, Chang Gung Memorial Hospital at Keelung, New Taipei, Taiwan

⁴Department of Diagnostic Radiology and Intervention, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

⁵Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan

email: chenkoting@gmail.com; haoliliu@mail.cgu.edu.tw

OBJECTIVES Coupling focused ultrasound (FUS) with systemic administration of microbubbles (MB) has been confirmed feasible in transiently opening the blood-brain barrier (BBB). NaviFUS, a novel device integrating the concept of neuronavigation and FUS-MB system, is able to intraoperatively steer the ultrasound energy precisely and repeatedly at targeted CNS area. The purpose of this study is to evaluate the safety and feasibility of using NaviFUS in treating recurrent glioblastoma patients.

METHODS A prospective, open-label, single-center, single-arm, dose escalation, first-in-human phase 1 clinical trial (NCT03626897) is conducted at Chang Gung Memorial Hospital, Taiwan. A total of 6 patients were recruited. Before FUS treatment, all patients received thin-slice contrast-enhanced magnetic resonance imaging (MRI) and computed tomography scanning to define the region of interest. A single FUS treatment was given to each patient with the sonication site receiving an escalating dose of ultrasound energy. Dynamic contrast-enhanced MRI was obtained immediately and 24 hours after FUS procedures, while heavy T2* weighted sequence was obtained to evaluate the occurrence of micro-hemorrhage.

RESULTS All FUS treatments were well-tolerated with no clinical or radiologic adverse events. All, except one patient in low-dose group, had significant signal intensity (SI) change at T1 contrast images, demonstrating successful BBB-opening. K^{trans} level was transiently elevated yet normalized, meaning BBB-closure, at 24 hours after treatment. No T2* SI change was observed.

CONCLUSIONS The results provide the support for a planned phase 2 trial to evaluate whether NaviFUS can effectively enhance the delivery of chemotherapeutic agents and yield a better tumor control.



Figure. Neuronavigation-Guided Focused Ultrasound Device (NaviFUS) for transcranial BBB opening in treating CNS diseases.

Alendronate might improve the skull density ratio of MRgFUS candidates with brain disorders

Hisashi Ito¹, Jordi Rumià², Shigeru Fukutake¹, Kazuaki Yamamoto³, Toshio Yamaguchi⁴, Takaomi Taira³, Tetsumasa Kamei¹

¹Department of Neurology, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Japan

²Functional Neurosurgery ResoFUS ALOMAR Barcelona University of Barcelona, Barcelona, Spain

³Department of Neurosurgery, Tokyo Women's Medical University, Tokyo, Japan

⁴Research Institute of Diagnostic Imaging, Shin-Yurigaoka General Hospital, Kawasaki, Japan

e-mail: hisashi.ito@tokushukai.jp

OBJECTIVES

The skull volume and skull density ratio (SDR) are two key factors determining the success of MRgFUS treatment for brain diseases. We examined the efficacy of Alendronate (Aln), one of the popular bisphosphonates for osteoporosis, to improve a SDR value.

METHODS

The objects were 6 Parkinson's disease patients (PD, 2 men, 4 women, 70.7±7.7 years old) and 1 Essential tremor patient (ET, man, 81 years old). All the patients desired MRgFUS treatment; however, we could not schedule their treatments as their SDR values were too low to perform MRgFUS. As they had untreated osteoporosis, we could administer Aln (35mg/week).

RESULTS

The SDR value elevated in 4 out of 7 patients following administration of Aln (Figure). No adverse reactions related with Aln were observed.

CONCLUSIONS

Aln increases the degree and uniformity of bone matrix mineralization and decreases the porosity of cortical bone. Although it will take several months, Aln may be a useful option for MRgFUS candidates with a low SDR value. Further investigations concerning the efficacy of Aln and other medicines to improve a SDR value are necessary.

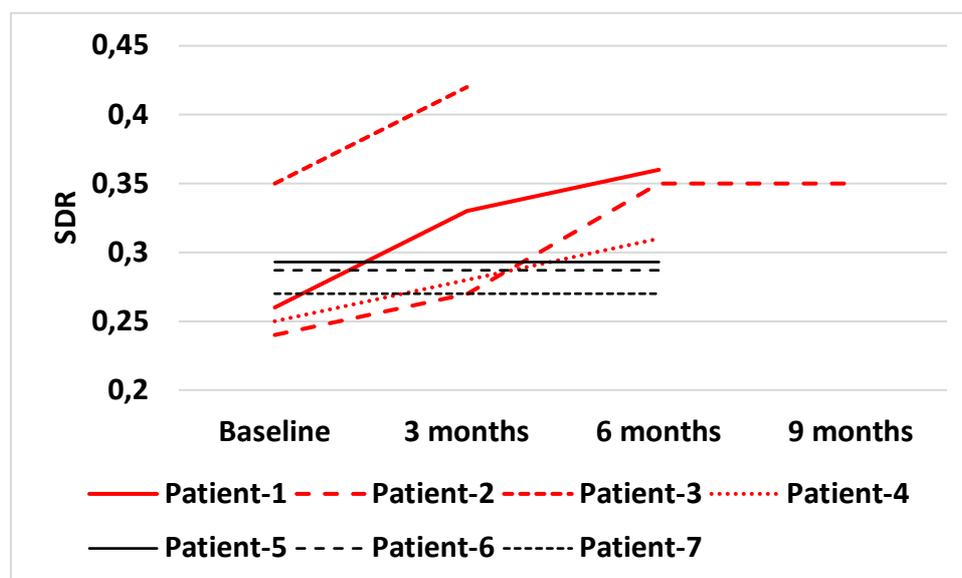


Figure. Changes in after administration of Aln (Patients 1-3, 5-7 were PD; Patient 4 was ET)

BEYOND THE THALAMUS - UNILATERAL MR GUIDED FOCUSED ULTRASOUND FOR THE TREATMENT OF ESSENTIAL TREMOR TARGETING THE VENTRALIS INTERMEDIUS NUCLEUS AND THE ZONA INCERTA

A.J. Jameel¹, P.G. Bain², D Nandi¹, B Jones¹, O Kirmi¹, W Gedroyc¹

¹Imperial College NHS Healthcare Trust, London. ²Imperial College of Science Technology and Medicine, London. E-mail: Ayesha.jameel@nhs.net; wladyslaw.gedroyc@imperial.ac.uk

INTRODUCTION:

Magnetic Resonance guided focussed ultrasound (MRgFUS) is non-invasive treatment for essential tremor (ET) that allows targeted thermal ablation of brain tissue under real time image guidance. Previous studies have demonstrated targeting the thalamic Ventral Intermedius Nucleus (Vim) to be an effective treatment in ET; this paper describes the world's first trial using MRgFUS to target both the thalamic Vim and the subthalamic Zona Incerta (ZI).

METHODS:

A prospective study enrolled 13 patients with medication refractory ET for unilateral MRgFUS procedure. Tremor severity was assessed using the Bain and Findley Spirals (BFS). Spirals were collated immediately pre-procedure, after targeting the Vim and after targeting the ZI. These spirals were anonymised, randomised and scored by three blinded movement disorder Neurology Consultants. The percentage improvement in the spiral scores after Vim ablation and after ZI ablation were compared and analysed.

RESULTS:

In all patients there was successful thermal ablation of the target tissue at the Vim and ZI. The mean percentage BFS improvement after Vim lesioning was 42.0% (11.1-81.8%). The mean percentage BFS improvement after Vim and ZI lesioning was 66.7% (18.8- 81.8%). The mean additional benefit of targeting the ZI was 24.6% (range 0% to 55.5%). There were no permanent significant adverse effects.

CONCLUSIONS:

Our study demonstrates the additional benefit of targeting the ZI alongside the Vim in a unilateral MRgFUS procedure for the treatment of ET. No significant permanent adverse events occurred after Vim and ZI ablation. Our study provides further evidence that MRgFUS is a safe, effective, curative treatment for ET.

Three-Year Follow-Up of Focused Ultrasound Thalamotomy for Essential Tremor

Introduction: We assessed clinical outcomes at 3-year follow-up of a controlled multi-center prospective trial to test the durability of efficacy and safety of transcranial Magnetic Resonance-guided Focused Ultrasound (tcMRgFUS) thalamotomy for medication-refractory essential tremor (ET) patients.

Methods: Outcomes were based on the Clinical Rating Scale for Tremor, including hand combined tremor-motor (scale of 0-32), functional disability (scale of 0-32), and postural tremor (scale of 0-4) scores, and total scores from the Quality of Life in Essential Tremor Questionnaire (scale of 0-100). Scores at 36 months were compared with baseline and at 6 months after treatment to assess for efficacy and durability. Adverse events were also reported.

Results:

- Measured scores remained improved from baseline to 36 months (all $P < 0.0001$).
- Range of improvement from baseline was between:
 - 38-50% in hand tremor;
 - 43-56% in disability;
 - 50-75% in postural tremor; and
 - 27-42% in quality of life.
- When compared to scores at 6 months, median scores increased for:
 - hand tremor (95%CI 0-2, $P = 0.0098$), and
 - disability (95%CI 1-4, $P = 0.0001$).
- During the 3rd follow-up year, all previously noted adverse events remained mild or moderate, none worsened, two resolved, and no new adverse events occurred.

Conclusions: Results at 3 years after unilateral tcMRgFUS thalamotomy for ET show continued benefit, and no progressive or delayed complications. Patients may experience mild degradation in some treatment metrics by 3 years, though improvement from baseline remains significant.

THE WORLD'S INITIAL EXPERIENCE OF BILATERAL TREATMENT OF ESSENTIAL TREMOR USING MR GUIDED FOCUSED ULTRASOUND. A.J. Jameel¹, P.G. Bain², D Nandi¹, B Jones¹, O Kirmi¹, W Gedroyc¹

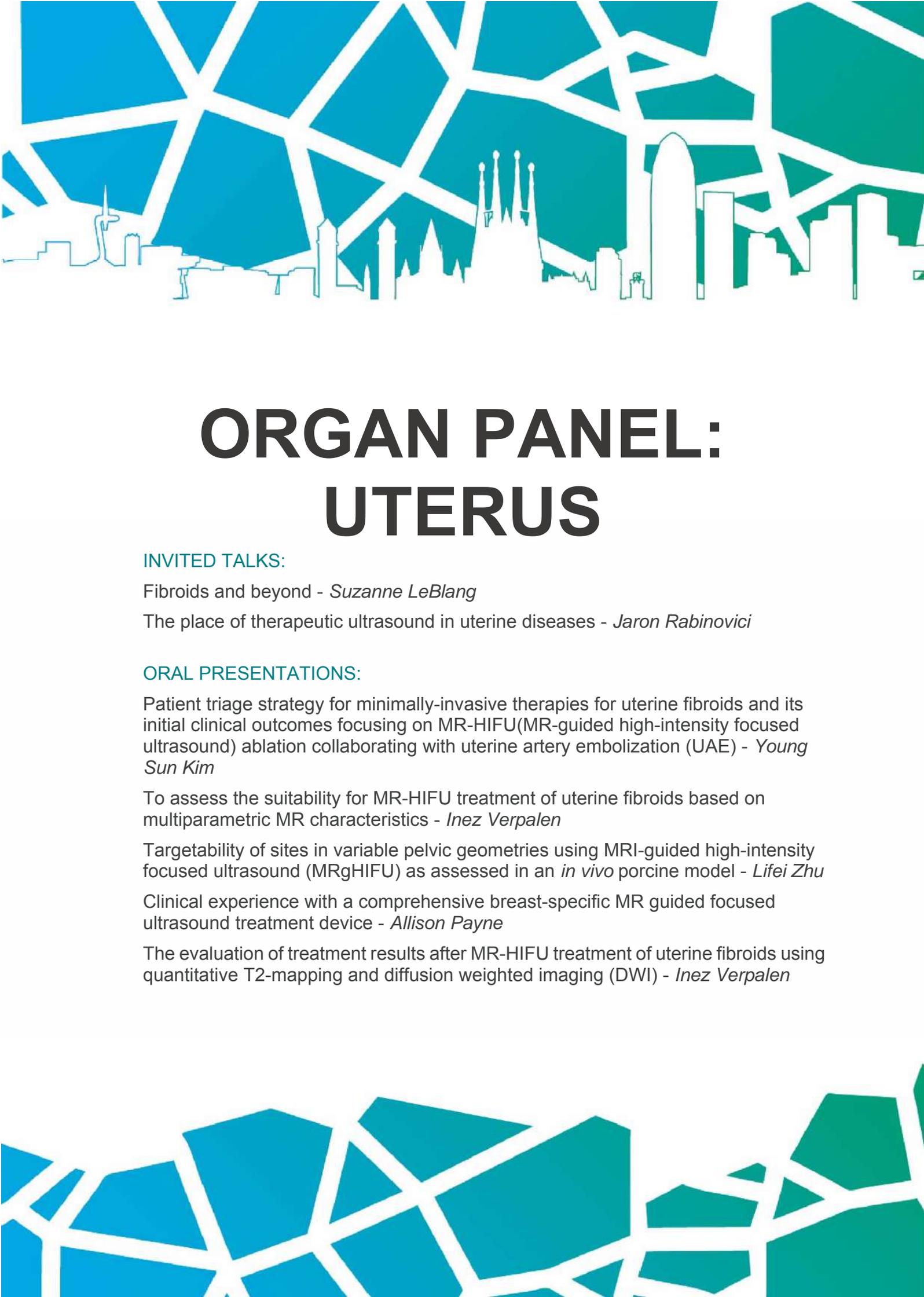
¹Imperial College NHS Healthcare Trust, London. ²Imperial College of Science Technology and Medicine, London. E-mail: ayesha.jameel@nhs.net ; wladyslaw.gedroyc@imperial.ac.uk

INTRODUCTION: Magnetic Resonance guided focused ultrasound (MRgFUS) is non-invasive treatment for essential tremor (ET) that allows targeted thermal ablation of brain tissue under real time image guidance. Previous studies have demonstrated the efficacy of unilateral MRgFUS treatment in ET. Bilateral treatment for ET has not been carried out with MRgFUS previously because of historical concerns regarding adverse events when bilateral Vim ablations were performed using unmonitored Radiofrequency Ablation. This paper describes the world's first cases of bilateral MRgFUS treatment of ET targeting both the Ventralis Intermedius Nucleus of the thalamus and the inferior Zona Incerta.

METHODS: This prospective study enrolled patients with medically refractory ET for Bilateral MRgFUS procedure. Treatments were separated by a minimum of 9 months between sides. Tremor severity and functional impairment were assessed at baseline and at regular intervals post-treatment for 12 months. The effectiveness of tremor suppression was monitored using parameters from the Clinical Rating Scale for Tremor (CRST), Quality of Life in Essential Tremor (QUEST) questionnaire, depression PHQ-9 and Bain and Findley Spiral (BFS) scores.

RESULTS: In all patients there was successful thermal ablation of the target tissues at the Vim and ZI with immediate improvement seen in BFS scores (see Figure 1). We describe the outcome and adverse effects experienced in this unique case group.

CONCLUSIONS: Our study demonstrates both the safety and efficacy of the world's first bilateral MRgFUS procedure for the treatment of ET. Our study provides further evidence that MRgFUS is a safe, effective, curative treatment for ET.



ORGAN PANEL: UTERUS

INVITED TALKS:

Fibroids and beyond - *Suzanne LeBlang*

The place of therapeutic ultrasound in uterine diseases - *Jaron Rabinovici*

ORAL PRESENTATIONS:

Patient triage strategy for minimally-invasive therapies for uterine fibroids and its initial clinical outcomes focusing on MR-HIFU(MR-guided high-intensity focused ultrasound) ablation collaborating with uterine artery embolization (UAE) - *Young Sun Kim*

To assess the suitability for MR-HIFU treatment of uterine fibroids based on multiparametric MR characteristics - *Inez Verpalen*

Targetability of sites in variable pelvic geometries using MRI-guided high-intensity focused ultrasound (MRgHIFU) as assessed in an *in vivo* porcine model - *Lifei Zhu*

Clinical experience with a comprehensive breast-specific MR guided focused ultrasound treatment device - *Allison Payne*

The evaluation of treatment results after MR-HIFU treatment of uterine fibroids using quantitative T2-mapping and diffusion weighted imaging (DWI) - *Inez Verpalen*

Fibroids and Beyond

Focused ultrasound treatment of uterine fibroids has improved the quality of life for women throughout the world. There are now multiple manufacturers in this market with varying applications of focused ultrasound technology. An overview describing the various manufacturers and the differences in mechanism of tissue ablation, guidance systems, patient preparation, and anesthesia requirements will be presented.

In addition, focused ultrasound is also addressing a wide assortment of other female pelvic pathologies. These include other diseases in the uterus such as adenomyosis and endometrial pathologies, as well as conditions outside the uterus in the cervix, ovaries, and vagina. A review of the status of these clinical applications will be presented.

PATIENT TRIAGE STRATEGY FOR MINIMALLY-INVASIVE THERAPIES FOR UTERINE FIBROIDS AND ITS INITIAL CLINICAL OUTCOMES FOCUSING ON MR-HIFU (MR-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND) ABLATION COLLABORATING WITH UTERINE ARTERY EMBOLIZATION (UAE)

Young-sun Kim, M.D.¹, Jae Wook Kim, M.D.¹, Ha-Jeong Kim, M.D.¹, Kun Woo Kim, M.D.¹

¹Uterine Fibroid Integrated Management Center, MINT Intervention Hospital, Seoul, Korea

e-mail: jeants.kim@gmail.com

OBJECTIVES

To provide patient triage strategy for minimally-invasive therapies for uterine fibroids including MR-HIFU ablation, UAE, and hysteroscopic/laparoscopic resection and to assess initial clinical outcomes of MR-HIFU ablation as compared to UAE

METHODS

From Oct 2017 to Sep 2018, a total of 356 women (mean age, 42.7) with 1408 fibroids (mean dominant lesion diameter, 6.0cm) were treated with either UAE (n=214), MR-HIFU ablation (n=120; GnRHa pretreatment, n=25) or hysteroscopic (n=18)/laparoscopic (n=4) resection. Treatment type was determined based on FIGO type, fibroid load, MR T2 signal intensity and complication risk, of which specific criteria will be presented.

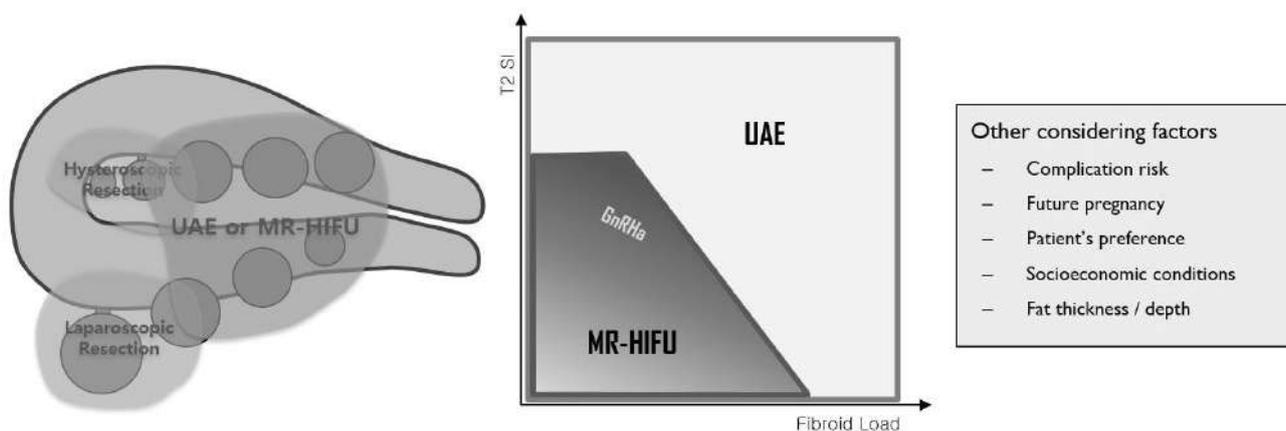
Fibroid feature, necrosis rate, additional treatment required for complete necrosis, complication and 3-month volume change treated with MR-HIFU ablation was analyzed as compared to UAE.

RESULTS

52.9% (9/17) of FIGO type 0 and 100% (3/3) of type 7 fibroids were treated with hysteroscopic and laparoscopic resection, respectively. Volume and T2 signal intensity ratio of the dominant fibroid treated with MR-HIFU ablation were significantly less than those treated with UAE (84.2 ± 86.8 mL vs. 238.7 ± 230.2 mL, $p < .001$; 2.1 ± 1.2 vs. 2.7 ± 1.5 , $p < .001$). Necrosis rates and additional treatment rates after MR-HIFU ablation vs. UAE were $95.3 \pm 12.0\%$ vs. $93.0 \pm 18.2\%$ ($p = .224$) and 5.0% (6/120) vs. 4.7% (10/214) ($p = .893$), respectively. Major/minor complication rates were 0% (0/120)/ 29.2% (35/120) and 7.9% (17/214)/ 15.9% (34/214) ($p = .284$), respectively. 3-month volume changes (3M/baseline) of MR-HIFU ablation and UAE were $35.9 \pm 20.5\%$ and $53.1 \pm 25.2\%$, respectively ($p < .001$).

CONCLUSIONS

Each modality for minimally-invasive therapy for uterine fibroids has complementary roles. Initial clinical outcomes of MR-HIFU ablation and UAE are comparable although fibroid features treated should be different.



CAPTION: Schematic drawings summarizing patient triage strategy for minimally-invasive therapies for uterine fibroids based on FIGO types, fibroid load, MR T2 signal intensity, and other considering factors

To assess the suitability for MR-HIFU treatment of uterine fibroids based on multiparametric MR characteristics.

I.M. Verpalen¹, M.A. Edens,² M.F. Boomsma¹

¹Department of Radiology, Isala, Zwolle, The Netherlands

²Department of Innovation and Science, Isala, Zwolle, The Netherlands

Email: i.m.verpalen@isala.nl

OBJECTIVES

This study investigates the value of multiparametric MRI protocol to predict treatment success of uterine fibroids due to fibroid characteristics.

METHODS

This single-centre prospective study included 64 women. Pre-treatment MR screening contained T2-weighted (to determine Funaki classification and the Scaled Signal Intensity (SSI)), quantitative T2-mapping and diffusion weighted imaging (with Apparent Diffusion Coefficient (ADC) mapping) sequences. Regions-Of-Interest were manually drawn using IntelliSpace Portal software (Philips). Treatment was performed using a clinical HIFU system (Sonalleve, V1, Profound Medical Inc, Mississauga, Canada) integrated into a 1.5-T MR scanner (Achieva; Philips Healthcare, Best, the Netherlands). Non-Perfused Volume (NPV) ratio, based on post-treatment contrast enhanced-T1-weighted images, and the Energy Efficiency Factor (EEF) were calculated and used as determinates of treatment success. Treatment failures due to inadequate heating were identified. Spearman's correlations between pre-treatment MR parameters and NPV ratio or EEF were investigated. Significant correlations were additionally analysed with a Receiver Operating Characteristic (ROC) curve resulting in a cut-off value.

RESULTS

No correlations were found for the ADC values (table 1). Although quantitative T₂-value was significant negative correlated with the NPV ratio, the association was low. The SSI and quantitative T₂-value were significant positive correlated with the EEF. The ROC curves of the EEF based on treatment success or failure (figure 1) resulted in a cut-off value of 67,95 ms for the quantitative T₂-value and 29,44 for the SSI.

CONCLUSIONS

Multiparametric MR characteristics of uterine fibroids were associated with failure of MR-HIFU therapy with a cut-off value of 29,44 for SSI and 67,95 ms for the quantitative T₂-value.

Table 1 Correlation between the screening MR parameters and NPV% or EEF.

	NPV% (RS)	P	EEF (RS)	P
SSI	-0,253	0,056	0,380	0,004
ADC (B-ALL)	-0,075	0,574	-0,033	0,809
ADC (B-LOW)	-0,067	0,617	-0,018	0,895
ADC (B-HIGH)	-0,055	0,682	0,046	0,736
ADC (B-0,800)	-0,118	0,379	-0,038	0,777
ADC (B-LONG TE)	0,160	0,231	-0,128	0,344
QUANTITATIVE T ₂ -VALUES	-0,270	0,041	0,285	0,003

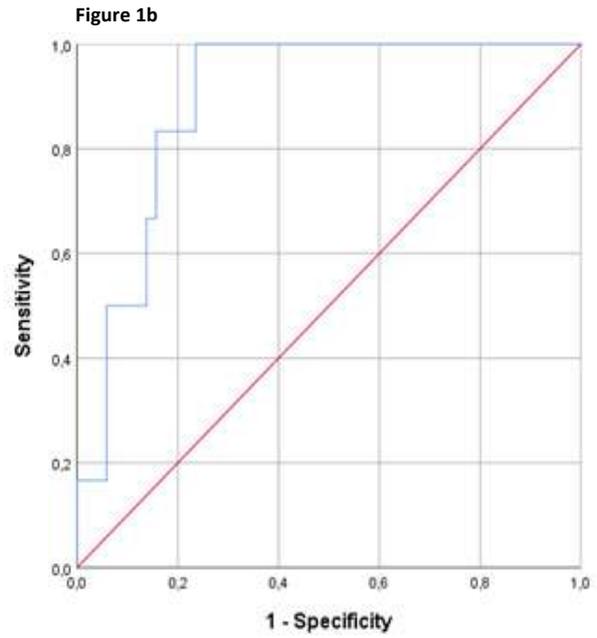
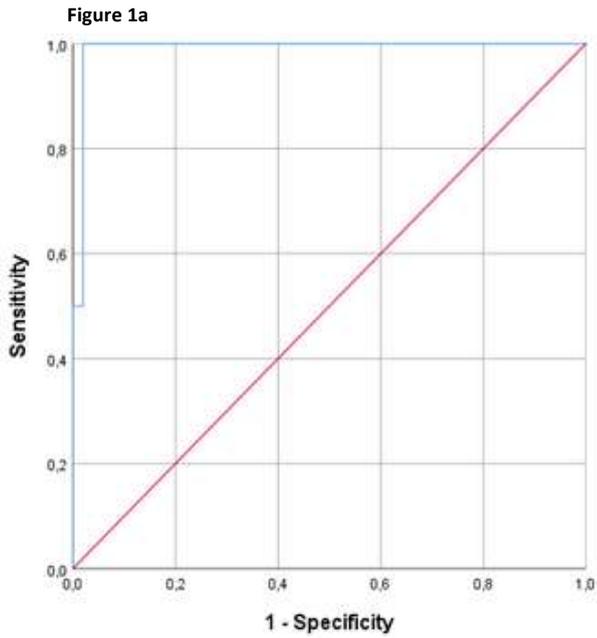


Figure 1a the ROC curve of the SSI, Area Under the Curve (AUC) 0,990. Figure 1b the ROC curve of the quantitative T₂, AUC 0,892.

TARGETABILITY OF SITES IN VARIABLE PELVIC GEOMETRIES USING MRI-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND (MRgHIFU) AS ASSESSED IN AN IN VIVO PORCINE MODEL

Lifei Zhu¹, Ari Partanen², H Michael Gach³, Lauren E. Henke³, Jessika A. Contreras³, Dennis E. Hallahan³, Imran Zoberi³, Hong Chen^{1,3}, and Michael B. Altman³

¹Department of Biomedical Engineering, Washington University in St. Louis, St. Louis, Missouri, 63130, USA

²Clinical Science, Profound Medical Inc., Mississauga, Toronto, Canada.

³ Departments of Radiation Oncology and Radiology, Washington University in St. Louis, St. Louis, Missouri, 63108, USA.

Email: lifeizhu@wustl.edu; maltman22@wustl.edu

OBJECTIVES

To assess the feasibility and safety of delivering localized and accurate mild hyperthermia therapy (MHT; 40-45°C) to a variety of clinically-relevant heterogeneous pelvic anatomical geometries using a commercial MRI-guided high-intensity focused ultrasound (MRgHIFU) system in an *in vivo* porcine model.

METHODS

Fourteen MHT sessions were delivered to 1-3 sites in seven pigs using a 1.5T clinical MRgHIFU system (Sonalleve V2, Profound Medical Inc.). MHT target sites were: muscle adjacent to ventral or dorsal urinary bladder wall, and the uterus. MHT target parameters were: 30-min duration, 18mm region-of-interest (ROI), and 42°C temperature. Temperature maintenance via feedback control was provided by multi-plane MR thermometry acquired every 3.7s. Contrast-enhanced T1-weighted MRI and gross pathology were performed to assess thermal damage.

RESULTS

Across all MHT sessions, the average difference between MR thermometry-measured average ROI temperature (T_{avg}) and target temperature was 0.45°C, the average ROI temperature standard deviation was 1.54°C, the average T_{avg} variation during 30-min was 0.80°C, and the average 10th to 90th percentile ROI temperature difference was 2.10°C. The average time for T_{avg} to reach >41°C or to cool to <40°C was 57.1s and 51.90s, respectively. No abnormally-perfused tissue within the ultrasound beam path was detected on MRI, nor was any thermal damage evident on gross pathology.

CONCLUSIONS

MRgHIFU MHT can be accurately and precisely administered to a variety of clinically-relevant pelvic targets. This, along with the lack of observed thermal tissue damage, suggests that administering MHT to pelvic targets in human patients may be feasible and safe with the Sonalleve MRgHIFU system.

Clinical experience with a comprehensive breast-specific MR guided focused ultrasound treatment device

Allison Payne¹, Robb Merrill¹, Emilee Minalga¹, Rock Hadley¹, Henrik Odéen¹, Stephanié Recco², Erik Dumont², Christine Tunon de Lara³, Gaeton MacGrogan³, Dennis Parker¹, Jean Palussiere³

¹University of Utah, 30 N 1900 E, Salt Lake City, UT 84132

²Image Guided Therapy, Inc., 2, Allée du Doyen Brus Pessac, France

³Institut Bergonié, 229 Cours de l'Argonne, Bordeaux, France

e-mail: allison.payne@hsc.utah.edu

OBJECTIVES

This abstract describes a comprehensive breast-specific MRgFUS system that integrates novel hardware, software and a streamlined treatment protocol. A phase I clinical trial is ongoing and initial results are presented.

METHODS

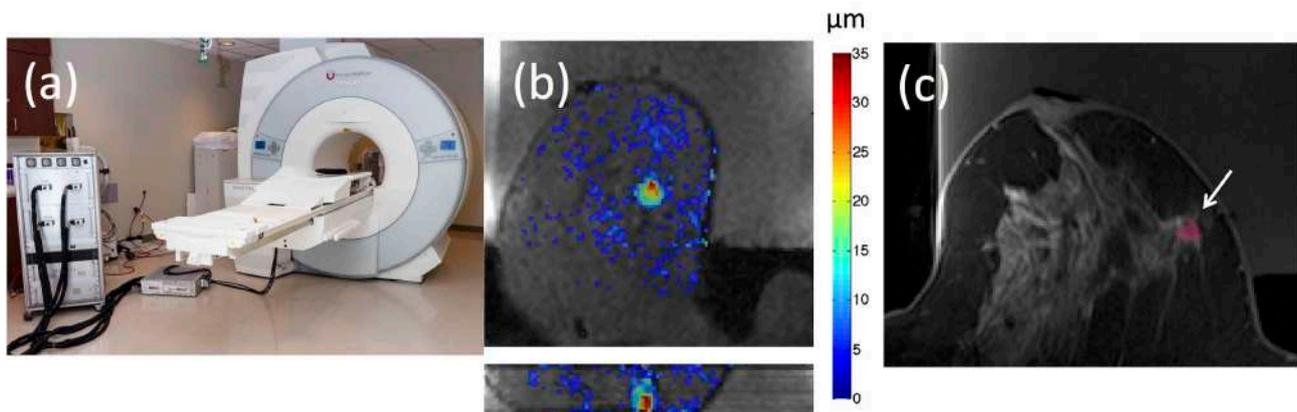
The system sits on top of the existing MRI table and consists of a modular support table, a treatment cylinder that houses a laterally-mounted FUS transducer, an 8-channel MRI receive imaging coil, 4-channel receive positioning coils, and an MR-compatible power generator. The positioning protocol uses information from the positioning coils to rapidly locate the focal spot. 3D MRI is used for treatment planning, monitoring and assessment.

RESULTS

At the time of submission, five patients have been treated. Patients have stage T0 breast cancer, <15mm in length. All treatments have been completed in <90 minutes, resulting in partial tumor destruction and improved palpability of the tumor. Representative volumetric MR-acoustic radiation force imaging and cumulative thermal dose images demonstrate the quality of imaging obtained during the procedure.

CONCLUSIONS

A successful first-in-human study with a new breast MRgFUS system is ongoing. Protocol streamlining and ongoing software improvements are further leveraging the high image quality to deliver an efficient, non-invasive treatment of stage T0 breast tumors demonstrating a more conservative treatment for breast cancer.



CAPTION: (a) Breast MRgFUS system installed in a 1.5T, 70cm bore MRI, (b) 3D MR-ARFI displacement map allowing accurate location of the FUS beam in fat, (c) thermal dose overlaid on contrast enhanced T1w post-treatment MRI.

The evaluation of treatment results after MR-HIFU treatment of uterine fibroids using quantitative T2-mapping and diffusion weighted imaging (DWI).

I.M. Verpalen¹, M.F. Boomsma¹

¹Department of Radiology, Isala, Zwolle, The Netherlands

Email: i.m.verpalen@isala.nl

OBJECTIVES

A contrast agent is required to visualize treatment outcome, the Non-Perfused Volume (NPV), after Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) treatment of uterine fibroids. The contrast agent may decompose when sonicated. Therefore, the NPV can only be visualized after therapy and target ablation of the remaining viable tissue during treatment is not possible. The aim of this study is to measure ablated fibroid tissue based on quantitative T2-mapping and diffusion weighted imaging (DWI) sequences.

METHODS

This prospective single-centre research included 42 patients. All treatments were performed using a clinical HIFU system (Sonalleve, V1, Profound Medical Inc, Mississauga, Canada) integrated into a 1.5-T MR scanner (Achieva; Philips Healthcare, Best, the Netherlands). The MRI protocol contained 3D T2-weighted, contrast enhanced (CE)-T1-weighted, quantitative T2-mapping and DWI sequences. Data were analysed using IntelliSpace Portal software (Philips). To analyse ADC values and quantitative T2 values pre- and posttreatment, Regions-Of-Interest (ROIs) were manually drawn in the fibroid and myometrium. Statistical analyses were performed using the IBM SPSS version 25.

RESULTS

ADC maps reconstructed by three combinations of low b-values showed the largest differences ($p < 0,001$) in ADC values (table 1). The combination of all b-values showed also significant difference ($p = 0,003$). The quantitative T2 values of the treated fibroid tissue showed a significant increase ($p < 0,001$) between pre- and post-treatment scans (table 2).

CONCLUSIONS

Significant differences in the ablated area of the treated fibroid were found in between the pre- and post-treatment scans for both ADC maps and quantitative T2 values. ADC maps reconstructed by low b-values showed the largest significant differences.

Table 1 pre- and post-treatment ADC maps of the fibroid and myometrium calculated by different b-value combinations.

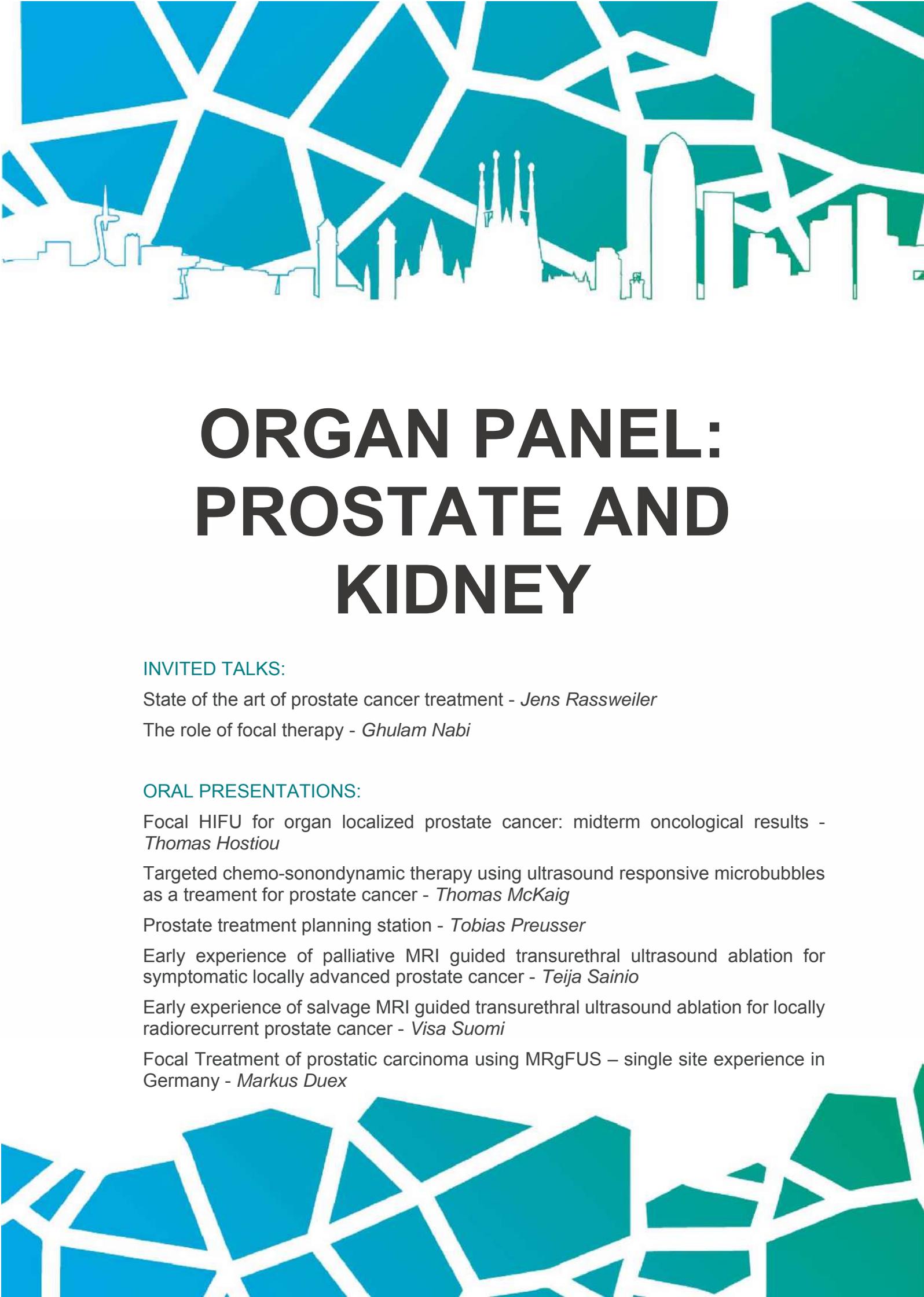
b-values	Fibroid				Myometrium			
	Pre (10 ⁻³ mm ² /s)	Post (10 ⁻³ mm ² /s)	Mean difference	<i>p</i>	Pre (10 ⁻³ mm ² /s)	Post (10 ⁻³ mm ² /s)	Mean difference	<i>p</i>
0, 50, 100	2,75 ± 0,83	1,68 ± 0,45	1,07	<0,001*	5,77 ± 2,82	4,85 ± 1,91	0,91	0,179*
400, 600, 800	1,03 ± 0,25	0,98 ± 0,27	0,05	0,357*	1,31 ± 0,35	1,22 ± 0,35	0,09	0,130
0, 200	2,05 ± 0,45	1,45 ± 0,37	0,60	<0,001*	3,90 ± 1,56	3,82 ± 1,26	0,08	0,980*
0, 800	1,34 ± 0,20	1,16 ± 0,32	0,18	<0,001	2,04 ± 0,44	1,85 ± 0,35	0,19	0,051*
All	1,23 ± 0,18	1,11 ± 0,30	0,12	0,003	1,47 ± 0,36	1,38 ± 0,34	0,09	0,216

Data presented as mean ± standard deviation. * Wilcoxon signed rank test.

Table 2 quantitative T2 values of the fibroid and myometrium, pre- and post-treatment.

Fibroid				Myometrium			
Pre (ms)	Post (ms)	Mean difference	<i>p</i>	Pre (ms)	Post (ms)	Mean difference	<i>p</i>
69,91 ± 29,01	84,89 ± 34,28	-15,00	<0,001*	106,54 ± 36,19	115,06 ± 38,01	-8,52	0,218*

Data presented as mean ± standard deviation. * Wilcoxon signed rank test.



ORGAN PANEL: PROSTATE AND KIDNEY

INVITED TALKS:

State of the art of prostate cancer treatment - *Jens Rassweiler*

The role of focal therapy - *Ghulam Nabi*

ORAL PRESENTATIONS:

Focal HIFU for organ localized prostate cancer: midterm oncological results - *Thomas Hostiou*

Targeted chemo-sonodynamic therapy using ultrasound responsive microbubbles as a treatment for prostate cancer - *Thomas McKaig*

Prostate treatment planning station - *Tobias Preusser*

Early experience of palliative MRI guided transurethral ultrasound ablation for symptomatic locally advanced prostate cancer - *Teija Sainio*

Early experience of salvage MRI guided transurethral ultrasound ablation for locally radiorecurrent prostate cancer - *Visa Suomi*

Focal Treatment of prostatic carcinoma using MRgFUS – single site experience in Germany - *Markus Duex*

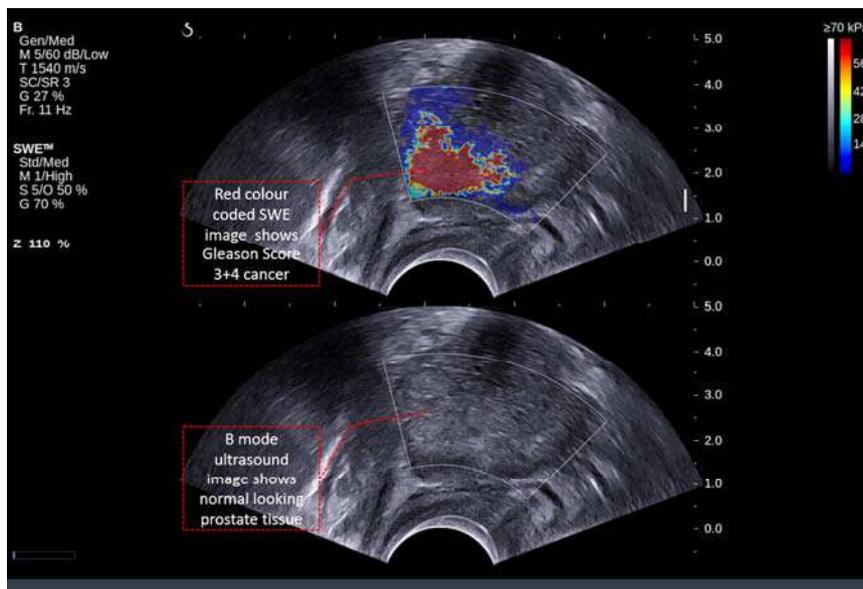
State of the art of Prostate Cancer Treatment

Jens Rassweiler, Department of Urology, SLK Kliniken Heilbronn, University of Heidelberg, Germany

The management of prostate cancer depends significantly on the stage and grade of the disease. Based on this, low risk, intermediate-risk and high-risk tumours are defined for localized cancer as well as metastatic versus non-metastatic disease. Determinants of the risk classification include PSA-value, Gleason Score, and clinical staging according to the TNM-classification. Low-risk tumors (PSA<10ng/ml, Gleason 6, T1c-T2) are managed preferably either by Active Surveillance, Focal Therapy or irradiation (ie. brachytherapy), because radical therapy (i.e. robot-assisted radical prostatectomy=RALP) are seen as too invasive for the mostly harmless disease. Patients with intermediate risk disease (PSA 10-20ng/ml, Gleason 7-8, T1c-T2) are candidates for either percutaneous radiotherapy or RALP, whereas high-risk patients (Gleason 9-10, T2-3b) require an extended lymph node dissection and RALP plus either adjuvant irradiation and/or androgen deprivation as a multimodal treatment concept. Metastatic disease is primarily treated with androgen deprivation. However, in case of an oligo-metastatic disease and fit patient, one might consider a combination of androgen deprivation and chemotherapy with doxetaxel in a neo-advent setting could be followed by RALP including extended lymph node dissection. Second-line therapy for metastatic disease include abiraterone / cortisone and enzalutamide. Third-line chemotherapy represents cabazitaxel. In case of lymph node recurrences / progression after RALP (i.e. detected by PSMA-PET/CT), laparoscopic second-look lymph node dissection might be useful.

Improving characterisation of localised prostate cancer using imaging: implications for focal therapy

The talk will focus on improving characterisation of localised prostate cancer and correctly identifying clinical significant prostate cancer. This is in order to improve treatment strategies. An increase, or 'upgrade', of Gleason Score (GS) in prostate cancer following Transrectal Ultrasound (TRUS) guided biopsies remains a significant challenge to overcome. Pre-biopsy magnetic resonance imaging (MRI) and Transrectal Ultrasound Shear Wave Elastography (SWE; Figure below) have the potential to narrow the discrepancy of histopathological grades between TRUS biopsy and radical prostatectomy (RP) using Prostate Imaging Reporting and Data System version 2 (PI-RADS v2.0) in the case of former and tissue stiffness in the case of later. We have a large experience of prospective recruitment to Transrectal ultrasound Shear wave elastography study and talk will describe its findings especially detection, correct characterisation with radical prostatectomy specimen as 'reference standard'. The lecture will also include long-term outcome prediction of biochemical relapse using tissue stiffness measurements on imaging as a biomarker. The data from this study was analysed using multivariate models and logistic regression analyses. Nomograms and clinical decision making impact will be discussed. The lecture will also describe use of pro-biopsy MRI PI-RADS scoring system as a biomarker to predict aggressive and clinically significant disease. Furthermore, included discussion will cover a method of improved orientation between histopathology and imaging using 3-D fabricated moulds.



FOCAL HIFU FOR ORGAN CONFINED LOCALIZED PROSTATE CANCER: MIDTERM ONCOLOGICAL RESULTS

T. Hostiou^{1,2}, A. Gelet^{1,2}, O. Rouviere^{2,3}, L. Badet¹, J-Y Chapelon², C. Lafon², S. Crouzet¹

¹Department of Urology and Transplantation Surgery, Edouard Herriot Hospital, Lyon, France

²INSERM Unit 1032, LabTau, Université de Lyon, Lyon, France

³Department of Radiology, Edouard Herriot Hospital, Lyon, France

e-mail: thomas.hostiou@chu-lyon.fr

OBJECTIVES

To evaluate midterm oncological results of focal HIFU therapy in low an intermediate risk prostate cancer.

METHODS

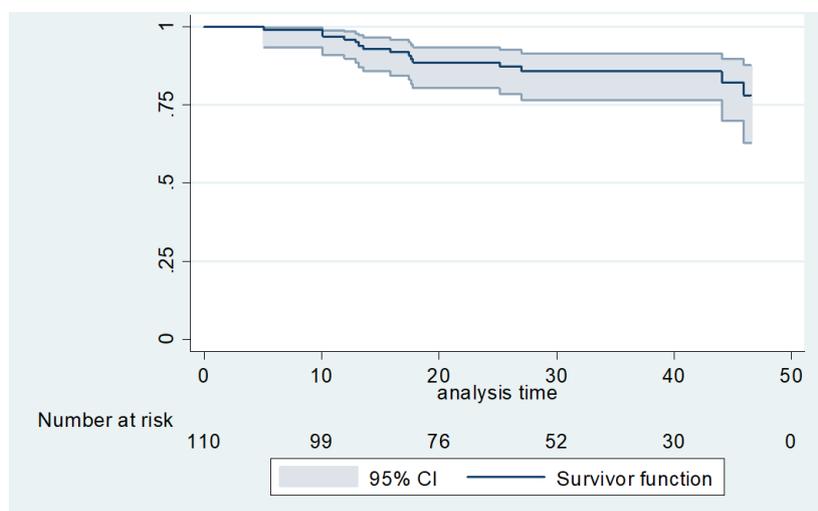
Single-center prospective evaluation of all patients treated for organ confined localized prostate cancer with focal HIFU from November 2009 to September 2015. Inclusion criteria: stage T1c-T2a, PSA <10ng/ml, Gleason score ≤7 (3+4), single tumor area identified by MRI and targeted biopsies. Follow-up: MRI-guided control biopsies (one per patient at 12 months). Primary endpoint: additional radical treatment (radical prostatectomy or radiotherapy) free survival (ARTFS) estimated with Kaplan Meyer method.

RESULTS

Mean follow-up: 39 months. 110 patients included, low risk: n=60, intermediate risk: n=50, Gleason 3+3: n=68, Gleason 3+4: n=42. Mean PSA: 5.96±2.5ng/ml. Number of patients without recurrence, with a non-significant recurrence (active surveillance) and with a significant-recurrence (radical treatment by 11 radiotherapy and 6 radical prostatectomy) were 78 (71%), 15 (14%), and 17(15.5%) respectively. At 40 months, ARTFS was 85% [CI: 77-92] for the entire cohort. There were significant differences of ARTFS according to the risk (low risk: 90% [CI 78-96], intermediate risk: 79% [CI 62-89], log-rank: 0.027) and the Gleason score (Gleason 3+3: 90% [CI 80-96], Gleason 3+4: 76% [CI 56-88] (log-rank: 0.005). In multivariate analysis, initial Gleason score (p=0.005), pre-HIFU PSA level (p=0.043) and nadir PSA post-HIFU (p=0.004) were significantly linked to initiation of a salvage radical treatment.

CONCLUSIONS

The study showed that Focal treatment with HIFU in selected patients with unilateral organ confined prostate cancer can achieve at midterm a satisfactory cancer control in low and intermediate risk patients.



CAPTION: Additional radical treatment free survival

TARGETED CHEMO-SONODYNAMIC THERAPY USING ULTRASOUND RESPONSIVE MICROBUBBLES AS A TREATMENT FOR PROSTATE CANCER

McKaig TJ, Nesbitt H, Callan B, McHale AP, Callan JF

¹School of Pharmacy and pharmaceutical sciences, University of Ulster, Coleraine, UK

e-mail: mckaig-t1@ulster.ac.uk

OBJECTIVES

Preparation and characterization of lipid stabilised microbubbles (MB) loaded with docetaxel (DTX) and Rose Bengal (RB). The resulting drug loaded MB (DTX-MB-RB) was tested for efficacy upon ultrasound stimulation in a murine model of prostate cancer.

METHODS

DTX-MB-RB were prepared with DTX incorporated in the hydrophobic shell of avidin functionalised MB with biotinylated RB attached to surface using the biotin-avidin interaction. MB size and number were determined using optical microscopy and MATLAB software. The DTX and RB loading was determined using HPLC and UV-Vis spectrophotometry respectively. Efficacy of DTX-MB-RB *in vivo* was determined using SCID mice bearing PC3 xenograft prostate cancer tumours. DTX-MB-RB was administered intravenously with low intensity ultrasound positioned at the tumour to rupture the MB and activate RB to produce reactive oxygen species (ROS).

RESULTS

The DTX-MB-RB produced had an average diameter of 1.65 μm and an average concentration of $2.4 \times 10^9/\text{mL}$. The amount of DTX and RB loaded in the MB was 0.599mg/mL and 0.640mg/mL respectively. *In vivo* results demonstrated that treatment with DTX-MB-RB + US was significantly more effective ($p \leq 0.01$) at controlling tumour growth than any of the control groups which included treatment with free DTX (10mg/kg). These results demonstrated that targeting chemo-sonodynamic therapy using ultrasound targeted microbubble destruction (UTMD) enables an enhanced therapeutic effect despite using significantly less (over 5-fold) toxic DTX.

CONCLUSIONS

UTMD mediated chemo-SDT is an effective alternative to standard chemotherapy for the treatment of prostate cancer.

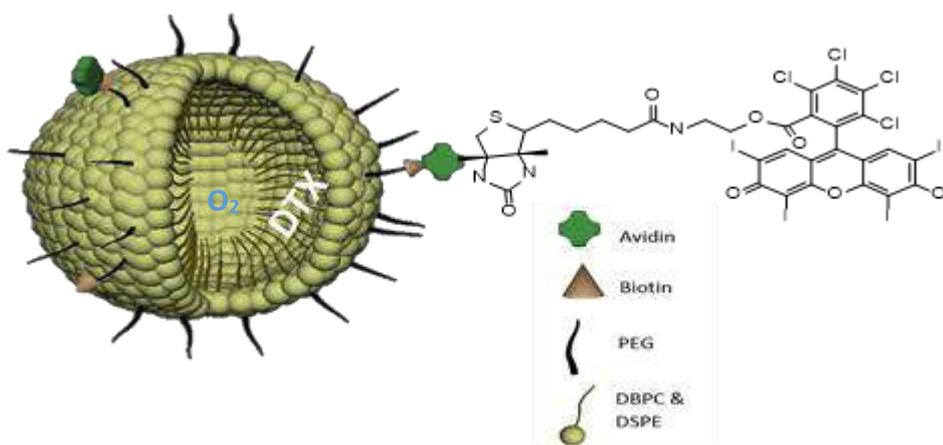


Figure 1: Schematic representation of the DTX-MB-RB conjugate.

PROSTATE TREATMENT PLANNING STATION

Jürgen Jenne^{1,2}, Christian Rieder¹, Sven Rothlübbers^{1,2}, Lennard Tautz¹, Jan Hendrik Moltz¹, Alba Malavé², Gilad Halevy³, Shlomi Rudich³, Caroline v. Dresky¹, Stefan Hoffmann², Johannes Heitz², Johannes Gregori², Yeruham Shapira³, Matthias Günther^{1,2}, Tobias Preusser^{1,4}

¹Fraunhofer MEVIS, Bremen, Germany

²mediri GmbH, Heidelberg, Germany

³INSIGHTEC, Tirat Carmel, Israel

⁴Jacobs University, Bremen, Germany

e-mail: juergen.jenne@mevis.fraunhofer.de

OBJECTIVES

Prostate Cancer is the second leading cause of death in American men. Due to PSA screening and better preventive examinations, an increasing number of small and well circumscribed prostate cancers are diagnosed. So a precise, non-invasive and less stressful therapy like a localized MRgFUS ablation could be a perfect therapy option. To support MRgFUS therapies in the prostate, tailored software tools for automatizing workflow, planning, guidance and follow up is essential.

METHODS

Supporting software tools include dedicated image processing algorithms and advanced visualization for detailed planning. Automatic segmentation tools based on machine-learning algorithms support the therapy planning stage. Motion detection of the prostate is continuously performed using acquired MR thermometry images. An automated quality assurance (AQUA) module was developed.

RESULTS

The prostate treatment planning station allows a detailed visualization of the MR images along with segmented structures and organs displayed as opaque overlay or mesh. Fully automated segmentation of the bladder, the catheterized urethra, the rectal wall, the prostate capsule and the adjacent cooling balloon is possible. Automated real-time motion tracking of the prostate capsule on consecutive images enhances the therapy precision. If changing imaging parameters, protocols, non-matching reference images and prostate motion show up, the AQUA module warns the physician instantaneously.

CONCLUSIONS

The prostate treatment planning station (PTPS) may simplify, speed up and improve the precision of prostate MRgFUS. Real-time prostate motion and deformation tracking and the automated detection of unwanted deviation from the treatment protocol by the AQUA software will lead to a safer therapy procedure.



Figure: Left: Advanced target visualization, right: Prostate motion detection

Early experience of palliative MRI guided transurethral ultrasound ablation for symptomatic locally advanced prostate cancer

M.Anttinen¹, Mäkelä P.², Suomi V.³, Kiviniemi A.², Saunavaara J.⁴, Sainio T.⁴, Blanco R.³, Boström P.J.¹

¹Turku University Hospital, Urology, Turku, Finland,

²Turku University Hospital, Radiology, Turku, Finland,

³Turku University Hospital, Radiology, Turku, Finland,

⁴Turku University Hospital, Medical Physics, Turku, Finland

mhjant@utu.fi, pietari.makela@tyks.fi, visa.suomi@tyks.fi

INTRODUCTION & OBJECTIVES

Advanced prostate cancer (PCa) may cause local symptoms commonly treated by palliative transurethral resection of prostate. MRI-guided transurethral ultrasound ablation (TULSA) may offer a palliative symptom control with reduced morbidity. The objectives are to evaluate feasibility, safety and efficacy of TULSA as a palliative intervention.

MATERIALS & METHODS

This prospective registered ethics-approved ongoing study includes advanced PCa-patients suffering from urinary retention and/or macrohematuria. After consent, patients undergo TULSA targeted to tumor component compressing and/or infiltrating prostatic urethra. Within first week catheter removal is attempted with bladder emptying confirmed by measuring post-void-residual. Patients are followed at 3-month intervals with flexible cystoscopy, uroflowmetry, patient reported outcome measures and safety assessed using Clavien Dindo Classification.

RESULTS

Five men have been treated with TULSA, all with urinary retention requiring permanent catheterization and hematuria with clotting requiring repeatedly hospitalization. Targeted ablation with TULSA was uneventful and successful in every study patient. Median sonication time was 17.9 min for target volumes of 16.5 cc. Median targeting accuracy \pm precision were 0.0 ± 0.8 mm, with median thermal dose coverage of 97%. One patient had extensive disease differing from others with ablation volume of 83 cc (sonication time 43.6 min, 73 % thermal dose coverage, -2.1 mm targeting accuracy). Foley catheter was removed successfully from two patients, both surviving without catheter at 6 months. Hematuria ceased in all study patients.

CONCLUSIONS

TULSA appears feasible and safe for palliative ablation of locally advanced PCa. TULSA seems to accomplish long-term control of hematuria and may relieve lower urinary tract obstruction in some patients.

EARLY EXPERIENCE OF SALVAGE MRI-GUIDED TRANSURETHRAL ULTRASOUND ABLATION FOR LOCALLY RADIORECURRENT PROSTATE CANCER

Anttinen M.¹, Mäkelä P.¹, Suomi V.², Kiviniemi A.², Saunavaara J.³, Sainio T.³, Blanco Sequeiros R.², Boström P.J.¹

¹Turku University Hospital, Urology, Turku, Finland,

²Turku University Hospital, Radiology, Turku, Finland,

³Turku University Hospital, Medical Physics, Turku, Finland

mhjant@utu.fi, pietari.makela@tyks.fi, visa.suomi@tyks.fi

OBJECTIVES

Many men with prostate cancer (PCa) experience local recurrence after primary radiation therapy. Objectives are to evaluate feasibility, safety and efficacy of MRI-guided transurethral ultrasound ablation (TULSA) for radiorecurrent PCa.

METHODS

This prospective registered ethics-approved ongoing trial enrolls men with biopsy-proven radiorecurrent PCa. Distant metastases are excluded with 18F-PSMA-PET/CT. After consent, patients undergo lesion-targeted TULSA. During the first year, follow-up includes mpMRI with non-perfused-volume (3 and 12 months) and 18F-PSMA-PET/CT at 12 months followed by transrectal ultrasound guided biopsies from ablated and suspicious regions on imaging. Safety is assessed using Clavien-Dindo Classification. Oncological response is evaluated by PSA and 12-month prostate-biopsies.

RESULTS

Four TULSA have been performed in three patients. One patient underwent repeated-TULSA due to thermometry artifact caused by fiducial marker resulting under treatment during the first treatment. One patient with diffuse bilobar disease had whole-gland, the others lesion-targeted TULSA. Median sonication time was 30 min for target volumes of 14 cc. At 3 months, NPV covered all lesions in every study patient. After whole-gland therapy, PSA decreased to 0.006 ng/ml. After lesion-targeted therapy PSA also decreased from 5.5 to 1.2 ng/ml, and 1.9 to 0.34 ng/ml. Further oncological follow-up is pending. One patient (whole-gland TULSA-treated) had prolonged catheterization, subsequent urinary tract infection and upper urinary tract dilatation treated with double-J-stents and oral antibiotics. No other treatment-related adverse events were reported. Foley catheters were removed successfully at first post-operative day in the other study patients.

CONCLUSIONS

TULSA appears feasible and safe as a salvage approach for radiorecurrent PCa with encouraging 3-month PSA-outcomes.

Focal Treatment of prostatic carcinoma using MRgFUS – single site experience in Germany

M. Düx¹, U. Witzsch²

¹Department of Radiology and Neuroradiology, Northwest Hospital, Frankfurt/Main, Germany

²Department of Urology, Northwest Hospital, Frankfurt/Main, Germany

e-mail: duex.markus@khnw.de, witzsch.ullrich@khnw.de, info@Mrgfus-Zentrum-Frankfurt.de

OBJECTIVES

Feasibility of focal treatment of prostatic carcinoma using MR-guided high focused ultrasound (MRgFUS).

METHODS

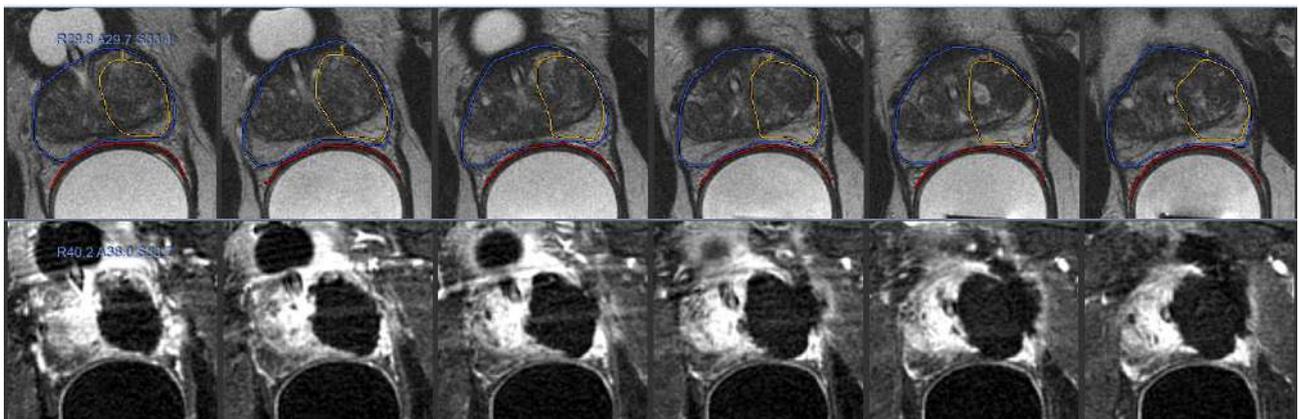
In June 2018 the MRgFUS center at Frankfurt, Germany, started focal therapy of prostate carcinoma. Men with prostate carcinoma of low/intermediate risk, Gleason score 6 or 7, have been offered focal ablation using MRgFUS as an alternative to active surveillance. Inclusion criteria: mpMRI of the prostate & MR fused biopsy of the prostate not older than 3 months, tumor board approval & considered fit for ITN.

RESULTS

11 patients with prostate carcinoma were considered for MRgFUS. For technical reasons 2 patients had two sessions of treatment, the remaining 9 patients were treated by one session only. 11/11 patients were successfully treated achieving homogeneous thermal necrosis covering the carcinoma. In all cases a minimum of 1 cm safety margin was planned and achieved as documented by post contrast MRI immediately after completion of focal treatment. Total table time was 5-6 hours in the beginning, dropping to a mean of 3,5 hours due to a learning curve. All patients did well after waking up from ITN, there was no haematuria, infection or pain that needed medical treatment. 10/11 patients reported no side effects during the hospital stay of 2-3 days post treatment. 1 patient suffered from right sided local thrombosis of gastrocnemius veins that was resolved by medical treatment. The urine catheter was routinely removed 2 days post treatment.

CONCLUSIONS

MRgFUS of prostate carcinoma is feasible, safe and achieves homogeneous thermal necrosis of the tumor and safety margins.



CAPTION: ax T2 weighted planning images and ax post treatment images with non-perfused volume covering tumor + safety margins. 73y old patient with localized prostate carcinoma, gleason score 6, left medial TZ, 12 macrospots, 3.516 - 6.276 joule.



ORGAN PANEL: MUSKULOSKELETAL

INVITED TALKS:

State of the art of percutaneous treatments in tumor bone lesions - *Francisco Aparisi*

Focused ultrasound treatment overview - *Pejman Ghanouni*

Other bone lesions - *Francesco Arrigoni*

Brief talk regarding Prof. Dux experience on facets - *Markus Duex*

ORAL PRESENTATIONS:

Intense Therapeutic Ultrasound for Musculoskeletal Pain Reduction Part 2; Clinical Data - *Michael Slayton*

Delivery of low intensity pulsed ultrasound to lumbar intervertebral discs using extracorporeal HIFU: a simulation study - *Matthew Adams*

Sacroiliac joint ablation in a chronic swine model using MRgFUS - *Roland Krug*

Focused Ultrasound and Radiotherapy for non-invasive palliative pain treatment in patients with bone metastasis - *Marcia Bartels*

Subacute and long term effects of MR-HIFU ablation on facet joints - *Sin Yuin Yeo*



State of the art of percutaneous treatments in tumor bone lesions.

Interventional radiology represents one of the pillars of minimally invasive surgery considered the future of surgery.

The basis of interventional radiology was the "needle", which allowed direct access or through the vascular path to the tumor lesions.

The initial objective was the biopsy, but soon the idea of taking a step forward and participating in the treatment arose.

The first effective results were obtained through vascular access by embolization or direct administration of medication.

In the second half of the twentieth century the pioneers began to inject corticosteroids, alcohols, cements, etc ... and filling techniques were born, some of them still in force today. An important chapter in filling techniques is the use of acrylic and biological cements products.

Through both we achieve pain control and structural recovery. Acrylics are inert materials with unknown long-term effects and biological ones allow bone regeneration.

At the end of the last century, termic radiofrequency was introduced as a very useful tool for treatment and with little aggressiveness.

Very soon, other procedures were added to this technique based on other physical effects such as cold, photocoagulation, ionization, etc ... Currently several of these techniques, are the basis of the treatment of benign lesions and are very useful support in malignant lesions. .

Probably some of these techniques will remain for years, but several of them will be replaced by others of less aggressiveness in which we do not need to cross the skin.

Other bone lesions

Osteoid Osteomas and Metastasis are the more common bone lesions treated with the FUS system. However, the minimally invasive profile of this system can allow to approach to multiple focal bone lesions different from those above mentioned, providing accessible by the system.

Osteoblastoma is one of this: when the lesion is on the bone surface, MRgFUS can represent a very good option of treatment; moreover with this solution the complexity of the surgical intervention is avoided (in particular when the lesion is intrarticular).

Moreover, we will present a little series of painful bone lesions (that were focal and benign) treated with MRgFUS: we will show safety and effectiveness of this type of treatment: the main requirements are the good exposure of the lesion to the US beam penetration and the certainty of diagnosis.

Background:

Lower back pain constitutes the majority of chronic pain settings. Lumbar facet joint osteoarthritis may account for 15-45% of severe lower back pain and may be subject to non-invasive thermal ablation using MR-guided high-focussed ultrasound (MRgFUS).

Materials and Methods:

The MRgFUS center at Frankfurt/Germany is performing thermal ablation of symptomatic lumbar facet joint osteoarthritis using MRgFUS since 2014. Patients with a long standing history of severe lumbar facet joint osteoarthritis or a positive response to facet joint interventions are recruited for thermal ablation using the ExAblate 2000 (Insightec, Haifa, Israel) magnetic resonance-guided focused ultrasound system. Evaluation and staging of the arthrosis is performed by MRI. Treatments are performed bilaterally at the levels L 3/4, L 4/5 and L 5/S 1, respectively.

Results:

Since 2014 > 300 patients have been treated using MRgFUS. All treatments were successfully completed. In the majority of cases a significant reduction in the NRS (average/worst) pain scores are achieved. Patients with pain relief report an improved mobility. Non-responders to pain treatment are still an unsolved problem. Retreatment is possible after initial pain control by MRgFUS.

Conclusion:

MRgFUS treatment of lumbar facet joint osteoarthritis is safe, non-invasive and effective with respect to pain control. There is no risk of nerve damage and retreatment is possible. The challenge of MRgFUS treatment of facet joint osteoarthritis is the selection of patients.

Intense Therapeutic Ultrasound for Musculoskeletal Pain Reduction Part 2; Clinical Data

M.H. Slayton, Ph.D.,
R.C. Amodei, RDMS,
K.B. Compton, MS
Guided Therapy Systems, Inc. Mesa, Arizona USA
e-mail: m.slayton@guidedtherapy.com

OBJECTIVES

Assess efficacy and safety of Intense Therapeutic Ultrasound (ITU) treatment for Musculoskeletal pain reduction in chronic Plantar Fasciitis and Lateral Epicondylitis, including initial European clinical data from commercial launch.

METHODS

Three studies evaluating 103 subjects, previously diagnosed as chronic participated; 91 ITU treated and 12 control/sham patients received 2 treatments, 2 – 4 weeks apart on subcutaneous musculoskeletal tissues along with Standard-of-Care treatments as prescribed by the Principal Investigators. Patients were followed up to 6 months after initial treatment receiving physical exams and diagnostic ultrasound imaging at each follow-up visit and providing feedback via Patient/Subject Reported Outcome Measure (SROMs) surveys specific to the treated anatomy. SROMs were compared to baseline reports. European initial clinical data includes results from 64 patients from two countries.

RESULTS

Subjects were previously diagnosed as chronic and had failed conservative standard-of-care therapies. After treatment, subjects meeting criterion of $\geq 25\%$ pain score reduction: TREATED(**SHAM TREATED**) VAS Pain Score; Wk 4: 68%(**40%**), Wk 8: 70%(**27%**), Wk 12: 86%(**25%**), Wk 26: 77%(**38%**).

Average Pain Score Reduction TREATED(**SHAM TREATED**): Wk 4: -29%(**-12%**), Wk 8: -37%(**-24%**), Wk 12: -48%(**-17%**), Wk 26: -42%(**-34%**). Subject Treatment Satisfaction: Wk 4: 67%(**73%**), Wk 8: 83%(**60%**), Wk 12: 82%(**25%**), Wk 26: 84%(**63%**). ITU is well tolerated by subjects. During all studies, no adverse events were reported. Initial European results 64 patients: VAS: WK 4: -45%, Wk 8: -78%, Wk 12: -88%.

CONCLUSIONS

ITU for pain reduction of musculoskeletal injuries is a safe and effective non-invasive treatment option, when conservative standard-of-Care therapies fail to relief musculoskeletal pain.

DELIVERY OF LOW-INTENSITY PULSED ULTRASOUND TO LUMBAR INTERVERTEBRAL DISCS USING EXTRACORPOREAL HIFU: A SIMULATION STUDY

M.S. Adams¹, J.C. Lotz², C.J. Diederich^{1,2}

¹Thermal Therapy Research Group, University of California San Francisco, San Francisco, USA

²University of California, Berkeley – University of California, San Francisco Graduate Program in Bioengineering, CA, USA.

e-mail: matt.adams@ucsf.edu; chris.diederich@ucsf.edu

OBJECTIVES

To investigate the feasibility of delivering localized low-intensity pulsed ultrasound (LIPUS) to lumbar intervertebral discs (IVDs) using an extracorporeal phased array while mitigating heating of adjacent tissues.

METHODS

3D anatomical models were generated from patient-specific CT scans that were segmented into IVDs, bone, bowel, and various soft tissues. Seven target regions in the annular wall and nucleus of each IVD from L2-S1 were delineated. A virtual acoustic point source was placed in each target region, and resultant acoustic emissions calculated using a linear full-wave equation solver and recorded extracorporeally. A generalized 2D phased array (8 x 8 cm planar, 1024 elements, 500 kHz) was positioned to maximize pressure recordings across the array surface, with derived driving pressure and time-reversed phase settings applied for forward acoustic and biothermal simulations.

RESULTS

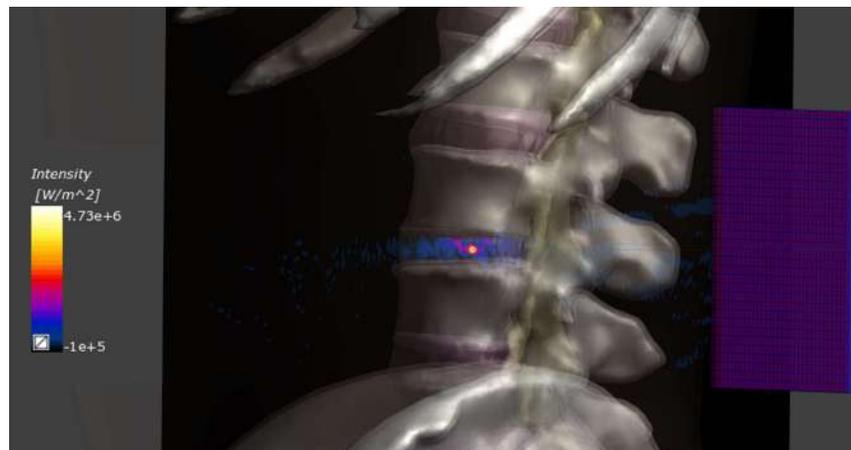
With the phased array positioned posterior to posterior-lateral of the body, intensity gain at the target point relative to array surface varied from 15-170 across all IVDs, with higher gain and smaller -3 dB intensity volume (<30 mm³) achieved in posterior and lateral annular wall regions. Improved localization of energy in the target site was produced in the L2-L5 IVDs compared to the L5/S1 IVD. For maximum prospective LIPUS exposure levels to the target region (1 W/cm² peak continuous-wave), steady-state peak temperature elevation varied 37.6-40°C.

CONCLUSIONS

Simulations suggest delivering targeted LIPUS to lumbar IVDs using an extracorporeal phased array similar to commercially-available platforms is feasible, which may have applications for disc injury repair and lower back pain management.

ACKNOWLEDGEMENTS

NIH R21EB024347.



CAPTION: Calculated LIPUS in L3/L4.

Sacroiliac joint ablation in a chronic swine model using MRgFUS

V. Rieke¹, E. Liebenberg², E. Ozhinsky³, R. Krug³

¹Department of Radiology and Imaging Sciences, University of Utah, Salt Lake City, USA

²Department of Orthopedic Surgery, University of California San Francisco, San Francisco, USA

³Department of Radiology and Medical Imaging, University of California San Francisco, San Francisco, USA

e-mail: viola.rieke@utah.edu; roland.krug@ucsf.edu

OBJECTIVES

We longitudinally evaluated the safety and effectiveness of MRgFUS ablation of the sacroiliac (SI) joint in a chronic swine model.

METHODS

Seven animals were treated with Insightec's Exablate 2000 (in-table) system at 3T using three energies (n=3 with 700J, n=3 with 1000J, n=1 with 1500J; duration=20secs at 1.35 MHz). Sonications were planned in oblique coronal slices lateral around the foramina targeting the lateral branches of the nerve roots. The left side of the animal was treated, the right side served as control.

After post-treatment imaging (baseline), the animals were recovered from anesthesia, assessed for pain, behavior, ambulation, and gait, followed for 5 weeks, and euthanized after a follow-up MR imaging session. The sacrum was removed for histopathological analysis (gross histology, H&E, Neurofilament 200 antibody) and confirmation of imaging results.

RESULTS

Temperature rise was clearly seen on MR temperature imaging showing contiguous lesions along the SI joint. The ablated region was well estimated by thermal dose measurements. Treatment effects were more pronounced on follow-up images than on baseline.

Animal assessment showed no signs of pain or impairment. At follow-up, treatment effects were still visible on MR and the lesion extend depended on applied energy.

H&E images clearly shows the ablated area within the targeted region. The depth of the lesions increased with increasing energy.

CONCLUSIONS

This study in a chronic swine model showed safety and effectiveness of MRgFUS sacroiliac joint ablation and histological results showed treatment effectiveness through successful nerve ablation.

ACKNOWLEDGEMENTS

This work was funded by the Focused Ultrasound Foundation and a Departmental Seed Grant.

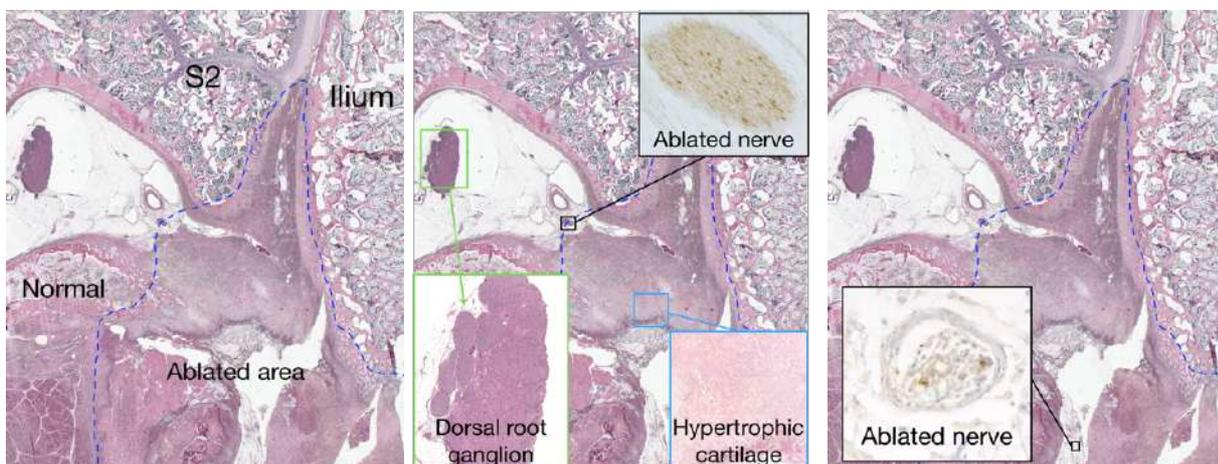


Figure: H&E and Neurofilament 200 histology of an animal treated with 1000 J.

The FURTHER study – a Horizon 2020 project:

Focused Ultrasound and RadioTHERapy for non-invasive palliative pain treatment in patients with bone metastasis

Marcia Bartels¹, Chrit Moonen¹, Ingrid Nijholt², Manon Braat¹, Wietse Eppinga¹, Wilbert Bartels¹, Clemens Bos¹, Stephanie Stock³, Holger Gröll³, Sin Yuen Yeo³, Dirk Müller³, Roberto Blanco⁴, Alessandro Napoli⁵, Martijn Boomsma², Erik Phernambucq², Alberto Bazzocchi⁶, Matthew Brown⁷, Nandita Desouza⁷, Jessica Foley⁸, Helena Verkooijen¹

¹Imaging Division, University Medical Center Utrecht, The Netherlands; ²Stichting Isala klinieken, Zwolle, the Netherlands; ³Klinikum der Universitaet zu Koeln, Germany; ⁴Varsinais-suomen sairaanhoitopiirin kuntayhtymä, Finland; ⁵Universita degli studi di Roma la sapienza, Italy; ⁶Alma mater studiorum - universita di Bologna, Italy; ⁷Institute of cancer research - royal cancer hospital, London, United Kingdom; ⁸Focused ultrasound foundation, Charlottesville, USA

E-mail: M.M.T.Bartels-6@umcutrecht.nl; H.M.Verkeoijen@umcutrecht.nl

OBJECTIVES

The current standard of care for patients with painful bone metastasis includes palliative external beam radiotherapy (EBRT). While EBRT is a well-established treatment option, it takes up to four weeks for EBRT to induce adequate pain relief, and 30-40% of patients do not respond to EBRT. Pain palliation may be improved by including magnetic resonance image guided high intensity focused ultrasound (MR-HIFU) as alternative or in addition to EBRT. The FURTHER study aims to evaluate the effectiveness and cost-effectiveness of MR-HIFU (alone or in combination with EBRT) as compared to standard-of-care as a palliative treatment option to relieve cancer induced bone pain.

METHODS

The FURTHER study is a prospective, multicenter, three-arm randomized controlled trial, performed at eight consortium institutes. A total of 216 patients with painful bone metastases will be randomized to receive EBRT only, EBRT followed by MR-HIFU in a timeframe of 4 hours to 7 days, or MR-HIFU only. Primary outcome of the trial will be pain response at 14 days after randomization. Secondary outcomes include pain response at 14 days after treatment, cost-effectiveness and evaluation of toxicity, adverse events, quality of life and survival in the first 6 months after treatment.

RESULTS & CONCLUSIONS

The FURTHER study is expected to start recruitment of patients in October 2019.

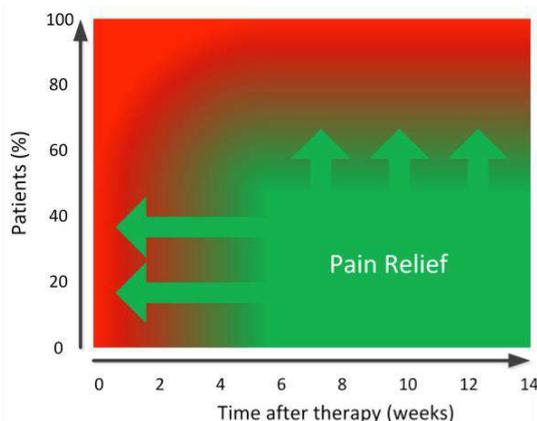


FIGURE 1: Radiotherapy achieves pain relief in 60-70% of patients after 4-6 weeks. There is a clinical need for more rapid pain relief, as well as treatment options for the patients that do not respond to EBRT.

SUBACUTE AND LONG TERM EFFECTS OF MR-HIFU ABLATION ON FACET JOINTS

S.Y. Yeo¹, P. Rademann², L. Sebeke¹, A.C. Maul², E. Heijman^{1,3}, J.D. Castillo¹, H. Schröder⁴, Holger Gröll¹

¹University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department of Diagnostic and Interventional Radiology, Cologne, Germany

²University of Cologne, Faculty of Medicine and University Hospital of Cologne, Center for Experimental Medicine, Cologne, Germany

³Philips Research Germany, Aachen, Germany

⁴University of Cologne, Faculty of Medicine and University Hospital of Cologne, Institute for Anatomy, Cologne, Germany

e-mail: sin.yeo@uk-koeln.de

OBJECTIVES

Magnetic resonance-guided high intensity focused ultrasound (MR-HIFU) is an attractive alternative non-invasive treatment to alleviate pain in patients with lumbar facet joint osteoarthritis. Here, we present the subacute and long term effects of MR-HIFU ablation of facet joints in pigs using MRI, computed tomography (CT) and histological analyses.

METHODS

Five female pigs were used in this study. For each pig, 4-5 lumbar facet joints were ablated using a Sonalleve[®] MR-HIFU system (Profound Medical) with the contralateral side serving as controls. For subacute analysis, MRI was performed at 7 days after MR-HIFU and two animals were euthanized for histology, whereas for long term effects, MRI and CT were performed at 1, 2, and 3 months post MR-HIFU.

RESULTS

At 7 days after MR-HIFU, edema and non-perfused volume was observed at the ablated area. Histological analysis confirmed ablation of facet joint. At 3 months follow-up, MRI showed reduction of tissue damage. Figure 1 shows representative CT images of facet joints after MR-HIFU and complete follow-up of all animals is currently pending. No MR-HIFU-related complications were observed.

CONCLUSIONS

MR-HIFU is a safe technique for facet joint ablation and soft tissue healing was noted at 3 months follow-up.

ACKNOWLEDGEMENTS

We thank colleagues from Experimental Medicine and Anatomy for in-vivo experiments and histology support.

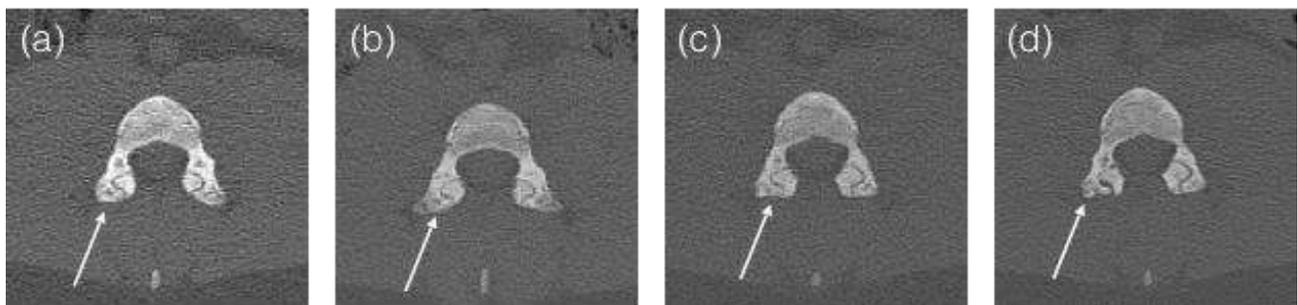
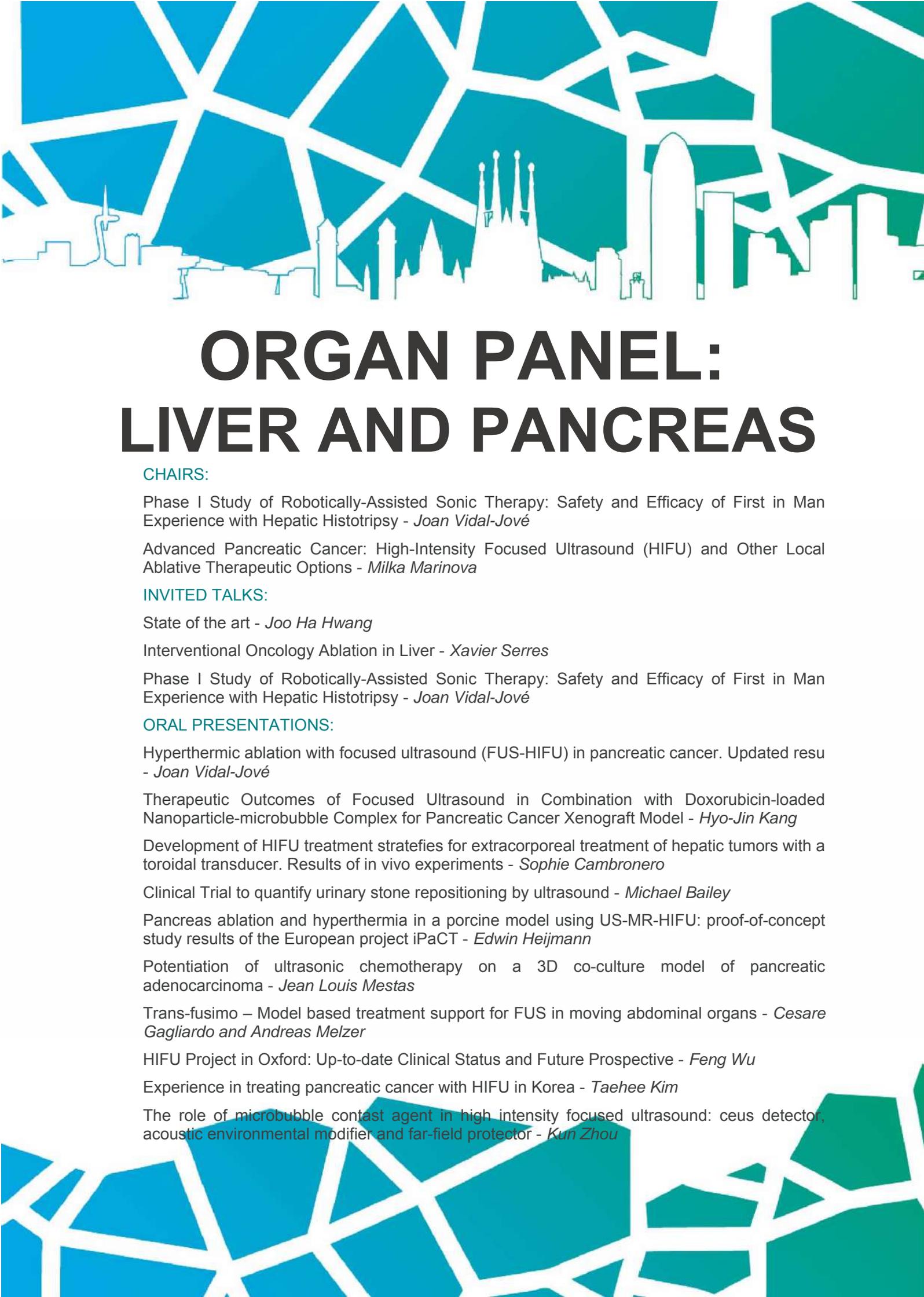


FIGURE 1: CT images of facet joints before(a), and at 1(b), 2(c), and 3(d) months after MR-HIFU (arrows).



ORGAN PANEL: LIVER AND PANCREAS

CHAIRS:

Phase I Study of Robotically-Assisted Sonic Therapy: Safety and Efficacy of First in Man Experience with Hepatic Histotripsy - *Joan Vidal-Jové*

Advanced Pancreatic Cancer: High-Intensity Focused Ultrasound (HIFU) and Other Local Ablative Therapeutic Options - *Milka Marinova*

INVITED TALKS:

State of the art - *Joo Ha Hwang*

Interventional Oncology Ablation in Liver - *Xavier Serres*

Phase I Study of Robotically-Assisted Sonic Therapy: Safety and Efficacy of First in Man Experience with Hepatic Histotripsy - *Joan Vidal-Jové*

ORAL PRESENTATIONS:

Hyperthermic ablation with focused ultrasound (FUS-HIFU) in pancreatic cancer. Updated results - *Joan Vidal-Jové*

Therapeutic Outcomes of Focused Ultrasound in Combination with Doxorubicin-loaded Nanoparticle-microbubble Complex for Pancreatic Cancer Xenograft Model - *Hyo-Jin Kang*

Development of HIFU treatment strategies for extracorporeal treatment of hepatic tumors with a toroidal transducer. Results of in vivo experiments - *Sophie Cambrono*

Clinical Trial to quantify urinary stone repositioning by ultrasound - *Michael Bailey*

Pancreas ablation and hyperthermia in a porcine model using US-MR-HIFU: proof-of-concept study results of the European project iPaCT - *Edwin Heijmann*

Potentiation of ultrasonic chemotherapy on a 3D co-culture model of pancreatic adenocarcinoma - *Jean Louis Mestas*

Trans-fusimo – Model based treatment support for FUS in moving abdominal organs - *Cesare Gagliardo and Andreas Melzer*

HIFU Project in Oxford: Up-to-date Clinical Status and Future Prospective - *Feng Wu*

Experience in treating pancreatic cancer with HIFU in Korea - *Taehee Kim*

The role of microbubble contrast agent in high intensity focused ultrasound: ceus detector, acoustic environmental modifier and far-field protector - *Kun Zhou*

**ADVANCED PANCREATIC CANCER:
HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU)
AND OTHER LOCAL ABLATIVE THERAPEUTIC OPTIONS**

Assoc. Prof. Dr. Dr. Milka Marinova, Prof. Dr. Holger Strunk

Background: Locally advanced pancreatic cancer is a life-limiting tumor with a wide range of incapacitating symptoms such as cancer associated pain. Several local ablative therapies with both thermal and non-thermal sources have recently received large attention as modern treatment options for local tumor control and symptomatic improvement. There are some currently available techniques including high-intensity focused ultrasound (HIFU) being one of the most exciting and innovative modalities.

Method: Our experiences with HIFU-treatment are based upon 110 pancreatic cancer patients (UICC III-IV). Outcomes as treatment-related changes in symptoms particularly in cancer pain and quality of life (QoL) as well as local tumor response, safety and survival have been compared to reported studies concerning HIFU, radiofrequency and microwave ablation, cryoablation, irreversible electroporation and stereotactic body radiation therapy.

Results: Even though all strategies appeared to be feasible, the unique feature of non-invasiveness represents a substantial advantage of HIFU procedure. In 85% of HIFU-treated patients a long-lasting pain relief was achieved; 50% of patients did not require any analgesic treatment 6 weeks post-ablation. Unfortunately, pain palliation and QoL outcomes are only rarely reported for other local treatment modalities. Tumor mass reduction could be achieved with all ablative therapies, with a mean tumor volume reduction of 60% after 6 months in HIFU-treated pancreatic tumors. Differences in treatment-associated morbidity were reported, however they are only partially comparable due to unbalanced study populations.

Conclusion: Various local ablative treatment modalities are available and feasible for tumor mass reduction of advanced pancreatic cancer but with different symptomatic benefit for patients. An effective and long-lasting reduction of cancer-related pain was observed following HIFU without insertion of needles or electrodes. Randomized controlled studies for head-to-head comparison of these modalities are warranted in the near future.

Lecture title: State-of-the-art in the application of focused ultrasound for the treatment of pancreatic cancer

Speaker: Joo Ha Hwang, MD, PhD, Professor of Medicine, Stanford University

Abstract

Focused ultrasound (FUS) is a novel non-invasive modality for treatment of various solid tumors including uterine fibroids, prostate cancer, hepatic, renal, breast and pancreatic tumors. FUS therapy utilizes mechanical energy delivered by ultrasound waves that are focused inside the body to induce thermal and/or mechanical effects in tissue. Multiple preclinical and non-randomized clinical trials have been performed to evaluate the safety and efficacy of FUS for the treatment of pancreatic tumors. Initially, ablative therapy with FUS demonstrated substantial tumor-related pain reduction after FUS treatment with minimal adverse effects. More recent studies have focused on the use of FUS to enhance drug delivery to pancreatic tumors, demonstrating extremely promising results. Drug delivery can be enhanced by FUS by both thermal and mechanical mechanisms. The most recent research that is demonstrating promising results in pre-clinical models is the application of FUS in stimulating the immune response and playing a role in immune therapy for the treatment of pancreatic cancer.

INTERVENTIONAL ONCOLOGY ABLATION IN LIVER

X. Serres¹

¹Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain

e-mail: xavierserresc@gmail.com

Chemotherapy (CT), Radiotherapy (RT), Surgery (S) and Interventional Oncology (IO) are the four pillars of oncological treatments. IO is one of the most promising areas, which is growing vertiginously. It is very exciting from a technical perspective but it is even more interesting from an anthropological point of view.

IO includes vascular treatments and ablation therapies; the latter might be thermal or non-thermal. Moreover, thermal ablations might work by heating or by freezing. However, ablation therapies can also be classified as chemical ablations (non-thermal; alcohol, acetic acid, bleomycin...) or energy-based ablations. The latter include techniques such as radiofrequency (thermal), microwaves (thermal), laser ablation and laser immunomodulation (thermal), cryoablation (thermal by freezing) or electroporation (non-thermal). Electroporation therapies may be irreversible for producing tumor ablations or reversible for increasing the permeability of tumor cells. Finally, focused ultrasound is a non-invasive technique that uses high intensity waves to produce heat (thermal ablation) or cavitation phenomena (non-thermal). The non-thermal ablation therapy that makes use of cavitation is called histotripsy.

All of these technologies have the same goal: to treat radically tumors in a safe manner without any damage to the patient.

Phase I Study of Robotically-Assisted Sonic Therapy: Safety and Efficacy of First in Man Experience with Hepatic Histotripsy

Joan Vidal Jove, MD, PhD^{1,2}, Xavier Serres, MD, PhD³, Eli Vlasisavljevich, PhD⁴, Jon Cannata, PhD⁵, Alex Duryea, PhD⁵, Ryan Miller, PhD⁵, Fred T. Lee, Jr., MD⁶, Timothy J. Ziemlewicz, MD⁶

¹FUS-HIFU Onco Ablation, Hospital Mutua Terrassa, University of Barcelona, Barcelona, Spain

²Comprehensive Tumor Center, Khwab Institute, Barcelona, Spain

³Department of Radiology, Vall D'Hebron University Hospital, Barcelona, Spain

⁴Biomedical Engineering and Mechanics, Virginia Tech University, Blacksburg, VA, USA

⁵Histosonics, Inc., Ann Arbor, MI, USA

⁶Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: jvidal@mutuaterrassa.es; tziemlewicz@uwhealth.org

OBJECTIVES

Robotically-assisted sonic therapy (RAST) is the automated treatment of a defined volume of tissue utilizing histotripsy. A Phase I trial was initiated to evaluate the safety and efficacy of RAST in patients with liver tumors.

METHODS

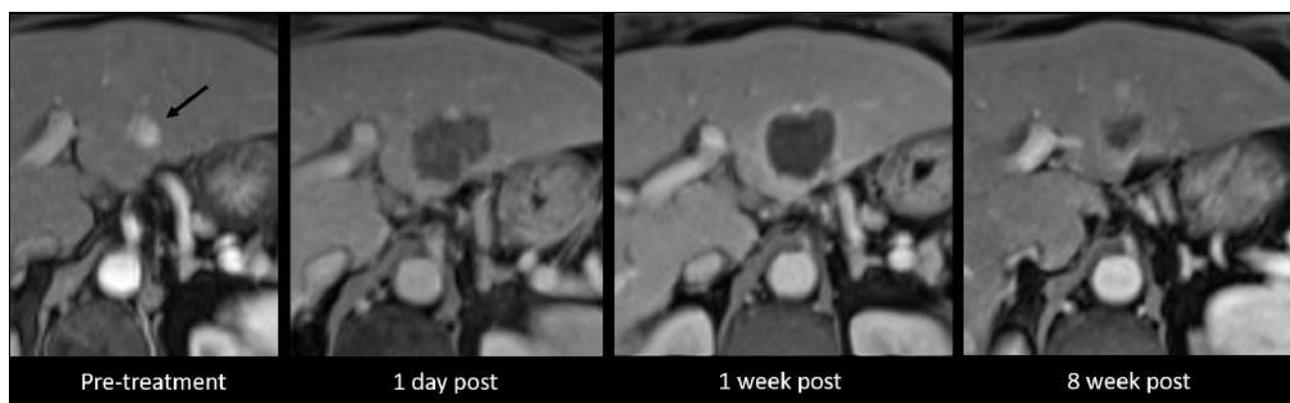
The primary endpoint is technical success, defined as creation of an ablation zone per the planned volume as assessed by MRI 1 day post-procedure. Secondary endpoints included safety (per CTCAE v4.0), local tumor control, and involution of ablation zone. Procedures were performed with the Robotic Histotripsy system (HistoSonics, Inc., Ann Arbor, MI) with the patient under general anesthesia. Follow-up MRI, laboratory draws, and clinical visits were scheduled at 1 day, 1 week, 1 month, and 2 months.

RESULTS

Five patients (mean 59, range 46 to 87 years) with multifocal liver malignancy (3 colorectal, 1 breast, 1 hepatocellular carcinoma) have undergone treatment of a single tumor. Average targeted tumor was 1.5 cm (0.5 to 2.3 cm) with volume of 2.5 mL (0.1 to 6.4 mL). Planned treatment volume averaged 10.5 mL (7.5 to 16.3 mL) with achieved volume of 13.0 mL (9.2 to 20.2 mL), meeting the primary endpoint. Ablation zone volume contraction averaged 36.7% at 1 week, 71.9% at 1 month, and 87.3% at 2 months. No device related adverse event has occurred. The 0.5 cm tumor was mis-targeted due to non-visualization with landmarks used for targeting. No definitive local tumor progression has occurred following appropriate targeting.

CONCLUSIONS

RAST can create a planned ablation volume without significant device-related adverse event.



HYPERTHERMIC ABLATION WITH FOCUSED ULTRASOUND (FUS-HIFU) IN PANCREATIC CANCER. UPDATED RESULTS OF A NINE-YEAR OBSERVATIONAL STUDY OF RETROSPECTIVE COHORTS IN PANCREATIC TUMORS

Vidal-Jove, Joan^{1, 3}; Jaen, Angels²; Velat, Manuela³; Perich, Eloi³

¹ Oncology Ablation HIFU Unit, Hospital University Mutua Terrassa, Barcelona

² Research Unit. Hospital University Mutua Terrassa, Barcelona

³ Interventional Oncology, Institut Khuab, Comprehensive Tumor Center Barcelona.
email: jvidal@khuab.com

OBJECTIVES

We describe our experience treating malignant pancreatic tumors, and compare it versus a cohort of patients treated with standard chemotherapy regimens only. This is a nine years observational comparative study of retrospective cohorts.

METHODS

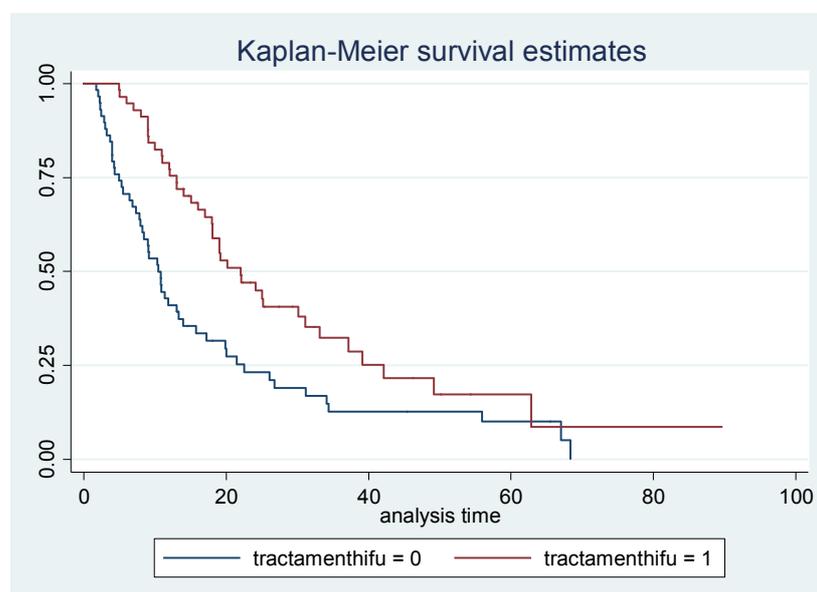
From February 2008 to May 2017 we have treated a total of 57 patients with non resectable pancreatic tumors, stage III and IV. They were treated with FUS-HIFU plus standard combinations of chemotherapy. We included stage IV patients that responded to chemotherapy. As control group, we have a cohort of 58 patients treated at the same institution and time.

RESULTS

The distribution of the pancreatic cases treated shows no differences in descriptive data. We specially analyze the 57 patients in the FUS-HIFU plus chemotherapy group. Clinical responses (ablation) were 82% in all cases. They were 12 complete responses (21%) at the end of the combined treatment. Complications included pancreatitis (2), skin burning grade III that required plastic surgery (2), duodenal perforation (1). One patient died from a delayed duodenal perforation. Median Survival is 23 months (6 mo - 4.3 year) and Overall Percent Survival is 18 % at 5 years follow up. Survival analysis between the two cohorts of patients shows a statistically significant benefit for the group of patients treated with FUS-HIFU plus chemotherapy ($p=0.0025$). Hazard ratio is 0.45.

CONCLUSIONS

FUS-HIFU is an effective and safe ablation of malignant pancreatic tumors. Compared with a similar cohort of patients, it shows survival advantage in non resectable stage III and IV cancer.



Abstract

Objectives: To evaluate the therapeutic effects of the doxorubicin-loaded nanoparticle-microbubble complex (DNMC) with focused ultrasound (FUS) in pancreatic cancer xenograft model.

Methods: Animals were treated in five groups (n=5 in each) with a doxorubicin (Dox) dose of 10mg/kg (toxicity study) and 4mg/kg (efficacy study), respectively: 1)control, 2)Dox only, 3)Dox with FUS, 4)DNMC only, and 5)DNMC with FUS. In further step, animals were treated in four groups (n=5 in each): 1)control, 2)Dox and microbubble (MB) mixture with FUS, 3)Dox-loaded nanoparticle (DoxNP) and MB mixture with FUS and 4)DNMC with FUS. Tumor growth was evaluated. Tumor apoptosis and fluorescence-based Dox amount were assessed in all tested treatment groups (n=3 in each).

Results: In toxicity study, all mice in “Dox only” and “Dox with FUS” died in the third week of experiment, while “DNMC only” or “DNMC with FUS” did not. In efficacy study, “DNMC with FUS” showed the significantly lowest tumor growth rate among groups in the third and fourth weeks. In further study, tumor growth rate in “DNMC with FUS” was lower than that of mice in “DoxNP and MB mixture with FUS” ($P<0.05$). In histopathological analysis, “DNMC with FUS” mice showed a higher Dox release in tumor than that of “Dox only”, “Dox with FUS” and “Dox and MB mixture with FUS” mice (all $P_s<0.05$). Tumor apoptosis rate of “DNMC with FUS” was significantly highest.

Conclusions: DNMC with FUS treatment presented enhanced anticancer effects with less toxicity.

DEVELOPMENT OF HIFU TREATMENT STRATEGIES FOR EXTRACORPOREAL TREATMENT OF HEPATIC TUMORS WITH A TOROIDAL TRANSDUCER. RESULTS OF IN VIVO EXPERIMENTS.

Sophie CAMBRONERO, Michel RIVOIRE, David MELODELIMA
LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, LYON, France
e-mail: sophie.cambronero@inserm.fr

OBJECTIVES

The liver is a particularly challenging organ for HIFU treatment due to the combined effects of respiratory-induced motion, partial blocking of the rib cage and high perfusion/flow. It has been shown, intra-operatively, that toroidal transducers can create large ablations in short treatment times. Numerical simulations, *in vitro* and *in vivo* experiments were conducted to evaluate the feasibility of an extracorporeal HIFU treatment of the liver with a toroidal transducer.

METHODS

The HIFU transducer has a toroidal shape with a radius of curvature of 70 mm focusing on a circle of 30 mm in diameter. The working frequency was 2.5 MHz. An ultrasound imaging probe operated at 7.5 MHz was placed in the center of the transducer.

The exposure parameters defined using numerical simulations were used in *in vitro* experiments and then *in vivo* in 3 pigs. The probe was held by hand. HIFU ablations were created in the liver using an acoustic power of 100 W for 40 seconds.

RESULTS

30 HIFU ablations were created *in vitro* to define optimal treatment parameters. Three lesions were created *in vivo* in the liver noninvasively without visible skin burns. All lesions were homogeneous and reproducible. The average diameter of these lesions was 7.7 ± 0.6 mm.

CONCLUSIONS

A truly noninvasive HIFU treatment of the liver is feasible using a toroidal transducer. Large volumes of ablation can be obtained in less than one minute. These results need to be confirmed and improved on a larger number of animals.

ACKNOWLEDGEMENTS

This project was partly funded by the FUS Foundation (N° RC17129CC).

CLINICAL TRIAL TO QUANTIFY URINARY STONE REPOSITIONING BY ULTRASOUND

MR Bailey,^{1,2} B Dunmire,¹ BW Cunitz,¹ J Thiel,¹ JC Dai,² Z. Liu,³ HC Chang,^{2*} PC Samson,² JD Harper,² MD Sorensen,^{2,4}

¹Center for Industrial and Medical Ultrasound, Applied Physics Laboratory, University of Washington, 1013 NE 40th St., Seattle, WA 98105, USA

²Department of Urology, University of Washington School of Medicine, 1959 NE Pacific Street, Box 356510, Seattle, WA 98195 USA

³Department of Biostatistics, Indiana University-Purdue University Indianapolis, 410 W. Tenth St., Suite 3000., Indianapolis, IN 46202, USA

⁴Division of Urology, Department of Veteran Affairs Medical Center, 1660 S Columbian Way, Seattle, WA 98108 USA

* Current Address: Kaiser Permanente Santa Clara Medical Center, Department of Urology, 710 Lawrence Expressway, Santa Clara CA 95051-5173
e-mail: mbailey@uw.edu

OBJECTIVES

Ultrasonic propulsion is an investigative modality to non-invasively reposition urinary stones. Our goals were to test safety and effectiveness of new exposures from a new transducer, and to use ureteroscopic observation to quantify stone repositioning.

METHODS

During surgery, ultrasonic propulsion was applied transcutaneously while stone targets were visualized ureteroscopically. Exposures were 350 kHz frequency, ≤ 200 W/cm² focal intensity, and ≤ 3 -second bursts per push. Ureteroscopic and ultrasound (US) videos were recorded and video clips with and without propulsion bursts were randomized and scored for motion ≥ 3 mm by independent reviewers blinded to the exposures. Subjects were followed with telephone calls, imaging, and chart review for adverse events.

RESULTS

Stone targets ranged from a collection of "dust" to 7 mm in size. Subjects received 16 ± 12 propulsion bursts for a total exposure time of 41 ± 39 s. All three endourologist reviewers scored stone movements ≥ 3 mm in 14 of 15 kidneys (93%) on the ureteroscopic videos. All three US video reviewers scored ≥ 3 mm movements in 11 of 15 kidneys (73%). This difference was likely due to motion out of the US imaging plane. Treatment successfully repositioned stones in two cases that would have otherwise required basket repositioning. No serious or unanticipated adverse events were associated with the experimental procedure.

CONCLUSIONS

Ultrasonic propulsion was shown to be safe, and it effectively repositioned stones in 93% of kidneys despite positioning and access restrictions caused by working in an operating room on anesthetized subjects.

ACKNOWLEDGEMENTS

Work supported by NIH grant P01-DK043881.

Pancreas ablation and hyperthermia in a porcine model using US-MR-HIFU: proof-of-concept study results of the European project iPaCT

E. Heijman^{1,2}, C.J. Ferrer³, L. Sebeke², R. Zitzmann¹, S.Y. Yeo², J. Castillo-Gómez², M. Ries³, J.H. Hwang⁴, C. Moonen³, H. Gröll², C. Bos³

¹Oncology Solutions, Philips Research, Eindhoven, NL

²University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department of Diagnostic and Interventional Radiology, Cologne, DE

³Image-guided molecular interventions, UMCU, Utrecht, NL

⁴Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, California, USA

e-mail: edwin.heijman@uk-koeln.de; C.J.Ferrer@umcutrecht.nl; lukas.sebeke@uk-koeln.de; rainer.zitzmann@philips.com; sin.yeo@uk-koeln.de; juan.castillo-gomez@uk-koeln.de; m.ries@umcutrecht.nl; jooaha@stanford.edu; C.Moonen@umcutrecht.nl; holger.gruell@uk-koeln.de; C.Bos@umcutrecht.nl

OBJECTIVES

Within the European FP7 project “iPaCT”, a novel HIFU system with simultaneous ultrasound- and MR-guidance (US-MR-HIFU) was developed for the treatment of pancreatic cancer. Here, we report on the first preclinical hyperthermia- and ablation experiments conducted with this system.

METHODS

The US-MR-HIFU tabletop contained a 256-element transducer with a Voronoi-tessellated Fermat-spiral pattern transducer with a 160 mm focal length and an f-ratio of 1. A custom dual tuned matching board with three accurately matched air coils per transducer element (Figure 1A) allowed concurrent usage of both 0.75 MHz for hyperthermia and 1.2 MHz for ablation of the therapeutic transducer. Preclinical experiments were carried out in a porcine model. Acoustic access to the pancreas was ensured by, a specialized diet, premedication, and an acoustically transparent coupling dome for bowel displacement and compression. Both apnea and respiratory triggering assured artifact free and stable thermometry during ablation and hyperthermia, respectively.

RESULTS

Pancreatic tissue was successfully ablated using 4mm (Figure 1B) and 8mm sonication cells as confirmed by both DCE MRI (Figure 1C) and histology. Hyperthermia was induced for more than 10 min with average temperature of 41°C.

CONCLUSIONS

The proof-of-concept study showed that hyperthermia and thermal ablation of the pancreas can be performed using two frequencies during an “one-stop shop” treatment with a US-MR-HIFU system.

ACKNOWLEDGEMENTS

iPaCT consortium: Philips, Imasonic, Neagen, University Hospitals of Utrecht and Cologne. The European FP7 Health program grant no. 603028 and BMBF “TSL-LIFU” (FKZ: 13XP5014A,D).

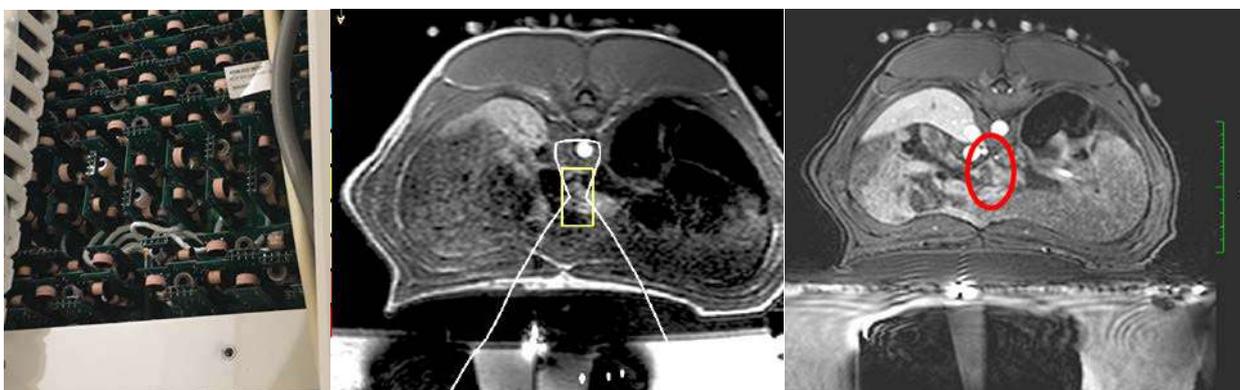


Figure 1: A: dual frequency matching board inside MR-HIFU tabletop. B: Planning of 4mm sonication in pancreas (300W, 25s, 1.2 MHz). C: DCE MRI of NPV volume in porcine pancreas.

POTENTIATION OF ULTRASONIC CHEMOTHERAPY ON A 3D CO-CULTURE MODEL OF PANCREATIC ADENOCARCINOMA

J.-L. Mestas¹, R. Leenhardt², E. Abou Ali², B. Bordacahar², M. Camus², F. Prat², C. Lafon¹

¹ Inserm, U1032, LabTau, Lyon, F-69003, France ; Université de Lyon, Lyon, F-69003, France

² INSERM U1066, Institut Cochin, Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, France.

e-mail: jean-louis.mestas@inserm.fr ; romainleni@gmail.com; frederic.prat@aphp.fr ;

OBJECTIVES

Pancreatic adenocarcinoma (PA) is experiencing a large increase in incidence, making it the fourth leading cause of cancer death. PA is characterized by increased chemoresistance due to its very dense tumor stroma. The aim of this work is to develop a 3D co-culture model (spheroid) associating PA cells with activated fibroblastic cells (FA) and to study the efficacy of inertial ultrasound cavitation (US) treatment in combination with chemotherapy.

METHODS

The tumor cells are derived from a murine PA cell line DT66066 derived from transgenic KPC mice. Fibroblasts are derived from mouse embryonic stem cells. After a development phase and model characterization, the therapeutic study focused on 8 groups (control, gemcitabine[Gem], US, US+Gem, US for 3 cavitation levels; N=6 in each group). Ultrasound device[1] has been adapted to treat spheroids one by one[2]. Treatment efficacy is evaluated at 24 hours by cell viability.

RESULTS

-Model development: the use of magnetic nanoparticles allowed rapid formation of PA/FA spheroids and improved their manipulation.

-Reproducible model: tumoral microenvironment was reconstituted by collagen fibers synthesized by fibroblasts

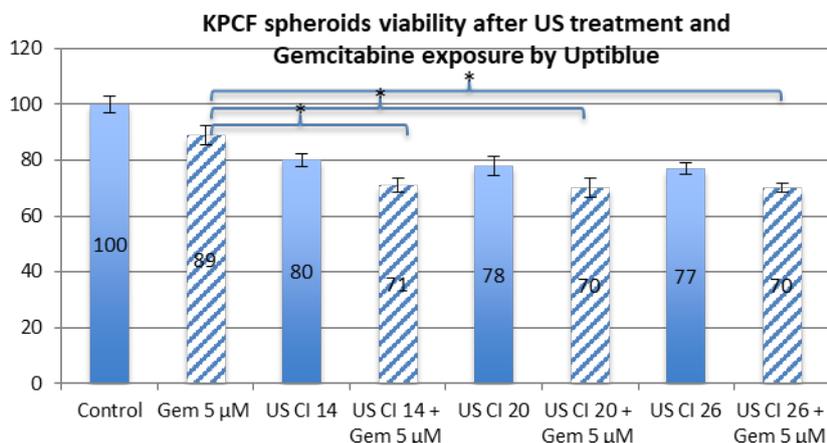
-Therapeutic application: (US+Gem) treatment resulted in a significant decrease in cell viability compared to Gemcitabine alone (p=0.0050). This treatment reduced tumor cell viability but did not impact fibroblasts.

CONCLUSIONS

This work led to the development of a relevant and reproducible model of three-dimensional co-culture of murine PA *in-vitro*. The US application with chemotherapy resulted in a significant reduction in cell viability compared with chemotherapy alone.

ACKNOWLEDGEMENTS

This work was funded by the Focused Ultrasound Foundation and ARC. The ultrasonic device was realized within the framework of the LabEx DevWeCan (ANR-10-LABX-0061).



1. Chettab A. et al. PLOS One, 2015

2. Abou Ali I. et al, PLOS One, 2018.

TRANS-FUSIMO - MODEL BASED TREATMENT SUPPORT FOR FUS IN MOVING ABDOMINAL ORGANS

S. Haase¹, M. Bezzi², T. Lango³, S. Muller³, Y. Levy⁴, Y. Shapira⁴, M. Midiri⁵,
M. Müller⁶, C. Tanner⁷, A. Melzer⁸, N. Naguib⁹, J.W. Jenne¹⁰, G. Sat¹¹, T. Preusser^{1,12}

¹Fraunhofer MEVIS, Bremen, Germany, ²Universita Degli Studi Di Roma La Sapienza, Rome, Italy, ³SINTEF AS, Trondheim, Norway, ⁴INSIGHTEC, Haifa, Israel, ⁵Università degli Studi di Palermo, Palermo, Italy, ⁶IBSmm, Brno, Czech Republic, ⁷ETH, Zurich, Switzerland, ⁸IMSat, University of Dundee, Dundee, UK, ⁹Johann Wolfgang Goethe University, Frankfurt, Germany, ¹⁰Mediri GmbH, Heidelberg, Germany, ¹¹GE Medical Systems, Haifa, Israel, ¹²Jacobs University, Bremen, Germany
e-mail: sabrina.haase@mevis.fraunhofer.de

OBJECTIVES

Treating liver tumors using FUS poses a great challenge due to the breathing motion of the target and the occlusion of the anatomical location of the malignancy by the rib cage. The EU project TRANS-FUSIMO aimed at the development and clinical translation of a system that supports conducting a focused ultrasound treatment in the moving liver.

METHODS

The TRANS-FUSIMO system contains real-time applicable motion compensation pipelines running during a sonication. Patient specific data is retrieved from the connected MRI to capture and track the motion of the liver and the target region. This data is then fed into a set of an abdominal organ models for the detecting deformations and tissue response. The FUS beam is steered according to this real-time information of the patient and the models.

RESULTS

To validate the TRANS-FUSIMO treatment system, its complete motion compensation pipeline and the models, phantom studies have been performed in static as well as moving scenarios. We showed that the software meets the defined requirements: System's safety requirements as well as functional ones. Furthermore, the in-vivo animal study showed that the software can sonicate safely in a living pig.

CONCLUSIONS

In ex-vivo and in-vivo experiments we could show that the TRANS-FUSIMO treatment system is capable of compensating organ motion through real-time motion detection, motion modelling and real-time beam steering.

ACKNOWLEDGEMENTS

The research leading to these results has received funding from the European Union's Seventh Framework Program (FP7/2007-2013) under grant agreement no. 611889 (TRANS-FUSIMO).

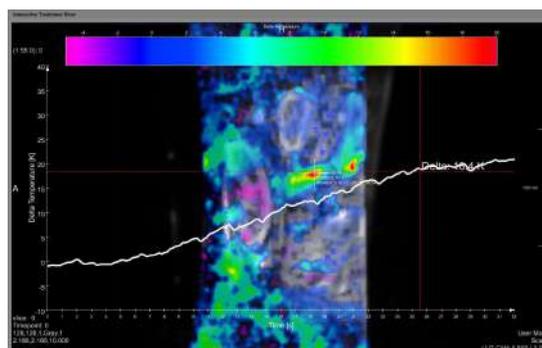


Figure: Temperature rise in in-vivo model using TRANS-FUSIMO system

HIFU Project in Oxford: Up-to-date Clinical Status and Future Prospective

Feng Wu^{1,2}, David Cranston^{1,2}

1. Nuffield Department of Surgical Sciences, University of Oxford,
Oxford, UK
2. HIFU Unit, Churchill Hospital, Oxford University Hospitals,
Oxford, UK

HIFU therapy has been used for more than 15 years in Oxford in the treatment of patients with solid tumours. It began with clinical trials related to thermal ablation of liver and kidney tumours and achieved a CE approval in 2005 for clinical applications in Europe. Since then, HIFU therapy has been increasingly exploited to provide a range of ultrasound therapies from tumour thermal ablation to targeted drug delivery in clinical trials. This talk reviews HIFU clinical development in Oxford with respect to its emerging clinical applications in gynaecology, neurosurgery, surgery and oncology. It presents up-to-date clinical results ranging from targeted drug delivery to thermal ablation for solid tumours. Future prospective and challenge of HIFU clinical use are also discussed in the presentation.

Experience in treating pancreatic cancer with HIFU in Korea.

TaeHee Kim¹

¹Seoul HICARE clinic , Seoul, Korea

e-mail: torog@hanmail.net

OBJECTIVES

The aim of this study was to long-term outcome of high-intensity focused ultrasound(HIFU) in advanced pancreatic cancer(PC) and discuss the usefulness of contrast enhanced ultrasound (CEUS)agent.

METHODS and RESULTS

In Korea, HIFU therapy for pancreatic cancer started in earnest in 2006 at St. Mary's hospital. In it's article about long-term outcome, patients with PC TNM stage 3 or 4 were included. HIFU treatment was performed without sever adverse event in 46 patients, 49 times. Average size of the PC lesion was 4.2cm(1.6-9.3). After HIFU treatment, ablating tumor volume was as follows: 90%-100% in 38 lesions, 90% to 50% in 8, and within 50% in 3. Overall survival (S1) from initial PC diagnosis was 12.4 months. Overall survival (S2) rates at 6, 12, and 18months from HIFU were 52.2%, 30.4%, and 21.79%, respectively, with a median survival of 7.0 months.

In my clinic data, 17 patients with pancreatic cancer with liver metastasis were included. Main purpose of treatment is pain control. It injected CEUS(sonazoid) 30 minutes before sonication. Average sonication power was 143.4w and average sonication time was 443.9s. HIFU treatment has been performed without sever adverse event. Average size of PC lesion was 4.8cm(2.7-10.1). All patient got the pain reduction more than 50% and 9 patients were more than 90%.

CONCLUSIONS

HIFU is safe and effective, which induced excellent local tumor control in most patients with advanced pancreas cancer. And also good option for pain control.

DISSCUSIONS

Because we used CEUS(sonazoid) for HIFU, sonication energy was lower than another HIFU centers. Some of the articles using CEUS for uterine myoma can be seen to increase the effect of HIFU treatment. It's worth studying about using CEUS for pancreatic cancer HIFU

THE ROLE OF MICROBUBBLE CONTRAST AGENT IN HIGH INTENSITY FOCUSED ULTRASOUND: CEUS DETECTOR, ACOUSTIC ENVIRONMENTAL MODIFIER AND FAR-FIELD PROTECTOR

Kun Zhou¹, Xing Chen¹, Jun Zhang¹, Yuhong Ma¹, Jingqi Wang¹, Lihui Huang¹, Hui Zhu¹, Zhechuan Mei²,

¹Clinical Center for Tumor Therapy, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

² Department of Gastroenterology, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

e-mail: zhoukunqq@ymail.com, zhoukun@hospital.cqmu.edu.cn,

OBJECTIVES

To discuss the clinical applications of microbubble contrast agent in HIFU treatment and evaluate the role of it.

METHODS

Microbubble contrast agent, was conducted into sonographic examination to make dynamic enhanced sono-images since 1990's. Ultrasound guided High Intensity Focused Ultrasound (USgHIFU) is used for benign tumors, malignancies, and some non-tumor diseases. The contrasted enhanced ultrasonography (CEUS) with microbubble contrast agent, is useful for evaluating the early therapeutic effect of percutaneous HIFU ablations.

The CEUS, with injection of adequate microbubble contrast agent, provided cavitation nuclei into the HIFU acoustic field. Clinical researchers thought it will helpful to generate cavitation. It made different if started HIFU sonication with different duration after CEUS with 1,2,3,5,8,10 min. Shorter the duration was, more the microbubble left in the HIFU acoustic field, stronger the cavitation generated. The cavitation was thought to enhance ablation of HIFU. A remarkable change is the massive grey scale change (MGSC). It means massive diagnostic ultrasound reflected from the ablated area. Similarly, the therapeutic ultrasound will be reflected from there, too. Clinical evidences supported that and it decreased the far field pain from the sacrum.

RESULTS

Microbubble contrast agent plays roles in HIFU treatment.

CONCLUSIONS

As conclusion, we believe that microbubble contrast agent is a good CEUS detector, available acoustic environmental modifier and potential far-field protector.



OTHER CLINICAL VASCULAR AND BENIGN HIFU APPLICATIONS

ORAL PRESENTATIONS:

Extra Corporeal Ultrasound-guided High-Intensity-Focused-Ultrasound (HIFU) treatment in superficial lower limb veins – First in Human study findings - *Michel Nuta*

Macroscopic and microscopic evaluation of HIFU thermal ablations of sheep veins at 30, 60 and 90 days - *Nesrine Barnat*

HIFU treatment of benign thyroid nodules in Spain. 12-months follow-up - *Pedro Pablo Ortiz Remacha*



Presentation title: Extra Corporeal Ultrasound-guided High-Intensity-Focused-Ultrasound (HIFU) treatment in superficial lower limb veins - First in Human study findings.

Author: Michel Nuta, MD – Theraclion

Background/Aim: A vast percentage of the population in age between 30 and 70 is affected by varicose veins. The standard treatment includes open surgery and endovenous thermal methods (radiofrequency/LASER) using a catheter inserted in the incompetent vein.

A first in human prospective study conducted by Alfred Obermayer, MD followed patients treated for incompetent lower limb veins to 3 months (M).

Methods: The Theraclion device generates HIFU which penetrates through soft tissues and causes localized hyperthermia responsible of irreversible protein denaturation and veinwall coagulation whereas overlying and surrounding tissues are spared. A piezoelectric transducer engender the ultrasound field. At the center of the transducer an imaging array allows perfect real time alignment of the focal point.

Results: We have several interesting examples of positive results after 3M follow-up. Most of the cases were performed without anesthesia and no severe adverse events, scars or skin pigmentation were observed.

- A) A female patient presenting recurrence after Great Saphenous Vein (GSV) stripping. No anesthesia was performed.
- B) A female patient presenting a refluxing stump and a neovascularization after GSV stripping as well as an active ulcer was treated over the stump and neo-vessels area. No anesthesia was performed.
- C) A male patient presenting a refluxing GSV and active ulcer was treated after unsuccessful surgery. Tumescence anesthesia was performed. The ulcer was healed at 3M.

Conclusion: In this study, the results are encouraging and are showing that this method could become a convincing, patient friendly alternative. More cases and longer follow-up will be required in the forthcoming multi-center studies.

MACROSCOPIC AND MICROSCOPIC EVALUATION OF HIFU THERMAL ABLATIONS OF SHEEP VEINS AT 30, 60 AND 90 DAYS

N. Barnat^{1,2}, A. Grisey², B. Gerold², J. Anquez², S. Yon², J. Aubry¹

¹ Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Paris, France

²Theraclion, Malakoff, France

e-mail: nesrine.barnat@espci.fr

OBJECTIVES

Venous insufficiency is a common medical disease currently treated by surgery or, less invasively, by sclerotherapy or endovenous thermotherapies like endovenous laser ablation (EVLA) or radiofrequency ablation (RFA). High-Intensity Focused Ultrasound (HIFU) is a promising non-invasive approach to thermally treat varicose veins. Short and long-term effects of HIFU treatments were studied macroscopically and microscopically in a sheep model. The vein aspect was compared with the commonly reported observations after EVLA and RFA.

METHODS

Eighteen saphenous veins (mean diameter 3.2 mm) in nine sheep were sonicated with a transducer operating at 3 MHz. Animals were split into three groups and followed-up for 30, 60 or 90 days post-treatment. In vivo B-mode imaging was used in conjunction to macroscopic and microscopic examination of veins.

RESULTS

Vein shrinkage was observed with B-mode imaging for all treated veins. At 30 days, histological examination showed vein wall coagulative necrosis, collagen hyalinization and localized necrosis of the perivascular tissues. Fibrous healing was observed at 60 days and was complete and considered to be stable at 90 days in all samples examined. Thrombotic occlusions were observed as illustrated in **Figure 1**. Neither perforation nor charring was observed in any of the targeted veins.

CONCLUSIONS

Histological findings after HIFU are characteristic of thermal injuries and are similar to the reported observations after EVLA and RFA, including fibrotic sealing of the vein lumen. These results support the strong potential of HIFU for treating varicose veins.

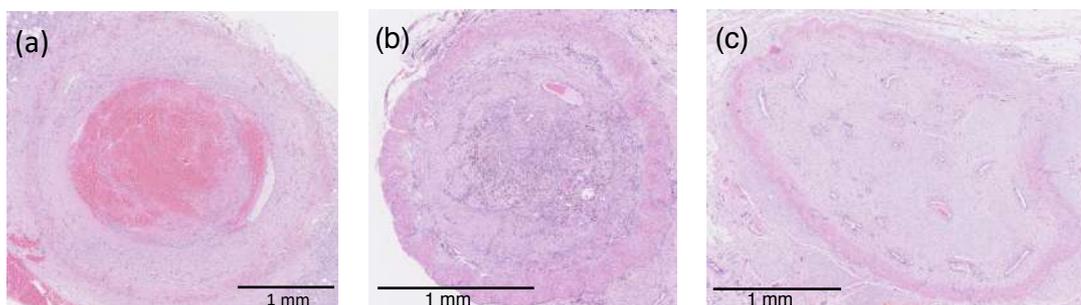


Figure 1: Veins extracted at 30 (a), 60 (b) and 90 (c) days post-treatment showing occlusion

HIFU TREATMENT OF BENIGN THYROID NODULES IN SPAIN. 12-MONTHS FOLLOW-UP.

P.P. Ortiz Remacha¹, J. Vidal Jové²

¹Endocrinology specialist. Expert in thyroid pathology. Human Anatomy and Embryology Department, Universidad de Zaragoza, Spain.

²Surgery specialist. Hospital Universitario Mutua de Terrassa, Barcelona, Spain.

E-mail: doctorortizremacha@gmail.com

OBJECTIVES

Assess the response of benign thyroid nodules to HIFU treatment depending on their volume and localization.

METHODS

60 patients with benign thyroid nodules (Bethesda Category II) were treated with HIFU (Echopulse® Theraclion). They were grouped in 3 categories by maximal nodule diameter as assessed by echography. Group 1: nodule diameter between 14 and 20 mm; Group 2: between 21 and 30 mm; Group 3: over 30 mm. Follow-up at 6 weeks, 6 and 12 months was done under echography. We define therapeutic success when the nodule size after treatment is inferior to 50% of its initial size. Nodules are described as superficial or deep taking the center line of the trachea as a reference.

RESULTS

Results from groups 1 and 2 are significantly different from those from Group 3. 80% of Group 1 cases reach therapeutic success with a single treatment. Groups 2 and 3, have respectively 50% and 20% of success. In cases from Groups 2 and 3 treatment is repeated up to 3 times. Deeper nodules and nodules located on the isthmus can only be treated partially.

CONCLUSIONS

The size of thyroid nodules is an important factor to design of the treatment strategy with HIFU. Nodules under 30 mm diameter are the best choice in terms of treatment speed, efficacy and obtained results. For bigger nodules, several sessions and a follow-up over 12 months are necessary to obtain satisfactory results. Deeper nodules and nodules located on the isthmus need a previous simulation treatment to assess the expected reduction.

POSTER SESSION I

- # 1 - Ultrasound transmission through human hair, *Pauline Agou*
- # 2 - Validation of neonatal lamb model for preclinical evaluation of MR-Guided Focused Ultrasound brain applications, *Matthew Alexander*
- # 3 - Estimation of the temperature increase during a HIFU treatment using ultrasound backscattered signals. Correlation with histological changes, *Victor Barrere*
- # 4 - Phase aberration correction in focused ultrasound fields with shock fronts, *Christopher Bawiec*
- # 5 - Modelling a Collaborative Robot with the IEEE 11073 SDC Standard for Combined Focused Ultrasound and Radiation Therapy, *Johann Berger*
- # 6 - HIFU localized hyperthermia for MR-Linac accelerators, *Giovanni Borasi*
- # 7 - Swine model for the evaluation of blood-brain barrier disruption with the sonocloud® Device using definity® and sonovue® microbubbles, *Guillaume Bouchoux*
- # 8 - Treatment of essential tremor (ET) and Parkinson disease (PD) tremor with MRgFUS: preliminary imaging and clinical results and their correlation, *Federico Bruno*
- # 9 - Magnetic resonance-guided focused ultrasound versus deep brain stimulation in medically-refractory essential tremor: A cost-consequence analysis in the Korean setting, *Lance Richard*
- # 10 - Post hoc prediction of blood-brain barrier opening with power cavitation imaging in non-human primates, *Mark Burgess*
- # 11 - Autophagy and dystrophic skeletal muscle regeneration are differentially modulated by different therapeutic ultrasound modalities, *Scott Burks*
- # 12 - Assessment of MR thermometry reliability for monitoring HIFU ablations in bone, *Paolo Cabras*
- # 13 - Acoustic holograms for transcranial focusing of arbitrary ultrasonic fields into the brain, *Francisco Camarena*
- # 14 - Simulation of temperature rise in mobile and elastic volume, *Elodie Cao*
- # 15 - Intensive HIFU simulation based on surrogate models using CIVA Healthcare platform application to parametric studies and sensitive analysis, *Sylvain Chatillon*
- # 16 - Cavitation Dose Painting for Predicting the Location and Concentration of Nanoclusters Delivered by Focused Ultrasound-Induced Blood-Brain Barrier Disruption, *Hong Chen*
- # 17 - Fusion MRI-Ultrasound guided histotripsy system, *Sang Won Choi*
- # 18 - Remote activation of engineered neural stem cells for the release of TNF α and IL15 via high-intensity focused ultrasound, *James Chu*
- # 19 - Multiple-focusing method for treatment time reduction in HIFU thermal ablation, *Euisuk Chung*
- # 20 - Development of a HIFU treatment using a toroidal transducer for pancreatic adenocarcinoma. Preliminary in vivo study, *Celia Cilleros*
- # 21 - Effect of bubble-bubble interactions on subharmonic emissions of a monodisperse bubble cloud, *Corentin Cornu*
- # 22 - Blood-brain tumor barrier opening with MR Image-guided focused ultrasound augments interstitial flow and facilitates nanoparticle-mediated transfection, *Colleen Curley*
- # 23 - #10yearschallenge: Our Roadmap to FURTHER - Focused Ultrasound and RadioTherapy in patients with bone metastases, *Cristina Marrocchio*
- # 24 - MRI-Guided focused ultrasound robotic system for experiments in mice, *Christakis Damianou*
- # 25 - Transient Acoustic Streaming in Confined Cavity from Pulsed HIFU Exposure, *Hussein Daoud*

- # 26 - Ultrasound-image based navigation guidance for 3D planning of conformal interstitial HIFU ablations, *Loïc Daunizeau*
- # 27 - Ultrasound-assisted drug delivery to solid tumours in silico, *Matheus de Andrade*
- # 28 - Ventilator Driven Motion Model for Pre-clinical Validation of MRgFUS Systems, *Andrew Dennison*
- # 29 - Pain relief and local tumor control after focused ultrasound surgery as treatment option for advanced pancreatic cancer patients, *Dobromir Dimitrov*
- # 30 - Delivery of basic fibroblast growth factor (bFGF) and control of endothelial network formation using acoustic droplet vaporization (ADV), *Mario Fabiilli*
- # 31 - Therapeutic response to free cabazitaxel and cabazitaxel loaded nanoparticles combined with ultrasound and microbubbles in a transgenic mouse prostate cancer model, *Stein-Martin Fagerland*
- # 32 - Ultrasonic-magnetic hybrid gene delivery system for Parkinson's disease treatment in mice model, *Ching-Hsiang Fan*
- # 33 - DNA damage induced by combined doxorubicin and unseeded controlled stable cavitation treatment in murine mammary tumor cells, *Cécile Fant*
- # 34 - The first coagulative necrosis point induced by HIFU treatment for isointense uterine fibroids on MRI T2WI : Retrospective analysis and theoretical simulation, *Li Faqi*
- # 35 - A theranostic polymer-based nanoparticle for use in sonodynamic therapy (sdt), *Sian Farrell*
- # 36 - Temporal proteomic immune changes of murine breast and melanoma tumor microenvironments without and with pulsed focused ultrasound , *Joseph Frank*
- # 37 - Acute evaluation of brain and cerebrospinal fluid biomarkers following blood brain barrier opening with pulsed focused ultrasound and definity using passive cavitation detection feedback, *Joseph Frank*
- # 38 - Experimental evaluation of the impact of ultrasound exposure parameters on necrotic lesions induced in tissue by a robotic ultrasound-guided HIFU ablation device for treating solid tumors in small animals, *Łukasz Fura*
- # 39 - Targeted delivery of multiple drug payloads to pancreatic tumours using an ultrasound responsive microbubble-liposome conjugate, *Jinhui Gao*
- # 40 - Transcranial MR acoustic radiation force imaging and simulation in sheep, *Pooja Gaur*
- # 41 - Unilateral mr guided focused ultrasound thalamotomy for essential tremor: a british experience, *Wladyslaw Gedroyc*
- # 42 - Ultrasound-stimulated Microbubble Indentation of Fibrin Clots, *David Goertz*
- # 43 - Multiple lesion generation during HIFU thermal therapy: numerical modeling & parametric study, *Pragya Gupta*
- # 44 - Stimulation of the rat dorsal root ganglion for chronic pain regulation with focused ultrasound, *Pohung Hsu*
- # 45 - Ultrasound-mediated skin erosion for hepatitis B immunization, *Yxin Hu*
- # 46 - Optimal overlapping protocol and robustness assessment of blood-brain barrier opening in humans using a single-element focused ultrasound transducer, *Sergio Jiménez Gambín*
- # 47 - Accuracy of Acute MR Predictors of Non-Perfused Ablation Volume in Multiple Tissue Types, *Sara Johnson*
- # 48 - New focused ultrasound protocol to improve blood-brain barrier permeability and doxorubicin delivery into the targeted rat brain, *Byeongjin Jung*
- # 49 - Ultrasound-Enhanced Drug Delivery for Treatment of Acanthamoeba Keratitis, *Bianca Karpinecz*
- # 50 - Mapping clinical HIFU thermal tissue ablation using simulation and MR-Imaging, *Maria Karzova*

- # 51 - Characteristics of therapeutic temperature monitoring of MR-Guided focused ultrasound therapy for bone and joint diseases, *Motohiro Kawasaki*
- # 52 - On-Demand, targeted light generation in bio-compatible elastomers using high-intensity focused ultrasound, *Gun Kim*
- # 53 - A new frequency domain passive acoustic mapping method using passive hilbert beamforming to reduce the computational complexity of fast fourier transform, *Pilsu Kim*
- # 54 - Cavitation nucleation by definity® infused through an ekosonic® catheter, *Maxime Lafond*
- # 55 - Pelvic soft tissue deformation estimation for patients in magnetic resonance guided high-intensity focused ultrasound (MRGHIFU) treatment positions, *Ngo Fung Daniel Lam*
- # 56 - Diminished expression of p glycoprotein is associated with PJNK-dependent pathway after blood-brain barrier disruption induced by MIR-Guided focused ultrasound, *Eunhee Lee*
- # 57 - Comparison of ray tracing and hybrid angular spectrum phase correction methods on focal spot pressure, *Steve Leung*
- # 58 - Theoretical Simulation and Experimental Study of HIFU Non-Fourier Bioheat Transfer Considering Thermoacoustic Lenses and Thermal Wave Effects, *Faqi Li*
- # 59 - Response to pain in the treatment of benign thyroid nodules with HIFU, *Pedro Pablo Ortiz Remacha*
- # 60 - Transcranial temperature rise comparison through phase corrections of embedded exablate function and kranion software, *Dong-Guk Paeng*
- # 61 - A clinical system for non-invasive blood-brain barrier opening using a neuronavigation-guided single-element transducer, *Antonios Pouliopoulos*
- # 62 - Simultaneous MR Thermometry and acoustic radiation force imaging of HIFU treatment based on echo-shifted sequence, *Yangzi Qiao*
- # 63 - Body Mounted Robot for High Intensity Focused Ultrasound, *Kevin Cleary*
- # 64 - A MRI Compatible Large Scale Array System for Low Intensity Therapeutic Ultrasound, *Weibao Qiu*
- # 65 - Volumetric and rapid MR-Acoustic radiation force imaging using simultaneous multislice imaging (SMS), *Bruno Quesson*
- # 66 - Repeated scanning ultrasound improves motor function and clears neuronal tau by autophagy in tau transgenic mice, *Jae Hee Song*
- # 67 - Neurostimulation by focused ultrasound in ex vivo mouse brain slices as measured with a microelectrode array (MEA) system, *Ivan Suarez Castellanos*
- # 68 - Development and characterization of a small animal hyperthermia system, *Steffen Tretbar*
- # 69 - Hepatic Ablation with Robotically Assisted Sonic Therapy (RAST) Through Full Rib Coverage in a Porcine Model, *Timothy Ziemlewicz*
- # 70 - Review of Robotic Assisted Sonic Therapy (RAST) in a Large Porcine Model and Implications for Future Development, *Timothy Ziemlewicz*
- # 71 - Synthetic schlieren tomography of focused ultrasound fields, *Aki Pulkkinen*
- # 72 - Gellan gum as a Tissue Mimicking Material for combined HIFU and Radiotherapy, *Alberto Sanchez-Pastor Gomis*
- # 73 - Validating Ultrasound Beam Prediction Modeling for Breast Tumor Treatment, *Allison Payne*
- # 74 - MR guided focused ultrasound thalamotomy for Essential Tremor: A 5 year single center experience, *Alon Sinai*
- # 75 - Ultrasound-induced blood spinal cord barrier opening in rabbits and mice, *Anne-Sophie Montero*

ULTRASOUND TRANSMISSION THROUGH HUMAN HAIR

P. Agou¹, H. A. S. Kamimura^{1,2}, A. Novell¹, B. Larrat¹

¹NeuroSpin, Commissariat à l'Énergie Atomique et aux Énergies Alternatives (CEA), Gif-sur-Yvette, France

²Molecular Imaging Research Center (MIRCen), Institut de Biologie François Jacob, Commissariat à l'Énergie Atomique et aux Énergies Alternatives (CEA), Fontenay-aux-Roses, France

e-mail: pauline.agou@cea.fr ; benoit.larrat@cea.fr

OBJECTIVES

Therapeutic transcranial focused ultrasound (TcFUS) protocols include patient's head shaving to facilitate the transducer acoustic coupling. However, little is known to what degree ultrasound transmission is affected by the hair presence. Avoiding hair shaving could improve patient's comfort and potential psychological burden, especially during repeated sessions. In this study, we investigated the influence of the acoustic frequency and the level of dissolved oxygen in the coupling medium on the ultrasound transmission through the human hair.

METHODS

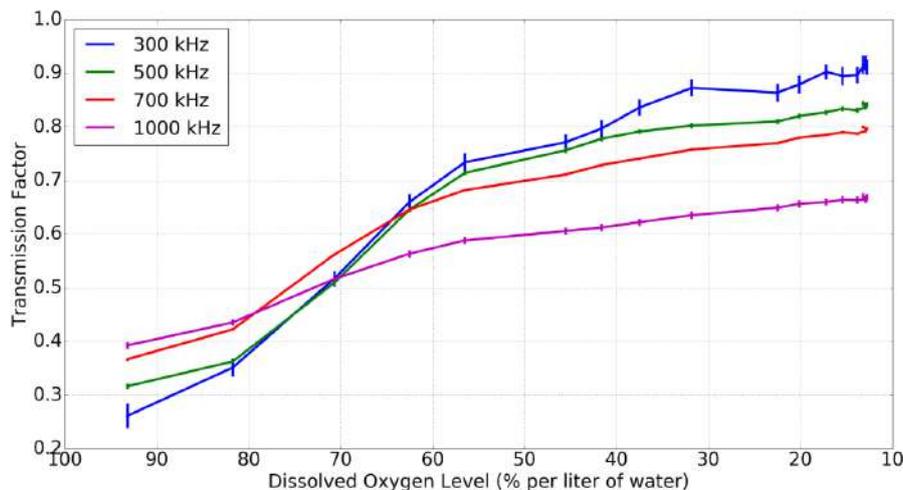
Strands of different types of hair were immersed in non-degassed water. The transmission factor (300-1000 kHz, $\Delta f=25$ kHz) through the hair was consecutively measured using a broadband transducer and a hydrophone while the dissolved oxygen level was gradually decreased from above 90% down to 15%. Transmission measurements in free water were used as reference.

RESULTS

The most attenuating sample presented transmission between 25% and 40% depending on the frequency. Degassing increased these values from 65% to 90%. However, final transmission decreases with frequency whereas the opposite trend was observed before degassing. As pressure measurements in free water were found independent of the degassing level, this observation could be explained by the ultrasound attenuation caused by large bubbles trapped in the hair.

CONCLUSIONS

In the range of investigated frequencies, a reasonable transmission factor through the hair was reached for sufficient degassing levels. This study demonstrates that TcFUS treatments could be achieved without head shaving with a compensation of ultrasound power.



CAPTION: Acoustic transmission factors through one hair sample as a function of dissolved oxygen level and frequency.

VALIDATION OF NEONATAL LAMB MODEL FOR PRECLINICAL EVALUATION OF MR-GUIDED FOCUSED ULTRASOUND BRAIN APPLICATIONS

H. Odéen¹, V. Rieke¹, D. Parker¹, K. Albertine², L. Hofstetter¹, J. Rolston³, A. Payne¹, M. Alexander^{1,3}
Departments of ¹Radiology and Imaging Sciences, ²Pediatrics, and ³Neurosurgery, University of Utah, Salt Lake City, Utah, USA
e-mail: matthew.alexander@hsc.utah.edu

OBJECTIVES

Developing novel MR-guided focused ultrasound (MRgFUS) therapies requires preclinical animal models to validate techniques prior to human use. Prior animal models have been limited by the need for removal of the skull to target the brain and use of MRgFUS equipment that is not clinically available.

METHODS

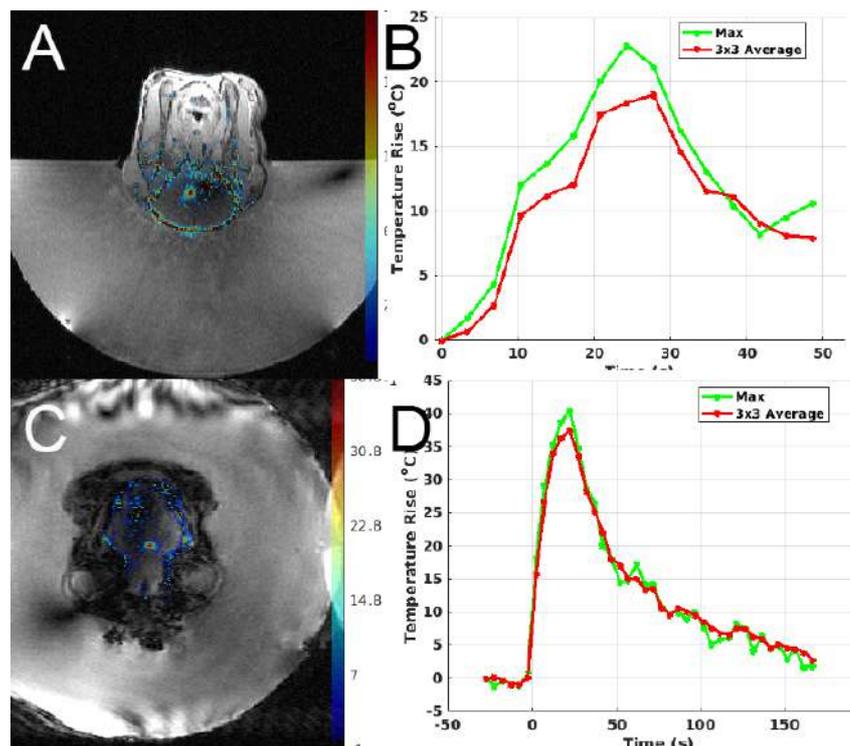
A neonatal lamb was euthanized, and its head was shorn and treated with depilating cream. The head of the lamb was positioned in the InSightec Exablate Neuro (IEN) MRgFUS array, submerging the head in degassed deionized water with the array in horizontal position. Various energies were delivered to multiple central brain structures through differing combinations of power and duration through the skull, which was co-registered following IEN protocol. MR thermometry was performed with the IEN 2D multi-echo gradient echo (ME-GRE) pulse sequence as well as a 3D segmented EPI sequence.

RESULTS

Using 2D ME-GRE, 9798 J (500W peak for 40s) achieved temperature rise of 19°C. Using 3D EPI, 25,651J (1000W peak for 30s) achieved temperature rise of 36°C. Temperature maps and graphs for these two sonications are provided in the figure. Pathology results are pending.

CONCLUSIONS

MRgFUS efficiently delivers energy to heat brain tissue in neonatal lambs to model potential new treatments for humans. This model improves on prior models since it does not require preoperative craniectomy and utilizes the clinically available IEN system. Further validation in living lambs is underway.



CAPTION: Temperature maps overlaid on magnitude images for 2D ME-GRE (A) and 3D EPI (C), and corresponding temperature vs. time curves (B) and (D), respectively.

ESTIMATION OF THE TEMPERATURE INCREASE DURING A HIFU TREATMENT USING ULTRASOUND BACKSCATTERED SIGNALS. CORRELATION WITH HISTOLOGICAL CHANGES.

Victor Barrere, David Melodelima

LabTAU, INSERM, Université Lyon 1, Univ Lyon, F-69003, LYON, France

e-mail: victor.barrere@inserm.fr; david.melodelima@inserm.fr

OBJECTIVES

Thermometry using ultrasound imaging is a challenge. Many methods have been suggested with limited success, mainly for temperatures higher than 55°C. Measuring the backscattered energy contained in the radiofrequency signals of ultrasound scanners may be promising. The aim of this study is to investigate if the increase of the backscattered energy is correlated with histological changes.

METHODS

Pulse-echo technique was used to measure changes in backscattered signals in liver tissues heated by a HIFU probe. The central frequencies of the pulse-echo transducer and of the HIFU transducer were 2.25 MHz and 3 MHz respectively. The sample was heated by HIFU up to 80°C and then cool down to 40°C. Attenuation, speed of sound and backscattered energy were calculated during heating and cooling. Samples were then fixed for histological analysis.

RESULTS

Twelve samples were treated. A +3 dB linear increase in backscattered energy (BSE) was observed between 37°C and 67°C. Histological analyses shown that intercellular space increased up to 175% at 55°C and then decreased to 50% at 80°C. The normalized size of cells increased up to 140% at 80°C.

CONCLUSIONS

The linear relationship between changes in the backscattered energy and actual temperature was observed up to 70°C. The increase in intercellular space combined with the increase of the size of the cells could explain the increase of the BSE. Successful temperature estimation may allow creating 2D temperature maps during HIFU treatments.

ACKNOWLEDGEMENTS

This project was partly supported by BPI France (project HECAM), and by SIRIC LyriCAN (INCa_INSERM_DGOS_12563).

PHASE ABERRATION CORRECTION IN FOCUSED ULTRASOUND FIELDS WITH SHOCK FRONTS

C.B. Bawiec¹, V.A. Khokhlova^{2,3}, O.A. Sapozhnikov^{2,3}, M. O'Donnell⁴, A.T. Peek², T.D. Khokhlova¹

¹Department of Medicine, University of Washington, Seattle, USA

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

⁴Department of Bioengineering, University of Washington, Seattle, USA

e-mail: bawiec@uw.edu

OBJECTIVES

Focused ultrasound therapies are often affected by aberrations induced by soft tissue heterogeneities. Aberrations are especially detrimental for treatments relying on shock front formation. If the therapeutic transducer is a multi-element array, correcting phases at different elements could mitigate aberration losses. In this work, an aberration correction method based on backscattering of nonlinear ultrasound waves at the array focus is proposed, validated through hydrophone measurements, and tested in tissue-mimicking phantoms (TMPs).

METHODS

A spherically focused 12-element ultrasound array (aperture 75mm, F#=1, 1.5 MHz) was coaxially aligned with an ultrasound imaging probe (ATL P7-4). Each focused element emitted a short (3-cycle) pulse through an aberrating layer into a TMP, and the backscattered signal was recorded by the imaging probe. The transmit time delay at each element restoring the shock amplitude at the focus was calculated based on cross-correlation between backscattered signals. Results were confirmed by replacing the TMP with a hydrophone.

RESULTS

The aberrating layer introduced time shifts (>200ns) between waveforms from individual elements that decreased shock amplitude by 60% compared to attenuated, but unaberrated beam. Using time delays estimated by the iterative cross-correlation algorithm from high-pass filtered backscattered signals, 50% of shock amplitude lost to aberrations was recovered by reducing the time shifts between individual waveforms.

CONCLUSIONS

The feasibility of the approach was confirmed, indicating that higher harmonics generated by separate elements at the focus provide sufficient spatial localization for phase correction feedback, even in the absence of a single-point scatterer.

ACKNOWLEDGEMENTS

Work supported by NIH R01GM122859 and R01EB007643

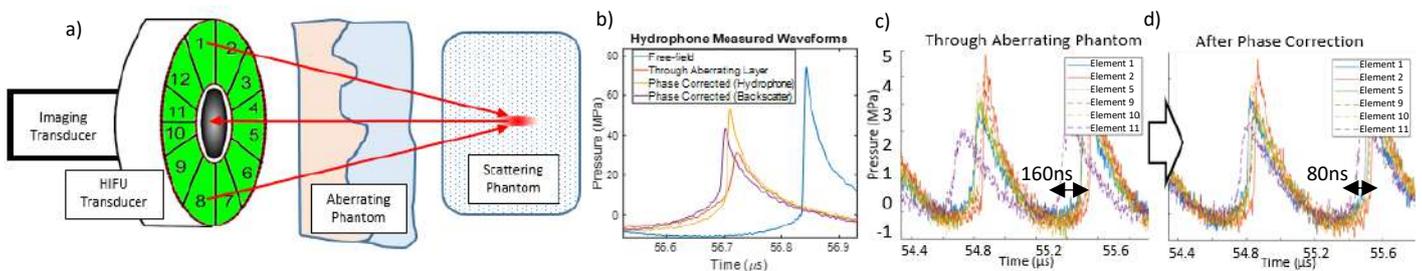


Figure Caption: a) Schematic of the experimental setup – imaging and HIFU arrays are coaxially aligned, an aberrating phantom of ballistic gel and PVA is placed in the acoustic path, and the focus is located in a gellan gum based scattering phantom. b-d) Focal waveforms as measured by a fiber optic hydrophone with all-elements turned on (b) and representative, individual element waveforms before and after phase correction (c and d, respectively).

Modelling a Collaborative Robot with the IEEE 11073 SDC Standard for Combined Focused Ultrasound and Radiation Therapy

Johann Berger¹, Michael Unger¹, Lisa Landgraf¹, Andreas Melzer¹

¹Innovation Center Computer Assisted Surgery, Leipzig, Germany

Introduction

Radiation therapy (RT) leads to negative side-effects. Applying hyperthermia (42 - 45°C) with focused ultrasound (FUS) showed improved radio-sensitization and, therefore, could improve treatment outcome. Evaluations to position ultrasound devices via collaborative robotics have been shown before. For a safe clinical integration, the goal of this work is the implementation and evaluation of a standardized communication between the robot and other devices.

Materials & Methods

A KUKA LBR iiwa 7 R800 robot (KUKA AG, Germany) was modelled within the *IEEE 11073 SDC* (Service-oriented Device Connectivity) standard. The interconnection with other devices was implemented and evaluated on a setup to position a Clarius L7 wireless ultrasound probe (Clarius Mobile Health Corp, Canada). For each robot-joint the critical states were represented in the SDC-conform descriptions to be shared via Ethernet, resulting in a total of 42 parameters. The software was implemented in C++ on a standard PC, accessing the KUKA-controller with ROS (Robot Operating System). The accessibility of each parameter and corresponding interaction-commands were evaluated with an SDC-consumer application.

Results

The SDC-provider functionality was successfully implemented, allowing for dynamic changes of the robot-state during interventions. All appliances (SDC standard compatible) in the robot's network can react to state changes and send movement and planning commands. After testing, 100% of the 42 parameters are safely accessible.

Conclusion

Implementing the medical device communication for the KUKA robot enables its integration into any networked operation room that supports the SDC standard. It is therefore ready to be implemented and evaluated for the application of FUS in a clinical environment.

HIFU LOCALIZED HYPERTHERMIA FOR MR-LINAC ACCELERATORS

G. Borasi¹, F. Cavaliere², F. Pezzotta², G. Durando³, D. Viganò², W. Merli², B. Caccia⁴, G. Caliano⁵

¹Università di Milano Bicocca, Dipartimento di Medicina, Milano, Italia

²Università di Milano, Dipartimento di Fisica, Milano, Italia

³Istituto Nazionale di Ricerca Metrologica, INRIM, Torino, Italia

⁴Istituto Superiore di Sanità, Roma, Italia

⁵Dipartimento di Ingegneria, Università di Roma tre, Roma, Italia

e-mail: giovanni.borasi@gmail.com

OBJECTIVES

To overcome the X-Ray Radiotherapy (RT) limitation, in particular for tumors containing radioresistant cells, the use of Hyperthermia (HT), which is an effective radio-sensitizer, may considerably improve the treatment outcome. The use of High Intensity Focused Ultrasound (HIFU) offers a new method to administer HT in a highly localized way ("stereotactic HT").

METHODS

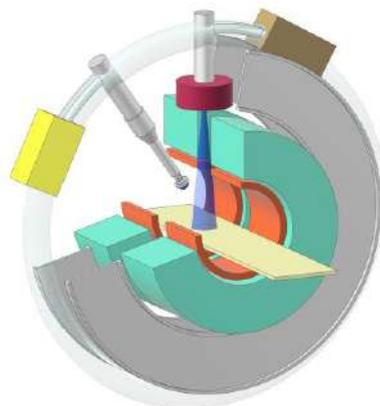
The problem of the length of the present standard HT treatment (1 h at 42.5 °C), can be overcome with the use of the experience gained with the "scanned ultrasound HT". The recent entry into the clinical field of high field (1.5 T) MR guided LINAC units give to the Radiotherapist not just the MR imaging quality and the real time organ movement control, but also the possibility of sophisticated analyses of the day by day progress of the RT effect (for example, by using ADC maps, tractography, and CEST spectroscopy).

RESULTS

Different solutions of MR guided HIFU systems for delivering localized HT are discussed.

CONCLUSIONS

Robotic HIFU devices can provide localized HT in the new MR-LINAC accelerators environment. In the near future, CMUT technology, integrated with MR multichannel surface coils, it's worth to be considered.



Schematic drawing of a 360° rotating robotic arm providing an existing MR-LINAC system with MR HT (see: B.W. Raaymakers et al. *Phys. Med. Biol.* **54** (2009) N229–N237).

The activities here presented will be developed in the framework of the 18HLT06 RaChy Project that received funding from the EMPIR program co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation program.

SWINE MODEL FOR THE EVALUATION OF BLOOD-BRAIN BARRIER DISRUPTION WITH THE SONOCLOUD® DEVICE USING DEFINITY® AND SONOVUE® MICROBUBBLES

G. Bouchoux¹, C. Deseaux¹, M. Canney¹, S. Robinson², O. Chevènement³, L. Fiette³, C. Lafon⁴, J.-Y. Chapelon⁴, A. Carpentier^{5,6}

¹CarThera, Institut du Cerveau et de la Moelle épinière (ICM), Paris F-75013, France

²Lantheus Medical Imaging, Inc., North Billerica, MA, USA

³IMMR, Institut Mutualiste Montsouris, Paris F-75014, France

⁴LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, LYON, France

⁵Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires La Pitié-Salpêtrière, Service de Neurochirurgie, F-75013 Paris, France

⁶Sorbonne Université, UPMC Univ Paris 06, F-75013 Paris, France

e-mail: guillaume.bouchoux@carthera.eu

OBJECTIVE

To compare the efficacy of blood-brain barrier disruption (BBBD) with the SonoCloud® device using two different ultrasound microbubble formulations, Definity® (Lantheus Medical Imaging Inc.), and SonoVue® (Bracco Imaging S.p.A) in a swine model.

METHODS

Six 39-45 kg white-landrace pigs were premedicated to prevent pulmonary hypertensive response to microbubbles (Loratadine 10 mg oral, Meloxicam 0.1 mg/kg intramuscular, Methylprednisolone 0.6 mg/kg intravenous), and anesthetized (propofol). Left and right hemispheres were sonicated sequentially (10-minute between treatments) with a 1-cm unfocused 1-MHz ultrasound transducer (0.8 MPa, 25-ms pulses, 0.5-Hz repetition, 270s) coupled with the dura mater. Microbubbles were injected during the first 50s of sonication. Three conditions were tested over 12 sonications: 1) 0.1 ml/kg SonoVue, 2) 10 µl/kg Definity®, and 3) 20 µl/kg Definity®. Evan's Blue (EB) was injected after the sonications. The animals were sacrificed after 30 minutes for histopathological analysis and evaluation of EB extravasation by infrared fluorescence (Odyssey® CLx, Li-Cor GmbH). The study was approved by the IMMR's Institutional Animal Care and Use Committee.

RESULTS

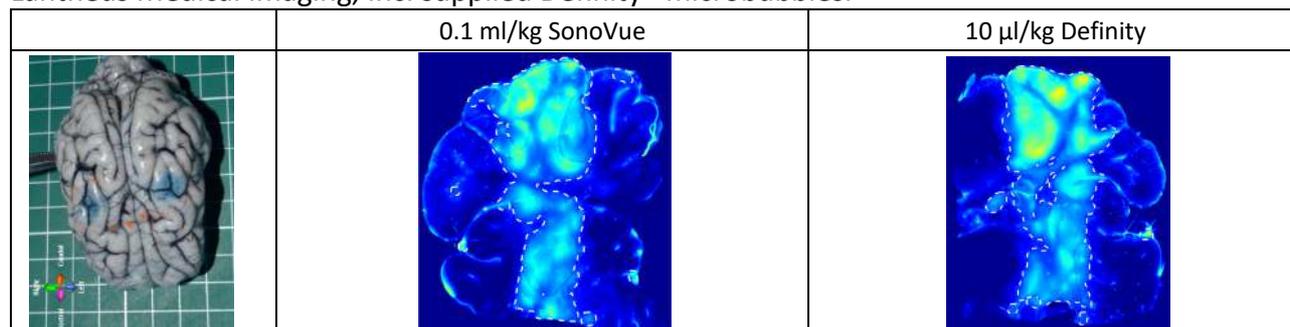
Deep and homogeneous BBBD was observed in a cylindrical region facing the emitter, with similar levels of disruption in terms of size and intensity (EB-enhanced area: 2.55±0.19, 2.66±0.68 and 2.76±1.11 cm² for conditions 1,2 and 3). BBBD was associated with similar microscopic findings for all conditions.

CONCLUSIONS

BBBD was obtained with similar efficiency and safety profiles using SonoVue® and Definity® in this swine model.

ACKNOWLEDGEMENTS

Lantheus Medical Imaging, Inc. supplied Definity® microbubbles.



EB distribution after BBBD with the SonoCloud® device (infrared fluorescence)

Treatment of essential tremor (ET) and Parkinson disease (PD) tremor with MRgFUS: preliminary imaging and clinical results and their correlation

Federico BRUNO, Francesco ARRIGONI, Alessia CATALUCCI, Marco VARRASSI, Luca PANEBIANCO, Maria Valeria Marcella MICELLI, Alessandro RICCI, Patrizia SUCAPANE, Carlo MASCIOCCHI

OBJECTIVES

To report our experience in the treatment of ET and PD tremor using MRgFUS thalamotomy and to evaluate the correlation between peri- and postprocedural imaging findings and treatment outcome

METHODS

We evaluated 30 patients subjected to unilateral Vim ablation using MRgFUS In the period February-December 2018 (16 ET, 14 PD tremor, mean duration of symptomatology 11.6 years). Pre and post-treatment evaluation included clinical evaluation using the Fahn-Tolosa-Marin scale (FTM) for and the QUEST score. Instrumental MRI findings (lesion and edema size) were assessed after treatment. Sonication parameters and intraprocedural findings (accumulated thermal dose, ATD) were also recorded in all procedures.

RESULTS

Treatment was effective (substantial and immediate reduction of tremor) in 28 out of 30 patients (93.3%). FTM scores decreased from mean values of 32.6 before treatment to 13.5 immediately after treatment. In patients followed-up at one month, we found a minimal increase in mean FTM values due to the reappearance of tremor in 6 patients. At 6 months, clinical evaluation showed a substantial stability of treatment effects. No major postoperative complications were recorded. We found a significant negative correlation between ATD size and FTM scores after the procedure ($p \leq 0.05$), while we did not find any statistically significant correlation with other periprocedural imaging findings.

CONCLUSIONS

MRgFUS thalamotomy is a safe and effective treatment option for tremor in patients with ET and PD. According to our preliminary results, intraprocedural ATD and MRI findings after the procedure may have a possible predictive value of treatment outcome after MRgFUS thalamotomy.

MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND VERSUS DEEP BRAIN STIMULATION IN MEDICALLY-REFRACTORY ESSENTIAL TREMOR: A COST-CONSEQUENCE ANALYSIS IN THE KOREAN SETTING

J.W. Chang¹, H.H. Jung¹, W. Ghosh², L. Richard³

¹Yonsei University College of Medicine (YUMC), Seoul, Korea

²Costello Medical Singapore Pte Ltd, Singapore

³INSIGHTEC Ltd, Tirat Carmel, Israel

e-mail: lancer@insightec.com

OBJECTIVES

To compare the costs and health outcomes associated with unilateral magnetic resonance-guided focused ultrasound (MRgFUS) versus unilateral deep brain stimulation (DBS) for the treatment of medically-refractory essential tremor (ET) in Korea using a cost-consequence analysis (CCA).

METHODS

The CCA was developed from the Korean healthcare system perspective. Outcomes included costs, tremor score changes, life years gained, and disutilities due to adverse events (AEs). Clinical, cost and resource utilisation data were obtained from published literature and supplemented by clinician expert opinion. The base case modelled changes in tremor symptoms and AEs following an initial procedure and subsequent procedures due to complications over a 13-month time horizon. Scenario analyses considered a 24-month time horizon and that DBS was more effective than MRgFUS after 6 and/or 12 months post-procedure. Deterministic and probabilistic sensitivity analyses were employed to identify key model drivers and assess uncertainty.

RESULTS

In the base case, MRgFUS resulted in total cost-savings of ₩2,468,249 per patient compared with DBS. The per patient procedural, follow-up and AE costs were lower for MRgFUS by ₩1,397,731, ₩138,056 and ₩932,462, respectively. MRgFUS was also cost-saving in the scenario analyses. Clinical outcomes and disutilities were comparable between interventions in the base case and scenario analyses. Model results were robust, and most sensitive to MRgFUS and DBS procedure costs.

CONCLUSIONS

These results demonstrate that MRgFUS is a lower cost intervention compared with DBS in medically-refractory ET patients in Korea, and may inform treatment decisions for patients who prefer to avoid invasive surgeries or are ineligible for DBS.

POST HOC PREDICTION OF BLOOD-BRAIN BARRIER OPENING WITH POWER CAVITATION IMAGING IN NON-HUMAN PRIMATES

M.T. Burgess¹, R. Ji¹, and E.E. Konofagou^{1,2}

¹Department of Biomedical Imaging, Columbia University, New York, NY, USA

²Department of Radiology, Columbia University, New York, NY, USA

e-mail: ek2191@columbia.edu

OBJECTIVE

The objective of this study was to investigate the potential of power cavitation imaging for ad hoc prediction of BBB opening areas in non-human primates (NHP).

METHODS

The putamen of an adult male NHP (macaque) was targeted using a neuronavigation-guided FUS system consisting of a 2.8 MHz imaging array placed through the central opening of a 250 kHz FUS transducer. Prior to BBB opening, an intravenous injection of Definity microbubbles was administered and power cavitation imaging (Burgess et al. Phys Med Biol. 2018 63(6)) was performed to localize acoustic cavitation activity. BBB opening was then performed using a long pulse FUS sequence (300 kPa peak negative pressure, 10 ms, 2 Hz, 120 seconds) and contrast-enhanced MRI was used to confirm BBB opening locations.

RESULTS

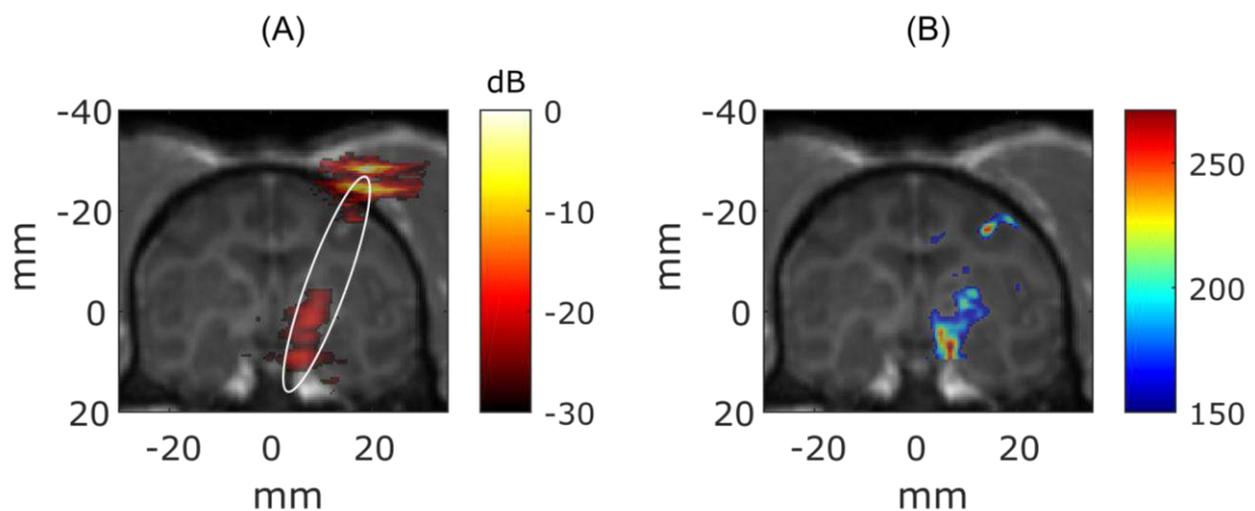
Power cavitation images acquired prior to BBB opening revealed the underlying acoustic cavitation activity throughout the focal region. Correlation of BBB opening with power cavitation images was assessed using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve indicated good correlation with a value of 0.81.

CONCLUSIONS

Power cavitation imaging can be used to predict the locations of BBB opening and therefore verify targeting accuracy. Ongoing work includes detection of BBB opening onset using the same technique.

ACKNOWLEDGEMENTS

Supported by National Institutes of Health (NIH) projects AG038961 and EB009041.



CAPTION: (A) Power cavitation image showing acoustic cavitation activity along the skull/tissue interface, cortex, and subcortical regions. White oval denotes focal area. (B) MRI showing locations of BBB opening denoted by contrast enhancement.

Autophagy and regeneration of dystrophic skeletal muscle are differentially modulated by different therapeutic ultrasound modalities.

S.R. Burks¹, R.M. Lorsung¹, J.A. Frank^{1,2}

¹Radiology and Imaging Sciences, NIH Clinical Center, Bethesda, USA

²National Institute of Biomedical Imaging and Bioengineering, Bethesda, USA

e-mail: scott.burks@nih.gov

OBJECTIVES

RNAseq in skeletal muscle suggested differential FOXO signaling following non-ablative pulsed focused ultrasound (pFUS) or low-intensity pulsed ultrasound (LIPUS). FOXO is a autophagy regulator and this study investigated molecular mechanisms of autophagy activation/repression by different ultrasound modalities and pathological outcomes in an murine muscular dystrophy model with impaired regeneration capabilities due to autophagic dysregulation.

METHODS

Hamstrings of NIH Swiss or MDX mice (n=6 per treatment group for all experiments) received pFUS (1MHz, 4MPa peak rarefaction, 100 10-ms pulses, 5% duty cycle) or LIPUS (1MHz, 160kPa peak rarefaction, 10000 1-ms pulses, 10% duty cycle). Some mice were given verapamil (5mg/kg) or digoxin (2mg/kg). Hamstrings were analyzed by immunohistochemistry and western blotting.

RESULTS

pFUS increased LC3-II expression (autophagic flux marker) following CaMKK and AMPK activation in normal and dystrophic muscle, while inhibiting mTOR (autophagy inhibitor). Voltage-gated-Ca²⁺-channel inhibition by verapamil blocked pFUS molecular changes. LIPUS decreased LC3-II expression and increased mTOR activation in both normal and dystrophic muscle. LIPUS activated hypoxia-inducible-factor-1a and repressed Wnt expression. Molecular LIPUS effects were blocked by the HIF1a inhibitor digoxin. pFUS increased dystrophic muscle regeneration (increased Pax7 and embryonic-myosin-heavy-chain (eMHC) expression), while LIPUS decreased regeneration. pFUS and LIPUS effects on regeneration were blocked by verapamil and digoxin, respectively.

CONCLUSIONS

In dystrophic muscle, pFUS induces autophagy and increases regeneration while LIPUS inhibits autophagy and further reduces regeneration. pFUS could be a potential muscular dystrophy therapy, while LIPUS, a common therapy in musculoskeletal disorders, could be contraindicated for dystrophic patients.

ACKNOWLEDGEMENTS

Supported by NIH Clinical Center and National Institute of Biomedical Imaging and Bioengineering

ASSESSMENT OF MR THERMOMETRY RELIABILITY FOR MONITORING HIFU ABLATIONS IN BONE

P. Cabras¹, F. Bing^{1,2,3}, K. Kim¹, E. Breton¹, A. Gangi^{1,2}, J. Vappou¹

¹ICUBE Laboratory, CNRS, University of Strasbourg, France

²Department of interventional Imaging, Strasbourg University Hospital, France

³CH Annecy Genevois, Metz-Tessy, France

e-mail: jvappou@unistra.fr, cabras@unistra.fr.

OBJECTIVES

Accuracy of MR-thermometry for monitoring HIFU ablations can be compromised since high spatial variations of temperature yield significant averaging effects. This study evaluates the effect of MR resolution along with HIFU focusing depth and tissue acoustical properties on the MR-thermometry accuracy in the case of bone HIFU treatment.

METHODS

In-vitro HIFU experiments were performed under MR guidance on bone samples embedded in gelatin. Three different shooting configurations were compared: focusing (1) at bone surface, (2) within and (3) beyond cortical bone. This set-up was reconstructed numerically by tissue segmentation and transducer registration. Thermo-acoustical simulations were performed on this realistic 3D model in order to evaluate the influence of voxel dimensions on the final temperature result. We considered two values of acoustic absorption for cortical bone (4.7&9.9 dB/MHz/cm) found in the literature. Simulation temperature results with two grid resolutions were compared (fine 0.5x0.5x0.5mm vs MR-like 2.7x2.7x5mm).

RESULTS

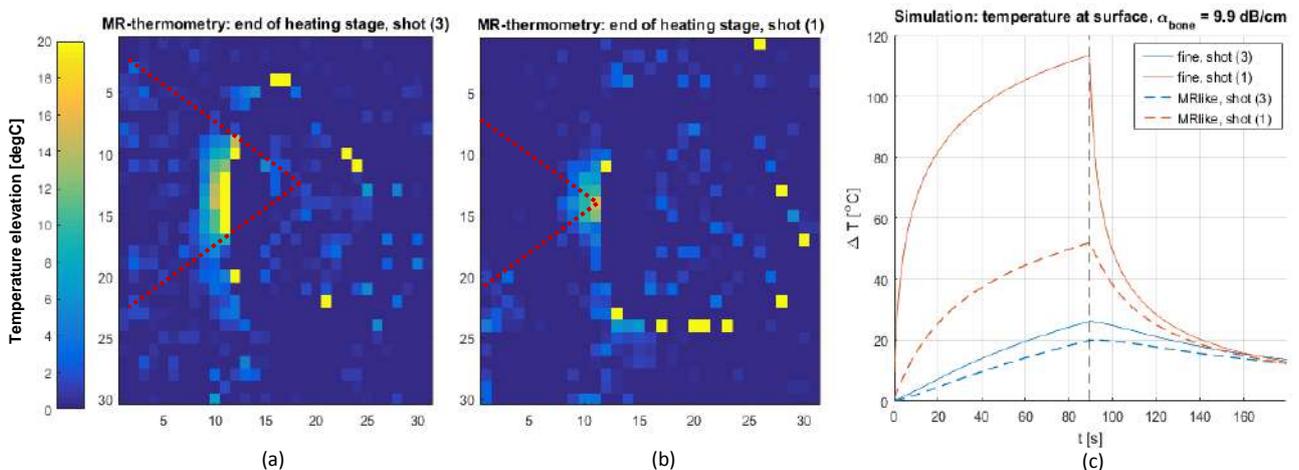
MR-like simulations with $\alpha_{\text{bone}}=4.7\text{dB/MHz/cm}$ were close to experimental results. Voxel dimensions weakly influence temperature values for shot (3), in which uniform temperature patterns were generated at the bone surface (Fig.(a)). For shots (1)&(2), simulations showed that temperature underestimation can be critical when dealing with highly absorbing bones ($\alpha_{\text{bone}}=9.9\text{dB/MHz/cm}$, Fig.(c)), where temperature variations within a voxel are higher.

CONCLUSIONS

MR-thermometry can be safely trusted when focusing beyond the cortical bone, while, in cases (1) and (2), it may underestimate focal temperature.

ACKNOWLEDGEMENTS

This project is funded by “Fond Unique Interministeriel” (UFOGUIDE 2017-2020).



CAPTION: In-vitro MR-thermometry results in the case of deep (a) and shallow (b) focusing. Simulated temperature evolution at bone surface for two grid resolutions (fine vs MR-like) (c).

ACOUSTIC HOLOGRAMS FOR TRANSCRANIAL FOCUSING OF ARBITRARY ULTRASONIC FIELDS INTO THE BRAIN

Sergio Jiménez-Gambín¹, Noé Jiménez¹, José María Benlloch¹, Francisco Camarena¹

¹ Instituto de Instrumentación para Imagen Molecular, Consejo Superior de Investigaciones Científicas, Universitat Politècnica de València, Valencia, Spain

e-mail: serjigam@upv.es; nojigon@upv.es; benlloch@i3m.upv.es; fracafe@fis.upv.es

OBJECTIVES

We design 3D printed lenses that generate acoustic holograms correcting the aberrations of the skull and producing ultrasonic fields with the shape of brain structures. Using experimental techniques on a human skull phantom (HSP), a multiple-point focusing lens is designed to simultaneously focus at both human hippocampi; a beam following an arbitrary curved trajectory, i.e., a self-bending beam; and a holographic plate producing a broad focus that overlaps with the left hippocampus (LH).

METHODS

Skull and LH shapes are obtained from CT-scans and MRI, respectively. Time-reversal (TR) method is used to obtain the magnitude and phase of the back-propagated field at the lens surface. Lens height is obtained assuming each element to vibrate as a Fabry-Pérot resonator. Resulting lenses are 3D printed with SLA techniques.

RESULTS

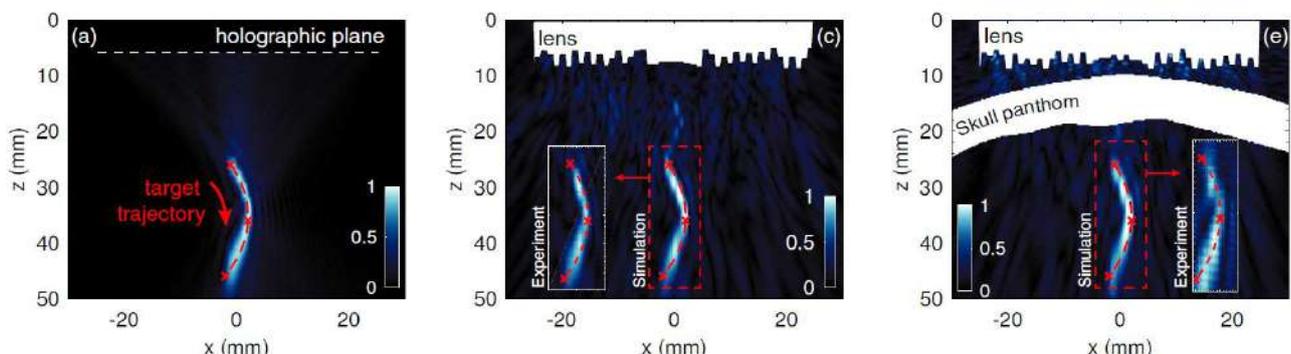
The three studied cases show similar results in simulation and experiment with and without the HSP: for the multi-focal beam, the reconstructed field accurately matches the target foci; for the curved trajectory beam, the holographic lens reconstructs the target acoustic image; for the broad focus beam, results present the same qualitative performance and provide a similar overall covering of the LH.

CONCLUSIONS

The reported holographic lenses can be used to control the spatial features of ultrasonic beams inside the skull in an unprecedented manner using single-element ultrasonic sources.

ACKNOWLEDGEMENTS

Supported by Generalitat Valenciana research programs APOSTD/2017/042 and GV/2018/011 and by Europea Union through the Programa Operativo del Fondo Europeo de Desarrollo Regional (FEDER) de la Comunitat Valenciana 2014-2020 (IDIFEDER/2018/022). Supported by Agència Valenciana de la Innovació (INNCON00/18/9).



CAPTION: Self-bending beam: a) theoretical pressure field in water, b) corresponding simulation; c) simulated field including the skull phantom. Experiments are shown in the corresponding insets.

SIMULATION OF TEMPERATURE RISE IN MOBILE AND ELASTIC VOLUME

E. Cao¹, P. Greillier¹, J. Robert¹, F. Bessi re^{1,2}, R. Loyet¹, F. Chavrier¹, JL. Dillenseger³, C. Lafon¹

¹ LabTAU, INSERM, Centre L on B erard, Universit  Lyon 1, Univ Lyon, F-69003, LYON, France

² Hospices Civils de Lyon, H pital Cardiovasculaire Louis Pradel, Lyon, France

³ Univ Rennes, Inserm, LTSI - UMR 1099, F-35000 Rennes, France

e-mail: elodie.cao@inserm.fr; cyril.lafon@inserm.fr

OBJECTIVES

Heart movements and deformations make cardiac procedures particularly challenging with high intensity focused ultrasound (HIFU). This study aims to prove that accurate modeling of temperature in elastic and mobile targets requires taking into account deformations and motions.

METHODS

Ultrasound pressure field is simulated using the Rayleigh integral method and a point-by-point estimation of the attenuation in the tissues. Temperature map is obtained by the discretization in finite volume of the Bio Heat Transfer Equation (BHTE) on a non-orthogonal, smooth and collocated tridimensional mesh with hexahedral cells. The equation is solved on a curvilinear coordinate system fitting in the grid. HIFU is produced with a 3-cm² truncated spherical transducer operating at 3 MHz. Compression, dilatation, rotation and 1-mm-translation are applied on a homogenous tissue matrix. Tests are performed on each configuration with 6-second sonication at 32 W.

RESULTS

When the target is not moving, the maximum temperature reaches 66 C. This temperature is 2 C greater in compression and rotation cases, 4 C lower with translation and 8 C lower in dilated configuration. Heated volume spread is 45% greater in dilatation case than in immobile matrix, and 25% greater in compression, rotation and translation cases. This heat diffusion leads to lesion size reduction and temperature rise in untargeted zones.

CONCLUSIONS

Significant variability is observed between immobile and elastic tissue matrices. Heart is affected by compression, dilatation, rotation and translation. Thus, this study demonstrates the necessity to consider these deformations in modeling studies when optimizing HIFU treatment strategies.

ACKNOWLEDGEMENTS

This work is supported by ANR-15-CE19-0016-SATURN and ANR-17-CE19-0017-CHORUS.

Intensive HIFU simulation based on surrogate models using CIVA Healthcare platform – application to parametric studies and sensitive analysis

Sylvain Chatillon¹, Raphaël Loyet², Laurie Brunel³, Françoise Chavrier², Nicolas Guillen³ and Stéphane Le Berre¹

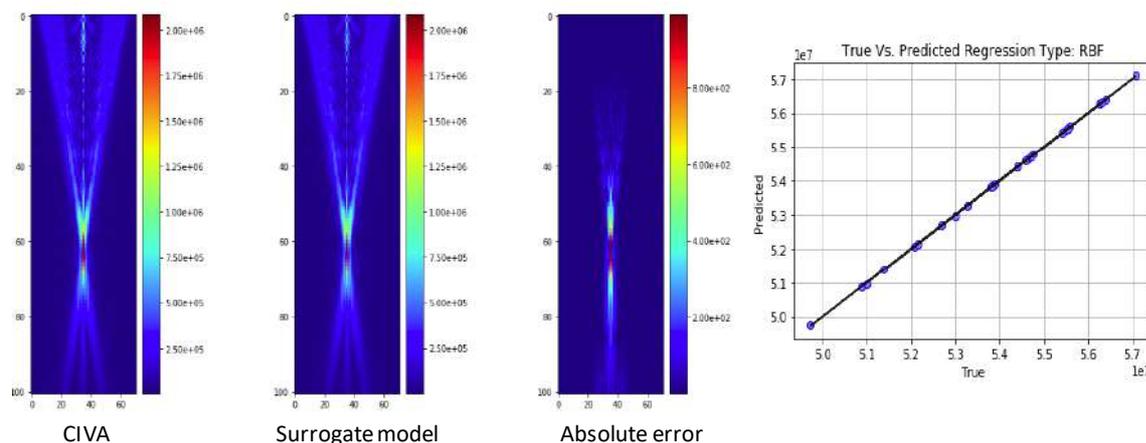
1 - CEA, LIST, F-91191, Gif-sur-Yvette cedex, France

2 - Univ. Lyon, Université Lyon 1, INSERM, LabTau, F-69003, LYON, France, 151 Cours Albert Thomas, Lyon 69424, France

3 – EDAP-TMS, 4 Rue du Dauphiné, 69120 Vaulx-en-Velin, France

For several years, CEA-LIST has been developing in partnership with INSERM, a HIFU simulation platform, CIVA Healthcare. It provides specific tools for the development and optimization of probes and therapeutic protocols in order to target clinical problematic of specific organs. The goal of this platform is to easily simulate the 3D pressure field induced by HIFU, in linear and non-linear regimes, and the corresponding thermal dose in tissues and phantoms.

Parametric studies for treatment optimization (probe design, protocol definition, etc...), sensitivity analysis, and tissue characterization using parametric inversion can be easily performed. A common feature of these studies is the need for a large amount of input data, which involves many simulations. This often makes these problems too expensive to deal with by standard numerical simulation approaches. In such contexts, it is often convenient to replace the computationally expensive direct solver with a surrogate model built from a database of simulation results, and acting as a quick and accurate surrogate restricted range of input parameters. This procedure breaks down into two stages. In a first step (off-line part), the database is adaptively constructed to maximize the fidelity of the associated interpolator computed from the pairs (I / O) of the database. In a second step, also known as the off line part, the interpolator, also called surrogate model, enables to generate signals in near real time for configurations covered by the range of the database.



Several applications based on the generation of surrogate models will be proposed. The first one concerns real-time pressure field computation. The second one, based on thermal simulations, deals with performance demonstration, treatment optimization and sensitivity analyses according to the uncertainties of the tissues parameters.

Work supported by French Nation Research Agency (ANR SATURN -15-CE19-0016)

Cavitation Dose Painting for Predicting the Location and Concentration of Nanoclusters Delivered by Focused Ultrasound-Induced Blood-Brain Barrier Disruption

Yaoheng Yang*¹, Xiaohui Zhang*², Dezhuang Ye³, Richard Laforest², Jeffrey Williamson⁴, Yongjian Liu², Hong Chen^{1,4, #}

1. Department of Biomedical Engineering, Washington University in St. Louis, MO, USA.
 2. Mallinckrodt Institute of Radiology, Washington University School of Medicine, MO, USA
 3. Department of Mechanical Engineering and Materials Science, Washington University in St. Louis, MO, USA.
 4. Department of Radiation Oncology, Washington University School of Medicine, MO, USA.
- e-mail: hongchen@wustl.edu;mack.yang@wustl.edu

OBJECTIVES

Focused ultrasound combined with microbubble-induced blood-brain barrier disruption (FUS-BBBD) is a promising technique for noninvasive and localized brain drug delivery. This study presented that passive cavitation imaging (PCI) was capable of predicting the location and concentration of nanoclusters delivered by FUS-BBBD.

METHODS

During FUS-BBBD treatment of mice, the acoustic emissions from FUS-activated microbubbles were passively detected by an ultrasound imaging system and processed offline using a frequency-domain PCI algorithm. After the FUS treatment, radiolabeled gold nanoclusters, ⁶⁴Cu-AuNCs, were intravenously injected into the mice and imaged by positron emission tomography/computer tomography (PET/CT).

RESULTS

The center of the stable cavitation dose (SCD) map acquired by PCI and the center of ⁶⁴Cu-AuNCs concentration map obtained by PET had an offset of 0.2 ± 0.2 mm and 1.2 ± 0.6 mm in the transverse and axial directions of the FUS beam, respectively. The SCD maps were found to be linearly correlated with the radioactivity maps (%ID/g) of ⁶⁴Cu-AuNCs on a pixel-by-pixel level.

CONCLUSIONS

These findings suggest that SCD maps can spatially “paint” the delivered nanoparticle concentration, a technique that we named as cavitation dose painting. This PCI-based cavitation dose painting technique in combination with FUS-BBBD opens new horizons in controlled brain drug delivery.

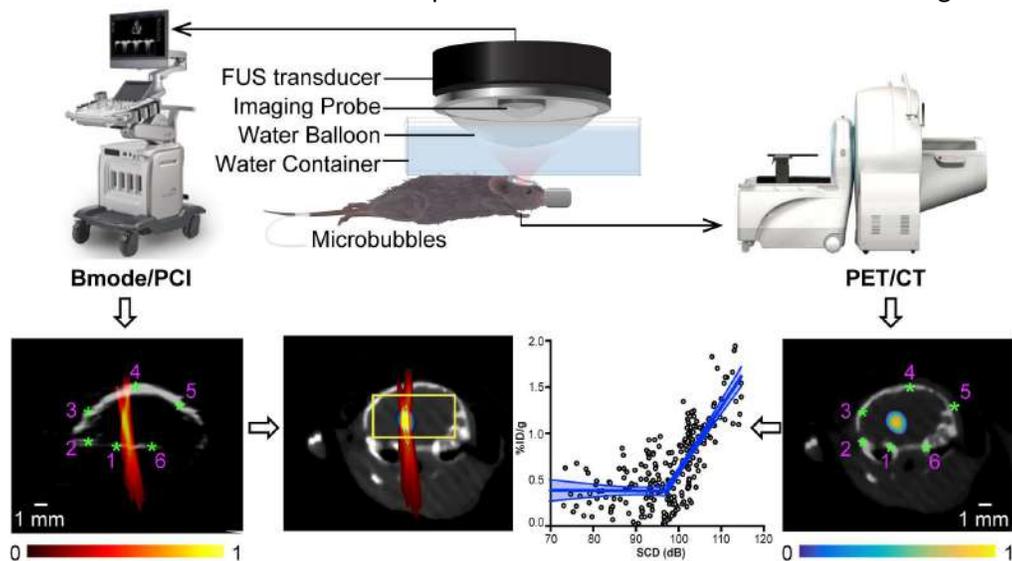


Figure 1. Illustration of the FUS-treatment setup, images acquisition, registration and the result of a pixel-by-pixel correlation between SCD maps and ⁶⁴Cu-AuNC concentration maps within the 2D region in the brain

FUSION MRI-ULTRASOUND GUIDED HISTOTRIPSY SYSTEM

S.W. Choi¹, T. Worlikar¹, T. Gerhandson¹, J. J. Macoskey¹, J. M. Balter², C. A. Cain¹, J. Sukovich¹, J. M. Greve¹, T. L. Hall¹, Z. Xu¹.

¹Biomedical Engineering, University of Michigan, Ann Arbor, Michigan, UNITED STATES

²Radiation Oncology, University of Michigan, Ann Arbor, Michigan, UNITED STATES

e-mail: csangwon@umich.edu

OBJECTIVE: Histotripsy has used B-mode imaging as real-time guidance to monitor therapy. However, tumors are often indiscernible with ultrasound, thus reducing histotripsy accuracy for tumor ablation. We tested a stereotactic fusion system that uses pre-treatment MR for treatment planning and ultrasound for real-time treatment monitoring. This system leverages the tumor imaging capability of MRI and real-time ultrasound feedback to improve histotripsy targeting accuracy.

METHODS: A stereotactic fusion system for small-animal histotripsy treatment (**Figure 1A**) was designed to have: 1) a stereotactic frame with three MRI fiducial markers to co-register MR images and to rigidly secure a subject, and 2) an ultrasound imager coaxially inserted into the histotripsy transducer. Custom treatment planning software allowed users to outline the treatment zone on pre-treatment MRI scans and create treatment focus grids. This system was tested on 10 liver phantoms. Post-MR images were used to compare the ablated to prescribed zones to determine accuracy.

RESULTS: Differences between the centers of prescribed and ablated zones (**figure 1B**) were 0.44 ± 0.45 mm and the ablation volume was $12.2 \pm 2.27\%$ larger than prescribed due to underestimation of the cavitation cloud size (estimated ~ 1 mm in diameter and 2 mm in height).

CONCLUSION: The fusion MRI-Ultrasound system displayed millimeter accuracy on phantoms. We plan to investigate the effectiveness of this system *in vivo* and to address impact of breathing motion on targeting.

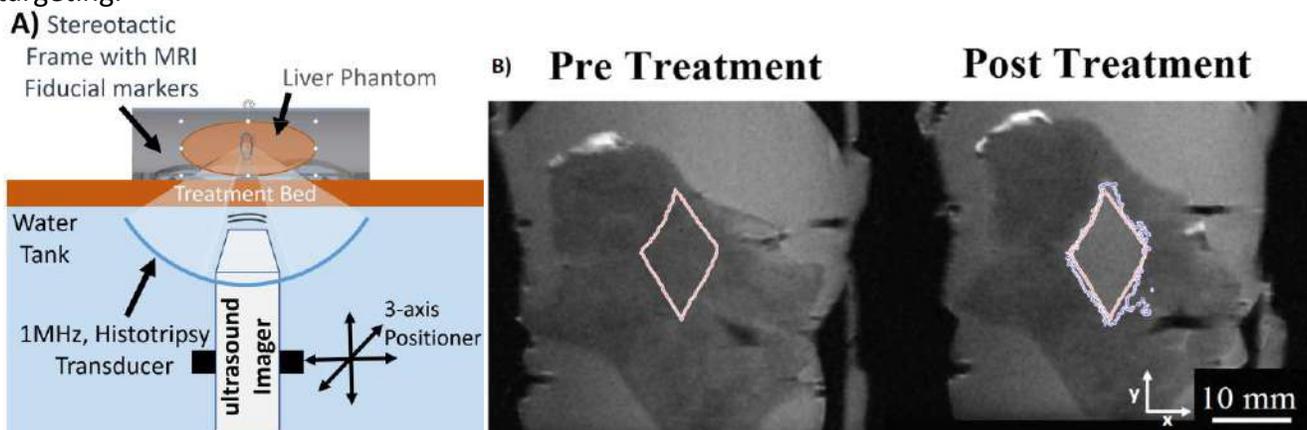


Figure 1: System Features (1A) and MR-guided histotripsy result on liver phantom (1B). Red diamond indicates the hand drawn prescribed region (left), and the blue diamond region (right) indicates the segmented ablation zone.

REMOTE ACTIVATION OF ENGINEERED NEURAL STEM CELLS FOR THE RELEASE OF TNF α AND IL15 VIA HIGH-INTENSITY FOCUSED ULTRASOUND

J.L. Chu^{1,2}, G. Kim^{1,2}, E. J. Roy^{2,3}, K.C. Li^{1,2,4}

¹Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

²Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

³Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

⁴Department of Bioengineering, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

e-mail: jchu6@illinois.edu; kingli@illinois.edu

OBJECTIVES

Cell therapies involving tumor-tropic stem cells take advantage of the preferential migration of stem cells towards cancer cells to target malignancies. However, uncontrolled systemic expressions of therapeutic transgenes can have devastating side effects that compromise the benefits of such approaches. High Intensity Focused Ultrasound (HIFU) can induce precise spatial-temporal controlled hyperthermia at desired anatomical locations. Combining this with heatshock promoter-controlled engineered neural stem cells (NSC) has the potential to achieve targeted expressions of therapeutic transgenes at the desired anatomical location.

METHODS

Primary NSCs isolated from the subventricular zone of C57BL/6 mice were transduced with lentivirus to enable heat-activatable expression of either tumor necrosis factor alpha (TNF α) or interleukin 15 (IL15) under the control of the heatshock protein 70 promoter (pHSP70). Transduced NSCs in the form of neurospheres were embedded in fibrin hydrogel and heat-activated via HIFU-induced hyperthermia (center frequency of 550 kHz) at 43 °C for durations ranging from 5 to 20 min. Activation of the NSCs were analyzed by ELISA assays against TNF α and IL15 as well as fluorescence of the co-transduced tdTomato reporter.

RESULTS

Upon HIFU-induced hyperthermia at 43 °C *in vitro*, transduced NSCs showed time dependent expressions of TNF α or IL15 as validated by ELISA assays and the fluorescence of tdTomato reporters.

CONCLUSIONS

Our results show promise for the combination of NSC-based cell therapy with the precision control of HIFU for targeted delivery of therapeutic transgenes. Precise control of these engineered NSCs provides potential avenues for treating malignancies in the brain such as glioblastoma.

ACKNOWLEDGEMENTS

This work is supported by the National Institute of Health (NIH) through Grant No. 5R01CA184091.

MULTIPLE-FOCUSING METHOD FOR TREATMENT TIME REDUCTION IN HIFU THERMAL ABLATION

Euisuk Chung¹, Pilsu Kim¹, Tai-Kyong Song¹

¹Department of Electronic Engineering, Sogang University, Seoul, Republic of Korea

e-mail: jes539@sogang.ac.kr, pskim@sogang.ac.kr, tksong@sogang.ac.kr

OBJECTIVES

Various scanning paths of a single HIFU focus have been suggested to reduce the HIFU treatment time. HIFU treatment time can be further reduced by exploiting thermal-diffusion effect more efficiently and by using a larger focal volume. For this, we present the multiple-focusing method using the same total acoustic power as that of single-focusing methods.

METHODS

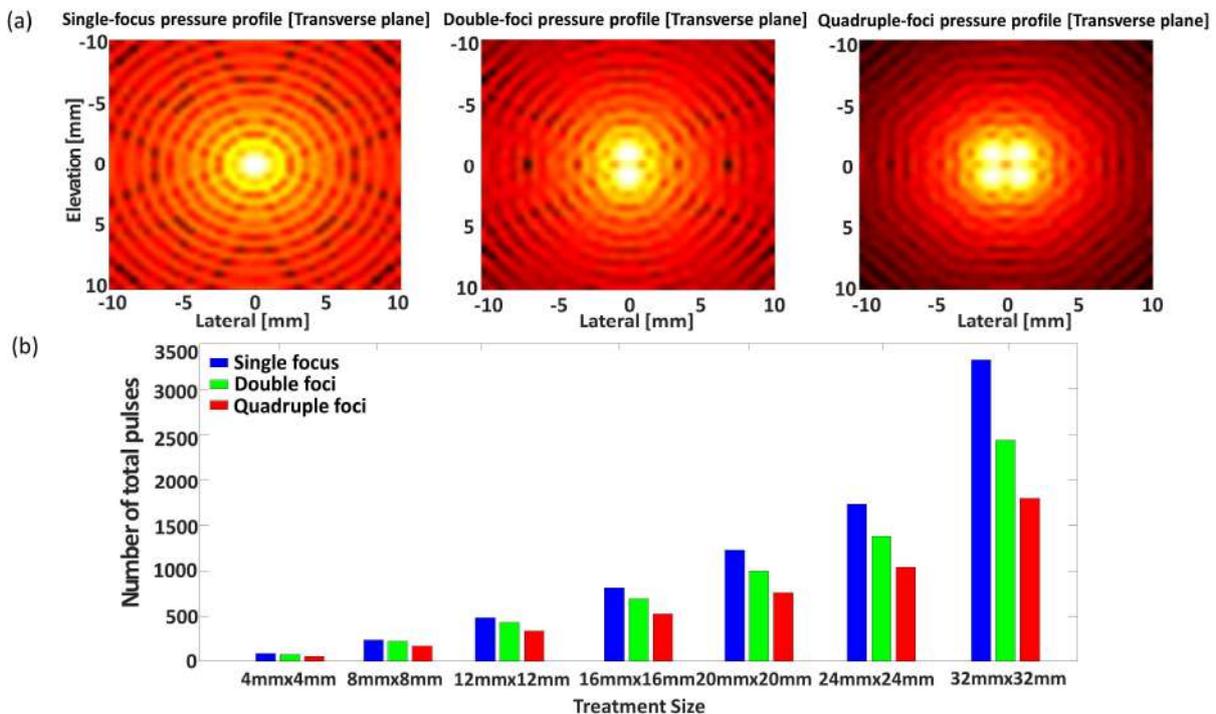
In this preliminary study, two multiple-focusing methods using double-foci and quadruple-foci are scanned along the spiral pattern in the single-focusing method, where each focus is apart by the diameter of the single focal spot from each spot as shown in Figure (a). The total acoustic power was set to 24W by delivering per each focus 6W for quadruple-foci, 12W for double-foci, and 24W for single-focus. FEM simulations with MATLAB were performed to predict the thermal coagulation by each method based on the CEM43 metric. To validate the simulation results, in-vitro experiments with a commercial BSA phantom were also conducted.

RESULTS

Treatment time reduction by the multi-focusing methods becomes more significant as the target treatment area increases as shown in Figure (b). For treatment area of 32mmx32mm, treatment times for double-foci and quadruple-foci are reduced to 74% and 54% of that of the single-focusing method, respectively. In addition, the peak temperature of the quadruple-foci method was 8°C lower than that of the single-focusing method.

CONCLUSIONS

Multiple-focusing methods can improve treatment time and over-heating problem.



CAPTION: (a) Transverse-plane pressure profiles: single-focus(left), double-foci(middle) and quadruple-foci(right). (b) Comparison of the total number of pulses about three methods for various treatment areas.

DEVELOPMENT OF A HIFU TREATMENT USING A TOROIDAL TRANSDUCER FOR PANCREATIC ADENOCARCINOMA. PRELIMINARY *IN VIVO* STUDY

C.Cilleros^{1,2}, A.Dupré¹, J.Vincenot², D.Melodelima¹

¹ LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, LYON, France

²EDAP TMS, 4 rue du Dauphiné, Vaulx-en-Velin, France

E-mail: celia.cilleros@inserm.fr

OBJECTIVES

Pancreatic adenocarcinoma is one of the most aggressive cancer. Regardless of the treatment used, the survival rate after 5 years is lower than 6%. It has been demonstrated that toroidal transducers can treat up to 60 cm³ of tissues in 370 seconds without the need to displace the HIFU probe. In this study we evaluated *in vivo* the use of this device for treating the pancreas and peripancreatic vessels.

METHODS

Eight pigs were included in this study. The device was used intra-operatively. The transducer has a toroidal shape with a radius of curvature of 70 mm focusing on a circle of 30 mm. The working frequency was 2.5 MHz. The diameter of the transducer was 70 mm. An ultrasound imaging probe working at 7.5 MHz was placed in the center of the HIFU transducer. Ablations were created in 370 seconds using an acoustic power of 85 watts.

RESULTS

In total eight lesions were created in the pancreas and around peri-pancreatic vessels. Homogenous ablations were obtained in all cases confirmed histologically. The average diameter of the pancreatic ablations was 17.7 ± 5.0 mm. These ablations were also homogeneous all around the peripancreatic artery and without occlusion as confirmed by Doppler examination.

CONCLUSIONS

Using this toroidal HIFU transducer it is possible to treat the most challenging region of the pancreas and its surrounding vessels without any occlusion. This may allow to treat locally-advanced pancreatic tumors which are the main contra-indication to curative resection.

ACKNOWLEDGEMENTS

This work was partly supported by the Cancéropôle Lyon Auvergne Rhône-Alpes (n° 171485A10).

EFFECT OF BUBBLE-BUBBLE INTERACTIONS ON SUBHARMONIC EMISSIONS OF A MONODISPERSE BUBBLE CLOUD

C. Cornu^{1,2}, M. Guédra², C. Inserra², W-S Chen¹

¹Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei 100, Taiwan

²Univ Lyon, Université Claude Bernard Lyon 1, Centre Léon Bérard, INSERM, UMR 1032, LabTAU, F-69003 Lyon, France

e-mail : corentin.c.cornu@gmail.com; claude.inserra@inserm.fr

OBJECTIVES

For therapeutic applications such as blood-brain barrier opening, the stable cavitation activity is mostly quantified by the subharmonic emissions due to the nonlinear response of the bubble population. Considering the free single bubble dynamics, the main cause of subharmonic emissions is the natural response of a bubble close to twice the resonant radius. Here, the main objective is to pinpoint the combined effects of (1) the interactions between bubbles and (2) the concentration of the bubble cloud on the subharmonic emission threshold.

METHODS

A simulation of the dynamic of a homogeneous, monodisperse bubble cloud is performed with a modified Keller-Miksis model. The results are compared with the analytical expression of the subharmonic threshold obtained by the asymptotic development of the Rayleigh-Plesset formula.

RESULTS

The interaction effect leads to a shift of the subharmonic resonant radius and a decrease of the corresponding pressure threshold. For a given sonication frequency, an optimal value of the number density of bubbles is obtained for a minimum subharmonic threshold.

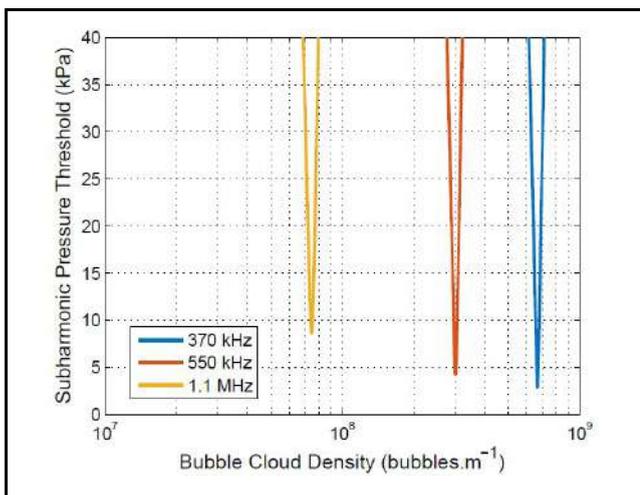


Fig.1: Subharmonic pressure threshold of a free 1 μm radius-sized bubble cloud as a function as the bubble density of the cloud. The results are presented for different transducer frequencies.

CONCLUSIONS

This result (Fig. 1) suggests that the choice of the sonication frequency and the size of contrast agents should not be based only on the resonant radius of individual bubbles, but also on the cloud density of contrast agents.

BLOOD-BRAIN TUMOR BARRIER OPENING WITH MR IMAGE-GUIDED FOCUSED ULTRASOUND AUGMENTS INTERSTITIAL FLOW AND FACILITATES NANOPARTICLE-MEDIATED TRANSFECTION

Colleen T. Curley¹, Brian P. Mead¹, Namho Kim², Karina Negron², G. Wilson Miller¹, William Garrison¹, Kathryn M. Kingsmore¹, Jennifer M. Munson^{1,3}, Alexander Klivanov¹, Jung Soo Suk², Justin Hanes², Richard J. Price¹; email: cc7fr@virginia.edu

¹. University of Virginia ². Johns Hopkins University ³. Virginia Polytechnic Institute and State University

OBJECTIVE

To examine the impact of interstitial flow on MR image-targeted brain tumor transfection with focused ultrasound (FUS) and non-viral brain penetrating nanoparticles (BPNs).

METHODS

Luciferase-BPNs (i.v.) were delivered to intracranial U87 gliomas using 0.45 or 0.55 MPa FUS and microbubbles (MBs). T1-weighted MR images acquired pre- and post-FUS were analyzed to assess interstitial flow[1]. Separately, zsGreen-BPNs were injected directly into tumors to examine the impact of BTB opening on BPN dispersion through tumor tissue.

RESULTS

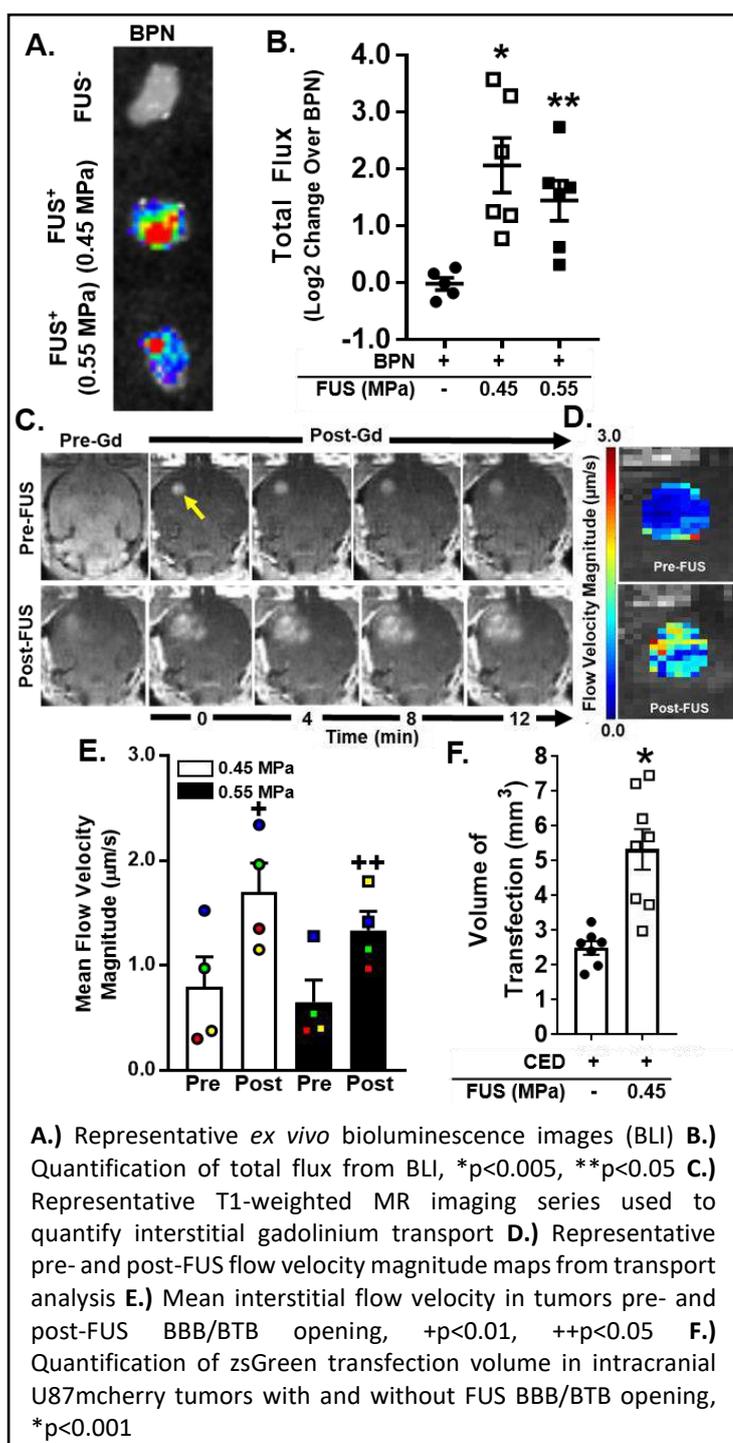
Blood brain/blood tumor barrier (BBB/BTB) opening with FUS+MBs increased transfection 4-fold (vs. EPR effect; **Fig 1 A, B**) and interstitial flow 2-fold (over untreated tumors; **Fig 1C,D,E**). BBB/BTB opening of U87 gliomas prior to injection of zsGreen-BPNs produced a two-fold increase in transfection volume (**Fig 1F**).

CONCLUSIONS

FUS-mediated BTB opening permits the MR image-targeted transfection of brain tumors with BPN. Convective flow augmentation during BTB opening is sufficient to markedly enhance the penetration of BPN through tissue, suggesting a central role for interstitial flow in transfection.

REFERENCES 1.Kingsmore, et al. APL Bioeng. 2018

ACKNOWLEDGEMENTS Supported by NIH R01CA197111 and R01EB020147.



#10yearschallenge: Our Roadmap to FURTHER - Focused Ultrasound and RadioTHERapy in patients with bone metastases

S.Dababou¹, A.Napoli¹, C.Marrocchio¹, R.Scipione¹, G.Alfieri¹, D.Fierro¹, C.Catalano¹

¹Department of Radiological Sciences, Sapienza University of Rome, V.le Regina Elena 324, Rome 00180, Italy.

e-mail: sdababou@gmail.com; alessandro.napoli@uniroma1.it, cristinamarrocchio@gmail.com, robertoscipione90@gmail.com, giuliaalfieri@hotmail.it, fierrodavide852@hotmail.com, carlo.catalano@uniroma1.it

OBJECTIVES

To assess and compare the clinical impact of MR-guided Focused Ultrasound (MRgFUS) and External Beam Radiation Therapy (EBRT) for pain palliation in patients with symptomatic non-spinal bone metastases.

METHODS

Patients with solid malignant tumors and one or more bone metastases were enrolled in the study. Included patients were ≥ 18 years of age, presented with symptomatic bone metastases (defined by pain score ≥ 4 at Visual Analogue Scale) confirmed at imaging, without contraindications to both MRgFUS and EBRT. Vertebral locations were excluded since they were not accessible to the ultrasound beam. Participants were randomly assigned (1:1 ratio) to receive MRgFUS or EBRT. Outcomes were compared at 1, 3, 6 and 12 months. The primary outcome was the reduction in pain with treatment response defined as a decrease of ≥ 2 points in worst pain by 1 month with stable or reduced opioid dose. Secondary outcomes included average pain, interference of pain with activity, mood, quality of life, and procedure-related adverse events.

RESULTS

281 patients (M: 151; F: 130) were enrolled and randomly assigned to MRgFUS (140) and to EBRT (141). Treatment response was achieved by 109 patients (77,9%) and 112 patients (79,4%) in the MRgFUS and EBRT arm respectively (adjusted odds ratio, 1.04; $p = 0.728$). No statistically significant differences were observed among the secondary outcomes between the two treatments. Results were stable along the whole follow-up period.

CONCLUSIONS

Pain palliation of symptomatic bone metastases achieved with MRgFUS was comparable to EBRT. This technique does not require radiation exposure and is performed in a single session. MRgFUS is limited to non-spinal locations.

MRI-GUIDED FOCUSED ULTRASOUND ROBOTIC SYSTEM FOR EXPERIMENTS IN MICE.

M. Giannakou¹, C. Damianou²

¹MEDSONIC, Limassol, Cyprus.

² Electrical Engineering Department, Cyprus University of Technology, Cyprus,

chistakis.damianou@cut.ac.cy

OBJECTIVES

An MRI-guided focused ultrasound (MRgFUS) system was developed that can be used for preclinical studies in mice in a 9.4 T magnet.

METHODS

A single element spherically focused transducer of 4 cm diameter, focusing at 6.5 cm and operating at 2 MHz was used. The positioning device incorporates only MRI compatible materials. The propagation of ultrasound is a bottom to top approach. The robotic system includes 2 linear axes (6 cm range each with 0.1 mm maximum motion error).

RESULTS

The system was tested successfully in agar/silica/evaporated milk phantom for various tasks such as MR compatibility, motion accuracy and functionality. High temperatures (60-80 oC) were achieved using the proposed system.

CONCLUSIONS

This simple and functional design can be a useful research tool for preclinical work on mice. This system has the potential to be marketed as a cost effective solution for performing experiments in mice. With minimum changes this robotic system can be converted into a device for performing interventions with focused ultrasound in humans mostly in the abdominal area and in breast.



FIG. 1: Schematic of the developed robotic system.

Transient Acoustic Streaming in Confined Cavity from Pulsed HIFU Exposure

H.S. Daoud, G.F. Oweis, R.Y. Seblany

M.S. Faculty of Engineering and Architecture, American University of Beirut, Beirut, Lebanon

e-mail: hsd08@mail.aub.edu ; goweis@aub.edu.lb; rys12@mail.aub.edu

OBJECTIVES

The study aims to investigate acoustic streaming from single, short HIFU exposure in millimetric confined cavity in emulation of exposure of confined bodily fluids such as in arteries and organ cavities. Acoustic streaming causes fluid mixing and induces shear stresses.

METHODS

A small, closed water cuvette was placed in a water bath near the focal center of a 60 mm, 1.6 MHz HIFU transducer of 1.5 mm transverse focal beam width (FWHM). The cubic cuvette had an acoustic window made from commercial cling film for the HIFU beam, and the water in it was seeded with 0.1 μm TiO_2 tracer particles to conduct particle image velocimetry PIV measurement. A thin laser sheet from a pulsed YAG laser was oriented coaxially with the acoustic beam to illuminate the tracers, which were imaged with a fast shutter camera. Digital image cross correlation was implemented to obtain the particles displacement field. Two cuvette sizes were used representing differing anatomical confinements: large one (20*20*30 mm) and small one (5*5*7 mm). The HIFU input powers was varied to test its effect.

In the experimental protocol, a single 30 ms long HIFU pulse was produced to stir the fluid. Two PIV tracer images were acquired for velocimetry: the first image was triggered 1 μs from the end of the HIFU exposure, while the trigger of the second image was adjusted (1 ms to 7.5 ms) according to the underlying streaming velocity to result in around 5 pixels of tracer displacement. Each experiment was repeated for 100 single HIFU pulses to obtain average measurements.

RESULTS

The streaming pattern in the larger cuvette (**Fig. 1a**) as manifested by regions of elevated velocity approximately delineates the geometric focusing pattern of the HIFU beam. In the smaller cuvette, however, (**Fig. 1b**), the pattern is significantly different, and is marked by a cigar-shaped region of high flow velocity. Interestingly there are cellular flow patterns of localized streaming outside the focal region but of smaller velocity, which are a manifestation of mass conservation. The peak velocity in the smaller confinement is almost one order of magnitude *larger* than in the bigger confinement as shown in **Fig 1c,d**. Lastly, the effect of the HIFU input power on the acoustic streaming velocity is much clearer in the small confinement as shown in **Fig. 1e**.

CONCLUSIONS

The size of confinement had a dramatic effect on the magnitude of the streaming velocities, with the smaller confinement exhibiting higher velocity for comparable input power. This is possibly caused by the acoustic energy density being higher in the smaller cuvette. The acoustic power correlated with the streaming velocity, and the sensitivity depended strongly on the size of the confinement.

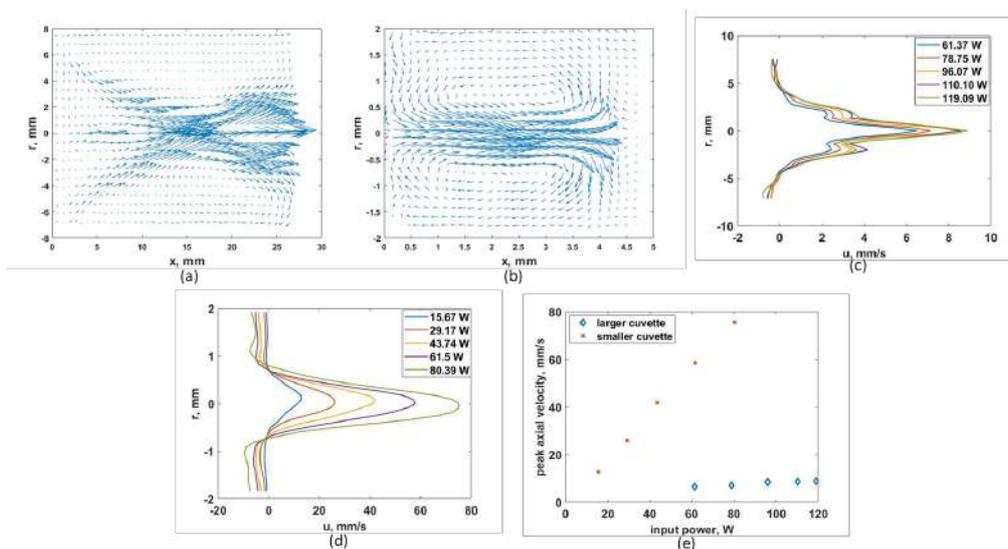


Figure 1: (a) Velocity vector field in the larger cuvette. (b) Velocity vector field in the smaller cuvette. (c) Radial profile of the axial streaming velocity in the larger cuvette at $x=22$ mm. (d) Radial profile of the axial velocity in the smaller cuvette at $x=1.7$ mm. (e) peak streaming velocity with input power for two confinement sizes.

ULTRASOUND-IMAGE BASED NAVIGATION GUIDANCE FOR 3D PLANNING OF CONFORMAL INTERSTITIAL HIFU ABLATIONS

L. Daunizeau¹, A. Nguyen¹, W.A. N'Djin¹, J.Y. Chapelon¹

¹ LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, Lyon, France
e-mail: loic.daunizeau@inserm.fr

OBJECTIVES

Interstitial image-guided HIFU therapy has the potential to overcome current limitations encountered with Radio Frequency ablation of hepatocellular carcinoma (HCC). To deliver a conformal and perfusion nondependent treatment, a platform has been developed for studying ultrasound-image based navigation guidance and 3D planning of conformal HIFU ablations. Here, we evaluated the imaging capability and the treatment strategy associated with this platform.

METHODS

The platform included a 3D navigation environment (3DSlicer), communicating with an ultrasound (US) scanner (Verasonics) and a robotic arm (KUKA). A prototype of dual-mode US catheter (64-elements linear-array, $f = 5$ MHz), allowing HIFU dynamic focusing and b-mode US imaging in 2D, was piloted to reconstruct 3D US image volumes of targeted tissues in situ. Image stream generated by the scanner was synchronized with the robot, and 3D b-mode volumes were reconstructed after rotation of the catheter. The ability to reconstruct accurate volumes was evaluated using tissue mimicking gel phantoms. Target volumes were segmented and used to define conformal HIFU treatment planning. Planning strategies were evaluated using numerical simulations of HIFU treatments (CIVA).

RESULTS

The platform allowed defining automatically the focal points positions and HIFU exposure durations. These planning strategies were tested in HIFU simulations to achieve conformal ablations (>20 cm³).

CONCLUSIONS

US-image based navigation guidance allowed 3D planning of interstitial HIFU treatments. This approach shows interest in an operative room, to deliver conformal treatments of HCC.

ACKNOWLEDGEMENTS

This work has been founded by FLI (WP3, 2014), BPI (HECAM, PIA, PSPC 2015), MESR (EDISS 2016) and labex DevWeCan.

ULTRASOUND-ASSISTED DRUG DELIVERY TO SOLID TUMOURS IN SILICO

M. O. de Andrade¹, A. Huc², N. Saffari¹

¹UCL Mechanical Engineering, University College London, London, UK

²ENSEIRB-MATMECA, Bordeaux, France

e-mail: matheus.andrade.15@ucl.ac.uk

OBJECTIVES

Poor prognosis in the treatment of solid tumours is often associated with elevated interstitial fluid pressure (IFP) and hypovascularisation at the tumour's core. High IFPs form a barrier to transcapillary transport of chemotherapeutics into the interstitium via convection. In this work, the ability of ultrasound (US) to overcome high IFPs and deliver chemotherapeutics to poorly vascularised regions of tumours is assessed in silico.

METHODS

Doxorubicin concentrations within a 24-hour window after drug administration were compared in silico for treatment with and without ultrasound. Mass-momentum conservation equations are solved in ANSYS Fluent 18.0® to estimate Darcian flow through a 2 cm diameter spherical tumour with a 1 cm diameter hypovascular core. Convection-diffusion equations are then employed to obtain drug concentrations across the tumour.

RESULTS

Results show a spike in free and bound drug concentrations in the centre of the tumour when sonication starts. The peak concentrations of free drug at the centre of the tumour can be raised up to three orders of magnitude during sonication. Such concentrations are negligible for treatment without ultrasound. Moreover, the average intracellular drug concentration at the centre of the tumour at 6, 12 and 24h after administration was at least 10 times higher with ultrasound.

CONCLUSIONS

These results clearly demonstrate the potential of ultrasound for promoting drug delivery in tumours that are unresponsive to conventional chemotherapy.

Ventilator Driven Motion Model for Pre-clinical Validation of MRgFUS Systems

A. Dennison¹, J. Joy¹, R. Coupar¹, A. Melzer¹

¹Institute for Medical Science & Technology, Division of Imaging Sciences & Technology, University of Dundee, Scotland, UK

e-mail: apdennison@dundee.ac.uk

OBJECTIVES

Establish a preclinical model for simulation of moving abdominal organ targets, in magnetic resonance guided focused ultrasound (MRgFUS), without imposing apnea (static) conditions. To design a re-usable respiratory motion phantom model, for use validating image guided motion tracking and FUS target delivery compensation, providing reproducible MR thermometry results.

METHODS

The model comprises of a ventilator driven expandable diaphragm to translate motion to a target carriage, mounted on MRI safe linear rails inside a degassed water tank and has a 1.5l water filled balloon provided return force to the carriage during ventilator exhalation. A DQA gel phantom (Insightec, Israel) fitted with a 3D printed MRI tracking collar, designed to mimic liver vessels provided an experimental target. A 1.5T MRI (GE, USA) scanner, an Exablate 2100 (Insightec, Israel) FUS transducer and the Trans-FUSIMO treatment system (TTS) were used to conduct multi-baseline MR thermometry for static and dynamic conditions.

RESULTS

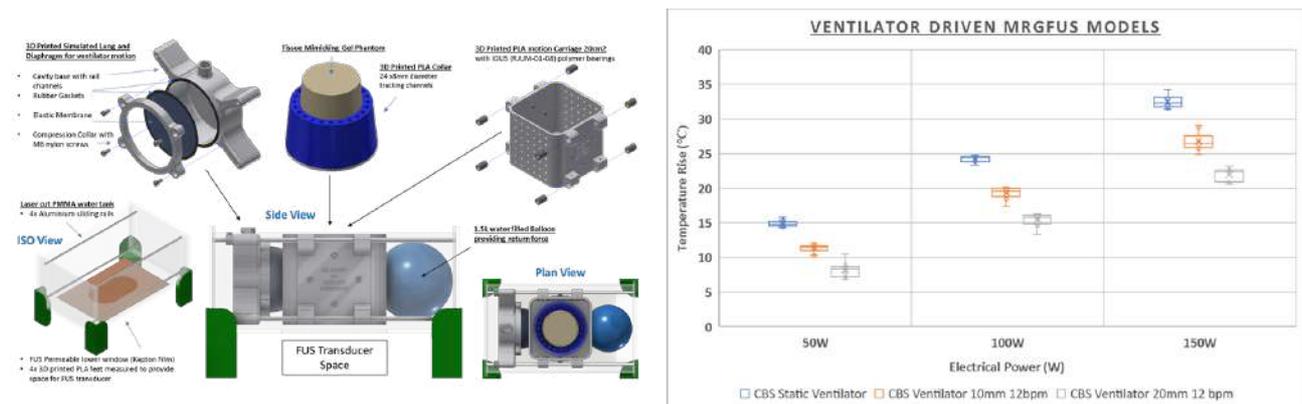
MRgFUS power was applied at (50W, 100W, 150W), duration 30s, target depth 70mm and a 12bpm motion cycle at 0, 10 and 20mm displacements. This was repeated (sample n=10) for each condition.

CONCLUSIONS

A pre-clinical validation model for MRgFUS performed under motion was successfully established.

ACKNOWLEDGEMENTS

Trans-FUSIMO Project (grant no 611889)



CAPTION: Left, diagram of ventilator driven motion model. Right, boxplot of MRgFUS thermometry summary results.

PAIN RELIEF AND LOCAL TUMOR CONTROL AFTER FOCUSED ULTRASOUND SURGERY AS TREATMENT OPTION FOR ADVANCED PANCREATIC CANCER PATIENTS

Dobromir Dimitrov¹, Nadya Stanislavova¹, Hyulia Feradova¹, Martin Karamanliev¹, Grigor Gortchev¹, Slavcho Tomov¹

¹ Department of HIFU therapy, University St. Marina Hospital, Medical University-Pleven, Bulgaria
e-mail: dobri_dimitrov@abv.bg

OBJECTIVES

Our objective is to study the use of focused ultrasound surgery (FUS) for pain relief and local tumor control in the treatment of advanced pancreatic cancer patients.

METHODS

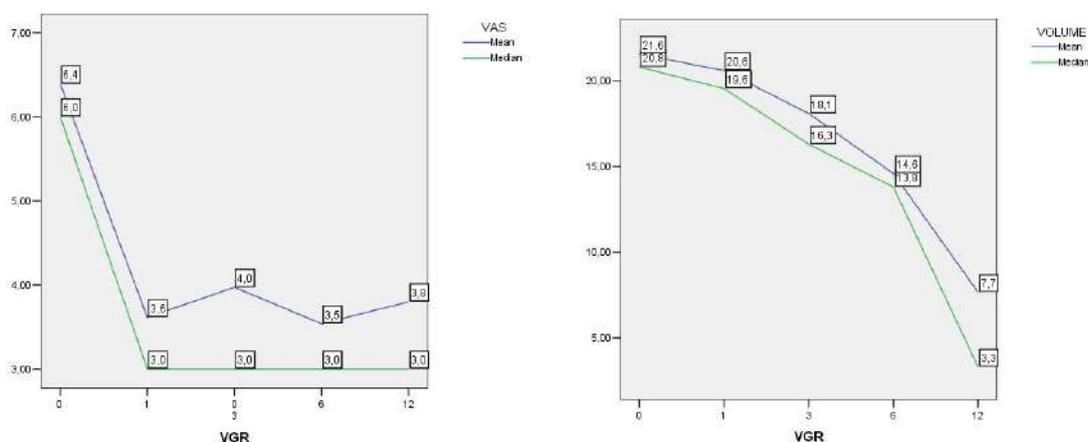
A single-center prospective study was conducted in the period 02. 2013 - 06. 2018 at the HIFU department, University hospital St. Marina – Pleven, Bulgaria. 47 advanced pancreatic cancer patients met the inclusion criteria and was treated by FUS. The mean age of the patients was 58.5 years. Mean tumor volume was 22.98ml and the localization was: in 34 patients (72.34%) in the head of the pancreas, in 9 patients (19.15%) in the body and in 4 patients (8.5%) in the tail.

RESULTS

The parameters of FUS of patients with advanced pancreatic cancer was: Sonication time /sec/ (mean, \pm SD) 694 \pm 338.2 and Average power /W/ 262 \pm 74.8. First hyperechogenic /grey scale/ changes were seen at mean time of 366.5 sec during FUS. No severe complications were observed. At least 2 cycles of chemotherapy were done in 42 of the patients. The mean tumor volume decreased to 20.6 ml after 1 month and 18.1 ml after 3 months and 14.6 ml after 6 months of the FUS treatment. Mean Visual Analog Scale (VAS) for pain decreased from 6.4 to 3.6 after FUS. The use of oral opioids and NSAIDs by the patients decreased at first month after FUS ($p=0.001$).

CONCLUSIONS

FUS is a safe and feasible method for treating advanced pancreatic cancer patients. In combination with chemotherapy FUS provide a good local tumor control, reducing patient's pain. Randomized trials are needed to substantiate this thesis.



CAPTION:

Figure 1 Visual analog scale changes after FUS treatment

Figure 2 Tumor volume changes after FUS treatment

Delivery of basic fibroblast growth factor (bFGF) and control of endothelial network formation using acoustic droplet vaporization (ADV)

Xiaoxiao Dong^{1,2}, Xiaofang Lu¹, Kailee Kingston¹, Emily Brewer¹, Oliver D. Kripfgans¹, J. Brian Fowlkes¹, Renny T. Franceschi¹, Zheng Liu², Andrew J. Putnam¹, and Mario L. Fabiilli¹

¹University of Michigan, Ann Arbor, MI, USA

²Army Medical University, Chongqing, China

e-mail: dongxx122@hotmail.com; mfabiill@umich.edu

OBJECTIVES

Blood vessel formation, a critical event in tissue regeneration, is regulated by pro-angiogenic growth factors in the local microenvironment. We demonstrate how ADV can temporally trigger release of bFGF from an acoustically-responsive scaffold (ARS), thereby stimulating *in vitro* vasculogenesis.

METHODS

The fibrin construct was polymerized in a 6-well BioFlex plate (Figure 1A,B). The inner gel (0.4 mL) was an ARS containing 1% (v/v) monodispersed (\varnothing : 6 μ m), perfluoroheptane double emulsion - with or without bFGF. The outer fibrin gel (1.5 mL) contained 75 endothelial cell-coated beads and 2.5×10^4 /mL fibroblasts. Constructs were cultured in complete media (day 0) and starvation media (days 1-8). On day 1, ADV was generated in ARSs with ultrasound (2.5 MHz, f-number: 0.83, 8.8 MPa peak rarefactional pressure, 100 Hz PRF). On day 8, the scaffolds were fixed, stained, and fluorescently imaged (Figure 1C). The length of endothelial tubules was quantified. Constructs, without ARSs, cultured in supplemented or starvation media, were positive and negative controls, respectively. bFGF release was quantified by ELISA.

RESULTS

Among the test groups, the longest tubules were observed when bFGF was released by ADV from the ARS (Figure 1D). This was confirmed using ELISA (Figure 1E).

CONCLUSIONS

ADV can control bFGF release and tubule formation.

ACKNOWLEDGEMENTS

This work is supported by NIH grant R01HL139656 and National Key R&D Program of China 2017YFC0107300.

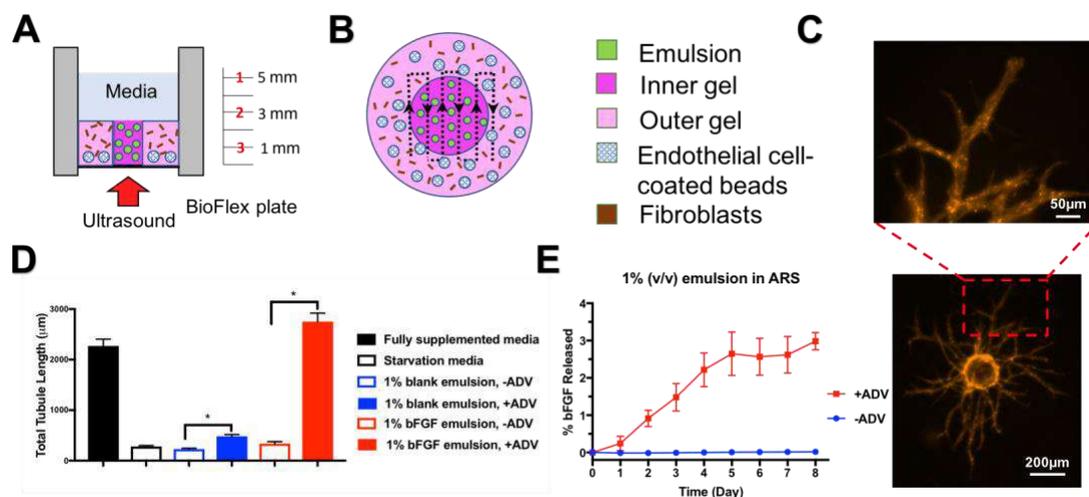


Figure 1. Side (A) and top (B) depictions of the ARS construct. C) Micrograph of fluorescently-stained endothelial tubules. D) Total tubule length after 7 days. E) Percent of bFGF longitudinally released from the construct.

THERAPEUTIC RESPONSE TO FREE CABAZITAXEL AND CABAZITAXEL LOADED NANOPARTICLES COMBINED WITH ULTRASOUND AND MICROBUBBLES IN A TRANSGENIC MOUSE PROSTATE CANCER MODEL

S.M.T. Fagerland^{1,2}, D.K. Hill², S. Berg^{2,4,5}, S. Snipstad^{1,3,5}, E. Sulheim^{1,3,5}, J. Kim², C.dL. Davies¹

¹Department of Physics, Norwegian University of Science and Technology, Trondheim, Norway

²Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

³Department of Biotechnology and Nanomedicine, SINTEF Industry, Trondheim, Norway

⁴Department of Health Research, SINTEF Digital, Trondheim, Norway

⁵Cancer Clinic, St. Olavs Hospital, Trondheim, Norway

E-mail: stein.m.fagerland@ntnu.no

OBJECTIVES

Ultrasound (US) in combination with microbubbles (MB) is reported to improve delivery of drugs and nanoparticles (NPs) in mouse xenografts. In the present study, we used the more clinically relevant Transgenic adenocarcinoma of the mouse prostate (TRAMP) model to evaluate the therapeutic response to free cabazitaxel (Cab) and Cab loaded polymeric NPs combined with US+MB.

METHODS

Diagnostic US was used to separate mice with premalignant prostates (PP) and poorly differentiated tumors (PDT). Mice with PP were divided into the groups: control, Cab, Cab with US+MB, Cab loaded NPs and Cab loaded NPs with US+MB. Mice with PDT were divided into the groups: control, Cab and Cab with US+MB. Treatment was repeated weekly for three successive weeks. The outcome measure was prostate volume for PP, and tumor volume PDT.

RESULTS

Preliminary data show that PP volumes were reduced in all groups during the treatment period compared to control. However, treated PPs regrew quickly, catching up with the control group by 6 weeks after treatment (Figure1). All PDT volumes were reduced by treatment and regrowth occurred in all mice except one receiving Cab and US+MB.

CONCLUSIONS

All treatments were effective in reducing PP and PDT volumes compared to control. However, preliminary data does not suggest an added effect from encapsulating Cab in NPs or combining with US+MB compared to treatment with free Cab without US+MB.

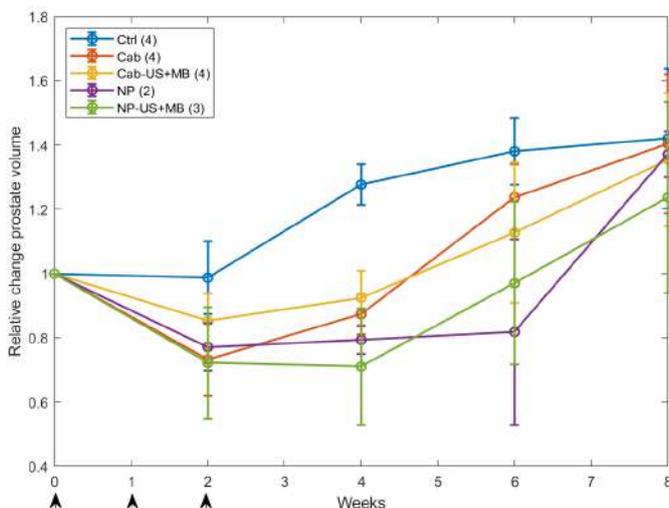


Figure1: Relative PP volumes over time. The arrows mark when treatment was given. Data points are average relative volume measurements with MRI and error bars show standard deviation. Number of mice per group is shown in the legend.

Ultrasonic-magnetic hybrid gene delivery system for Parkinson's disease treatment in mice model

Ching-Hsiang Fan ¹, Chih-Kuang Yeh ¹

¹ Department of Biomedical Engineering and Environmental Sciences, National Tsing Hua University, Hsinchu, Taiwan

OBJECTIVES

Genetic treatment with plasmid glial cell-line derived neurotrophic factor (pGDNF) has the potent effect for Parkinson's disease (PD). However, pDNA transfection rate by transcranial ultrasound (US) was hampered by cell membrane, lysosome, and nucleus envelope. We proposed the polyethylenimine (PEI)-superparamagnetic iron oxide-pDNA loaded microbubbles (PSp-MBs) with US and two steps magnetism to increase gene transfection rate. The intracellular accumulation of PSp was enhanced by concurrently performing US and 1st magnetism. The PEI allowed PSp escaping from lysosome degradation. Finally, the amount of pDNA entering nucleus was increased by 2nd magnetism.

METHODS

The plasmid green fluorescence protein (pGFP) and pGDNF were used to quantify transfection rate and repair dopaminergic neurons in SH-sy5y neuron-like cell and genetic PD mice (MitoPark), respectively. PSp (150±4.7 nm) was delivered by 1-MHz US (0.3 MPa, 0.5 % of duty cycle, 1 min), PSp-MBs (1±0.2 μm), and 1st magnetism (0.37 T). The 2nd magnetism (60 min) was applied to promote pDNA entering nuclear. The motor balance and willingness of animals were assessed weekly by beam walking test and open field test, respectively.

RESULTS

The transfection rates were boosted ~11%, ~7%, and 2% by cavitation-magnetic hybrid enhanced membrane permeabilization, proton sponge effect and magnetic-assisted cytoskeleton-reorganization, respectively. In vivo data suggested that the system improved 1.8 fold and 1.6 fold of motor balance and willingness compared to untreated PD mice, respectively.

CONCLUSIONS

This study proposed a novel US-magnetic hybrid gene delivery platform and potentially could be integrated with other therapeutic genes for treating neurodegenerative diseases in future.

DNA DAMAGE INDUCED BY COMBINED DOXORUBICIN AND UNSEEDED CONTROLLED STABLE CAVITATION TREATMENT IN MURINE MAMMARY TUMOR CELLS

C.Fant¹, A. Granzotto², T. Moraes-Vieira¹, J-L. Mestas¹, J. Ngo¹, M. Lafond¹, C. Lafon¹, N. Foray², F. Padilla^{1,3,4}

R.O. Cleveland³

¹ LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ-Lyon, F-69003, LYON, France

² Inserm U1052 unit, Groupe de Radiobiologie, 69008 Lyon, France

³ Department of Radiation Oncology, University of Virginia School of Medicine, Charlottesville, VA, USA

⁴ Focused Ultrasound Foundation, Charlottesville, VA, USA

e-mail: cecile.fant@inserm.fr; frederic.padilla@inserm.fr

OBJECTIVES

Doxorubicin (DOX) induces cell cytotoxicity through DNA damage. Recent studies reported that DNA damage could occur in different cell lines after exposition to cavitation ultrasound (US). We evaluate *in vitro* whether a combined treatment with doxorubicin and stable cavitation can potentiate DOX cytotoxicity through increased DNA damage.

METHODS

Mouse mammary cancer cells 4T1 were treated *in vitro* using a confocal device to generate and monitor pulsed cavitation ultrasound, with or without addition of DOX. After treatment, DNA damages were assessed by scoring γ -H2AX foci number in cell nuclei by immunofluorescence. To assess a bystander effect through calcium release, untreated cells were exposed to the supernatant of sonicated cells, with or without the addition of calcium chelator PBS. Cell viability and cell proliferation were assessed at 72hrs post treatment.

RESULTS

Cells treated with stable cavitation, with or without DOX, elicited double strand breaks (DSB) displayed by γ -H2AX foci. Without DOX, these DSB did not impact cell proliferation or viability. Compared to treatment with DOX alone, the combination of stable cavitation and DOX led to premature DSB, significant decrease of cell viability and proliferation. The exposure of untreated cells to sonicated cells supernatant showed 40% of untreated cells with γ -H2AX foci from 10 min after treatment. The addition of PBS in the supernatant counteracted this effect.

CONCLUSIONS

A combined treatment of 4T1 tumor cells with DOX and controlled stable cavitation led to premature DSB, possibly induced by a bystander effect mediated by calcium release, and to significant decreases in cell proliferation and viability.

ACKNOWLEDGEMENTS

This work was supported by the LabEx DEVweCAN (ANR-10-LBX-0061) of the University of Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR). FP is supported by the Merkin Fellowship of the Focused Ultrasound Foundation.

The first coagulative necrosis point induced by HIFU treatment for isointense uterine fibroids on MRI T2WI : Retrospective analysis and theoretical simulation

Chengbi Guo¹, Chenghai Li¹, Huan Liu¹, Haoran Huang¹, Faqi Li^{1,2}

¹State Key Laboratory of Ultrasound Engineering in Medicine Co-founded by Chongqing and the Ministry of Science and Technology, Chongqing Key Laboratory of Ultrasound in Medicine and Engineering, College of Biomedical Engineering, Chongqing Medical University, Chongqing 400016, China

²National Engineering Research Center of Ultrasound Medicine, Chongqing 401121, China

e-mail: lifq@cqmu.edu.cn

OBJECTIVES

High-intensity focused ultrasound (HIFU) is a safe and effective non-invasive new technique for the treatment of uterine fibroids. However, how to select irradiation dose (acoustic power, irradiation time, interval time, and irradiation times) to achieve the coagulative necrosis at the first treatment point is a major problem in HIFU treatment. Currently, it relies on the experience of doctor because of the lacks of the evidence for dose delivery. Therefore, the study was expected to provide the basis for the irradiation dose of HIFU treatment of isointense uterine fibroids on MRI T2WI.

METHODS

We analyzed retrospectively the irradiation dose and the range of coagulative necrosis (corresponding to the hyperechoic area on the ultrasound image) for the first HIFU treatment point of 111 cases of isointense uterine fibroids on MRI T2WI, and then simulated the range of coagulative necrosis under each irradiation dose. The layered media model (degassed water, skin, fat, rectus abdominis, bladder, uterine fibroid) was used in simulation, and the thickness of each layer was measured through the B-mode ultrasound image. KZK equation and Pennes biological heat conduction equation were combined to calculate the temperature distribution within the tissue. Thermal dose in tissue was calculated with the equivalent thermal dose model, and threshold of thermal lesion was set at 240EM.

RESULTS

The area of coagulative necrosis by simulated theoretically for the first HIFU treatment point of 111 cases of isointense uterine fibroids on MRI T2WI was between 3.406 mm² - 248.844 mm², and the hyperechoic area on the ultrasound image was between 12.994 mm² - 204.24 mm². The sperman correlation coefficient of the two groups was 0.8232 (p=0.000).

CONCLUSIONS

The results indicated that the theoretical simulation may also provide a reference for the radiation dose of the HIFU treatment of isointense uterine fibroids on MRI T2WI.

A THERANOSTIC POLYMER-BASED NANOPARTICLE FOR USE IN SONODYNAMIC THERAPY (SDT)

S. Farrell, H. Nesbitt, J.F. Callan, A.P. McHale

School of Pharmacy and Pharmaceutical Sciences, Ulster University, Coleraine, Co. Derry, BT52 1SA Northern Ireland

e-mail: farrell-s6@ulster.ac.uk, ap.mchale@ulster.ac.uk

OBJECTIVES

To prepare and characterize a PLGA-based nanoparticle harboring Rose Bengal as a sonosensitiser and indocyanine green as a near infrared imaging agent for use in SDT.

METHODS

Particles containing Rose Bengal (RB) and indocyanine green (ICG) were prepared with PLGA using a solvent diffusion approach. Particles were characterized using dynamic light scattering and spectrophotometry. Stimulus-responsive toxicity was assessed using human pancreatic tumour and human xenograft pancreatic tumours (BxPC3) in SCID mice.

RESULTS

Particles had an average diameter of 220-250 nm and polydispersity indices of 0.110-0.250. 1 mg of nanoparticles contained 49 μg of RB and 4.5 μg of ICG, indicating encapsulation efficiencies of 39% and 33%, respectively. Ultrasound-mediated toxicity in combination with nanoparticles was demonstrated against target cell lines *in vitro*. *In vivo* studies confirmed that ICG payload within the nanoparticle is sufficient to enable nIR fluorescence imaging, demonstrating nanoparticle accumulation at the tumour following intravenous administration (Fig.1a). A reduction in tumour growth was also demonstrated *in vivo* in tumour-bearing animals treated with nanoparticles in combination with relatively low intensity ultrasound.

CONCLUSIONS

A PLGA-based nanoparticle encapsulating Rose Bengal has been formulated for use in SDT. The nanoparticles are relatively non-toxic until they are exposed to ultrasound and generate cytotoxic reactive oxygen species that elicit a targeted anti-tumour effect. The level of ultrasound required to trigger nanoparticle has no impact on tumour growth.

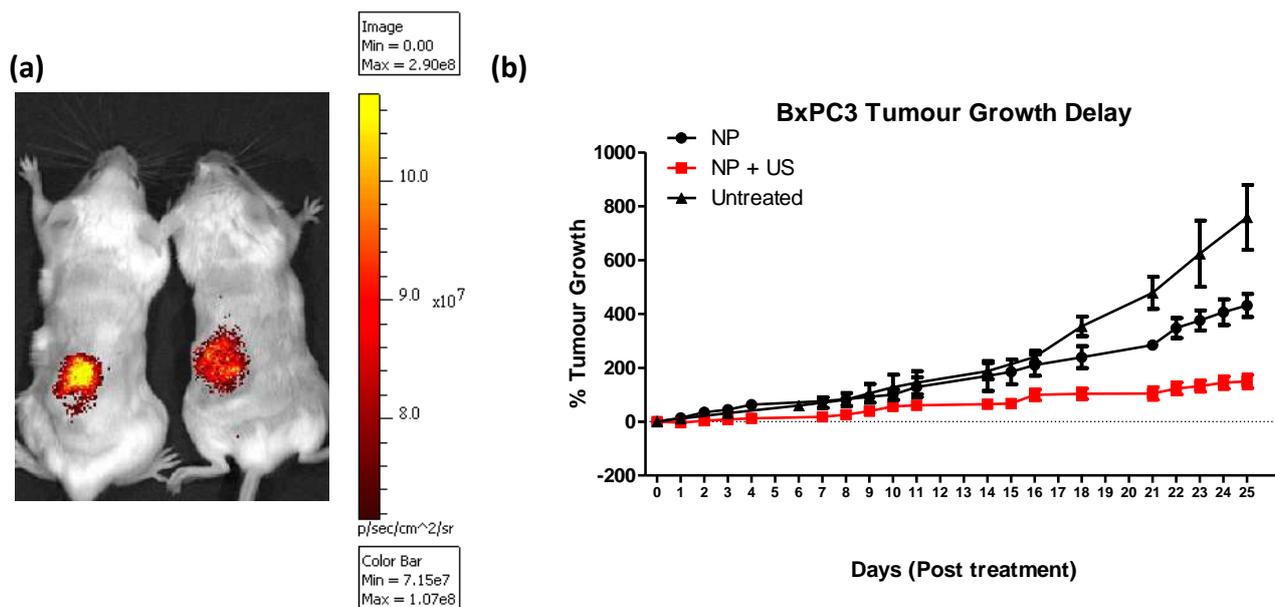


Figure 1: (a) Real time nIR fluorescence of animals 24 h after intravenous administration of nanoparticles and (b) The effect of ultrasound on animals treated with nanoparticles (n=4 per group).

Temporal proteomic immune changes of murine breast and melanoma tumor microenvironments without and with pulsed focused ultrasound

Gadi Cohen¹, Rebecca Lorsung¹, Parwathy Chandran¹, Jennifer Colon Mercado¹, Scott R. Burks¹ and Joseph A. Frank^{1,2}

¹Frank Lab, Radiology and Imaging Sciences, Clinical Center, ²National Institute of Biomedical Imaging and Bioengineering, NIH, Bethesda, MD

Pulsed focused ultrasound (pFUS) ablation has been successfully used as a noninvasive treatment of solid malignancies. pFUS has been shown to release tumor debris and other protein antigens that can stimulate an immune response within the tumor microenvironment (TME). Here, we explored the temporal expression differences in cytokines, chemokines and trophic factors (CCTF) in TME of mouse xenograft models following pFUS treatment. Mice were subcutaneously inoculated with B16 melanoma or 4T1 breast tumors cells into the bilateral hind limbs (n=6/group/time-point). The natural history of proteomic changes with tumor size was started when masses reached ~5mm in diameter (day 1). Proteomic analysis demonstrated a shift over 11 days towards immunosuppressive TME in untreated tumors. We also evaluated the acute effects of pFUS at 1MHz at PNP=6MPa on CCTF. We investigated the influence of pFUS on days 1, 5 or 9 compared with controls 24hrs post sonication. Tumor growth was significantly slowed compared to controls along with increased expression levels of anti-tumoral CCTF. Next, we monitored the CCTF changes over 72hrs post-pFUS. Following pFUS, a unique CCTF profile with a shift towards anti-tumoral TME within first 24hrs specifically with increases in proinflammatory CCTF. Our natural history results provide insight into change in CCTF in the TME associated with tumor growth that could have implications with the timing of pFUS-treatment and its effect on the TME. pFUS modulates the TME with increased acute expression of primarily pro-

inflammatory CCTF that could potentially be harnessed as complementary approaches in cancer immunotherapy.

ACUTE EVALUATION OF BRAIN AND CEREBROSPINAL FLUID BIOMARKERS FOLLOWING BLOOD BRAIN BARRIER OPENING WITH PULSED FOCUSED ULTRASOUND AND DEFINITY USING PASSIVE CAVITATION DETECTION FEEDBACK

Jennifer M. Colon Mercado¹, Jaclyn A. Witko¹, Maggie Sundby¹, Scott Burks¹, Joseph A. Frank^{1,2}

¹Frank Laboratory, Radiology & Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, United States

²National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, Bethesda, MD, United States

e-mail: jennifer.colonmercado@nih.gov;jaclyn.witko@nih.gov;maggie.sundby@nih.gov;
scott.burks@nih.gov;jfrank@cc.nih.gov

OBJECTIVES

Pulsed focused ultrasound (pFUS) in combination with microbubble (MB) infusion has been used to cause blood-brain barrier disruption (BBBD) to improve delivery of neurotherapeutics to treat CNS disease. pFUS+MB has been shown to induce a sterile inflammatory response (SIR) with temporal changes in expression of cytokines, chemokines and trophic factors (CCTF) in the brain. Cerebrospinal fluid (CSF) biomarkers are routinely used to monitor inflammation in traumatic brain injury (TBI) but have not been evaluated post-pFUS+MB.

METHODS

pFUS (548KHz) was used with passive cavitation detection feedback (PCD, $1.5f_0$, $2.5f_0$ < $3.5f_0$ baseline, FUS Instrument) with bolus infusion of Definity (20 μ l/kg) to sonicate 9 foci in the rat cortex. Brain and CSF was obtained at 2 and 6 hours (hrs) post-pFUS for proteomic analysis.

RESULTS

Following pFUS+MB to the left cortex significant elevations (ANOVA $p < 0.05$) in proinflammatory CCTFs were detected including IL1 α , IL1 β , TNF α , Fraktalkine, IP10, MIP1 α and RANTES at 6hrs post-sonication at 2 and 6 hrs compared to contralateral cortex. Importantly, CSF showed significant (ANOVA $p < 0.05$) increases in proinflammatory proteins IL1 α , IL1 β , IP10, MCP1 post-sonication. The increased expression of proinflammatory CCTF in the CSF may originate either from the parenchyma or the meninges. Ex-vivo 7T MRI revealed areas of hypointense voxels in sonicated brain and histological examination demonstrated areas of micro-hemorrhages despite using PCD feedback to control PNP.

CONCLUSIONS

pFUS+Definity under PCD monitoring opened BBB and resulted in increased expression of proinflammatory CCTF in the brain and the CSF indicative of a SIR that could be potentially have important clinical implications.

EXPERIMENTAL EVALUATION OF THE IMPACT OF ULTRASOUND EXPOSURE PARAMETERS ON NECROTIC LESIONS INDUCED IN TISSUE BY A ROBOTIC ULTRASOUND-GUIDED HIFU ABLATION DEVICE FOR TREATING SOLID TUMORS IN SMALL ANIMALS

Ł. Fura¹, W. Dera², C. Dziekoński², T. Kujawska¹

¹ Department of Ultrasound, Institute of Fundamental Technological Research of the Polish Academy of Sciences, Warsaw, Poland

² Department of Theory of Continuous Media and Nanostructures, Institute of Fundamental Technological Research of the Polish Academy of Sciences, Warsaw, Poland

e-mail: lfura@ippt.pan.pl

OBJECTIVES

We have designed and built a robotic Ultrasound Imaging-guided HIFU (USigHIFU) ablation device for destroying solid tumors in small animals. Before the device is used, series of experimental studies on *ex vivo* tissues were needed to assess the location and extent of necrotic lesions induced. The objective of this studies was to evaluate the impact of sonication parameters on necrotic lesions induced in tested tissue during less than 3s. The results of this studies were necessary to determine the step and speed of the HIFU beam movement to cover with necrosis the whole treated volume.

METHODS

The HIFU beam was generated by a bowl-shaped, 64mm transducer (*f*-number 0.98) operating at 1.08MHz or 3.21MHz. Multiple thermal lesions were created within *ex vivo* pork loin tissue at a 12.6mm depth below its surface during 3s of exposure. Beams with the same duty-factor and varying pulse duration (30 μ s-300ms) or with the same pulse duration and varying duty factor (0.2-0.8) propagated in two-layer media: water/tissue (50mm/40mm) were studied. The *in situ* intensity was estimated assuming nonlinear propagation model.

RESULTS

Dependence of lesion dimensions on frequency, pulse duration and duty-factor was determined.

CONCLUSIONS

Lesion extent depended strongly on frequency and duty-factor, but slightly on pulse duration. The lesions created by shorter pulses were hardly visible on ultrasound images. Based on the experimental results the HIFU beam acoustic parameters, the step and speed of its movement to cover the whole treated tissue volume were designated.

ACKNOWLEDGEMENTS

The financial support of the National Science Centre (Grant 2016/21/B/ST8/02445) is gratefully acknowledged.

TARGETED DELIVERY OF MULTIPLE DRUG PAYLOADS TO PANCREATIC TUMOURS USING AN ULTRASOUND RESPONSIVE MICROBUBBLE-LIPOSOME CONJUGATE

Jinhui Gao, Heather Nesbitt, Anthony P McHale and John F Callan.

Biomedical Sciences Research Institute, Ulster University, Coleraine, Northern Ireland, UK. BT52 1SA.

E-mail: gao-j2@ulster.ac.uk

OBJECTIVE

To deliver a combination of Irinotecan (IR) / Oxaliplatin (OX) chemotherapy and Sonodynamic Therapy (SDT) to pancreatic tumours using lipid stabilised microbubbles (MBs) conjugated to liposomes. Treatment efficacy was determined in Panc-01 3D spheroids and an *in vivo* murine model incorporating BxPC-3 ectopic xenografts.

METHODS

IR and OX were loaded into the shell of biotin-functionalised MBs and liposomes respectively. The drug loaded MBs and liposomes were conjugated together using an avidin bridge. Any remaining free biotin sites on the liposomes were used to facilitate attachment of the SDT sensitiser biotin-Rose Bengal (biotin-RB), again using an avidin bridge. Particle size was determined using light microscopy (MBs) and Dynamic Light Scattering (liposomes) while drug loading was determined using UV-Vis spectroscopy (biotin-RB / IR) and HPLC (OX). 3D Panc-01 spheroids were treated with the MB-liposome conjugate and subjected to ultrasound for 30 seconds (power=3.0W/cm², frequency=1MHz, duty cycle=50%). Cell viability was determined using propidium iodide staining and MTT assay. SCID mice, bearing human xenograft BxPC-3 tumours, were treated with an intravenous suspension of the MB-liposome conjugate and exposed to 3.5min ultrasound using the parameters defined above. Animals were also treated with MB-liposome conjugate without ultrasound for comparative purposes. In each case the effect of the treatment on tumour growth was determined.

RESULTS

The IR loaded MB (Conc.:8.84× 10⁸/ml, Diameter: 2.19µm±1.09 µm) and the OX loaded liposomes (Diameter:152nm±8.5nm) were prepared successfully. The IR, OX and biotin-RB loadings were 1607.2µM±169µM, 71.2µM±22µM and 554.4µM±29µM respectively. Results from the 3D spheroid and *in vivo* studies demonstrated a significant improvement in spheroid viability and tumour control for the MB-liposome conjugate compared to the other control groups tested.

CONCLUSIONS

Chemo-Sonodynamic Therapy, delivered using a microbubble-liposome conjugate and ultrasound activation, is a promising approach for the targeted treatment of pancreatic tumours. Importantly, MB-liposome conjugate achieved significant multiple drug payload compare to MB alone.

TRANSCRANIAL MR ACOUSTIC RADIATION FORCE IMAGING AND SIMULATION IN SHEEP

P. Gaur¹, N. Li², S. A. Leung³, M. Mohammadjavadi¹, K. Butts Pauly¹

¹Radiology, Stanford University, Stanford, USA

²Electrical Engineering, Stanford University, Stanford, USA

³Bioengineering, Stanford University, Stanford, USA

e-mail: pgaur@stanford.edu

OBJECTIVES

In lieu of a temperature rise in non-ablative applications of focused ultrasound, targeting can be predicted with simulation or validated with magnetic resonance acoustic radiation force imaging (MR-ARFI). In this study, we compare the prescribed *in vivo* transcranial focal spot location with the simulated location and the MR-ARFI measured location.

METHODS

Ten sheep were studied using a 550 kHz transducer array (ExAblate 2100, Insightec Ltd) and repeated bipolar MR-ARFI sequence at 3T (Signa Excite, GE Healthcare), without phase aberration correction. Twelve focal spots were evaluated: one location in each of eight sheep, and two locations in two sheep. Combining two MR-ARFI acquisitions with alternating bipolar gradients yielded one image per location. Simulation using the hybrid angular spectrum method was performed retrospectively using CT images of the *ex vivo* skull caps obtained from each sheep (Discovery CT750 HD, GE Healthcare; 120 kVp, BONEPLUS reconstruction kernel).

RESULTS

The in-plane (x,y) differences between prescribed focal spot locations and peak MR-ARFI and simulated focal spot locations are shown in Fig. 1. The median root-mean-square deviation (RMSD) from the prescribed focal spot location for MR-ARFI was 2.5 mm and for simulation was 1.2 mm. The median RMSD between MR-ARFI and simulated focal spot locations was 1.7 mm.

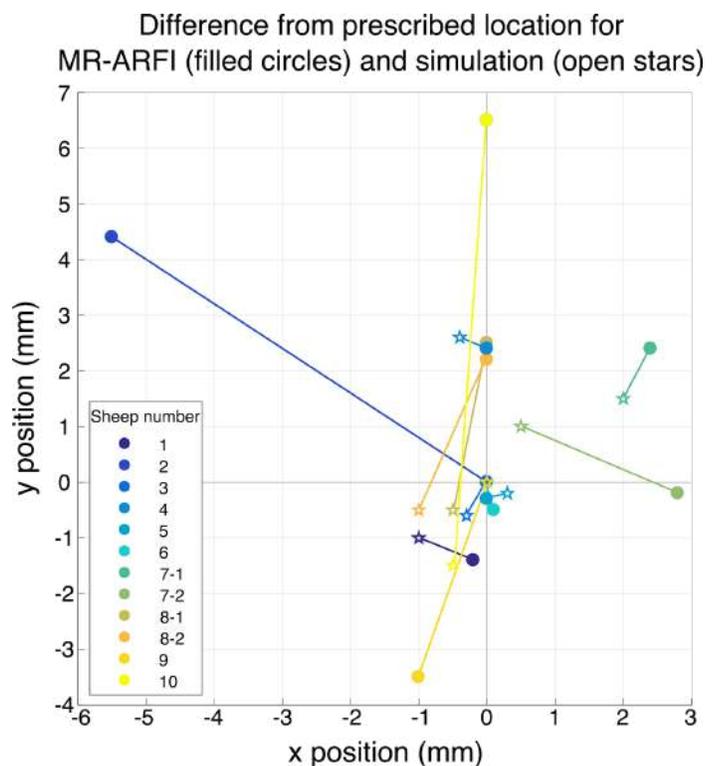
CONCLUSIONS

Simulation captured some but not all of the changes in focal spot location that were seen on MR-ARFI.

ACKNOWLEDGEMENTS

Supported by NIH T32 CA009695, R01 MH111825, RF1 MH116977, R01 CA227687.

CAPTION: *In vivo* MR-ARFI and simulated focal spot locations relative to the prescribed location (indicated by 0,0).



UNILATERAL MR GUIDED FOCUSED ULTRASOUND THALAMOTOMY FOR ESSENTIAL TREMOR: A BRITISH EXPERIENCE. A.J. Jameel¹, P.G. Bain², D Nandi¹, B Jones¹, O Kirmi¹, W Gedroyc¹

¹Imperial College NHS Healthcare Trust, London. ²Imperial College of Science Technology and Medicine, London. E-mail: Ayesha.jameel@nhs.net; wladyslaw.gedroyc@imperial.ac.uk

INTRODUCTION:

Magnetic Resonance guided focussed ultrasound (MRgFUS) is non-invasive treatment for essential tremor (ET) that allows targeted thermal ablation of brain tissue under real time image guidance. In ET the target is a specific thalamic nucleus - the ventralis intermedius nucleus. This paper describes the first UK experience of unilateral MRgFUS thalamotomy in essential tremor.

METHODS:

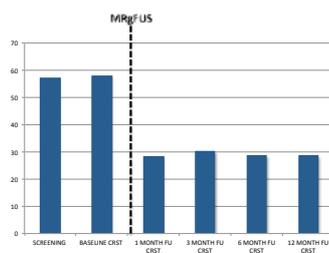
A prospective study enrolled 13 patients with medically refractory ET for unilateral MRgFUS thalamotomy. Tremor severity and functional impairment was assessed at baseline and at regular intervals post-treatment for 12 months. The effectiveness of tremor suppression was monitored using parameters from the Clinical Rating Scale for Tremor (CRST), Quality of Life in Essential Tremor (QUEST) questionnaire, depression PHQ-9 and Bain and Findley Spiral (BFS) scores.

RESULTS:

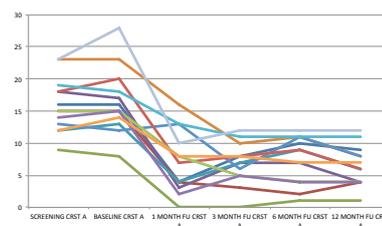
In all patients there was successful thermal ablation of the target tissue and improvement in all tremor scores, which remained stable over the 12 months. All CRST parameters improved (Figure1) - the tremor score of the treated arm by 73.5% and its BFS by 56.9%. Furthermore the non-treated arm tremor score improved 38.4%. The QUEST and PHQ scores improved by 38% and 36.8% respectively, demonstrating the psychosocial impact of reducing tremor on patient's lives. There were no permanent significant adverse effects.

CONCLUSIONS:

Our study demonstrates the efficacy of unilateral MRgFUS thalamotomy on ET with profound improvement in all tremor scores, including functional impairment and quality of life. The bilateral effect demonstrated warrants further analysis and investigation. Our study provides further evidence that MRgFUS thalamotomy is a safe, effective, curative treatment for ET.



Mean CRST score from screening to 12 month follow up.



Individual whole body tremor score (CRST-A) from screening to 12 month follow up.

ULTRASOUND-STIMULATED MICROBUBBLE INDENTATION OF FIBRIN CLOTS

K. Kiezun^{1,2}, C. Acconcia², D. Goertz^{1,2}

¹ Department of Medical Biophysics, University of Toronto, Toronto, Canada

² Sunnybrook Research Institute, Toronto, Canada

e-mail: kevin.kiezun@sri.utoronto.ca; chrisacc@sri.utoronto.ca; goertz@sri.utoronto.ca

OBJECTIVES

Rapid indentation of the boundary of a fluid filled porous viscoelastic medium is well established to be associated with fluid transport within the medium. Fibrin clots, relevant to blood clots, are an example of such a medium. Previously, we used high-speed microscopy to demonstrate that cyclical indentations of the clot boundary, associated with radiation forces on the time-scale of the pulse repetition frequency, can be induced by ultrasound stimulated microbubbles. The objective of this work is to investigate how such deformations, occurring at a far different timescale than oscillations, can facilitate the transport of fluid and therapeutic agents into the medium.

METHODS

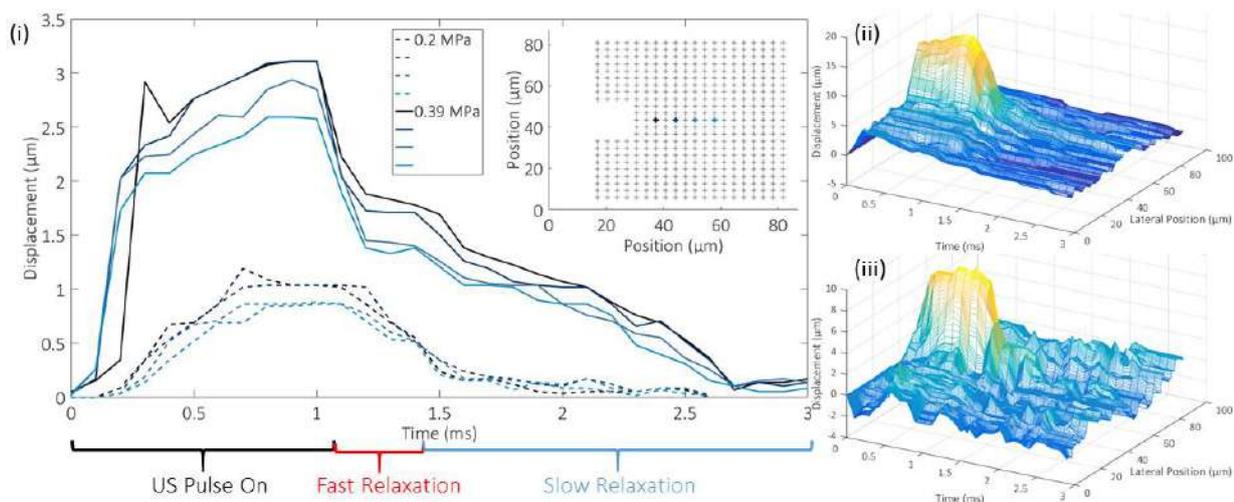
Digital image correlation was applied to high speed microscopy (10kFps) to quantify the spatial distribution of displacements and strain within fibrin clots ($2.97 \pm 1.02 \mu\text{m}$ pore size) subject to indentation by individual Definity™ microbubbles ($n=36$) positioned via optical tweezers and stimulated by pulsed ultrasound (1-MHz, 1-ms duration, 15% duty cycle).

RESULTS

Significant deformation, on the scale of pore size, is observed away from the boundaries as a result of single microbubble indentation. Furthermore, there are indications of an asymmetry in fibrin network recovery post-indentation characterized by a rapid primary relaxation followed by a prolonged secondary relaxation.

CONCLUSIONS

The scale of deformation observed suggests that fluid flow is occurring. Indications of an asymmetry in fibrin network recovery imply the existence of multiple recovery timescales and allow for the potential of net fluid transport.



CAPTION: (i) Displacement along axis of indentation for 3.09 μm microbubble (0.2MPa) and 3.92 μm diameter microbubble (0.39MPa). Colour indicates position. Corresponding boundary deformations for (ii) 3.09 μm and (iii) 3.92 μm microbubble.

MULTIPLE LESION GENERATION DURING HIFU THERMAL THERAPY: NUMERICAL MODELING & PARAMETRIC STUDY

Pragya Gupta¹, Atul Srivastava²

¹IITB Monash Research Academy, Indian Institute of Technology Bombay, Mumbai, India

²Department of Mechanical Engineering, Indian Institute of Technology Bombay, Mumbai, India

e-mail: ¹pragya.gupta@monash.edu; atulsr@iitb.ac.in

OBJECTIVES

The selective destruction of tumor cells in a calculated and controlled manner requires the optimization of source parameters to avoid the under and over exposure of high intensity focused ultrasound (HIFU) on the tissue. The main objective here is to reduce the total treatment time and minimize the damage of healthy intervening tissue.

METHODS

Three scanning methods raster scan, spiral scan center to outward and spiral scan outward to center have been chosen to deliver acoustic energy and placement of multiple lesion at the desired location. Time parameter (heating, cooling and transducer moving), as well as the inter-spatial gap between lesions, affects the temperature rise and the extent of a cool down period. In this study, non-linear Westervelt equation is used to calculate the pressure distribution in two-layered medium (water and tissue).

RESULTS

As the transducer moves from one lesion to another, the heat from the previously generated lesion starts diffusing and hence raises the temperature of the surrounding region, which makes the next targeted lesion pre-heated. Figure 1(a) shows the maximum temperature reached for each lesion during various scanning method. It can be clearly seen that spiral scan (outside to center) results into the highest temperature compared to the other two. Figure 1(b) shows the temperature distribution contour in x-z focus plane during the spiral scanning (outside to center).

CONCLUSIONS

The optimization of source parameters is required to avoid the under and over exposure of HIFU on the tissue, which is important in deciding the efficacy of this mode of thermal therapy.

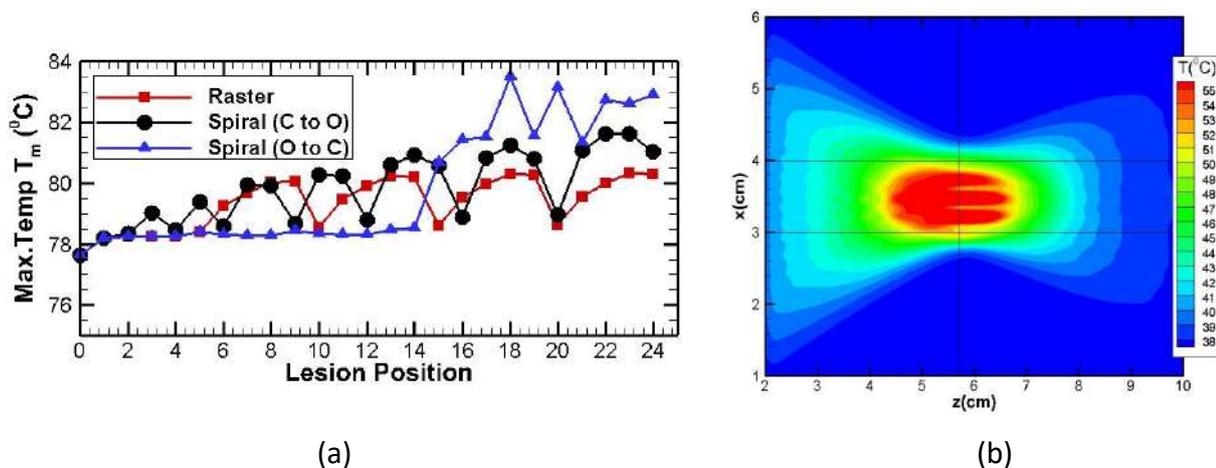


Figure 1. a) Maximum temperature reached during each lesion generation for different scanning methods and, b) Temperature contour plot in x-z plane for the spiral (outward to center) scanning done in x-y. plane.

STIMULATION OF THE RAT DORSAL ROOT GANGLION FOR CHRONIC PAIN REGULATION WITH FOCUSED ULTRASOUND

Po-Hung Hsu¹, Ya-Tin Lin², Jin-Chung Chen², and Hao-Li Liu³

¹Center for Advanced Molecular Imaging and Translation, Chang Gung Memorial Hospital, Taoyuan, Taiwan

²Graduate Institute of Biomedical Sciences, Department of Physiology and Pharmacology, Chang Gung University, Taoyuan, Taiwan

³Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan
e-mail: phhsu@cgmh.org.tw

OBJECTIVES

Chronic pain remains a significant health problem with patients suffered from inflammation, diabetes, or cancer. Currently, analgesic drugs and nerve block are the major effective treatments to chronic pain. However, analgesic drug administration encounters substantial side-effects such as resistance to drugs and surgery infections. Focused ultrasound (FUS) has demonstrated its utility to modulate neurons and has potential to provide a non-invasive, non-pharmacological mean to regulate chronic pain. In this study, we aimed to evaluate whether the use of FUS-mediated rat DRG modulation may serve as an alternative to produce analgesic effect to relieve neuro-inflammatory pain.

METHODS

We conducted *in-vitro* experiment to confirm ultrasound-mediated effects by measuring calcitonin gene-related peptide (CGRP) released level. In *in-vivo* experiments, a hind-paws neuro-inflammatory models was applied to evaluate the behavior response before and after FUS treatment. Immunohistochemistry (IHC) staining was also applied to detect CGRP release level *ex vivo* to quantitatively validate the proposed mechanism.

RESULTS

In *in vitro* experiments, we confirmed that CGRP release showed a 23.2% down-regulated level after FUS stimulation compared to the control group. Animal behavior response also showed positive improvement up to 81%, which implies the animals have better tolerances to pain after FUS stimulation on DRGs. Furthermore, IHC results also indicated similar trend in rat spinal cord. This preliminary results showed significant change *in vitro* and convinced improvement *in vivo*.

CONCLUSIONS

This study reveals that FUS neuronal stimulation demonstrate its utility in modulating dorsal root ganglion neurons non-invasively and non-pharmacologically, expanding the applicability of focused ultrasound toward peripheral nerve regions, and may expand the clinical relevance of using focused ultrasound as a non-invasive tool to perform neuromodulation.

ULTRASOUND-MEDIATED SKIN EROSION FOR HEPATITIS B IMMUNIZATION

Yaxin Hu^{1,2}, Mei Yang^{1,2}, Yang Mo^{1,2}, Xin Chen^{1,2}

¹School of Biomedical Engineering, Health Science Center, Shenzhen University, Shenzhen, China

²National-Regional Key Technology Engineering Laboratory for Medical Ultrasound, Shenzhen, China

e-mail: yxhu@szu.edu.cn

OBJECTIVES

Transdermal immunization is attractive since the skin has a large population of immune cells. This study aims to develop a transdermal immunization method using the spatially-confined ultrasound erosion effect.

METHODS

Acoustically-transparent skin patch containing 6 μ g Hepatitis B antigen was designed. To label the skin erosion area, a black tissue staining dye of Indian ink was also included in the patch. High-intensity ultrasound pulses (16.5 MPa peak negative pressure, 75 cycles per pulse, 4 kHz pulse repetition frequency, 60 s duration) were generated by an annular focused 3.3-MHz transducer. A 5-MHz transducer was placed at the center of the 3.3 MHz transducer to work in the pulse-echo mode for precise skin location (Figure A) and passive cavitation detection (Figure B).

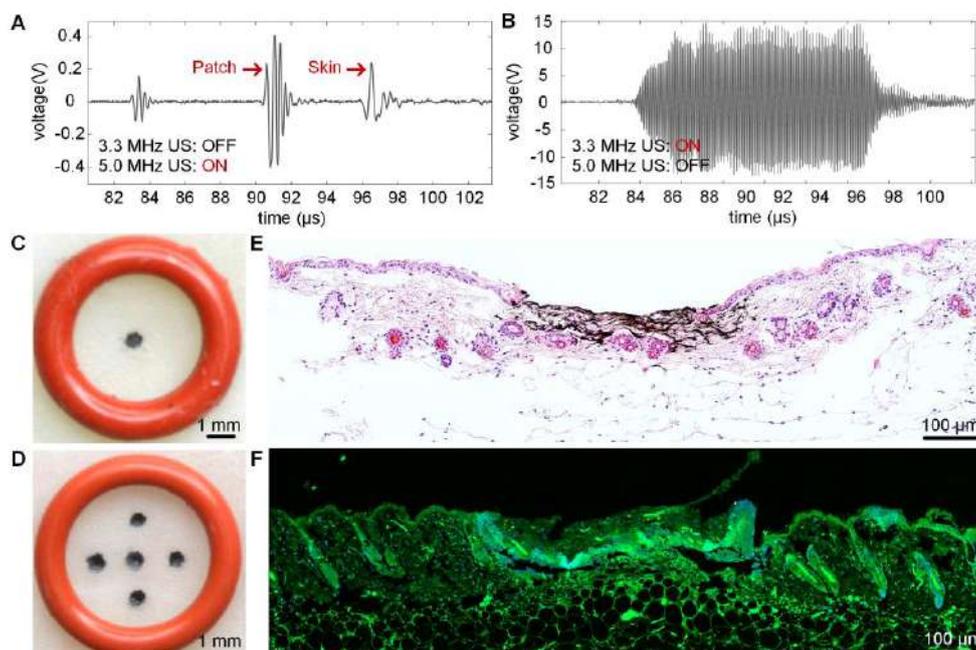
RESULTS

As shown in Figure C, the proposed ultrasound method created a single skin erosion site of sub-millimeter diameter at the center of the patch. Particularly, skin erosion array (5 sites) could also be created to control the total dosage of the delivered vaccine (Figure D). In the H&E staining results, the depth of skin erosions were measured to be less than 200 μ m (Figure E). Immunofluorescence labelling of skin sections showed the number of skin immune cells was increased at the time of 24 hours after immunization. ELISA assay of the blood serum showed that this method triggered the *in-vivo* production of murine antibodies against Hepatitis B.

CONCLUSIONS

Hepatitis B antigens were successfully presented to the murine immune systems via the ultrasound-created skin erosion areas.

CAPTION: ultrasound-mediated skin erosion



OPTIMAL OVERLAPPING PROTOCOL AND ROBUSTNESS ASSESSMENT OF BLOOD-BRAIN BARRIER OPENING IN HUMANS USING A SINGLE-ELEMENT FOCUSED ULTRASOUND TRANSDUCER

Sergio Jiménez-Gambín¹, Noé Jiménez¹, Andrei Marin¹, Francisco Camarena¹

¹ Instituto de Instrumentación para Imagen Molecular, Consejo Superior de Investigaciones Científicas, Universitat Politècnica de València, Valencia, Spain

e-mail: serjigam@upv.es; nojigon@upv.es; ancrism2@alumni.uv.es; fracafe@fis.upv.es

OBJECTIVES

The blood-brain barrier (BBB) restricts the diffusion of therapeutic drugs to the brain. BBB disruption is safely achieved by using focused ultrasound and microbubbles. Single-element transducers can be used to cover a complex and big structure such as the left hippocampus (LH). This numerical study addresses the optimal transcranial targeting of the LH of an adult human with specific transducer positions and its robustness as a potential clinical technique is assessed.

METHODS

k-space method was used to simulate a 500 kHz single-element focused transducer. The skull acoustic properties were obtained from CT-scans and the LH location from a 3D brain atlas. The LH was divided into 2 and 4 parts to optimize the overlapped volume with the number of sonications. Positioning errors of ± 1 mm and ± 1 deg were considered to evaluate the robustness of the technique.

RESULTS

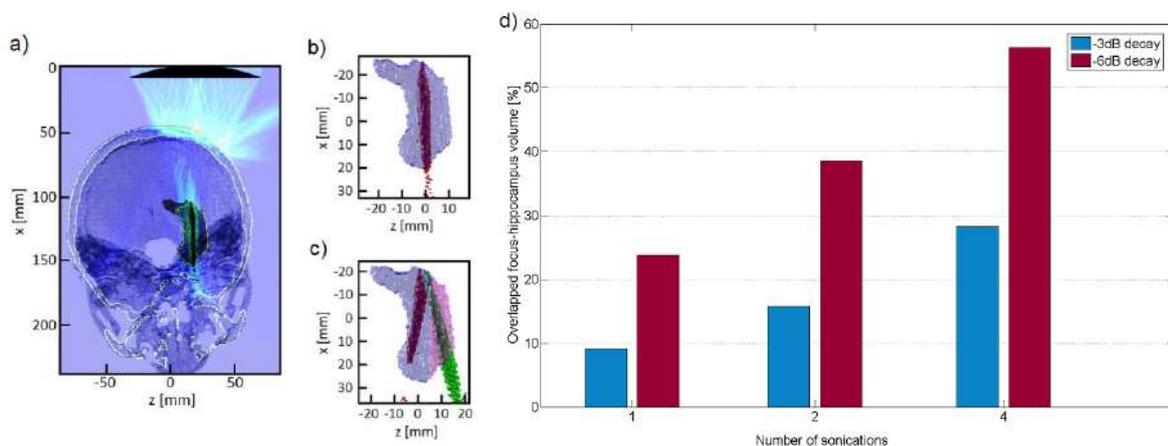
The LH overlapped volume increases with the number of sonications, from 23% (1 sonication) to 57% (4 sonications). The robustness of the system is submillimetric against a positioning error of the transducer of ± 1 mm, and about ± 1 mm when introducing an incidence angle error of ± 1 deg.

CONCLUSIONS

Single-element proposed system has demonstrated the ability to cover high percentage of the LH and targeting errors are submillimetric.

ACKNOWLEDGEMENTS

Supported by Generalitat Valenciana research programs APOSTD/2017/042 and GV/2018/011 and by Europea Union through the Programa Operativo del Fondo Europeo de Desarrollo Regional (FEDER) de la Comunitat Valenciana 2014-2020 (IDIFEDER/2018/022). Supported by Agència Valenciana de la Innovació (INNCON00/18/9).



CAPTION: a) *k*-space simulation including skull and brain; b) one sonication of the LH; c) two sonications of the LH; d) overlapped volume of the LH as a function of the number of sonications.

Accuracy of Acute MR Predictors of Non-Perfused Ablation Volume in Multiple Tissue Types

S.L. Johnson¹, B. Zimmerman¹, H. Odèn², S. Joshi¹, and A. Payne²

¹ Biomedical Engineering, University of Utah, Salt Lake City, USA

² Radiology and Imaging Sciences, University of Utah, Salt Lake City, USA

sara.l.johnson@utah.edu

OBJECTIVES

The study objective is to evaluate the accuracy and optimal thresholds of clinical thermal ablation treatment metrics using voxel-wise analysis of registered MRgFUS ablation treatment response images.

METHODS

VX2 tumor cells were injected into the quadriceps of n=8 New Zealand white rabbits and targeted with MRgFUS (256-element phased array transducer; Imasonic; 940 kHz) one week later for thermal ablation. Treatments were monitored with 3D segmented EPI MR thermometry. Contrast-enhanced T1w (CE-T1w) images were acquired 40 minutes (Day 0) and 3 days (Day 3) after treatment completion. Max Temperature Projection (MTP), and Cumulative Thermal Dose (CTD), and Day 0 CE-T1w non-perfused volume (NPV) maps were registered to Day 3 CE-T1w images using intensity-based elastic registration (registration error=1.2±0.54 mm). After concatenating data from all animals (N_{muscle}=114,185; N_{tumor}=6,050 voxels), Day 0 NPV, MTP, and CTD were evaluated as binary treatment outcome predictors of Day 3 CE-T1w NPV.

RESULTS

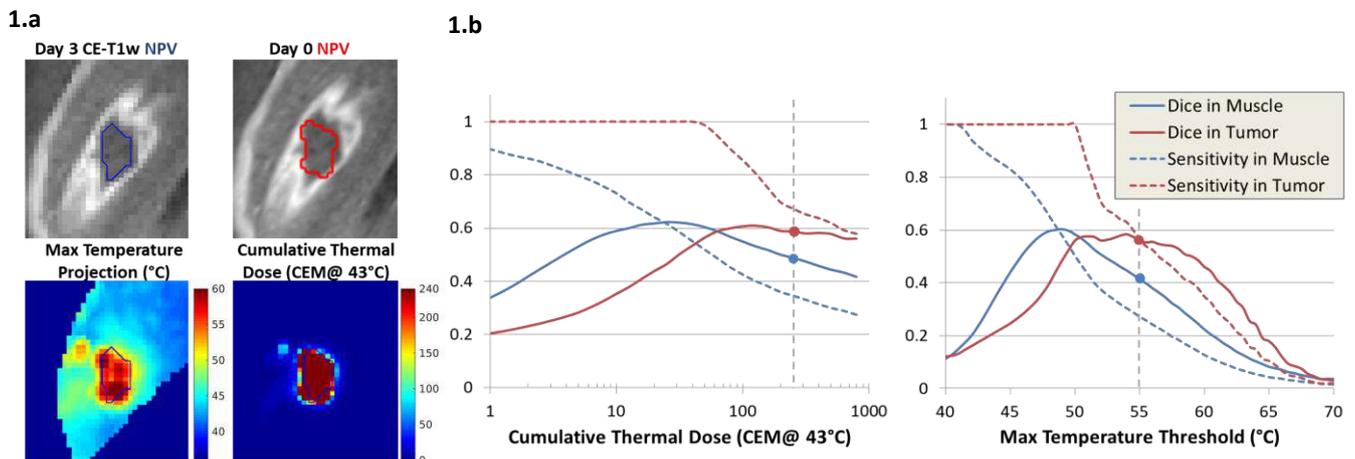
The Dice coefficients for Day 0 NPV, MTP (threshold = 55°C), and CTD (threshold = 240 CEM@43°C) are 0.72, 0.43, and 0.50, respectively. However, the peak Dice coefficients in both muscle and tumor tissues occur at MTP and CTD thresholds lower than the clinically accepted values (Figure 1b), with the optimal damage threshold in muscle being significantly lower than in tumor tissue.

CONCLUSIONS

Though requiring additional scanning time, Day 0 CE-T1w imaging outperformed temperature-based metrics for predicting the final NPV. Damage thresholds for healthy and solid tumor tissue were assessed *in vivo*.

ACKNOWLEDGEMENTS

This work is funded by NIH 5R37CA224141.



CAPTION: 1.a. Example of NPV, MTP, and CTD parameter maps in one animal. **1.b.** Dice and Sensitivity as a function of CTD and MTP threshold values.

NEW FOCUSED ULTRASOUND PROTOCOL TO IMPROVE BLOOD-BRAIN BARRIER PERMEABILITY AND DOXORUBICIN DELIVERY INTO THE TARGETED RAT BRAIN.

Byeongjin Jung¹, Eun-hee Lee¹, Mun Han¹, Juyoung Park^{1, *}

¹ Medical Device Development Center, Daegu-Gyeongbuk Medical Innovation Foundation, Daegu, Republic of Korea

e-mail: jyp@dgmif.re.kr

OBJECTIVES

Despite recent advances in Focused ultrasound (FUS) technique to disrupt blood-brain barrier (BBB) and drug delivery into the targeted brain, the safety and efficiency of drug delivery protocol of the FUS treatment is important. The main object of this study is to achieve safe and efficient BBB permeability and to improve the efficiency of drug delivery by development of an optimal new protocol using MRgFUS system.

METHODS

Two different methods of focused ultrasound were used to disrupt the BBB. The FUS protocol (F) is 0.5, 1.0 or 2.0Mpa, 10ms tone burst, 1Hz pulse repetition frequency and 120sec total duration without microbubble and BBBD protocol (B) is 0.65 or 0.72Mpa, 10ms tone burst, 1Hz pulse repetition frequency and 120sec total duration along with microbubble intravenous injection. The FUS+BBBD protocol (FB), which is the new protocol mentioned here, FUS protocol was applied before BBBD protocol (Figure 1A). Doxorubicin (DOX) concentration was quantified using fluorometric detector after extracting targeted brain regions.

RESULTS

The signal intensity of T1-weighted MR images after Gd-DTPA increased gradually as the power of FUS protocol increased (F 0.5MPa < F 1.0MPa < F 2.0MPa) (Figure 1B and C). In addition, DOX concentration was increased by 1.5 times, 3 times and 3.5 times at F 0.5MPa, F 1.0MPa and F 2.0MPa, respectively (Figure 1D). However, hemorrhage and petechiae was found at 2MPa but no damage at 1MPa (Figure 1E).

CONCLUSIONS

The 1MPa optimal new protocol would be efficient BBB opening and effective drug delivery brain disorders without damages.

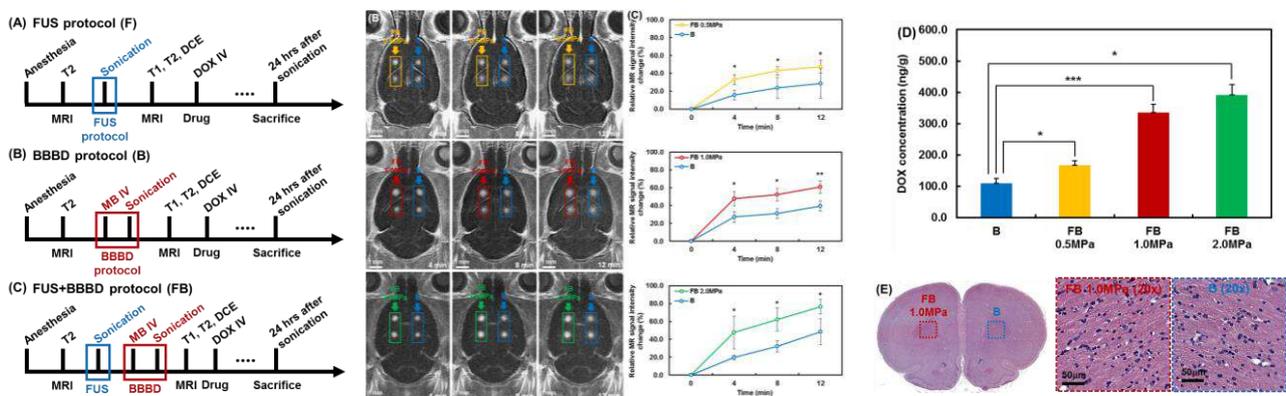


Figure 1: Schedule of each protocol (A), MR images (B), MR signal intensity (C), Doxorubicin concentration (D), H&E staining (E)

Ultrasound-Enhanced Drug Delivery for Treatment of *Acanthamoeba* Keratitis

B. Karpinecz¹, N. Edwards¹, V. Zderic¹

¹Department of Biomedical Engineering, The George Washington University, Washington, DC
e-mail: biancakarpinecz@gwu.edu; natalieedwards@gwu.edu; zderic@gwu.edu

OBJECTIVES

The aim of this study was to determine the effectiveness of using ultrasound to increase transcorneal drug delivery for the treatment of *Acanthamoeba* keratitis using polyhexamethylene biguanide (PHMB).

METHODS

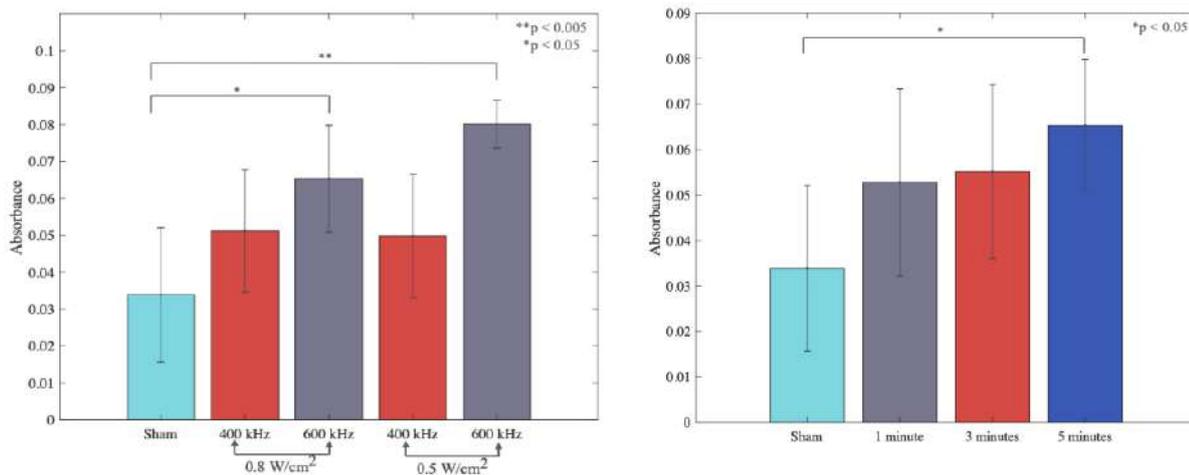
Dissected rabbit corneas were placed in a diffusion cell setup with PHMB. Each cornea was exposed to PHMB for 60 minutes, with the experimental group receiving 5 minutes of ultrasound. Ultrasound transducers were operated at 0.8 W/cm² or 0.5 W/cm² at 400 kHz or 600 kHz and placed at the near field to far field transition distance from the cornea. The 0.8 W/cm² at 600 kHz group was tested with reduced treatment times. Histology slides were used to evaluate structural damage.

RESULTS

Application of ultrasound increased the amount of PHMB passing through the cornea, with the 600 kHz groups reaching statistical significance. At an intensity of 0.8 W/cm², the increase in PHMB concentration in the receiver compartment was 1.51 times for 400 kHz and 1.93 times for 600 kHz. The 0.5 W/cm² group showed an increase of 1.47 times for 400 kHz and 2.36 times for 600 kHz. The 3-minute ultrasound application group showed a 1.63 times increase, while the 1-minute treatment group showed a 1.56 times increase. Some cornea structural changes were observed.

CONCLUSIONS

This study suggests the possibility of ultrasound-mediated drug delivery as an effective and minimally invasive treatment for *Acanthamoeba* keratitis.



Experimental Results: Increases in drug concentration for the 5-minute treatment group (left) and for reduced treatment times (right).

MAPPING CLINICAL HIFU THERMAL TISSUE ABLATION USING SIMULATION AND MR-IMAGING

M.M. Karzova¹, W. Kreider², A. Partanen³, O.A. Sapozhnikov^{1,2}, T.D. Khokhlova⁴, P.V. Yuldashev¹, and V.A. Khokhlova^{1,2}

¹Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Clinical Science, Profound Medical Inc., Mississauga, ON, Canada

⁴Division of Gastroenterology, School of Medicine, University of Washington, Seattle, WA

e-mail: masha@acs366.phys.msu.ru

OBJECTIVES

Clinical MR-guided HIFU is typically applied using strategies that rely on linear ultrasound propagation and heat diffusion to create a uniform ablation zone. In this study, a model for HIFU tissue heating and ablation was developed and validated by comparing the predictions to MR thermometry images obtained during HIFU ablation and to photographs of ablated tissue volumes.

METHODS

The linearized 3D Westervelt equation with boundary conditions obtained from holography measurements was used to simulate acoustic heat sources in tissue. These heat sources were further used with the bioheat equation to simulate temperature fields and volumetric tissue ablation based on a thermal dose of 1.76 seconds at 56°C. Simulations and experiments in *ex vivo* bovine liver on the Sonalleve V2 clinical MR-HIFU system (Profound Medical Inc., Canada) were performed for 1.2 MHz HIFU exposures at 200 W acoustic power, CW irradiation, and trajectories of 24 discrete foci located on concentric rings with radii of 2 and 4 mm. MR temperature maps were acquired during HIFU exposures using the proton resonance frequency shift thermometry method.

RESULTS

MR-based temperature maps and simulations were in good agreement for the dimensions and values of the temperature distributions in tissue for both sagittal (Fig. a) and coronal (b) planes. In addition, the numerically calculated lesion volume of 785 mm³ matched the ablated volume in gross lesion photograph (c), resulting in ablation speed of 2.4 cm³/min.

CONCLUSIONS

A numerical model to predict linear HIFU tissue heating and ablation was developed and validated for use. The model may further allow development and characterization of nonlinear pulsed shock wave exposures with high peak power and low duty cycle to create more precise, predictable, and heat diffusion-independent ablation volumes on clinical HIFU systems.

ACKNOWLEDGEMENTS

Supported by FUSF and NIH R01EB007643.

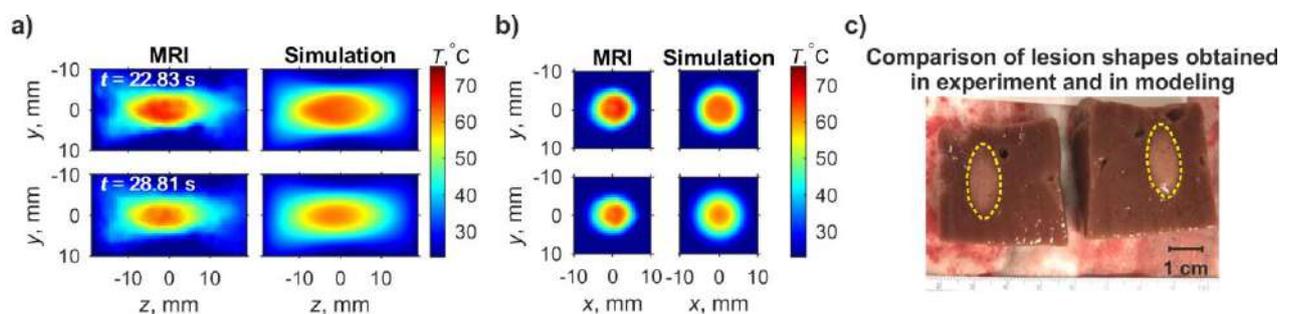


FIGURE CAPTION: Temperature distribution in *ex vivo* bovine liver assessed by MR thermometry and simulation in sagittal (a) and coronal (b) planes at 22.8 s and 28.8 s. (c) Thermal lesions in *ex vivo* bovine liver with superimposed contour of numerically simulated ablated region.

CHARACTERISTICS OF THERAPEUTIC TEMPERATURE MONITORING OF MR-GUIDED FOCUSED ULTRASOUND THERAPY FOR BONE AND JOINT DISEASES

M. Kawasaki^{1,2}, S. Muramatsu², H. Namba², K. Kiyasu², R. Takemasa², M. Ikeuchi², T. Ushida³

¹Pain Medical Center, NHO Shikoku Medical Center for Children and Adults, Kagawa, JP

²Department of Orthopaedic Surgery, Kochi Medical School, Kochi University, Kochi, JP

³Multidisciplinary Pain Center, Aichi Medical University, Aichi, JP

e-mail: kawasaki-koc@umin.net

OBJECTIVES

The aim of this study is to clarify the characteristics of therapeutic temperature monitoring during and after ultrasound irradiations (sonications) of MR-guided focused ultrasound (MRgFUS) for bone and joint diseases.

METHODS

Recorded data of temperature monitoring in 11 patients with bone metastatic pain (BMp) and 13 patients with lumbar facet joint osteoarthritic pain (LFJp), who underwent MRgFUS therapy using the ExAblate 2000 system (InSightec), were retrospectively analyzed. The target temperature irradiated to painful lesions was 60°C for BMp and 55°C for LFJp, while obtaining a real-time thermal feedback using the proton resonance frequency shift method. Frequency of the sonication that the highest temperature reached the target temperature was 134 of total 209 times in the BMp group and 87 of total 147 times in the LFJp group. Location of the highest temperature inside the irradiated area and changes in temperature for 10 seconds after sonication were investigated.

RESULTS

The percentage of sonication that the highest temperature was located deep in the irradiated area was 24.8% of all sonications in the BMp group and 6.9% in the LFJp group. The rate at which temperature remained or increased after sonication was 85.7% of all sonications in the BMp group and 89.7% in the LFJp group.

CONCLUSIONS

Therapeutic ultrasound energies in the treatment for bone metastasis were shown to reach deeper than those in the treatment for lumbar facet joint osteoarthritis. Furthermore, focused ultrasound therapy for bone and joint diseases was found not to cool easily after sonication once bone temperature increased.

ON-DEMAND, TARGETED LIGHT GENERATION IN BIO-COMPATIBLE ELASTOMERS USING HIGH-INTENSITY FOCUSED ULTRASOUND

G. Kim^{1,2}, Q. Wu^{1,3}, A.J. Halmes^{1,3}, J.L. Chu^{1,2}, M.L. Oelze^{1,2,4,6}, J.S. Moore^{1,2,3,5}, K.C. Li^{1,2,6}

¹Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801, United States

²Carle Illinois College of Medicine, University of Illinois at Urbana–Champaign, Urbana, Illinois 61820, United States

³Department of Chemistry, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801, United States

⁴Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois 61801, United States

⁵Department of Materials Science and Engineering, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801, United States

⁶Department of Bioengineering, University of Illinois at Urbana–Champaign, Urbana, Illinois 61801, United States

e-mail: gunkim@illinois.edu; kingli@illinois.edu

OBJECTIVES

Targeted, remote light generation is potentially useful in biomedical applications such as optogenetics where a light source is used to trigger a cellular response. Here we introduce a new HIFU-based platform that exploits polymer mechanochemistry to spatiotemporally control the emission of light.

METHODS

1.5 wt% of covalently incorporated 1,2-dioxetane mechanophore was embedded as a crosslinker in a 5 mm thick PDMS film. Upon scission of the dioxetane, the mechanophore generated an excited state ketone and in the process emitted luminescence. The luminescence was enhanced by an energy acceptor, 9,10-diphenylanthracene (DPA). In a tank of degassed water, a HIFU transducer (550 kHz) was employed to generate continuous wave ultrasound for seven seconds that triggered the prepared dioxetane–functionalized PDMS film.

RESULTS

Blue luminescence (ca. 470 nm) was observed from the PDMS film through remote, non-invasive control by HIFU. However, the measured intensity ($0.2 \mu\text{W}/\text{cm}^2$) was weaker than the reported threshold ($< 2.6 \mu\text{W}/\text{cm}^2$) for optogenetic applications. This low intensity is due to the weakly-dispersible DPA and can be overcome by adopting a more soluble hexyl-functionalized DPA (HDPDA). Incorporating 7.5 wt% HDPDA into PDMS improved the solubility of the energy acceptor and the emitted light intensity by 70-fold, up to $14.3 \mu\text{W}/\text{cm}^2$. This increased intensity is above the threshold and thus promising for optogenetic activation.

CONCLUSIONS

This study demonstrates the promise of HIFU as a stimulus that is capable of on-demand, spatiotemporally resolved mechanoluminescent transduction, which can potentially leverage the advantages of existing optogenetic technology.

ACKNOWLEDGEMENTS

This work is supported by NIH through Grant No.5R01CA184091.

A NEW FREQUENCY DOMAIN PASSIVE ACOUSTIC MAPPING METHOD USING PASSIVE HILBERT BEAMFORMING TO REDUCE THE COMPUTATIONAL COMPLEXITY OF FAST FOURIER TRANSFORM

Pilsu Kim¹, Jae Hee Song², Tai-Kyong Song¹

¹ Department of Electronic Engineering, Sogang University, Seoul, Republic of Korea

² Queensland Brain Institute, University of Queensland, St Lucia Campus, Brisbane, QLD, Australia

e-mail: pskim@sogang.ac.kr; jae.song@uq.edu.au; tksong@sogang.ac.kr

OBJECTIVES

Frequency domain passive acoustic mapping (FD-PAM) is widely utilized for focused ultrasound therapy as a guidance imaging. FD-PAM requires a large number of computation for fast Fourier transforms (FFTs) to produce the frequency components. Here, we propose a frequency domain PAM method using passive Hilbert beamforming (PHB-PAM), which can significantly reduce the number of input samples for FFT.

METHODS

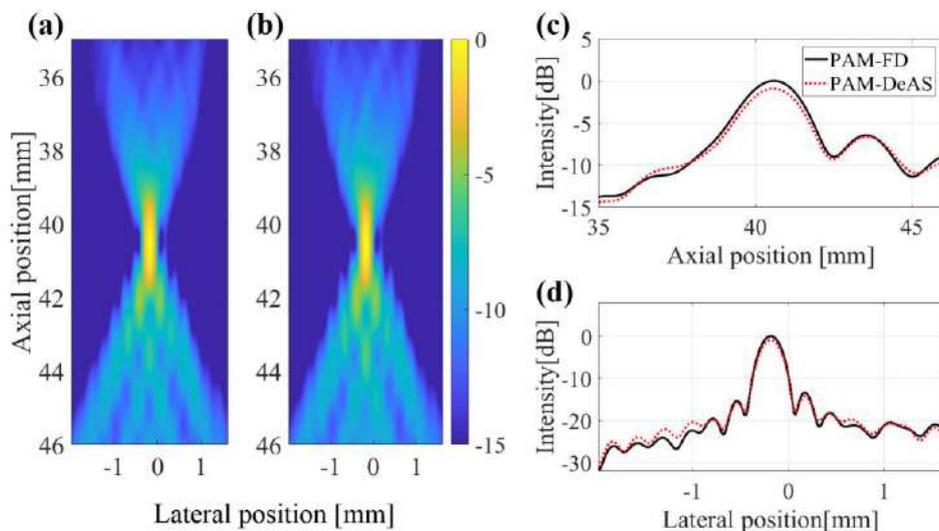
To eliminate redundant calculation for FFT, the PHB-PAM perform decimation using a band-limited analytic signal before FFT execution. The maximum decimation rate M is determined by the sampling rate f_s and the frequency bandwidth (BW) for PAM reconstruction ($f_s/BW \geq M$). In addition, we introduce the frequency conversion and accompanying phase shift methods to perform the passive beamforming using the resultant FFT output. We evaluated the performance of PHB-PAM compared to FD-PAM by varying M from 4 to 128. Moreover, computational complexity was investigated by implementing FFT on single FPGA.

RESULTS

The Figure shows representative results reconstructed by FD-PAM with 2048 samples and PHB-PAM with 32 samples. In spite of reduced samples for FFT, PHB-PAM provides comparable image quality to FD-PAM (2D cross-correlation coefficient = 0.99). In addition, all required hardware resource to generate frequency components was reduced by more than 33%.

CONCLUSIONS

We proposed the PHB-PAM method which provides good image quality with reduced samples for FFT.



CAPTION: PAM images obtained using (a) FD-PAM and (b) PHB-PAM when $f_s = 40$ MHz, $M = 64$, and $BW = 622.5$ kHz. The intensity profiles in the (c) axial and (d) lateral directions.

CAVITATION NUCLEATION BY DEFINITY® INFUSED THROUGH AN EKOSONIC® CATHETER

Maxime Lafond¹, Himanshu Shekhar¹, Nuria Salido¹, Kevin J. Haworth^{1,2}, Alex Hannah³, Curtis Genstler³, Christy K. Holland^{1,2}

¹ Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA

² Department of Biomedical Engineering, University of Cincinnati, Cincinnati, Ohio, USA

³ EKOS Corporation, Bothell, Washington, USA

e-mail: lafondme@ucmail.uc.edu

OBJECTIVES

Concomitant anti-inflammatory infusion and intravascular nucleation agent insonation provides an alternative to drug-eluting stents to prevent restenosis following intervention in arteries. The study objective was to determine if flow dynamics and interaction with a catheter lumen during infusion modifies the nucleation agent and cavitation activity.

METHODS

Acoustic attenuation spectroscopy of Definity® was performed following 0.3, 2.0 and 4.0 ml/min infusions through the drug delivery ports of an FDA-cleared EkoSonic® catheter. Additionally, cavitation activity was assessed in an arterial flow-mimicking model. Intra-vascular transducers (EkoSonic®, EKOS Corp.) were operated at 2.3 MHz, 0.78 MPa peak negative pressure, 15 ms pulse duration, and 18% duty cycle. An L11-5v array connected to a Vantage ultrasound scanner was placed in the transverse plane of the catheter axis. Fifty frames of passively received channel data were recorded for each infusion. Passive cavitation imaging (PCI) was performed by independently beamforming inharmonics (inertial cavitation), ultraharmonics (stable cavitation), and harmonics. Cavitation activity was calculated from the PCI pixel amplitudes within the tube lumen.

RESULTS

Attenuation dropped by 5 dB in the 5–15 MHz frequency range with 0.3 and 4.0 ml/min infusions (Figure 1). At 2 MHz, attenuation decreased by 12, 7, and 9.5 dB for 0.3, 2.0 and 4.0 ml/min infusion rates, respectively. Both 2.0 and 4.0ml/min infusion rates increased stable (+10dB) and inertial (+4dB) cavitation activity compared to the 0.3 ml/min infusion ($p < 0.01$).

CONCLUSIONS

This study demonstrates the nucleation of sustained cavitation from Definity® infused through an EkoSonic® catheter.

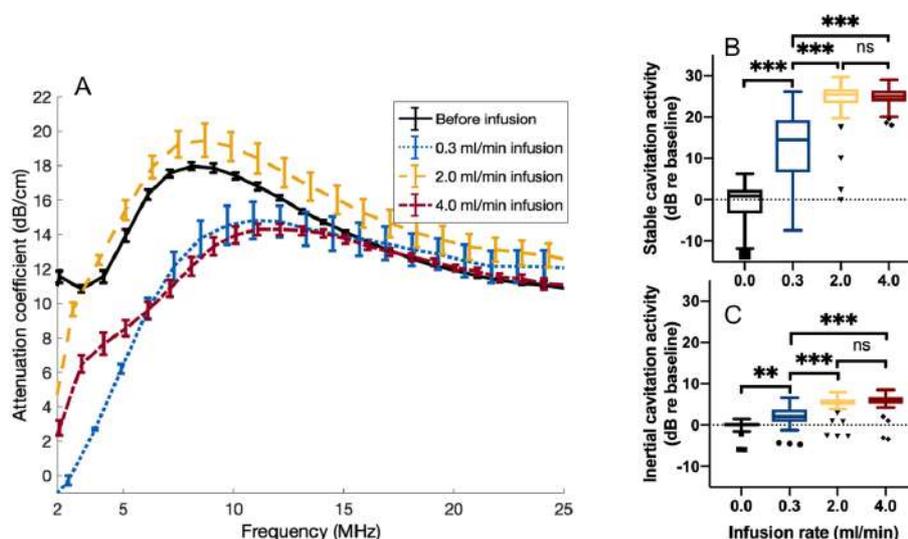


Fig. 1: Attenuation spectroscopy (A). Stable (B) and inertial (C) cavitation measurements.

PELVIC SOFT TISSUE DEFORMATION ESTIMATION FOR PATIENTS IN MAGNETIC RESONANCE GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND (MRGHIFU) TREATMENT POSITIONS

Daniel Lam^{1*}, Ian Rivens¹, Sharon Giles^{2,3}, Emma Harris¹, Nandita de Souza³, Gail ter Haar¹;

¹Therapeutic Ultrasound, Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, United Kingdom

²MRI Unit, The Royal Marsden NHS Foundation Trust, London, UK.

³Cancer Research UK Cancer Imaging Centre, Division of Imaging and Radiotherapy, The Institute of Cancer Research, London, UK.

E-mail: Daniel.Lam@icr.ac.uk

OBJECTIVES

Triaging is required to determine whether a patient is suitable for magnetic resonance-guided high intensity focused ultrasound (MRgHIFU). Typical referral image datasets are obtained for the supine patient. Accurate triaging depends on the ability to estimate patient deformation in the treatment position.

METHODS

Referral (supine on the MR couch) and Treatment (lying angled on a Sonalleve treatment bed) DIXON 3D magnetic resonance image datasets were acquired for 5 volunteers. The datasets were registered using ≥ 12 pelvic bone landmarks. Body outline, fat and non-fatty soft tissues were segmented automatically. Pelvic and femoral bones were segmented manually. Clinically-relevant measures of tissue deformation were defined and quantified. Three simple procedures for prediction of the deformation from a referral image dataset were studied. The difference in geometric accessibility of the tumor with the Sonalleve transducer between the corrected referral image data and that of the (ground-truth) treatment dataset was quantified to judge the effectiveness of each correction -- device and clinical limitations were taken into account.

RESULTS

The best correction achieved no worse than 11% volume disagreement and 7 mm maximum depth disagreement.

CONCLUSIONS

The prediction techniques proposed to estimate deformation for the triage software are suitable in light of simplicity. Triage software development can proceed.

ACKNOWLEDGEMENTS

Research funded by Philips. Technical support was provided by Profound Medical.

Comentado [DL1]: Total wordcount 250 words

DIMINISHED EXPRESSION OF P GLYCOPROTEIN IS ASSOCIATED WITH pJNK-DEPENDENT PATHWAY AFTER BLOOD-BRAIN BARRIER DISRUPTION INDUCED BY MRI-GUIDED FOCUSED ULTRASOUND

Eun-Hee Lee¹, Hyo Jin Choi¹, Mun Han¹, Juyoung Park^{1, *}

¹ Medical Device Development Center, Daegu-Gyeongbuk Medical Innovation Foundation, Daegu, Republic of Korea

e-mail: jyp@dgmif.re.kr

OBJECTIVES

P-glycoprotein (P-gp) is a major huddle for drug delivery and highly expressed at the blood-brain barrier (BBB). Previous studies have shown that the down-regulation of P-gp expression was induced by focused ultrasound (FUS)-mediated BBB disruption (BBBD), but the precise molecular mechanism involved remain unclear. This study aimed to investigate the transcriptional and translational regulatory mechanisms of P-gp after FUS-BBBD.

METHODS

The BBB was disrupted in twelve target-points with ultrasound beams combined with microbubble. Blood vessel was isolated and assessed P-gp expression in protein and RNA level using quantitative real-time PCR and immunoblot analysis. Immunofluorescence was performed to determine activation of JNK in the BBB-disrupted vessel comparing with non-sonicated contralateral vessel.

RESULTS

The extent of BBB disruption was acquired by T1-weighted images after Gd-DTPA administration. The signal enhancement of target regions was gradually increased over-time (Figure 1A). When the BBBD was produced by MRgFUS, P-gp was expressed the lowest level at 24 hours both RNA and protein. Pearson's correlation analysis showed a significant positive correlation between P-gp mRNA and protein expression levels (Figure 1C). In addition, it was found that pJNK was strikingly activated in BBB disrupted blood vessel compared with its contralateral region (Figure 1D).

CONCLUSIONS

P-gp expression of cerebral blood vessel can be temporarily modulated by MRgFUS. Our data suggests that pJNK signaling pathway may be involved in transcriptional and translational regulation of P-gp.

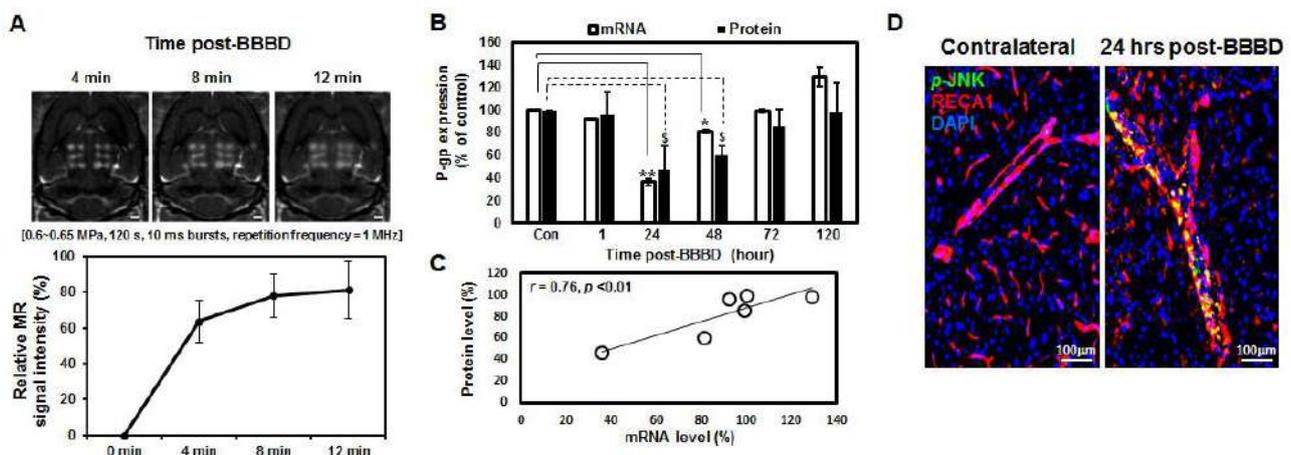


Figure 1: MR images and MR signal intensity (A) and the correlation of the mRNA and protein expression level of P-gp (B, C), Immunostaining of pJNK/RECA1 (D).

COMPARISON OF RAY TRACING AND HYBRID ANGULAR SPECTRUM PHASE CORRECTION METHODS ON FOCAL SPOT PRESSURE

S.A. Leung¹, T.D. Webb², D. Moore³, J. Snell^{3,4}, K. Butts Pauly^{1,2,5}

¹Department of Bioengineering, Stanford University, Stanford, California, USA

²Department of Electrical Engineering, Stanford University, Stanford, California, USA

³Focused Ultrasound Foundation

⁴Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA

⁵Department of Radiology, Stanford University, Stanford, California, USA

E-mail: stevenleung@stanford.edu

OBJECTIVES

Currently, brain ablation treatments use a ray tracing algorithm to phase correct aberrations due to skull. Prior studies have shown that simulation methods perform well for phase correction. However, they take many hours to run. The hybrid angular spectrum (HAS) method requires substantially less compute time, often running 100x-1000x faster than FDTD and PSTD methods. This study aims to evaluate the performance of the HAS method for phase correction.

METHODS

A degassed human skull was attached to a skull holder, which in turn was secured to an InSightec Exablate 4000 head transducer. Elements were fired individually and their signals measured with an Onda HNA-0400 hydrophone. Recorded signals were computationally phased and summed to achieve the resulting focal spot pressure.

A CT scan of the skull was performed on a GE system at 120 kVp using the boneplus reconstruction kernel. A skull model was generated from the CT images and assigned acoustic properties using the parameter set from Leung *et al.* 2018. The ray tracing and HAS methods were used to estimate phase corrections using the skull model. Hydrophone phase corrections were estimated using the measured data.

RESULTS

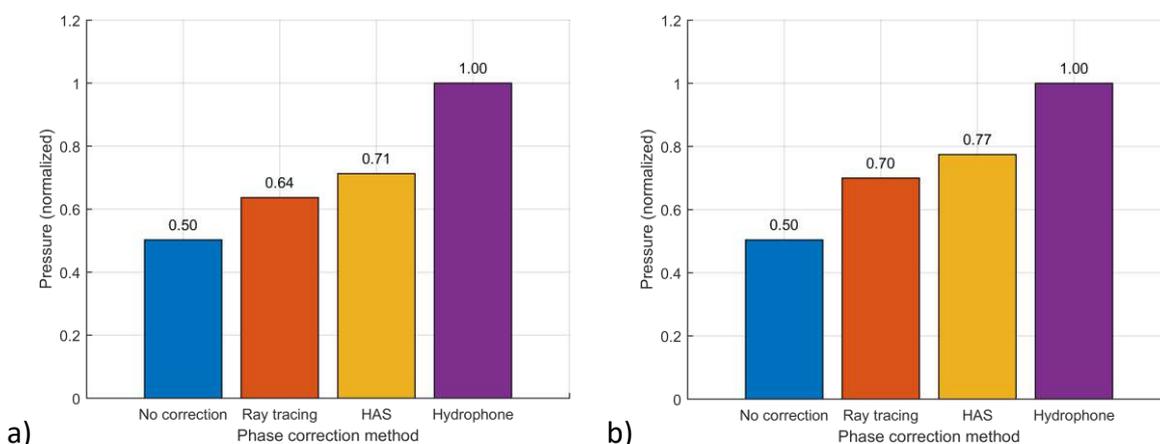
Results from two skulls are shown below. Compared to ray tracing, HAS resulted in a focal spot with a 11% and 10% increase in pressure for skulls A and B, respectively, which is equivalent to a 23% and 21% increase in intensity.

CONCLUSIONS

The HAS method is a promising method for phase correction.

ACKNOWLEDGEMENTS

Supported by InSightec and Focused Ultrasound Foundation.



CAPTION: Focal spot pressure as a result of different phase correction methods. HAS phase correction was more effective than ray tracing for both a) skull A and b) skull B.

Theoretical Simulation and Experimental Study of HIFU Non-Fourier Bioheat Transfer Considering Thermoacoustic Lenses and Thermal Wave Effects

Huan Liu 1, Jihui Liu, Yalu Liu, Chengbin Guo, Qi Wang, Faqi Li*

Department of Biomedical Engineering of Chongqing Medical University, State Key Laboratory of Ultrasound Engineering in Medicine Co-founded by Chongqing and the Ministry of Science and Technology, National Engineering Research Center for Ultrasound Medical, Chongqing 400016, China

e-mail: lifq@cqmu.edu.cn

OBJECTIVES:

To investigate the effects of thermoacoustic lens effect (structured sound velocity, acoustic attenuation with temperature during HIFU irradiation) and thermal wave effect on HIFU heat transfer during HIFU irradiation.

METHODS:

Theoretical simulation and experimental measurements of HIFU fixed-point irradiation (two sets of irradiation parameters of the same irradiation dose of 277320 J/cm^2 : $1039.95 \text{ W/cm}^2 \times 267 \text{ s}$, $1386.6 \text{ W/cm}^2 \times 200 \text{ s}$) focus temperature of fresh isolated bovine liver tissue Rise. Among them, the theoretical simulation is to use the Pennes bioheat transfer equation, the second is to use the thermal wave model of bio-heat transfer (TWMBT) model, and the third is to consider the thermoacoustic lens effect and The cyclic iteration method of the Twmbt model.

RESULTS:

Using the Pennes bioheat transfer equation theory to simulate the HIFU fixed-point irradiation (irradiation parameters of $1039.95 \text{ W/cm}^2 \times 267 \text{ s}$ and $1386.6 \text{ W/cm}^2 \times 200 \text{ s}$), the initial stage of irradiation ($0 \sim 48 \text{ s}$ for The focal temperature rise of $1039.95 \text{ W/cm}^2 \times 267 \text{ s}$, $0 \sim 57 \text{ s}$ for $1386.6 \text{ W/cm}^2 \times 200 \text{ s}$) was significantly higher than the experimentally measured temperature rise. The temperature rise of the focus simulated by the TWMBT model agreed well with the experiment in the initial stage of irradiation, but the maximum temperature rise in irradiation (27°C for $1039.95 \text{ W/cm}^2 \times 267 \text{ s}$, 36.5°C for $1386.6 \text{ W/cm}^2 \times 200 \text{ s}$) is lower than the experimental measurement results (32.5°C for $1039.95 \text{ W/cm}^2 \times 267 \text{ s}$, 41.5°C for $1386.6 \text{ W/cm}^2 \times 200 \text{ s}$). The temperature rise of the focus with the thermoacoustic lens effect and the TMWBT model (32°C for $1039.95 \text{ W/cm}^2 \times 267 \text{ s}$, 42°C for $1386.6 \text{ W/cm}^2 \times 200 \text{ s}$) was consistent with the experimental results throughout the HIFU irradiation.

CONCLUSIONS:

The theoretical simulation and experimental results of HIFU non-Fourier bioheat transfer considering thermoacoustic lens and thermal wave effect are more consistent.

RESPONSE TO PAIN IN THE TREATMENT OF BENIGN THYROID NODULES WITH HIFU

P.P. Ortiz Remacha¹, J. Vidal Jové²

¹Endocrinology specialist. Expert in thyroid pathology. Human Anatomy and Embryology Department, Universidad de Zaragoza, Spain.

²Surgery specialist. Hospital Universitario Mutua de Terrassa, Barcelona, Spain.

e-mail: doctorortizremacha@gmail.com

OBJECTIVES

Assess the efficacy of an oral analgesia protocol in the HIFU treatment of benign thyroid nodules of different sizes.

METHODS

60 patients with benign thyroid nodules (Bethesda Category II) were treated with HIFU (Echopulse® Theraclion). They were grouped in 3 categories by maximal nodule diameter. Group 1: nodule diameter between 14 and 20 mm; Group 2: between 21 and 30 mm; Group 3: over 30 mm. All patients followed the same pre-treatment oral analgesia protocol: Lorazepam 1 mg + Paracetamol 1.000 mg + Dexketoprofene 25 mg). Assessment was made using a categorical 6-grade scale (CS).

RESULTS

Patients describe pain as “tolerable” in 50% of cases. In 30% of cases pain is marked as “almost intolerable”, which needed to lower the delivered power by 5-10 W. Lastly, in 20% of cases pain was marked as “intolerable” leading the treatment to finalize without being totally performed.

Pain sensitivity does not depend on the nodule size, but is less and less tolerated for Group 3 nodules of longer treatment durations, as oral analgesia efficacy decreases in time.

CONCLUSIONS

Treatment of benign thyroid nodules with HIFU is painful. Other countries perform total anesthesia, conscious sedation, or relaxation. Our protocol for oral analgesia is successful for nodules that do not require long treatment times, and on patients that feel relaxed and have a better self-control management. Sedation should be offered for patients with previous intense pain experience in order to finalize a 2nd treatment.

TRANSCRANIAL TEMPERATURE RISE COMPARISON THROUGH PHASE CORRECTIONS OF EMBEDDED EXABLATE FUNCTION AND KRANION SOFTWARE

D.-G. Paeng^{1,2,3}, J. Snell^{2,4}, D. Moore², C. Jin⁵, J. Lee¹, M.Eames²

¹Ocean System Engineering, Jeju National University, Jeju, Korea

²Focused Ultrasound Foundation, Charlottesville, VA, USA

³Radiation Oncology, ⁴Neurological Surgery, University of Virginia, Charlottesville, VA, USA

⁴Robotics Engineering Department, DGIST, Daeju, Korea

e-mail: paeng@jejunu.ac.kr; jsnell@fusfoundation.org

OBJECTIVES

This study is to measure temperature rise at the focus of the phantom through an ex-vivo human skull and to compare them between two phase correction methods, one in using the ExAblate 4000 software (InSightec, Israel) and the other using Kranion software. Kranion software was developed as a 3-dimensional visualization tool based on acoustic ray theory mainly for transcranial focused ultrasound planning. Our previous hydrophone measurements showed the equivalent peak negative pressures, 0.77 and 0.78 MPa in one plane and 1.24 and 0.91 MPa in the orthogonal plane targeting the center, and 1.09 and 1.19 MPa and 1.85 and 1.31 MPa targeting 1 cm left of the center, for ExAblate-based and Kranion-based phase corrections, respectively.

METHODS

The ExAblate 650 kHz FUS transducer was positioned vertically with an ex-vivo human skull mounted on a purpose built frame with phantom material placed at the focal area inside the skull. ExAblate-based and Kranion-based phase correction files were read into the ExAblate CPC and the transducer array elements were driven by the two phase corrections with a fixed amplitude. Temperature rise was measured at two focal positions in the phantom, the geometrical center and 1 cm left of the center using MR thermometry. The power was varied over 4 levels from 88 W to 600 W for 15 and 30 seconds to compare the resulting temperature.

RESULTS

Kranion-based phase correction resulted in 2 to 3°C lower peak temperature rise at the geometrical center in the phantom inside the skull cadaver compared to the ExAblate-based phase correction for all energy levels from 2320 J to 9000 J. At the off-centered target, the peak temperature rise by Kranion-based correction was lower by 2°C in lower energy but the difference was larger by up to 6°C for higher energy. The peak temperatures by ExAblate-based phase correction were similar (< 1 °C) between two focal positions for all energy levels, but temperature rises by the Kranion-based calculation at higher energies were much lower for off-centered target though starting temperature rise was the same below 3000 J.

CONCLUSIONS

The lower temperature rise (2 to 3°C) at the geometrical focus by Kranion-based phase correction compared to ExAblate-based phase correction is mainly due to lower peak pressure. Further research is required for this lower peak pressure and temperature, off-centered target case, and compensation methods.

ACKNOWLEDGEMENTS

Supported by Focused Ultrasound Foundation.

A CLINICAL SYSTEM FOR NON-INVASIVE BLOOD-BRAIN BARRIER OPENING USING A NEURONAVIGATION-GUIDED SINGLE-ELEMENT TRANSDUCER

A.N. Pouliopoulos¹, S.W. Wu¹, M.T. Burgess¹, M.E. Karakatsani¹, H.A.S. Kamimura¹, E.E. Konofagou^{1,2}
¹Department of Biomedical Engineering, ²Department of Radiology, Columbia University, NY, USA.
email: a.pouliopoulos@columbia.edu; ek2191@columbia.edu

OBJECTIVES

Blood-brain barrier (BBB) opening clinical trials using focused ultrasound (FUS) are conducted with either an implanted transducer or a multi-element array within an MRI system. Here, we describe a clinical system based on a neuronavigation-guided FUS transducer that can achieve a large treatment envelope non-invasively while eliminating the need of on-line MRI.

METHODS

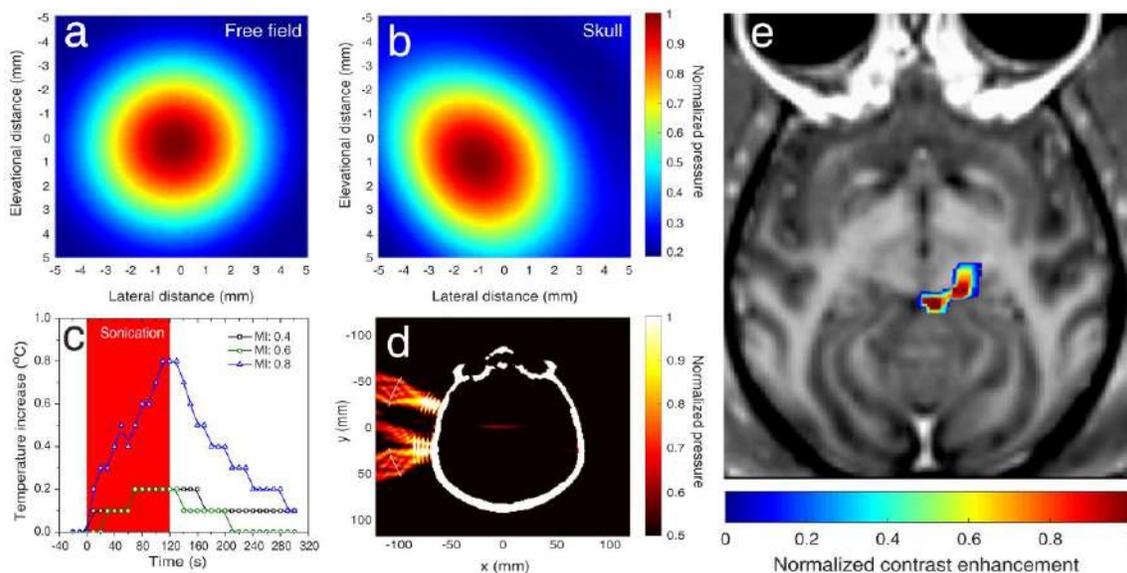
A 0.25-MHz, single-element FUS transducer was developed for clinical BBB opening applications. Human skull-induced beam aberrations and temperature increase were estimated during therapeutic sonication (MI: 0.4-0.8). K-Wave simulations were performed to determine whether the system was able to reach the human brain midline. *In vivo* feasibility was shown in a non-human primate (NHP) at MI of 0.4 (PL: 10 ms, PRF: 2 Hz) and 1x Definity microbubbles.

RESULTS

Numerical simulations showed that the system can target the human midbrain. Transcranial transmission through a human skull caused a 1-mm lateral and 3-mm axial focal shift. A temperature increase of 0.2-0.8°C was measured within the MI range of 0.4-0.8. Contrast-enhanced T₁-weighted imaging revealed a 150 mm³ BBB opening in the NHP caudate at a MI of 0.4, without damage as assessed by susceptibility- and T₂-weighted imaging.

CONCLUSIONS

The neuronavigation-guided, single-element FUS system transcranially induced a safe BBB opening in a NHP brain with minimal distortion at clinically-relevant ultrasound parameters and FDA-approved Definity microbubble dosage.



CAPTION: a)-b) Beam transverse profile in free field and through a human skull. c) Skull heating. d) Numerical simulations of ultrasound propagation through a human skull. e) BBB opening at MI of 0.4 and Definity microbubbles at clinical dose.

SIMULTANEOUS MR THERMOMETRY AND ACOUSTIC RADIATION FORCE IMAGING OF HIFU TREATMENT BASED ON ECHO-SHIFTED SEQUENCE

Yangzi Qiao¹, Chao Zou¹, Xin Liu¹, Hairong Zheng¹

¹Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China
 e-mail: yz.qiao@siat.ac.cn; chao.zou@siat.ac.cn; xin.liu@siat.ac.cn; hr.zheng@siat.ac.cn

OBJECTIVES

Simultaneous MR thermometry (MRT) and acoustic radiation force imaging (ARFI) based on echo shifted (ES) sequence was proposed to monitor the high intensity focused ultrasound (HIFU) treatment. The proposed method provided a real-time monitoring of transient acoustic property change and temperature rise simultaneously within 4 seconds.

METHODS

Echo-shifted (ES) sequence delays the collection of echo by one TR (Fig.1(a)). Crusher gradient C (Fig.1(a)) after imaging gradient can be used for displacement encoding. Meanwhile ES was intrinsically sensitive to temperature. All experiments were conducted on 3T MR system (uMR790, United Imaging Healthcare, Shanghai, China). The *ex vivo* porcine samples were sonicated by an MR-compatible HIFU transducer (0.8MHz, Imasonics, France). HIFU pulses were interleaved off/on in the successive TRs to separate the phase change induced by displacement from that induced by both displacement and temperature. The imaging parameters were: TE/TR = 6.4/15.3ms, Resolution = 2.0*2.0*5.0mm³, FA = 10°, C = 198.8mT/m*ms, T_{offset} = 3ms. The total acquisition time of a pair of images was 3.9s.

RESULTS

The acquired temperature change and displacement at focus was given in Fig. 1(b). The max temperature change induced by HIFU pulse was 18.2° C. While the acquired displacement slightly increased from 7.98 to 8.75μm. The displacement and temperature map acquired during HIFU on was shown in Fig. 1(c) and (d). The two maps were in good accordance with each other.

CONCLUSIONS

ES sequence can provide a fast and simultaneous temperature and displacement measurement during HIFU ablation.

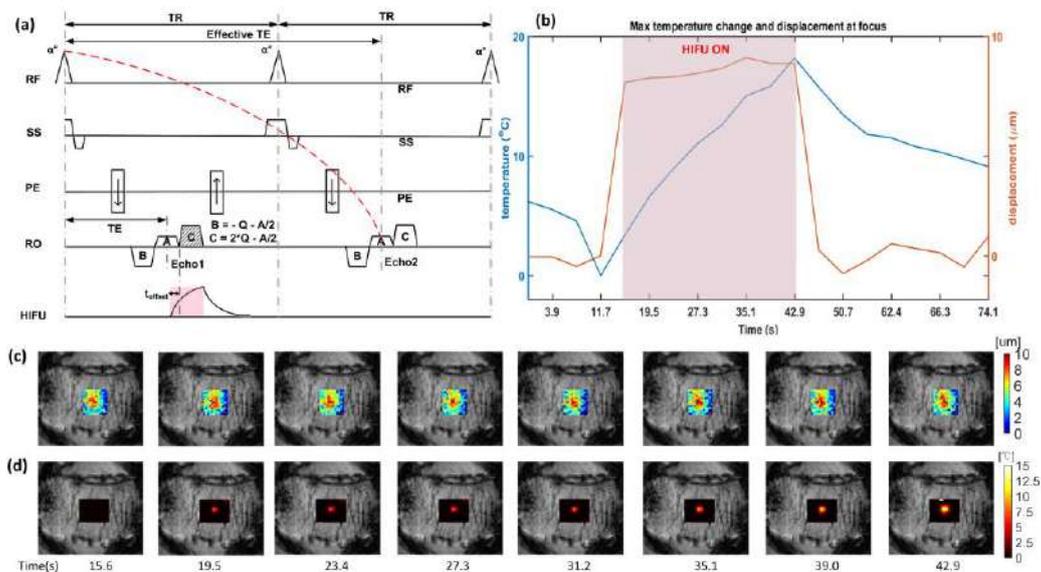


FIGURE 1: (a) The echo-shifted sequence; (b) the calculated temperature change and displacement at focus. (c) the displacement map and (d) the temperature map acquired during HIFU on

Body Mounted Robot for High Intensity Focused Ultrasound

Kevin Cleary¹, Reza Monfaredi¹, Pavel Yarmolenko¹, Karun Sharma¹, Niravkumar Patel², Iulian Iordichita², Andrew Dennison³, Lukasz Priba³, Andreas Melzer³

¹Children's National Health System, Washington, DC, USA

²Laboratory for Computational Sensing and Robotics (LCSR), Johns Hopkins University, MD, USA

³Institute of Medical Science & Technology, University of Dundee, Dundee, UK

A prototype concept for a body mounted robot for high intensity focused ultrasound was tested in a cadaver study at the University of Dundee. A single annular array transducer was attached to a four degree MRI compatible robot. The robot was mounted to the lumbar spine using straps. The robot was able to manipulate the transducer probe to different angles to simulate focused ultrasound treatment. Future work will be to refine the concept.

Methods: The body-mounted robot used for this study provides 4 degrees-of-freedom for positioning and orienting the needle guide to a prescribed needle trajectory; it is manufactured from materials compatible with the MRI environment and does not affect the image quality. The robot is registered to the scanner coordinate system using fiducial markers attached to the robot base and then based on the prescribed target and skin entry points, it aligns the needle guide to the planned trajectory. The robot has shown a targeting accuracy of 2.08 mm in MRI phantom studies. Thiel embalmed cadavers from the University of Dundee Anatomy Department were used for this study. Thiel embalmed cadavers offer significant advantages over traditional formalin embalmed and fresh cadavers including improved tissue flexibility, texture and tone, low infection risk and odor. Imaging was performed with a 1.5T GE Signa HDx scanner (GE, Milwaukee, USA) using a 5CH DuoFLEX phased array coil (24cm paddle combined (4CH) with an interventional loop coil (1CH) at the Institute for Medical Science and Technology. A mounting ring was strapped on the shoulder and hip with the square paddle underneath the cadaver and the loop coil around the mounting ring. 3D-volume Fast Spin Echo (3D CUBE) images were acquired for registration of the robot with the image space, planning needle insertion trajectory and needle placement confirmation post insertion.

Results: On one female and one male cadaver, a total of 13 targeting attempts were made to position an 18 gauge cannula and finally the FUS transducer. For targeting spine facet joints Level L2-L5 the robot was registered to the scanner coordinate system only for the first attempt and then the same registration was used for the remaining attempts. All attempts were successful with an average procedure time of 20 minutes. However, for the first targeting attempt, the total time was more than 1 hour as it involved the complete clinical workflow including robot attachment, registration to the scanner coordinate system, learning curve for the robot assisted trajectory planning and contrast agent injection. For the remaining 9 targeting attempts, the average time was 12 minutes. In future studies we want to optimize the clinical workflow to reduce the total procedure time to less than 1 hour.

Conclusions: The study showed the feasibility of using the robotic device but identified issues that must be resolved before moving to clinical trial, particularly in terms of robot mounting and mounting the FUS transducer.

Funding Sources: This work is supported by the National Institutes of Health (NIH) grant EBO20003. The IMSaT MRI surgical Suite has been supported by the European Commission ERDF program and by the Norther Research Partnership (NRP) of Scotland.

A MRI Compatible Large Scale Array System for Low Intensity Therapeutic Ultrasound

Juan Zhou, Jincheng Li, Haibo Zhong, Xudong Shi, Guofeng Li, Yongchuan Li, Teng Ma, Xiaojing Long, Hairong Zheng, Weibao Qiu

¹ Institute of Biomedical and Health Engineering, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, 1068 Xueyuan Avenue, Shenzhen 518055, China;

² Shenzhen key laboratory of ultrasound imaging and therapy, Shenzhen 518055, China;

E-mail: hr.zheng@siat.ac.cn; wb.qiu@siat.ac.cn

OBJECTIVES

Neurological diseases such as Alzheimer and Parkinson affect the health of millions of people and are still lacking in treatment. Low intensity ultrasound recently draws substantial attention for non-invasive neurostimulation, which may provide a powerful solution for the treatment of neurological diseases. In addition, Low intensity ultrasound has also been shown for temporarily open the patient's blood-brain barrier (BBB), allowing the drug to reach the brain lesion for treatment. In order to ensure a safe treatment, magnetic resonance imaging (MRI) is usually employed to monitor the temperature and displacement caused by the ultrasound. Therefore, MRI compatible ultrasound system is required for the brain therapy, and it is still not an easy work for the society.

METHODS

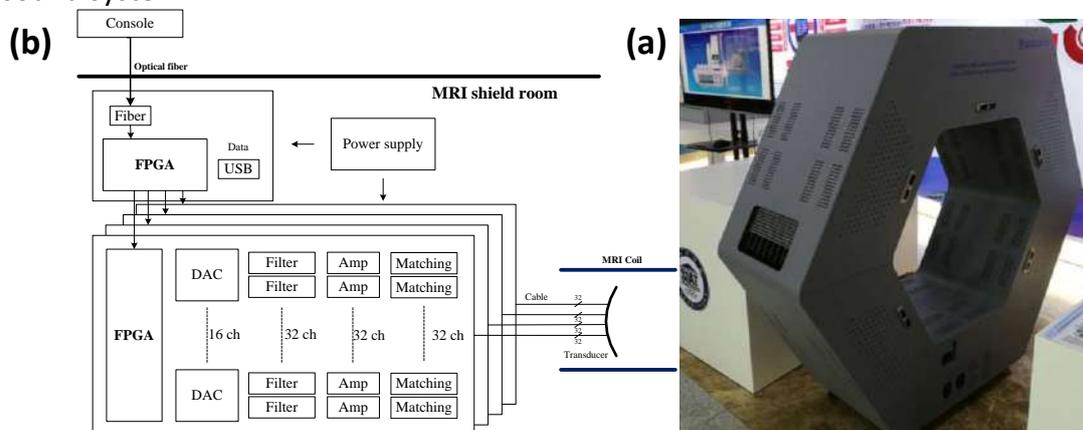
We have developed a MRI compatible ultrasound array system with 1024+ channels for low intensity therapeutic application. The system is implemented by cascading at least eight 128-channel subsystems. The clock synchronization between subsystems is performed through optical fibers, including data loading and signal control. The accuracy of the fiber clock synchronization can be in picosecond level. The system performs beamforming by using the issued parameters to form single or multi-points focus at any positions of the acoustic field by exciting the ultrasound transducer.

RESULTS

The system can generate an acoustic focus at predetermined location under MRI guidance and the acoustic power can be in MPa level. The phase difference errors for all channels are less than 7 ns, which means the phase errors of the proposed ultrasound system are less than 3 degree when the center frequency of transducer is 1 MHz. The system has been applied for primate animal studies.

CONCLUSIONS

A MRI compatible array system has been proposed for low intensity ultrasound therapy. Fiber based clock synchronization scheme has been used, and it offers a good way for large scale ultrasound system.



CAPTION: (a) Block diagram of the ultrasound array system; (b) A prototype of 1024-channel ultrasound array system.

Volumetric and rapid MR-Acoustic radiation force imaging using simultaneous multislice imaging (SMS)

Pierre Bour^{1,2,3}, Valéry Ozenne^{1,2,3}, Stanislas Rapacchi⁴, Rainer Schneider⁵, Franck Mauconduit⁶, Wadie Ben Hassen⁶, and Bruno Quesson^{1,2,3}

¹IHU-LIRYC, PESSAC, France, ²Univ. Bordeaux, Centre de recherche Cardio-Thoracique de Bordeaux, Bordeaux, France, ³INSERM U1045, Bordeaux, France, ⁴Center for Magnetic Resonance in Biology and Medicine - UMR 7339, Marseille, France, ⁵Siemens Healthcare, Saint-Denis, France, ⁶Siemens Healthcare, Erlangen, Germany

OBJECTIVE

In this work, we have investigated the benefits of simultaneous multislice acquisitions to monitor volumetric temperature and displacement information at the focus. The potential artifacts induced on focus definition due to different acceleration factors was investigated.

METHODS

We integrated a bipolar Motion Encoding Gradient to encode micrometric tissue displacement in a simultaneous multislice single shot gradient-echo echo-planar imaging sequence. Sequence parameters were: 12 slices, 10% gap, FOV = 260x260 mm², spatial resolution = 2.3x2.3x3 mm³, TE/TR/FA = 36 ms/101 ms/60°, GRAPPA 2, 6/8 partial, Fourier and pixel bandwidth = 1955 Hz/pixel. HIFU protocol: ARFI pulse duration = 7 ms, acoustic power = 220 W. Validation was performed on fresh ex vivo pig samples.

RESULTS

The temporal resolutions for acquiring the 12 slices were 1130 ms, 608 ms, 408 ms and 309 ms for SMS = 1,2,3 and 4, respectively.

The displacement profile dimensions along X, Y and Z axis (see figure 1b), measured at half the maximum displacement amplitude were [5.9, 6.0, 5.6, 5.7], [5.9, 5.8, 5.9, 5.8] and [20.6, 20.4, 18.4, 18.6] mm, for MB = [1, 2, 3, 4], respectively.

CONCLUSIONS

The study demonstrates the feasibility of sub-second volumetric monitoring of tissue displacement using slice-acceleration and GRAPPA. ARFI focus size was preserved for acceleration factors 1 up to 4.

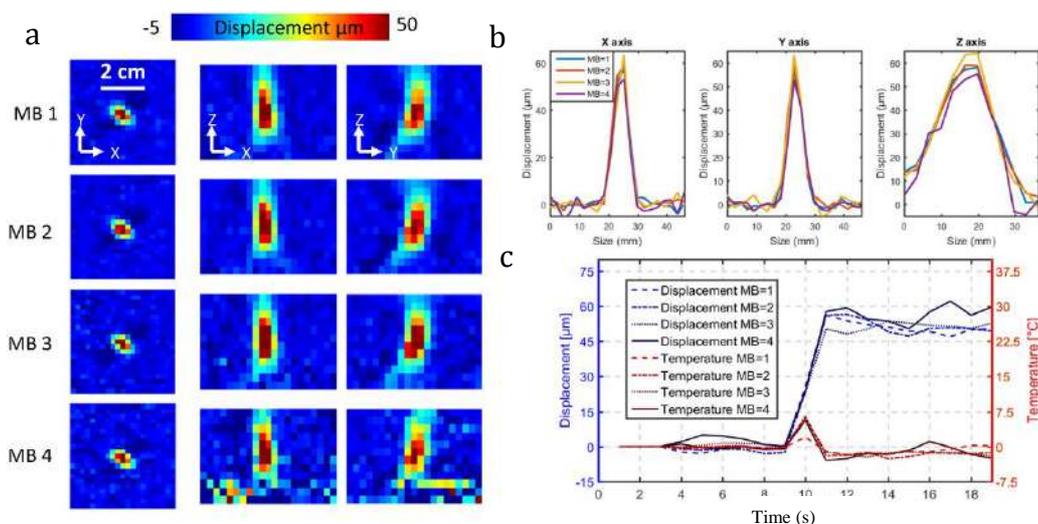


Figure 1: A) shows displacements at the focus in three orthogonal directions. B) Displacement profiles of the focus along X, Y and Z axis. C) Displacement and temperature monitoring for a pixel at the focus.

REPEATED SCANNING ULTRASOUND IMPROVES MOTOR FUNCTION AND CLEARS NEURONAL TAU BY AUTOPHAGY IN TAU TRANSGENIC MICE

J. H. Song¹, R. Pandit¹, G. Leinenga¹, J. Götz¹

¹Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane QLD 4072, Australia; e-mail: j.goetz@uq.edu.au

OBJECTIVES

Tauopathies are characterized by the intracellular deposition of pathological tau. A major obstacle in developing effective treatments for tauopathies is the blood-brain barrier that restricts access of therapeutic agents to the brain. An emerging technology utilises low-intensity ultrasound with microbubbles to transiently open this barrier. Ultrasound on its own, without a therapeutic agent, has previously been shown by us to reduce amyloid plaques and pathological tau in transgenic mice (Leinenga & Götz, *Science Transl Med* 2015, Nisbet et al., *Brain* 2017). The main objective of this study was to assess the effect of ultrasound on tau transgenic mice with tau-dependent motor and memory deficits.

METHODS

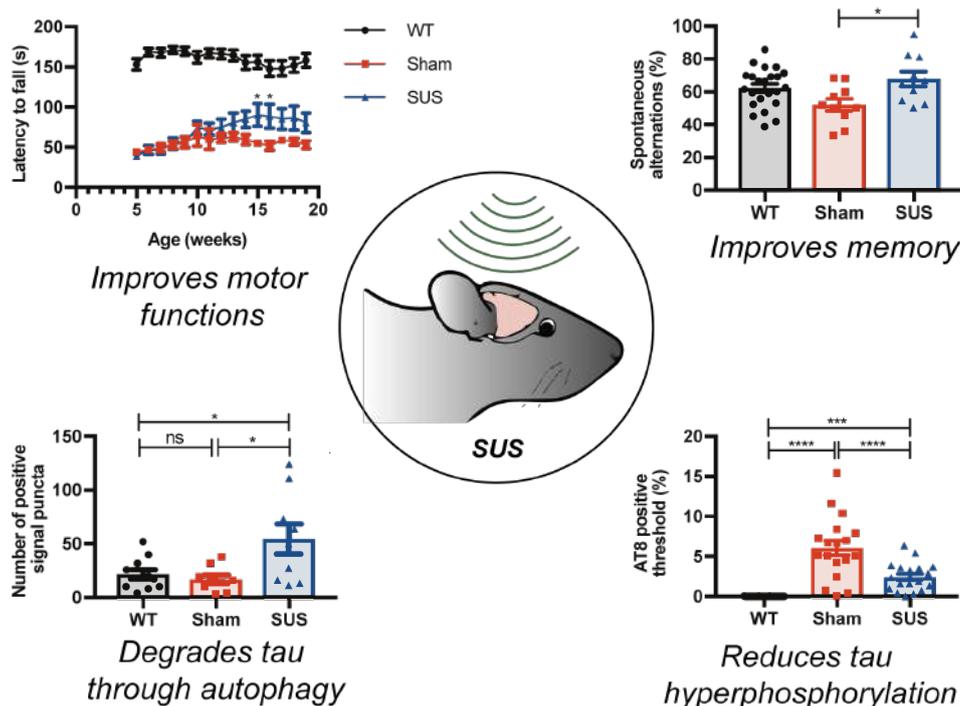
To assess the effect of ultrasound on pathological tau, we performed repeated scanning ultrasound (SUS) treatments over a period of 15 weeks. The effect of repeated SUS treatments on tau pathology was assessed histologically and biochemically, along with analysing motor and memory functions.

RESULTS

The SUS treatment regime significantly reduced tau pathology and improved associated behaviours. As a mechanism of action, we ruled out enzymatic changes and proteasomal tau degradation. We found that ultrasound treatment induced an increase in autophagy in neurons of the treated mice.

CONCLUSIONS

Our findings (Pandit et al, in revision) indicate that repeated ultrasound treatments reduce hyperphosphorylated tau potentially via induction of autophagy in neurons. These results further supports the safety and therapeutic potential of low-intensity ultrasound to treat neurodegenerative disorders.



CAPTION: Effects of scanning ultrasound on tau in tau transgenic mice

NEUROSTIMULATION BY FOCUSED ULTRASOUND IN EX VIVO MOUSE BRAIN SLICES AS MEASURED WITH A MICROELECTRODE ARRAY (MEA) SYSTEM

I.M. Suarez-Castellanos¹, W.A. N'Djin¹, J. Vion-Bailly¹, E. Dossi², A. Carpentier³, G. Huberfeld^{2,4}, J.Y. Chapelon¹

¹ LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, Lyon, France

² Center for Interdisciplinary Research in Biology, Collège de France, CIRB - CNRS UMR 7241 / INSERM U1050, Paris, France

³ Research Laboratory on Advanced Surgical Technologies (LRTCA), La Pitié-Salpêtrière Hospital, Paris 6 Sorbonne University Paris, France

⁴ Neurophysiology department, Sorbonne University, AP-HP, La Pitié-Salpêtrière Hospital
e-mail: ivan.suarez@inserm.fr

OBJECTIVES

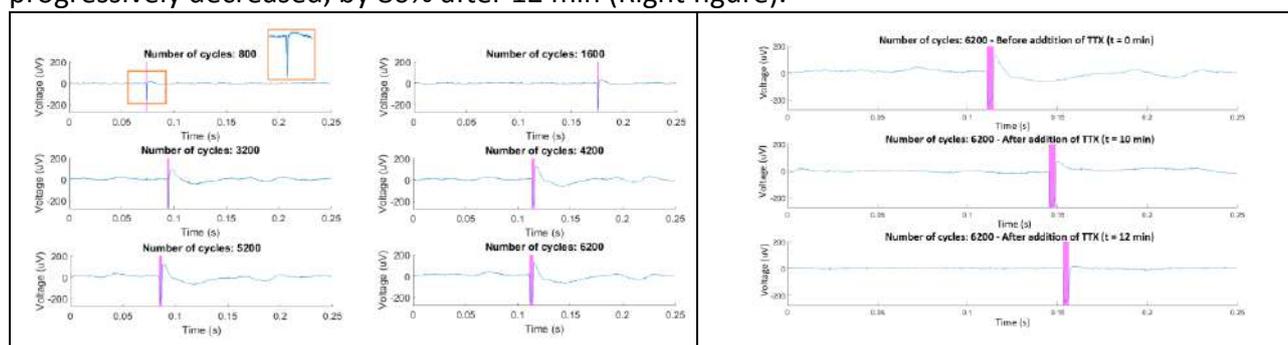
The objective of this project was to study the activities and the underlying cellular mechanisms elicited by Focused Ultrasound (FUS) neurostimulation in *ex vivo* mouse brain slices using a MicroElectrode Array (MEA) System. Here, a proof of concept is presented.

METHODS

A mixed FUS/MEA platform was developed for spatial-temporal recording of neural responses induced by FUS exposures in brain. The FUS system consisted of a 1.78-MHz transducer (\varnothing : 15 mm, R_c : 15 mm). Mouse hippocampal slices were placed in a MEA chip and perfused with artificial cerebrospinal fluid. Low energy FUS (1.1 MPa, 800 – 6200 cycles) was applied before and after perfusion with sodium channel blocker TTX to confirm the nature of the recorded signals.

RESULTS

MEA recordings repeatedly exhibited a characteristic signal composed of a negative deflection associated to FUS-induced artifacts (Vertical pink lines in figures below - duration: 0.5 – 3.5 ms) and a positive deflection, similar to that recorded through electrical stimulation, attributed to neural responses. Neural response magnitudes increased 6-fold (amplitude: 20 – 130 μ V, duration: 1.6 – 5.5 ms) when increasing the number of FUS cycles (800 to 6200). After adding TTX, a blocker of sodium channels sustaining action potential propagation, the magnitude of the response progressively decreased, by 86% after 12 min (Right figure).



CONCLUSIONS

Low energy pulsed FUS can generate neuronal population responses from ex-vivo sliced mouse brains.

ACKNOWLEDGEMENTS

This project was supported by the French National Research Agency (ANR-16-TERC-0017), LabEx DevWeCan, and the Focused Ultrasound Foundation (Centers of Excellence).

Development and characterization of a small animal hyperthermia system

S. Tretbar¹, M. Fournelle¹, D. Speicher¹, F.J. Becker¹, A. Melzer²

¹Ultrasound Department, Fraunhofer IBMT, Sankt Ingbert, Germany

²Innovation Center Computer Assisted Surgery, Leipzig, Germany

e-mail: steffen.tretbar@ibmt.fraunhofer.de

OBJECTIVES

Hyperthermia is known to improve the effect of radiotherapy in cancer treatment. For systematic assessment of the effect of ultrasound, we developed a platform consisting of a multichannel electronics system and different 11x11 element matrix arrays for inducing local hyperthermia in small animal models.

METHODS

The system is a modified version of Fraunhofer IBMT's ultrasound research platform DiPhAS allowing pulse durations up to 50 μ s at up to 1 kHz PRF. The 11x11 matrix arrays (1x1 cm² footprint) were realized by processing the piezoceramic material directly on the PCB used for contacting of the array. The overall dimension (especially the thickness) was a main constraint during design of the transducer. Accordingly, the individual elements were contacted to the PCB through the backing of the array.

RESULTS

A soundfield study showed that a focus with extent of $\sim 1,3 / \sim 6$ mm (lateral and axial FWHM) could be generated at arbitrary locations in the volume with an I_{SPTA} up to 5 W /cm². The measured sound field were in good agreement with the simulations (deviation <10%). For testing of the hyperthermia capabilities of the system, tissue like phantoms (e.g. PVCP) were sonicated and the generation of spatially confined temperature increase by 10°C within < 20 s could be demonstrated.

CONCLUSIONS

A small animal hyperthermia system for generation of local hyperthermia spots was developed and characterized. Its capabilities for generating spatially confined hotspots were demonstrated on tissue-mimicking phantoms.



CAPTION: Integrated 11x11 matrix array for generation of hyperthermia in small animal models

Hepatic Ablation with Robotically Assisted Sonic Therapy (RAST) Through Full Rib Coverage in a Porcine Model

E. A. Knott¹, K. Longo¹, J. Swietlik¹, X Zhang², E. Vlasisavljevich³, Z. Xu⁴, F.T. Lee Jr¹, T.J. Ziemlewicz¹

¹Department of Radiology, University of Wisconsin, Madison, WI, USA

²Department of Pathology, University of Wisconsin, Madison, WI, USA

³Department of Biomedical Engineering, Virginia Tech University, Blacksburg, VA, USA

⁴Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

e-mail: knott2@wisc.edu; zziemlewicz@uwhealth.org

OBJECTIVES

Robotically Assisted Sonic Therapy (RAST) is the automated delivery of histotripsy. The purpose of this study was to determine the feasibility of creating hepatic ablations with a clinical prototype RAST system through full rib coverage.

METHODS

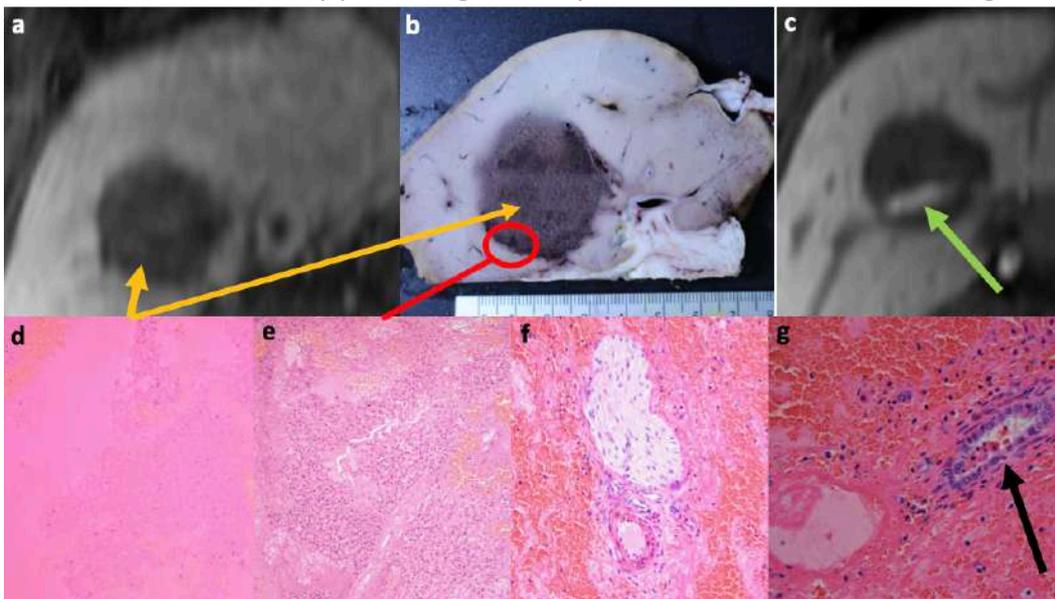
Six female swine were positioned in a left lateral decubitus position and the RAST therapy transducer (Histosonics, Inc.) placed over the ipsilateral ribcage. A 3 cm (14.1 cm³) spherical treatment was created in the right hepatic lobe with continuous ultrasound monitoring. Animals underwent magnetic resonance (MR) imaging and body wall edema and lung injury were scored (0=none, 3=substantial). Swine were then sacrificed, underwent necropsy, and the liver, lung, and body wall (overlying the ablation zone) harvested for histologic evaluation.

RESULTS

Ablation zones were created at an average depth of 7.3 cm and were 13.7 ± 2.0 cm³. Histology demonstrated no viable tissue within the ablation zone with a 2.8 (± 0.2) mm transition zone between complete necrosis and untreated liver. Imaging demonstrated mild chest wall (severity mean score = 1.6 ± 0.8) and lung (severity mean score = 1.0 ± 0.7) injury in 4/5 swine. Histopathology demonstrated no correlative abnormality at the chest wall. Lung histology showed minor hemorrhage in the alveolar space, with bronchioles and blood vessels well-preserved and a sharp transition between this hemorrhagic area and normal lung parenchyma.

CONCLUSIONS

RAST is effective in safely producing clinically relevant ablation zones through full rib coverage.



CAPTION: MRI (a) and gross pathology (b) with complete histological cell lysis (d) and sharp transition between ablation and normal tissue (e). MRI (c) and pathology (g) of intact bile duct within the ablation zone.

Title: Review of Robotic Assisted Sonic Therapy (RAST) in a Large Porcine Model and Implications for Future Development

Authors: Katherine C. Longo MD¹, John Swietlik MD¹, Emily Knott, Amanda Smolock MD PhD², Tim Ziemlewicz, MD¹, Fred Lee, MD¹

¹University of Wisconsin Hospital and Clinics, Department of Radiology

²Jefferson University Medical Center, Department of Interventional Radiology

Email:Klongo@uwhealth.org

OBJECTIVES:

Robotically Assisted Sonic Therapy (RAST) is a non-thermal focused ultrasound therapy utilizing histotripsy. The goal of this exhibit is to describe the developments achieved with this technology to date and to discuss the potential for future applications with RAST.

METHODS:

RAST uses the mechanism of histotripsy to destroy tissue at the cellular level by pressure-induced acoustic cavitation. When histotripsy is combined with motorized micropositioners to allow treatment of a defined volume, it is termed RAST.

RESULTS:

We have performed RAST in 87 porcine models to date (66 liver, 9 kidney, 2 kidney and liver, 4 thymus and 6 fat). In liver and renal models, RAST has been safely used to create 2.5 to 3 cm ablation spheres. Pathologic analysis demonstrates a sharply demarcated acellular tissue homogenate with a thin transition to normal adjacent tissue. RAST has very recently been applied to subcutaneous fat with promising results that are currently under evaluation.

Potential future applications for RAST include pancreatic tumors and uterine fibroids. The tissue selective nature of cavitation caused by histotripsy holds promise for pancreatic tumors where the pancreatic duct limits interventions. RAST may offer the ability to treat uterine fibroids without associated thermal effects seen in currently used HIFU.

CONCLUSIONS:

Robotic assisted sonic therapy (RAST) combines the focused ultrasound treatment modality of histotripsy with robotic micropositioners to perform non-invasive, non-thermal ablations. RAST has been safely applied to porcine liver, kidney, and fat with promising results. Potential future applications for RAST include pancreatic tumors and uterine fibroids.

Synthetic schlieren tomography of focused ultrasound fields

A. Pulkkinen¹

¹Department of Applied Physics, University of Eastern Finland, Finland
e-mail: Aki.Pulkkinen@uef.fi

OBJECTIVES

Synthetic schlieren tomography (SST), or background-oriented schlieren (BOS), is a technique to determine refractive index field distribution in opaque medium. The technique relies on a reference image obtained with medium in its ambient state, and another image obtained with refractive index perturbation. Acousto-optic effect induces said perturbations as a consequence of an acoustic field. In this work, the technique is used to estimate the ultrasound field as produced by a focused ultrasound transducer operating in medically relevant parameter scale.

METHODS

A measurement setup was developed based on a consumer level camera, stroboscopically driven custom circuitry driving a LED light source, and rotational stage for the ultrasound transducer. The setup was used to obtain a tomographic dataset of a ultrasound field radiated by a focused transducer. An approach based on optical flow algorithm, inverse Radon transform, and plane-wave approximation was developed to estimate the ultrasound field based on the images. The results were compared to hydrophone scans.

RESULTS

An estimate of the three dimensional ultrasound field was obtained. Qualitative comparison to hydrophone scans showed good agreement between the fields.

CONCLUSIONS

SST can be used to estimate ultrasound fields and could serve as a cheap technique to perform noninvasive measurements of the field in optical fashion.

ACKNOWLEDGEMENTS

This work has been supported by the Academy of Finland Project No. 286247 and 312342 Centre of Excellence in Inverse Modelling and Imaging.

Gellan gum as a Tissue Mimicking Material for combined HIFU and Radiotherapy

A. Sanchez-Pastor Gomis^{1,2,3}, I. Rivens¹, P. Miloro², C.H. Clark², B. Zeqiri², G. Ter Haar¹

¹Institute of Cancer Research, Sutton, UK

²National Physical Laboratory, Teddington, UK and Royal Surrey County Hospital, Guildford, UK

³University College London, London, UK

e-mail: alberto.sanchez-pastor@icr.ac.uk

OBJECTIVES

As the effects of combined Hyperthermia and Radiotherapy are being explored, gellan gum gels' suitability as a TMM (Tissue Mimicking Material) for the development of dosimetry phantoms for combined Radiotherapy and HIFU (High Intensity Focused Ultrasound) has been studied.

METHODS

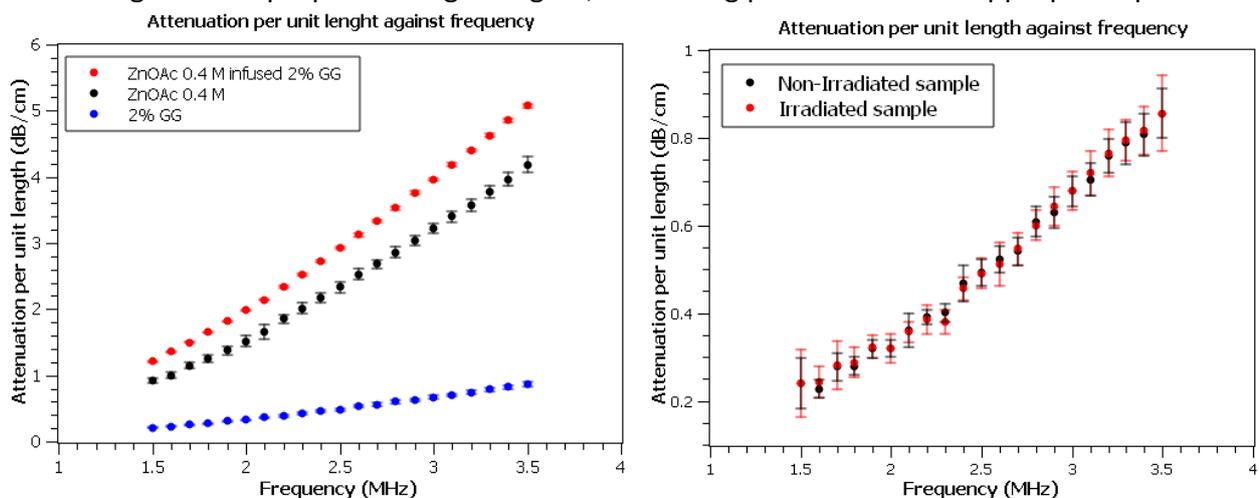
Gellan gum gels have been modified by the addition of zinc acetate, silicon oxide and glycerol in order to match acoustic properties of human tissues. Through-Transmission Substitution method has been used to characterize the acoustic attenuation and speed of sound of the samples. Gels have been measured pre- and post-irradiation with 3 kGy in order to exceed the radiotherapy dose we estimated a dosimetry phantom would receive over a year. The contribution of scatter and absorption to acoustic attenuation has been estimated by using a calorimetric method.

RESULTS

The effects of zinc acetate, silicon oxide and glycerol on the different properties of the gels have been quantified. A comparison of acoustic and thermal properties pre- and post-irradiation will be presented to assess the long term viability of the phantoms.

CONCLUSIONS

Gellan gum, zinc acetate, silicon oxide and glycerol have been characterized sufficiently to allow fine-tuning acoustic properties of gellan gum, facilitating production of an appropriate phantom.



Left: Additivity of attenuation of 2% gellan gum (GG) and zinc acetate. Right: Comparison of attenuation of irradiated and non-irradiated gellan gum

VALIDATING ULTRASOUND BEAM PREDICTION MODELING FOR BREAST TUMOR TREATMENT

M. Dearden^{1,2}, D. Christensen¹, A. Payne²

¹Department of Biomedical Engineering, University of Utah, Salt Lake City, USA

²Department of Radiology and Imaging Sciences, University of Utah, Salt Lake City, USA

e-mail: megan.dearden@utah.edu

OBJECTIVES

This study aims to experimentally validate a rapid ultrasound beam modeling algorithm in heterogeneous tissue-mimicking phantoms.

METHODS

Three heterogeneous phantoms (102x30 mm, 250 bloom, 70% milk) were constructed with a ballistics gelatin recipe containing inclusions of canola oil. Acoustic properties were measured using through-transmission and radiation force techniques. With the phantom placed in the near-field of the ultrasound beam, a scanning hydrophone (Onda, HNR-0500) was used to measure the 2D pressure patterns created at the geometric focus of the focused ultrasound beam (f=940 kHz, 256 elements). Numerical models were created of the phantom using MRI scans, and the experimental data was compared to pressure patterns simulated with the Hybrid Angular Spectrum (HAS) acoustic simulation algorithm.

RESULTS

Representative results are shown. The experimental and simulated peak pressures differed by 6.6% (Figure 1). The average difference for full width half maximum of the beam over all three directions was $14 \pm 8\%$. The root mean square difference normalized was 12.1%.

CONCLUSIONS

HAS is a full-wave acoustic simulation algorithm shown to accurately predict pressure of a focused ultrasound transducer in heterogeneous environments. Because HAS is significantly faster than other acoustic modeling techniques (runs in seconds rather than hours), it is a potentially valuable clinical tool. Experimental validation using magnetic resonance temperature imaging techniques in both phantoms and *in vivo* environments is ongoing.

ACKNOWLEDGEMENTS

This work was funded by NIH 5R37 CA224141.

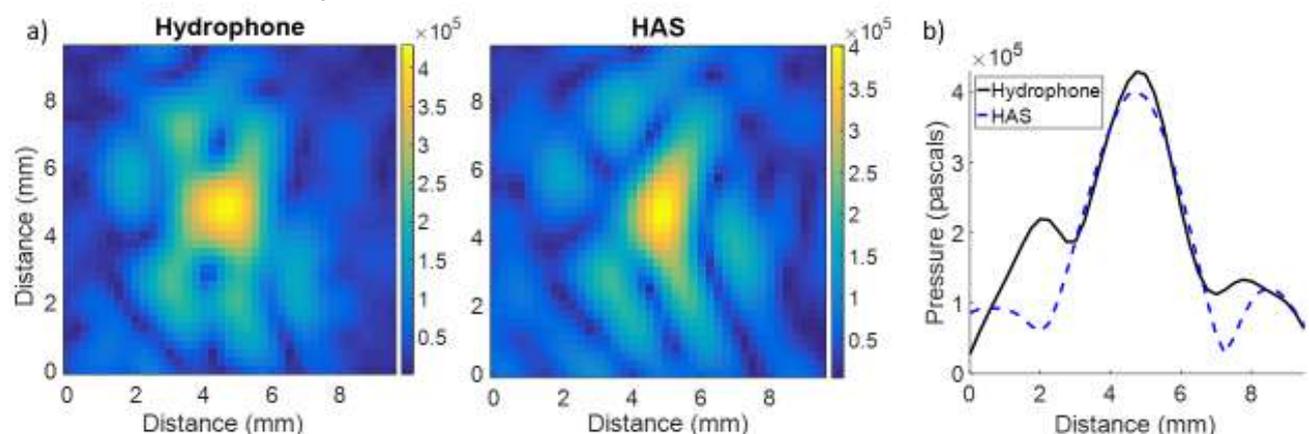


FIGURE 1: Comparison of hydrophone measurement and HAS simulation in (a) transverse plane and (b) transverse peak pressure trace after propagating through a heterogeneous phantom.

MR guided focused ultrasound thalamotomy for Essential Tremor:

A 5 year single center experience

Constantinesco M, Sinai A, Nassar M, Eran A, Schlesinger I.

MRI guided focused ultrasound (MRgFUS) is a new technology that enables VIM thalamotomy through an intact skull for tremor relief. The intracranial target tissue is heated gradually to 55-60°C, while the patient is awake, monitoring for maximal efficacy and adverse events.

We report our experience in treating patients with medication resistant Essential Tremor (ET) over a 5-year period.

Fifty-five ET patients treated with unilateral MRgFUS VIM thalamotomy were assessed using the Clinical Rating Scale for Tremor (CRST) score and the Quality of Life in ET Questionnaire (QUEST). Tremor was significantly improved immediately following MRgFUS thalamotomy in all 55 patients and ceased completely in 26 patients. CRST scores significantly decreased from 45.7 ± 12.8 to 19.6 ± 11.0 at 1 year [$p < 0.0001$]. During a 5 year follow-up period, CRST scores remained significantly improved (19.4 ± 15.6 at 2 years [$p < 0.0001$], 24.1 ± 18.2 at 3 years [$p < 0.01$] and 22.2 ± 21.0 [$p < 0.01$] at 4 years, as compared to baseline). Significant return of tremor was seen in 6 patients. QUEST scores showed significant improvement from 44.8 ± 19.5 to 21.3 ± 22.0 at 1 year [$p < 0.0001$] and remained significantly lower during follow-up. Adverse events were mild and reversible except for 5 patients, 2 with gait ataxia, 2 with hypogausia 1 of them with lip paresthesia and 1 with lip paresthesia. MRgFUS thalamotomy for ET in patients with medication resistant disabling tremor was effective, safe and provided long-term tremor relief with improvement in quality of life. Adverse events were mostly mild and reversible. Additional larger studies are needed to substantiate our results.

ULTRASOUND-INDUCED BLOOD SPINAL CORD BARRIER OPENING IN RABBITS AND MICE

AS Montero^{1,2}, F Bielle³, L Goldwirt⁴, A Lalot⁵, K Beccaria^{2,6}, PF Pradat⁷, F Salachas⁷, S Boillée⁸, C Lobsiger⁸, A Carpentier^{1,2}

1. Sorbonne Université, Neurosurgery department, AP-HP, Hopital de la Pitie Salpetriere, Paris, France.
2. Sorbonne Université, Advanced Surgical Research Technology Laboratory, Paris, France
3. Sorbonne Université, Department of Neuropathology, AP-HP, Hopital de la Pitie Salpetriere, Paris, France.
4. Pharmacology Department, AP-HP, Hopital de Saint-Louis, AP-HP, F-75010 Paris, France
5. Univ Paris Descartes, Laboratoire de Recherches Biochirurgicales, Hôpital Georges Pompidou, Paris, France
6. Université Paris Descartes, Department of Pediatric Neurosurgery, AP-HP, Hopital Necker, Paris, France.
7. Centre de Reference Maladie Rare Département neurologie. Hôpital de la Pitié-Salpêtrière, Paris, France
8. Inserm U 1127, CNRS UMR 7225, Sorbonne Université, UMR S 1127, ICM, F-75013, Paris, France

email : annesophie.montero@live.fr, alexandre.carpentier@aphp.fr

OBJECTIVES

The blood spinal cord barrier (BSCB) considerably limits the delivery and efficacy of treatments for spinal cord diseases. The blood brain barrier (BBB) can be safely and transiently opened with low intensity pulsed ultrasound (LIPU) when microbubbles are simultaneously administered intravenously. This technique was tested on the BSCB in two animal models in this work: rabbit and mice.

METHODS

Twenty-three segments of rabbit spinal cord and 42 segments of mice spinal cord were sonicated with unfocussed LIPU and compared to non-sonicated segments as controls. BSCB disruption was assessed using quantitative measurement of Evan's blue dye (EBD). Tolerance was assessed by histological and clinical analysis. Multiple sonications (up to 10) were repeated with clinical and histological evaluations to evaluate a potential cumulative toxicity.

RESULTS

An increased EBD concentration indicating BSCB disruption was clearly observed in sonicated segments compared to controls on both rabbit ($p=0.004$) and mice models ($p=0.0009$). With a safe acoustical pressure, clear BSCB opening was obtained in 56 to 80% of sonications. Excessively increasing acoustic pressure resulted in a risk of neurological deficit. On one rabbit, which received 10 sonications, repetitive BSCB disruptions showed no evidence of cumulative toxicity. This was confirmed on 18 mice which received sonications weekly during 5 weeks.

CONCLUSIONS

BSCB can be disrupted using an unfocused pulsed ultrasound device in combination with microbubbles without acute neurotoxicity even in the case of repeated sonications.



CAPTION: External view of the spinal cord. Blue coloration is observed on the sonicated segment of the mice spinal cord.

POSTER SESSION 2

- # 76 - Tailoring Microbubble Shell Composition For Therapeutic Ultrasound Applications, *Antonios Pouliopoulos*
- # 77 - Registration of In Vivo Magnetic Resonance Images To Volumetric Histopathology, *Blake Zimmerman*
- # 78 - Simultaneous rapid and multi-slice MR-temperature and MR-displacement imaging during transcranial focused ultrasound in non-human primate, *Bruno Quesson*
- # 79 - Focused Ultrasound Immunomodulation in Melanoma, *Christopher Margraf*
- # 80 - Physics based, validated reliable modeling of single element focused ultrasound transducer (SEFT), *Cristina Pasquinelli*
- # 81 - From 2D to 3D real-time passive cavitation imaging of pulsed cavitation ultrasound therapy, *Daniel Suarez*
- # 82 - Oxygen Generating Nanoparticles for Improving Sonodynamic Therapy in Hypoxic Tumours, *Dean Nicholas*
- # 83 - A surface acoustic wave-based platform for cellular mechanotransduction investigation, *Defei Liao*
- # 84 - Modeling of Carbon nanotube transducer considering acoustic characteristics of the human skull, *Dong-Guk Paeng*
- # 85 - Cell-cycle-dependences of membrane permeability and viability observed for HeLa cells undergoing multi-bubble-cell interactions, *Dongxin Yang*
- # 86 - Engineering acoustically activated nanodroplets for bone fracture repair, *Eleanor Stride*
- # 87 - Novel Acoustic Coupling Bath to Improve MRI Guidance for Focused Ultrasound Surgery, *Eli Vlaisavljevich*
- # 88 - Therapeutic ultrasound phased array with arbitrarily shaped, densely packed, removable modular elements, *Ellen Yeats*
- # 89 - A preliminary study for evaluation of sonodynamic therapy in combination with BBB-opening by FUS, *Eun-Joo Park*
- # 90 - Integrin-dependent calcium signaling induced by single impulsive bubbles, *Fenfang Li*
- # 91 - Stroboscopic Schlieren Imaging of Ultrasound Fields with Large Field of View, *Florian Steinmeyer*
- # 92 - Mechanism of HIFU interaction in flooded lung and their consequences on ablation schemes for FUS on lung cancer, *Frank Wolfram*
- # 93 - Predicting high intensity focused ultrasound thalamotomy lesions using magnetic resonance thermometry and 3D Gaussian modelling, *Graham Seasons*
- # 94 - Safety and feasibility of temporary blood-brain barrier disruption with the sonocloud-3 implantable ultrasound device in recurrent glioblastoma, *Guillaume Bouchoux*
- # 95 - Design of 1024-element hemispherical arrays for ultrasonic brain therapy, *Hansol Yoon*
- # 96 - NaviFUS: A Neuronavigation-Guided Focused Ultrasound (NaviFUS) Medical Device Design, *Hao-Li Liu*
- # 97 - MRgFUS treatment of desmoid tumor with preparatory nerve protection using MR-guided hydrodissection, *Heikki Pärssinen*
- # 98 - Rapid prototyped microvessel networks for ultrasound mediated targeted drug delivery research, *Helen Mulvana*
- # 99 - Low-intensity focused ultrasound stimulation to frontal eye-field modulates human antisaccade behavior, *Hyungmin Kim*

- # 100 - Modelling for MRGHIFU treatment of recurrent gynaecological tumours, *Ian Rivens*
- # 101 - Manipulation during MR-HIFU treatment of fibroids located in the retroverted uterus or rectosigmoid region, *Inez Verpalen*
- # 102 - Modulation of electrical activity of individual neurons by focused ultrasound as measured with a whole-cell patch-clamp setup, *Ivan Suarez Castellanos*
- # 103 - Feasibility studies in mice and sheep to validate ultrasound-mediated blood-brain barrier opening for potential therapeutic interventions, *Jae Hee Song*
- # 104 - Design of an Acoustic Reflective Casing for Neurostimulation Studies with Microscopy, *Jak Loree-Spacek*
- # 105 - The clinical research of efficacy and safety of ultrasound hyperthermia combined with TPF regimen in the treatment of advanced oral squamous cell carcinoma, *Jian Meng*
- # 106 - Evaluation of a Mobile Ultrasound Device for Robot Assisted Focused Ultrasound Applications, *Johann Berger*
- # 107 - The interaction of a shockwave with a vapour bubble during boiling histotripsy, *Ki Joo Park*
- # 108 - Quantitative acoustic coupling evaluation in US-guided focused ultrasound surgery, *Laura Morchi*
- # 109 - In-vivo Validation of a Model-Based Control Algorithm for MR-HIFU Hyperthermia, *Lukas Sebeke*
- # 110 - Intratumoral microdistribution and therapeutic response of enzyme sensitive liposomes in human prostate cancer xenografts after ultrasound mediated delivery, *Marieke Olsman*
- # 111 - Development of a HIFU treatment of breast tumors using a toroidal transducer. Preliminary experiments in human samples, *Marine Sanchez*
- # 112 - Acoustic droplet vaporization in acoustically responsive scaffolds: A frequency and volume fraction study, *Mario Fabilli*
- # 113 - How do culture containers influence ultrasound field during in vitro sonication experiments?, *Martin Snehota*
- # 114 - Numerical and experimental study on the cavitation enhanced temperature elevation in soft tissue during high intensity focused ultrasound, *Maxim Solovchuk*
- # 115 - Quality of Life after MR guided focused ultrasound thalamotomy for tremor, *Michael Schwartz*
- # 116 - Intense Therapeutic Ultrasound for Musculoskeletal Pain Reduction Part I; Technical and Preclinical Data, *Michael Slayton*
- # 117 - Acoustic modeling and focus quality through the ribcage with a dual mode ultrasound random phased array, *Muhammad Zubair*
- # 118 - A fast parallel computing method for transcranial ultrasound phase correction based on k-space propagation models and acoustic holography method, *Nan Wu*
- # 119 - Targeting immunosuppression for enhanced focused ultrasound efficacy in TNBC, *Natasha Sheybani*
- # 120 - Evaluation of different in-vitro setups concerning transferability into clinical application of extracorporeal shockwave lithotripsy, *Nina Reinhardt*
- # 121 - Fast scanning for holographic characterization of sources, *Oleg Sapozhnikov*
- # 122 - Real-time closed-loop control of transcranial fus-induced localized thermal lesions in vivo with minimal collateral damage, *Emad Ebbini*

- # 123 - Is age a limiting factor in the treatment of benign thyroid nodules with HIFU?,
Pedro Pablo Ortiz Remacha
- # 124 - Semi-automatic and automatic segmentation of CT images for modeling therapeutic ultrasound beams in a human body, *Petr Yuldashev*
- # 125 - A comparison study of high-speed photography and passive acoustic mapping for monitoring of focused ultrasound induced cavitation bubbles, *Pilsu Kim*
- # 126 - MR-HIFU mild hyperthermia with radiation and chemotherapy for rectal cancer: Phase I study in recurrent rectal cancer, and retrospective study for primary disease, *Robert Staruch*
- # 127 - Fast volumetric liquefaction of large hematomas ex vivo using continuous HIFU focus translation, *Sergey Tsysar*
- # 128 - Study of the effect of cranial holes due to emissary veins and inhomogeneities in the thickness of the skull when focusing a transcranial ultrasound beam, *Sergio Jiménez Gambín*
- # 129 - Tailor-Made polymeric microbubbles combined with ultrasound for blood brain barrier opening, *Shani Tsirkin*
- # 130 - Ultrasonic imaging of tissue displacement induced by short burst exposure of therapeutic ultrasound for estimation of ultrasonically heated region, *Shin Yoshizawa*
- # 131 - Experimental setup for characterization of low intensity ultrasound for targeting the cortical region in the brain, *Shirshak Shrestha*
- # 132 - Effects of physical parameters on estimating acoustic intensity in focused ultrasound field using infrared camera, *Simon Yu*
- # 133 - Magnetic resonance-guided focused ultrasound thalamotomy in essential tremor: One-year clinical experience in a single center, *Stefano Tamburin*
- # 134 - High intensity applicator for parallelized sonication of well-plates, *Steffen Tretbar*
- # 135 - In vivo measurements of sacral thickness and sacral nerve lateral branch depth for focused ultrasound ablation of patients with sacral iliac joint pain: Predictors for patient candidacy, *Suzanne Leblang*
- # 136 - Pore Eccentricity Improves CT Based Estimates of Acoustic Velocity in Human Skull Bone, *Taylor Webb*
- # 137 - Apparent diffusion coefficient classification predicts outcome of magnetic resonance-guided high-intensity focused ultrasound treatment of uterine fibroids, *Teija Sainio*
- # 138 - Tissue-selective Ablation with Robotically Assisted Sonic Therapy (RAST): Radiologic-Pathologic Findings, *Timothy Ziemlewicz*
- # 139 - Potential for Thyroid Ablation with Robotically Assisted Sonic Therapy (RAST) with histotripsy: Proof-of-concept in a Porcine Model, *Timothy Ziemlewicz*
- # 140 - High frequency (20 mhz) focused ultrasound - a novel method for dermal intervention, *Torsten Bove*
- # 141 - Preclinical MRI-Guided focused ultrasound hyperthermia in 7 t MRI, *Upasana Roy*
- # 142 - Robotic high-intensity focused ultrasound for prostate cancer treatment: 10 years follow-up, *Viacheslav Solovov*
- # 143 - High intensity ultrasound treatment monitoring by passive elastography: an in vitro feasibility study, *Victor Barrere*

- # 144 - Feature selection for classifying the treatment outcome of high-intensity focused ultrasound therapy in uterine fibroids, *Visa Suomi*
- # 145 - A Modified PMN-PT Ceramic based 2D Array Transducer for Low-intensity Ultrasound Therapy, *Weibao Qiu*
- # 147 - In vitro focused ultrasound hyperthermia for radiosensitization of human cancer cells, *Xinrui Zhang*
- # 148 - Reducing secondary hot spots in/off axial focus shifting for phased High-Intensity focused Ultrasound system by using frequency modulation waveform A simulation study, *Xiongfei Qu*
- # 149 - Long-term results of MR Guided focused ultrasound VIM-thalamotomy in parkinson's patients with medication-refractory disabling tremor, *Alon Sinai*
- # 150 - Transscleral drug delivery mediated by low-frequency ultrasound, *Yaxin Hu*
- # 151 - Suppression of cavitation generation outside focal region by split-aperture transmission methods, *Yui Tanaka*
- # 152 - Robotic Driven Motion Model for Static vs Dynamic MRgFUS Systems, *Andrew Dennisson and Andreas Melzer*

MODELLING FOR MRgHIFU TREATMENT OF RECURRENT GYNAECOLOGICAL TUMOURS

S. Anand^{1,2}, D. Lam¹, I. Rivens¹, S. Giles¹, N. de Souza¹, G. ter Haar¹

¹Division of Radiotherapy and Imaging, Institute of Cancer Research : Royal Marsden NHS Trust, Sutton, London, UK

²Barcelona,

e-mail: s.anand@icr.ac.uk; d.lam@icr.ac.uk; ian.rivens@icr.ac.uk; g.terhaar@icr.ac.uk

OBJECTIVES

Treatment of recurrent gynaecological cancer within the pelvis is debilitating and has poor long term outcome. MRgHIFU is a novel potential salvage treatment, however, early clinical trials demonstrate that effective focal heating without significant pre-focal absorption is elusive.

METHODS

Three typical clinical scenarios were identified with the tissue beneath the skin and before the tumour being (i) fat only (F) (ii) fat then soft tissue (FS) or (iii) fat, soft tissue, fat (FSF). K-wave software was used to investigate the importance of reflection, refraction and attenuation using a single element transducer in up to 3 layers of media. Results were compared with experimental data obtained using fat and soft tissue acoustic phantoms.

RESULTS

Quantification of the effects of (i) refraction and reflection on the size and shape of the focus (ii) these plus attenuation on the ability to achieve focal heating in absence of unwanted thermal side effects will be presented. The agreement between theory and experiment, and the implications for clinical treatments will be discussed.

CONCLUSIONS

By understanding the impact of refraction, reflection and attenuation on both focal and pre-focal heat deposition, it may be possible to improve the current status of clinical treatment.

ACKNOWLEDGEMENTS

Supported by Phillips N.V., Profound Medical, MRC, EPSRC, Ari Partanen, Thomas Andrea.

Manipulation during MR-HIFU treatment of fibroids located in the retroverted uterus or rectosigmoid region.

I.M. Verpalen¹, M. van 't Veer-ten Kate¹, E. de Boer¹, R.D. van den Hoed¹, M.F. Boomsma¹

¹Department of Radiology, Isala, Zwolle, The Netherlands

Email: i.m.verpalen@isala.nl

OBJECTIVES

Magnetic Resonance-High Intensity Focused Ultrasound (MR-HIFU) is a completely non-invasive treatment of symptomatic uterine fibroids. However, the clinical applicability is often limited due to bowel-interference in the sonication pathway or the limit in focal depth of the MR-HIFU system. Bowel-interference mitigation strategies have been widely used, but manipulation techniques are not well described for inaccessible uterine fibroids located in the retroverted uterus or rectosigmoid region.

METHODS

Pre-treatment MRI was conducted to assess eligibility. MR-HIFU treatments were performed under conscious sedation using a clinical HIFU system (Sonalleve, V1, Profound Medical Inc, Mississauga, Canada) integrated into a 1.5-T MR scanner (Achieva; Philips Healthcare, Best, the Netherlands). Patient preparation included a micro-enema, oral premedication, Foley catheter and intravenous line. If necessary, manipulation techniques were used. Bladder filling, rectal filling (with a solution of water, ultrasound gel and psyllium fibers) and bladder emptying was often sufficient. However, a retroverted uterus required manually repositioning of the uterus, called anteversion (figure 1a). A speculum and/or rectal filling was used for fixation. Fibroids located in the rectosigmoid region (uterus anteverted) unresponsive to rectal filling needed rectal insertion of a balloon device catheter causing anterior displacement (figure 1b) to safely continue MR-HIFU treatment.

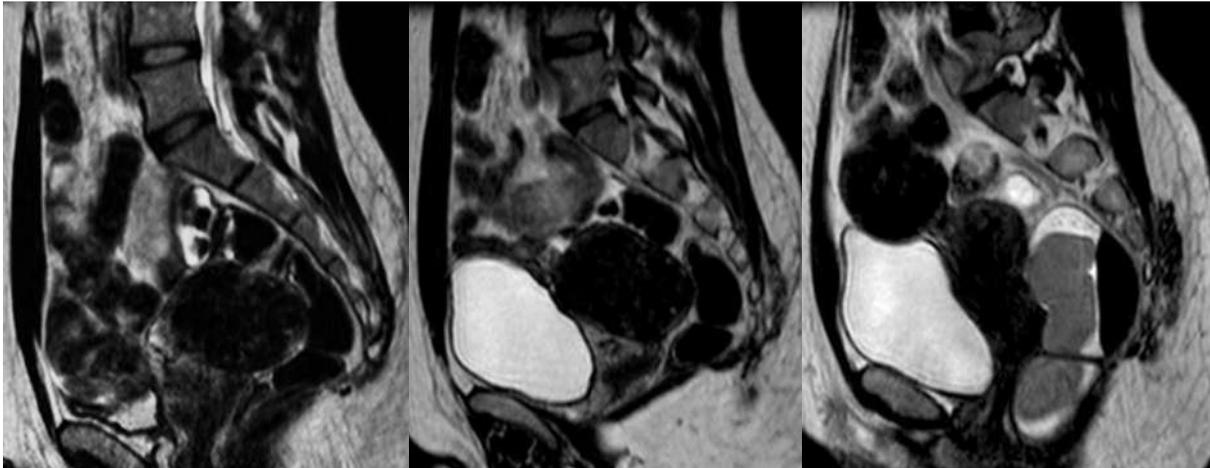
RESULTS

After implementation of the manipulation techniques, our screening failure rate and treatment failure rate due to bowel-interference or unreachable fibroids decreased to 0%. No complications or thermal injuries to the bowel or uterus occurred from the manipulation.

CONCLUSIONS

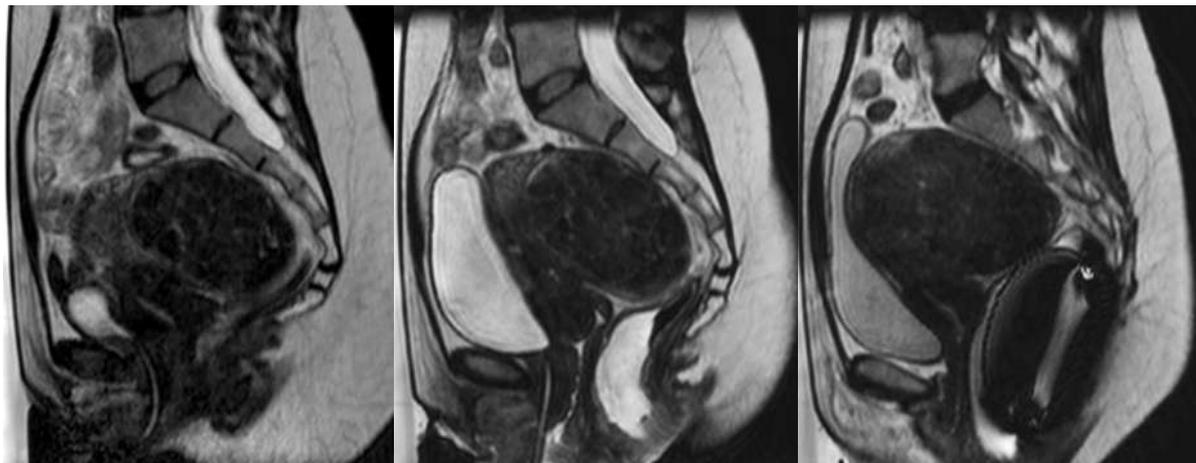
We implemented different manipulation techniques which has led to a decrease in our screening and treatment failure rates.

Figure 1a



A uterine fibroid and a retroverted uterus. The image on the left shows the position of the fibroid without manipulation. The middle image shows the image after bladder filling. After anteversion of the uterus manually and fixation of the uterine position with rectal filling (image on the right), the fibroid was accessible for MR-HIFU therapy.

Figure 1b



A uterine fibroid located on the posterior wall of an anteverted uterus. The image on the left shows the position of the fibroid without manipulation. The middle image shows the image after bladder and rectal filling, also we tried to manually move the fibroid, but the fibroid did not move anteriorly. The image on the right shows the rectal balloon device inserted which is filled with water and surrounded by the ultrasound gel, the fibroid is now accessible for MR-HIFU treatment.

MODULATION OF ELECTRICAL ACTIVITY OF INDIVIDUAL NEURONS BY FOCUSED ULTRASOUND AS MEASURED WITH A WHOLE-CELL PATCH-CLAMP SETUP

I.M. Suarez-Castellanos¹, M. Perier¹, J. Vion-Bailly¹, A. Birer¹, W.A. N'Djin¹

¹LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, Lyon, France

e-mail: ivan.suarez@inserm.fr

OBJECTIVES

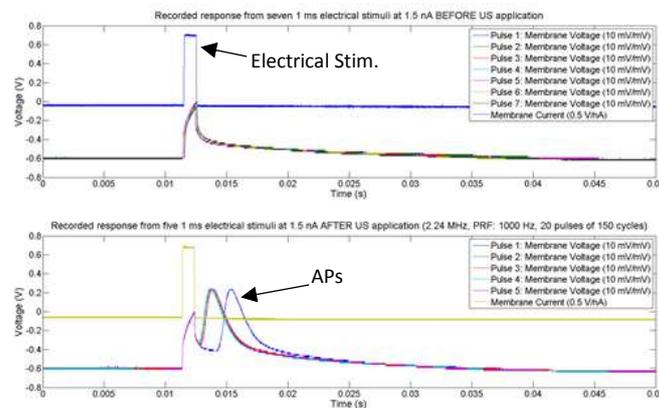
Full characterization of the mechanisms involved in Neuromodulation by Low-Energy Focused Ultrasound (LEFUS) is necessary for further development of this promising technology. The aim of this work was to integrate a LEFUS-system with a patch-clamp platform for study of LEFUS-modulated electrophysiological responses from cultured neurons.

METHODS

Mouse primary neurons and human neural progenitor cells were plated onto 35-mm diameter Petri dishes. Electrophysiological activity in the neurons was recorded using a whole-cell patch-clamp setup in current-clamp mode. The LEFUS system consisted of a 2.24-MHz planar transducer (PZT4, \varnothing : 10-mm), coupled with a conical waveguide filled with agarose gel for focusing and transmission of the ultrasound wave to the Petri dish. LEFUS exposures were administered as trains of twenty pulses (150 cycles / pulse, $p = 32.3$ kPa, PRF = 1 kHz). Activation thresholds to electrical stimulation were determined before and after application of LEFUS.

RESULTS

Electrophysiological patch-clamp measurement was successfully performed before, during and after LEFUS exposures. Preliminary data suggests that the activation threshold of an ultrasound-treated neural cell could be modulated. In a first set of experiments, the activation threshold required for triggering an action potential (AP) was both elevated and lowered following FUS treatment.



Lowering of neuronal activation threshold following LEFUS

CONCLUSIONS

These results provide an initial indication that the electrophysiological activity of individual neurons can be modulated using LEFUS. Further studies are currently being conducted to support this observation.

ACKNOWLEDGEMENTS

This project was supported by the French National Research Agency (ANR-16-TERC-0017) the LabEx DevWeCan, and the Focused Ultrasound Foundation (Centers of Excellence).

FEASIBILITY STUDIES IN MICE AND SHEEP TO VALIDATE ULTRASOUND-MEDIATED BLOOD-BRAIN BARRIER OPENING FOR POTENTIAL THERAPEUTIC INTERVENTIONS

J. H. Song¹, D. Blackmore¹, R. Pandit¹, M. Pelekanos¹, G. Leinenga¹, J. Götz¹

¹Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane QLD 4072, Australia; e-mail: j.goetz@uq.edu.au

OBJECTIVES

Scanning ultrasound (SUS) with retro-orbitally injected microbubbles can be effectively used to transiently open the blood-brain barrier (BBB) and thereby remove toxic protein aggregates and ameliorate memory functions in mouse models of Alzheimer's disease (Leinenga et al., Science Translational Medicine 2015). To develop SUS into a treatment modality for human patients it is important to establish the technology in larger animals and prove long-term safety.

METHODS

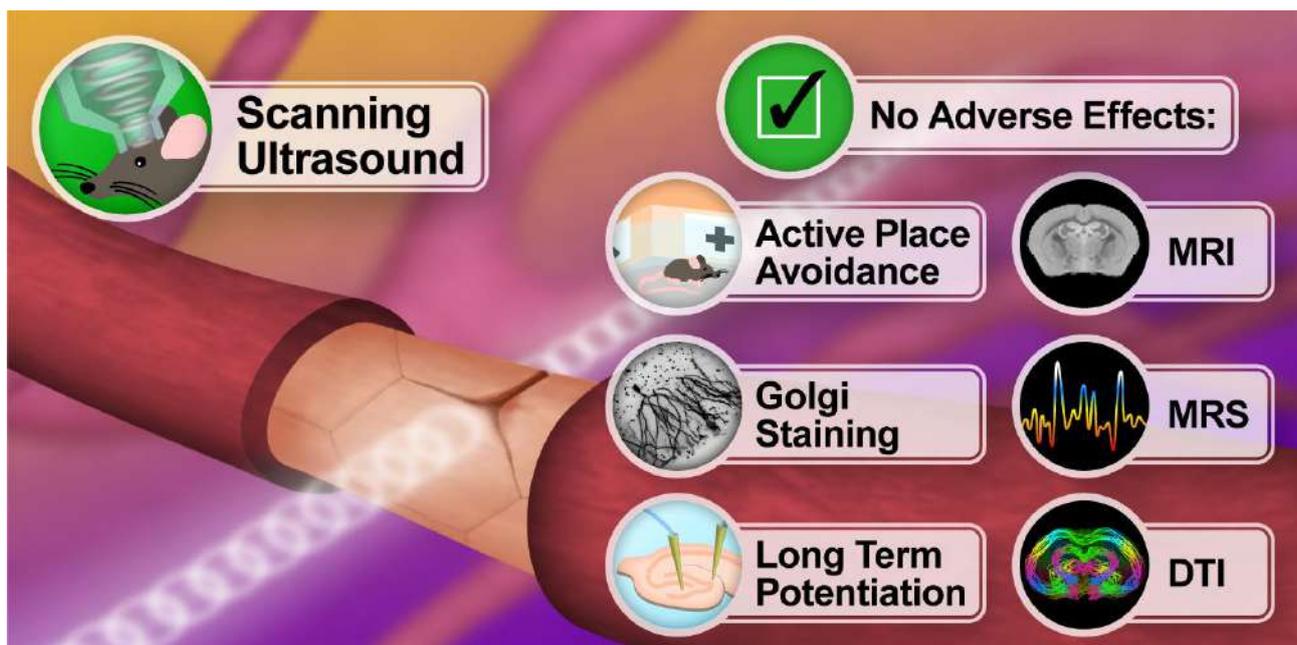
In a stepwise manner, we used 20 sheep to establish a sonication protocol using a spherically focused transducer, assisted by ex vivo simulations based on CT scans. BBB opening was assessed by Evans blue staining and a range of histological tests. To assess long-term safety, we treated 12 month-old wild-type mice weekly over six weeks with SUS, followed by a multimodal analysis until animals were 18 months of age.

RESULTS

The non-recovery protocol allowed for BBB opening in areas relevant for AD, including the cortex and hippocampus through the intact sheep skull. - In mice, we found that spatial memory and neuronal morphology were not adversely affected nor was long-term potentiation as a cellular correlate of memory.

CONCLUSIONS

Our study firstly establishes sheep as a novel animal model for ultrasound-mediated BBB opening and highlights opportunities and challenges in using this model. Secondly, the multimodal analysis in mice indicates that therapeutic ultrasound is safe in the long-term, underscoring its validity as a potential treatment modality for diseases of the brain (Blackmore et al., Theranostics, 2018).



CAPTION Multimodal analysis of ultrasound-treated aged mice demonstrates long-term safety

DESIGN OF AN ACOUSTIC REFLECTIVE CASING FOR NEUROSTIMULATION STUDIES WITH MICROSCOPY

J. Loree-Spacek,¹ A. Coreas,¹ S. Pichardo¹

¹ Depts. of Radiology, Biomedical Engineering, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

e-mail: jak.loreespacek1@ucalgary.ca

OBJECTIVES

Studies of neurostimulation effects using microscopy require specialized devices that are compatible with the optical system. This numerical study presents a method employing optimization and finite-element modeling to design a hollow polycarbonate casing that focuses the ultrasound beam via reflection. The device should facilitate sonication of rodent brain slices while maintaining compatibility with optical and electrophysiological assessments.

METHODS

A multi-objective optimization to design the casing geometry was run using the genetic algorithm *gamultiobj* (MATLAB R2018a, Mathworks). Choosing a flat circular transducer with diameter 10mm and operating frequency 200kHz, the acoustic pressure field was computed by interfacing with the finite-element software COMSOL Multiphysics. The optimization maximized length and minimized width of the focal spot extending from the casing.

RESULTS

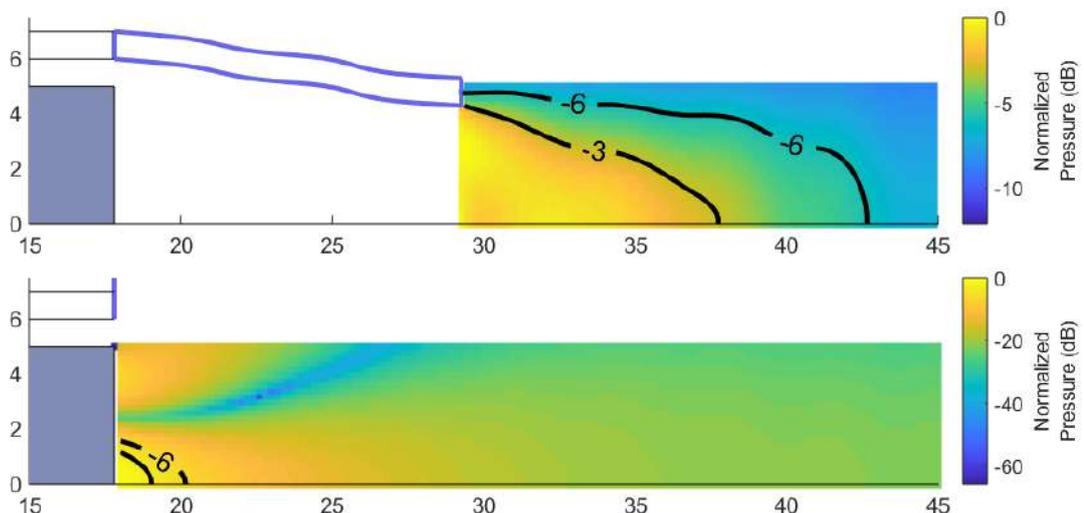
The procedure yielded a geometry defined by five fixed-length segments, interpolated with splines. The design measures 11.5mm from the transducer surface and produces a region of concentrated pressure (-6dB from maximum) extending 13.4mm past the casing's tip.

CONCLUSIONS

This study demonstrates the feasibility of a flat transducer and printable casing to produce optimal focal zones for neurostimulation studies. This design strategy leads to setups that are effective and easily fabricable, while exploiting the accuracy of finite-element modeling.

ACKNOWLEDGEMENTS

Authors acknowledge the financial support of the Natural Sciences and Engineering Research Council of Canada and the support from CMC Microsystems for access to simulation tools.



CAPTION: Simulations of a transducer with (top) and without (bottom) a reflective casing. Model is axisymmetric about the horizontal axis, and pressure is normalized to peak value. Visualized in MATLAB 2018a.

Aim : To evaluate the efficacy and safety of ultrasound hyperthermia combined with TPF regimen in the treatment of advanced oral squamous cell carcinoma(OSCC) through stage IV study. Methods:From 2015 to 2018, 37 patients with advanced OSCC diagnosed by pathology were randomly divided into experimental group and control group.Among them, the ultrasonic thermochemotherapy group was the experimental group (n ~ 17), and the TPF chemotherapy group was the control group (n ~ 20).The experimental group was treated with local ultrasound hyperthermia at 42 °C for 40 min, 5 times every other day, 21 days for 1 cycle, 2 cycles.The control group received only 2 cycles of TPF regimen chemotherapy.Compare the efficacy, long-term survival rate and toxicity in both groups.Results: In the experimental group, the effective rate was 82.35% (14 / 17), 4 cases were completely relieved.The effective rate of the control group was 50% (10 / 20).The disease control rate of the experimental group was 94.12% (16 / 17), while that of the control group was 85% (17 / 20). The main adverse effects of ultrasound hyperthermia were mild scalding (9/17) and first degree pain (10/17) , but the course of treatment was completed as scheduled. There was no significant adverse reaction during the course of chemotherapy. The patient's facial shape and function were preserved well, and the quality of life was improved. Conclusion: Ultrasound hyperthermia combined with TPF chemotherapy is a minimally invasive, effective and safe adjuvant therapy for advanced OSCC, with mild adverse reactions, tolerability, safety and feasibility.

Evaluation of a Mobile Ultrasound Device for Robot Assisted Focused Ultrasound Applications

Michael Unger¹, Johann Berger¹, Lisa Landgraf¹, Andreas Melzer¹

¹Innovation Center Computer Assisted Surgery, University Leipzig, Leipzig, Germany

Email: michael.unger@medizin.uni-leipzig.de

Introduction

To realize clinical combination of focused ultrasound hyperthermia (FUS-HT) to support Radiation therapy (RT) a mobile FUS system and communication between the two modalities is needed. The aim of this study was to evaluate the measurement accuracy of a mobile ultrasound device (US) device as a basis for the robotic positioning of a FUS transducer during FUS-RT intervention.

Materials and methods

To perform flexible positioning of a FUS transducer a KUKA LBR iiwa 7 R800 (KUKA AG) robotic setup as described in [1] was applied in this study. In a first step, a Clarius L7 mobile imaging ultrasound device (Clarius Inc.) was attached to the robot. A software module to acquire and process the US images in real time was implemented in C++ on a standard PC using the *Listen API* provided by the vendor.

To simulate a target for the robot two lesions in a phantom (Abdominal Triple Modality Phantom, CIRS Inc.) were segmented via US (spatial resolution = 146 μm per pixel) and magnetic resonance imaging (Philips Ingenia 3T; TR=4182ms; TE=80ms; SliceThickness=1mm; Pixel Spacing = 0.76 mm;).

Results

The mean positioning accuracy of the ultrasound probe by the robot was 2.94 mm. The mean measurement error between the MRI and US segmented images was 0.54 mm (horizontal) and 1.95 mm (vertical).

Discussion and Conclusion

This study showed that a US-guided robotic system would allow accurate positioning of a FUS transducer. The measurement error of the mobile US device was of less than 2 mm. Thus, real time monitoring during treatment and using the special information as an input for positioning adjustments is feasible, e.g. for motion compensation.

References

[1] Berger J, Unger M, Landgraf L, Bieck R, Neumuth T, Melzer A. Assessment of Natural User Interactions for Robot-Assisted Interventions. In: Current Directions in Biomedical Engineering. 2018.

THE INTERACTION OF A SHOCKWAVE WITH A VAPOUR BUBBLE DURING BOILING HISTOTRIPSY

K.J. Pakh¹, S. Lee², P. G lat³, M.O. de Andrade³, M.J. Choi⁴, H. Kim¹, N. Saffari³

¹Center for Bionics, Biomedical Research Institute, Korea Institute of Science and Technology (KIST), Seoul, Republic of Korea; ²Dept. of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea; ³Dept. of Mechanical Engineering, University College London, London, UK; ⁴Dept. of Medicine, Jeju National University, Jeju, Republic of Korea.
e-mail: kipahk@kist.re.kr

OBJECTIVES

Boiling histotripsy (BH) is a promising High-Intensity Focused Ultrasound (HIFU) technique that can be used to mechanically fractionate solid tumours. Whilst a number of studies have shown the effects of shockwave heating in creating a boiling vapour bubble at the HIFU focus, not much is known about the subsequent formation of cavitation clouds during BH exposure. The aim of the present study is, therefore, to investigate what causes this bubble cluster formation.

METHODS

The k-Wave MATLAB toolbox that numerically solves the generalised Westervelt equation was employed to simulate 2D nonlinear acoustic fields scattered by a vapour bubble at the HIFU focus in liver. A vapour bubble was exposed to 1 MHz HIFU fields with peak positive P_+ and negative P_- pressures of 51 and -9.8 MPa at the HIFU focus. The size of the bubble was varied to investigate the changes in the pressure amplitude of the acoustic fields backscattered by the bubble.

RESULTS

Numerical results of the 2D spatial distribution of acoustic pressure fields around a vapour bubble depicted in Figure 1 show the presence of strong negative pressure fields between the HIFU source and the bubble, with P_- of -30 MPa. This value is above the cavitation clouds' intrinsic threshold of -28 MPa.

CONCLUSIONS

A numerical study of the interaction of a shockwave with a vapour bubble in liver was performed. Our results reveal that the shock scattering effect involved in cavitation cloud histotripsy also appears during the course of BH, resulting in the subsequent formation of bubble clouds.

ACKNOWLEDGEMENTS

Supported by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIT) (No. CAP-18-01-KIST) and a grant of National Research Foundation of Korea (NRF) (Grant No. 2017R1A2B3007907) funded by the Korean government.

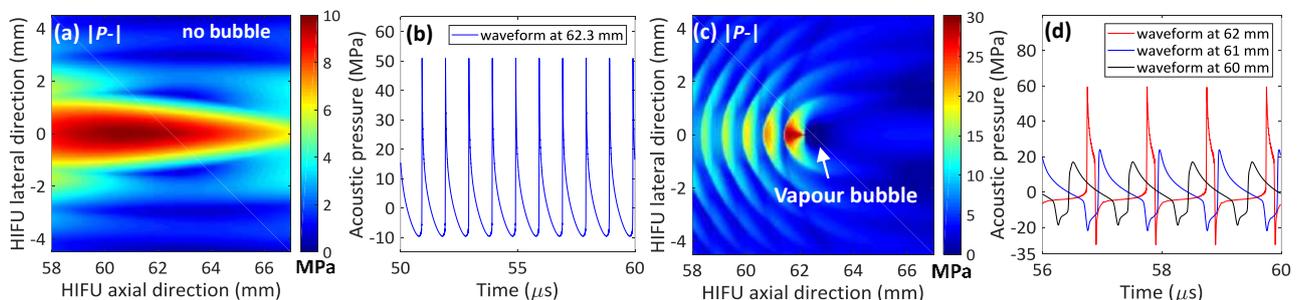


Figure 1. Simulated (a) 2D negative pressure fields and (b) acoustic waveforms at the HIFU focus without a vapour bubble in liver. (c) and (d) are respectively computed 2D negative pressure fields and acoustic waveforms with the presence of a vapour bubble at the HIFU focus. The size of the bubble of 0.77 mm (half of the wavelength) and a number of 160 grid points per wavelength at 1 MHz were used in the simulations. The HIFU beam propagates from left to right.

QUANTITATIVE ACOUSTIC COUPLING EVALUATION IN US-GUIDED FOCUSED ULTRASOUND SURGERY

L. Morchi^{♦,1}, A. Mariani^{♦,1}, A. Cafarelli¹, A. Diodato¹, S. Tognarelli¹, A. Menciassi¹

[♦]These authors equally contributed to the work.

¹The BioRobotics Institute, Sant'Anna School of Advanced Studies, Pisa, Italy

e-mail: laura.morchi@santannapisa.it

OBJECTIVE

A correct acoustic coupling between the therapeutic transducer and the patient's body is crucial for efficient and safe Ultrasound-guided Focused Ultrasound (USgFUS) treatments. Unfortunately, nowadays clinicians verify the coupling by only qualitatively inspecting Ultrasound images. This study introduces a quantitative metrics for evaluating the quality and correctness of the acoustic coupling in a pre-operative phase.

METHODS

Different acoustic coupling conditions were replicated using the position control of a robotic USgFUS platform (www.futuraproject.eu). The coupling system consisted in a 150µm latex membrane attached to the FUS transducer and filled with deionized and degassed water. An Agar-based phantom was used as skin simulator (Fig.1a). For each coupling condition, *i.e.* robot position (z), a safe low-energy FUS sonication (1W power, 1s duration, 1.2MHz frequency) was executed and the related RF echoes were recorded through the 2D confocal imaging probe. The introduced Acoustic Coupling (AC) coefficient is calculated from the frequency peak (P_z) - at the working frequency of the FUS transducer - of the reflected RF signals.

RESULTS

Fig.1b shows a sigmoidal trend between AC coefficient and robot position (bigger the value of the robot position (z), better the acoustic coupling) until reaching a plateau, where the AC samples are statistically equivalent.

CONCLUSIONS

The introduced AC coefficient paves the way to preoperatively quantify the quality and correctness of the acoustic coupling in a USgFUS clinical set-up, thus ensuring the safety and efficacy of the FUS treatment.

ACKNOWLEDGEMENTS

Research supported by FUTURA2020 project (grant agreement 801451) and River Global Capital Ltd.

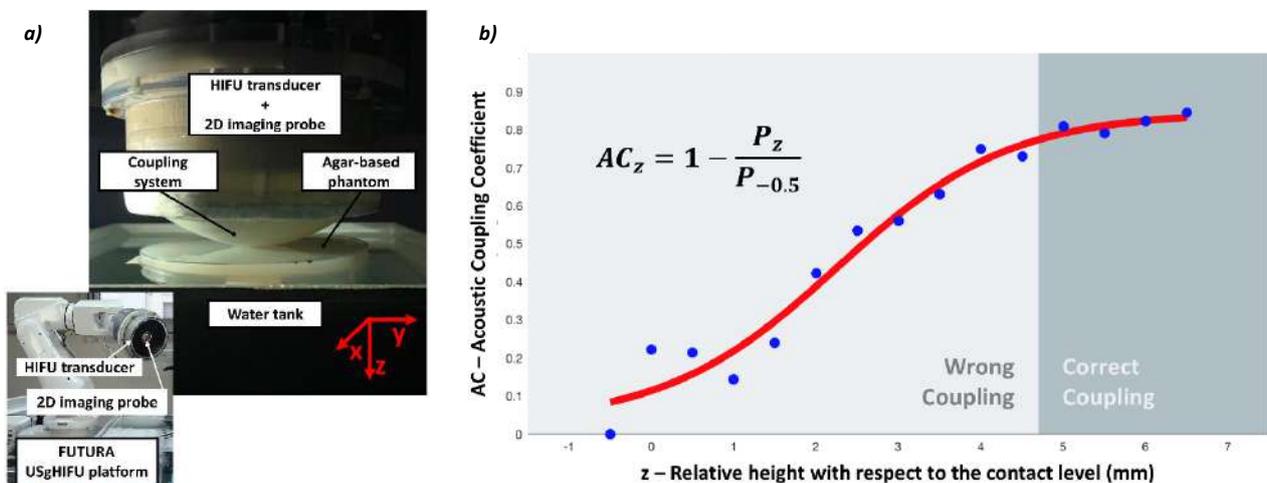


Figure 1: a) USgFUS platform components (bottom left) and experimental set-up (centre): to simulate different coupling conditions, the coupling system was moved along the z-axis towards the phantom. b) AC coefficient (defined in the upper left) as a function of the robot position, normalized with respect to a non-contact condition ($z=-0.5$ mm).

IN-VIVO VALIDATION OF A MODEL-BASED CONTROL ALGORITHM FOR MR-HIFU HYPERTHERMIA

L. Sebeke^{1,2}, P. Rademann³, A. Maul³, E. Heijman^{2,4}, J.D. Castillo², S.Y. Yeo², H. Gröll^{1,2}

¹Eindhoven University of Technology, Department of Biomedical Engineering, Eindhoven, The Netherlands

²University of Cologne, Faculty of Medicine and University Hospital of Cologne, Department of Diagnostic and Interventional Radiology, Cologne, Germany

³University of Cologne, Faculty of Medicine and University Hospital of Cologne, Center for Experimental Medicine, Cologne, Germany

⁴Philips Research Germany, Aachen, Germany

e-mail: lukas.sebeke@uk-koeln.de; holger.gruell@uk-koeln.de

OBJECTIVES

Development of a novel model-based feedback control algorithm for the generation of highly homogeneous temperature profiles using magnetic resonance guided high-intensity focused ultrasound (MR-HIFU) and its in-vivo evaluation for the application of mild hyperthermia.

METHODS

A controller for local hyperthermia based on the Model Predictive Control (MPC) paradigm was developed and implemented on a clinical MR-HIFU system (3T Achieva[®], Philips Healthcare, Best, The Netherlands & Sonalleve[®] V2, Profound Medical, Toronto, Canada). Its performance was assessed in a side-by-side comparison to the current state of the art controller using a tissue-mimicking phantom material and validated in-vivo on various regions of the porcine thigh.

RESULTS

The newly developed MPC algorithm outperforms the current state of the art controller in-vitro and produces highly homogeneous temperature distributions in-vivo (**Figure 1**).

CONCLUSIONS

The finely tuned heating power allocation enabled by model-based optimization produces more homogeneous temperature distributions and smaller target temperature tracking errors compared to current controllers. Case-by-case tailoring of the model parameters to the respective target tissue likewise facilitates consistently high performance in-vivo.

ACKNOWLEDGEMENTS

Supported by the European Union FP7 Health program Health (“IPaCT”, grant agreement no. 603028) and German Federal Ministry of Education and Research (“TSL-LIFU”, FKZ: 13XP5014A,D).

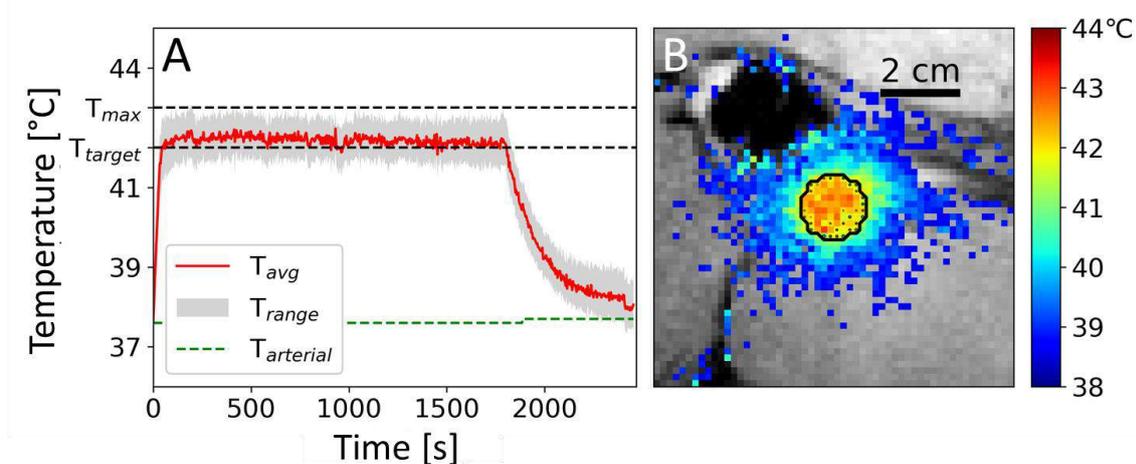


Figure 1: (A) Temperature evolution inside the target area during an MPC-mediated MR-HIFU hyperthermia treatment in porcine thigh muscle. (B) Representative temperature map acquired after establishment of the steady-state temperature distribution.

INTRATUMORAL MICRODISTRIBUTION AND THERAPEUTIC RESPONSE OF ENZYME SENSITIVE LIPOSOMES IN HUMAN PROSTATE CANCER XENOGRAFTS AFTER ULTRASOUND MEDIATED DELIVERY

Marieke Olsman¹, Kristine Andreassen¹, Viktoria Sereti², Sofie Snipstad^{1,3,4}, Annemieke van Wamel¹, Sigrid Berg^{4,5,6}, Andrew Urquhart², Thomas Lars Andresen², Catharina de Lange Davies¹

¹ Department of Physics, Norwegian University of Science and Technology, Trondheim, Norway

² Department of Health Technology, Center for Nanomedicine and Theranostics, Technical University Denmark, DTU Healthtech, Lyngby, Denmark

³ Department of Biotechnology and Nanomedicine, SINTEF Industry, Trondheim, Norway

⁴ Cancer Clinic, St. Olavs Hospital, Trondheim, Norway

⁵ Department of Health Research, SINTEF Digital, Trondheim, Norway

⁶ Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

email: marieke.olsman@ntnu.no

OBJECTIVES

Focused ultrasound (FUS) in combination with microbubbles (MBs) has shown to improve the delivery of nanoparticles (NPs) to tumors. We compared the effect of FUS+MBs on the intratumoral microdistribution and therapeutic response of three liposomes: clinically used (C), enzyme sensitive (ES) and non-enzyme sensitive (NES) in tumors growing in mice.

METHODS

Subcutaneous prostate cancer xenografts were treated with fluorophore labelled liposomes and FUS (1 MHz, mechanical index (MI) of 0.4 or 0.8) in combination with SonoVue™ MBs. Mice were euthanized 3 hours post treatment. Frozen tissue sections were imaged by confocal laser scanning microscopy and data on relative total NP count (RTNP), relative extravasated NP count (RENP), average distance travelled (ADT), and maximal penetration depth (MPD) into the extracellular matrix were extracted. The therapy study is ongoing and tumor sizes are measured with a calliper.

RESULTS

FUS+MBs increased the RTNP of the C and NES liposome, 1.8x and 1.7x, respectively (table 1). No effect on the RTNP was observed for the ES liposome. Improved extravasation was observed for the C and NES liposomes, 2.8x and 1.6x, respectively. Effect on the ES liposome was limited to the MI=0.8 group (1.3x increase). For all liposomes, the ADT differed minimally while the MPD was doubled.

CONCLUSION

FUS+MBs increased the RENP for all three liposomes and most efficiently for the C and NES liposomes. The RTNP was only improved for the C and NES liposome. Furthermore, FUS+MBs doubled the MPD even when the RTNP and RENP increase was limited (ES liposome), demonstrating the therapeutic potential of FUS+MBs.

Table 1. The RTNP, RENP, ADT and MPD of each liposome and treatment group including their standard deviations. Values for the RTNP and RENP are normalized to values of the No US group.

Liposome	Clinically used liposome (C)			Enzyme sensitive liposome (ES)			Non-enzyme sensitive liposome (NES)		
	No US	MI=0.4	MI=0.8	No US	MI=0.4	MI=0.8	No US	MI=0.4	MI=0.8
RTNP [au]	-	1.8x	2.0x	-	1.0x	1.0x	-	1.1x	1.7x
RENP [au]	-	2.8x	3.0x	-	1.0x	1.3x	-	1.6x	1.7x
ADT [µm]	2.4±3.6	7.2±10.8	4.8±8.4	3.6±4.8	4.8±9.6	4.8±7.2	2.4±4.8	8.4±10.8	4.8±7.2
MPD [µm]	16.8±30.0	38.4±50.4	33.6±46.8	20.4±32.4	33.6±50.4	27.6±42.0	15.6±19.2	33.6±45.6	31.2±51.6

DEVELOPMENT OF A HIFU TREATMENT OF BREAST TUMORS USING A TOROIDAL TRANSDUCER. PRELIMINARY EXPERIMENTS IN HUMAN SAMPLES.

Marine Sanchez¹, Victor Barrere¹, Nicolas Chopin², David Melodelima¹

¹LabTAU, INSERM, Centre Leon Berard, Universite Lyon 1, Univ Lyon, F-69003, LYON, France

²Centre Leon Berard, Lyon

Email: marine.sanchez@inserm.fr

OBJECTIVES

We report here the first use of a completely non-invasive treatment of human breast tissues using a toroidal HIFU transducer.

METHODS

The toroidal transducer has a radius of curvature of 70 mm, a diameter of 70 mm and was divided into 32 concentric rings of equal areas (78 mm²). The operating frequency was 2.5 MHz. A toroidal transducer creates two focal zones leading to large, fast and homogeneous ablations (8 cc/min). A 7 MHz ultrasound imaging probe was placed at the center of the HIFU transducer.

Experiments were conducted in 23 human samples of normal breast tissues recovered from mastectomies. The free-field acoustical power used varied between 100 to 140 watts and was applied from 45 to 180 seconds. The tissue attenuation was measured using pulse-echo method before and after HIFU.

RESULTS

Ten HIFU ablations were created with an average diameter of 22.5 ± 4.4 mm. Ablations were placed at an average depth of 15.1 mm while preserving the skin integrity. The HIFU-treated breast tissues have a higher attenuation (0.27 ± 0.08 Np.cm⁻¹.MHz⁻¹) when compared to the untreated tissues (0.16 ± 0.09 Np.cm⁻¹.MHz⁻¹). The treated zone was observed immediately after HIFU as hyperechoic in ultrasound images. Histological analyses confirmed homogeneous ablations in the breast.

CONCLUSIONS

This study shows the feasibility of a fast and fully noninvasive treatment of 10-15 mm diameter breast tumor using a toroidal transducer. Based on these results, Phase I-II clinical trials will be conducted with the toroidal HIFU transducer to treat breast cancer.

Acoustic droplet vaporization in acoustically responsive scaffolds: A frequency and volume fraction study

Mitra Aliabouzar, Xiaofang Lu, Oliver D. Kripfgans, J. Brian Fowlkes, and Mario L. Fabiilli
University of Michigan, Ann Arbor, MI, USA
e-mail: aliabouz@umich.edu; mfabiill@umich.edu

OBJECTIVES

We study the effects of frequency of excitation and volume fraction of phase shift emulsions, embedded in acoustically-responsive-scaffolds (ARS), on the acoustic droplet vaporization (ADV) threshold.

METHODS

Monodispersed perfluorohexane (PFH) double emulsions (\varnothing : $13.2 \pm 0.8 \mu\text{m}$) were made by microfluidic techniques. ARSs were prepared by combining 10 mg/mL bovine fibrinogen, varying volume fractions of double emulsions (0.05, 0.2 and 1 % (v/v)), and 2 U/mL bovine thrombin in custom-made cylindrical sample chambers. ADV studies were carried out at excitation frequencies of 2.25, 5, and 10 MHz at 37 °C. An active vaporization detection method was used to determine the ADV threshold based on the scattered response at 2.25 MHz. Using the same setup, effective attenuation of ARSs was measured before and after ADV. ADV efficiency was quantified by Coulter Counter.

RESULTS

ADV threshold increased with the frequency of excitation in both active and attenuation methods. ADV threshold inversely correlated with the volume fraction of double emulsions at the lowest excitation frequency. At higher frequencies, due to high acoustic reflectivity of PFH emulsions, the ADV threshold correlated directly with the volume fraction of emulsions. At higher applied pressures, the suprathreshold focal volume increased, along with the ADV efficiency.

CONCLUSIONS

Propagating media can affect the generation of nonlinearly distorted waves, diminishing the amplitude of harmonics at higher frequencies and higher volume fractions of double emulsions. The high reflectivity of PFH, possibly due to high impedance mismatch, may play a critical role in ADV threshold determination.

ACKNOWLEDGEMENTS

This work is supported by NIH grant R01HL139656

HOW DO CULTURE CONTAINERS INFLUENCE ULTRASOUND FIELD DURING *IN VITRO* SONICATION EXPERIMENTS?

M. Snehota¹, J. Vachutka¹

¹Department of Medical Biophysics, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic

e-mail: m.snehota@email.cz

OBJECTIVES

In vitro sonication experiments encounter several issues affecting final ultrasound dose received by sonicated samples such as standing waves formation or attenuation of ultrasound energy by culture containers. The main scope of this work is to assess the influence of common culture containers in these experiments.

METHODS

Ultrasound was generated by circular plane piston unfocussed transducer s/n: PA192 (Precision Acoustics) at 3.5 MHz and 0.1 W in continuous mode. Ultrasound field was measured by 0.5 mm needle hydrophone SN: 1057 (Precision Acoustics) in water tank with distilled water. We placed several types of common culture dishes, culture plates and test tubes at last axial maximum. Additionally, several PVC and copper tubes were placed lengthwise to ultrasound axis. Values measured behind each object were compared to reference values of free field.

RESULTS

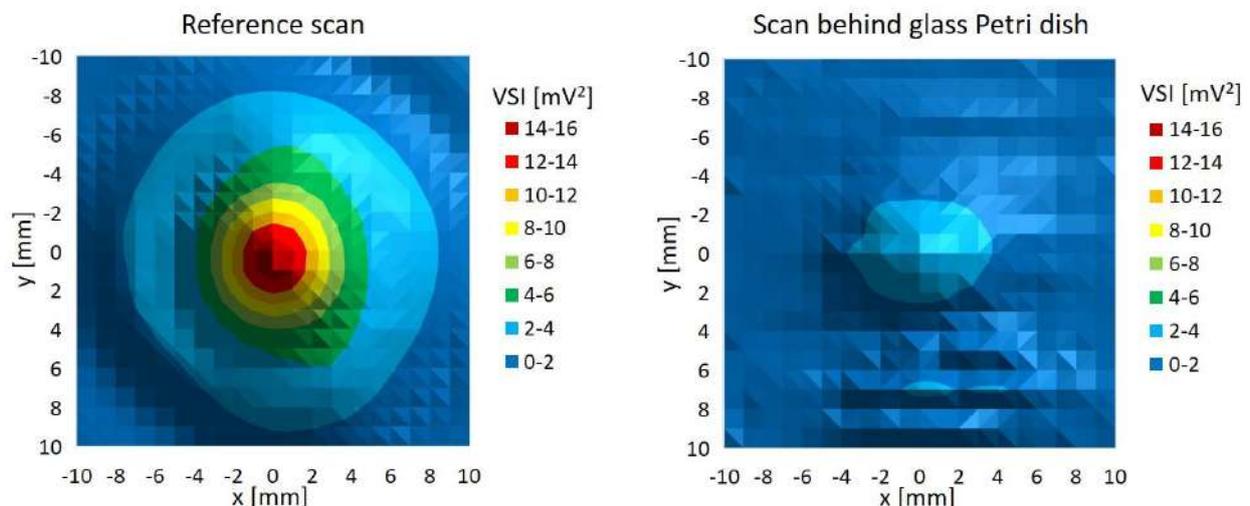
Plastic containers attenuated ultrasound intensity by 5 - 27 %. Glass containers attenuated ultrasound intensity by 77 - 90 % (Figure). Curved surfaces of test tubes focused ultrasound energy to hot spot. In case of main lobe of ultrasound beam encountering narrower object (e.g. 48 well plate), hot and cold spots were created. The narrower and longer the tubes, the hotter (max 472 %) and colder (max 3 %) spots were created when compared to corresponding values.

CONCLUSIONS

Common culture containers significantly influence ultrasound field during sonication experiments *in vitro*. Influence of standing waves also needs further assessment.

ACKNOWLEDGEMENTS

This work was supported by the Grant Project NPU LO1304.



CAPTION: Glass Petri dish significantly attenuates ultrasound energy.

Numerical and experimental study on the cavitation enhanced temperature elevation in soft tissue during high intensity focused ultrasound

M. A. Solovchuk^{1,2}, E. Zilonova², T.W.H. Sheu²

¹ Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes, Zhunan, Taiwan

² Engineering Science and Ocean Engineering Department, National Taiwan University, Taipei, Taiwan

e-mail: solovchuk@gmail.com

OBJECTIVES

At high ultrasound intensities during focused ultrasound therapy the formation of gas/vapor bubbles might take place. This effect is known as acoustic cavitation. Without the formation of bubbles, the necrosed area has a well-defined ellipsoidal shape and can be well predicted by acoustic and bioheat equations. However, the appearance of bubbles makes the treatment more complicated. The goal of this work is to design the mathematical model for the cavitation enhanced temperature elevation during focused ultrasound therapy and validate it by comparing with the experimental data.

METHODS

For the modeling of ultrasound wave propagation, nonlinear Westervelt equation with relaxation effects taken into account has been used. For the modeling of bubble dynamics Gilmore-Akulichev cavitation model has been used. Zener viscoelastic model is employed in order to simulate some important soft tissue features such as elasticity and relaxation time. The above mentioned equations have been coupled with the bioheat equation for the simulation of temperature elevation. The temperature measurements have been performed using MRI both in-vivo (animal experiments) and ex-vivo. The porcine muscle was exposed to ultrasound heating for 30s with the electric power ranged from 120 W to 180W.

RESULTS

Good agreement between the developed mathematical model and measured by MRI temperature has been obtained. The temperature peaks equal to 75-100 °C in the experimental data were demonstrated in the simulations by the consideration of the bubble cloud consisting of 50 – 65 bubbles per 2mm×2mm×2mm.

CONCLUSIONS

The developed in this paper theoretical model is capable to describe the heating process of the tissue even in the case of the bubbles' formation. Moreover, the large difference in the simulation results with and without bubbles should urge one to take into account the cavitation phenomena in the formulation of the mathematical model and can be used for the better understanding of the treatment process.

QUALITY OF LIFE AFTER MR GUIDED FOCUSED ULTRASOUND (MRgFUS) THALAMOTOMY FOR ESSENTIAL TREMOR

N. Scantlebury¹, Y. Meng^{1,6}, N. Lipsman^{1,6}, J. Jain², D. Dawson^{3,4,5}, M.L. Schwartz^{1,6}.

¹Division of Neurosurgery, Sunnybrook Health Sciences Centre,

²Division of Neurology, Sunnybrook Health Sciences Centre,

³Rehabilitation Sciences Institute, University of Toronto,

⁴Rotman Research Institute, Baycrest Centre, Toronto,

⁵Department of Occupational Science and Occupational Therapy, University of Toronto,

⁶Department of Surgery, University of Toronto.

e-mail: m.schwartz@utoronto.ca

OBJECTIVES/METHODS

32 patients with medication-refractory essential tremor treated with unilateral MRgFUS thalamotomy between 2014 and 2017 were evaluated with the Clinical Rating Scale for Tremor (CRST) and the Quality of Life in Essential Tremor questionnaire (QUEST) at baseline, 6 months and 12 months post-treatment.

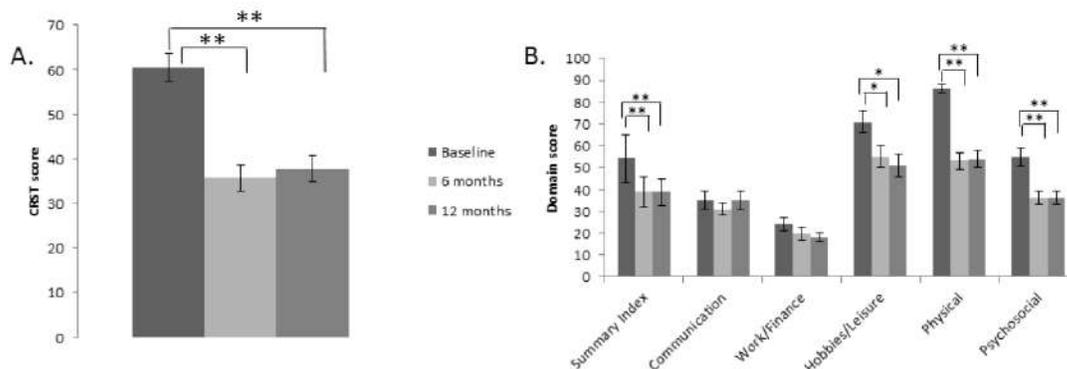
RESULTS

Mean age at treatment: 71.5±7.6 years and mean tremor duration: 29.1±17.4 years. Tremor severity (CRST) was improved from baseline at both 6 and 12-month follow-up (Figure 1A). Using QUEST, in which higher scores reflect poorer satisfaction, patients rated 30 statements about domains that contribute to daily life. Patients reported improvement in the physical and hobbies/leisure domains 6 months after treatment that were maintained at 1 year (Figure 1B). Patients anecdotally reported increased independence in everyday activities. Patients also indicated improvements in the psychosocial domain at 6 and 12 months, perhaps because of regained independence. As vocal tremor did not improve with unilateral thalamotomy, there was no change in the communication domain. Furthermore, no change in the work/finance domain was demonstrated, perhaps because 26 of the 32 participants had either retired by the time of treatment or had never worked outside the home.

CONCLUSION

There was a correlation with CRST in 3 domains at 6 months and 1 year: physical (R=0.40 and R=0.62), psychosocial (R=0.40 and R=0.50) hobbies/leisure (R=0.45 and R=0.34).

The summary index (mean of percentage scores across the five domains) at 6 and 12 months was significantly improved from baseline, indicating that improvements in quality of life persist one year after treatment.



Intense Therapeutic Ultrasound for Musculoskeletal Pain Reduction Part 1; Technical and Preclinical Data

M.H.Slayton, Ph.D.¹

J.K. Barton, Ph.D.²

R.C. Amodei, RDMS¹

¹CEO, Guided Therapy Systems, Inc.: Mesa, Arizona USA

²University of Arizona; Tucson, Arizona USA

e-mail: m.slayton@guidedtherapy.com

OBJECTIVES

Assess feasibility of Intense Therapeutic Ultrasound (ITU) to create thermal coagula in musculoskeletal tissues and the impact of such treatments in ex-Vivo and in-Vivo rabbit model for subsequent clinical trials.

METHODS

ITU was tested on explanted porcine tissue to assess the size and depth of thermal coagula when simulating treatment. A pilot study was performed on 22 white rabbits to determine the impact of the treatment. For each rabbit, the right Achilles was partially cut to simulate a tear, while the contralateral tendon was left uncut. Rabbits were tested at 1, 4, 14 and 28 days after surgery and treatment. Tests included: ultrasound imaging (US), optical coherence tomography (OCT), mechanical strength testing, gene expression analysis (PCR), histology and atomic force microscopy (AFM) of sectioned tissue.

RESULTS

In rabbit studies US imaging showed enhanced healing of treated sites, MPM: inflammatory infiltrate, collagen synthesis, OCT birefringence banding caused by collagen organization. Days 14-28 tendons had smooth appearance and histology. Result trends in gene expression indicated initial decrease in growth and collagen followed by sharp increase. No difference in failure loads for all tendons suggested healing occurred by 14 days restored mechanical properties and no harm caused to tendon tissues.

CONCLUSIONS

Results suggest that ITU does not cause decreased mechanical strength of tendon, nor any other detrimental impact, while upregulating genes associated with inflammation and healing, with increased collagen expression at later timepoints.

ACOUSTIC MODELING AND FOCUS QUALITY THROUGH THE RIBCAGE WITH A DUAL MODE ULTRASOUND RANDOM PHASED ARRAY

Muhammad Zubair¹, Robert Dickinson¹

¹Department of Bioengineering, Imperial College, South Kensington campus, London
e-mail: m.zubair14@ic.ac.uk; Robert.dickinson@ic.ac.uk

OBJECTIVES

A major difficulty in the clinical use of High Intensity Focused Ultrasound (HIFU) for ablating liver tumor is the transmission of sufficient energy through the ribs to induce tissue necrosis while minimizing the energy in side-lobes. It is thus of paramount importance to determine the position of ribs and calculate acoustic intensity distribution near the ribs to optimize the efficacy of the HIFU system in terms of peak intensity levels in the focal plane and low intensity levels in the rib plane.

METHODS

Though Random Phased Arrays are optimized for therapy only, the highly directional elements and the availability of almost 40% bandwidth encouraged us to assess its imaging capabilities. A 1 MHz 256-element random phased array, made by Acublate Ltd, London, UK is used both in therapeutic and imaging modes. Control code was developed to generate the correct drive signals for generating a single focus and set of foci at a desired target position, and for processing the receive signals for image reconstruction of the target volume. In imaging mode, the random phased array was integrated with Verasonics system via custom-built connectors to acquire raw RF data. Synthetic Aperture 3D beamforming technique was used to achieve 3D volumetric images of the region of interest including Rib phantoms and ex-vivo ovine ribs in water bath.

RESULTS

Acoustic field distributions were calculated in the focal plane in an xy Cartesian coordinate grid with spatial step of 0.2mm. Patterns of multiple heating foci were generated and steered at ± 15 mm off the array axis and ± 20 mm along the axis. Ribs 8 to 12 of the left side of the rib cage were used in simulation after truncating them from the spine. The input acoustic power was set to 15W and the effect on intensity at the focal spot due to shadowing of the ribs and focus deterioration due to periodic structure of the ribs were calculated for various different array-rib configurations.

CONCLUSIONS

The effect on focal quality caused by the ultrasonic propagation through the ribs were quantified in various different scenarios that may come across the surgeon in a clinical setting.



Fig.1. Two Ovine ribs (left),
3D image (right)

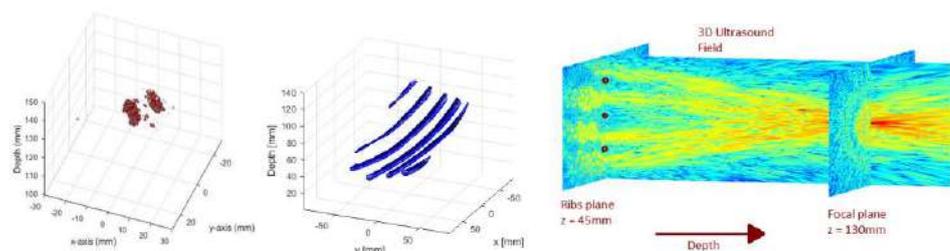


Fig. 2. Anatomical correct ribs (left), 3D acoustic
field (right)

A FAST PARALLEL COMPUTING METHOD FOR TRANSCRANIAL ULTRASOUND PHASE CORRECTION BASED ON K-SPACE PROPAGATION MODELS AND ACOUSTIC HOLOGRAPHY METHOD

Nan Wu¹, Guofeng Shen¹, Yazhu Chen¹, Xiongfei Qu¹

¹School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China
e-mail: saturnnan@sjtu.edu.cn

OBJECTIVES

The noninvasive transcranial ultrasonic brain therapy requires a multi-element ultrasound transducer and phase correction algorithms to compensate the aberrations caused by heterogeneous acoustic medium of skulls. The present work utilizes a fast parallel hybrid acoustic simulation (HAS) based on k-space pseudospectral method (KSPM) and acoustic holography method to calculate the corrected phase.

METHODS

A 37-element concave phased array transducer (800 kHz) was designed in the simulation. The parameters of the skull were converted from the CT images. Each element of the array corresponded to one channel, which consisted of two stages: a k-Wave stage was used to simulate the acoustic field containing a part of parietal through the method of KSPM; a holography stage was used to calculate the homogeneous medium region. The multi-channel could be calculated by multiple GPUs in parallel compared with the method of time reversal (TR) by one GPU.

RESULTS

The axial results of the sound pressure after the phase correction by the method of HAS and TR are shown in Figure a. The computational time of phase correction for different thread counts are shown in Figure b.

CONCLUSIONS

A sharp focus can be acquired through the HAS as well as the TR, and the accuracy of the results are nearly the same. The HAS (multiple GPUs in parallel) could reduce more computational time.

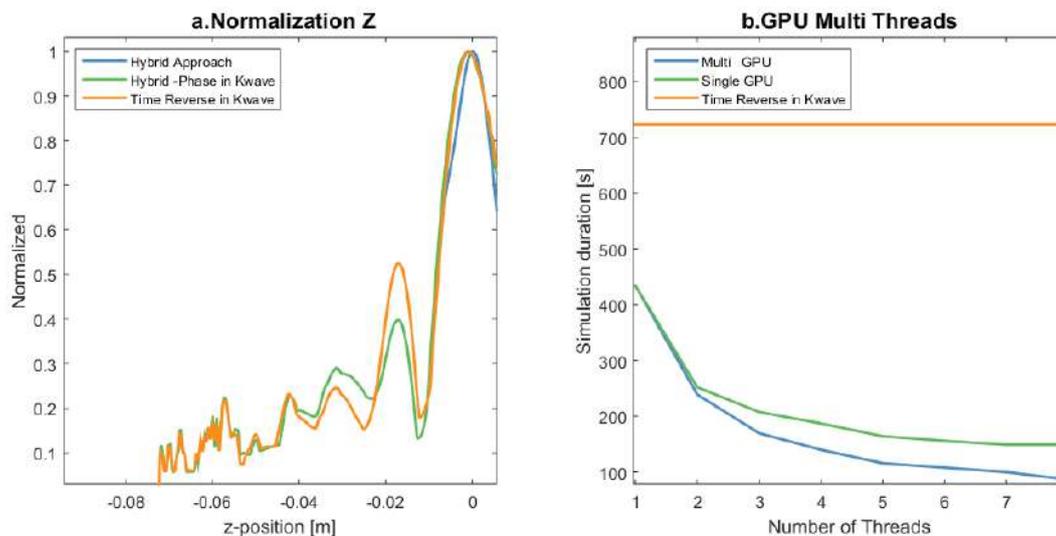


Figure: a. Axial results of the sound pressure after phase correction by the method of HAS and TR correction; b. Consumption time of GPU operating as a function of thread counts.

TARGETING IMMUNOSUPPRESSION FOR ENHANCED FOCUSED ULTRASOUND EFFICACY IN TNBC

A.R. Witter¹, N.D. Sheybani², E.A. Thim², R.J. Price², T.N.J. Bullock¹

¹ Department of Pathology, University of Virginia, Charlottesville, Virginia, USA

² Department of Biomedical Engineering, University of Virginia, Charlottesville, Virginia, USA

e-mail: ar.witter@virginia.edu; nds3sa@virginia.edu; rprice@virginia.edu; tb5v@virginia.edu

OBJECTIVES

Focused ultrasound (FUS) ablation has been shown to cause tumor cell damage and to elicit immunomodulatory effects, however whether these effects are sufficient to overcome the prevalent immunosuppression in aggressive, metastatic disease like triple-negative breast cancer (TNBC) remains unclear. These studies aim to refine immunotherapeutic interventions in combination with partial thermal ablation (tFUS) in order to optimize immune-mediated anti-tumor responses in metastatic TNBC.

METHODS

Spontaneously metastasizing TNBC (4T1 cell line) was implanted in the flank of Balb/C mice. Two weeks post-inoculation, tumors were ultrasonically coupled to an ultrasound-guided 3 MHz FUS system and partially thermally ablated at 30W derated acoustic power for 4 seconds in order to reach temperatures exceeding 60°C. Gemcitabine, poly(I:C) with FGK45, or GR-1 depleting antibody were used to attenuate myeloid cell immunosuppression. Tumor outgrowth was monitored by digital caliper measurements and immunophenotyping and functional assessments were analyzed via flow cytometry.

RESULTS

Initial experiments indicate that tFUS promotes immune activation within tumor-draining lymph nodes but does not control tumor growth. Combination of tFUS with gemcitabine leads to sustained tumor control and reduced mortality.

CONCLUSIONS

While tFUS promotes DC activation in tumor bearing mice, approaches to enhance immunogenicity in the tumor microenvironment are needed to gain durable responses. Our approach of reducing the myeloid-driven immunosuppression and utilizing tFUS to drive an anti-tumor immune response could prove promising across many tumor types.

ACKNOWLEDGEMENTS

Support from the Focused Ultrasound Foundation and NIH 2T32CA009109-41.

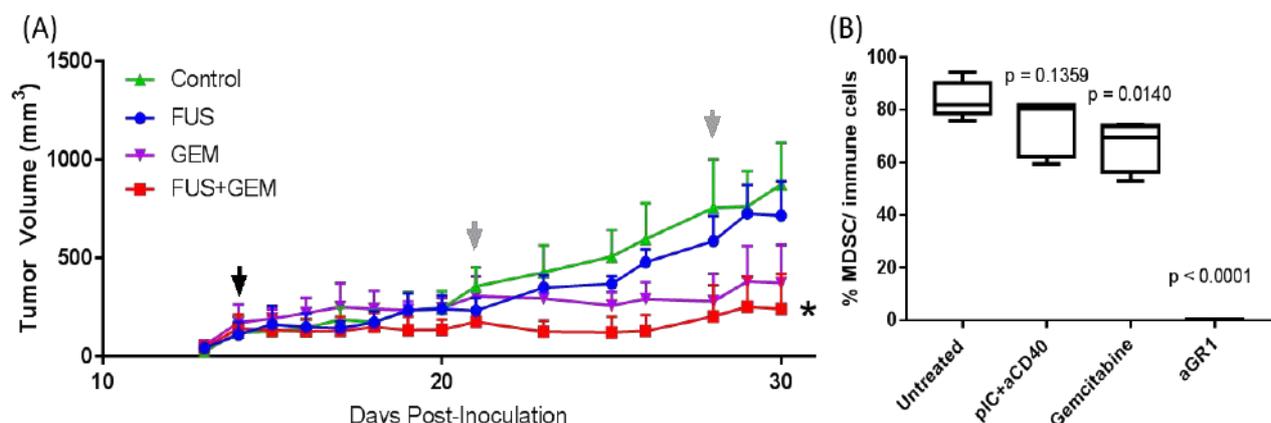


FIGURE: (A) Gemcitabine + tFUS treatment leads to sustained tumor control. (B) Interventions that lead to reduced immunosuppressive myeloid cells in circulation.

EVALUATION OF DIFFERENT IN-VITRO SETUPS CONCERNING TRANSFERABILITY INTO CLINICAL APPLICATION OF EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY

N. Reinhardt¹, J. Hahn¹, C. Bach², K. Radermacher¹, M. de la Fuente¹

¹Chair of Medical Engineering, Helmholtz-Institute for Biomedical Engineering, RWTH Aachen University, Aachen, Germany

²Department of Urology, University Hospital Aachen, Aachen, Germany

e-mail: reinhardt@hia.rwth-aachen.de

OBJECTIVES

A common practice to evaluate the efficiency of shockwave lithotripsy is to position a phantom stone in the focal area of the applied shockwaves within a water tank. Thereby many factors are neglected, especially the impact of the surrounding tissue. Thus the objective is to investigate the influence of different in-vitro setups on sound fields and stone comminution in order to evaluate transferability into clinical application.

METHODS

A kidney phantom, made of gel-wax and paraffin, with similar acoustic properties to kidney tissue was developed. It was analysed in a testing rig comprising a piezoelectric research lithotripter and compared to a latex stone holder and porcine tissue. The influence on the sound field was investigated by pressure measurements with a fibre optic hydrophone while the amount and location of cavitation was determined by B-mode ultrasound. Moreover, the efficiency in stone comminution was analysed by fixed-dose fragmentation of gypsum stones.

RESULTS

Sound field measurements behind phantom and tissue showed attenuation of the shock front as well as a reduced negative pressure in contrast to the latex holder. Cavitation amount and location differed for all setups. Stone fragmentation was less efficient in the kidney phantom (fragmentation coefficient $f=7.45\%$) than in the latex holder ($f=30.44\%$).

CONCLUSIONS

Frequency-dependent material damping caused decreased peak pressures while negative pressure was absorbed by cavitation resulting in less efficient stone fragmentation behind tissue. Therefore, adapting in-vitro conditions closer to the in-vivo situation is necessary in order to analyse fracture mechanisms.

ACKNOWLEDGEMENTS

Supported by Richard Wolf GmbH, Knittlingen, Germany.

FAST SCANNING FOR HOLOGRAPHIC CHARACTERIZATION OF SOURCES

W. Kreider¹, C. Hunter¹, V.A. Khokhlova^{1,2}, O.A. Sapozhnikov^{1,2}

¹Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

²Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

e-mail: wkreider@uw.edu; olegs2@uw.edu

OBJECTIVES

Acoustic holography provides an efficient and accurate way of reconstructing ultrasound fields in 3D based on 2D hydrophone scans. However, to characterize sources operating at megahertz frequencies with apertures on the order of 10 cm, holograms often include tens of thousands of measurement points. Typical measurement systems use a motorized positioner to scan a single hydrophone through the measurement region point-by-point, with measurement times in excess of 5 hours. Here we evaluate the potential for accelerating such measurements.

METHODS

A custom scanning program was developed to synchronize motion along one linear positioner axis with the excitation of a source and associated hydrophone measurements. The positioner comprised lead screws driven by stepper motors (Velmex, Inc., Bloomfield, NY); hydrophone signals were recorded using a 14-bit digitizer with deep memory (Gage Razor 14, DynamicSignals LLC, Lockport, IL). Positional uncertainties were evaluated by comparing point-by-point and continuous line scans in measuring the focal lobe of a 4.2 MHz source (aperture 4.5 cm, F-number 1).

RESULTS

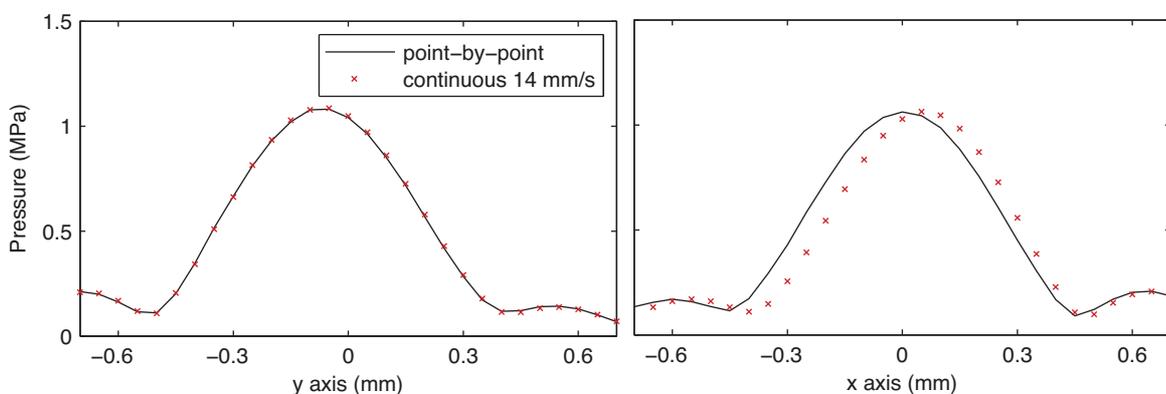
Continuous scans at speeds up to 14 mm/s were tested and not found to introduce any measurable position uncertainty for movement in one direction transverse to the acoustic beam; scans in the other transverse direction introduced relative displacements on the order of 50 μm . Differences between these directions are related to both the geometry of fixturing used to hold the hydrophone and the tank orientation. Uncertainty appears to be related to compliance in the fixturing.

CONCLUSIONS

Although care must be taken with regard to fixturing, continuous scanning can be implemented with negligible loss of accuracy, thereby enabling accurate holograms to be recorded in less than an hour.

ACKNOWLEDGEMENTS

Supported by NIH R01EB025187 and R01EB007643.



CAPTION: Pressure magnitudes measured in the focal plane of a 4.2 MHz source. With the hydrophone supported by a vertical tube (2.5 cm diameter, 110 cm length) aligned with the y axis, no measurable uncertainty in position is introduced by recording measurements during continuous hydrophone motion in the y direction. In contrast, scanning transverse to the tube axis in the x-direction appears to cause a relative displacement.

REAL-TIME CLOSED-LOOP CONTROL OF TRANSCRANIAL FUS-INDUCED LOCALIZED THERMAL LESIONS IN VIVO WITH MINIMAL COLLATERAL DAMAGE

P. D. O'Brien¹, H. Aldiabat¹, K. Schiabe², R. Aravali¹, W. C. Low², E. S. Ebbini¹

¹Electrical and Computer Engineering, University of Minnesota, Minneapolis, USA

²Neurosurgery, University of Minnesota, Minneapolis, USA

e-mail: obrie844@umn.edu, aldia001@umn.edu, schai003@umn.edu, aravalli@umn.edu, lowwalt@umn.edu, ebbin001@umn.edu

OBJECTIVES

The feasibility of using real-time monitoring and closed-loop control of short-exposure tFUS shots to spare the skull and scalp tissue is investigated. In particular, the use of 200-msec tFUS shots with initial intensities above the threshold with real-time closed-loop control at 400 frames per second (fps) is investigated. The goal is to establish the feasibility of forming localized tissue necrosis while sparing the scalp and intervening brain tissues.

METHODS

Anesthetized rats (~300 g) were treated under IACUC-approved protocol. A dual-mode ultrasound array (DMUA) operating at 3.2 MHz is used for imaging and lesion formation. A stereotaxic guidance system is used to locate the target tissue with reference to the skull suture lines identified on 3D DMUA imaging. Once the target is located, real-time imaging before, during and after tFUS application is performed at 400 fps with real-time tracking of thermal and mechanical echo changes. Initial tFUS intensities ~10 kW/cm² are used. Following the detection of signature tFUS-induced tissue changes, the beam intensity is reduced to main the heating at the target while minimizing the power deposition to the skull. Histological evaluation was performed 2 – 5 days after treatment.

RESULTS

The figure shows a sagittal slide from a treated rat with two distinct lesions placed at -4.2 and -5.2 from bregma. Histological analysis confirmed the localized thermal coagulative necrosis within the lesion boundaries shown. Only minor blisters were observed on the scalp.

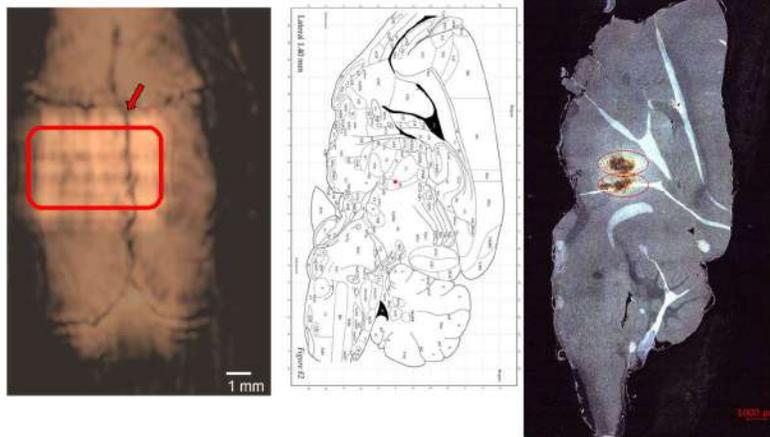
CONCLUSIONS

The results demonstrate the use of CLC of tFUS beams for localized thermal coagulative necrosis with minimal collateral damage.

ACKNOWLEDGEMENTS

Funded by grant R01 NS098781 from the National Institutes of Health

CAPTION: Left: A C-scan of the skull surface derived from 3D DMUA imaging data with the tFUS wavefront highlighted (arrow points to bregma). Center: The closest sagittal section from rat brain atlas showing the target region. A composite fluorescence/bright field slide showing two tFUS-induced lesions. Damage within the area marked by the two ellipses.



IS AGE A LIMITATING FACTOR IN THE TREATMENT OF BENIGN THYROID NODULES WITH HIFU?

P.P. Ortiz Remacha¹, J. Vidal Jové²

¹Endocrinology specialist. Expert in thyroid pathology. Human Anatomy and Embryology Department, Universidad de Zaragoza, Spain.

²Surgery specialist. Hospital Universitario Mutua de Terrassa, Barcelona, Spain.

E-mail: doctorortizremacha@gmail.com

OBJECTIVES

Understand the efficacy and limitations of HFU treatments of benign thyroid nodules on elder patients.

METHODS

60 patients with benign thyroid nodules (Bethesda Category II) were treated with HIFU (Echopulse® Theraclion). Patients over 70 years old constituted a subgroup of 8 subjects. Clinical data from both groups was collected. Both groups had the same oral analgesia protocol and post-treatment follow-up after 6 weeks, 6 months, and 12 months, by echography.

RESULTS

The results from the subgroup of advanced age confirm the need for two treatment sessions. During the first treatment with oral analgesia, patients feel more pain, are nervous and show some anatomical limitations; the treatment is performed only partially. The second treatment is realized with sedation and concluded without further issues.

CONCLUSIONS

The efficacy of the treatment of benign thyroid nodules with HIFU on elder patients is improved if sedation is used instead of oral analgesia. Anatomical limitations linked to cervical arthrosis and scoliosis, as well as higher psychological vulnerabilities, can explain this choice.

SEMI-AUTOMATIC AND AUTOMATIC SEGMENTATION OF CT IMAGES FOR MODELING THERAPEUTIC ULTRASOUND BEAMS IN A HUMAN BODY

A.S. Bobina¹, P.V. Yuldashev¹, M.S. Avetisian³, V.A. Khokhlova^{1,2}

¹Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Faculty of Computational Mathematics and Cybernetics, M.V. Lomonosov Moscow State University, Moscow, Russia

e-mails: ana06.97@mail.ru; {petr, vera}@acs366.phys.msu.ru; avetisian@gmail.com

OBJECTIVES

Quantitative characterization of ultrasound fields inside the human body is a challenge. One of the critical problems in non-invasive ultrasound surgery applications therefore is the development of patient-specific treatment protocols. The goal of this study was to provide methods for reconstructing inhomogeneities of biological tissues for acoustic propagation models.

METHODS

Spatial distributions of the density and sound speed were extracted from computed tomography images as functions of Hounsfield units. Segmentation of CT images allowed definition of tissue types at each voxel followed by the assignment of absorption and nonlinear coefficients known from the literature. The segmentation was performed either by semi-automatic method or using deep learning neural network. The one-way numerical model based on the linearized Westervelt equation was used to propagate the ultrasound beam through the inhomogeneous medium.

RESULTS

Representative single slice of semi-automatic segmentation of CT data in the plane perpendicular to spine is shown in (a). Skin, fat, muscle, kidney, and bone tissues were identified. Hundreds of semi-automated segmented slices were used to train a neural network, which showed less than 1% difference from results of the semi-automatic method (b and c). Linear simulation results for acoustic pressure amplitude normalized to the source pressure generated by a 1 MHz transducer (10 cm diameter and 9 cm focal distance) showed significant distortions of the focal maximum due to the presence of tissue inhomogeneities (e-g versus d-f).

CONCLUSIONS

Semi-automatic and neural network based methods are developed for reconstructing spatial distributions of acoustic parameters from CT images of a human body for taking into account effects of heterogeneous biological tissues in treatment planning of therapeutic exposures.

ACKNOWLEDGEMENTS

Work supported by FUSF and student stipends from "Basis" Foundation.

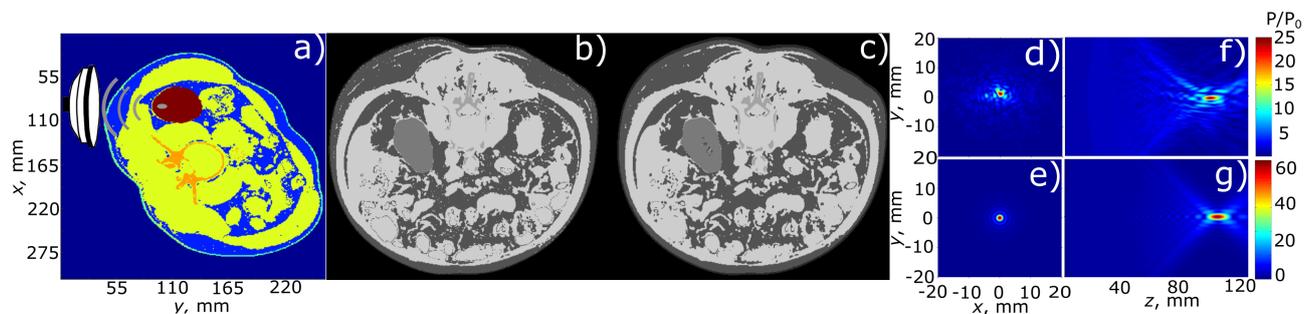


FIGURE CAPTION: a) HIFU transducer relative to the segmented CT image; results of b) semi-automatic and c) neural network segmentation; modeled acoustic pressure amplitude in a linear beam in the body (d, f) and in water (e, g) in the focal (d,e) and axial (f,g) planes.

A COMPARISON STUDY OF HIGH SPEED PHOTOGRAPHY AND PASSIVE ACOUSTIC MAPPING FOR MONITORING OF FOCUSED ULTRASOUND INDUCED CAVITATION BUBBLES

Pilsu Kim¹, Sua Bae¹, Jae Hee Song², Tai-Kyong Song¹

¹ Department of Electronic Engineering, Sogang University, Seoul, Republic of Korea

² Queensland Brain Institute, University of Queensland, St Lucia Campus, Brisbane, QLD, Australia

e-mail: pskim@sogang.ac.kr; suabae89@gmail.com; jae.song@uq.edu.au; tksong@sogang.ac.kr

OBJECTIVES

Although passive acoustic mapping (PAM) has been utilized for cavitation monitoring during focused ultrasound (FUS) therapy, its spatial accuracy has been assessed only in indirect ways such as comparing the cavitation location estimated by PAM with the location of the thermal lesion or BBB opening site. Here, we evaluate the spatiotemporal accuracy of PAM by comparing with high-speed photography (HSP) for FUS-induced cavitation.

METHODS

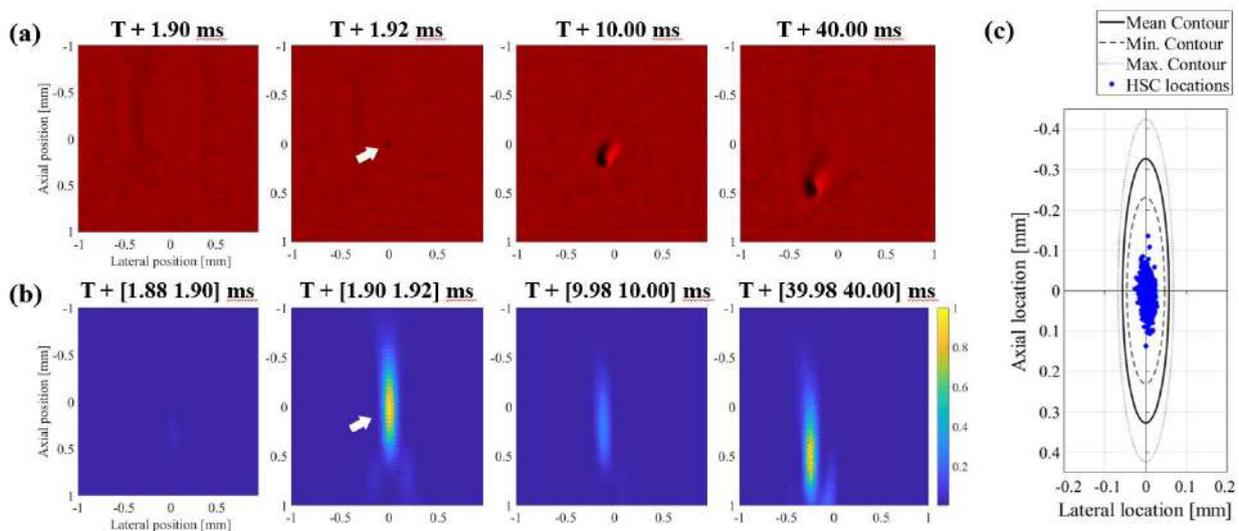
We conducted simultaneous monitoring with PAM and HSP during FUS sonication. All equipment were synchronized by an electric trigger. Poly-acrylamide phantom was insonated for 50ms by a 1.1-MHz transducer to induce cavitation. The cavitation is captured by a high-speed camera at 50kfps and an ultrasound system with a linear-array transducer. The image registration was conducted using the first frame showing cavitation from both imaging modalities.

RESULTS

Cavitation nucleation is simultaneously observed at T+1.92ms in HSP and PAM. Observed cavitation had traveled a distance of 0.547mm and -0.170mm in the axial and lateral direction. The mean discrepancies of the cavitation locations detected by HSP and PAM were 0.0064 ± 0.0052 mm and 0.0192 ± 0.0175 mm for lateral and axial direction ($N = 1881$ frames), which were 5.57% and 2.93% of the lateral and axial width of -6dB contour in PAM.

CONCLUSIONS

We verified that PAM provides high spatiotemporal accuracy in the localization of FUS-induced cavitation by simultaneous observation with PAM and HSP.



CAPTION: Cavitation images obtained by (a) HSP and (b) PAM. The first observation of cavitation is indicated by a white arrow. (c) Relative cavitation locations of HSP compared to those detected by PAM.

MR-HIFU mild hyperthermia with radiation and chemotherapy for rectal cancer: Phase I study in recurrent rectal cancer, and retrospective study for primary disease

William Chu¹, Yuexi Huang², Samuel Pichardo³, Kaitlyn Perry¹, Merrylee McGuffin¹, Robert Staruch⁴, Ari Partanen⁴, Shun Wong¹, Greg Czarnota^{1,2}, Kullervo Hynynen^{1,2}

¹ Sunnybrook Health Sciences Centre and University of Toronto, Toronto ON, Canada

² Sunnybrook Research Institute, Toronto ON, Canada

³ Cumming School of Medicine, University of Calgary, Calgary AB, Canada

⁴ Profound Medical, Mississauga ON, Canada

e-mail: william.chu@sunnybrook.ca

OBJECTIVES

For rectal cancer, mild hyperthermia (HT) with MR-HIFU may improve cancer control and quality of life by sensitizing tumors to radiation (RT) and chemotherapy (CT). We report on an ongoing phase I trial of MR-HIFU HT with RT+CT for locally recurrent rectal cancer, and a retrospective study evaluating tumor targetability for primary rectal cancer.

METHODS

The phase I trial has enrolled six patients with inoperable recurrent rectal cancer fit for re-irradiation and chemotherapy, and a HIFU-accessible MRI-visible lesion. Patients received 30.6 Gy (17 fractions) and daily oral capecitabine, plus MR-HIFU HT (Sonalleve) before RT on days 1/8/15. Primary objectives are safety (acute toxicity) and treatment feasibility. Secondary objectives include late toxicity, pain palliation, QoL, HT accuracy, and radiologic response. With research ethics board approval, we retrospectively identified 102 patients diagnosed with rectal cancer. Targetability by MR-HIFU was determined by the size and location of the tumor and surrounding structures.

RESULTS

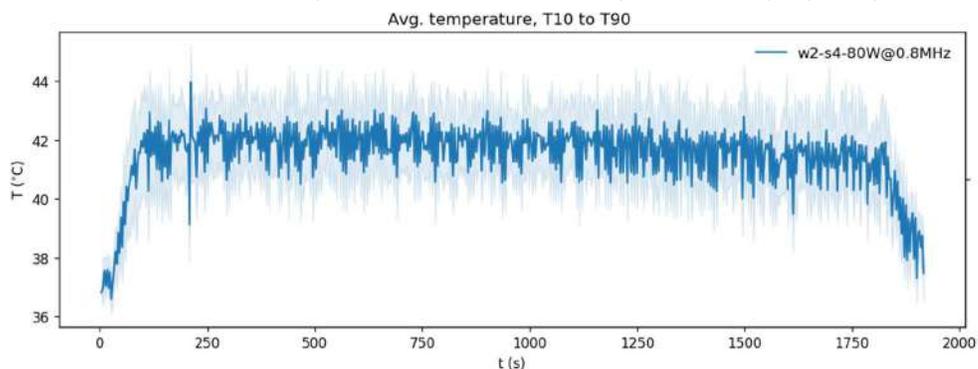
One patient withdrew after 1/3 HT sessions due to scheduling and sedation difficulties. Five patients completed HT+RT+CT. There were no intraoperative complications, no adverse events attributable to HT/RT/CT, and no unintended damage. Best HT sessions had mean (T90,T10) temperatures of 41.7 (40.6,42.9)°C. Sonication and MRI suite times were 36±13 and 226±78 min. For the retrospective study, the first 46/102 primary rectal tumors measured 50±18mm (craniocaudally) at depths of 84±17mm; 33 had tumors that abutted prostate/bowel/cervix/bladder/uterus. Width of the sciatic notch (acoustic window) was 58±14mm.

CONCLUSIONS

MR-HIFU HT has been safely delivered in five patients with recurrent rectal cancer, and targetability appears feasible for primary tumors.

ACKNOWLEDGEMENTS

Both clinical studies are funded by Canadian Cancer Society. RS, AP employed by Profound Medical.



CAPTION: Mean (T90, T10) temperature in 18mm diameter target for MR-HIFU HT patient 5.

FAST VOLUMETRIC LIQUEFACTION OF LARGE HEMATOMAS *EX VIVO* USING CONTINUOUS HIFU FOCUS TRANSLATION

S.A. Tsysar¹, P.B. Rosnitskiy¹, M.M. Karzova¹, E.M. Ponomarchuk¹, O.A. Sapozhnikov^{1,2}, T.D. Khokhlova³, A.D. Maxwell⁴, V.A. Khokhlova^{1,2}

¹Physics Faculty, M.V. Lomonosov Moscow State University, Moscow, Russia

²Center for Industrial and Medical Ultrasound, University of Washington, Seattle, USA

³Division of Gastroenterology, Department of Medicine, University of Washington, Seattle, USA

⁴Department of Urology, School of Medicine, University of Washington, Seattle, USA

e-mail: sergey@acs366.phys.msu.ru

OBJECTIVES

The main goal of this work was to perform fast volumetric mechanical disintegration of coagulated human blood using a pulsed HIFU exposure protocol and continuous translation of the focus.

METHODS

Ex vivo coagulated human blood (30x30x30 mm³) was enclosed in agar gel and positioned in degassed water in front of a 1.5 MHz HIFU transducer with F# = 0.77 (Fig. 1a,b). Pulsed sonications were performed at 240V and 1% duty cycle with 0.2 ms pulses containing high-amplitude shocks of 170 MPa and peak focal pressures of $p_+ = 155$ MPa, $p_- = 25$ MPa. The transducer focus was continuously translated within the targeted volume along 6 layers of folded meanders with 2 mm spacing between the lines and layers with the speed of 9.5 mm/s (Fig. 1c,d).

RESULTS

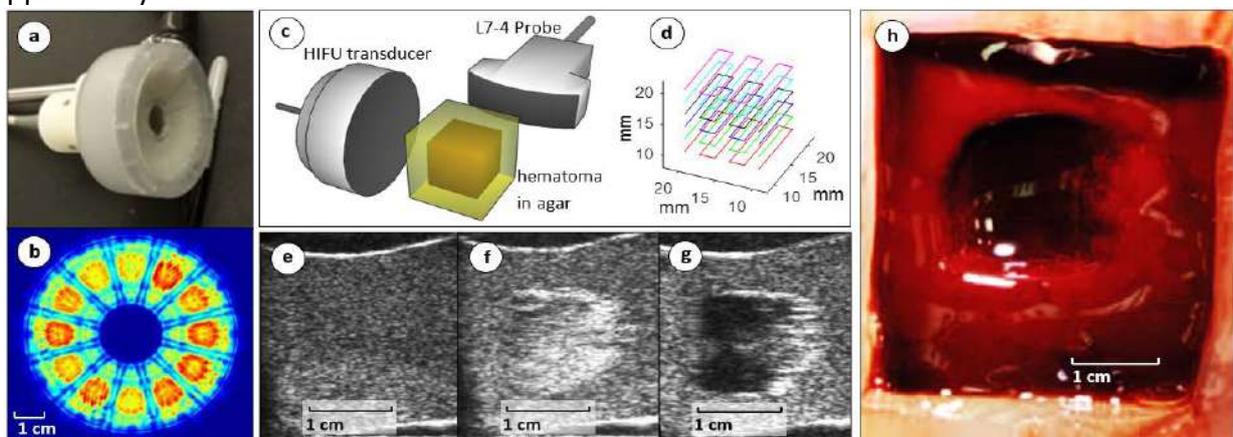
The treated sites were clearly observed in real time on B-mode images (Fig. 1e,f,g) as hyperechoic regions during the treatment and hypoechoic volume after the treatment. Lesion formation rate was 2.5 cm³/min for 1.8 cm³ treated volume. Similarly sized volumetric lesion consisting of discrete single boiling histotripsy lesions (135V, 10 ms, 1% DC, 4 mm step, 5 pulses per focus) was obtained at maximum effective ablation rate of 0.75 cm³/min.

CONCLUSIONS

Proposed method of lesion formation by sub-millisecond pulsed ultrasound combined with continuous mechanical translation of the focus provides full liquefaction of hematoma with clinically acceptable rate.

ACKNOWLEDGEMENTS

Supported by NIH GM122859 and RFBR 18-02-00991.



CAPTION: (a): 1.5 MHz 12-element HIFU transducer; (b): hologram of the transducer; (c): diagram of the experiment; (d): Focal spot trajectories; (e,f,g): B-images of volumetric lesion respectively: before HIFU, during HIFU exposure and 10 min after; (h): typical volumetric liquefied lesion.

STUDY OF THE EFFECT OF CRANIAL HOLES DUE TO EMISSARY VEINS AND INHOMOGENEITIES IN THE THICKNESS OF THE SKULL WHEN FOCUSING A TRANSCRANIAL ULTRASOUND BEAM

María Cristina Dejoz-Díez¹, Sergio Jiménez-Gambín¹, Andrei Marin¹, Noé Jiménez, Francisco Camarena¹

¹ Instituto de Instrumentación para Imagen Molecular, Consejo Superior de Investigaciones Científicas, Universitat Politècnica de València, Valencia, Spain
e-mail: madedie3@etsii.upv.es; serjigam@upv.es; ancrism2@alumni.uv.es; nojigon@upv.es; fracafe@fis.upv.es

OBJECTIVES

Skull bones present inhomogeneities due to variations in the thickness of the skull and, in addition, the appearance of emissary veins cause the existence of some of the skull holes. In transcranial focused ultrasound applications acoustic beams encounter in their path these tissues causing strong beam aberrations. The aim of this study is to numerically evaluate the impact of these inhomogeneities in the quality of an ultrasonic transcranial beam.

METHODS

Ultrasound fields produced by a 500 kHz single-element focused transducer were simulated using *k*-space methods. The acoustic properties of the skull were obtained from two CT-scan sets. In all simulations ultrasound beams were set to propagate through the parietal hole.

RESULTS

The robustness of single-element 500 kHz focused ultrasound has been proven with two skull CT-scan sets, one with a significant hole and the other homogeneous. The results show that the main focus retains good quality and only small increases in acoustic intensity are detected in the hole area due to inner resonances. The local increase of the energy density can lead to skull overheating in therapeutically applications. In addition, variations of the skull thickness produce the appearance of secondary foci, as well as to varying both the gain and the width of the main focus.

CONCLUSIONS

In the treatment planning it is recommended to avoid the areas of the skull where there exist strong irregularities in the thickness within the coverage of the acoustic beam, since the quality of the focus of single element focused transducers can be compromised.

ACKNOWLEDGEMENTS

Supported by Generalitat Valenciana research programs APOSTD/2017/042 and GV/2018/011 and by Europea Union through the Programa Operativo del Fondo Europeo de Desarrollo Regional (FEDER) de la Comunitat Valenciana 2014-2020 (IDIFEDER/2018/022). Supported by Agència Valenciana de la Innovació (INNCON00/18/9).

ULTRASONIC IMAGING OF TISSUE DISPLACEMENT INDUCED BY SHORT BURST EXPOSURE OF THERAPEUTIC ULTRASOUND FOR ESTIMATION OF ULTRASONICALLY HEATED REGION

S. Yoshizawa¹, H. Yabata², S. Umemura²

¹Graduate School of Engineering, Tohoku University, Sendai, Japan

²Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan

e-mail: syoshi@ecei.tohoku.ac.jp

OBJECTIVES

The objective of this study is to develop a method for the estimation of an ultrasonically heated region by ultrasound imaging before a HIFU treatment.

METHODS

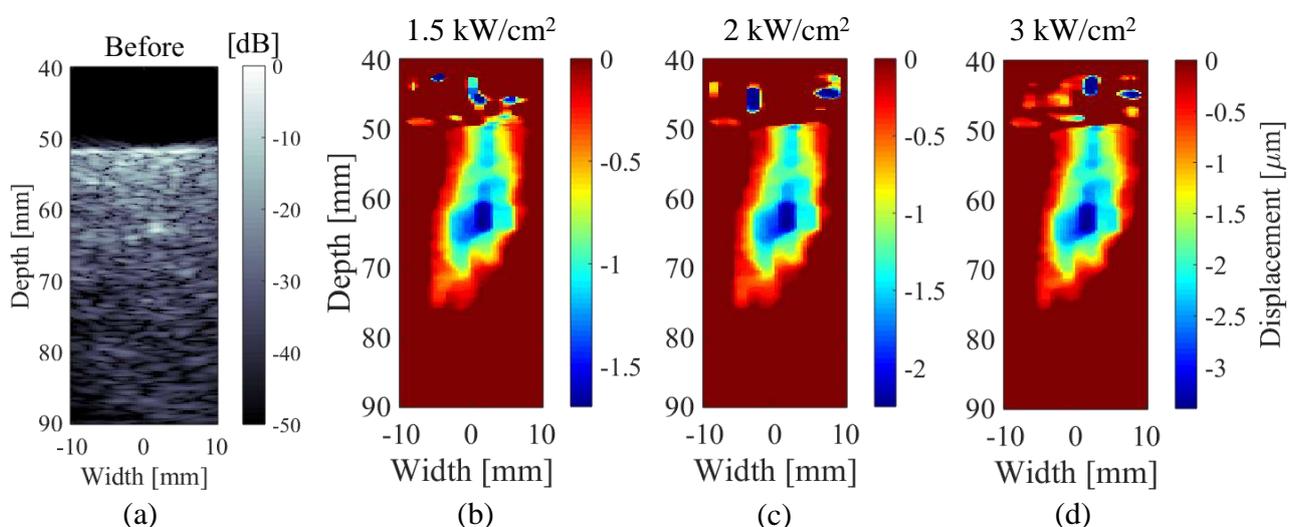
When the acoustic absorption of a target tissue can be assumed to be in proportion to the acoustic attenuation, it would be practical to estimate the relative distribution of the HIFU absorption from the tissue displacement induced by acoustic radiation force when exposed to a short burst of HIFU. In this study, a 128-ch array transducer was used as a HIFU source and placed in a water tank. The transducer has a diameter of 147.8 mm and a focal length of 120 mm, and was driven at 1.25 MHz for 2 ms. A diagnostic probe was set in the center hole of the HIFU transducer. Plane waves at 3.5 MHz were transmitted from the diagnostic probe to acquire the tissue displacements 2.6 ms after the start of the HIFU exposure.

RESULTS

The B-mode image of the chicken breast tissue before the HIFU exposure and displacement distributions after the HIFU exposure at three different intensities are shown in Figs. (a) – (d). The geometric focal point of the HIFU transducer was located at a depth of 70 mm. The displacement distributions approximately proportional to the acoustic intensities were obtained in the shallower region than the geometric focal point.

CONCLUSIONS

The proposed method would be helpful to estimate a HIFU heating region before the HIFU treatment.



CAPTION: (a) B-mode images of the target tissue. Displacement distributions induced by the exposure of 2-ms HIFU burst at (b) 1.5, (c) 2.0, and (d) 3.0 kW/cm².

EXPERIMENTAL SETUP FOR CHARACTERIZATION OF LOW INTENSITY ULTRASOUND FOR TARGETING THE CORTICAL REGION IN THE BRAIN

Shirshak Shrestha¹, Christopher Krasnichuk², Samuel Pichardo³

¹Department of Biomedical Engineering, University of Calgary, Calgary, Canada

²Department of Electrical Engineering, Lakehead University, Thunder Bay, Canada

³Departments of Radiology and Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

e-mail: shirshak.shrestha@ucalgary.ca; samuel.pichardo@ucalgary.ca; cjkrasni@lakeheadu.ca

OBJECTIVES

Low Intensity Focused Ultrasound (LIFU) is being studied as a non-invasive technique to perform neurostimulation in the cortex tissue. Inspired by a previous characterization setup [1], this study presents a method to verify the focusing of the acoustic pressure in regions close to the skull inner face where cortical targets are located.

METHODS

A custom-made force-sensitive device mimicking a needle hydrophone was 3D-printed to locate stereotactic landmarks in the skull phantom fixation frame. Both frame and skull phantom were scanned with Computed Tomography (CT). The device was mounted on a 3-axis cartesian positioning system to identify the landmarks when pressed against them. The locations of the landmarks were registered with a CT scan of the skull phantom to locate it in the 3D space. The force-sensitive device was also used as a redundancy to stop the positioning system given hydrophone touching the phantom.

RESULTS

The distance between the 6 landmarks located in the skull phantom fixation frame using the force resistive device and the 3-axis cartesian positioning system was found to be within 1.22% of the actual distance. This registration precision is slightly better than previous work using optical registration method (3%) [1].

CONCLUSIONS

The force resistive device improves on locating the skull to scan the inner surface of the calvaria. This method allows for data collection close to the inner skull enabling studies of ultrasound effects for targeting the cortical regions of the brain.

REFERENCES

1. V. Chaplin et al. 2018 Phys. Med. Biol. 63 105016

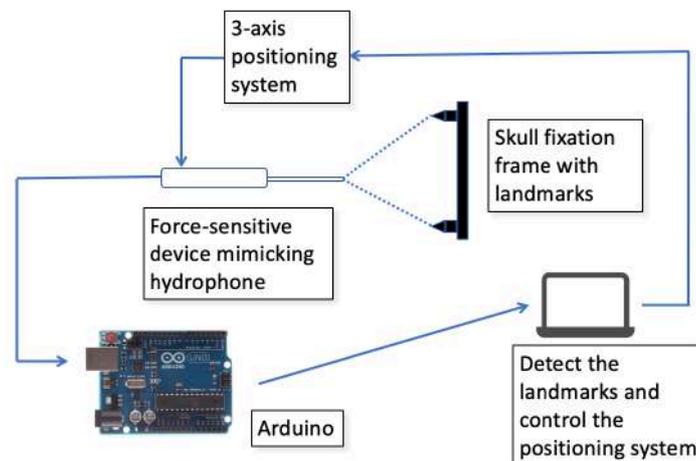


Figure 1: 2D Setup Schematic

EFFECTS OF PHYSICAL PARAMETERS ON ESTIMATING ACOUSTIC INTENSITY IN FOCUSED ULTRASOUND FIELD USING INFRARED CAMERA

Yu Ying^{1,3}, Shen Guofeng², Qiao Shan³, Wu Hao³, Qu Xiongfei², Wu Nan², Ma Xiao²

¹ School of Computer Science, Jiangxi University of Traditional Chinese Medicine, Nanchang, Jiangxi, CHINA

² School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, CHINA

³ Shanghai Shende Health Care Co., Ltd, Shanghai, CHINA

e-mail: 59920079@qq.com; shengguofeng@sjtu.edu.cn

OBJECTIVES

Recently, infrared thermometry has been used to estimate acoustic intensity in the focused ultrasound field at full power or in the therapy mode. According to the theoretical framework of quantitative method for estimating harmonic intensity in focused field, the thermal field acquired by infrared camera at same plane with different thickness of absorber could be used to estimate the intensity amplitude of fundamental and parameters for harmonics. In this paper, the effects of different thickness of absorber and heating time were discussed.

METHODS

The beam distribution in the absorber was performed by a free software HIFU-Simulator. The heat deposition in the absorber was calculated basing on the standing wave model. Thermodynamic formulas were used to calculate the temperature rise on the absorber/air.

The equal interval of thickness was set to 1, 2 and 3 mm. The symbol D11, D12; D21, D22; D31, D32 mean the thickness of three absorbers are 1,2,3; 2,3,4; 1,3,5;2,4,6;1,4,7,2,5,8; respectively. The comparisons of derived acoustic intensities and theoretical value were carried out at different location in the sound field (Z1 ~ Z5) and heating time. Sound power was set to 100 W. The heating time was set to 40 to 100 ms.

The PDTI (percentage difference of total intensity on beam axis), and PDFI (percentage difference of fundamental intensity on beam axis), and PDBW (percentage difference of -6 dB beam width of total intensity) were used to evaluate the effect of the thickness in changing and heating time.

RESULTS

The PDTI decreased with the increase of heating time when the interval of thickness was 1 and 2 mm. The minimum of it was 0.02% when the thickness of absorbers is D21 and heating time is 100 ms. When the interval of thickness was setting to 3 mm, the minimum of PDTI was find at 60 ms at D31 and 80 ms at D32. The overestimation happened in the focal plane (Z1) and far field (Z3).

The indicator PDFI in the focal plane decreased with the increase of heating time at D11 and D12. The minimum of PDFI in the focal plane was find at heating time is 80 and 40 ms for D21, D22 and D31, D32, respectively. The PDFI in other position (Z2, Z3, Z4, Z5) decreased with the increase of heating time for all thickness of absorber.

The PDBW had same trend for thickness settings. In the near field (Z4, Z2), the PDBW increased with the increase of heating time, but in the focal plane and far field (Z5, Z3) the trend was opposite.

CONCLUSIONS

In this paper, the effects of choosing different thickness of absorber and heating time were discussed. The choosing of thickness of absorber and heating time will lead to great influence to the estimation. Generally, the bigger interval of thickness and longer heating time would lead to better results.

ACKNOWLEDGEMENTS

The paper is supported by program or foundation (2017YFC0108900, 11774231, 20151BAB202014, 81727806, 17441906400, 15441900700).

MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND THALAMOTOMY IN ESSENTIAL TREMOR: ONE-YEAR CLINICAL EXPERIENCE IN A SINGLE CENTER

S. Tamburin^{1,2}, G. Ricciardi¹, T. Bovi¹, M. Longhi¹, R. Foroni¹, A. Nicolato¹, B. Bonetti¹, M. Tinazzi^{1,2}, E. Ciceri¹, S. Montemezzi¹

¹Verona University Hospital, Verona, Italy

²University of Verona, Verona, Italy

e-mail: stefano.tamburin@univr.it

OBJECTIVES

Magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy of the ventralis intermedius (Vim) nucleus is emerging as a minimally invasive treatment for patients with disabling and medication-refractory essential tremor (ET). We report our preliminary one-year experience on 15 patients with ET treated from January 2018 to February 2019 in a single center.

METHODS

From January 2018 to February 2019, 15 patients (7 men, 8 women, age: 70.7 ± 7.5 years) underwent MRgFUS thalamotomy of the Vim nucleus for disabling and refractory ET (tremor duration: 27.2 ± 12.2 years) with a 3T magnetic resonance scanner at Verona University Hospital.

RESULTS

At baseline the total Clinical Rating Scale for Tremor (CRST) score was 42.9 ± 15.8 , and the Quality of Life in Essential Tremor Questionnaire (QUEST) score was 38.5 ± 13.6 . At one-month follow-up, the total CRST score was 8.8 ± 5.2 and the QUEST score was 7.6 ± 4.5 . Response persisted in the majority of patients at three- and six-month follow-up. Side effects related to Vim nucleus thalamotomy included transitory ataxia, ballism, and mild lower-limb hypaesthesia.

CONCLUSIONS

Our data confirm that MRgFUS thalamotomy of the Vim nucleus is an effective treatment for disabling and refractory ET.

High intensity applicator for parallelized sonication of well-plates

S. Tretbar¹, M. Fournelle¹, M. Benecke¹, F.J. Becker¹, A. Melzer²

¹Ultrasound Department, Fraunhofer IBMT, Sankt Ingbert, Germany

²Innovation Center Computer Assisted Surgery, Leipzig, Germany

e-mail: steffen.tretbar@ibmt.fraunhofer.de

OBJECTIVES

For systematic assessment of the influence of ultrasound on biological systems, in-vitro studies need to be performed in a reproducible and standardized way. Furthermore, for achieving statistical significance, parallelized approaches involving multi-well plates are preferable over studies in single petry dishes. For this purpose, we developed a second generation ultrasound applicator allowing to deliver high intensities to cells in 96-well culture models.

METHODS

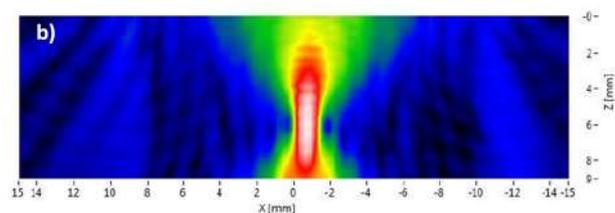
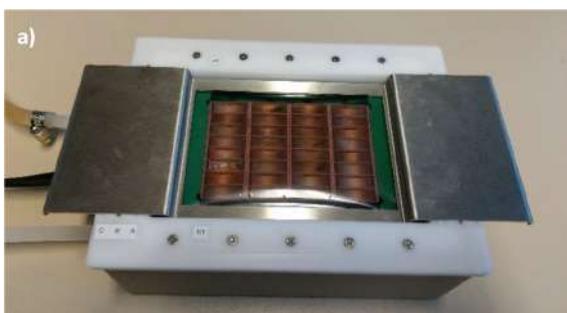
An earlier system consisting of 96 unfocused transducers was taken as the basis for the development of a high-intensity cell applicator. Cylindrically focused transducers with a curvature radius of 13 mm and a frequency of 1 MHz were integrated in a table-top device. Small bars were added in order to separate the sound fields of neighboring elements. A geometry of 8x4 transducers was chosen, so that a third of a 96-well-plate can be sonicated simultaneously. Water cooling was realized to prevent overheating of the piezo-elements.

RESULTS

When driven with a single channel amplifier (AG 1016, T&C Power Conversion Systems), acoustic intensities (I_{SPTA}) of more than 10 W/cm^2 could easily be achieved. A focus spot of $1,3 \times 5,5 \text{ mm}^2$ (FWHMs in the XY-dimension) was realized, which guarantees that the sound exposure is confined to a single well.

CONCLUSIONS

A high power applicator for sonication of well plates was realized and characterized. With a low inter-transducer intensity variation (standard deviation $\sim 10\%$), it can be used for parallelized in-vitro sonication experiments in applications such as hyperthermia or ultrasound mediated drug delivery.



CAPTION: 8x4 elements high-power applicator (a) and XZ-soundfield of a single element (b)

IN VIVO MEASUREMENTS OF SACRAL THICKNESS AND SACRAL NERVE LATERAL BRANCH DEPTH FOR FOCUSED ULTRASOUND ABLATION OF PATIENTS WITH SACRAL ILIAC JOINT PAIN: PREDICTORS FOR PATIENT CANDIDACY

J. Jaraki¹, D. Kushner¹, R. Aginsky², A. Hananel, MD, MBA, BsCs², F. Steinberg, M.D.³, S. LeBlang, M.D.³

¹Florida Atlantic University Charles E. Schmidt College of Medicine, Boca Raton, FL, USA

²FUS Mobile

³University MRI, Boca Raton, FL, USA

Email: jude.jaraki@gmail.com

BACKGROUND: To evaluate candidacy for focused ultrasound ablation of lateral branches of the sacral nerves in patients with sacral iliac joint (SIJ) pain.

METHODS: 50 CT scans of the sacrum were retrospectively evaluated in 23 male and 27 female patients, and charts were reviewed for age and BMI. Bilateral measurements were obtained from 2D and 3D images and included: distance between the lateral aspect of the posterior sacral foramina to the medial margin of the SIJ (LSIJ), depth from the skin to the midpoint of LSIJ at various angles without interacting with the spinous processes, AP thickness of the sacrum measured at LSIJ midpoint, as well as other anatomical measurements. A regression model evaluated the most statistically and clinically significant predictors for the distance from the skin to the LSIJ midpoint at these angles.

RESULTS: The average depth from the skin to the sacral LSIJ midpoint perpendicularly decreased as the vertebral levels increased. The average perpendicular skin distances were 57.2 mm at S1 and 40.97 mm at S2. The average AP diameter at S1 was 40.72 mm and increased at S2 to 44.79 mm then decreased through S3 and S4.

CONCLUSIONS: The average distance from the skin to the posterior border of the sacrum at the LSIJ was 49.1 mm and decreased as the vertebral level increased. To date, no clinical studies have published in vivo measurements of the posterior sacrum. These results will help determine the feasibility of noninvasive FUS ablation of the lateral sacral branches for patients with sacroiliac joint pain.

PORE ECCENTRICITY IMPROVES CT BASED ESTIMATES OF ACOUSTIC VELOCITY IN HUMAN SKULL BONE

T. D. Webb¹, S. A. Leung², P. Ghanouni³, J. J. Dahl³, K. Butts Pauly^{1,2,3}

¹Electrical Engineering, Stanford University, Stanford, CA

²Bioengineering, Stanford University, Stanford, CA

³Radiology, Stanford University, Stanford, CA

e-mail: taylor.webb@utah.edu

OBJECTIVES

Transcranial MR guided focused ultrasound treatments (tcMRgFUS) rely on CT based predictions of acoustic velocity to estimate phase corrections necessary to focus through the skull. Recent work shows that CT only accounts for about half of the variation in velocity in the skull. We examine how pore structure, information not easily captured by clinical CT, contributes to velocity in the skull.

METHODS

Bores with a diameter of 13 mm were removed from two dried *ex-vivo* skulls. Each bore was separated into up to three samples, one for each bone layer. The samples were sanded to achieve flat and parallel interfaces. Each fragment was imaged with clinical and micro CT imaging. Clinical images were used to estimate an average Hounsfield unit (HU) value and micro CT images were used to identify the average eccentricity, pore size, and porosity in each fragment. Combinations of HU with eccentricity (ϵ), pore size, and porosity were then correlated with the velocity measured in each fragment to see if information about pore structure improved predictions of velocity.

RESULTS

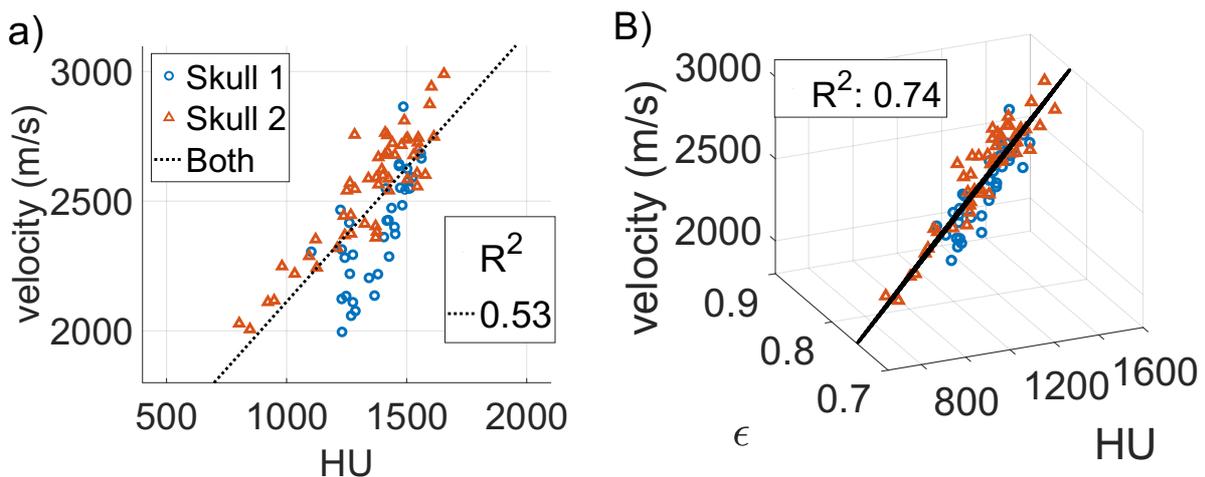
When combined with HU, measurements of pore eccentricity improve predictions of velocity (R^2 -squared increased from 0.53 to 0.74, see Figure). Other parameters produced no improvement.

CONCLUSIONS

Information about pore structure improves predictions of acoustic velocity in human skull bone.

ACKNOWLEDGEMENTS

NIH R01 MH111825, the FUS Foundation, GE Healthcare, InSightec.



CAPTION: (a) The correlation between velocity and HU appears to be strongly patient dependent. (b) Including eccentricity improves the R^2 -squared value and reconciles much of the difference between the skulls.

APPARENT DIFFUSION COEFFICIENT CLASSIFICATION PREDICTS OUTCOME OF MAGNETIC RESONANCE-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND TREATMENT OF UTERINE FIBROIDS

T. Sainio¹, J. Saunavaara¹, G. Komar², K. Joronen³, A. Perheentupa³ and R. Blanco Sequeiros²

¹Department of Medical Physics, Turku University Hospital, Turku, Finland

²Department of Radiology, Turku University Hospital, Turku, Finland

³Department of Obstetrics and Gynecology, Turku University Hospital, Turku, Finland

e-mail: teija.sainio@tyks.fi, jani.saunavaara@tyks.fi, gaber.komar@tyks.fi, Kirsi.joronen@tyks.fi, antti.perheentupa@tyks.fi, Roberto.blanco@tyks.fi

OBJECTIVES

The qualitative Funaki classification is typically used in screening and efficacy assessment of magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) uterine fibroid therapy. The aim of this study is to create a quantitative apparent diffusion coefficient (ADC) classification to screen patients and predict the MR-HIFU treatment outcome.

METHODS

Forty-two patients with 48 uterine fibroids underwent diffusion weighted imaging (DWI) as part of routine clinical screening protocol, based on which ADC maps were constructed and average quantitative ADC values obtained. Correlation between the pretreatment ADC values and immediate therapeutic outcomes (NPV ratios [NPVr]) was assessed. Optimal ADC cut-off values were determined to predict outcomes (NPVr of <30%, 30-60%, or >60%), resulting in three classification groups. Whole model was examined using receiver operating characteristic (ROC) curve analysis, and significance was tested with Chi-square test.

RESULTS

Statistically significant negative correlation (Pearson's $r = -0.40$, $p < 0.005$) was found between ADC values and outcomes. ROC curve analysis indicated optimal ADC cut-off values of $980 \times 10^{-6} \text{ mm}^2/\text{s}$ (NPVr >60%) and $1800 \times 10^{-6} \text{ mm}^2/\text{s}$ (NPVr <30%) producing ADC classification into three groups: ADC I (NPVr >60%), ADC II (NPVr 30-60%) and ADC III (NPVr <30%). ADC classification resulted in whole model area under the curve value of 0.79 ($p = 0.0007$).

CONCLUSIONS

ADC mapping could provide a method to quantitatively evaluate uterine fibroid HIFU suitability. ADC classification could offer a novel inclusion/exclusion criteria. Inclusion criteria could be ADC I ($\text{ADC} < 980 \times 10^{-6} \text{ mm}^2/\text{s}$) and ADC II ($\text{ADC} 980-1800 \times 10^{-6} \text{ mm}^2/\text{s}$), and exclusion criteria ADC III ($\text{ADC} > 1800 \times 10^{-6} \text{ mm}^2/\text{s}$).

ACKNOWLEDGEMENTS

Supported by The Finnish Cultural Foundation, TYKS Foundation and Instrumentarium Science Foundation.

Tissue-selective Ablation with Robotically Assisted Sonic Therapy (RAST): Radiologic-Pathologic Findings

E. A. Knott¹, K. Longo¹, J Swietlik¹, X Zhang², E. Vlasisavljevich³, Z. Xu⁴, F.T. Lee Jr¹, T.J. Ziemlewicz¹

¹Department of Radiology, University of Wisconsin, Madison, WI, USA

²Department of Pathology, University of Wisconsin, Madison, WI, USA

³Department of Biomedical Engineering, Virginia Tech University, Blacksburg, VA, USA

⁴Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

e-mail: knott2@wisc.edu; tziemlewicz@uwhealth.org

OBJECTIVES

Robotically Assisted Sonic Therapy (RAST) is the automated delivery of histotripsy. This exhibit will use MRI, CT, and pathology to demonstrate the ability of RAST to create effective ablations while sparing collagen-rich structures, such as vessels, bile ducts, bowel and urothelium.

METHODS

RAST hepatic or renal ablations were performed in female adult swine with a prescribed spherical shape of clinically relevant size (2-3 cm diameter). Following ablations, animals underwent MRI or CT, were sacrificed, and necropsy performed with pertinent tissues harvested for pathologic evaluation. Imaging and pathologic features were reviewed by abdominal radiologists and pathologists in consensus for radiologic-pathologic correlation.

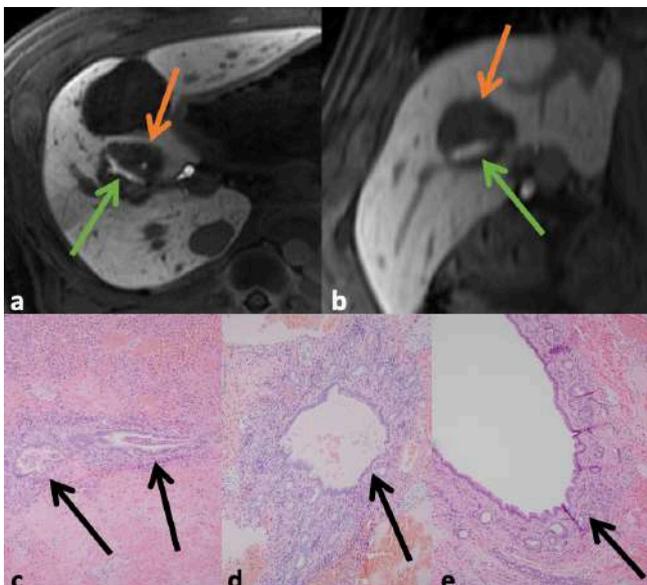
RESULTS

Liver: Imaging demonstrated complete destruction of targeted hepatocytes with a well circumscribed peripheral rim. MRI findings included intact bile ducts and vessels traversing ablation zones. On pathology, the central ablation zones had no viable hepatocytes and there was sharp demarcation from surrounding liver. Large bile ducts and arteries were preserved within ablation zones. Large veins appeared more susceptible to injury than arteries with evidence of portal venous thrombosis, though the collagen scaffolding of these vessels was intact.

Kidney: Imaging demonstrated generalized sparing of the collecting system with excretion of contrast into the ureter. At histopathology there were occasional patchy disruptions of the urothelium, though the underlying collagen matrix was intact with no urinary leaks detected upon retrograde injection of the ureter.

CONCLUSIONS

RAST appears to demonstrate tissue selectivity in the porcine model, a finding which could extend the indications for ablation and increase the safety of procedures.



CAPTION: (a) and (b) MR images of hepatic RAST ablation zones (orange) with traversing patent bile ducts (green). Histology images (c, d, e) of preserved bile ducts within ablation zones (arrow).

Potential for Thyroid Ablation with Robotically Assisted Sonic Therapy (RAST) with histotripsy: Proof-of-concept in a Porcine Model

J Swietlik¹, K. Longo¹, E. A. Knott¹, Z. Xu², F.T. Lee Jr¹, T.J. Ziemlewicz¹

¹Department of Radiology, University of Wisconsin, Madison, WI, USA

²Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

e-mail: jswietlik@uwhealth.org; zziemlewicz@uwhealth.org

OBJECTIVES

Given the growing incidence of small thyroid cancers identified with cross-sectional imaging there is need for non-invasive treatment options. The purpose of this study was to evaluate the feasibility of creating precise ablation zones within superficial soft tissues of a porcine thyroid model using histotripsy/RAST.

METHODS

Four swine underwent ablations targeted within the thymus/thyroid with a custom therapy transducer (Histosonics, Inc.). Each animal had 2 ablations prescribed (one left, one right), a 1.0 cm spherical ablation zone (0.5 cm³) and a 1.0 x 1.0 x 2.0 cm ovoid ablation zone (1.1 cm³). Thymus was included in the ablation zone due to the similarity in anatomic position of the porcine thymus to the human thyroid and the diminutive size of porcine thyroid. MRI was obtained following the procedure and ablations were reviewed for size and characteristics. The animals were sacrificed immediately following imaging, and the ablation zones were removed at necropsy for histologic analysis.

RESULTS

RAST created circumscribed ablation zones similar to the prescribed volume. Mean depth of the superficial aspect of the ablation zones was 1.9 cm (1.3-2.2cm). The 1.0 cm sphere ablation zones had a mean volume of 0.68 cm³ (SD +/-0.11). While the ovoid ablation zones had a mean volume of 1.20 cm³ (SD +/-0.40). MRI showed well demarcated ablation zones with central non-enhancement consistent with necrosis. There was mild edema in overlying muscle in 2/8 ablations.

CONCLUSIONS

RAST is capable of creating precise ablations in a porcine thyroid model without significant damage to the overlying structures.

HIGH FREQUENCY (20 MHz) FOCUSED ULTRASOUND - A NOVEL METHOD FOR DERMAL INTERVENTION

Torsten Bove¹ and Tomasz Zawada¹, Jørgen Serup²

¹TOOsonix A/S, Denmark

²Department of Dermatology, Bispebjerg University Hospital, Denmark.

e-mail: torsten.bove@toosonix.com

OBJECTIVES

High intensity focused ultrasound (HIFU) at high frequencies is not well explored, and commercial systems with frequencies above 15 MHz are not available. High frequencies however allow very small focal zones, and thereby precise confinement of lesions in e.g. the dermis layer of human skin. The objective of the work is to demonstrate a method and a HIFU system working at 20 MHz suitable for a wide range of indications in dermatology.

METHODS

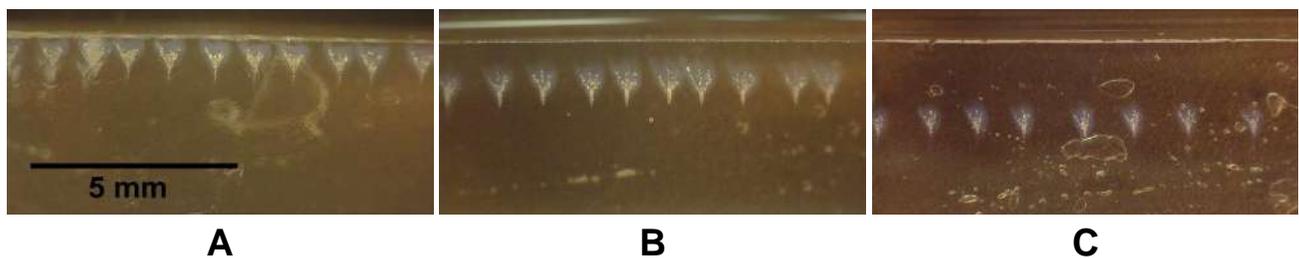
A new 20 MHz HIFU system has been used in the presented experiments. Tissue mimicking phantoms gel were used to verify acoustic field distribution and depth of treatments. The system was used to demonstrate the safety in a minipig animal study. Human experimental treatments were used to verify the efficacy of the method for tattoo removal, basal cell carcinoma and actinic keratosis.

RESULTS

Pre-clinical, animal studies and human clinical results are presented. Treatment on human skin demonstrate efficient removal of tattoos, regardless of color. The results indicate that a protocol for tattoo removal in 2 or 3 sessions is feasible. Initial treatments of basal cell carcinoma and actinic keratosis show similar encouraging results with significant removal and/or reduction of symptoms from single treatments.

CONCLUSIONS

High frequency HIFU has been used for research-based human treatment. A very effective method for tattoo removal as well as promising preliminary results in basal cell carcinoma and actinic keratosis is demonstrated. The method therefore has the potential to supplement or replace lasers and/or photodynamic therapy in both hospital and dermatology clinics.



Cross section of 20 MHz HIFU lesions in tissue mimicking gel made with an acoustic energy of 1.05 J (7 W, 150 ms). Focal depths are 1.7 mm (A), 2.2 mm (B) and 2.7 mm (C).

PRECLINICAL MRI-GUIDED FOCUSED ULTRASOUND HYPERTHERMIA IN 7 T MRI

Upasana Roy¹, Robbert van Gorkum², Marc Fournelle³, Sebastian Greiser⁴, Daniel Speicher³, Thomas Grunwald⁴, Sebastian Kozerke², Steffen Tretbar³, Lisa Landgraf¹, Andreas Melzer¹.

¹Innovation Center Computer Assisted Surgery, Leipzig, Germany.

²Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland.

³Fraunhofer Institut für Biomedizinische Technik, St. Ingbert, Germany.

⁴Fraunhofer Institute for Cell Therapy and Immunology, Department of Cell Therapy, Leipzig, Germany.

Email: upasana.roy@medizin.uni-leipzig.de

OBJECTIVES

Magnetic resonance imaging guided focused ultrasound (MRgFUS) allows precise and non-invasive 3D positioning of hyperthermia treatment at 41-46°C (Reike *et al.* JMRI 2008) which may allow to radio-sensitize tumor cells for Radiation Therapy (FUS-RT). The purpose of this study was validation of the implementation of a preclinical FUS system and MRI based thermometry for FUS-RT hyperthermia in a preclinical 7 T MRI scanner.

METHODS

A novel MRI conditional FUS array transducer for preclinical use has been developed and produced (11 x 11 elements, copper shielding, aperture size of 10 x 10 mm, frequency 960 kHz) (Fig. 1 A). Installation of the transducer was realized at 7 T MRI (PharmaScan 7T, Bruker). The transducer was placed on top of an agar-milk tissue phantom coupled via gel and fixed inside the rat body coil (Bruker). For PRF thermometry FLASH sequence was used to image the phantom during FUS heating, with: TE 7 ms, TR 180 ms, FOV 6 cm, slice thickness 2 mm, number of slices 10 and matrix 128 x 128; total acquisition time: 24 s. Sonication was manually started at intensity of 4.8 W/cm² for 60 s. Real temperature monitoring was confirmed by using fiber optic (Luxtron) inside the phantom.

RESULTS

Images showed zipper artifact of 0.7 mm thickness oriented in the phase-encoded direction with presence of the transducer (Fig. 1 B) and 2.4 fold reduction of the signal-to-noise ratio (SNR). The SNR, with transducer and FLASH sequence parameters, was 36. The temperature of the phantom was increased by 6°C during sonication (measured with fiber optic) with $\leq 0.8^\circ\text{C}$ temperature discrepancy in comparison to PRF thermometry (Fig. 1 C).

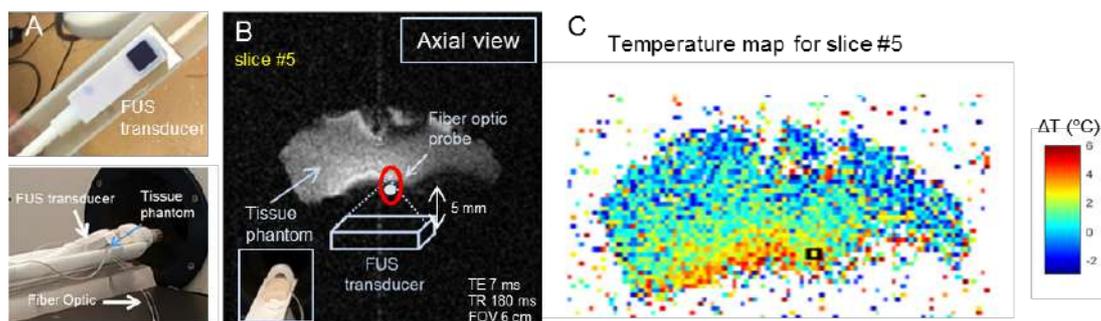


Fig. 1: **Preclinical MRgFUS hyperthermia in 7 T MRI.** (A) Experimental setup with FUS transducer (top) fixed on top of tissue phantom in the rat bed and position of temperature measurement system (fiber optic) (bottom). (B) MR image of the tissue phantom along axial direction with schematic drawing of transducer position and its focus point with respect to the phantom. (C) Temperature distribution in slice number 5 calculated with PRF thermometry.

CONCLUSIONS

This study showed that FUS heating and MRI based temperature control is feasible in a small animal 7 T MRI. *In vivo* experiments in xenografted mice are now being conducted combining MRgFUS hyperthermia and radiation therapy.

ROBOTIC HIGH-INTENSITY FOCUSED ULTRASOUND FOR PROSTATE CANCER TREATMENT: 10 YEARS FOLLOW-UP

V.A. Solovov¹

¹Samara Oncology Centre, Samara, Russia

e-mail: samarasdc@yahoo.com

OBJECTIVES

To report the results of the rHIFU treatment of patients with different stages of prostate cancer (PC) including localized PC, locally-advanced, and failure after external beam radiotherapy (EBRT) and radical prostatectomy (RPE).

METHODS

The current analysis included the results of treatment of 1250 patients in the Samara Oncology Center between Sep 2007 – September 2018: 731 with localized PC, 468 with locally-advanced PC, 51 – after the EBRT and RPE failure. Mean follow-up is 78 months (range 6-120). The oncology follow-up consisted of the PSA evaluation, the MRI and a transrectal biopsy in the case of rising the PSA.

RESULTS

In group with localized PC after 10 years, the progression was observed in 6.1% of the patients with low risk, in 8.2% with an average risk of progression.

In group with locally-advanced PC after 10 years, the progression was observed in 36.8% of the patients with high risk of progression.

In group with EBRT and RPE failure at after 10 years, the progression was observed in 19.1.

The local recurrence was diagnosed after in average of 12 (6-18) months after the initial treatment.

15 (1.3 %) patients needed to undergo a second treatment due to a local recurrence.

CONCLUSIONS

The HIFU ablation is a safe, minimally invasive treatment for a localized and a locally advanced prostate cancer, effective in 85.8% of the cases.

HIGH INTENSITY ULTRASOUND TREATMENT MONITORING BY PASSIVE ELASTOGRAPHY: AN *IN VITRO* FEASIBILITY STUDY

B. Giammarinaro, V. Barrère, D. Melodelima, S. Catheline

LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, Lyon, FRANCE

E-mail : bruno.giammarinaro@inserm.fr

OBJECTIVES

High Intensity Focused Ultrasounds (HIFU) is a non-invasive modality of treatment allowing thermal ablation in soft tissue by locally increasing temperature. Thermal lesions can be observed as a change in tissue elastic properties, and so in shear wave velocity, by elastography. In human body, a natural noise due to cardiac activity or arterial pulsatility can be used to characterize the elasticity in using noise correlation techniques; it corresponds to passive elastography. The objective is here to study the feasibility of using passive elastography technique during a high intensity ultrasound (HIU) treatment.

METHODS

Experiments were performed in *in vitro* bovine livers, heated with a plane transducer up to 80°C and imaged with a high framerate ultrasound-imaging device. Shear waves displacements were computed with Loupas motion estimator from IQ data and then used in the passive elastography algorithm to obtain shear waves velocity maps. This process was executed every minute during treatments as well as during heating and cooling periods.

RESULTS

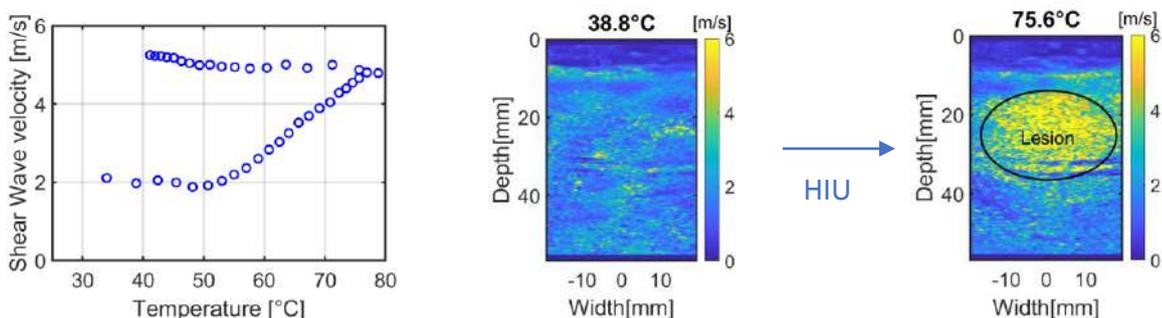
Four experiments were performed and led to the creation of four thermal lesions. Shear waves velocity maps were obtained for each lesion and corresponding increases in shear wave velocity were observed.

CONCLUSIONS

A first study of monitoring by passive elastography has been performed and the lesion formation has been successfully observed. Further experiments should be dedicated to evaluate the *in vivo* feasibility.

ACKNOWLEDGEMENTS

Work supported by BPI France (project HECAM).



CAPTION

Average shear wave velocity during a treatment (left); Shear Wave velocity maps before (center) and after (right) heating.

FEATURE SELECTION FOR CLASSIFYING THE TREATMENT OUTCOME OF HIGH-INTENSITY FOCUSED ULTRASOUND THERAPY IN UTERINE FIBROIDS

V. Suomi¹, G. Komar¹, T. Sainio², K. Joronen³, A. Perheentupa³ and R. Blanco Sequeiros¹

¹Department of Radiology, Turku University Hospital, Turku, Finland

²Department of Medical Physics, Turku University Hospital, Turku, Finland

³Department of Gynaecology, Turku University Hospital, Turku, Finland

e-mail: visa.suomi@tyks.fi

OBJECTIVES

The aim of this study was to utilise different feature selection methods in order to select the most important parameters from clinical patient data for high-intensity focused ultrasound (HIFU) treatment outcome classification in uterine fibroids.

METHODS

The study was retrospective using patient data from 89 uterine fibroid HIFU treatments conducted at the hospital. A total of 39 features were extracted from the patient data and 14 different filter-based feature selection methods were used to select the most important features via majority voting. The selected features were then used in a support vector classification (SVC) model to evaluate the performance of these parameters in predicting HIFU therapy outcome. The therapy outcome was defined as non-perfused volume (NPV) ratio in three classes: <30%, 30-80% or >80%.

RESULTS

The most important features ranked by their median majority vote from the feature selection methods are shown in Fig. 1. The ten most prominent features in order were: fibroid diameter, subcutaneous fat thickness, fibroid volume, fibroid distance, Funaki type I, fundus location, gravidity, Funaki type III, submucosal fibroid type and urinary symptoms. The maximum F1-micro classification score was 0.63 using top 10 features from Mutual Information Maximisation (MIM) and Joint Mutual Information (JMI) feature selection methods.

CONCLUSIONS

Classification performance of HIFU therapy outcome prediction in uterine fibroids is highly dependent on the chosen feature set which should be determined prior using different classifiers.

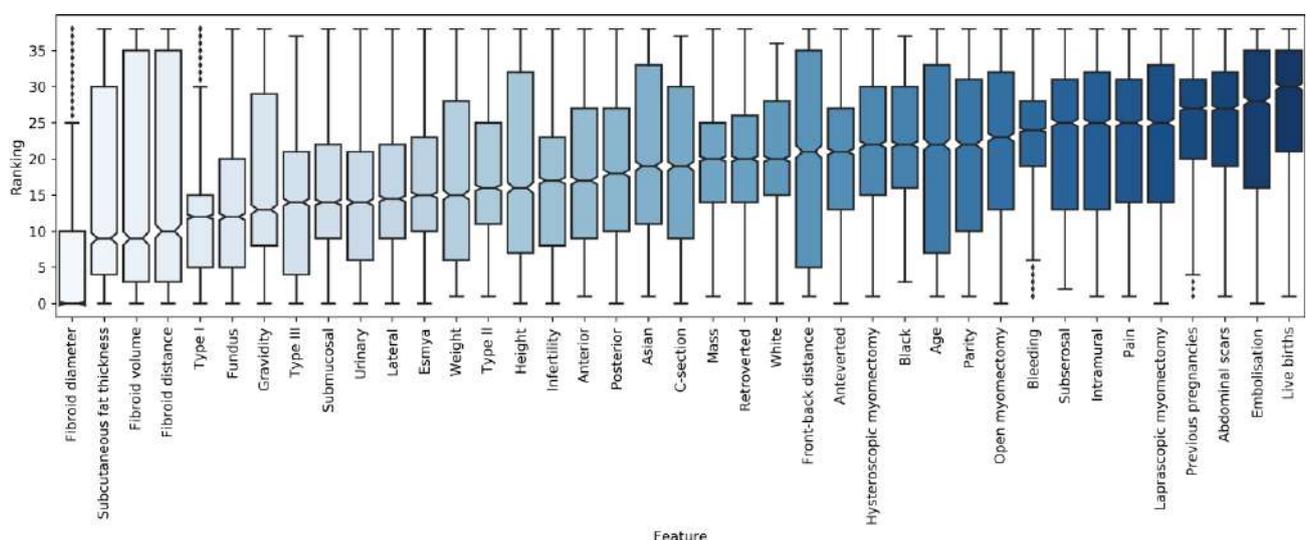


Figure 1: Feature importance hierarchy in predicting HIFU treatment outcome in uterine fibroids. The features are ranked by their median value based on the majority vote from 14 different filter-based feature selection methods.

A Modified PMN-PT Ceramic based 2D Array Transducer for Low-intensity Ultrasound Therapy

Zhiqiang Zhang¹, Min Su¹, Fei Li², Rong Liu¹, Ruilin Cai¹, Thomas Shrout², Hairong Zheng¹, Weibao Qiu¹

¹ Institute of Biomedical and Health Engineering, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China

² Department of Materials Science and Engineering, The Pennsylvania State University, University Park, PA 16802, USA

e-mail: hr.zheng@siat.ac.cn; wb.qiu@siat.ac.cn

OBJECTIVES

Low-intensity ultrasound has drawn great attention in the past years for many non-invasive therapeutic applications on brain diseases, such as brain neuro-stimulation, blood-brain barrier (BBB) opening, and thrombolysis. Two-dimensional (2D) array can achieve full three-dimensional control of the ultrasound beam. Therefore, it can produce multiple focal points at the same time, which is an idea tool for non-invasive treatment. In this work, a high performance 2D array with modified PMN-PT piezoceramic has been developed for low-intensity ultrasound therapy.

METHODS

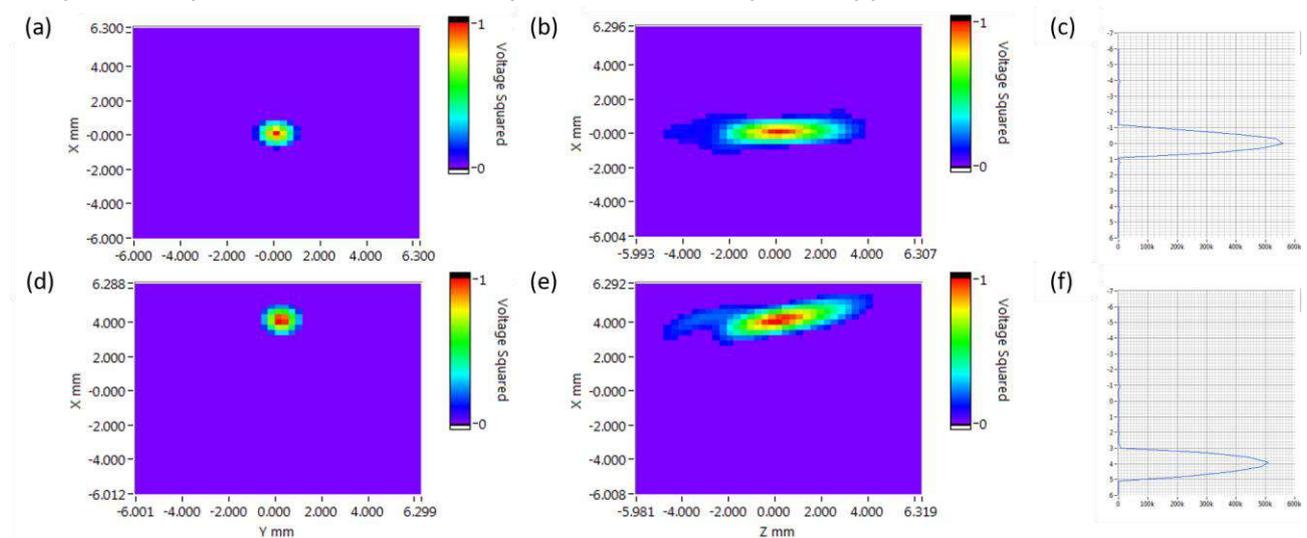
In order to optimize the power output of 256 elements 2D array transducer, modified PMN-PT piezoceramic with ultrahigh clamped dielectric permittivity was used to minimize the electrical impedance of array elements. The center frequency was designed to be 1 MHz considering the tradeoff between ultrasound beam resolution and ultrasonic attenuation of the skull. The element pitch was designed to be 0.71λ , enabling a large steering range of the ultrasound beam.

RESULTS

A 2D array transducer with 1 MHz center frequency, and 0.71λ pitch was successfully developed. The ultrasound beam of the array can be steered at a large range. The acoustic pressure of the proposed array is about 3 times higher than that of 2D array made of PZT-5H ceramic. The resolution of developed 2D array is less than 2 mm when focus length is smaller than 15 mm.

CONCLUSIONS

A high performance 2D array transducer with low electrical impedance has been developed, and it can potentially be used in low-intensity ultrasound therapeutic applications.



CAPTION: The spatial distribution of acoustic pressure from 2D array with a focus at (0,0,8) in the lateral (a) and axial (b) planes, and lateral resolution (c); The spatial distribution of acoustic pressure from 2D array with a focus at (4,0,8) in the lateral (d) and axial (e) planes, and lateral resolution (f).

IN VITRO FOCUSED ULTRASOUND HYPERTHERMIA FOR RADIOSENSITIZATION OF HUMAN CANCER CELLS

X. Zhang¹, M. Unger¹, I. Patties², L. Landgraf¹, A. Melzer¹

¹Innovation Center Computer Assisted Surgery, University of Leipzig, Leipzig, Germany

²Department of Radiooncology, University of Leipzig, Leipzig, Germany

e-mail: xinrui.zhang@medizin.uni-leipzig.de

OBJECTIVES

Hyperthermia (HT; 40-46°C) has been reported to sensitize cancer cells to radiation therapy (RT). Focused ultrasound (FUS) displays for the first time a suitable technique to generate local HT. In this study, impact of combined FUS-HT and RT treatment on human cancer cells was investigated *in vitro*.

METHODS

Human glioblastoma (T98G), prostate (PC-3), and head and neck cancer cell lines (FaDu) were seeded in ultrasound-penetrable 96-well plates (Greiner Bio One). We have used a special sonicator for cell culture plates developed at IMSaT (University Dundee) and modified by us comprised by a programmable VXM motor controller and a NEMA 17 stepper motor (VELMEX Inc.). FUS-HT (45°C, 30min) was induced using customized 1.14MHz transducer at 214W/cm². Temperature was monitored by thermal camera (Optris). HT (45°C, 30min) in thermal cycler worked as control. Single RT was applied at 10 Gy with an X-Ray device (DARPAC 150-MC; 1.28Gy/min) afterwards. Effects on metabolic activity (WST-1, Roche) and DNA double-strand breaks (γ H2A.X, Cell signalling) were evaluated.

RESULTS

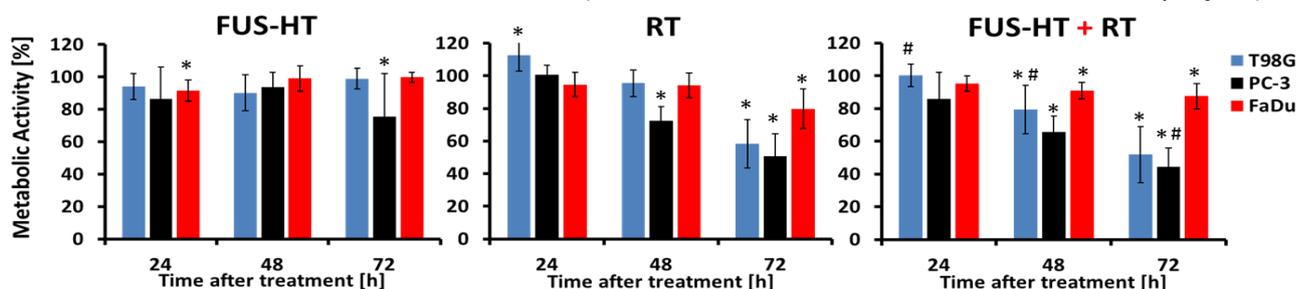
Combination of HT+RT leads to a significantly ($p < 0.05$) decreased metabolic activity (T98G:27%; PC-3:50%; FaDu:55%) compared to single RT (T98G:65%; PC-3:76%; FaDu:85%) 72h after treatment. Metabolic activity was also reduced in FUS-HT+RT group (T98G:52%; PC-3:45%; FaDu:88%). FUS-HT+RT enhances the number of residual DNA double-strand breaks in PC-3 cells (8.57foci/nucleus) compared to RT alone (5.32 foci/nucleus) 1h post treatment.

CONCLUSIONS

Our data indicate that FUS-HT is an effective tool to radiosensitize cancer cells *in vitro*. Comparison to control group revealed importance of consistent temperature level. New *in vitro* FUS systems are needed and under investigation.

ACKNOWLEDGEMENTS

Our project is funded by Bundesministerium für Bildung und Forschung (BMBF) under grant No.03Z1L511 (SONO-RAY project).



CAPTION: Combination of FUS-HT and RT showed the highest impact on cell metabolic activity in a time dependent manner. Data were normalized to untreated control, which were set as 100%. n=9, * significantly different from control group ($p < 0.05$), # significantly different from RT ($p < 0.05$)

Reducing secondary hot spots in/off axial focus shifting for phased High-Intensity focused Ultrasound system by using frequency modulation waveform – A simulation study

Xiongfei Qu¹, Guofeng Shen¹, Yazhu Chen¹, Nan Wu¹

¹ School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

e-mail: quxiongfei@sjtu.edu.cn

OBJECTIVES

Phased High-Intensity focused Ultrasound (pHIFU) has been widely used in tumor ablation and thalamotomy. However, a large focus shifting distances usually results in a series of secondary hot spots. The objective of this work is to evaluate the influences of secondary hot spots in/off axial focus shifting for pHIFU system using frequency modulation waveform.

METHODS

A 64-element concave phased array transducer model (1.36MHz) based on Fermat's Spiral were used in this study. First, propagation of frequency modulation wave through homogeneous medium was calculated in a linear acoustic model using spatial impulse response approach. Influences of the acoustic intensity at a large space around the focus with different shifting distance in/off axial were investigated. Then, the nonlinearity at the focus was evaluated using KZK Texas Code. Finally, temperature and thermal dose distribution were calculated from bio-heat transfer equation (BHTE).

RESULTS

The acoustic fields of sine wave and frequency modulation wave have been simulated and the -15dB envelope surface of acoustic intensity are shown in Figure.

CONCLUSIONS

The acoustic intensity at secondary hot spots could be considerably reduced by using frequency modulation waveform without compromising the intensity at the main lobe.

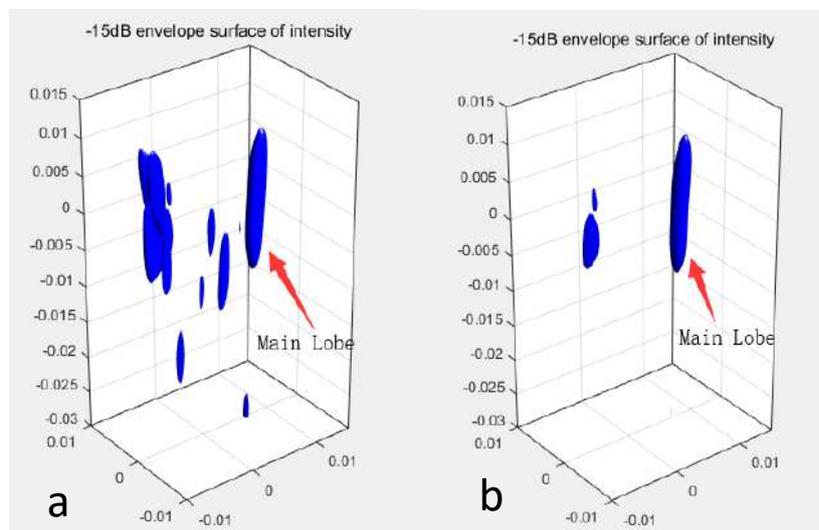


Figure: a. The -15dB envelope surface of acoustic intensity by using sine wave; b. The -15dB envelope surface of acoustic intensity by using frequency modulation wave.

**LONG-TERM RESULTS OF MR GUIDED FOCUSED ULTRASOUND VIM-
THALAMOTOMY IN PARKINSON'S PATIENTS WITH MEDICATION-REFRACTORY
DISABLING TREMOR**

I. Schlesinger^{1,2}, A. Sinai³, A. Eran⁴, M. Nassar¹, M. Constantinescu³

¹Department of Neurology, Rambam Health Care Campus, Haifa, Israel

²Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

¹Department of Neurosurgery, Rambam Health Care Campus, Haifa, Israel

¹Department of Radiology Rambam Health Care Campus, Haifa, Israel

OBJECTIVES

Long term results of MR-guided focused ultrasound (MRgFUS) VIM-thalamotomy in Tremor-Dominant Parkinson's Disease (TDPD) patients are lacking. We report our single center 5-year experience with VIM MRgFUS thalamotomy.

METHODS

Between Feb-2014 and Mar-2019, thirty-four TDPD patients underwent unilateral MRgFUS VIM thalamotomy and were assessed by the motor part of the Unified PD rating scale (UPDRS) and the PDQ-39 quality of life questionnaire.

RESULTS

In all patients treatment resulted in immediate cessation of tremor in the treated hand. Twenty-seven were male, mean age was 63.4 ± 9.3 years, with a mean disease duration of 6.7 ± 4.6 years. UPDRS scores decreased from 25.6 ± 7.7 to 13.4 ± 8.6 (34 patients, $p < 0.001$) at 1 month, to 11.8 ± 8.2 (30 patients, $p = 0.0001$) at 6 month, to 10.6 ± 7.0 (19 patients, $p < 0.0001$) at 1 year, 8.6 ± 6.6 (11 patients, $p < 0.001$) at 2 years, 11.4 ± 7.9 (8 patients, $p = 0.0004$) at 3 years, 11.2 ± 9.0 (6 patients, $p = 0.02$) at 4 years and 7.0 ± 4.0 (2 patients) at 5 years due to decreased tremor and rigidity. PDQ-39 scores significantly improved from 42.8 ± 21.1 to 24.5 ± 18.4 at one year ($p = 0.002$) and remained lower than baseline over time. In 5 patients tremor returned to the same degree as before MRgFUS. Adverse events after the procedure were mild and resolved within 3 months in all patients.

CONCLUSIONS

MRgFUS thalamotomy for TDPD is an effective, durable and safe procedure that provides long-term tremor relief and in some cases reduced rigidity, with subsequent improvement in quality of life. Additional studies are needed to substantiate our favorable results.

TRANSSCLERAL DRUG DELIVERY MEDIATED BY LOW-FREQUENCY ULTRASOUND

Yaxin Hu^{1,2}, Ying Zhu^{1,2}, Xinyu Zhang^{1,2}

¹School of Biomedical Engineering, Health Science Center, Shenzhen University, Shenzhen, China

²National-Regional Key Technology Engineering Laboratory for Medical Ultrasound, Shenzhen, China

e-mail: yxhu@szu.edu.cn

OBJECTIVES

Drug delivery to the posterior segment of the eye is challenging due to the existence of anatomic and physiologic barriers. Here, we propose a drug delivery method for back of the eye using the mechanical effects of low-frequency ultrasound via the transscleral route.

METHODS

Ultrasound pulses were edited in a function generator, powered by a 53-dB amplifier and produced by a low-frequency transducer (40 kHz center freq.). With two duty cycle settings of 25% and 50%, ultrasound pulses of I_{spta} values of 0.04-0.21 W/cm² and 0.08-0.42 W/cm² were applied on the porcine sclera, respectively (as shown in Figure A). Sclera sections of 10- μ m thickness were imaged under the fluorescence microscope to calculate the diffusion depth of Dextran-FITC. Sclera sections were also stained by H&E method to examine the safety of ultrasound. Total fluorescence intensities of Dextran-FITC delivered into the porcine eyes were measured by small animal imaging system.

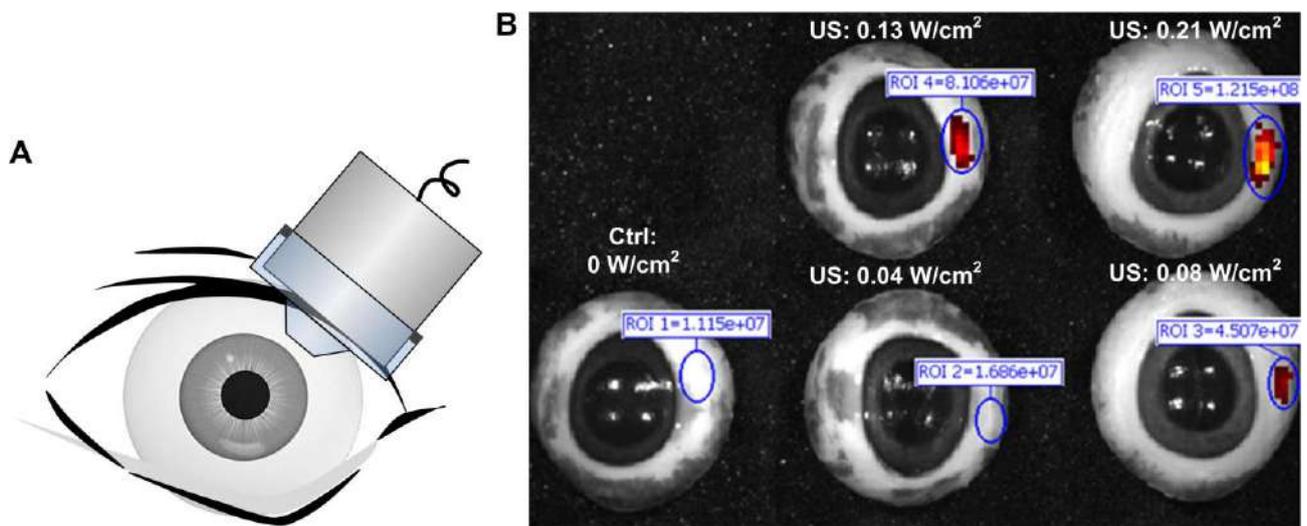
RESULTS

Compared with the sham-exposure group, ultrasound groups had enhanced transscleral deliveries of Dextran-FITC. The measured transscleral delivery efficiencies of ultrasound groups of I_{spta} values of 0.04, 0.08, 0.13 and 0.21 W/cm² were 28.5%, 35.0%, 46.3% and 63.5%, respectively. The total amount of Dextran-FITC delivered into the porcine eye also increased with the ultrasound I_{spta} value (Figure B). H&E staining results of sclera sections showed that the collagen structure was disturbed when the I_{spta} value exceeded 0.42 W/cm².

CONCLUSIONS

Low-frequency ultrasound can deliver 70-kDa Dextran-FITC into the porcine sclera.

CAPTION: ultrasound-mediated transscleral drug delivery



SUPPRESSION OF CAVITATION GENERATION OUTSIDE FOCAL REGION BY SPLIT-APERTURE TRANSMISSION METHODS

Y. Tanaka¹, S. Umemura¹, S. Yoshizawa²

¹Graduate School of Biomedical Engineering, Tohoku University, Sendai, Japan

²Graduate School of Engineering, Tohoku University, Sendai, Japan

e-mail: yui.tanaka.p3@dc.tohoku.ac.jp

OBJECTIVES

In a HIFU treatment, there is a problem of a long treatment time. “Trigger HIFU sequence” consisting of “trigger pulses” and “heating bursts” has been investigated to reduce the treatment time by cavitation-enhanced ultrasonic heating. The trigger pulse is a high-intensity pulse to generate cavitation bubbles, and the heating burst is a low- to moderate-intensity burst to heat tissue. In this research, a split-aperture transmission methods are proposed for the suppression of cavitation outside the focal region. Cavitation generation region by the methods was investigated using a high-speed camera.

METHODS

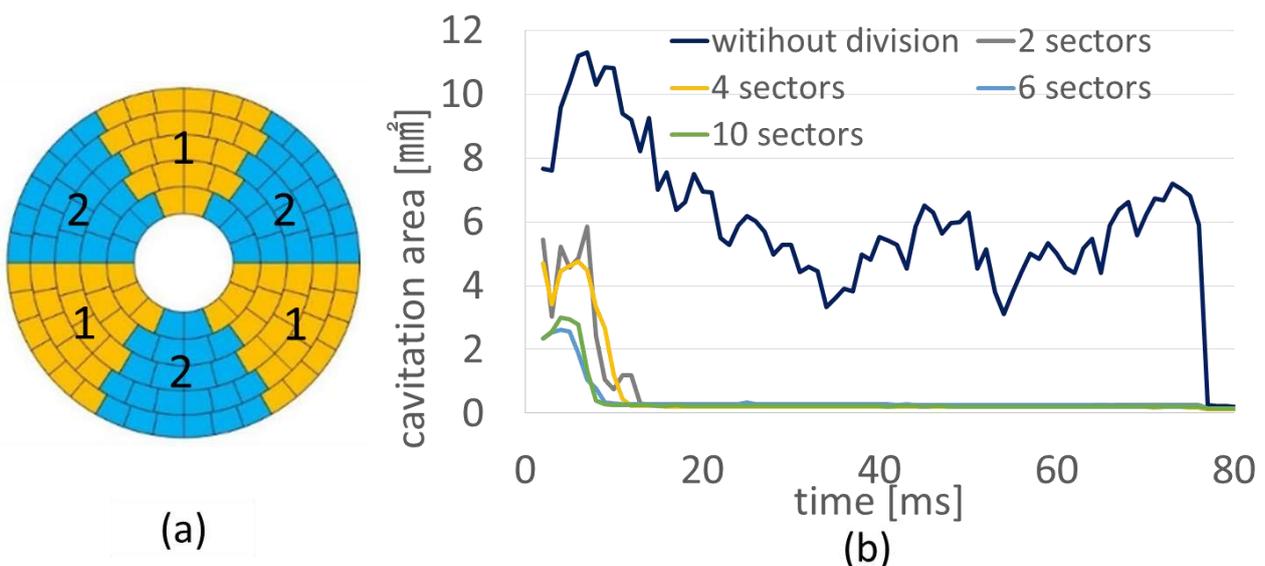
A 128-ch array transducer with a diameter of 147.8 mm and a focal length of 120 mm was driven at 1 MHz. Cavitation bubbles generated on a sapphire glass placed 4 mm toward the transducer from the HIFU focal point were observed with a high-speed camera. For the split-aperture transmission, the transducer were divided into two element groups which consist with 2 – 10 sectors in total. Adjacent two sectors belonged to different element groups. After a trigger pulse exposure at 930 W for 0.1 ms, heating bursts were alternately transmitted from the two element groups at 58 W once every 0.05 ms for 75 ms. The division pattern into 6 sectors is shown in Fig (a).

RESULTS

The cavitation area was effectively suppressed by the split-aperture transmission methods.

CONCLUSIONS

In a HIFU treatment, the split-aperture transmission methods will reduce the risk of side effects caused by unwanted cavitation bubbles such as a skin burn.



CAPTION: (a) an example of a divided transducer

(b) relation between cavitation generation area and time

Robotic Driven Motion Model for Static vs Dynamic MRgFUS Systems

R. Coupar¹, A. Dennison¹, J. Joy¹, A. Melzer¹

¹Institute for Medical Science & Technology, Division of Imaging Sciences & Technology, University of Dundee, Scotland, UK

e-mail: rzcoupar@dundee.ac.uk

OBJECTIVES

To compare Magnetic Resonance guided Focused Ultrasound (MRgFUS) for static and dynamic conditions using a MR safe robotic driven motion model. To establish a preclinical validation model simulating the scenario of moving abdominal organs under image guided FUS treatment.

METHODS

An MR safe robot (INNOMOTION) was used to slide a DQA gel phantom (Insightec, Israel) with a 3D printed tracking collar, suspended in a degassed water tank, creating a 0 to 2cm linear motion path. An ExAblate 2100 FUS system (Insightec, Israel) coupled below the water tank was used to apply power (50, 75 and 100W) for 30s. A 1.5T MRI (GE, USA) was used to acquire monitoring images with an Echo Planar imaging sequence. Multi-baseline MR thermometry for static and dynamic conditions was conducted using the Trans-FUSIMO Treatment System (TTS).

RESULTS

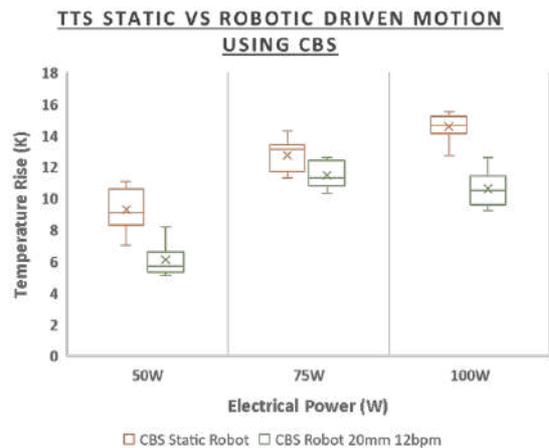
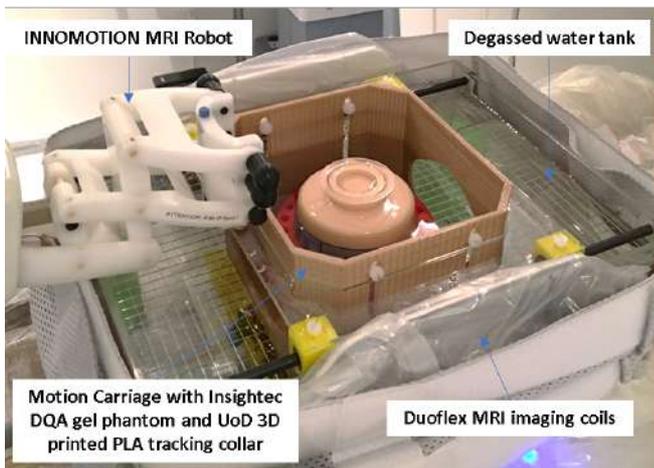
MR Thermometry results were taken at a sample depth of 70 mm from the transducer plane. This was repeated (sample n=10) for each experimental condition (power and range).

CONCLUSIONS

The Robotic model was successfully established for MRgFUS under simulated dynamic motion.

ACKNOWLEDGEMENTS

Trans-FUSIMO Project (grant no 611889)



CAPTION: Left, photograph of robotic driven motion model. Right, boxplot of MRgFUS thermometry summary results.

TAILORING MICROBUBBLE SHELL COMPOSITION FOR THERAPEUTIC ULTRASOUND APPLICATIONS

Lin Zhang¹, Antonios N. Pouliopoulos², Elisa E. Konofagou^{2,3}

¹Bronx High School of Science, New York, USA, ²Department of Biomedical Engineering,

³Department of Radiology, Columbia University, New York, USA

e-mail: zhangl3@bxscience.edu; a.pouliopoulos@columbia.edu; ek2191@columbia.edu

OBJECTIVES

Microbubbles typically serve as ultrasound contrast agents. Consequently, their performance under therapeutic ultrasound exposures is less well-known. Here, we investigated the cavitation emissions and temporal stability of lipid-shelled microbubbles with varying shell composition exposed to a 1-ms-long therapeutic pulse.

METHODS

C₄F₁₀ microbubbles with 15:1, 9:1 and 5:1 molar ratios of 1,2-distearoyl-sn-glycerol-3-phosphocholine (DSPC) and 1,2-distearoyl-sn-glycero-phosphoethanolamine-PEG₂₀₀₀ (DSPE-PEG₂₀₀₀) were manufactured in-house. Lipid amounts were also decreased by 5x and 10x, maintaining the DSPC:DSPE-PEG₂₀₀₀ 9:1 ratio. Microbubbles within a 4-mm vessel of a 5%-gelatin phantom were exposed to 10 therapeutic pulses (0.5MHz, 500 cycles, 400kPa_{pk-neg}; n=5 batches). Acoustic emissions were recorded with a 7.5MHz passive cavitation detector.

RESULTS

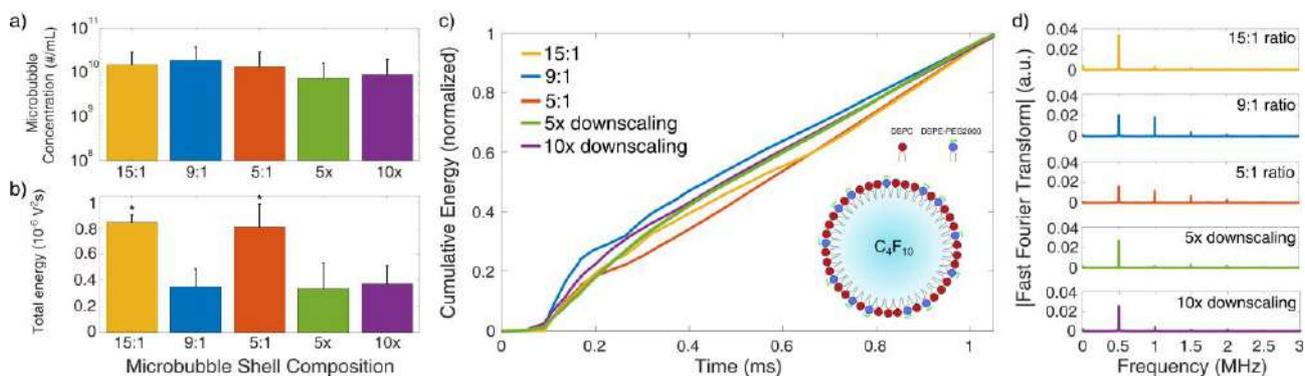
Although microbubble concentration was not significantly different, 15:1 and 5:1 ratios produced acoustic emissions with higher energy than the 9:1. Higher energy was correlated with increased temporal stability during the 1-ms pulse, as indicated by the cumulative energy evolution. Lipid decrease did not affect acoustic emissions or temporal stability. The amplitude of higher harmonics increased with reduced lipid ratio and decreased with lipid downscaling.

CONCLUSIONS

Microbubbles with lipid shells composed at 15:1 or 5:1 ratio may be more suitable for therapeutic applications such as blood-brain barrier opening. Decrease of the lipid amount did not affect microbubble response but may lower manufacturing cost.

ACKNOWLEDGEMENTS

This work was supported through a Focused Ultrasound Foundation Global Internship.



CAPTION: a) Microbubble concentration did not change with different shell compositions. b) Acoustic energy was significantly higher for the 15:1 and 5:1 ratio. c) Cumulative energy during the 1-ms pulse. d) Frequency content for each microbubble formulation.

REGISTRATION OF IN VIVO MAGNETIC RESONANCE IMAGES TO VOLUMETRIC HISTOPATHOLOGY

B.E. Zimmerman¹, S. Johnson¹, J. Shea², H. Odéen³, E. Hillas², C. Winterton³, R. Merrill³, S. Joshi¹, and A. Payne³

¹Biomedical Engineering, University of Utah, Salt Lake City, UT, USA

²Department of Surgery, University of Utah, Salt Lake City, UT, USA

³Department of Radiology and Imaging Sciences, University of Utah, Salt Lake City, UT, USA

e-mail: blakez@sci.utah.edu, allison.payne@hsc.utah.edu

OBJECTIVES

As MR guided focused ultrasound (MRgFUS) expands to include oncological targets, accurate evaluation of tumor viability immediately after MRgFUS procedures is critical. Histopathology is the gold standard for evaluating tumor viability after any cancer therapy. Common clinical MR assessment metrics do not always predict the tumor viability as seen in histopathology images. In this work, we present a rigorous in vivo MR to volumetric histopathology registration pipeline that estimates the deformation at every histopathology processing step.

METHODS

MRgFUS ablation was performed on a rabbit VX2 tumor model using a preclinical MRgFUS system in a 3T MRI scanner. Post-treatment imaging was performed four days after ablation, the animal was euthanized, and the treated tissue was excised. Methods reflective of clinical processing were used to process the excised tissue for histopathology. Novel landmark free registration methods were developed to register MR and histopathology. Our methods estimate an affine to explicitly correct the gross slicing step during standard clinical processing.

RESULTS

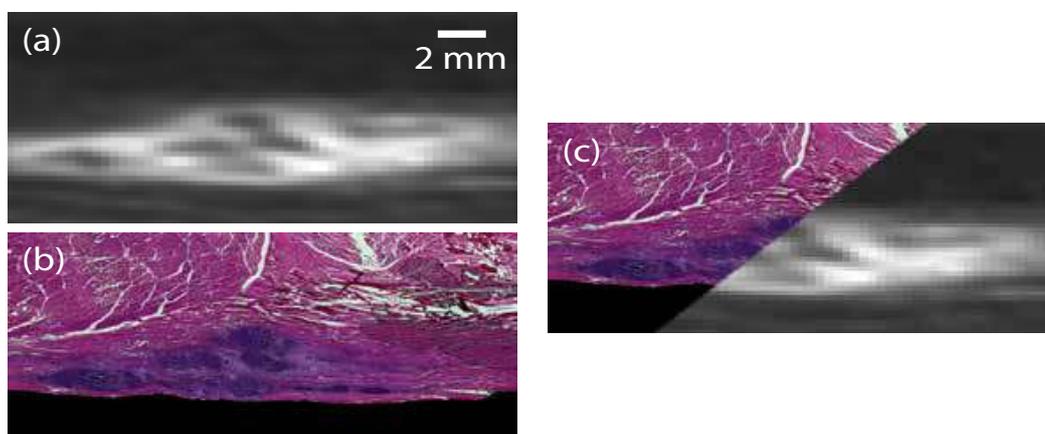
The result of transforming MR to histopathology images can be seen in Figure 1. Initial analysis of the registration reveals high correlation between necrotic nodules seen on hematoxylin and eosin (H&E) stained histopathology images and registered in vivo contrast enhanced T1w MR images.

CONCLUSIONS

The developed algorithm provides detailed volumetric registration between acute MRgFUS MR images and histopathology images for validating quantitative MR metrics for MRgFUS treatment assessment.

ACKNOWLEDGEMENTS

This work is supported by 5R37CA224141 and 1R03EB026132.



CAPTION: (a) Contrast enhanced T1w MR slice through VX2 tumor. (b) Registered H&E stained histopathology section. (c) Overlay between the registered T1w MR slice and the histopathology image.

Simultaneous rapid and multi-slice MR-temperature and MR-displacement imaging during transcranial focused ultrasound in non-human primate.

Valéry Ozenne^{1,2,3}, Charlotte Constans⁴, Pierre Bour^{1,2,3}, Mathieu Santin⁵, Romain Valabregue^{5,6}, Harry Ahnine⁵, Pierre Pouget⁶, Stephane Lehericy^{5,6}, Jean-Francois Aubry⁷, Bruno Quesson^{1,2,3}

¹IHU Liryc, Electrophysiology and Heart Modeling Institute, Fondation Bordeaux Université, Bordeaux, France.

²Univ. Bordeaux, Centre de recherche Cardio-Thoracique de Bordeaux, U1045, Bordeaux, France.

³INSERM, Centre de recherche Cardio-Thoracique de Bordeaux, U1045, Bordeaux, France.

⁴Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Univ Paris Diderot, Sorbonne Paris Cité, Paris, France

⁵ICM, Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, Paris, France

⁶UPMC Université Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, Paris, France.

⁷Physics for Medicine Paris, Inserm, ESPCI Paris, CNRS, PSL Research University, Paris, France.

e-mail: valery.ozenne@ihu-liryc.fr, charlotte.constans@gmail.com, pierre.bour@ihu-liryc.fr, mathieu.santin@icm-institute.org, romain.valabregue@upmc.fr, harry.ahnine@gmail.com, pierre.pouget@upmc.fr, stephane.lehericy@upmc.fr, jean-francois.aubry@espci.fr, bruno.quesson@u-bordeaux.fr

OBJECTIVES: To evaluate a multi-slice, sub-second MRI sequence allowing simultaneous measurements of temperature and displacement in the brain during transcranial focused ultrasound therapy in nonhuman primates. Experimental data were compared to numerical simulations for validation purposes.

METHODS: A single-shot gradient echo EPI (4 slices, 2 mm³ isotropic, 1 Hz update frequency, 60 repetitions) incorporating bipolar motion encoding gradients (MEG, 5 ms duration, 54 mT/m) was used at 3T. For each slice, a focused ultrasound (single element transducer, 850 kHz, 63 mm focal length, F/D=1) pulse of 4-8 ms was synchronized on the MEG (MR-ARFI). A total of 25 acquisitions were performed in 3 different sets of experiments, with alternative emissions periods of ultrasound (20 off – 20 on - 20 off). Experimental displacement patterns were compared to in silico ARFI simulations with different peak-to-peak voltages applied to the transducer.

RESULTS: The temporal standard deviation of the displacement and of the temperature in the brain were 0.4 μm and 0.2 $^{\circ}\text{C}$, respectively. Maximum displacement at the focus was 2 μm with an average value around 1.5 μm . Temperature elevations were observed near the skull (2.1 $^{\circ}\text{C}$). A good spatial correspondence (see figure) can be observed at the focus between experimental and simulated displacement for different applied voltages to the transducer.

CONCLUSIONS: The rapid, multi-slice acquisition and real-time implementation of image visualization is clinically applicable and may improve safety operation conditions for clinical applications of transcranial HIFU.

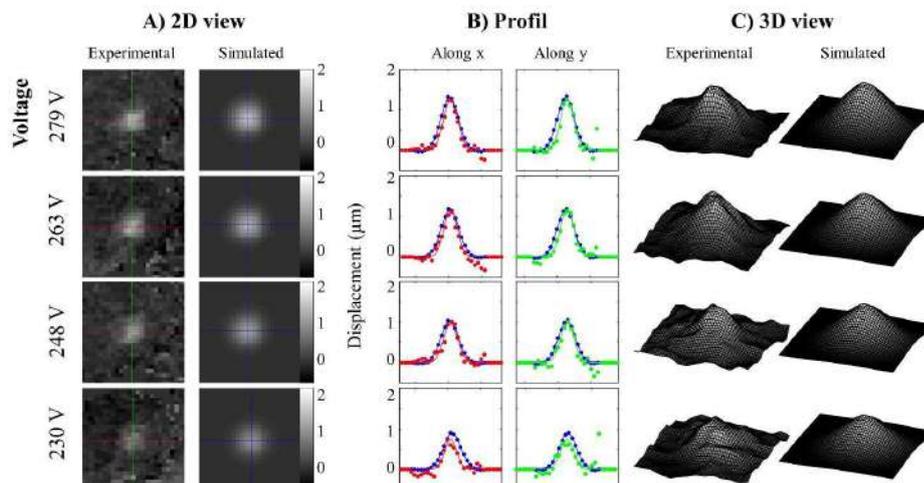


Figure: Comparison between experimental and simulated displacement for different peak-to-peak voltage applied to the transducer

FOCUSED ULTRASOUND-INDUCED IMMUNOMODULATION IN MELANOMA

Christopher J. Margraf¹, Alexandra R. Witter¹, Alexander S. Mathew², Natasha D. Sheybani², Richard J. Price², Timothy N. J. Bullock¹

¹University of Virginia School of Medicine Department of Pathology

²University of Virginia School of Medicine Department of Biomedical Engineering

Email: cjm3sn@virginia.edu

OBJECTIVES

This project aims to use high-intensity focused ultrasound to stimulate an anti-tumor immune response in melanoma. An explanation for the weak immunogenicity of melanomas is the lack of available antigen and immune-stimulatory materials (DAMPs) from tumor damage. Methods of increasing antigen availability could support melanoma immunotherapy. This study investigates how ablative ultrasound (FUS) can enhance antigen acquisition by dendritic cells (DCs), and whether these cells increase expression of costimulatory molecules critical for generating anti-tumor responses.

METHODS

C57Bl/6 mice were inoculated with B16F1 melanoma cells expressing chimeric ZsGreen fluorescent protein and MHC class I and MHC class II restricted peptides derived from ovalbumin. Tumor cells were injected subcutaneously into the lower right flank. Thermally ablative FUS treatment (20-30% ablation) was administered on day 15 post-inoculation. Tumors, tumor-draining lymph nodes, and spleens were harvested 24 hours post-treatment. Cells were processed and stained for flow cytometry. The ZsGreen marker was used to map antigen trafficking and uptake.

RESULTS

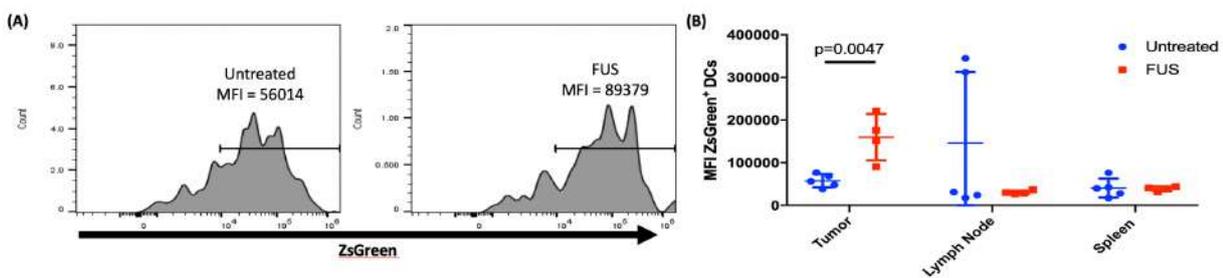
Thermally ablative FUS increased the amount of tumor antigen acquired by tumor resident DCs, but there is no evidence of increased antigen in draining lymph nodes or in other myeloid cells. DCs in tumors but not lymph nodes expressed higher levels of costimulatory molecules.

CONCLUSIONS

Ablative FUS increases antigen availability and DC activation. Further studies need to be conducted to determine DC migration and T cells activation.

ACKNOWLEDGEMENTS

This work was supported by the Focused Ultrasound Foundation.



CAPTION: 24 hours post-FUS antigen uptake increased in DCs. Mean fluorescent index via flow cytometry (A) and t-test (B) were used (n=4-5).

PHYSICS BASED, VALIDATED RELIABLE MODELING OF SINGLE ELEMENT FOCUSED ULTRASOUND TRANSDUCER (SEFT)

Cristina Pasquinelli^{1,2}, Hazael Montanaro^{3,4}, Hyunjoo J. Lee⁵, Niels Kuster³, Esra Neufeld³, Axel Thielscher^{1,2,*}

¹ DRCMR, Hvidovre, Denmark

² DTU, Kgs. Lyngby, Denmark

³ ITIS, Zürich, Switzerland

⁴ ETH, Zürich, Switzerland

⁵ KAIST, Daejeon, South Korea

*e-mail: axelt@drcmr.dk

OBJECTIVES

Transducer models for the simulation of transcranial focused ultrasound stimulation (TFUS) are often not accurate when only based on the specifications of the manufacturer, but require adaptations based on hydrophone measurements. We investigated the importance of creating a transducer model that is based on a real physical representation of the geometry and internal transducer structure, rather than an 'effective' model optimized to fit hydrophone measurements in water.

METHODS

A SEFT operating at 500 KHz has been characterized through measurements in a water tank with and without obstacles of varying shape (plate, pig and sheep skull) printed from a material with known acoustic properties (Veroblack) at different positions. We compared an 'effective' model with our new physical model accounting for internal structure, using the gamma method (spatial and intensity tolerance: 5mm and 15%). We calculated the percentage of points outside this tolerance (failure %) as well as the deviations of the position of maximum intensity (max) and intensity and the full width at half maximum (FWHM).

RESULTS

The results are shown in the Table.

CONCLUSIONS

While 'effective' transducer models can well reproduce the acoustic distribution in water, they are significantly less accurate than physical representation-based models when obstacles are introduced.

		Failure [%]	Deviation (% normalized by tolerance) of		
			Position of max	FWHM	Intensity
Water background	Effective model	0.4	-88	-157	-
	Physical model	0	-28	37	-
Obstacle plate	Effective model	19	-135	-220	-77
	Physical model	0	-72	-57	5.4
Sheep skull	Effective model	4	-100	-88	-17
	Physical model	0	-92	38	-42
Pig skull	Effective model	25	-42	-	-284
	Physical model	0	-41	-	100

TABLE: Results of the comparison. In one case the obstacle was too close to the focus to measure the FWHM. The deviations are normalized to the chosen tolerances, i.e. values outside the range from -100 to 100 exceed the tolerance limits.

FROM 2D TO 3D REAL-TIME PASSIVE CAVITATION IMAGING OF PULSED CAVITATION ULTRASOUND THERAPY

D. Suarez Escudero^{1,2}, M. Tanter¹, M. Pernot¹

¹Institute Physics for Medicine Paris, Inserm U1273, ESPCI Paris, CNRS FRE 2031, PSL University, 17 rue Moreau, 75012 Paris, France

²Cardiawave SA, 29 rue du Faubourg Saint Jacques, 75014, Paris, France

E-mail : daniel.suarez@cardiawave.com

OBJECTIVES

Pulsed cavitation ultrasound therapy (PCUT) is a non-invasive medical therapeutic approach that relies on the mechanical effects generated by cavitation bubbles. The visualization of the bubble cloud is often limited on conventional ultrasound B-Mode imaging by the poor contrast, particularly in deep and moving organs such as the liver and the heart and remains moreover qualitative for the operator. Our goal is to develop a new monitoring imaging mode to better identify and quantify the cavitation cloud in real-time and in moving organs.

METHODS

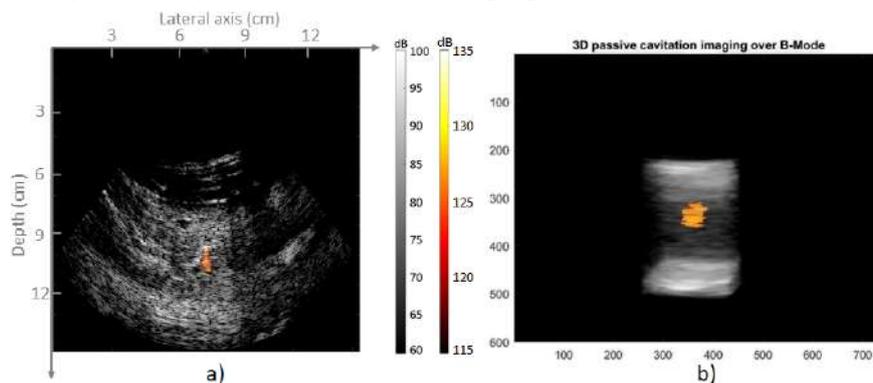
We propose a passive coherent ultrasound imaging approach combined with a spatiotemporal singular value decomposition filter to detect and map the bubble cloud with high sensitivity and high contrast. The mapping of the bubble cloud is overlaid to the conventional B-Mode, which permits to locate the cavitation phenomena in relation to the anatomic image in real-time. We performed experiments on the liver of three pigs to investigate the feasibility of our method *in vivo*. Finally, we extended the technique to volumetric imaging *in vitro* on tissue mimicking phantoms.

RESULTS

In vitro, at a maximal motion speed of 10 mm s^{-1} , the Contrast-to-Noise Ratio (CNR) for passive cavitation imaging is up to 10 times higher than for active cavitation imaging, with a temporal resolution of about 100 ms. *In vivo* results show that the CNR achieved for the passive acquisitions was significantly higher than the CNR achieved by the active acquisitions for all animals (average CNR of 6.7 ± 0.9 compared to 1.9 ± 1.0 , $p < 0.05$ where p is the p-value). Finally, we successfully mapped cavitation in 3D in phantoms and in particular we proved its feasibility with under-sampled matrix probes for cheap and efficient volume beamforming.

CONCLUSIONS

We demonstrated the feasibility and robustness of 2D passive cavitation imaging *in vivo*. We extended the technique to 3D passive cavitation imaging *in vitro*.



CAPTION: a) 2D cavitation map over B-Mode *in vivo* b) 3D cavitation map over B-Mode *in vitro*

Oxygen Generating Nanoparticles for Improving Sonodynamic Therapy in Hypoxic Tumours

Nicholas, D. M.¹, Sheng, Y.¹, Nesbitt, H., McHale, A.P.¹, Callan, J.F.¹

¹School of Pharmacy and Pharmaceutical Sciences, Ulster University, UK.

Email: d.nicholas@ulster.ac.uk, ap.mchale@ulster.ac.uk

OBJECTIVES

To produce pH-responsive calcium peroxide (CaO₂ NPs) nanoparticles compatible with transient oxygenation of the tumour microenvironment in order to enhance oxygen-driven therapies such as sonodynamic therapy (**Figure 1a**).

METHODS

CaO₂ NPs were prepared by pH-mediated precipitation from CaCl₂ solution and coated with a pH sensitive polymer, prepared from 2-(dimethylamino)ethyl methacrylate, methyl methacrylate and ethyl acrylate and ABCN. Coating was achieved by solvent-based precipitation of the polymer on to the nanoparticle surface from a solution of polymer.

RESULTS

When placed in contact with aqueous media, particles fail to generate O₂ at pH 7.2, whereas decreasing the pH to 6.4 results in detectable oxygen generation. Tumour pO₂ was measured in mice bearing ectopic Mia PaCa-2 pancreatic tumours after IV administration of pH responsive CaO₂ NPs. **Figure 1b** reveals no significant change in pO₂ in the 20 min before injection. However, 10 min after injection, pO₂ levels in the treatment group increased dramatically reaching 16 mmHg before levelling off at ~6 mmHg 30 min after injection. Data indicate that use of the CaO₂ NPs together with SDT leads to enhanced toxicity.

CONCLUSIONS

CaO₂ nanoparticles that enable the generation of oxygen in response to a decrease in pH in the have been developed. Following administration to tumour-bearing mice, a decrease in tumour hypoxia has been demonstrated *in vivo*. No overt adverse effects were noted in subjects and we suggest that use of this preparation could play a significant role in enhancing cancer treatment modalities such as SDT.

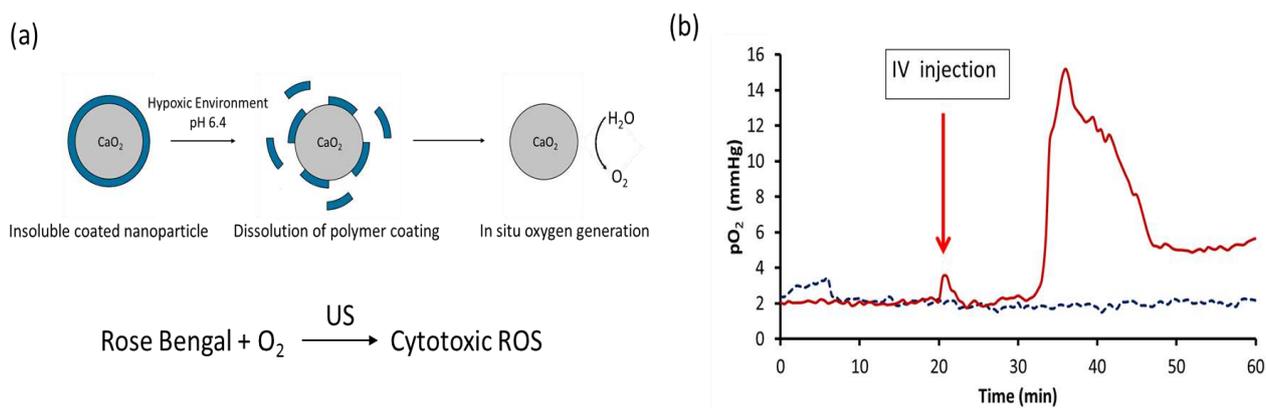


Figure 1: (a) pH dependent generation of oxygen by pH responsive CaO₂ NPs and production of cytotoxic ROS in sonodynamic therapy (b) Tumour pO₂ for mice bearing ectopic Mia Paca-2 tumours during an IV injection of CaO₂ NPs (solid red line) or vehicle only (dotted blue line).

A SURFACE ACOUSTIC WAVE-BASED PLATFORM FOR CELLULAR MECHANOTRANSDUCTION INVESTIGATION

Defei Liao, Fenfang Li, Eric Esch, Ricky Park, and Pei Zhong

Department of Mechanical Engineering and Materials Science, Duke University, Durham, NC 27708

e-mail: defei.liao@duke.edu; pzhong@duke.edu

OBJECTIVES

We constructed a surface acoustic wave (SAW)-based platform to investigate whether Piezo1, a mechanically activated ion channel, may play a significant role in US-induced mechanotransduction.

METHODS

SAW pulses were generated by a focused interdigital transducer of 33 MHz, coupled into culture medium, and excited leaky pressure waves toward individual cells grown in a glass-bottom petri dish. HEK293T cells with Piezo1 either genetically knocked out (P1KO) or transfected (P1KO-TF) were treated by SAW for 60 s at an estimated peak pressure of 0.35 MPa with 0.5 Hz repetition frequency and 50% duty cycle. Fluorescence images were taken to monitor the intracellular Ca^{2+} transient (fura-2) and membrane poration (PI), and bright-field images for cell morphology changes.

RESULTS

Our results showed that the intracellular calcium ratio increased dramatically in P1KO-TF cells (peak ratio change: $36 \pm 12\%$) compared to P1KO cells (peak ratio change: $10 \pm 6\%$). Furthermore, the calcium response of P1KO-TF cells showed increased rise time (103 ± 21 s) and prolonged -6dB duration (345 ± 103 s), compared to P1KO cells (85 ± 17 s in rise time and 55 ± 26 s in duration). Neither PI uptake nor cell morphology change was observed after the SAW stimulation.

CONCLUSIONS

The SAW-based platform was capable of eliciting intracellular calcium signaling in both P1KO and P1KO-TF HEK293T cells, suggesting multiple pathways exist. The significantly increased calcium response in the P1KO-TF cells indicates that Piezo1 may play an important role in modulating US-induced calcium signaling.

ACKNOWLEDGEMENTS

Supported by NIHR37DK052985; Dr. Jorg Grandl provided the HEK293T Piezo1 knockout cell line.

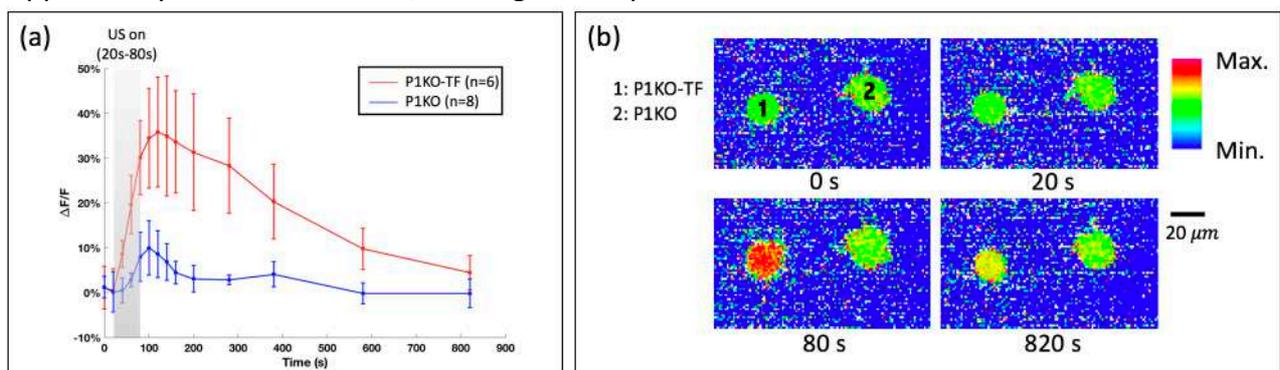


Figure 1. Intracellular Ca^{2+} transients induced by 33MHz US (stimulation from 20 to 80 s): (a) Normalized ratio change in fluorescence ($\Delta F/F$) and (b) representative ratio images of P1KO-TF and P1KO HEK293T cells at 0, 20, 80, and 820 s.

Modeling of Carbon nanotube transducer considering acoustic characteristics of the human skull

C. LEE¹, J. LEE¹, S. Min¹, D-G. Paeng^{1,2}

¹Department of Ocean System Engineering, Jeju national University, Jeju, Korea

²Department of Radiation Oncology, University of Virginia, Charlottesville, VA, USA

e-mail: cjddk7467@naver.com; paeng@jejunu.ac.kr

OBJECTIVES

This is a proof-of-concept study to design the surface of carbon nanotube (CNT) transducer for the optimal energy transmission through human skull at the brain target tissue. CNT transducer surface considering sound speed and density of the human skull was designed by applying the acoustic inverse ray method for better focus with higher pressure and confirmed by numerical simulation.

METHODS

Three-dimensional surface of the CNT transducer was designed by tracking the same phase at a specific time using the MATLAB and Sim4Life software when the point source at the focal point propagates with and without skull. The aperture and focal length of the CNT transducer are 8 cm and 5 cm, respectively. The skull was modelled as a homogeneous medium with density of 1098kg/m^3 , sound speed of 2813.69m/s , and attenuation of 32.73np/m at 0.6 MHz continuous wave.

RESULTS

We performed simulations to compute the axial and lateral sound pressures through the skull using Sim4life software. Transmitted sound pressure from the conventional PZT transducer (named TR2 without skull) was computed as a reference. Sound pressure reduced through the skull (TR2 with skull) was recovered about two times from 6 MPa to 13 MPa at the focus by the skull-specific surface of the designed CNT transducer (TR1) as shown in Fig. 1.

CONCLUSIONS

CNT transducer was designed considering acoustic characteristics of the human skull, which could compensate the focal distortion and increase sound pressure at the focus. In the future, the designed CNT transducer surfaces will be fabricated and the experimental measurement will be performed.

ACKNOWLEDGEMENTS

Thanks to Focused Ultrasound Foundation for research fund and ZMT for free license of Sim4Life

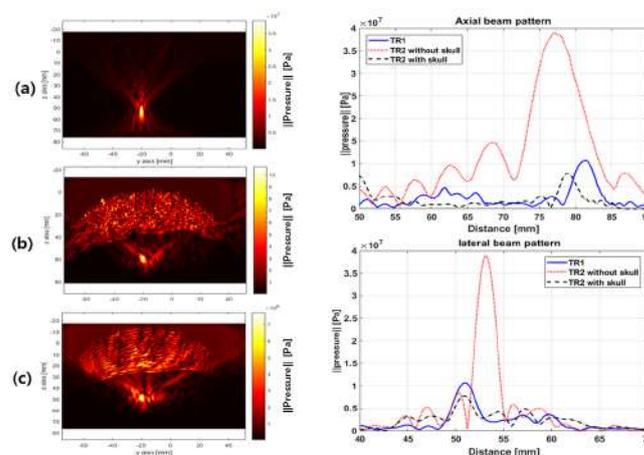


Fig. 1(a) Pressure field from the conventional transducer (TR2) without the skull as a reference. (b) Pressure field from TR2 with the skull. (c) Pressure field from the designed CNT transducer (TR1) considering sound speed and shape of the skull. Axial and lateral pressures near the focus were plotted in (d) and (e), respectively.

Cell-cycle-dependences of membrane permeability and viability observed for HeLa cells undergoing multi-bubble-cell interactions

Dongxin Yang¹, Yanye Yang¹, Xiasheng Guo¹, Juan Tu¹, Dong Zhang^{1,2}

¹Key Laboratory of Modern Acoustics (MOE), School of Physics, Nanjing University, Nanjing 210093, China

²The State Key Laboratory of Acoustics, Chinese Academy of Science, Beijing 10080, China
e-mail: juantu@nju.edu.cn; dzhang@nju.edu.cn

OBJECTIVES

As a biophysical process, the biological effects of microbubble-mediated sonoporation can be affected by many factors. In our previous studies, the impact of cell cycle phase on sonoporation-induced cellular responses was investigated at a single cell level, more efforts were made in the present work to investigate the cell-cycle-dependent manner in the multi-bubble-cell interaction system.

METHODS

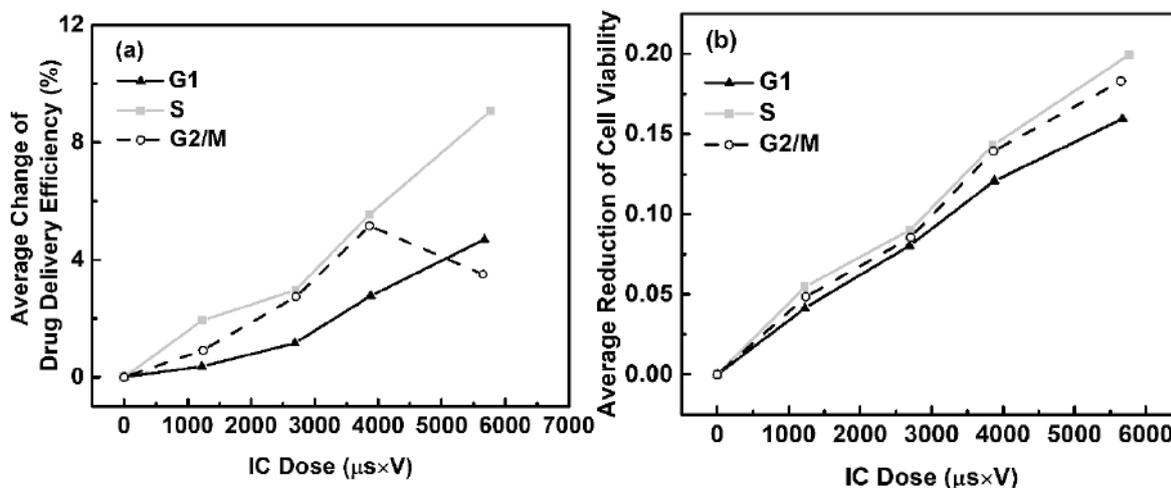
HeLa cells were synchronized at individual cell cycle phases of G₁, S and G₂/M. By employing a focused US exposure apparatus coupling with passive cavitation detection (PCD) system, systemic experiments were performed to study the impact of cell cycle phase on the microbubble cavitation activity and multi-bubble sonoporation-induced cellular responses of HeLa cells.

RESULTS

The results indicated that: (1) the microbubble cavitation activity should be independent on cell cycle phases; (2) G₁-phase cells with the largest Young's modulus were the most robust against microbubble-mediated sonoporation; (3) G₂/M-phase cells exhibited the greatest accumulated Fluorescein Isothiocyanate (FITC) uptake with the lowest viability; (4) S-phase cells with the lowest stiffness exhibited the greatest enhancement in sonoporation-facilitated membrane permeabilization without further scarifying their viability.

CONCLUSIONS

With the help of microbubble inertial cavitation (IC) activity, the greatest enhancement of drug delivery efficiency could be achieved for the cells synchronized in S phase without further reducing their viability. Therefore, S phase might be the most preferable cell phase for long-term sonoporation facilitated drug/gene delivery treatment.



CAPTION: The average changes in (a) the drug delivery efficiency and (b) the cell viability induced by multi-bubble IC activity for cells in different periods.

ENGINEERING ACOUSTICALLY ACTIVATED NANODROPLETS FOR BONE FRACTURE REPAIR

Q. Wu¹, J. May^{2,3}, S. Ferri^{2,3}, A. Polydorou^{2,3}, J. Owen¹, N.D. Evans^{2,3}, D. Carugo³, E. Stride¹

¹Department of Engineering Science, University of Oxford, Oxford, UK

²Faculty of Medicine, University of Southampton, Southampton, UK

³Faculty of Engineering and Physical Sciences, University of Southampton, Southampton, UK

e-mail: eleonor.stride@eng.ox.ac.uk; d.carugo@soton.ac.uk; n.d.evans@soton.ac.uk

OBJECTIVES

There are currently no clinically approved systemic therapies for bone fracture healing. The aim of this work was to investigate the use of ultrasound responsive nanodroplets for the targeted delivery of an osteogenic drug (BIO). In particular, the influence of nanodroplet composition and manufacturing process on drug encapsulation efficiency and acoustic response were investigated.

METHODS

Phospholipid nanodroplets (NDs) were prepared by either sonication or through condensation of a microbubble precursor. Both perfluoropentane (PFP) and perfluorobutane (PFB) were investigated as the core material and the ratio of phospholipid and emulsifier in the coating was also varied. The size distribution, concentration and stability of the droplets at 4, 20 and 37°C was measured and the liquid to vapour phase transition determined as a function of ultrasound frequency and pressure. In vivo, 1 mm drill-hole defects were made in the femurs of male MF1 mice. Nanodroplets with fluorescent dye, DiR, were injected 1-hour post-surgery and imaged at 24 hrs using IVIS.

RESULTS

All NDs were stable at both 4°C and 37°C and the diameter was found to be sensitive to the manufacturing method, lipid coating composition and volume of perfluorocarbon (Fig. 1A&B). The 50% phase-transition pressure thresholds for PFP NDs were 0.92 MPa and 3.1 MPa at 0.5 MHz and 1 MHz respectively (Fig.1C). For PFB NDs the threshold was 1.1MPa at 1 MHz and the encapsulation efficiency of BIO was 48±8%. In vivo, DiR-labelled nanodroplets were seen to accumulate specifically at bone fracture sites at 24 hours (Fig.1D).

CONCLUSIONS

A protocol was established to produce phospholipid NDs with clinically acceptable diameter, size distribution and stability. The phospholipid NDs could be induced to vaporize at moderate ultrasound intensities, encapsulate an osteogenic agent and accumulate preferentially at a fracture site in vivo. They thus offer a potential method of targeted delivery for fracture treatment.

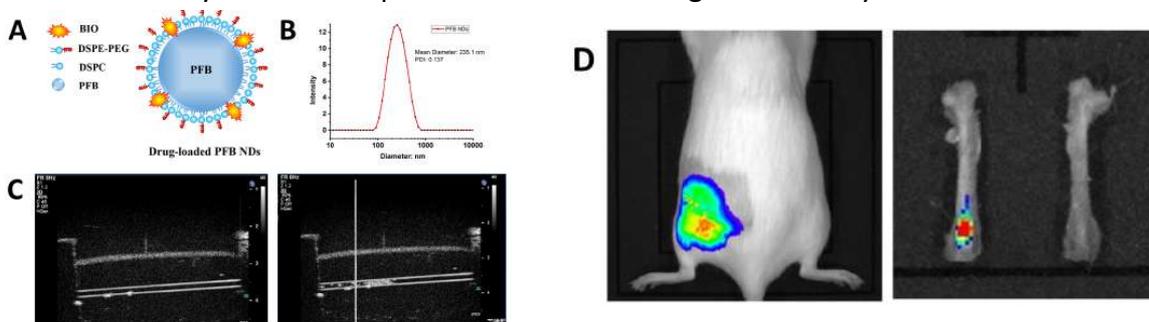


Figure 1. (A) Schematic and (B) size distribution of BIO-loaded PFB NDs; (C) B-mode images of phospholipid NDs in the flow channel before and after focused ultrasound exposure; (D) DiR-labelled NDs accumulated at a fracture site as shown by whole animal imaging and in extracted femurs

Novel Acoustic Coupling Bath to Improve MRI Guidance for Focused Ultrasound Surgery

S.P. Allen¹, T. Steeves², E. Vlaisavljevich³, A. Fergusson⁴, R.M. Davis⁵, C.H. Meyer^{1,6}

¹Department of Biomedical Engineering, University of Virginia, Charlottesville, USA

²Department of Mechanical Engineering, Virginia Tech, Blacksburg, USA

³Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, USA

⁴Graduate Program in Translational Biology, Medicine, and Health, Virginia Tech, Blacksburg, USA

⁵Department of Chemical Engineering, Virginia Tech, Blacksburg, USA

⁶Department of Radiology, University of Virginia, Charlottesville, USA

e-mail: spa5c@virginia.edu

OBJECTIVES

To reduce errors in guidance magnetic resonance imaging (MRI) for focused ultrasound surgeries by using aqueous superparamagnetic iron oxide nanoparticles (SPIOs) as MRI-invisible acoustic coupling media.

METHODS

Aqueous 0.75 mM Fe SPIO mixtures (US7568, US-Nano-Research, Houston, TX) were used as coupling media while sonicating a gel target with a 30 cm diameter, 650 kHz hemispherical transducer (ExAblate Neuro 4000, Haifa, Israel) situated in a 3T scanner (MR750, GE, Waukesha, WI). Sonications consisted of 10 s bursts with transmitted acoustic power ranging from 50 to 600 W. Anatomical turbo-spin-echo and gradient-echo thermometry MR images were also acquired.

The intrinsic cavitation threshold pressure for various aqueous SPIO mixtures was also estimated by depositing 100 highly focused, shocked, 5 cycle, 700 kHz acoustic pulses at a rate of 1 Hz into the media using a custom transducer (Histosonics, Ann Arbor, MI) in a water tank. Negative acoustic pressures were incremented from -8 to -42 MPa. To prevent settling, the SPIOs were periodically and gently agitated. Cavitation activity was detected with both an optical camera and a passive detection element. Cavitation probability curves were then computed by fitting the observed relative cavitation frequency to a Gaussian cumulative distribution function.

RESULTS

Aqueous SPIOs suppressed 90-98% of the coupling medias' MR signal relative to degassed water, caused ~2 °C less temperature elevation in sonicated gel targets relative to degassed water, and decreased the intrinsic cavitation threshold pressure by ~17% relative to degassed water.

CONCLUSIONS

SPIOs effectively suppress the MRI conspicuity of the coupling media, slightly depress thermal deposition in gel targets, and non-trivially depress the intrinsic cavitation threshold pressure.

ACKNOWLEDGEMENTS

The authors would like to thank the Ivy Biomedical Innovation Fund for support.

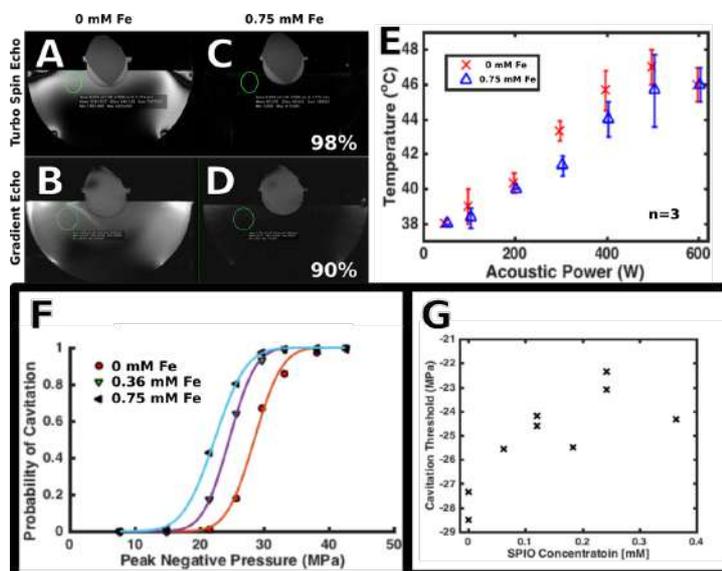


Figure 1: (A-D) Gradient echo and turbo spin echo images of a gel target in the transducer using (A-B) 0 mM Fe SPIO coupling medium and a (C-D) 0.75 mM Fe SPIO coupling medium. The SPIOs suppress at least 90% of the coupling medium's MR signal. (E) Estimated peak temperature in a gel target as a function of transmitted acoustic power for two coupling media. The presences of the SPIOs marginally attenuates the peak temperature achieved in the gels. (F) Example estimated cavitation probability curves for three coupling media compositions. (G) Intrinsic 0.5 cavitation probability threshold pressures as a function of SPIO concentration (mM).

THERAPEUTIC ULTRASOUND PHASED ARRAY WITH ARBITRARILY SHAPED, DENSELY PACKED, REMOVABLE MODULAR ELEMENTS

J.E. Lundt¹, T.L. Hall¹, A. P. Duryea², T.I. Gerhardson¹, Z. Xu¹

¹Department of Biomedical Engineering, University of Michigan, Ann Arbor, USA

²Histosonics, Inc., Ann Arbor, USA

e-mail: lundt@umich.edu

OBJECTIVES

Our lab has previously fabricated transducers with modular circular elements with packing densities of ~60%. Here we present a novel design amenable to readily accessible fabrication techniques for a therapeutic ultrasound array with high packing-density (>90%) and easily replaceable modular elements.

METHODS

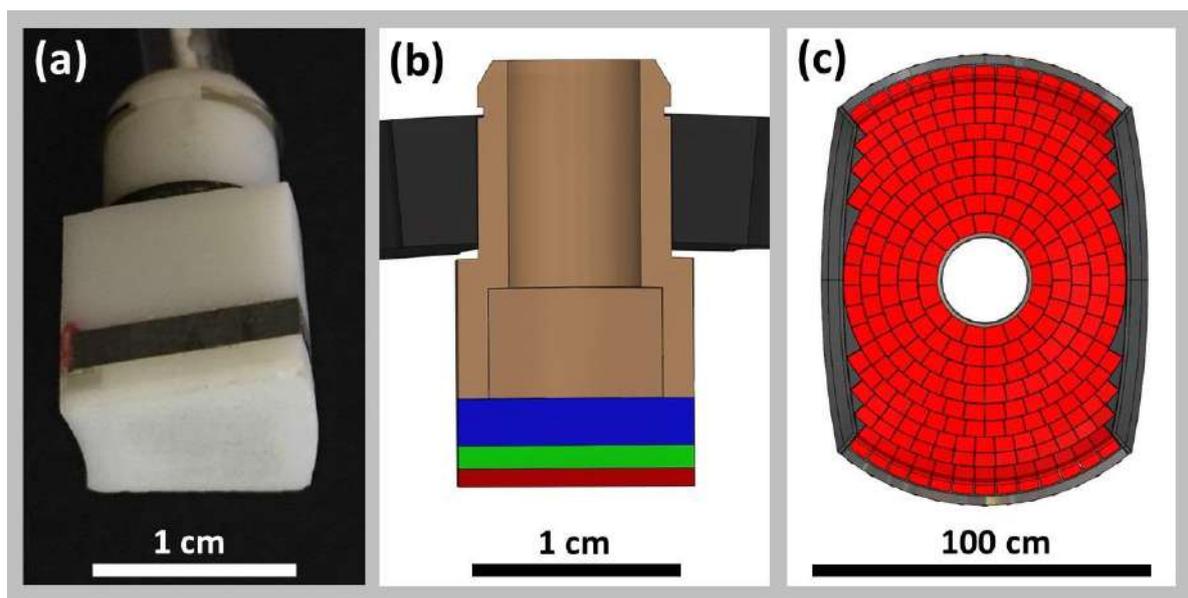
A 750 kHz phased array was designed for histotripsy liver-ablation based on human CT scans (N=16) and simulation. There were 260 total elements with 9 unique arc-segment shapes of approximately equal aspect ratio which nested in concentric rings. Sheets of piezoceramic material were water-jet cut into individual elements and bonded flush between a 3D printed backing-mount and two matching layers as shown in figures (a) and (b). Modules were coated with a 125-micron layer of epoxy for water-sealing and electrical insulation and mounted in an aluminum scaffold. Ceramic-edge-to-ceramic-edge spacing separating adjacent piezoceramic components was 0.5 mm.

RESULTS

The resulting design had a 165 mm x 234 mm aperture with 92% active area. P- at the focus was estimated to be 224 MPa assuming simple linear summation of individual module output. The FWHM electronic focal steering range was simulated to be 35.4, 32.5, and 54.4 mm in the two transverse-directions and axial-direction, respectively.

CONCLUSIONS

This study presents a novel method for fabricating a therapeutic array with densely packed, modular elements.



CAPTION: (a) Image of assembled module prior to epoxy coating. (b) CAD cross-section of module in scaffold. (b) red: first matching layer; green: second matching layer; blue: piezoceramic; brown: backing-mount. (c) CAD rendering of transducer. View along acoustic axis. Modules appear in red. (42 words)

A preliminary study for evaluation of sonodynamic therapy in combination with BBB-opening by FUS

Eun-Joo Park^{1,2*}, Yuri Cheon¹, Yundeok Ahn¹, Jae Young Lee^{1,3}

¹Department of Radiology, Seoul National University Hospital, Seoul, Korea

²Biomedical research institute, Seoul National University Hospital, Seoul, Korea

³Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

e-mail: ejpark@snuh.org, yr861117@gmail.com, duck512@gmail.com, leeju4u@snu.ac.kr

OBJECTIVES

This experiments were designed as preliminary studies to investigate the possibility of 5-ALA mediated sonodynamic therapy (SDT) in combination with BBB/BTB opening as an active brain cancer treatment.

METHODS

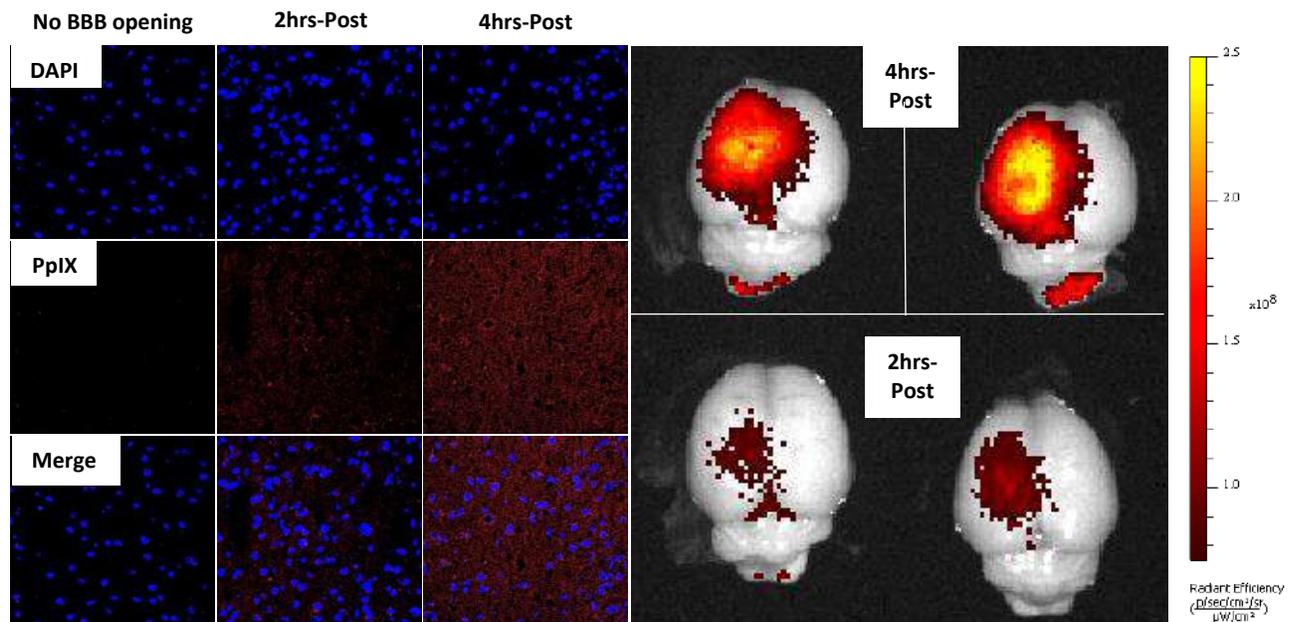
The levels of 5-ALA-induced PpIX over time and ROS generated by ultrasound were evaluated in C6 rat glioma cells *in vitro*. The ROS levels were measured for six different ultrasound treatment conditions. SD rats were used in an *In vivo* study. The levels of PpIX were measured by fluorescence images at two or four hours after the BBB opening and the administration of 5-ALA.

RESULTS

In vitro study showed the maximum level of 5-ALA induced PpIX at two hours after the treatment, while *in vivo* study showed higher PpIX level at four hours after the BBB opening and IV injection of 5-ALA.

CONCLUSIONS

This work is a preliminary study to obtain proper treatment protocol for our ongoing project, sonodynamic therapy in the brain. Based on the results from *in vitro* and *in vivo* studies, the evaluation of sonodynamic therapy for brain cancer is currently in progress and the results will be presented at the conference.



Fluorescence images of the 5-ALA induced PpIX in tissue (a) and whole brain (b). Higher PpIX concentration is observed at four hours of BBB opening and 5-ALA administration.

INTEGRIN-DEPENDENT CALCIUM SIGNALING INDUCED BY SINGLE IMPULSIVE BUBBLES

Fenfang Li¹, Ricky Park¹, George Sankin¹, Christopher Gilchrist², Brent Hoffman², and Pei Zhong^{1,2}

¹Department of Mechanical Engineering and Materials Science, ²Department of Biomedical Engineering, Duke University, Durham, NC 27708

e-mail: fenfang.li@duke.edu; pzhong@duke.edu

OBJECTIVES

How to tune ultrasound and cavitation activity to achieve maximum therapeutic gain with minimal adverse effects is important and challenging in therapeutic ultrasound. Here we investigate whether mechanosensitive channel Piezo1 and integrin-mediated pathway may play an important role in Ca²⁺ signaling induced by single impulsive bubbles.

METHODS

Laser-generated single bubbles ($D_{max} = 90 - 110 \mu\text{m}$) are utilized to stimulate HEK293T cells with Piezo1 either genetically knockout (P1KO) or transfected (P1KO-TF). Integrin-binding RGD beads ($6 \mu\text{m}$) are attached to cell surface to amplify shear flow-induced drag to the cells. Bubble dynamics and flow field are characterized by high-speed imaging while intracellular Ca²⁺ transient and membrane poration are monitored by fluorescence imaging.

RESULTS

The strength of bubble-generated impulsive shear flow (within $20 \mu\text{s}$) can be tuned by the normalized standoff distance ($\gamma = S_d/R$) (peak flow velocity decrease from 6 m/s at $\gamma = 1.1$ to 2 m/s at $\gamma = 1.7$) (Fig.1A). Single impulsive bubbles cannot elicit Ca²⁺ response without membrane poration, even with the presence of Piezo1 (Fig. 2B). In contrast, impulsive stretch of integrin-binding RGD beads can elicit a significant Ca²⁺ response without membrane poration, with or without Piezo1 (Fig. 1C). We are investigating the key molecular players in this process.

CONCLUSIONS

Piezo1 does not mediate cellular Ca²⁺ response without membrane poration produced by single impulsive bubbles, possibly due to the high shear strain rate. Impulsive stretch of integrin-binding RGD beads provides an effective means to elicit Ca²⁺ signaling without cell injury.

ACKNOWLEDGEMENTS

Supported by NIHR37DK052985; Dr. Jorg Grandl provided HEK293T P1KO cell line & Piezo1 plasmids.

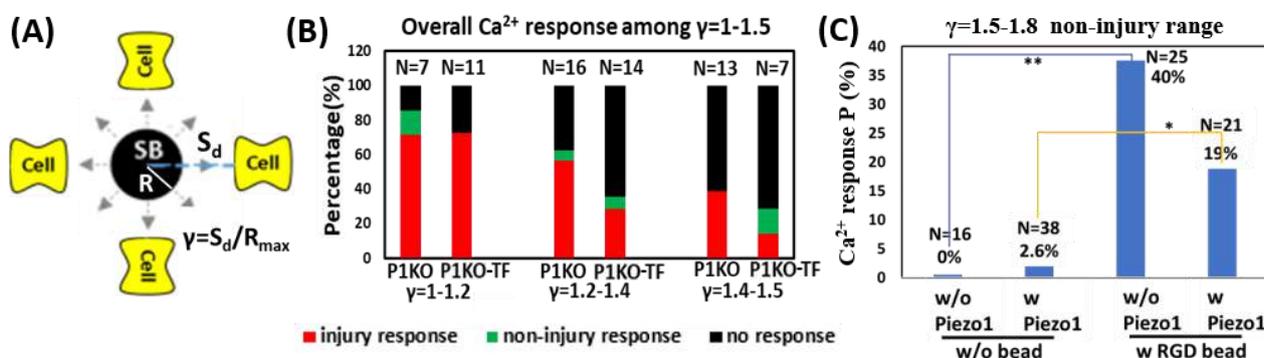


Figure 1: Intracellular Ca²⁺ signaling induced by single bubble (SB). (A) Schematic diagram of the experiment. (B) Three different Ca²⁺ responses elicited in P1KO and P1KO-TF cells in the range of $\gamma = 1-1.5$. (C) Ca²⁺ response probability in the non-poration range of $\gamma = 1.5-1.8$, either with or without Piezo1 and RGD bead attachment.

Stroboscopic Schlieren Imaging of Ultrasound Fields with Large Field of View

Florian Steinmeyer¹, Adrian Dittmaier^{1,2}, Maximilian Jahrsdörfer^{1,3}

¹Faculty for Applied Mathematics, Physics and Humanities, Technische Hochschule Nürnberg, Germany

²Karlsruhe Institute of Technology, Karlsruhe, Germany

³Siemens Healthineers, Forchheim, Germany

E-mail: florian.steinmeyer@th-nuernberg.de

OBJECTIVES

Schlieren imaging is an established means of qualitatively and - to a degree - quantitatively characterising ultrasound fields. We present a stroboscopic system with ~ 10 cm field of view capable of visualising amplitude and phase of an ultrasound field based on low-cost LED light sources.

METHODS

In a Toepler type Schlieren system a 628 nm red LED (3 mm, 12.5 Cd in 25° angle) is pulsed with the transducer frequency (3.1 MHz) and a pulse width of 16 ns (FWHM) from a dual channel frequency generator (Keysight 33500B). The piezocomposite transducer ($D = 70$ mm, $f = 72$ mm, Imasonic, Voray sur l'Ognon, France) is fed through a lab-build impedance matching system and a power amplifier (E&I, Rochester, NY, A300-B1). The transducer is mounted in a glass walled water bath. Light is collimated and focused by 120 mm diameter lenses ($f = 250$ mm). A knife edge stops direct light. Refracted light is observed with either a Sony DSC-RX100V or a Panasonic GX-80 digital camera. The DSC is capable of 960 frames per second and electronic shutter speed down to 31 μ s while the GX-80 was equipped with a zoom lens (12mm-60mm) improving spatial resolution.

RESULTS

Ultrasound wave fields can be recorded with optical resolution using LED sources and consumer market digital cameras. Imaging examples of a focussed ultrasound field and of cavitation with short exposure time are shown in Fig a) and b) respectively.

CONCLUSIONS

Stroboscopic imaging allows fast, non-invasive and comprehensive visualisation of ultrasound wave fields including phase resolution. Further image reconstruction may allow full 3D wave field detection within minutes.

ACKNOWLEDGEMENTS

We are grateful to Staedtler Stiftung, Nuremberg, Germany for partial financial support.

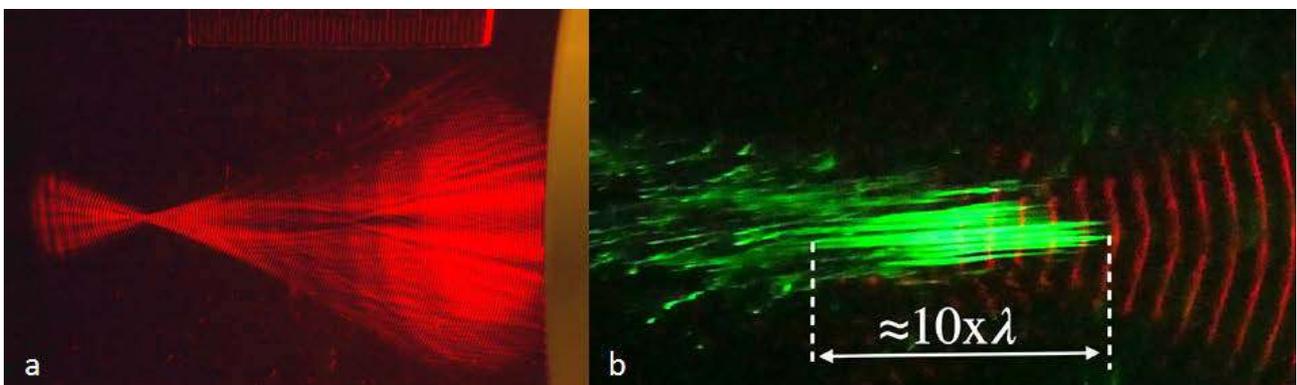


Fig a) Stroboscopic image of a 3.1 MHz focussed wave field. Note the braided interference pattern. Scale at top of image is 45 mm. **Fig b)** Cavitation bubbles in water at 130 W ultrasound power are illuminated by a green laser (not pulsed). Bubble track length within shutter time (1/16000 s) allows estimation of bubble speed to 80 m/s.

Mechanism of HIFU interaction in flooded lung and their consequences on ablation schemes for FUS on lung cancer

Wolfram, Frank¹; Thomas G Lesser¹

¹ SRH Waldklinikum Gera / Lung Cancer Centre

e-mail: Frank.Wolfram@SRH.de

OBJECTIVES

FUS for lung cancer requires partial One Lung Filling (OLF). Previous work showed that during OLF atypical acoustic properties in lung, as a tissue-saline compound, exists. Those might impact the ablation process and require adaption of ablation schemes. Therefore this work investigates the HIFU interaction on flooded lung and lung cancer (NSCLC) tissue and compares experimental with simulation results showing strength and limitations of lung FUS.

METHODS

HIFU (1,1MHz @ 2.400W/cm²) was targeted into lung parenchyma and cancer tissue using an ex-vivo human lung model under thermal monitoring. Based on previously determined acoustic properties, a simulation of the corresponding heat induction were performed using the HIFU Simulator 1.2 and a customized 3D Bio-Heat solver.

RESULTS

In central NSCLC temperature rises exponentially, reaching ablative values above 80°C, whilst in lung only 45°C are monitored at the end of 10 sec HIFU exposure. Values are in agreement with simulation for NSCLC but are overestimated in flooded lung, therefore absorption coefficients were corrected, taking scatter losses in lung into account. Simulations of focal position at the tumour-lung interface, showed temperature decay towards the lung parenchyma (Fig. 1a). An optimal ablation process for lung cancer is achieved by using volumetric ablation schemes providing sufficient safety margins (Fig. 1b).

CONCLUSIONS

During OLF atypical but superior conditions for HIFU ablations exists reaching ablative temperature in NSCLC sparing healthy parenchyma. To ensure radicality, volumetric ablation schemes should be applied for lung FUS.

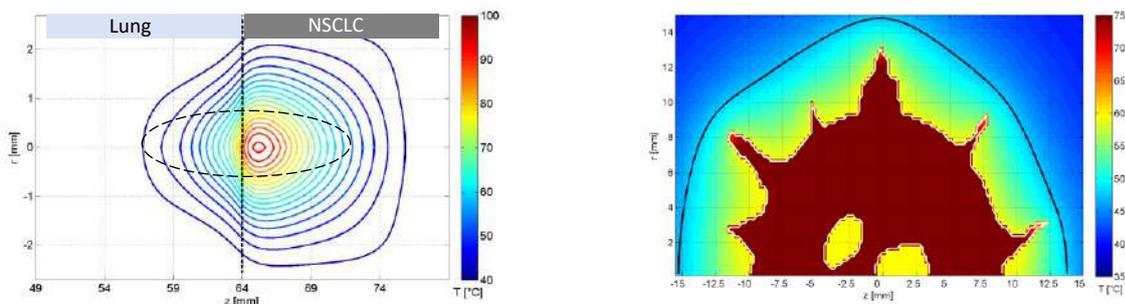


Fig. 1 Simulation of HIFU temperature induction a) focus (dashed line) placed at tumour –lung tissue interface (dotted line) showing temperature decay towards lung and b) during volumetric ablation on an irregular lung tumour model @ 6 min, black line indicate lethal dose (240CEM43)

Predicting high intensity focused ultrasound thalamotomy lesions using magnetic resonance thermometry and 3D Gaussian modelling

Graham M. Seasons^{1,2,6}, Erin L. Mazerolle PhD^{1,2}, Robyn Warwaruk-Rogers BN³, Paul Romo⁴, Tejas Sankar MDCM⁵, Davide Martino MD^{2,3}, Zelma HT Kiss MD PhD^{2,3}, Samuel Pichardo PhD^{1,2,3}, and G Bruce Pike PhD^{1,2,3*}

¹Department of Radiology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

²Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

³Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

⁴Seaman Family MR Research Centre, Foothills Hospital, Calgary, Alberta, Canada

⁵Division of Neurosurgery, Department of Surgery, University of Alberta, Edmonton, Alberta, Canada

⁶Department of Electrical Engineering, University of Alberta, Edmonton, Alberta, Canada
e-mail: gseasons@ualberta.ca

OBJECTIVES

To predict magnetic resonance guided focused ultrasound (MRgFUS) thalamotomy lesion volume, shape, and location in tremor patients.

METHODS

Twelve patients with medication-refractory tremor underwent MRgFUS thalamotomy using an InSightec ExAblate 4000 system integrated with a 3T GE MR scanner. Two-dimensional gradient-echo MR thermometry images were acquired intra-operatively (bandwidth: 279 Hz/pixel, thermal coefficient: -0.00909 ppm/°C) before being temporally filtered using a general linear model approach to reduce noise. Thermometry images across all sonications were aligned and fit using a 3D Gaussian model to approximate a patient specific temperature distribution. To analyze individual sonications, three-dimensional temperature distributions were approximated from each 2D sonication using the axial relationships derived from the fitted model, before calculating the accumulated thermal dose (ATD). ATD distributions were then correlated with the T1w lesion volume acquired one day post-operatively across patients, and regression slopes were plotted against thermal dose thresholds. We also considered shape and location overlap between the predicted and actual lesions by calculating the Dice-Sørensen coefficient (DSC).

RESULTS

The ATD with greatest correlation with T1w lesion volume was 59.6 cumulative equivalent minutes at 43°C (CEM43). Predicted lesions at this threshold were associated with an average DSC of 0.531 (range: 0.355-0.636). Alternately, when ATD was allowed to vary across patients to optimize DSC, the average ATD was 99.2 CEM43, with an average DSC of 0.551 (0.377-0.674).

CONCLUSIONS

3D modelling of the thermal dose distribution was achieved using multiple orthogonal 2D temperature maps and gave very good predictions of day 1 T1w lesions with maximal correlation occurring at approximately 60 CEM43.

SAFETY AND FEASIBILITY OF TEMPORARY BLOOD-BRAIN BARRIER DISRUPTION WITH THE SONOCLOUD-3 IMPLANTABLE ULTRASOUND DEVICE IN RECURRENT GLIOBLASTOMA

A. Carpentier^{1,2}, M. Canney³, G. Bouchoux³, C. Desseaux³, A. Vignot³, C. Lafon⁴, J.-Y. Chapelon⁴, A. Idbaih⁵

¹Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires La Pitié-Salpêtrière, Service de Neurochirurgie, F-75013 Paris, France

²Sorbonne Université, UPMC Univ Paris 06, F-75013 Paris, France

³CarThera, Institut du Cerveau et de la Moelle épinière (ICM), Paris F-75013, France

⁴LabTAU, INSERM, Centre Léon Bérard, Université Lyon 1, Univ Lyon, F-69003, LYON, France

⁵Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, F-75013, Paris, France

e-mail: alexandre.carpentier@aphp.fr

OBJECTIVES

The blood-brain barrier (BBB) limits penetration of drug therapies to the brain. An implantable ultrasound device, SonoCloud, was developed to temporarily disrupt the BBB in patients with recurrent glioblastoma (rGBM) prior to carboplatin chemotherapy to enhance brain drug concentrations. The safety of repeated BBB disruption with a single emitter device, SonoCloud-1, was demonstrated in 19 patients¹. Here, the safety of BBB disruption in a larger region was evaluated using a three-emitter device, SonoCloud-3 (SC3).

METHODS

Patients were implanted with the SC3, which consisted of three 1-MHz, 10-mm diameter ultrasound transducers, during tumor debulking at recurrence. The device was activated monthly at two escalating acoustic pressure levels (0.90 and 1.03 MPa) in combination with injection of SonoVue® microbubbles (0.1 mL/kg). Magnetic resonance imaging was performed after sonications followed by carboplatin infusion at AUC4-6.

RESULTS

Sonications were performed monthly in six patients, confirming clear BBB opening at 1.03 MPa. No unexpected safety issues related to the larger sonication volume were observed over the 24 sonications. One recurrent IDH wild type GBM patient received 12 monthly sonications with SC3 and remains without tumor recurrence after a follow-up of more than 19 months since inclusion.

CONCLUSIONS

These results in six patients using the SC3 provide additional safety data on the effects of disrupting the BBB in rGBM patients prior to carboplatin chemotherapy. This bridge study supports the development of a larger device, SonoCloud-9, which will be used in a new clinical study starting in 2019.

ACKNOWLEDGEMENTS

Supported by CarThera and APHP.

1 Carpentier A, Canney M, Vignot A, *et al*. Clinical trial of blood-brain barrier disruption by pulsed ultrasound. *Sci Transl Med* 2016; **8**. DOI:10.1126/scitranslmed.aaf6086.

DESIGN OF 1024-ELEMENT HEMISPHERICAL ARRAYS FOR ULTRASONIC BRAIN THERAPY

Hansol Yoon¹, Pilsu Kim¹, Tai-Kyong Song¹

¹Department of Electronic Engineering, Sogang University, Seoul, Korea, Republic of

e-mail: yoonhs@sogang.ac.kr; pskim@sogang.ac.kr; tksong@sogang.ac.kr

OBJECTIVES

Ultrasonic brain therapy requires the concentration of ultrasound power at the steered foci. We evaluate the steering capabilities of three types of 1024-element arrays on a 150-millimeter-radius hemisphere and examine the effects of element size and curvature to optimize the steering performance.

METHODS

Three array types with circular elements are assessed: annular, random (minimum interelement distance of 4λ) and sunflower arrays. The narrow-band responses of these arrays working at 1 MHz are calculated using the Rayleigh-Sommerfeld integral in a $75 \times 75 \times 150 \text{ mm}^3$ volume with a 0.25 mm step. Steering capabilities are compared under two conditions: 1) the maximum grating lobe pressure is at least 10 dB lower than the focal pressure; 2) the difference between the steered and the non-steered focal pressure is below 3 dB.

RESULTS

The sunflower array has the smallest grating lobes over the steering range (0-20 mm) [Fig. 1(a)]. Moreover, its element size can be increased up to 5.5λ , leading to 5.28 dB pressure increase at the geometrical focus. Although the 3 dB steering range is reduced (0-15 mm), using larger elements also lowers the artifacts [Fig. 1(b)]. Additionally, the same performance is obtained by using (easy-to-fabricate) flat elements.

CONCLUSIONS

Hemispherical sunflower arrays are optimal for brain therapy regarding its good steering capability and element packing property.

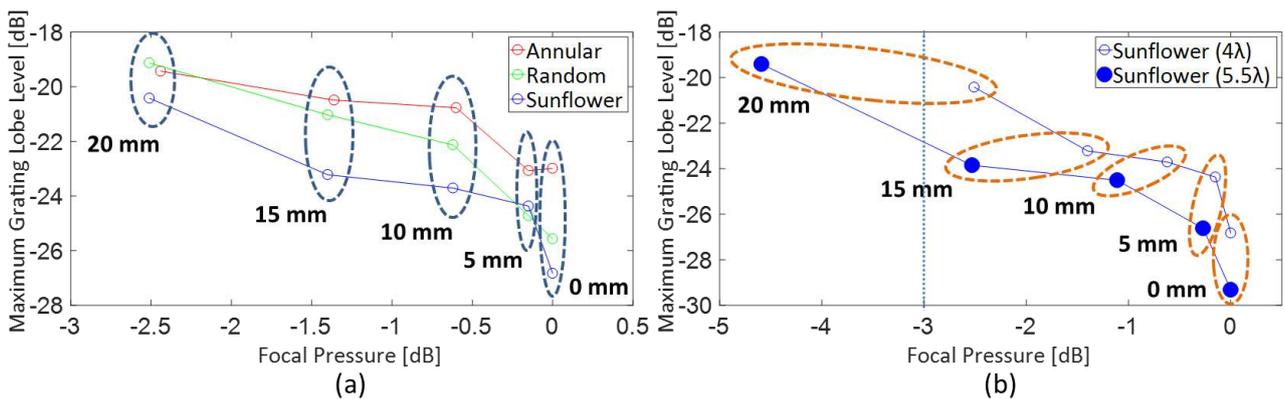


Fig. 1. (a) Maximum grating lobe levels of three arrays with the same element size (4λ) in the lateral steering range (0-20 mm). (b) Effects of using larger elements in the sunflower array. All focal pressures are normalized to 0 dB.

NaviFUS: A Neuronavigation-Guided Focused Ultrasound (NaviFUS) Medical Device Design

Wen-Ting Tsai¹, Hao-Li Liu^{1,2,3}, Kuo-Chen Wei³

¹NaviFUS Co. Ltd., Taipei, Taiwan

²Department of Neurosurgery, Chang Gung Memorial Hospital at Keelung, New Taipei, Taiwan

³Department of Electrical Engineering, Chang Gung University, Taoyuan, Taiwan

email: wtttsai@navifus.com

OBJECTIVES Current focused ultrasound (FUS) has been well-developed in its technological breakthrough for brain treatment, and now has been encountered to obtain fast development in CNS disease treatment. Currently it relies on MR to guide FUS energy targeting at deep brain location to its thermal sensitivity. However, for non-thermal FUS intervention, alternative approach other than MR guidance should be developed to reduce FUS system development complexity improve flexibility to incorporate with current clinical tools during interventions. Here we present a new concept in guiding FUS energy based on neuronavigation.

METHODS

NaviFUS is a device with its concept to incorporate with neuronavigation for FUS energy guidance, and is designed to transcranially deliver focal energy into the deep brain. The system comprise 256-channel transmit channel, with the selected channels is operated under dual transmit/receive mode for backscattered RF-channel data acquisition. Before intervention, the patient requires acquire CT image to obtain cranial bone information and perform personal treatment planning for investigator's approval. During operation, NaviFUS incorporates with the neuronavigator once the treatment plan been imported. With the developed algorithm, FUS spot can be visualized and guided during the entire intervention process.

RESULTS

The system is operated with the frequency suitable for transcranial use. The system is now able to produce nearly sufficient therapeutic power level for non-thermal treatment use. The electrical steering distance of centimeter-wide off axis at focal depth. Multiple channel backscattered RF data now allow real-time PCD monitoring during intervention. The overall treatment procedure can be limited to be less than 1 hour. The system is currently undergoing clinical feasibility testing to open the blood-brain barrier opening for recurrent GBM patients, and ready to conduct feasibility testing to perform neuromodulation for epilepsy patients.

CONCLUSIONS

NaviFUS is a feasible solution to perform precise and targeted non-thermal FUS intervention in the deep brain.



Figure 1. Neuronavigation-Guided Focused Ultrasound Device (NaviFUS).

MRgFUS treatment of desmoid tumor with preparatory nerve protection using MR-guided hydrodissection

H.E. Pärssinen¹, R.T. Blanco-Sequeiros¹

¹Radiology department, Turku University Hospital, Turku, Finland

e-mail: heikki.parssinen@tyks.fi

CLINICAL HISTORY

A 47 years old female slowly developed radicular pain on her left buttock. MRI showed a large 20cm long tumor with varying zones of enhancement and scar-like signal poor tissue in gluteus maximus and quadratus femoris muscles. The tumor dislocated the ischial nerve. Biopsy confirmed desmoid tumor.

MATERIALS AND METHODS

Surgical treatment was considered but discarded due to large resection area and resulting side effects. MRgFUS treatment with Philips Sonalleve (Amsterdam, Netherlands) was chosen to contain the symptoms. Proximity of ischial nerve to the treatment area was a concern that was dealt with MR-guided hydrodissection, here an injection of a mixture of 20ml Lidocain 10mg/ml and 50ml of NaCl 9mg/ml with MRI compatible needle (20G, 150mm, Invivo, Gainesville, USA) between tumor and the nerve creating a buffer to avoid heating of the nerve during sonications. The treatment was performed under general anesthesia.

RESULTS

Post-treatment contrast enhanced MRI showed 90% non-enhancing area of the tumor. Following the treatment lower limb sensomotory functions were normal and shrinkage of the tumor volume was observed. Due to significant pain reduction the patient could return to work.

CONCLUSIONS

Desmoid tumors pose a challenge to current standard treatment. MRgFUS shows potential in treating cases where invasive treatment is not feasible. Hydrodissection can be considered to protect critical structures at risk during the treatment.



Figure: Hydrodissection in balanced gradient echo.

Rapid prototyped microvessel networks for ultrasound mediated targeted drug delivery research

R. Domingo-Roca¹, B. Saltin², J.F.C. Windmill², J.C. Jackson², H. Mulvana¹

¹Medical and Industrial Ultrasonics, University of Glasgow, Glasgow, UK.

²Center for Ultrasonic Engineering, University of Strathclyde, Glasgow, UK.

e-mail: roger.domingo-roca@glasgow.ac.uk ; helen.mulvana@glasgow.ac.uk

OBJECTIVES

Understanding the deterministic factors within the complex microvasculature – fluid system is essential to exploit targeted drug delivery, and particularly important in the development of ultrasound-mediated targeted drug delivery (UmTDD), as a clinically applicable technology. Thus, it is essential and highly useful to develop an engineered method that provides accurate understanding of all the parameters influencing drug delivery efficiency to clinically apply this technology. In this work, we present the design of a new protocol that allows us to systematically investigate variables of potential influence in UmTDD.

METHODS

Structure of micro-vessel networks was acquired using X-ray microCT of porcine pig mesentery. An ASIGA 3D printer was used to 3D-print simplified versions of the structures obtained from microCT scans.

Acoustic measurements were conducted in a water tank filled with outgassed water at room temperature using a single-element broadband 3.5 MHz transducer. Signals were received using a calibrated needle hydrophone.

RESULTS

Flow velocity and Reynolds numbers were determined to establish the experimental parameters required to replicate biological flow conditions *in vivo* and match those observed in the human body. The acoustic attenuation coefficient, speed of sound, and B/A nonlinear coefficient of the 3D-printed material (poly(ethylene glycol) diacrylate, PEGDA) were fully characterized, providing tissue-like values.

CONCLUSIONS

The ability to accurately replicate microvessel networks will be essential to study the physical phenomena underpinning UmTDD efficiency and applicability. This protocol provides a platform to rapidly prototype any structure that is suspected to play a key role in UmTDD treatments.

ACKNOWLEDGEMENTS

This research has been conducted thanks to the funding provided by the Carnegie Trust for the Universities of Scotland, Grant number 50354.

Low-intensity focused ultrasound stimulation to frontal eye-field modulates human antisaccade behavior

T.Y. Park¹, S.-H. Yeo², H. Kim¹

¹Center for Bionics, Korea Institute of Science and Technology, Republic of Korea

²School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, United Kingdom

e-mail: hk@kist.re.kr

OBJECTIVES

Low-intensity focused ultrasound (LIFU) stimulation on the frontal eye field (FEF) has been previously shown to be capable of modulating saccade behavior of monkeys (Deffieux et al. 2013). In this study, we are to demonstrate the neuromodulatory effects of human visuomotor behavior induced by LIFU stimulation on FEF.

METHODS

Two healthy subjects were recruited and performed an antisaccade experiment with randomized LIFU stimulation to left FEF while measuring eye movement by electrooculography (EOG). The location of the subject-specific FEF on the MRI was determined by the radiologist. Acoustic simulation was performed to calculate optimal path to the left FEF. Transducer guide was designed based on the anatomical MRI scan of each subject. LIFU sonication with pulse repetition frequency of 360 Hz, tone-burst duration of 1 ms and estimated in-situ spatial-peak temporal-average intensity of 1.2-1.5 W/cm² at -300 to 200 ms with respect to the target onset was applied, while subjects were performing the antisaccade test with 25% frequency of stimulation trials.

RESULTS

Comparison of the latencies of control and stimulation trials suggests that LIFU on FEF has no or only weak effect on the latency of either correct or incorrect antisaccade for both sides and both subjects. However, in terms of the error rate, i.e. the proportion of incorrect trials, there are significant reductions in error rate for both sides and both subjects ($p < 0.05$).

CONCLUSIONS

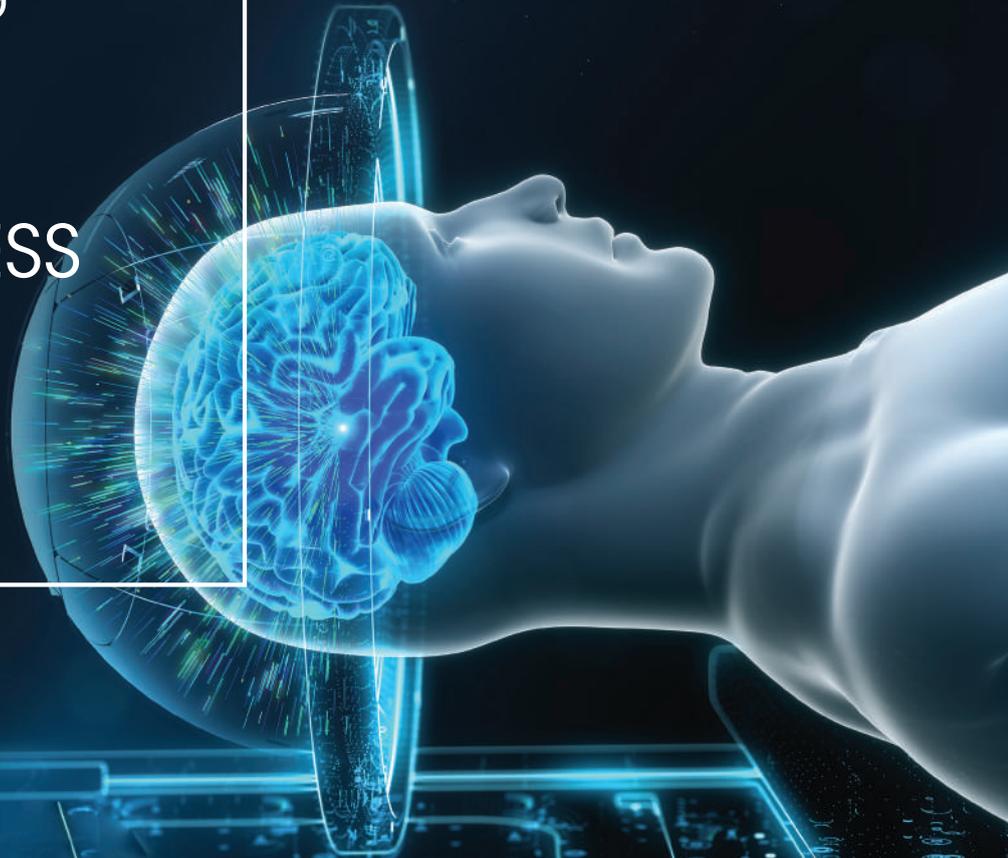
LIFU stimulation on human FEF during performing antisaccade task has shown to be effective in inhibiting erroneous prosaccade toward the target.

ACKNOWLEDGEMENTS

Supported by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIT) (No. CAP-18-01-KIST) and the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2015M3C7A1064833).

The logo for INSIGHTEC, featuring the word in a white, sans-serif font with a blue vertical bar and a horizontal line intersecting the letter 'H'.

Transforming
Patient Lives
through
**INCISIONLESS
SURGERY**



NEUROSURGERY | WOMEN'S HEALTH | ONCOLOGY

MR-guided Focused Ultrasound is a proven technology based on 20 years of research, development and clinical results.



Redefining surgery
by making 0 cuts



Minimal to no risk
of infection¹



Single session
treatments



Safe & effective with
minimal side effects¹

www.insightec.com

 @company/insightec

 @INSIGHTEC.MRgFUS

 @INSIGHTEC

¹Information for Prescribers: <https://www.insightec.com/media/31393/exablate-neuroinformationforprescribers0usa.pdf>
Safety Information: <https://www.insightec.com/safety-information>

INSIGHTEC Ltd. © 2019. All rights reserved.

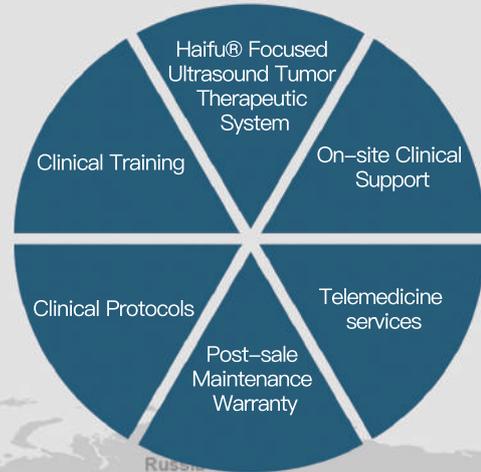


(Model JC200, CE marked)

Indications

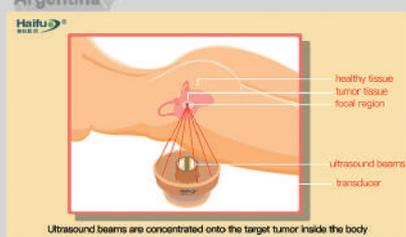
- Uterine fibroids
- Adenomyosis
- Breast tumor
- Liver tumor
- Pancreatic cancer
- Bone tumor
- Kidney tumor
- ...

Total Solution Provider

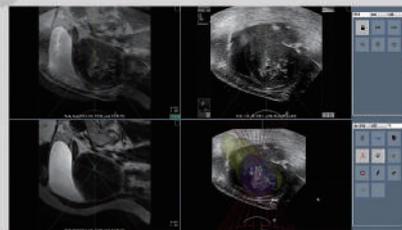


ABOUT US

Chongqing Haifu Medical Technology Co. Ltd, China, takes the lead in Focused Ultrasound Surgery. More than **200** Haifu® HIFU centers in **26** countries and regions, completed over **120,000** cases of benign and malignant tumors by 2018 and over **27,000** cases of uterine fibroids and adenomyosis in 2018.



(Treatment Presentation)



(Double-image guided HIFU)



Mutua Terrassa University Hospital (Barcelona, Spain)



Churchill Hospital of Oxford University (Oxford, UK)



Bonn University Hospital (Bonn, Germany)



Your partner
in advancing the field



FOCUSED
ULTRASOUND
FOUNDATION

Funding Research

We fund investigator-initiated clinical, preclinical, and technical projects in a competitive, peer-reviewed process.

Cultivating Leaders

We offer educational opportunities for early and mid-career researchers through fellowships and internships.

Fostering Collaboration

We host workshops, summits, and symposia to stimulate innovation and drive progress.

Overcoming Barriers

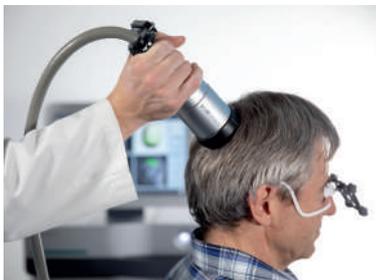
We partner with stakeholders to help with regulatory and reimbursement hurdles.

Visit fusfoundation.org to learn more.

Transcranial Pulse Stimulation (TPS®)

An innovative treatment method for Alzheimer's disease

Visit us at the 19th International Symposium of ISTU and 5th European Symposium of EUFUS, 13 – 15 June 2019 in Barcelona, Spain, on our Booth No. 3.



Advantages of TPS®

- Painless and without side effects
- Outpatient treatment (30 minutes/session)
- Adjuvant cognitive training not required
- Shaving of the scalp not required



BodyTrack® software

- Use of personalized MRI data
- Visualization of MRI data in 3 planes (axial, coronal, sagittal)
- Coloured visualization of the treatment region
- Real-time visualization of pulse distribution

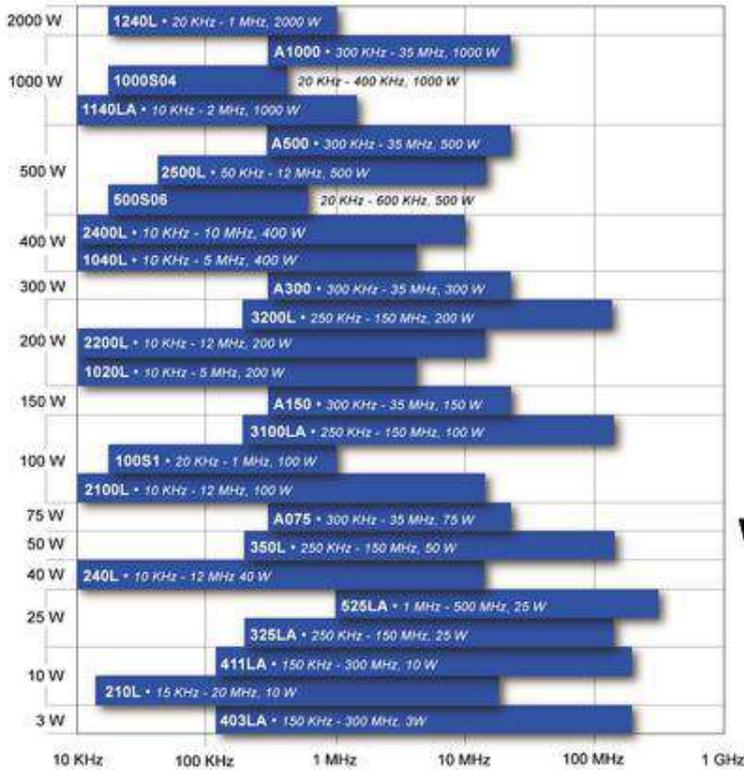


NEUROLITH® system

- Focused stimulation of deep cerebral regions
- Personalized 3D visualization of patient's head
- 3D infrared camera system for precise cerebral tracking
- Patient database



RF Amplifier Power/Frequency Chart



E&I supports the vast and exciting developments in medical research and treatment in the application of therapeutic ultrasound. We have a proven track record of manufacturing robust RF amplifiers; known throughout the industry for their ruggedness and reliability

www.eandiltd.com sales@eandiltd.com



We can work with you from Research to Production, Benchtop to Module.
Please contact us to learn more about our OEM Solutions.

The information shown herein refers to products of 3rd party manufacturer's and thus are in their regulatory responsibility. Please contact the 3rd party manufacturer for further information.

The solution for the treatment of essential tremor

Exablate Neuro for Siemens Healthineers MR systems

MR imaging plays an increasingly important role in planning, guiding and monitoring minimal invasive procedures. As a leading imaging equipment vendor it is our clear target to provide an open platform and well defined interfaces to enable both companies and researchers to seamlessly integrate with the MR environment.

With Access-i and other developments in the space of MR image guidance for therapy we aim to remove boundaries and restrictions toward a more widespread clinical adoption of MR in therapy.

siemens-healthineers.com/mri

Strategic Partner

INSIGHTEC
Therapy In Focus

Magnetic Resonance

SIEMENS
Healthineers

Verasonics and Sonic Concepts introduce the HIFUPlex™ portfolio

HIFUPlex™ brings together Verasonics' Vantage systems with Sonic Concepts' transducers to address the full range of applications in focused ultrasound, and to meet a wide range of budgets.

- Choose from 6 standard sets of HIFU and imaging transducers
- Provides researchers and developers an upgrade pathway from any Vantage configuration, as well as from non-USgFUS solutions using Sonic Concepts' Transducer Power Output™(TPO)
- The Vantage software now includes a simple graphical user interface, with interleaving scripts that control the major parameters of HIFU and imaging from the same transmitters

SONIC
CONCEPTS

 **Verasonics**®
The leader in Research Ultrasound™

Please visit the Verasonics and Sonic Concepts booths to see HIFUPlex™

HIFUPlex™



SPONSORS

Platinum Sponsors



Gold Sponsors



Bronze Sponsors



Sponsors



EXHIBITORS



INSIGHTTEC

MEGGITT

PROFOUND
MEDICAL

SIEMENS
Healthineers

SONIC
CONCEPTS

#S-Sharp

STORZ MEDICAL

THERACLION

Verasonics
The leader in Research Ultrasound™



ISTU 2020

2020 Annual Meeting of the International Society for
Therapeutic Ultrasound

May 17 (Sun) to 20 (Wed), 2020
HICO, Gyeongju, Korea



International Society for Therapeutic Ultrasound

WELCOME TO
GYEONGJU

Save the Date

7th International Symposium on Focused Ultrasound



November 8-12, 2020
Hilton McLean Tysons Corner
McLean, Virginia USA



FOCUSED
ULTRASOUND
FOUNDATION

