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Director of Extramural Research
Focused Ultrasound Foundation
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November 7, 2012

Dear Dr. Eames,

I am writing to provide you and the Foundation the final report on the execution of the project entitled "*MR-Guided Focused Ultrasound Ablation of Visceral Fat: A new treatment for metabolic syndrome*".

Background

The overarching goal of the research is to develop a non-invasive approach for the treatment of metabolic syndrome. The main hypothesis of the project is that HIFU ablation of visceral fat can improve insulin action in obese rats and provide a non-invasive treatment for type 2 diabetes and other diseases associated with metabolic syndrome. The hypothesis is being tested with two specific aims that are centered on: 1) technique development, and 2) animal experiments.

We estimate that the entire research program will cost approximately $500,000 to conduct, and we are grateful to the Focused Ultrasound Foundation for the grant of $100,000 which allowed us to purchase the equipment. At this point we are still seeking funds to cover the remainder of the metabolic syndrome project, but as you can see from the progress reported below, the hardware that has been acquired with the support from your foundation has given us a tremendous start. We have made significant progress on aim 1 and, the grant has enabled exciting new programs in other directions relevant to human disease.

Progress

1) We ordered a pre-clinical Sonalleve MR-guided HIFU system from Philips in early 2011. The system was delivered in late 2011. The system is now operational and being used on our 3T MR system. All animal experiments have been performed under animal use protocols.

2) The HIFU system has been optimized for use on rats with the creation of a new stage and MR imaging coils.

3) We have developed high-speed imaging approaches for monitoring temperature changes and thermal dose. One of the approaches we are investigating is the use of magnitude images for temperature monitoring.

4) We have used the system to support simple ablations in pig livers in collaboration with Dr. Rupak Banerjee at the University of Cincinnati.

5) We have launched a research collaboration with Dr. John Bissler in our institution. Together we are exploring the utility of MR-guided HIFU in treating preclinical models of angiomyolipomas, a tumor found in patients with Tuberous Sclerosis Complex.

6) Although efforts to secure research funding from the NIH for the metabolic syndrome effort have been unsuccessful thus far, the HIFU hardware acquired with Foundation support has permitted us to successfully compete for the following grant awards:

   A) Sponsor: Department of Defense (grant W81XWH-11-1-0299)
   PI: Yu Li, PhD
   Title: Non-invasive MR-guided HIFU Therapy of TSC-Associated Renal Angiomyolipomas

   B) Sponsor: St Baldrick's Foundation
   PI: Yu Li, PhD
   Title: MR-guided HIFU for cancer therapy

   C) Sponsor: Tuberous Sclerosis Alliance
   PI: John Bissler, MD
   Title: MRI-Guided High Intensity Focused Ultrasound for TSC-Associated Renal and Pulmonary Disease

7) The progress with the preclinical HIFU system has encouraged us to pursue human research opportunities. We have secured funding from our institution to purchase a clinical Sonalleve system from Philips to perform clinical HIFU treatments and related research. Our first clinical target will be bone ablation in pediatric patients. The pre-clinical and clinical systems will have common control software and we anticipate substantial benefit for translational studies.

8) Several publications describing our HIFU experimental results are in preparation. This includes an abstract for presentation at next year's ISMRM.

Additional details of our progress can be found in the attached documents. We at Cincinnati Children's Medical Center are very grateful for the support the FUS Foundation has provided and we look forward to the research opportunities it enables as we pursue our mission of improving the practice of healthcare for our patients.

Please feel free to call me if you have any questions.

Thank you,

Charles Dumoulin, PhD
Director, Imaging Research Center
Cincinnati Children's Hospital Medical Center

Attachments:

A) Abstract for next year's ISMRM describing initial results acquired with the preclinical HIFU system

B) Annual report to the DOD for grant W81XWH-11-1-0299: "Non-invasive MR-guided HIFU Therapy of TSC-Associated Renal Angiomyolipomas", Yu Li, PhD -- Principal Investigator

C) Project narrative for the St. Baldrick's Foundation application describing preliminary results using HIFU monitored with high-speed MR imaging in mouse models of disease.

Attachment A

Abstract for next year's ISMRM describing initial results acquired with the preclinical HIFU system

Introduction: Magnetic Resonance (MR) is routinely used to monitor thermal therapy in clinical applications of High Intensity Focused Ultrasound (HIFU). MR-thermometry typically relies on changes in signal phase arising from the proton resonance frequency (PRF) sensitivity to temperature [1-2]. Little attention has been paid to MR signal magnitude dependencies on temperature. In this work, we investigated the potential of MR magnitude images for HIFU thermometry.

Methods and Materials: A small pre-clinical HIFU system was used in our experimental investigation. This system includes a 3.0 MHz 8-channel sectional HIFU transducer with a focal length of 5 centimeters, a MR-compatible radiofrequency driving system, and a stand-alone console that controls HIFU transmission and communicates with the MR scanner. A section of pig kidney tissue was positioned at the focal spot using a flat stage placed on top of the transducer (Fig. 1a). Water provided acoustic interface between the transducer surface and the sample tissue. The HIFU transducer and the sample tissue were placed at the isocenter of a 3.0 Tesla clinical whole-body MR scanner. A single-channel small-loop receive coil was used to image the sample tissue. HIFU thermal treatments were performed with the same power (2 W) and phase in each channel. The sonication was kept on for ~ 12 seconds and then turned off. The experiment lasted ~ 30 seconds. MR imaging was run continuously over the entire session using a multi-shot Echo Planar Imaging (EPI) sequence (TR/TE=200/16 ms, Flip angle=15°, EPI factor=7, FOV=160 mm, slice number=4, slice thickness=2 mm, matrix 160×160). Real-time MR thermometry was obtained using standard PRF method. Both magnitude and phase time-series images were exported for post-processing.

Results: Figure 1(a) gives real-time temperature mapping using the PRF method. A focal lesion of ~3 mm was formed at a distance of ~ 45 mm from the transducer surface. PRF imaging showed a temperature rise of ~20°C at the focal spot. Figure 1(b) shows the phase and magnitude difference maps between the two EPI images at the beginning and end of the sonication session. It can be seen that both magnitude and phase show significant changes at the focal spot. Figure 1(c) gives the time plots for magnitude and phase changes at the center of the focal spot. They both agree well with the PRF temperature measurement, implying magnitude imaging may be useful in temperature measurement. However, our further investigation indicates that the temperature change may introduce complicated spatial and temporary behaviors in MR magnitude images. For example, Figure 1(d) shows the plots of magnitude changes along the line ***x*** in the magnitude difference map at three different times (3, 12 and 28 seconds). It can be seen that the spatial pattern of magnitude changes is varying with time. As a result, the magnitude changes may manifest as temporal pulsation waves at some voxels (e.g. voxel ***A*** in Figure 1d) instead of monotonic curve like in Figure 1(c).

Discussion: MR magnitude is sensitive to temperature owning to several physical mechanisms. First, the use of a short TR in EPI sequence gives T1 contrast in MR magnitude. Second, temperature introduces MR phase inhomogeneities within imaging voxels. The phase inhomogeneities may generate T2* contrast in magnitude images. Finally, tissue movement induced by HIFU pressure may affect MR magnitude. The magnitude changes observed in our experiments are associated with all of these contrast mechanisms. The mixing effects of these mechanisms introduce complexity of magnitude changes in spatial and temporal space. Since these underlying mechanisms are different from how MR phase changes with temperature, MR magnitude may provide information complementary to MR phase in MR thermometry. We expect that MR magnitude and phase be used together to improve HIFU treatment.

Reference: [1]. Cline HE et. al., Magn. Reson. Med. 1994; 31: 628-636. [2]. Rieke V et. al., Magn. Reson. Med. 2004; 51: 1223-1231.

Acknowledgement: This work is supported by DOD grant 10604719 and St. Baldrick Foundation research grant.

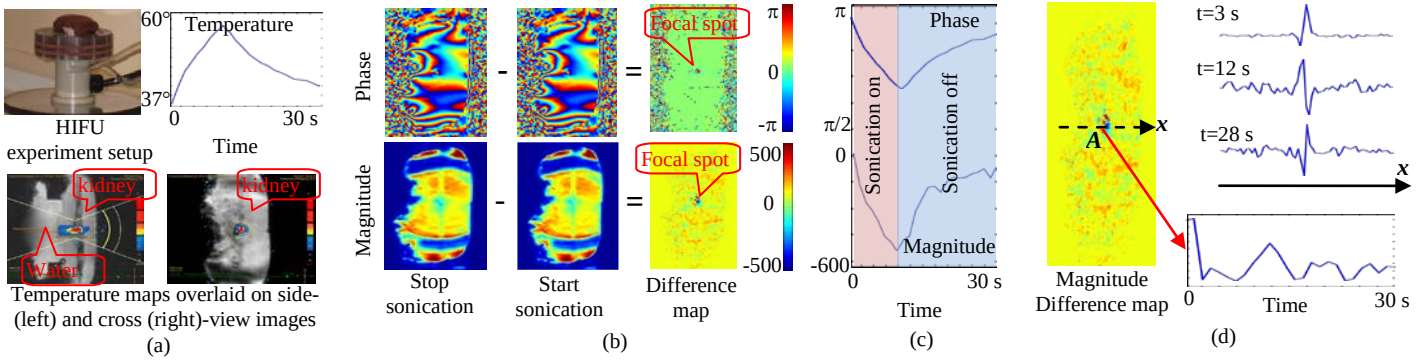

Figure 1. *In-vitro MR-guided HIFU experiment. (a) Experimental setup and temperature mapping using the PRF method. The time plot shows the temperature measurement at the focal spot (red spots in temperature maps). (b)Phase and magnitude difference maps are generated from EPI images at the beginning and end of sonication session. Both magnitude and phase show significant changes at the focal spot during HIFU treatment. (c) Both the time plots of the phase and magnitude changes agree well with temperature measurement in (a). (d). The magnitude changes along the line* ***x*** *in the magnitude difference map are plotted at three different times. The temporal variation of the magnitude changes induces pulsation waves at some voxels. For example, magnitude changes at voxel A increases and decreases alternatively with time. It is believed this complexity is generated due to the mixing effects of multiple temperature-associated contrast mechanisms in MR magnitude imaging.*

Attachment B

Annual report to the DOD for grant W81XWH-11-1-0299: "Non-invasive MR-guided HIFU Therapy of TSC-Associated Renal Angiomyolipomas", Yu Li, PhD -- Principal Investigator

AD_____

Award Number:

W81XWH-11-1-0299

TITLE:

Non-invasive MR-guided HIFU Therapy of TSC-Associated Renal Angiomyolipomas

PRINCIPAL INVESTIGATOR:

Yu Li

CONTRACTING ORGANIZATION:

Cincinnati Children's Hospital Medical Center

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14. ABSTRACT

This report is a summary of our first year's work on the proposed research. During this period, our effort was focused on technological development for thermal ablation in mice. Our goal was to establish a small-animal MR-guided HIFU experimental system that enables simultaneous HIFU ablation and MR guidance. This goal was achieved and our experimental results demonstrated the basic function of the experimental system in in-vitro studies. We have laid the groundwork for the feasibility investigation of mouse tumor ablation in the second year. Based on the current progress, we will continue work on our technological improvement of MR-guided HIFU system for in-vivo studies. We believe this system will be ready for animal experiments after several further in-vitro studies in two or three months.

15. SUBJECT TERMS
MR-guided HIFU, renal angiomyolipoma, tumor, ablation, thermal therapy, TSC

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Introduction

The overarching goal of our research is to develop a non-invasive technique for clinical management of TSC-associated renal angiomyolipomas. TSC is a genetic tumor predisposition syndrome characterized by the growth of lesions in multiple organ systems. Approximately 80% of TSC patients develop renal angiomyolipomas, a type of lesion composed of variable amounts of fat, smooth muscle, and vascular tissue. Renal angiomyolipomas are often benign and present with multiple lesions in each kidney. Patients with renal angiomyolipomas may experience discomfort, flank pain, hydronephrosis, hematuria, and hypertension. These lesions can also lead to acute hemorrhaging or chronic loss of renal function.

The technique we are developing uses High Intensity Focused Ultrasound (HIFU) to ablate tumors and magnetic resonance (MR) imaging to monitor ablation. MR-guided HIFU enables “surgical procedures” to be performed deep within the body without incisions or punctures, providing a risk-free therapeutic approach to managing renal angiomyolipomas. The physical mechanisms underlying HIFU is that a HIFU transducer constructed with a concave shape and/or multiple elements has the ability to focus acoustic energy into a target volume having a diameter of a few millimeters. The focused acoustic energy induces a rapid rise in temperature (e.g. 70°C to 100°C), resulting in thermal necrosis of tissues in the target volume. Although HIFU offers the capability of thermal ablation, non-invasive thermal therapy is possible only if the focal spot of HIFU can be controlled within the body using the feedback information provided by medical imaging guidance. MR is superior to other imaging modalities because it provides both excellent soft-tissue visualization and the ability to monitor thermal delivery (temperature mapping).

The proposed research is a two-year pre-clinical study that aims to investigate whether MR-guided HIFU offers the ability to ablate renal angiomyolipomas in a mouse tumor model. From this animal study, we expect to gain research experience that will benefit future clinical study on non-invasive thermal therapy of renal angiomyolipomas in human subjects. The obtained experimental results will be used to apply for grant funding that will support our further work on MR-guided HIFU. In the proposed work, we had planned our first year on the development of an MR-guided HIFU experimental system for thermal ablation in mouse kidneys. The technical challenge we expected to meet was the respiratory movement of kidneys in mouse ablation. We proposed to use parallel MR imaging technology to track the respiration in order to enable real-time MR guidance for HIFU ablation in mouse.

This report is a summary of our first year's work on the proposed research. During this period, our effort was focused on technological development for thermal ablation in mice. Our goal was to establish a small-animal MR-guided HIFU system and enable efficient thermal delivery deep within the mouse body. The following list highlights the primary progresses we have made:

1. An animal HIFU system was purchased and installed on our research Philips 3T MR scanner at the Cincinnati Children's Hospital Medical Center (CCHMC) Imaging Research Center (IRC).
2. A feedback control MR-guided experimental system was established using the Philips 3T MR scanner and the installed animal HIFU system.
3. MR temperature mapping using MR phase signals was demonstrated in in-vitro studies (phantom and pig liver).
4. We found that respiratory movement in mice does not affect thermal therapy as significantly as expected. Instead, the primary challenge in our work arises from the interface between transducer and mouse body. This finding changed our technological focus in research development.
5. We constructed a mechanic stage that can provide a water interface for ultrasound wave propagation. This will be used to tackle the new technical issues we found in our work.
6. The whole MR-guided HIFU experimental system was demonstrated functional. Based on this ground work, we will proceed animal studies in the second year.

Our first year's work laid the groundwork for the feasibility investigation of mouse tumor ablation we planned for the second year. Based on the current progress, we will continue work on our technological solution to mouse thermal ablation and improve the performance of MR-guided HIFU system. We believe this system will be ready for animal experiments in two or three months after several in-vitro studies. We expect to start animal ablation in the first half of the second year of this research.

Body

Proposed Task 1: Design and development of an MR-guided HIFU experimental system for thermal ablation in a phantom study (Stage 1: Months 1-12).
An MR-guided HIFU experimental system will be designed for thermal ablation. The MR coil hardware will be constructed and integrated with a HIFU system for small animal research in a Philips 3.0 T multi-channel whole body MR imaging system. The software components will be developed for MR guidance and HIFU control. The basic function of the entire system will be tested using a phantom.

Research accomplishment: A small-animal HIFU system (Philips HealthCare, Vantaa, Finland) was purchased and installed on the IRC Philips 3.0 Tesla MRI scanner at the Cincinnati Children's Hospital Medical Center. This system includes an eight-channel 3.0 MHz sectored ultrasound transducer, a high-efficiency generator for acoustic power control, and a stand-alone console that can be used to control the HIFU power transmission and communicate with the MRI scanner. Figure 1 shows the experimental setup scheme and pictures for thermal ablation in phantoms and animals. This setup allows the HIFU console to synchronize MRI scanning when running HIFU thermal ablation. The acoustic power delivery from the HIFU transducer can be dynamically updated by the HIFU console based on MRI information. This provides a feedback control for the thermal delivery deep within the body.

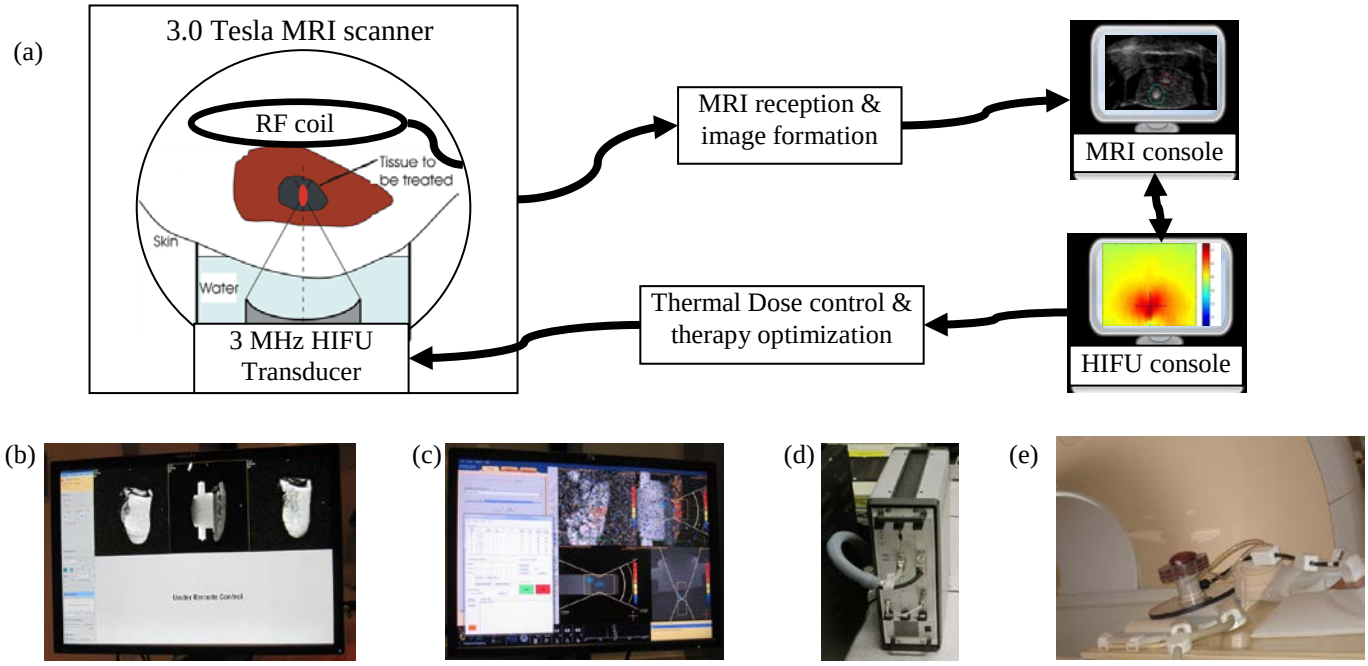

Figure 1. *A feedback control system for preclinical thermal therapy was established using MR-guided HIFU in the CCHMC IRC. The feedback control loop is formed using a 3.0 Tesla 32-channel Philips Achieva MR scanner (Philips HealthCare, Best, the Netherlands) and a Philips small-animal HIFU system (Philips HealthCare, Vantaa, Finland). This system uses an eight-channel 3 MHz sectored transducer (IMASONIC, Voray sur l'Ognon, France) for acoustic transmission. (a) Experimental setup scheme. (b) MRI console. (c) HIFU console). (d) High-efficiency generator for HIFU transducer. (e) Transducer, cables and phantoms inside the MRI scanner.*

New challenges were found in our preliminary studies: Using a few preliminary experiments with the established MR-guided HIFU experimental system, we found a new challenge in small-animal HIFU ablation. As shown in Figure 2, a HIFU ablation experiment was conducted using a homogeneous phantom. A HIFU lesion of ~ 2 millimeter was successfully developed within the target region. The MR phase signals showed dynamic variation associated with temperature rise within the HIFU lesion, indicating the temperature can be effectively monitored during the ablation. However, in our first attempted in-vivo study (mouse ablation), we found the HIFU lesion cannot be formed although we kept the mouse static using sedation during the HIFU ablation. As shown in Figure 3, the temperature mapping indicated that a focal spot could not be produced within the static target region in the mouse. After further investigation, we found that the problem arises from

the interface between transducer and the animal body. Since the animal body is small with respect to the focal length of the transducer (5 centimeter), we have to put water between the transducer and the animal body as acoustic interface. However, the small air bubbles in the water introduce phase incoherence of the acoustic waves transmitted from different channels of the HIFU transducer. As a result, the acoustic energy cannot be focused within the target region due to phase cancellation of acoustic waves.

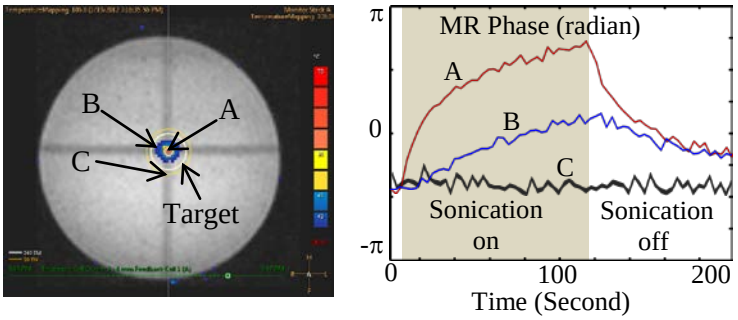

Figure 2. *HIFU thermal ablation and temperature mapping in a homogeneous phantom. A HIFU lesion of ~ 2 mm can be formed using feedback control in Figure 1. The plots show MR phase signals change with temperature and provide an approach to tracking and optimizing HIFU thermal delivery. The color maps overlaid on the MR image gives the temperature mapping in HIFU ablation.*

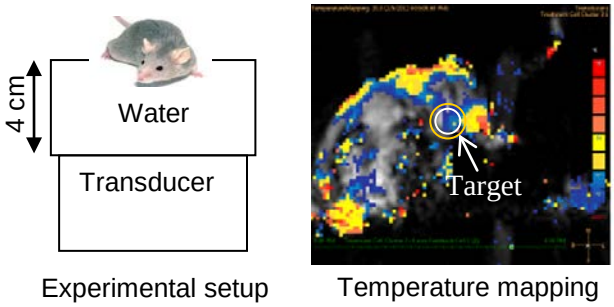

Figure 3. *First attempted mouse HIFU ablation. Because there are air bubbles in the ware interface between the transducer and the animal body, a HIFU lesion cannot be effectively formed. The temperature mapping shows the acoustic energy is spread over the whole body.*

Proposed Task 1a: Hardware development (Months 1-4).
A radiofrequency (RF) coil will be designed and developed for abdominal imaging in mice. The number of receive channels will be determined experimentally for optimum SNR and imaging acceleration performance in mouse imaging. This coil will be integrated with a HIFU system for small animal research on a Philips 3.0 Tesla multi-channel MR imaging system.

Research accomplishment: A small-animal MRI coil was constructed (Figure 4a). This coil provided better SNR for mouse imaging than other coils on the IRC Philips 3T MRI scanner. The SNR gain factor was estimated to be ~ 3 over the commercial small-animal coil provided by Philips HealthCare. A mechanic stage (Figure 4b) was built for holding/stabilizing the animal/phantom and the coil in HIFU experiments within the MRI scanner. This stage has an empty space inside and is sealed outside. The sealed space is used to accommodate water for interfacing acoustic pathway between the transducer and the target. There are two tubes (Figure 4b) connected to the internal space inside the stage. These tubes are used to fill the water into the stage and remove the air bubbles in the water. This design will be used to address the interface problem we found in our first attempted in-vivo experiments. We expect to try in-vivo experiments using this new design in the coming two or three months.

(a) (b)

Figure 4*. An MRI coil (a) was built for mouse imaging on Philips 3T scanner. A mechanic stage (b) was constructed for holding/stabilizing the mouse and the coil within the MRI scanner. Inside the stage, water will be used as the interface between the HIFU transducer and the animal.*

All the hardware has been tested on the MRI scanner. The test demonstrated that the hardware is MR compatible. In addition, we experimentally compared our MR imaging results with those using commercial hardware. The experiments showed that our hardware offers better MR imaging quality than commercial hardware provided by Philips HealthCare. The new hardware we developed has been integrated with MR scanner system and ready for MR-guided HIFU experiments in the in-vitro and in-vivo studies.

Proposed Task 1b: Software development (Months 5-10).
Dynamic parallel imaging and motion correction methods will be developed on Philips 3.0 Tesla multi-channel MR imaging system. Real-time reconstruction will be implemented. Four major imaging methods, T_1 weighted imaging, T_2 weighted imaging, stiffness weighted imaging, and phase imaging, will be developed using parallel

imaging. Data processing methods will be developed to extract multi-source information, including lesion position, temperature, acoustic force under HIFU, and tissue destruction in therapy, from real-time MR images. A control algorithm will be developed to dynamically optimize the localization and power of HIFU focal spot based on real-time and multi-source feedback information.

Research accomplishment: The software development work has been accomplished in collaboration with Philips HealthCare during the last several months. This collaboration includes the setting up of the imaging protocols for animal HIFU ablation, the configuration of software for feedback control of HIFU transducer, and the verification of MR guidance for HIFU ablation. Currently, we have a software package installed on the HIFU console. This package includes a standard Philips clinical software, Sonalleve (*Philips HealthCare, Vantaa, Finland*), and a small-animal HIFU software. The prior one provides the capability of communication with MRI console and processing MRI data. The latter one provides the capability of communicating with the HIFU generator and extracting information from Sonalleve. This package provides a feedback control algorithm for HIFU ablation. A standard Philips MRI protocol was installed on Philips 3T MRI scanner. These protocols provide the capability of imaging animals with different strategies during HIFU ablation and monitoring the thermal delivery in real time. An echo-planar imaging protocol has been developed in combination with our new MR coil and used in MR guidance for HIFU ablation. The temporal resolution for this sequence can reach 1 second. This imaging speed was found sufficient for real-time guidance even when motion exists. We are working on the integration of echo-planar imaging with T1-weighted, T2-weighted, stiffness weighted, and phase imaging methods.

Proposed Task 1c: Test of basic function (Months 11-12).
A phantom model will be designed and developed to simulate the body of a mouse. MR-guided HIFU experimental system will be tested and optimized in a phantom study. Its ability to ablate a pre-selected target in the phantom will be evaluated.

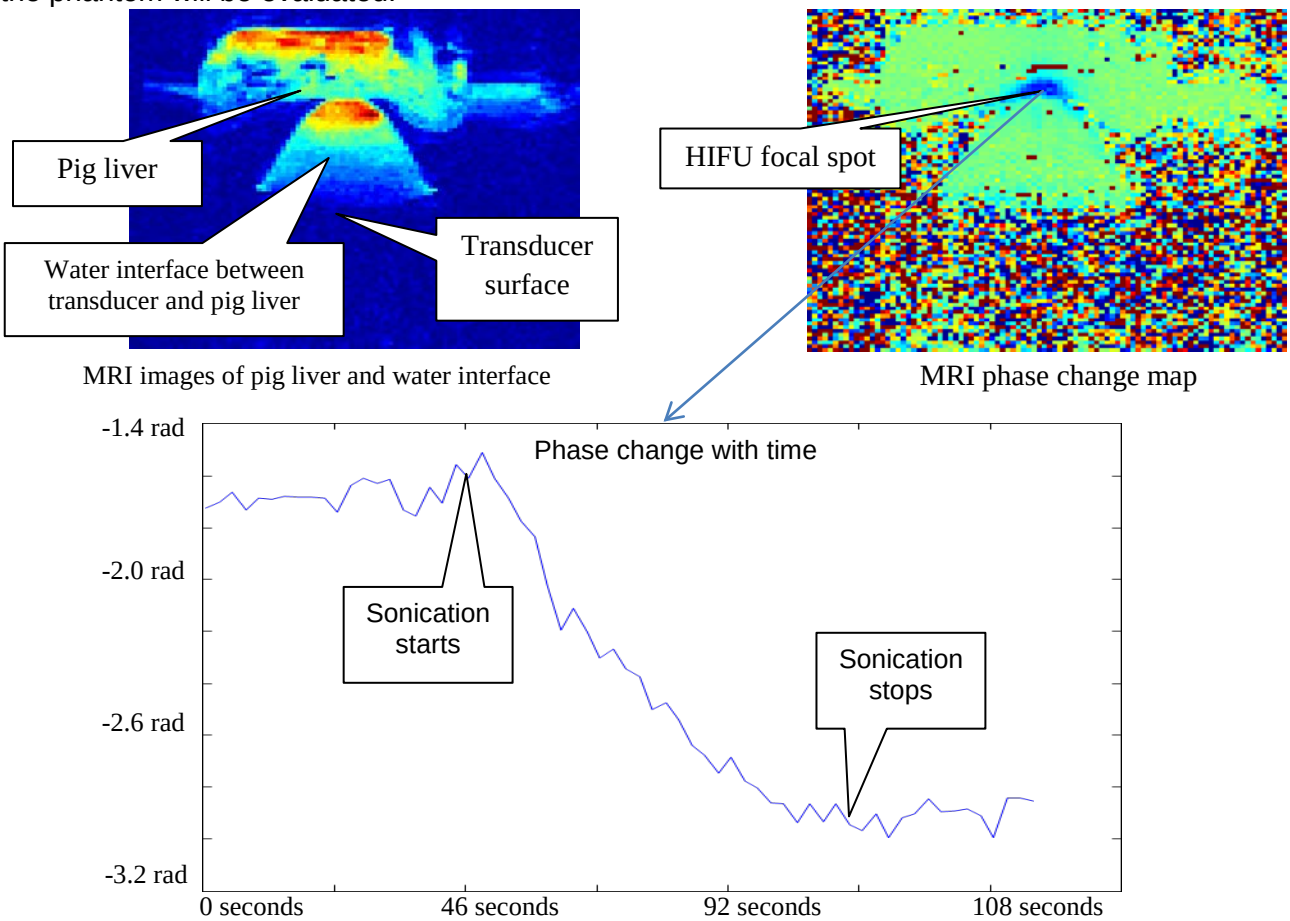

Figure 5. *An in-vitro study (ablation of pig liver) using the established MR-guided HIFU system in Figure 1. The MR phase change mapping shows the acoustic energy is focused within a small local spot of ~ 2 millimeters. The plot shows the phase change with sonication in the center of focal spot. This study demonstrates the basic function of the experimental system we developed in the first year.*

Research accomplishment: We have tested the small-animal MR-guided HIFU experimental system in in-vitro studies. Figure 5 shows an experimental study on MR-guided HIFU using a piece of pig liver. It was found that HIFU offers the capability of deliver ultrasound energy into a small local spot of ~ 2 millimeters. This demonstrates the potential of HIFU to ablate tumors deep within the mouse body. However, in this study on pig liver, we also found that the interface between the transducer surface and the target plays a critical role in HIFU ablation. In the experiment, we used water as interface. The bubbles in the water significantly reduced the efficiency of thermal delivery. We found that HIFU ablation may fail due to the existence of bubbles. We will change the experimental design using the mechanic stage (Figure 4b) developed in the last several months. We expect that this new design can improve the water interface performance and make the in-vivo studies feasible. We expect to start mouse ablation using MR-guided HIFU experimental system in Month 15.

Key Research Accomplishments

1. A small animal MR-guided HIFU experimental system was established at the Cincinnati Children's Hospital Medical Center (CCHMC) Imaging Research Center (IRC).
2. Thermal ablation and MR guidance capability was demonstrated using the established experimental system in in-vitro studies.
3. MR imaging speed using EPI sequence was found sufficient for real-time feedback in HIFU thermal delivery. This addressed the challenge arising from that respiratory movement in mice.
4. We found that the water interface between the transducer surface and the animal body is crucial to the thermal delivery. To address this issue, we constructed a mechanic stage that can provide a water interface for ultrasound wave propagation.
5. All the hardware and software are ready for mouse ablation experiment. We will make a final adjustment of the system in the coming two months before the start of mouse ablation.
6. The small-animal MR-guided HIFU experimental system was demonstrated functional in in-vitro studies. We will proceed our animal studies in the second year.

Reportable Outcomes

1. Based on our preliminary results we obtained in this study, we applied for St. Baldrick foundation research grant. This grant was awarded in July 2012 and provided a support on the purchase of a needle hydrophone system that can measure the acoustic pressure in in-vitro studies. This will provide a direct way to evaluate HIFU transmission in soft tissue and a new technique to monitor HIFU ablation in real time. We are working on how to integrate the new project with the DOD project in order to deliver the best experimental outcomes in a more efficient way.
2. Based on this study, we have developed our collaboration relationship with two research groups at the University of Cincinnati: Dr. Donald French's group [1-2] and Dr. Christy Holland's group [3]. Dr. French is working on inverse imaging problem for HIFU treatment planning and Dr. Holland is working on cavitation mechanisms in cardiac applications of HIFU. We are working on combining these different research projects together for enhancing our ongoing MR-guided HIFU project.

Conclusion

In summary, we have established a small-animal MR-guided HIFU system for mouse ablation and demonstrated the basic function of this new system. The first year of this research has seen the success in technological development. This will lay groundwork for animal studies in the second year of this research. We expect to deliver more promising outcomes by proceeding animal studies in the coming time.

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Attachment C

Project narrative for the St. Baldrick's Foundation application describing preliminary results using HIFU monitored with high-speed MR imaging in mouse models of disease.

Research Project Narrative

Introduction

At Cincinnati Children's Hospital Medical Center (CCHMC), we are developing a non-invasive technique for human cancer therapy. This technique uses High-Intensity Focused Ultrasound (HIFU) to ablate tumors, and Magnetic Resonance (MR) guidance to monitor ablation. MR-guided HIFU enables "surgical procedures" to be performed deep within the body without incisions or punctures, providing a risk-free therapeutic approach to the management of adolescent and childhood cancers. The proposed project aims to address a technical challenge to MR-guided HIFU for cancer therapy: How can we establish real-time feedback control for thermal therapy in a physiological environment with tissue inhomogeneity and dynamic changes (e.g. respiration, blood flow)?

Thermal ablation using HIFU relies on the delivery of acoustic energy into a small volume deep inside living tissue. HIFU transducers are typically constructed with a concave shape and/or multiple elements to focus acoustic energy into a target volume having a diameter of a few millimeters. The focused acoustic energy induces a rapid rise in temperature (e.g. 70°C to 100°C), resulting in the thermal necrosis of tissue in the target volume. Although the potential of HIFU for thermal ablation was realized as early as in 1940s, cancer therapy with HIFU was not likely possible until MR was introduced as imaging guidance in 1990s. Compared with other imaging modalities, MR offers superior soft tissue contrast, accurate heating quantification and rich anatomical and pathological information. This makes MR an ideal approach to monitoring HIFU thermal delivery in cancer therapy. MR-guided HIFU first found application in the clinical management of uterine fibroids. Up to date, over 7000 patients with symptomatic fibroids have been treated in the United States. This success demonstrated the potential capability of MR-guided HIFU in the clinical management of human cancers. However, subsequent research on the treatment of other types of human tumors met a fundamental challenge: Physiological complication (tissue inhomogeneity and dynamics) deep in the human body may reduce the efficiency of HIFU thermal delivery. The imaging speed afforded by available MR techniques is not sufficient for tracking a large amount of physiological information in real time. As a result, a stable feedback control loop cannot be established in HIFU therapy. This challenge has been reported in a number of HIFU applications for clinical management of renal, prostate, breast and liver tumors. To date, it is a technical barrier to the clinical use of MR-guided HIFU for cancer therapy.

Specific Aims

This project will address the speed challenge to MR guidance in HIFU control using high-speed MR techniques based on high-density coil arrays. We hypothesize that the feedback control based on high-speed MR techniques can enable thermal therapy in a physiological environment with tissue inhomogeneity and dynamic changes. To demonstrate this hypothesis, the following specific aims will be pursued:

Specific Aim 1: Techological development and translation of high-speed MR imaging for HIFU guidance in a animal model. New radiofrequency (RF) coil arrays for MR imaging will be developed for a preclinical MR-guided HIFU system established in CCHMC (Figure 1). A new high-speed MR technique, correlation imaging, will be translated into HIFU application in animal studies.

Specific Aim 2: Preclinical demonstration of HIFU feedback control in animals using high-speed MR guidance. A mouse angiomyolipoma model (Figure 2) will be used. Thermal therapy using MR-guided HIFU will be applied to 15 mice. Tumor volumes will be measured using MR imaging before and after the treatment. Statistical analysis on the measured volume will be used to evaluate the thermal therapy.

Significance

The proposed research will address the imaging speed challenge to thermal control of MR-guided HIFU in a physiological environment with tissue inhomogeneity and dynamic changes. As thermal control is currently a critical barrier to HIFU applications in cancer therapy, this research will lay a strong foundation for human use of MR-guided HIFU in subsequent clinical studies that aim to improve the clinical management of human cancers. The techniques developed in this research, although preclinical, will lead to a non-invasive approach to the clinical treatment of multiple types of cancers. This will produce substantial impact on both adolescent and childhood cancer research. In addition, non-invasive surgery allows for cancer treatment with minimal risk of physiological function loss. Since the prevention of such loss early in life can disproportionally improve an individual's life quality, this research will especially benefit those patients with childhood cancer. From this perspective, this research will impact childhood cancer research more significantly.

Preliminary Data

1) Feedback control of MR-guided HIFU for preclinical thermal therapy. At Cincinnati Children's Hospital Medical Center, we are developing MR-guided HIFU technology for human cancer therapy. A feedback control system for preclinical thermal therapy in animals has been established using MR-guided HIFU in the Imaging Research Center (IRC) (Figure 1). This system enables HIFU therapy in an animal model during MR imaging. By enabling direct communication between MR and HIFU consoles, the system offers the ability to establish a feedback control loop for thermal therapy.

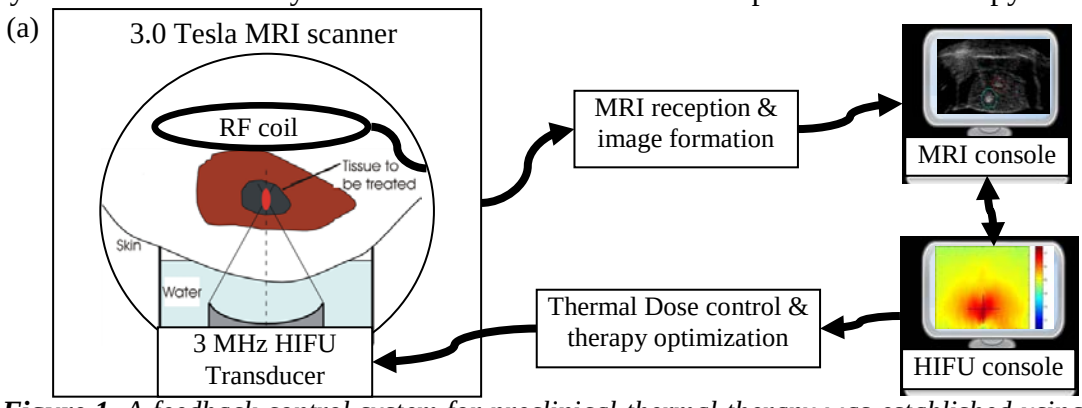

Figure 1. *A feedback control system for preclinical thermal therapy was established using MR-guided HIFU in the CCHMC IRC. The feedback control loop is formed using a 3.0 Tesla 32-channel Philips Achieva MR scanner (Philips HealthCare, Best, the Netherlands) and a Philips small-animal HIFU system (Philips HealthCare, Vantaa, Finland). This system uses a single channel RF coil for animal imaging and an eight-channel 3 MHz sectored transducer (IMASONIC, Voray sur I'Ognon, France) for acoustic transmission. Multi-channel RF coil array for mouse imaging is being developed to support high-speed MR imaging in this work.*

2) Mouse angiomyolipoma model for preclinical investigation of MR-guided HIFU in a physiological environment: A renal tumor model has been developed in our collaborative work with the Pediatrics and Cell Biology Laboratory at CCHMC (Figure 2). Based on this work, renal angiomyolipoma model in mice will be used for our investigation. Renal angiomyolipoma is a type of tumor composed of variable amounts of fat, smooth muscle, and vascular tissue. Acoustic interaction in angiomyolipomas may become complicated due to high tissue inhomogeneity and human dynamics. For example, fat favors HIFU thermal delivery due to high absorption rate. Blood flow introduces heat loss, deviation in temperature measurement, and imaging artifacts. Smooth muscle is not as MR sensitive as fat and blood. Therefore, all the critical challenges that can be met in cancer therapy with MR-guided HIFU are present, providing an ideal environment for our experimental study in the proposed project.

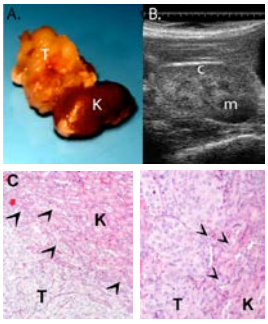

Figure 2. *Renal tumor model for preclinical HIFU investigation. (A) Photograph of full size renal cell carcinoma tumor "T" and a mouse kidney "K" after injection of 786-0 cells into the kidney. (B) Mouse renal ultrasound for injection localization of coronal mouse kidney demonstrating renal cortex "c" and medullary pyramids "m". (C) Hematoxylin and eosin stained sections show renal parenchyma "K" infiltrated by malignant neoplasm "T" composed of large polygonal cells with pale abundant cytoplasm and large nuclei with open chromatin and prominent nucleoli. The arrowheads point to the infiltration sites.*

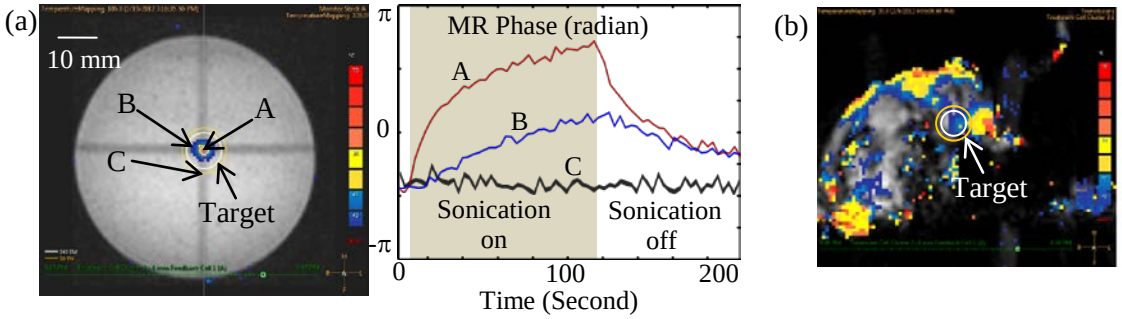

Figure 3. *Temperature mapping (color overlay on MR image) of HIFU experiments in a phantom and a mouse. (a) In a static and homogeneous environment (phantom), a HIFU lesion of ~ 2 mm can be formed using feedback control in Figure 1. The plots show MR phase signals change with temperature and provide an approach to tracking and optimizing HIFU thermal delivery. (b) In a dynamic and inhomogeneous environment (mouse), a HIFU lesion cannot be effectively formed for two reasons: 1) The complexity of HIFU acoustic interaction increases with physiological complication (tissue inhomogeneity and dynamics). To form a good focal spot as in (a), HIFU thermal control requires more feedback information including tissue structure, acoustic interaction, and temperature mapping. 2) Although MR imaging offers the capability of extracting all the physiological information needed for HIFU control, the real-time MR guidance is limited by a tradeoff between imaging speed and information: When collecting a large amount of physiological information, a feedback control loop cannot be established in* ***real time*** *due to insufficient imaging speed. This will be the primary challenge to be addressed in the proposed project.*

3) Preliminary MR-guided HIFU experiments in phantom and mouse: Using the MR-guided HIFU system (Figure 1), we demonstrated that the feedback control can generate a HIFU lesion of ~ 2 mm in a homogeneous and static phantom (Figure 3a).

However, HIFU energy cannot be effectively focused in a mouse because MRI is not sufficiently fast to track the physiological information with significant tissue inhomogeneity and dynamics (Figure 3b). In the proposed research, we will develop new technology to address this challenge in order to establish a HIFU focal spot.

4) Correlation imaging for high-speed MR imaging: The principle investigator of this proposal is an experienced scientist with a research focus in the field of high-speed MR. Prior to joining the CCHMC, he worked with Philips HealthCare for 6 years. In MR industry, he developed several parallel imaging techniques for high-speed MR using multi-channel RF coil arrays. Based on his industrial research work, a new high-speed MR technique, correlation imaging, has been developed in the CCHMC IRC. By synergistically combining multi-channel coil array technology and information-sharing mechanism underlying clinical MR data, correlation imaging offers the ability to overcome the imaging speed limit in conventional parallel imaging technology. This technology has been demonstrated in neuroimaging and neonatal imaging applications (Figure 4). In the proposed project, we will use correlation imaging to address the tradeoff between imaging speed and information in MR guidance for HIFU thermal therapy in a physiological environment (Figure 3b).

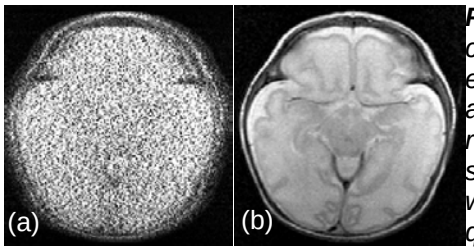

Figure 4. *Comparison of correlation imaging and conventional parallel imaging in neonatal brain MR exams. The imaging is accelerated by a factor of 32 (data acquisition time is ~ 60 ms). This speed is sufficient for real-time MR guidance in HIFU thermal therapy. At this speed, conventional parallel imaging technology fails (a) while correlation imaging provides high diagnostic image quality in this application.*

Experimental Design

The experimental study in this work aims to demonstrate that the tumor volumes in animals are effectively reduced after thermal therapy using HIFU with feedback control established based on high-speed MR guidance. We will use MR imaging to measure the volume of tumors. The measured volumes before and after the thermal therapy will be compared and their mean difference will be used as statistical metrics. Since this is paired sample statistics, the sample size for this statistical comparison is calculated using equation: $N= t^2 \sigma^2/ m^2$, where N is the sample size, t is the confidence level (t = 1.96 for a 95% confidence level), σ is the standard deviation of measured volumes, and m is the margin of error. Based on our experimental experience with mouse angiomyolipoma models (an ongoing study in parallel to this proposal), σ is estimated to be <10% of the tumor volumes. Assuming a 5% margin of error in our MR imaging measurement, N is calculated to be 15.

Methods

In the CCHMC IRC, we have developed a MR-guided HIFU system (Figure 1) and a mouse angiomyolipoma model (Figure 2). This provides a preclinical experimental platform for the investigation of thermal therapy feedback control in a physiological environment with tissue inhomogeneity and dynamic changes. In the proposed research, we will introduce correlation imaging developed by the principle investigator in order to

overcome the speed challenge to MR guidance for mouse renal HIFU therapy. We expect that MR guidance based on correlation imaging will provide all the anatomical, pathological, acoustic interaction, temperature mapping, and thermal dose distribution information needed for HIFU control in real time and thus a real-time feedback control system can be established in a physiological environment with significant tissue inhomogeneity and dynamics including respiration and blood flow. We will experimentally demonstrate our hypothesis using a one-year research plan as follows:

Specific Aim 1: Techological development and translation of high-speed MR imaging for HIFU guidance in a animal model. Multi-channel RF coil array for mouse imaging will be developed for preclinical MR-guided HIFU system (Figure 1). Correlation imaging will be translated into MR-guided HIFU application for real-time collection of anatomical, pathological and temperature information needed for HIFU thermal control.

Specific Aim 2: Preclinical demonstration of HIFU feedback control in animals using high-speed MR guidance. A preclinical study on mice will be performed (N=15). Thermal therapy will be applied to 15 mice using MR-guided HIFU. Tumor volumes will be measured using MR imaging before and after treatment. We will experimentally demonstrate that feedback control system based on correlation imaging will enable effective thermal ablation of renal angiomyolipoma in MR-guided HIFU. We expect that the treatment will significantly reduce the tumor volume in the sense of statistics (See the section "Experimental Design").