Development of and pilot results from a large animal study to measure cerebrospinal fluid pressure before, during and after spinal cord injury

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ABSTRACT

The mechanical interactions between cerebrospinal fluid (CSF), spinal cord and dura associated with spinal cord injury (SCI) are not well understood. A better understanding of these interactions is important to develop, and define current limitations of animal, synthetic and computational models of SCI. Furthermore, CSF drainage to increase spinal cord tissue perfusion in patients immediately after an acute SCI is currently being assessed at our institution; however, CSF pressures cranial to the SCI site cannot be measured in patients. In this study we developed an in vivo large animal model to quantify CSF pressures experienced during an acute SCI, and to quantify CSF pressure variation cranially and caudally in the hours following SCI with a sustained complete subarachnoid occlusion and subsequent decompression. Four of the six pigs tested received a spinal cord injury. The peak pressures observed during SCI (range 6.2-19.7 mmHg) were greater than baseline pressure pulsations coupled with respiration (maximum peak-peak 5 mmHg), but less than the previously published result for a single cat SCI (50 mmHg, Hung et al., 1975). Two animals were of suitable condition to continue post-injury monitoring for two hours. The cranial and caudal CSF pressures both tended to decrease after injury in the presence of a complete subarachnoid occlusion. Following decompression, cranial CSF pressure increased and caudal pressure decreased. These trends were not as expected and may be due to physiological responses associated with the spinal cord injury or anaesthesia. This pilot study has provided valuable data, methodology, and experience which will be built upon in the continuation of our research program.

INTRODUCTION

The complex mechanical interactions between the spinal cord and the surrounding cerebrospinal fluid (CSF) and dura, during and immediately following spinal cord injury (SCI) are not well understood. A better understanding of these interactions is important to develop new animal, synthetic and computational models of SCI as well as to define the limitations of those currently in use. Such information will be valuable in the development of alternative predictive measures of individual SCI risk, and also for treatment strategies, including CSF drainage.

There have been very few studies that have attempted to measure cerebrospinal fluid pressure (CSFP) in relation to a SCI injury. Hung et al. (1975) reported the CSFP measured during a single drop-weight SCI in an *in vivo* cat model. Pintar et al. (1996) used a gelatin/collagen spinal cord model to measure spinal cord pressures resulting from a series of drop-weight tests simulating SCI. We have previously observed a pressure wave traveling through the CSF and spinal cord away from the point of impact in an *ex vivo* bovine SCI model (Jones et al., 2008) and this pressure wave may have implications for injury severity.

CSF drainage in the lumbar region to promote spinal cord tissue perfusion is currently being assessed at our institution as a SCI treatment. This strategy is currently used to decrease the risk of spinal cord tissue ischaemia in surgeries requiring aortic ligation (Kahn and Stansby, 2003). Preliminary results from the Vancouver General Hospital study were different than expected (Kwon, 2007) and measuring CSFP cranial to the SCI site may help to elucidate these findings. CSFP cannot be measured cranial to the SCI site in patients due to risk of a higher spinal level injury, therefore an animal model may provide valuable insight.

The aim of this study was to develop an *in vivo* large animal model to quantify CSFP experienced during an acute SCI, and to quantify CSFP variation cranially and caudally in the hours following SCI. We hypothesized that: (1) CSFP would exhibit a transient increase at the time of SCI; (2) CSFP would gradually increase cranial to the injury and decrease caudal to the injury in the presence of a sustained complete subarachnoid occlusion; and, (3) this trend would be reversed following a subsequent decompression.

METHODS

The University of British Columbia Animal Care Committee approved all procedures *(#A07-0363)*. Six (6) farm bred, 30-35 kg, female domestic white Yorkshire pigs were used.

Surgical Preparation

Animals were pre-anaesthetized with Ketamine hydrochloride, 10-20mg/kg IM, endotracheally intubated, and maintained on Isoflurane (2-2.5% in O_2) for the entire procedure. Mechanical ventilation was maintained 10-12 breaths/min and tidal volume 10-12 mL/kg. Temperature was maintained at 38.5-39.5 °C with a heating pad and rectal temperature probe. Sodium pentobarbital analgesic (120 mg/kg) and neuromuscular blocker Pancuronium (0.02-0.15 mg/kg), were administered periodically as required. An intravenous catheter was placed in the

lesser sapheneous artery (hind leg) for blood pressure monitoring and recording. Hydration was maintained with lactated Ringer's solution administered intravenously. ECG pads were attached to monitor and record cardiac activity. Animals were euthanised at completion of the entire procedure with intravenous Euthanyl.

Following anaesthetic administration and prior to the study herein, the animals underwent an unrelated procedure involving measurement of intervertebral disc pressure both percutaneously and directly with surgical exposure of a lower lumbar disc from the posterior approach. The same lumbar location was used for the current study.

Laminectomies of approximately three and six spinal levels were performed in the thoracic and lumbar regions, respectively. The ligamentum flavum and posterior epidural fat were removed to expose the dura mater and spinal cord. Pedicle screws and a rod were inserted across three vertebral levels in the lower thoracic region (Figure 1) for holding the drop-weight device.

Spinal Cord Injury Device

The drop-weight device consisted of an articulating arm and guide-cylinder (length 500 mm, ϕ1/2") mounted on a plastic base that attached to the implanted pedicle screws (Figure 1). The laminae were resected to slightly more than ½" in the region of the SCI site and the guide cylinder was positioned vertically over the spinal cord (Figure 2). The spinal cord injury was carried out by dropping a 50 g spherical (ϕ1/2") stainless steel weight through the guide cylinder from a height of approximately 450 mm. After impact a further 100 g was added statically to ensure subarachnoid occlusion.

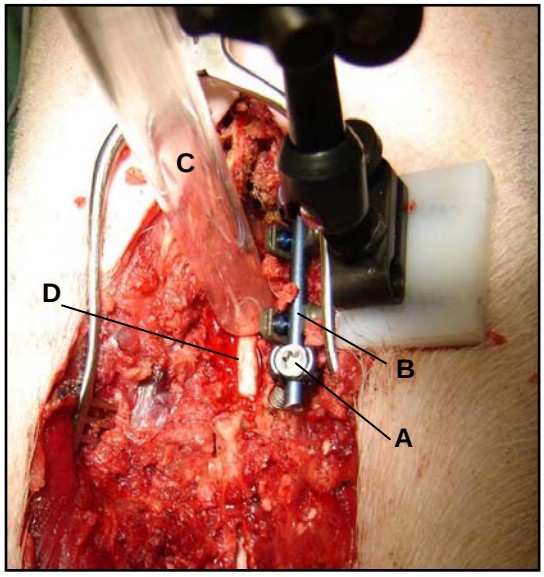


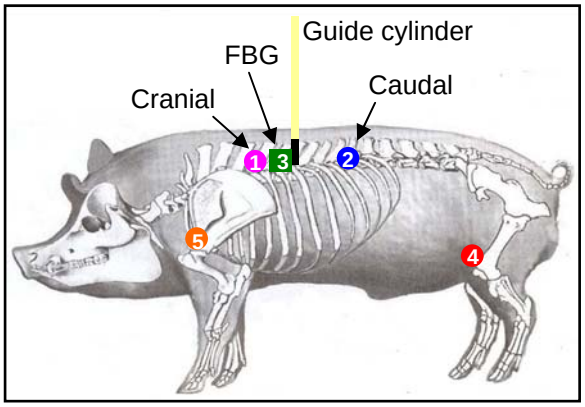
Figure 1 (left): Drop weight device. (A) Articulating arm with guide cylinder and pedicle attachment; (B) 50g drop weight with ½" spherical end, dropped from ~50 cm (C) 100 g static weight.;

Figure 2 (right): Photo of drop weight device guide cylinder installed and aligned above spinal cord. (A) Pedicle screw head; (B) Rod; (C) Guide cylinder; (D) Spinal cord.

Pressure Measurement Devices

Two catheters (19 gauge) were implanted under the dura in the thoracic and lumbar laminectomy sites, with the catheter tip approximately one spinal level above (CSFP-U) and three spinal levels below (CSFP-L) the injury site (Figure 3, ; FBG transducer at 3; ECG at 5.). Catheter insertion sites were sealed with cyanoacrylate adhesive. The catheters were connected to saline-filled tubes and two standard clinical catheter transducers (Transpac IV Monitoring Kit, Hospira Inc., Lake Forest IL, USA). The data were collected with a HP clinical monitor and custom Labview Program, at 120 Hz, 0.2 mmHg resolution.

A single Fibre Bragg Grating pressure sensor (FBG, ϕ0.4 mm) was implanted with the tip approximately 10 mm cranial to the injury site (implanted length approximately 20 mm) and the insertion site was sealed with cyanoacrylate adhesive (Dennison et al., 2008) (Figure 3, Figure 4). The FBG consists of a single optical fibre sheathed in plastic from approximately 20 mm from its tip. The sensing face is located on the cross-sectional end of the fibre.



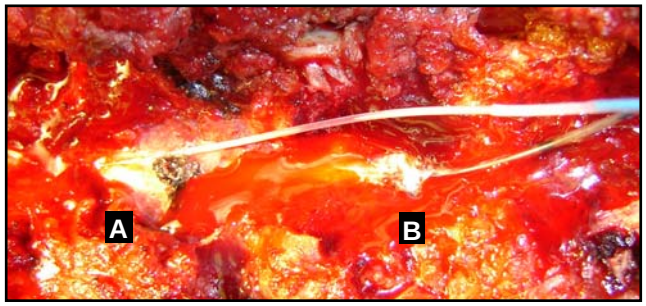


Figure 3 (left): Schematic indicating placement of instruments. Catheter sensors at 1,2,4; FBG transducer at 3; ECG at 5.

Figure 4 (right): FBG transducer (A) and catheter sensor (B) inserted under dura, cranial to SCI site.

Protocol

Baseline pressures were obtained following completion of surgical procedures. The SCI was carried out, and data collected for approximately 10 minutes. The static 100 g weight was then added gently, and data collected for approximately 1 hour. All weights were removed from the guide cylinder and the remaining posterior elements between the thoracic and lumbar laminectomies were removed to simulate a surgical decompression of the spinal cord. Data was then collected for a final 1 hour, after which the animal was euthanised.

RESULTS

Two of the six animals died prior to SCI. SCI CSFP was successfully measured in four animals, and of these, two survived the two hours post-SCI CSFP measurement. The data from the FBG sensor requires further analysis and will not be presented here.

The strongest cyclic variation in baseline CSFP was coincident with the chest motion from mechanical ventilation, with a frequency of approximately 5 Hz. Similar respiration synchronicity has been reported for the spinal CSF of anaesthetised rats, both spontaneously and mechanically ventilated (Budgell and Bolton, 2007; Kusaka et al., 2004). Intracranial and upper cervical CSF flow pulsation has been correlated with the cardiac cycle using cardiac gated MRI in humans (Wagshul et al., 2006; Linninger et al., 2007) and pressure measurements in animal models (Linninger et al., 2005); however, this was not a dominant waveform in our measurements. The magnitude of pressure fluctuations (range 1.2-5 mmHg) was consistent with those measured in humans (McConnell, 1994).

The instantaneous peak CSFP during SCI, measured by the catheter sensors, is shown in Figure 5. The increase in pressure is relative to the pressure immediately prior to injury, and ranged from 8.5 to 17.3 mmHg for the cranial CSFP and 6.2 to 19.7 mmHg for the caudal CSFP.

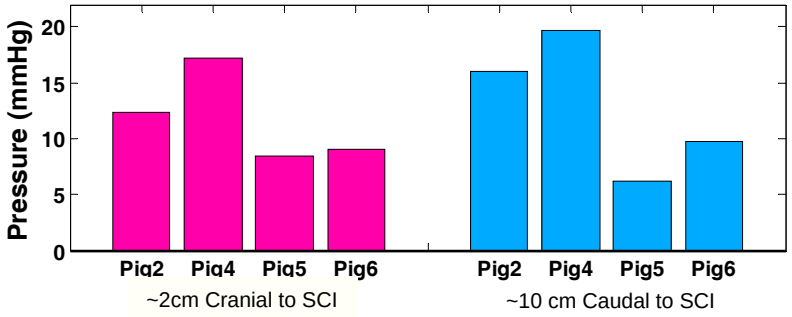


Figure 5: Peak CSFP (mmHg) at injury for four animals. Values expressed as a pressure change from immediately prior to injury.

The post injury and post decompression results are detailed in Table 1. There was a general trend of decreased CSFP both cranial and caudal to the injury site following SCI. After decompression the cranial CSFP generally increased, while the caudal CSFP decreased, in both animals.

Table 1: CSFP results in mmHg for two animals (Pig5, Pig6). Values expressed as a change from the pre-injury mean pressure.

	Immediately post-injury	**0.5 hr post-injury**	**1 hr post-injury**	**Immediately post-decompress.**	**0.5 hr post-decompress.**	**1 hr post-decompress.**
CSFP-U	-0.10, 0.64	-5.80, 0.07	-5.60, 0.28	-5.5, -0.06	-3.73, 0.17	-4.51, 2.46
CSFP-L	2.45, 1.76	0.65, -0.07	-0.05, 0.35	0.30, -0.21	-0.01, -0.04	-0.54, -2.07

DISCUSSION

The peak CSF pressures during SCI measured by the catheter sensors in the current study were somewhat lower than the single value reported by Hung et al. (1975). They measured an *in vivo* peak pressure of 50 mmHg, 2.5 cm cranial to a 20gm-15cm drop-weight impact on a cat spinal cord using a piezoresistive pressure transducer connected to a needle inserted under the

dura. It is difficult to compare this result with the current study due to different drop weights and heights, and the different anatomic scales of the two animal models. In addition, Hung et al. did not report a pulsatile waveform prior to the impact, so it is not known what baseline reference value was used.

In the hour following SCI, there was a general trend of reduction in CSFP both caudal and cranial to the injury site. We had hypothesised that CSFP would increase cranial to the injury, due to the production of CSF in the ventricles in the brain, and decrease caudal to the injury due to the subarachnoid occlusion. Following decompression, the cranial CSFP tended to increase relative to the pressure immediately after decompression, while the caudal CSFP tended to decrease relatively. We expected the cranial pressure to decrease and the caudal pressure to increase following removal of the subarachnoid occlusion.

It is unclear why the post-injury and decompression results did not agree with our hypotheses. To the authors' knowledge there is no similar post-injury study reported in the literature. Physiological responses to either the SCI, anaesthetic or surgical procedure may have included a down-regulation of CSF formation or an increase in CSF reabsorption. A systemic shift in venous pressure may have caused increased reabsorption. The compliance of the central nervous system (both brain and spine) may have also contributed to the pressure trends. There may have been a leakage of CSF from around the catheter insertion sites; however, this was not visible during the procedure or when saline was introduced at the completion of each test.

CONCLUSIONS

We successfully measured CSFP at multiple spinal levels in a newly developed *in vivo* porcine SCI model both during and after an acute SCI. Marked pressure increases above the baseline level were observed during SCI. There were trends of decreased CSFP after injury, as well as increased and decreased cranial and caudal CSFP, respectively, after decompression. These trends were not consistent with our hypotheses and this may be due to physiological responses associated with the spinal cord injury, surgical procedure or anaesthesia. Our research program will continue to build on the methods described herein, and the valuable data and experience gained in this pilot study will contribute to the development of a physical model of the system.

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