2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Intraoperative Monitoring of Spinal Cord Perfusion using Ultrasound in an Ovine Model

Elias Shaaya[1], Jonathan Calvert[2], Kirk Wallace[3], *Member, IEEE*, Samuel Parker[2], Radu Darie[2], Sohail Syed[1], Jared Fridley[1], Gautam Parthasarathy[3], Steven Duclos[3], and David A. Borton[4 †], *Member, IEEE*

***Abstract*— Ultrasound imaging can be used to visualize the spinal cord and assess localized cord perfusion. We present *in vivo* data in an ovine model undergoing spinal cord stimulation and propose development of transcutaneous US imaging as a potential non-invasive imaging modality in spinal cord injury.**

***Clinical Relevance*— Ultrasound imaging can be used to aid in prognosis and diagnosis by providing qualitative and quantitative characterization of the spinal cord. This modality can be developed as a low cost, portable, and non-invasive imaging technique in spinal injury patients.**

I. Introduction

Ultrasound (US) imaging is a widely available and commonplace technique applied to diagnostics and interventional guidance in numerous clinical subspecialties, including cardiovascular, radiologic, obstetric, and point of care applications. Neurosurgeons use intraoperative US routinely to identify anatomic landmarks in the brain and spine, particularly during tumor resection [1], and to assess degree of neural element compression. US imaging presents many advantages over other standard medical imaging techniques such as portability, cost, and ease of use. However, the use of bedside US as a routine imaging modality for assessing the spinal cord has yet to be developed. This is mainly due to the acoustic impendence mismatch between the bony spine and the soft tissue of the spinal cord, preventing clear imaging of spinal cord structures. Post-laminectomy, where all or part of the dorsal vertebrae are removed as part of routine spine surgeries, bedside US could potentially be used to image the spinal cord.

Development of bedside US imaging of the spinal cord would be especially beneficial in the field of spinal cord injury (SCI). A laminectomy is routinely performed as part of the standard of practice in the acute phase of SCI, which allows decompression of the spinal cord at the level of injury [2]. This should allow visualization of the local site of SCI and the surrounding cord penumbra. Currently, the standard clinical imaging technique used for visualizing SCI is Magnetic Resonance Imaging (MRI), which is typically conducted in the acute phase of injury to assess the location and severity of the SCI [3]. While MRI is useful during the initial assessment of acute SCI, it is limited in the post-surgical setting due to imaging artifact arising from implanted spinal hardware. This makes visualization of the spinal cord in the chronic SCI patient more challenging.

Furthermore, Doppler US is capable of measuring blood flow through arteries and veins, including those in the spinal cord. Orthostatic hypotension and hemodynamic instability are common clinical issues for individuals in the chronic phase of SCI [4]. Application of Doppler US directly to the spinal cord could provide quantitative information regarding blood flow rate in the spinal cord and aid in evaluating the effectiveness of treatments on these hemodynamic values. One specific research technique that has recently been shown to modulate hemodynamic values and improve orthostatic hypotension in individuals with chronic SCI is epidural electrical stimulation (EES), where stimulation is delivered below the SCI lesion [5]. Development of techniques such as Doppler US of the spinal cord may allow further insight into the mechanisms by which EES modulates blood flow through and near the SCI to reduce orthostatic hypotension and hemodynamic instability.

Here, our goal was to perform a proof-of-concept evaluation of spinal cord imaging using US in an ovine model. We evaluated US imaging intra-operatively in an *in vivo* ovine animal model as well as post-mortem in a separate ovine animal. We were able to characterize the spinal cord *in vivo* and visualize blood flow using the Doppler function of the US. Moreover, our sheep had two epidural electrodes implanted on the epidural surface of the lumbosacral spinal cord. We were able to observe real-time changes in blood flow with different stimulation parameters rostral to the site of stimulation. Additionally, we were able to evaluate differences in spinal cord structure in our post-mortem model following an acute SCI during surgery.

II. Methods

A. Subjects

All study procedures were conducted with the approval of the Brown University Institutional Animal Care and Use

*This work was sponsored in part by the Defense Advanced Research Projects Agency (DARPA) BTO under the auspices of Dr. Doug Weber and Alfred Emondi through the [Space and Naval Warfare Systems Center, Pacific OR DARPA Contracts Management Office] Grant/Contract No. D15AP00112 (DAB) and D19AC00015 (DAB).

† Corresponding author, david_borton@brown.edu

1. E. Shaaya, S. Syed, and J. Fridley are with the Department of Neurosurgery, Brown University and Rhode Island Hospital, 593 Eddy St, Providence, RI 02903 (e-mail: elias_shaaya@brown.edu, sohail_syed@brown.edu, jared.fridley@lifespan.org).

2. J. S. Calvert, S. Parker, and R. Darie are with the School of Engineering, Brown University, 184 Hope Street, Providence, RI 02912 USA (e-mail: jonathan_calvert@brown.edu, samuel_parker@brown.edu, radu_darie@brown.edu)

3. K. Wallace, G. Parthasarathy, and S. Duclos are at GE Research, Niskayuna, NY 12309 USA. (e-mail: wallacek@ge.com, partha@ge.com, duclos@ge.com).

4. D. A. Borton is Assistant Professor at the School of Engineering and Carney Institute for Brain Science Brown University, 184 Hope Street, Providence, RI 02912 USA (phone: 401-863-2963, e-mail: david_borton@brown.edu) and a Biomedical Engineer at the Center for Neurorestoration and Neurotechnology, Rehabilitation R&D Service, Department of Veterans Affairs, Providence, RI, USA

Committee (IACUC) and in accordance with the National Institutes of Health Guidelines for Animal Research (Guide for the Care and Use of Laboratory Animals). Two male sheep aged 1 year and weighing approximately 80 kg were used for this study. Animals were kept in separate cages in a controlled environment on a 12-h light/dark cycle with ad libitum access to water and were fed twice daily.

B. Ultrasound Equipment

We used a GE Vivid™ iq Ultra Edition portable ultrasound system with a L8-18i intraoperative probe to image the spinal cords of the two sheep. High resolution (sub-mm), broadband (16 MHz center frequency) 2D image cross-sections of the spinal cord were visualized in real time and representative clips were stored as DICOM files.

C. Experimental Procedure

We imaged the spinal cord in two sheep that were previously implanted with epidural spinal cord electrodes. The first set of experiments occurred post-mortem. In the first animal (S1), an acute SCI had occurred in a previously planned surgical procedure. The animal was found to be plegic in the hind legs and the decision was then made to euthanize him. The post-mortem US experiment occurred approximately 8 hours post-euthanasia and the cord images were taken at that time. During the experiment, we imaged the cord using Aquasonic 100 gel to fill the volume of the surgical field and couple the ultrasound signals.

In the second animal (S2), we made measurements intra-operatively while the animal was under general anesthesia. We attempted to visualize the cord transcutaneously but were unsuccessful. We dissected down to the dura and flooded the surgical field with sterile saline and imaged through that medium. We also used the ColorFlow and Power Doppler capabilities of the US to visualize and record arterial and venous blood flow to and from the spinal cord. Pulse Wave (spectral) Doppler was used to measure blood flow speed and record temporal flow profiles in spinal cord vessels specified within the operator specified region of interest. We exposed the cord above and below the electrodes and made measurements at each site. We also measured the blood flow while stimulating different areas of the cord using the previously implanted epidural electrodes. Images from both experiments were saved electronically for further analysis.

D. Epidural Electrical Stimulation (EES)

The *in vivo* intraoperative procedure was performed in a sheep (S2) that was implanted with two EES electrode arrays approximately six months prior to the US evaluation. Briefly, the sheep was implanted with two custom-made 24 contact electrode arrays (Micro-leads Medical, Somerville, MA) spanning the L4-L6 vertebral bodies. The electrode leads and ground and reference wires implanted within the back musculature and spine were tunneled subcutaneously and externalized. The electrode wires connected to a Grapevine Nano2+Stim front end (Ripple Neuro, Salt Lake City, UT) which enabled stimulation across all 24 contacts on both EES arrays. An electrode configuration was selected, and a range of 5-10 stimulation amplitude (0-1500 μA) and stimulation frequency (10-100 Hz) combinations were swept through in a randomized order. Each unique stimulation combination was applied 10-15 times for each electrode configuration. Pulse width was held constant with a cathodic phase of 167 μs and an anodic phase of 500 μs. Stimulation was delivered as 300 ms bursts.

III. RESULTS

We started the experiments with an attempt to transcutaneously image the spinal cord in S1. When the US probe was first applied on the skin surface dorsal to the spinal cord, we were unable to visualize discernable spinal cord anatomy (**Figure 1**). The US was not powerful enough to penetrate the subcutaneous tissue and reach the spinal cord. However, following surgical dissection and a laminectomy, we were able to clearly visualize the spinal cord using US with the US probe placed directly onto the epidural surface of the spinal cord (**Figure 1**). The gray-white junctures were clearly visible. We were able to see the butterfly shape of the axial cord with clear margins between grey and white matter. The US was able to distinguish between the myelinated axons and the cell bodies and clearly depict the architecture of the cord.

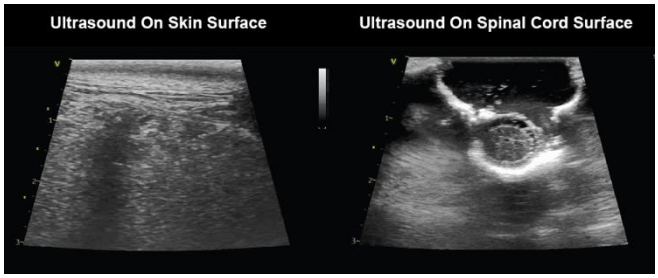

Figure 1. Transcutaneous ultrasound could not penetrate through the intact skin, muscle, and bone for sufficient visualization of the spinal cord (left). Following surgical dissection and a laminectomy to reveal the epidural surface of the spinal cord, visualization of the spinal cord and its grey and white matter structures could be achieved by placing the ultrasound probe directly onto the surface of the spinal cord (right).

We then sought to determine whether we could distinguish damaged cord from healthy tissue. In S1, we imaged the intact cord rostral to the injured section then imaged the contused cord **(Figure 2)**. When imaging the intact spinal cord, the gray-white junctures were visible in the standard "butterfly" pattern. However, the contused cord presented an altered pattern without clear gray-white junctures. The disruption of the architecture of the spinal cord was apparent on US. The architecture of the spinal cord had been altered due to the injury and that was apparent on the US images.

We then turned our attention to evaluating imaging quality through sonolucent material (Aquaflex, Parker Labs). We placed a 2cm block of sonolucent material between the US probe and the epidural surface of the spinal cord. The images produced were of similar quality as when imaging using the Aquasonic 100 gel. The spinal cord and its architecture were clearly visualized, and intact and contused cords could be easily distinguished. Sonolucent materials allow for the penetration of US waves and aid in the visualization of the cord.

In the second set of experiments, we wanted to see the effects of EES on blood flow and whether US could be used to visualize that. In S2, we were able to observe spinal cord

blood flow and modulate the blood flow values by applying stimulation caudal to the US site (**Figure 3**). When the animal was at rest, the blood flow pattern was symmetric, with regions of blood flow in both directions. When EES was applied, spikes PW (spectral) Doppler could be observed at distinct times when the stimulation was applied. Interestingly, following epidural electrical stimulation of different areas of the cord, the ColorFlow Doppler indicated distinct spatial locations of increased blood flow were related to the regions of stimulation: midline stimulation resulted in increased blood flow along the center of the spinal cord, while stimulation applied lateral to midline resulted in increased blood flow along the ipsilateral side of the spinal cord. In addition, we were able to replicate the imaging findings of S1 in S2: the healthy spinal cord could be clearly visualized with crisp borders between white and grey matter.

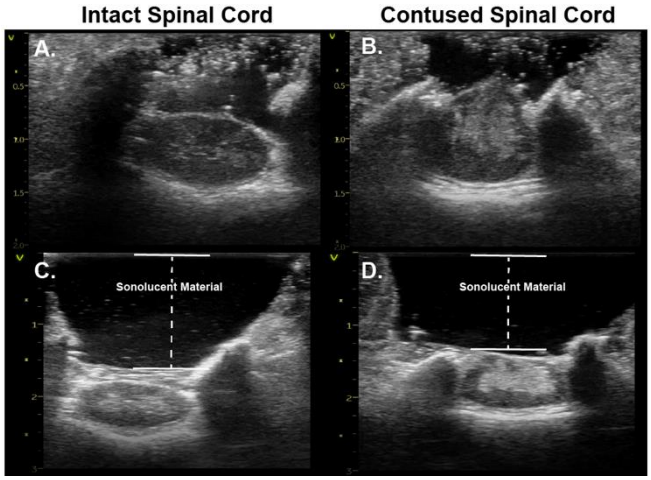

Figure 2. Visualization of the spinal cord using US in a post-mortem animal model. **A.** US image of the intact spinal cord with the US probe directly on the surface of the spinal cord. Note the established "butterfly" pattern of the grey and white matter tracts. **B.** US image of the contused spinal cord with the US probe placed directly on the surface of the spinal cord. The contusion had occurred during a previous surgery while the animal was alive. Note the non-standard appearance of the grey and white matter tracts. **C, D.** The same images as **2A** and **2B** with approximately 2cm of sonolucent material (Aquaflex, Parker Labs) placed in between the ultrasound probe and the surface of the spinal cord.

IV. Discussion

Currently, diagnostic imaging of the spinal cord consists mainly of Magnetic Resonance Imaging (MRI), which is time consuming and costly. Moreover, some patients cannot tolerate MRIs due to claustrophobia or anxiety. Spinal hardware artifact can also limit the view of the spinal cord on MRI, making evaluation of the cord challenging. Patients with certain implanted metal devices (e.g., pacemakers, metal mesh, shrapnel, etc.) cannot obtain MRIs. The alternative imaging modality for a patient unable to undergo MRIs is a myelogram followed by a spinal CT. However, this imaging modality involves injecting contrast dye in the subdural space, which carries a risk of infection, CSF leak, and potential neurologic injury [6]. US has the potential to be a disruptive bedside imaging modality in patients post-laminectomy. Spinal US may provide an inexpensive, rapid, and non-invasive tool to image the spinal cord.

Blood pressure in spinal cord injury patients is usually closely monitored and titrated after injury. Patients have their mean arterial pressure (MAP) maintained above 85 mmHg usually for 7 days post-injury. This is believed to maintain adequate spinal cord perfusion, which can be inhibited due to post-traumatic swelling [7]. Currently, clinicians can either rely on MAP measurements from an arterial line or can measure spinal intradural pressures using a lumbar drain and

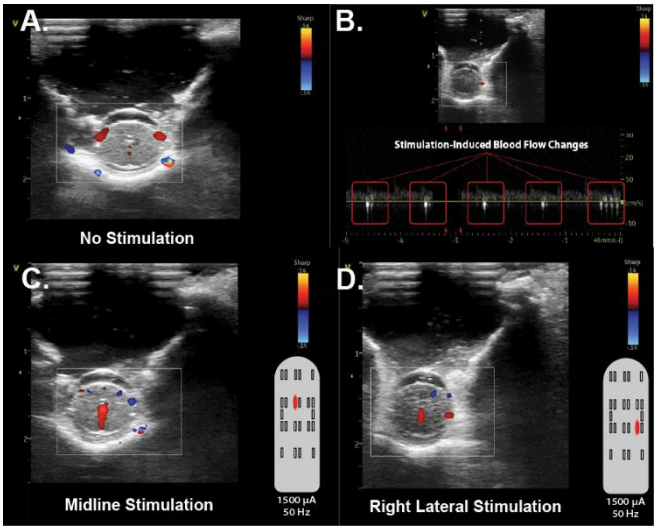

Figure 3. Visualization of blood flow changes during epidural electrical stimulation caudal to the US site. **A.** Power Doppler US image of the blood flow along the spinal cord while the subject was at rest. **B.** PW Doppler sensitivity to stimulation induced motion. Periods of stimulation are indicated in red boxes. **C.** Doppler US image of spinal cord blood flow following stimulation at a midline contact on the EES array. **D.** Doppler US image of spinal cord blood flow following stimulation at a contact positioned laterally right from midline on the EES array.

titrate the blood pressures accordingly [8]. Relying on MAP readings is an indirect way to assess spinal cord perfusion and can be insensitive for small variations. Lumbar drains, however, pose their own set of challenges. They are at risk for infection and their placement carries a risk of neurological injury from a hematoma. Moreover, they are uncomfortable for patients, can get disconnected, and can get clogged and require replacement. Development of direct real-time measurement of spinal cord perfusion would replace current treatment options. Currently, several studies have described the ability of real time spinal cord perfusion measurements using rat models of spinal cord injury [9,10]. We show that similar measurements are able to be done in a large animal model. Developing the ability to measure spinal cord perfusion at the bedside percutaneously would improve patient care and has the potential to improve outcomes. This would be greatly useful in patients with SCI that need adequate spinal cord perfusion to aid their recovery.

In the *in vivo* animal, we were able to show that blood flow to the spinal cord was modulated with change in the location of epidural spinal stimulation. Epidural stimulation is actively being studied in patients with chronic SCI for restoration of motor function in individuals with chronic paralysis and cardiovascular function in individuals with severe orthostatic hypotension [11]. Developing a closed loop system that can assess changes in spinal cord perfusion with US can help develop stimulation protocols for patients with SCI as well as

help elucidate the underlying mechanisms in SCI recovery. Real-time spinal cord perfusion using US has the potential to become a cornerstone of SCI treatment.

Patients after a decompression and fusion surgery are usually monitored with imaging, either MRI to assess the degree of decompression or CT to assess hardware integrity. US could potentially replace MRI imaging of the cord for long-term spinal cord monitoring. In an ongoing study, Shaaya et al. have found that the spinal cord can be visualized transcutaneously using US in patients who have undergone cervical laminectomy and fusion. Patients in that study had undergone cervical decompression with or without fusion at least 3 months prior to their US examination. This preliminary work could further help develop US in the modality of choice for chronic spinal cord imaging.

Finally, given recent advances in ultrasound imaging technologies and implantable biomaterials, a future area of collaborative work between our teams is to resolve the imaging conundrum presented in **Figure 1** and develop an ultrasound imaging platform capable of providing quantitative data on spinal perfusion and hemodynamics with intact lamina.

The work presented here represents the first steps toward developing this US platform by developing a baseline understanding of the capabilities of acquiring clinical US images of the intact and contused spinal cord, spinal cord blood flow values, and validation of a sonolucent material through which to acquire spinal cord images.

ACKNOWLEDGMENTS

We would like to thank the staff and faculty at the Brown University Center for Animal Resources and Education for assisting with this study. Additionally, we would like to thank Aaron Gregoire for assisting with animal surgery, preparation, and training.

REFERENCES

[1] Harel, Ran, and Nachshon Knoller. “Intraoperative Spine Ultrasound: Application and Benefits.” *European Spine Journal* 25.3 (2016): 865–69.

[2] Boakye, Maxwell, et al. "Laminectomy and fusion after spinal cord injury: national inpatient complications and outcomes." *Journal of neurotrauma* 25.3 (2008): 173-183.

[3] Bozzo, Anthony, et al. "The role of magnetic resonance imaging in the management of acute spinal cord injury." *Journal of neurotrauma* 28.8 (2011): 1401-1411.

[4] Claydon, V. E., J. D. Steeves, and A. Krassioukov. "Orthostatic hypotension following spinal cord injury: understanding clinical pathophysiology." *Spinal cord* 44.6 (2006): 341-351.

[5] Squair, Jordan W., et al. "Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury." *Nature* 590.7845 (2021): 308-314.

[6] Rosenblum, Jordan D. “Complications of Neuroimaging.” 121 (n.d.): 1743-EOA.

[7] Catapano, Joshua et al. “Higher Mean Arterial Pressure Values Correlate with Neurologic Improvement in Patients with Initially Complete Spinal Cord Injuries.” *World Neurosurgery*, 96, (2016): 72-79.

[8] Yue, John et al. “Clinical Implementation of Novel Spinal Cord Perfusion Pressure Protocol in Acute Traumatic Spinal Cord Injury at U.S. Level I Trauma Center: TRACK-SCI Study.” *World Neurosurgery*, 133, (2020): e391-e396

[9] Dubory, Arnaud, et al. “Contrast Enhanced Ultrasound Imaging for Assessment of Spinal Cord Blood Flow in Experimental Spinal Cord Injury.” *Journal of Visualized Experiments*, 99 (2015): 52536.

[10] Soubeyrand, Marc, et al. “Very High Resolution Ultrasound Imaging for Real-Time Quantitative Visualization of Vascular Disruption after Spinal Cord Injury.” *Journal of Neurotrauma,* 21 (2014): 1767–75.

[11] Rejc, Enrico et al. “Spinal Cord Imaging Markers and Recovery of Volitional Leg Movement With Spinal Cord Epidural Stimulation in Individuals With Clinically Motor Complete Spinal Cord Injury.” *Frontiers in systems neuroscience*, 14, (2020): 559313.