Implementing Magnetic Resonance Guided Focused Ultrasound to Open the Blood Spinal Cord Barrier: Procedures and Data Analysis Techniques

Example

Applicant: ___________

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Faculty Mentor: _______________

Department: Radiology and Imaging Sciences

State the Problem/Topic of Research or Creative Work

MRI-guided focused ultrasound (MRgFUS) is a non-invasive energy delivery technique that can deliver focal energy deep in the body (many centimeters) without damaging non-targeted tissues. Both thermal and mechanical damage effects can be used. Currently MRgFUS is FDA approved to treat uterine fibroids, bone metastases, essential tremor and prostate disease. Using magnetic resonance imaging as guidance, MRgFUS implements ultrasound to excite microbubbles which mechanically open the cell membrane for further treatment. As a result, it may be used to bypass the blood spinal cord barrier (BSCB). Spinal cord injury (SCI) currently affects between 238,000 to 332,000 people in the United States alone[1] and results in a greatly decreased quality of life for those affected. Following an injury to the spinal cord, a glial scar forms over the damaged area. The glial scar greatly decreases the permeability of the spinal cord and inhibits the ability of the spinal cord to regenerate[2]. While useful acutely for protection of the injured site, the decreased permeability of the scar prevents treatment such as gene therapy. MRgFUS is a tool that can be used to increase permeability and allow for the use of other beneficial treatments.

Few methods currently prove effective in repairing a SCI due to the inability to deliver therapeutics past the BSCB and glial scar. MRgFUS has been proven to effectively open the blood brain barrier (BBB) for chemical delivery, but very few studies have been conducted testing the effect of MRgFUS on the BSCB and the glial scar that forms after injury. The project aims to effectively develop a method to increase the permeability of the injury site without causing further damage to the spinal cord. To accomplish this task, the MRgFUS parameters specifying safe and accurate delivery to the injured site need to be determined. MRgFUS excites microbubbles injected into the rat, and during excitation, these microbubbles begin to oscillate at a high frequency which mechanically stretches the openings between cells of the spinal cord. This process is known as sonoporation.

In this project, I have been using semi-automatic data analysis techniques with MR images obtained during MRgFUS procedures. I will continue to use these techniques throughout the summer semester in addition to directly assisting with the MRgFUS procedures. Following data acquisition and segmentation of the images, automatic algorithms will be used to determine contrast enhancement that indicates the amount of BSCB opening. Using this data, we will be evaluating the effects of different exposure parameters and determining the best parameters to efficiently cause sonoporation in the spinal cord.

Relevant Background/ Literature Review

Spinal cord injury (SCI) leads to a large drop in life expectancy for those afflicted by the condition. In 2016, a study conducted by the University of Alabama found that for paraplegics who injured their spinal cord at age twenty experienced a 19 year drop in life expectancy compared to the national average[4]. For tetraplegics, the average life expectancy dropped by as much as 28 years[4]. Those with SCI are more prone to diseases such as septicemia due to many not noticing the development of injuries or sores. Prolonged non-treatment of an injury can lead to the development of infection leading to further complications. Additionally, the quality of life of those affected greatly diminishes in most circumstances. In those afflicted, sensory and motor deficits are common, and many experience bowel and bladder dysfunction, the inability to control defecation and urination[5]. As a result, SCI can completely render an individual dependent on others to survive. Gene therapy is among one of the methods which may improve spinal cord regeneration[7]. However, a major issue behind repairing spinal cord injury is the lack of permeability in the blood spinal cord barrier (BSCB) and the glial scar. The glial scar forms upon injury to protect the damaged site, but it additionally decreases permeability. A possible solution to this issue may be magnetic resonance guided focused ultrasound (MRgFUS). Currently in human trials for certain conditions not related to the spinal cord, MRgFUS has been proven to open the blood brain barrier (BBB) for delivery of desired molecules. Several researchers at the Tokyo University of Pharmacy and Life Sciences succeeded in opening the blood brain barrier for delivery of oligonucleotides and genes[6]. Due to the similar nature of the BSCB to the BBB, the effectiveness of MRgFUS on opening the BSCB will be tested in our experiments.

Specific Activities to be Undertaken and a Timetable Allotted for Each Activity

Over the course of the spring semester, our lab examined MRI images of thirty rats before and after the addition of contrast, as well as after subjection to MRgFUS sonoporation to gain a further understanding of the effect of MRgFUS on the permeability of the glial scar. The first task of the project was to segment existing MR images for data processing using Seg3D2, a program developed by the NIH center for Integrative Biomedical Computing at the Scientific Computing Institute at the University of Utah. I created a segmented model of the spinal cord from a dicom image set for approximately thirty rats and evaluated the opening metrics of the glial scar and the surrounding spinal cord via MATLAB for each one. Additional MRgFUS procedures which will take place from April to June, and these data sets will be collected and analyzed with the above method. Images will be collected on eight separate dates with each date consisting of eight rats. With an approximate time of 2 hours required for the data analysis of each image set, it is expected that this part of the project will require upwards of 128 hours to complete.

The MRgFUS procedures will be conducted between the months of April and June. On each of the eight study dates, approximately eight rats will be subjected to focused ultrasound and imaged with a contrast agent to quantify opening of the glial scar and the BSCB. For the first step of the procedure, the rats will be anesthetized and prepped for ultrasound sonication by removing hair around the injury site. The subject will then be placed above the transducer in a holder with its back partially submerged in degassed warm water. The first MRI images will then be collected using a gadolinium contrast agent. After microbubble administration, sonications will be applied from 2 to 5 locations with a spacing of 2 mm between each. The MRgFUS will be administered in 20 ms bursts for the duration of 3 minutes. The last MRI images will be collected for the rat, and preparation for the next rat will begin. As this experiment for eight rats is expected to take approximately nine hours including the setup for the procedure, the total time spent across the semester conducting these experiments will be approximately 72 hours.

In addition, I will be conducting acoustic loss experiments to determine the effect that the size of the subject exhibits on the energy lost as ultrasound passes through the spine. This part of the project will aid with understanding the effect of a rat's size on the opening metric collected during data analysis. To begin the experiment, approximately 10 rats with a measured weight will be selected and dissected to remove a portion of the spine, back muscle and layer of skin. Hydrophone testing will then be conducted with each of the specimens to determine the acoustic loss parameters within the spine. This data will then be used to adjust the opening metrics of each rat based off of their measured weight. The dissection process including cleanup requires 1 hour and 30 minutes to complete while hydrophone testing can take up to 2 hours. Therefore, this experiment will require around 35 hours to complete.

Relationship of the Proposed Work to the Expertise of the Mentor

Dr. ___________, an assistant professor in the Radiology and Imaging Science department dedicates her research to discovering improvements in MRgFUS and MRI technology. Dr. __________, an expert in MRI, ultrasound, and biothermal heat transfer, has worked on many MRgFUS projects with a focus in breast cancer and neurological treatments. For my project, Dr. ________ will act as project manager in addition to my mentor, and I will be working in conjunction with her research on the application of MRgFUS for SCI. Furthermore, we will meet weekly to discuss approaches for each procedure and data analysis. Once exceeding 120 hours with UROP, further funding exists for me to work as an undergraduate research assistant in her lab. Under her guidance, I have vastly improved my research abilities and understanding of imaging technology and I hope to continue to do so.

Relationship of the Proposed Work to Your Future Goals

I am currently a junior undergraduate at the University of Utah pursuing a major in biomedical engineering and a minor in chemistry. Additionally, at the end of next spring, I intend on applying for medical school. Working in the ________________ under Dr. ________ has taught me valuable problem solving and time management skills and continues to offer more insight into the development of medical technology. Due to my intentions of studying neurology, studying methods for improving SCI rehabilitation offers insight into the biology of the spinal cord that will prove useful as a physician. It also grants me with the vision of how future neurological injuries may be treated. SCI can be entirely debilitating to those affected, and I seek to improve the quality of life of the people with the injury. Participation in the UROP program has provided me with the opportunity to expand my research abilities and grants me with the time and skills I require to accomplish my goals.

References

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