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A Direct Comparison Between Norepinephrine and Phenylephrine for Augmenting Spinal Cord Perfusion in a Porcine Model of Spinal Cord Injury

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ABSTRACT

Current clinical guidelines recommend elevating the mean arterial blood pressure (MAP) to increase spinal cord perfusion in patients with acute spinal cord injury (SCI). This is typically achieved with vasopressors such as norepinephrine (NE) and phenylephrine (PE). These drugs differ in their pharmacologic properties and potentially have different effects on spinal cord blood flow (SCBF), oxygenation (PO_2), and downstream metabolism after injury. Using a porcine model of thoracic SCI, we evaluated how these vasopressors influenced intraparenchymal SCBF, PO_2, hydrostatic pressure, and metabolism within the spinal cord adjacent to the injury site.

Yorkshire pigs underwent a contusion/compression SCI at T10 and were randomized to receive either NE or PE for MAP elevation of 20 mm Hg, or no MAP augmentation. Prior to injury, a combined SCBF/PO_2 sensor, a pressure sensor, and a microdialysis probe were inserted into the spinal cord adjacent to T10 at two locations: a 'proximal' site and 'distal' site, 2 mm and 22 mm from the spinal cord injury, respectively. At the proximal site, NE and PE resulted in little improvement in SCBF during cord compression. Following decompression, NE resulted in increased SCBF and PO_2, while decreased levels were observed for PE. However, both NE and PE were associated with a gradual decrease in the L/P ratio after decompression. PE was associated with greater hemorrhage through the injury site than control animals.

Combined, our results suggest that NE promotes better restoration of blood flow and oxygenation than PE in the traumatically injured spinal cord, thus providing a physiologic rationale for selecting NE over PE in the hemodynamic management of acute SCI.

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INTRODUCTION

The hemodynamic management of acute SCI is currently one of the few aspects of clinical care where physicians can potentially improve neurologic outcome in acute SCI patients. Despite considerable preclinical evidence that hypoperfusion and ischemia are significant contributors to secondary damage after traumatic SCI,[1, 2] translating this knowledge into improved neurologic outcomes in human SCI has been challenging. Early non-controlled clinical studies reported that elevating mean arterial pressure (MAP) to 85-90 mmHg for 5-7 days via aggressive fluid and vasopressor support improved mortality rates and neurological outcome after acute SCI.[3, 4] Guidelines have subsequently been established that recommend augmenting the MAP to 85-90 mmHg for the first 7 days post-injury in acute SCI patients, using vasopressors and/or intravenous fluids to achieve this.[5] More recent data has supported the notion that such aggressive hemodynamic management can influence neurologic outcome.[6, 7] Thus, there is a strong practical rationale to better understand the hemodynamic management of acute SCI and optimize treatment guidelines – both in defining the optimal MAP targets and how to best achieve them.

A number of different vasopressors are used clinically to elevate the MAP in the acute neurotrauma setting, including phenylephrine (PE), dopamine (DA) and norepinephrine (NE).[8, 9] While all of these vasopressors can effectively increase MAP, they each have unique pharmacologic properties, based on their affinity for alpha-adrenergic, beta-adrenergic, and dopamine receptors.[10] Although the systemic effects of these vasopressors are well described, their actions on the specific microvascular beds within the CNS may not be predictable, particularly after injury.[11, 12] As such, they may have different effects on perfusion within the injured central nervous system (CNS).[9] Whether one vasopressor is more effective than another at restoring perfusion and downstream metabolic needs of the acutely injured spinal cord is unknown. The decision about which vasopressor to use in acute neurotrauma is typically left to the discretion of the treating physician, whose choice may be based on desired pharmacologic activity, personal

familiarity/experience, and institutional bias/tradition. This has resulted in considerable variations in clinical practice for both traumatic brain injury (TBI) and SCI.[13-15]

Therefore, in this study we conducted a direct comparison of phenylephrine (PE), norepinephrine (NE), and dopamine (DA) in a large animal (pig) model of SCI to determine how these commonly used vasopressors affect the oxygenation, perfusion, hydrostatic pressure, and downstream metabolic responses within the parenchyma of the injured spinal cord. To achieve intraparenchymal measurements of these parameters, we used female Yorkshire pigs that were subjected to a combination of contusion SCI with persistent compression at the T10 level.[16]

METHODS

All animal protocols and procedures employed in this study were approved by the Animal Care Committee of the University of British Columbia and were compliant with the policies of the Canadian Council on Animal Care.

Animals & Experimental Groups

Female Yorkshire pigs acquired from a local distributor weighing 25-32 kg were transported to our animal facility 1 week before surgery. Upon arrival, the animals were housed in groups of 2-4 in an indoor pen bedded with sawdust and toys (chains, balls) with access to an adjoining outdoor pen. Animals were given water *ad libitum* and fed 1.5% of their body weight twice a day (Hog Grower, Hi-Pro Feeds, Chilliwack, BC, Canada). Animals were distributed into four groups: 1) Control (no MAP support), 2) Norepinephrine (NE), 3) Phenylephrine (PE), and 4) Dopamine (DA).

All four groups received a T10 contusion injury followed by 3 hours of compression and then 3 hours of post-decompression observation. In the middle of each 3-hour period, the NE, PE and DA group received a 1-hour infusion of NE (4 mg in 250 ml of 0.9% NaCl/1.25% dextrose), PE (1ml in 250 ml of 0.9% NaCl/1.25% dextrose) or DA (400mg in 250 ml of 0.9% saline/1.25% dextrose) respectively to raise MAP ~20 mmHg and measure

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responses inside the injured cord. The control group received no vasopressor infusion and the MAP was left untreated. A schematic of the experimental design is shown in Figure 1.

During vasopressor infusion, I.V. maintenance fluids rates (0.9% NaCl/1.25% dextrose) were independently adjusted to ensure a total fluid infusion of 7ml/kg/hr for all experimental groups. The experiment for each animal typically began at 08:00 am; IV line insertion, surgical exposure, laminectomy, insertion of probes, stabilization and collection of baseline measurements would take until approximately 06:00 pm. The three hours of observation with compression and then 3 hours post-decompression would last until midnight, at which time the animal was euthanized and the cord harvested for histologic analysis.

Carotid Artery and Jugular Vein Catheterization

Tracheal intubation and mechanical ventilation was performed as described previously.[17] Anesthesia was maintained with a combination of isoflurane (0.5% in 100% O_2) and Propofol (8-20 mg/kg/hr; Baxter, Allison, Ontario, Canada). All animals received ketoprofen (3 mg/kg) via intravenous administration and fentanyl (15-30 μg/kg/hr; Sandoz Canada, Boucherville, Quebec, Canada) delivered via continuous rate infusion (CRI). After a surgical plane of anesthesia was reached, the animal was placed on the surgical table in the supine position. A longitudinal incision was made at the base of the neck ~3 cm left of the midline. The left external jugular vein (EJV) and common carotid artery (CCA) were exposed by blunt dissection. A 20-gauge intravenous catheter was inserted into the CCA and connected to a blood pressure transducer system for measurement of MAP (Edward Lifesciences Inc, Irvine, CA). A 7F triple lumen venous catheter (Arrow International, Reading, PA) was inserted and advanced ~16 cm towards the heart for infusion of vasopressors and fluids. To secure both catheters, two ligatures caudal to the site of insertion were carefully tied around the vessels in addition to being sutured to the musculature. The wound was closed in layers with the catheters exiting the skin through the primary incision site.

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Contusion / Compression Spinal Cord Injury Technique

After catheter insertion, the animal was gently turned into the prone position. A skin incision was made along the dorsal midline of the thoracic region of each animal. Using electro-cautery (Surgitron® Dual Frequency RF/120 Device; Ellman International, Oceanside, NY), the semispinalis, multifidus and longissimus lumborum muscles were separated from the dorsal spinous processes, laminae and transverse processes. A T9 to T13 laminectomy was performed and widened to expose the dura and spinal cord with sufficient clearance for sensor positioning and weight drop injury.

The SCI was delivered by a weight drop impactor device, which was securely fixed to the spine using an articulating arm (660, Starrett, Athol, Massachusetts, USA) mounted via bilaterally inserted T6 and T8 pedicle screws and rods. This arm enabled the guide-rail to be precisely positioned and aligned, allowing for the impactor to fall straight vertically onto the exposed dura and cord at T10. The tip of the impactor (diameter: 0.953 cm) was outfitted with a load cell (LLB215, Futek Advanced Sensor Technology, Irvine, CA, USA) to record the force at impact. The guide rail was equipped with a Balluff Micropulse® linear position sensor (BTL6-G500-M0102-PF-S115, Balluff Canada Inc., Mississauga ON, Canada) to record the impactor position from 10 cm above the impact (for calculation of impact velocity and cord displacement). A custom controller was used to operate the device and filter the force and position data collected with the simultaneous USB DAQ module (DT9816-S, Data Translation Inc., Marlboro, MA, USA). A LabVIEW (National Instruments, Austin, TX, USA) program enabled remote operation of the device and real-time data collection feedback. Immediately after the weight drop contusion injury (weight: 50 g; height: 20 cm), a 3-hour compression period was maintained on the contused spinal cord by placing an additional 100 g weight onto the impactor (150 g total).

Insertion of Intraparenchymal Blood Flow/O_2, Pressure, and Microdialysis Probes

To consistently insert the monitoring probes into the desired location within the spinal cord and stabilize their position for the duration of the experiment, a custom-made sensor holder was created (Figure 2). The sensor holder was attached rigidly to the spine via

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bilateral T9, T11, T12, and T14 pedicle screws (Select™ Multi Axial Screw, Medtronic, Minneapolis, MN) and 3.5 mm titanium rods (Medtronic, Minneapolis, MN). The location of the sensor holder was locked in place by sliding the device over the rod and adjusting the height of the pedicle screws. Additional transverse connecting bridges were fixed between two poly-axial pedicle screws to produce a stable, rigid construct. Six custom-made introducers with a lumen wide enough to fit one sensor/probe were inserted through precision-drilled holes in the sensor-holder (45-degree angle), entering the dura at 12 and 32 mm from the centre of the intended impact. Subsequently, the sensors were guided through the introducers and advanced another 7.8 mm, placing the sensors in the ventral aspects of the white matter. The distance between the tips of the blood flow/oxygen, pressure and microdialysis probes was ~0.5-1.0 mm.

The final location of the tip of the sensors were situated approximately 2 mm and 22 mm away from the edge of the impactor, herein described as the “proximal” (2 mm) and “distal” (22 mm) measurement sites. To prevent CSF leakage, cyanoacrylate glue was applied to the dural surface where the catheters entered. After sensor insertion, we waited for 2 hours to allow for a period of physiologic ‘stabilization’. We then commenced recording the ‘baseline’ samples for a period of 60 minutes prior to the actual spinal cord injury.

Intraparenchymal Spinal Cord Blood Flow and Partial Pressure of Oxygen (PO_2) Measurements

For measurement of blood flow and oxygen, we utilized a single multi-parameter probe that contains a device for measuring blood flow and another for measuring partial pressure of oxygen (PO_2) at the tip. This probe, with a tip diameter of 450 μm (NX-BF/OF/E, Oxford Optronix, Oxford, UK), was attached to the OxyLab/OxyFlo combined channel monitor (Oxford Optronix OxyLab, Oxford, UK) with LabChart Pro software for interpretation (ADInstruments, Colorado Springs, Colorado, US). Spinal cord tissue partial pressure of oxygen (PO_2) was measured by a fluorescence quenching technique which

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monitors the mean time between photon absorption and emission of the oxygen-sensitive fluorescent ruthenium lumiphor dye after being excited by a short pulse of light (luminescence lifetime). In the presence of oxygen, the fluorescence lifetime is quenched proportionally to the oxygen concentration. The OxyLab system measures the reduced lifetime of luminescence of the reflected signal and displays a value for partial pressure of oxygen (PO_2) in mmHg according to the Stern Volmer equation. Since the luminescence-based oxygen sensing technique is sensitive to temperature changes, a thermocouple transducer is incorporated into the sensor for temperature corrections for variations from 30-44^{o}C. Blood flow is determined via laser-Doppler flowmetry (LDF) where light from the probe tip is projected into the tissue, scattered and then reabsorbed by a sensor. Only the laser light backscattered from moving cells undergoes a Doppler shift, which creates Doppler frequencies at the detectors and produces a voltage output which can be interpreted as blood flow by the OxyFlo monitor (in arbitrary perfusion units, APU). The numeric calculation of LDF is dependent on the relative concentration of local red blood cells in the tissue and the velocity.

Intraparenchymal Spinal Cord Pressure Measurement

Spinal cord pressure was characterized using custom-manufactured fiber-optic combined Fabry-Perot interferometry pressure sensors (FOP-LS-NS-1006A, FISO Technologies Inc., Harvard Apparatus, Quebec, Canada) with a tip diameter of 333 μm. The sensor tip is comprised of two parallel reflecting mirrors on either side of an optical cavity. The first mirror is semi-reflective and the second is a flexible membrane. As pressure is applied, the membrane deflects, reducing the cavity length. The reduced cavity lengths cause phase shifts in the reflected light, which are distinguished by a detector. Transducers are calibrated in such a way that each cavity length corresponds to a specific pressure value, with the transducers being capable of measuring pressure changes of ± 300 mmHg, with a resolution of ± 0.3 mmHg. Transducers were connected to a chassis-mounted signal conditioner module (EVO-SD-5/FPI-LS-10, FISO Technologies Inc., Harvard Apparatus, Quebec, Canada) with internal atmospheric pressure compensation, which is particularly

valuable for long-term animal studies. The data was acquired digitally through the Evolution software (FISO Technologies Inc., Harvard Apparatus, Quebec, Canada) at a frequency of 1 Hz.

Intraparenchymal Spinal Cord Microdialysis

Microdialysis probes (CMA11, CMA Microdialysis, Harvard Apparatus, Quebec, Canada) with an outer diameter of 380 μm, 2 mm membrane length and a 6-kDa cut-off were used to sample the extracellular fluid for energy related metabolites. Probes were continuously perfused with artificial CSF (Perfusion Fluid CNS, CMA Microdialysis, Harvard Apparatus, Quebec, Canada) using a subcutaneous implantable micro-pump at a flow rate of 0.5 μl/min (SMP-200, IPrecio, Alzet Osmotic Pumps, Durect Corporation, Cupertino, CA, USA). Dialysates were collected in micro tubes, capped, and frozen on dry ice every 15 minutes, from the beginning of the baseline period to 6 hours post-injury; providing a sample volume of 7.5 μl sufficient for the exploration of five metabolites (lactate, pyruvate, glucose, glutamate and glycerol). Samples were analyzed within a week of collection using the ISCUS^{flex} Microdialysis Analyzer (M Dialysis, Stockholm, Sweden).

Eriochrome Cyanine Histochemistry

For differentiating grey and white matter, Eriochrome Cyanine R histochemistry was performed on spinal cord sections as described previously.[17, 18] Dried sections were cleared in xylene, rehydrated in a reverse ethanol series followed by distilled water (dH_2O), then left in a solution containing 0.16% Eriochrome Cyanine R, 0.5% sulphuric acid and 0.4% iron chloride (in dH_2O) to stain myelinated fibres. Following staining, sections were differentiated in 0.5% ammonium hydroxide. After differentiation, the grey matter was counterstained in Neutral Red then rinsed in dH_2O. Finally, sections were dehydrated and cleared, and then mounted onto silane-coated SuperFrost^{TM} Plus slides (Fisher Scientific, Pittsburgh, PA). Sections were examined for hemorrhage using a Zeiss AxioImager M2 microscope. Pictures were taken of sections at 800μm intervals throughout the lesion site to measure the distribution (in mm^2) of *hemorrhage.*

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Data Acquisition and Analysis

SCBF and PO_2 were recorded continuously at a sampling rate of 10 Hz. To mitigate movement artifacts in the oxygenation and blood flow data, a post-processing filter was applied (smoothing type: median filter, window width: 601 samples / 1 minute of sampling). Microdialysis samples were collected every 15 minutes, from the beginning of the baseline period to 6 hours post-injury. The lactate to pyruvate (L/P) ratio was calculated from the measured values of lactate and pyruvate concentrations. To account for absolute differences in the baseline recordings, all values were expressed as a percentage change from baseline (%Δ) as a function of time (hours). For comparisons of SCBF, PO2, spinal cord pressure, and metabolic responses between the three independent groups, the Kruskal-Wallis test followed by Dunn's post hoc test was used. Between group differences at each time point was determined using multiple t-test. Calculated p-values were corrected for multiple testing using Bonferroni adjustment. Differences between groups were considered significant if more than two consecutive points in the time course were statistically significant at $p < 0.05$. The data was collected over 6 hours at 15-min intervals for microdialysis samples and 1-min intervals for SCBF/PO2/SCP recordings; these are plotted as mean values ± SEM. For both parameters, a 1-hour mean and its corresponding 95% confidence interval (95% CI) were calculated based on six time periods: 0 to 1 hour before injury (the baseline pre-injury period), 0 to 1 hour after injury (the immediate post-SCI period with sustained compression), 1 to 2 hours after injury (the vasopressor infusion #1 during sustained compression), 2-3 hours after injury (the post-infusion period #1 during sustained compression), 3-4 hours after injury (the immediate post-decompression period), 4 to 5 hours after injury (the vasopressor infusion #2 with the cord decompressed), and 5 to 6 hours after injury (the post-infusion period #2 with the cord decompressed).

Due to the practical challenges of constantly titrating vasopressor dosages throughout the experiment, the surgery research team was not blinded to the intervention. However, for the data analysis of physiologic/metabolic responses (e.g. blood flow, microdialysis) and histology, the research team was blinded to the intervention groups.

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The hemorrhage data was plotted as mean values ±SEM for different positions (spaced 800 μm apart) along the length of the spinal cord (total 5600 μm). For the analysis of hemorrhage, we fit linear generalized estimating equations (GEE) models predicting the absolute (in mm^2) and relative (%) extent of hemorrhage within each axial section through the length of the injury site. We used the autoregressive working correlation structure per lowest quasi information criterion (QIC). This was sensible given the large number of records per subject (pig) and that adjacent records contain data collected from points on the spinal cord immediately adjacent in physical proximity (hence high correlation). The analysis was performed through the region of cord in which hemorrhage was detected (16.8 mm on either side of the epicenter) and directly around the epicenter of injury (2.8 mm on either side). Results were Bonferroni-adjusted for multiple comparisons among the levels of intervention (PE, NE, control) and estimates were reported with 95% confidence intervals.

RESULTS

In total, 22 animals were randomized to receive NE (n=9), PE (n=9), or no MAP support (n=4). An additional 4 animals were randomized to receive dopamine. However, the dopamine experiments had to be stopped prematurely as all animals rapidly experienced severe tachycardia (e.g. heart rates exceeding 200 beats/minute) upon institution of dopamine at dosages required to increase MAP by 20 mm Hg. The dopamine experimental group was therefore excluded from this study.

Biomechanical Features of Spinal Cord Contusion Injury Across Groups

All animals received a contusion SCI by dropping a 50 g weight from a 20 cm height at the T10 level of the spinal cord followed by 3 hours of compression (150 g total weight). To determine the consistency of the injury, we measured force, displacement and velocity of the impact. On average, the maximum impact force applied to the exposed spinal cord measured at the tip of the impactor was 3,315 ± 119 kdynes (mean ± SEM). The impactor

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tip traveled approximately 3 mm from initial contact with a velocity of 1.6-1.7 m/s at impact. Between the three experimental groups (NE, PE, Control) no significant differences were observed for maximal impact force, displacement, or velocity ($p>0.05$). (Table 1).

Hemodynamic Parameters

To maintain a target MAP of 20 mmHg above pre-SCI levels (i.e. target MAP: of 75-85 mmHg; Figure 3A), the average PE dose was 0.7 ± 0.1 (range 0.14–2.8) μg/kg/min, and the average NE dose was 0.1 ± 0.04 (range 0.02–1.18) μg/kg/min. No differences in target MAP between the NE and PE group were observed during the compressed (NE mean: 77 mmHg, 95% CI: 69-84 mmHg; PE mean: 76.62 mmHg, 95% CI: 73-80 mmHg) or decompressed state of the spinal cord (NE mean: 73 mmHg, 95% CI 67-79 mmHg; PE mean: 76 mmHg, 95% CI: 71-80 mmHg). Raising MAP with NE by ~20 mmHg significantly increased heart rate (HR) over time, while PE showed a tendency to decrease HR (Figure 3B). As described earlier, DA was utilized in 4 animals (at an average dose of 41.7 ± 8.8 (range 17–118) μg/kg/min) but this induced severe tachycardia, which prompted us to stop the experiment.

Intraparenchymal Responses at Proximal Measurement Site (2-mm probe position)

Post-injury Changes in Intraparenchymal Pressure, SCBF, PO_2 and Pressure: Measures of SCBF and PO_2 adjacent to the injury site decreased precipitously immediately after SCI (Figure 4A-B). During the first hour after SCI, the drop in SCBF (control mean: 26% of pre-injury values, 95% CI: 10-42; PE mean: 33%, 95% CI: 25-42%; NE mean: 35%, 95% CI: 22-48%) or PO2 (control mean: 2%, 95% CI: -0.23-4%; PE mean: 3%, 95% CI: 0.68-5%; NE mean: 11%, 95% CI: -12-35%) was relatively similar between the three groups. During the period of sustained compression, no recovery of SCBF or PO_2 was observed in the control group where the MAP remained relatively constant throughout the three-hour period. During compression, a ~20 mmHg MAP elevation with NE resulted in an increase to 58% (95% CI: 28-89%) in SCBF, while PE had a minimal effect on SCBF (mean: 39%, 95% CI: 25-52%) (Figure 4A). Notably, there was much variability in the increases of SCBF within the

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NE group. The MAP increase of 20 mmHg had minimal effect on PO_2 during this period of sustained compression, regardless of which vasopressor was used (Figure 4B). Compression of the spinal cord during the first 1 hour resulted in increased spinal cord pressure (SCP) to a mean value of 365% (95% CI: 280-449%), 358% (95% CI: 238-478%), and 461% (95% CI: 137-785%) above pre-injury levels for respectively the control, PE and NE group. MAP augmentation by 20 mmHg with NE or PE during compression did not appreciably change the intraparenchymal pressure (Figure 4C).

Following decompression, SCBF (control mean: 43%, 95% CI: 16-71%; PE mean: 83%, 95% CI: 45-121%; NE mean: 71%, 95% CI: 41-102%) and PO_2 levels (control mean: 3%, 95% CI: -9-15%; mean PE: 26%, 95% CI: -1-53%; mean NE: 28%, 95% CI: -8-63%) recovered partially for all three groups, although the extent was much greater in both vasopressor groups than in the control group. After decompression, only NE infusion increased both SCBF (mean: 91%, 95% CI: 53-129%, p=0.048) and PO_2 (mean: 48%, 95% CI: -7-102%), while PE infusion resulted in a slight drop of SCBF (mean: 70%, 95% CI: 34-106%). The SCP rapidly declined after decompression, and was again not influenced by changes in MAP in the NE or PE groups.

Post-injury Changes in Microdialysis Measurements: Time-dependent changes in microdialysis markers of excitotoxicity (glutamate), phospholipid degradation (glycerol) and energy metabolism (glucose, lactate, and pyruvate) induced by the injury are summarized in Figure 5. Glucose levels in the control group rapidly decreased after contusion to 23% of pre-injury values (95% CI: 5-42%) during the first hour and steadily decreased to almost zero at the end of the 3-hour compression period (mean: 4%, 95% CI: 2-7) (Figure 5A). Decompression was associated with a small increase in glucose, yet levels persisted well below pre-injury values (mean: 24%, 95% CI: -7-54%). In contrary to the gradual drop in glucose levels for the control group during the 3-hours of compression, glucose held steadily at approximately 15% of baseline levels during the 1-hour infusion period in both the PE (mean: 15%, 95% CI: 5-24%) and NE group (mean: 19%, 95% CI: 9-28%). For the first hour after vasopressor infusion was ceased, glucose levels tended to be

higher in the NE group (mean: 19%, 95% CI: 7-29%, p=0.05) compared to the control animals (mean: 4%, 95% CI: 2-7%).

Glutamate levels sharply increased after SCI, reaching peak values of ~3000% within 15 minutes after contusion (Figure 5B). For the control group, glutamate levels remained >2000% throughout the 6 hour observation period. During the compressed state of the spinal cord, MAP augmentation with either NE or PE resulted in negligible changes in glutamate levels. However, following decompression the glutamate levels trended downwards within 45 minutes in the NE group (notably 15 minutes before vasopressor infusion) (mean 1067%, 95% CI: 11-2123%). During NE infusion after decompression glutamate decreased to 587% (95% CI: -147-1322%) and remained at this level during the 1-hour period following cessation of NE infusion (mean: 554%, 95% CI: -238-1346%). Compared to the control group, glutamate values in the NE group tended to be lower after decompression (control mean: 3924%, 95%: -1029-8877%; NE mean: 1067%, 95% CI: 11-2123) and during the second NE infusion (control mean: 2924%, 95% CI: -1226-7074%; NE mean: 587% (95% CI: -147-1322%). Although the decline in glutamate was greater with NE than PE (mean percent decrease of 1000% vs. 500%), this difference was not statistically significant.

Glycerol levels exhibited a value of 295% (95% CI: 120-470%) 1 hour after contusion and remained at this level throughout the compression period (Figure 5C). Immediately after decompression, levels rose again and remained high at 573% (95% CI: 253-893%) until the end of the study. In the PE and NE groups, this rapid post-contusion increase in glycerol was not observed, even before the vasopressor was infused (PE mean: 147%, 95% CI: 89-205%; NE mean: 170%, 95% CI: 115-226%, p=0.04). Notwithstanding the lower glycerol levels in the two vasopressor groups post-injury, neither PE nor NE had an appreciable impact on glycerol levels during the compression or post-decompression period.

In the control group, elevated lactate (Figure 5D) and decreasing pyruvate levels (Figure 5E) were observed during the entire compression period, resulting in a marked rise

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in L/P ratio to 1107% of baseline (95% CI: -105.1-2320%) during the first hour (Figure 5F). After decompression, both lactate and pyruvate levels steadily increased, but then decreased again. As lactate levels did not change in direct proportion to pyruvate, the L/P ratio gradually declined to ~485% (95% CI: 281-690%). As in the control group, a similar increase in L/P ratio was observed acutely after SCI and during the first hour of compression for both the PE (mean: 456%, 95% CI: 274-639%) and NE group (mean: 526%, 95% CI: 202-850%), without significant changes during vasopressor infusion. However, in both NE and PE groups, the L/P ratio started to drop within 30 minutes of decompression (i.e. 30 minutes before the 2nd infusion) and continued to decline until static levels of ~250% were reached (i.e. 30 minutes after initiation of the infusion). For both the PE (mean: 241%, 95% CI: 158-323%) and NE groups (mean: 288%, 95% CI: 142-433%), the L/P ratio values were significantly lower 1.0 hour after decompression and onwards compared to SCI-control animals (mean: 485%, 95% CI: 281-690%). The response in L/P ratio was not significantly different between the NE and PE treated animals at any time.

Intraparenchymal Responses at Distal Measurement Site (22-mm probe position)

Post-injury Changes in Intraparenchymal Pressure, Blood Flow, PO_2 and Pressure: Compared to the 2-mm probe location, slight changes in SCBF, PO_2, and pressure after SCI were observed at the 22 mm position (i.e. the more distal of the two sensor positions) (Figure 6). An increase in SCBF was found in the control within 15 minutes after SCI and after spinal cord decompression to 177% (95% CI: -0.13-353%) during the last hour of the study (Figure 6A), while PO_2 gradually increased over time to 193% (95% CI: 50-337%) above pre-injury values (Figure 6B). Despite the lower SCBF (control mean: 152%, 95% CI: 75-228%; PE mean: 116%, 95% CI: 90-141%; NE mean: 100%; 84-115%) and PO_2 (control mean: 138%, 95% CI: 30-246%; PE mean: 101%, 95% CI: 57-145%; NE mean: 126%, 95% CI: 54-199%) injury response after SCI compared to the SCI-control group, augmenting MAP by 20 mmHg using NE or PE during compression and decompression resulted in a further increase in SCBF and PO_2 levels. After ceasing NE infusion, SCBF and PO_2 values in the NE group dropped immediately to pre-infusion levels and showed a declining trend thereafter. Conversely, SCBF and PO_2 in the PE group gradually continued to increase even

after infusion was stopped until the end of the experiment. Neither vasopressor infusion had a noticeable effect on spinal cord pressure (Figure 6C).

Post-injury Changes in Microdialysis Markers: Glucose, glutamate, glycerol, lactate, pyruvate and L/P ratio patterns after SCI at the 22-mm position were far less pronounced (Figure 7). Between the experimental groups no significant differences were observed ($p>0.05$)

Spinal Cord Tissue Hemorrhage

As expected, hemorrhage was observed within the spinal cord in all animals acutely after injury, particularly at and around the site of contusive/compressive injury. Quantification on axial sections through the length of the injury revealed a greater percentage of the cross-sectional area being occupied by hemorrhage in the vasopressor-treated animals as compared to control animals, with the PE group having generally more extensive hemorrhage than the NE group (Figure 8). As illustrated in Figure 8, at the epicenter of injury the hemorrhage occupied, on average, 16% of the cross-sectional area in the PE group (95% CI: 7-25%), as compared to 11% in the NE group (95% CI: 8-16%). In control animals, the hemorrhage occupied, on average, 6% of the cross-sectional area through the injury epicenter (95% CI: 4-8%).

To assess the extent of hemorrhage through the lesion site, we considered the entire length of cord from -16.8 mm to +16.8 mm on either side of the injury epicenter (0) where hemorrhage was generally identified (Figure 8), and also the central zone of -2.8 mm to +2.8 mm to represent the area of cord directly subjected to the physical contusion/compression injury. When considering the percentage of the cross-sectional area occupied by hemorrhage (and after applying the Bonferroni correction for multiple comparisons), the PE group had significantly greater hemorrhage (mean: 3%, 95% CI: 2-4%, $p=0.040$) than control animals (mean: 1%, 95% CI: 1-2%) through the wide (±16.8 mm) zone of injury around the epicenter and also through the central (±2.8 mm) epicenter zone (PE mean: 11%, 95% CI: 7-15%, $p=0.013$; Control mean: 5%, 95% CI: 4-5%). While there was seemed to be slightly more hemorrhage in the NE group than the control group

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(as per Figure 8), this difference was not statistically significant through the wide (NE mean: 2%, 95% CI: 1-2%) or central zone of injury (NE mean: 6%, 95% CI: 4-8%). Also, the differences in hemorrhage between NE and PE were not statistically significant through either the wide (p=0.250) or central zone of injury (p=0.103). While this analysis utilized the percentage of cross-sectional area occupied by hemorrhage on each axial section, an analysis utilizing the absolute area of hemorrhage (in mm^2) on each axial l section produced the same results. Statistically significant differences ($p<0.05$ after Bonferroni correction) were found between PE and control through the wide (p=0.049) and central zones of injury (p=0.038), with no significant differences between NE and control and between NE and PE.

DISCUSSION

In summary, we compared the effect of the vasopressors norepinephrine (NE) and phenylephrine (PE) on spinal cord oxygenation, perfusion, pressure, and downstream metabolic responses after acute SCI. NE and PE were studied because they are both commonly utilized to augment MAP in the clinical setting of TBI and SCI.[13-15] Dopamine was included in the original study design but had to be abandoned due to severe tachycardia that it induced in the animals. Immediately adjacent to the spinal cord injury site, MAP augmentation with NE resulted in a modest improvement in SCBF during compression and after decompression, while PE had little effect during compression and appeared to even reduce SCBF following decompression. NE was also associated with reduced glutamate and L/P ratio levels following decompression. Both vasopressors were associated with increased hemorrhage in the spinal cord, although this was more apparent in the PE group of animals. These results suggest a physiologic rationale to choosing NE over PE in the hemodynamic management of acute SCI.

Current clinical practice guidelines recommend that MAP be augmented for 5-7 days using appropriate intravascular fluid and vasopressor support.[5] However, there are no recommendations regarding the optimal vasopressor for MAP augmentation, leaving the choice of vasopressor up to physicians or their institutional preference and resulting in considerable variability in clinical practice. For example, a retrospective study of pediatric

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TBI patients at a single American level 1 trauma center reported that vasopressor usage varied widely, with the first-line treatment most commonly being PE (57%), followed by DA (29%), NE (10%), and epinephrine (4%).[13] In a series of 114 adult TBI patients from the same institution, PE was again the most commonly used vasopressor (43%), followed by NE (30%), DA (22%), and vasopressin (5%).[14] In a series of 131 acute SCI patients at another American level 1 trauma center, DA was the most commonly used vasopressor (48%), followed by PE (45%), NE (5.0%), epinephrine (1.5%) and vasopressin (0.5%).[15] In contrast, at our own institution and in other Canadian institutions, the vasopressor of choice is NE, followed by DA. These observed variations in practice simply illustrate the variability that exists with respect to vasopressor utilization in acute SCI and TBI and highlight the paucity of scientific and clinical evidence that would support one agent over another.

Importantly, while different vasopressors may achieve comparable augmentation of MAP, these agents each have unique pharmacologic properties and therefore they are likely to have differential (and unpredictable) effects on microvascular beds within the CNS, particularly after injury. To our knowledge, a direct comparison of norepinephrine and phenylephrine and their potentially differential effects on tissue hemodynamics within the traumatically injured spinal cord has not been reported. The differential effects of vasopressors in animal models of neurotrauma have been much more extensively studied in the context of TBI than SCI. As reviewed by Pfister et al., comparative studies of vasopressors in TBI have suggested that norepinephrine may have a more predictable effect on cerebral blood flow over dopamine and phenylephrine.[19] For example, in a rodent model of traumatic brain injury (controlled cortical impact, CCI), Kroppenstedt et al. observed that norepinephrine and dopamine differentially influenced pericontusional cortical perfusion and extracellular glutamate levels, with norepinephrine providing better restoration of blood flow [20, 21] and dopamine causing worsening vasogenic edema.[22] A more recent comparison of norepinephrine versus phenylephrine in a porcine model of non-impact inertial brain injury revealed that norepinephrine resulted in higher tissue oxygenation, but phenylephrine resulted in better normalization of metabolic responses and ultimately, less tissue injury.[23]

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It is, however, important to acknowledge that human studies report conflicting results with respect to the differential effects of various vasopressors in the setting of acute CNS trauma. Ract et al. reported in a cross-over study of 19 patients with severe TBI that dopamine resulted in increased ICP as compared to norepinephrine without significantly improving other hemodynamic parameters such as transcranial Doppler mean velocity in the middle cerebral artery.[12] Steiner and colleagues also performed a direct cross-over comparison of norepinephrine and dopamine in TBI patients and found norepinephrine to provide more consistent increases in transcranial Doppler mean velocity[24] and more consistent increases in brain tissue oxygenation than dopamine.[25] Roy et al. evaluated 63 patients with acute subarachnoid hemorrhage treated with phenylephrine and norepinephrine and found that phenylephrine resulted in worse neurologic recovery, a higher likelihood of delayed infarct, and less likelihood to be discharged home.[26]

How MAP augmentation influences the compromised spinal cord tissue adjacent to an area of persistent compression is a question of considerable clinical relevance. Even with growing clinical enthusiasm for "early" surgical decompression, acute SCI patients wait many hours (to days) before surgical decompression, and during this pre-operative period of time are typically admitted to an intensive care setting where MAP augmentation with vasopressors is undertaken. While our results would suggest a benefit of NE over PE, it is notable that NE did not fully restore SCBF or oxygenation while the spinal cord remained compressed. This supports the importance of decompressing the persistently compressed spinal cord as soon as possible after injury. In most rodent and mouse models of SCI, persistent compression after traumatic spinal cord injury is either non-existent or lasts for only 1 minute.[27] In such models, the question of how MAP augmentation influences tissue hemodynamics in the 'penumbra' around the persistently compressed spinal cord would be practically difficult (if not impossible) to address. Our data would suggest that the effect of such MAP augmentation (either with norepinephrine or phenylephrine) on improved tissue hemodynamics directly adjacent to the SCI site is at best very modest while compression is still applied.

Journal of Neurotrauma
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The finding of decreased SCBF with PE after decompression is also intriguing. This could be interpreted to be the result of the alpha-adrenergic agonist effect of PE causing severe vasoconstriction on microvasculature around the injury site. This stands in contrast to other animal TBI studies in which PE has been shown to improve cerebral perfusion and oxygenation,[28, 29] although this may be associated with increased intracranial pressure and vasogenic edema.[30, 31] In a clinical study of TBI where brain oxygenation was monitored with Licox probes, PE increased cerebral perfusion pressure *without* improved cerebral oxygenation.[32] In the setting of anesthesia-induced hypotension, PE was also found to reduce cerebral oxygenation by 14%,[33, 34] findings that are also supported by other investigators studying the effects of PE on cerebral oxygenation in other non-traumatic settings.[33, 35, 36] While these studies suggest that PE has potential disadvantages in the setting of neurotrauma, it is worth noting that it was one of the most commonly utilized vasopressors in the large series of acute SCI patients reported by Inoue et al.[15] Clearly, there is room for further study on the use of such vasopressors, particularly in the setting of traumatic SCI.

The finding of increased hemorrhage within the parenchyma of the vasopressor animals (worse in PE in particular) is also intriguing. Others have reported on the occurrence of intracranial hemorrhage as the result of oral or systemic phenylephrine administration.[37] This is potentially the result of increased cerebral blood flow and increasing vascular resistance causing the rupture of weak vessels.[38, 39] Such could certainly be an issue in the traumatically injured spinal cord with both norepinephrine and phenylephrine, where the spinal cord microvasculature is known to be vulnerable immediately after injury.[1] Our observations of increased hemorrhage within the spinal cord serve as a warning around the aggressive hemodynamic resuscitation of acute SCI, in that we may unintentionally be promoting some degree of increased bleeding within the spinal cord with our enthusiastic measures to augment MAP with vasopressors. This was in fact demonstrated by Soubeyrand et al. in a rodent model of SCI, where NE did not significantly modify blood flow but did increase intraparenchymal hemorrhage at the injury site.[40] The conflicting issue that requires further study is that while MAP augmentation (typically achieved with vasopressors) appears to be associated with

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improved neurologic outcome in human SCI, intraparenchymal hemorrhage (which appears to be increase with vasopressors) is associated with worsened neurologic outcome. Our data highlight the fact that while vasopressors are routinely utilized, fluid-based resuscitation should not be overlooked as an adjunct to the hemodynamic management of acute SCI. What is clearly needed here to inform optimal hemodynamic management practices is a real-time assessment of SCPP at the injury site, as has been proposed in many elegant studies by Papadopoulos and colleagues.[41]

We were also interested to note that the MAP augmentation had fairly modest effects on our metabolic responses to injury as measured by microdialysis. We chose to evaluate these responses as potential downstream effects of alterations in SCBF and PO_2. It could be interpreted that the rapid changes in SCBF and PO_2 that were observed with MAP augmentation are not reflected as quickly in changes to local lactate, pyruvate, and glucose levels, or simply that the changes were not of sufficient magnitude to alter these downstream metabolic responses. This lack of responsiveness in the microdialysis measures of metabolism to perfusion/oxygenation was also observed by Johnston et al. in their study of 11 TBI patients, where norepinephrine was found to significantly increase cerebral perfusion pressure and cerebral blood flow, but had no effect on glucose, lactate, pyruvate, L/P ratio, or glycerol as measured by microdialysis.[25] It is interesting however that the L/P ratio and the glycerol levels were reduced post-decompression in both the NE and PE groups at the most proximal measurement site (2mm), suggesting that while the effects of MAP augmentation on metabolic responses were not observable during the actual vasopressor infusion, there was still some beneficial effect that was manifested later when the cord was decompressed.

We employed our pig model of thoracic SCI for these experiments to take advantage of the larger size of the spinal cord as compared to rodents and the similarities to humans with regards to cardiovascular physiology and spinal cord vasculature.[42-44] While these features allowed for the study of intraparenchymal responses over time, there are some limitations that should be acknowledged. The issue of hypotension requiring vasopressor support is common in human SCI after injuries to the cervical spine and upper thoracic

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spine above T6. In our pig model of SCI, the injury is performed at T10 as this mid/low thoracic level was the most technically straight-forward location for the impact when we developed the pig model a number of years ago. As in humans, there is variability in normal physiologic MAPs in healthy conscious Yucatan mini-pigs, ranging between 86 and 123 mmHg.[45-48] With the combination of anaesthesia and the traumatic SCI at T10, we did observe MAP to drop to around 55-60 mmHg, and a vasopressor-induced elevation of MAP by 20 mm Hg would bring the animals back to a more normotensive level. This MAP augmentation would arguably still represent a mild degree of relative hypotension, and most certainly not *hyper*tension. An upper thoracic injury in the pig such as at T2 would likely induce different systemic hemodynamic effects, and while it would not necessarily change the impact of different vasopressors on intraparenchymal responses, it would be a more clinically relevant experimental paradigm. We are currently exploring the technical development of such a model with the contusion/compression injury occurring at T2.

Additionally, a limitation of our experimental paradigm in the pig is that the long-term functional effect of norepinephrine versus phenylephrine versus control was not studied. Under the current experimental paradigm with 3 hours of observation with persistent spinal cord compression and 3 hours of observation post-decompression, the entire experiment lasts from early in the morning (approx. 0700hrs) to late at night (approx. 2400). For this reason, we could not practically extend the duration of observation or vasopressor infusion beyond the current design. We recognize that an hour of MAP augmentation before and after decompression is unlikely to represent clinical reality in which patients are on vasopressors for many hours/days post-injury. Furthermore, we acknowledge that this brief period of intra-operative MAP augmentation may not have a meaningful effect on long-term functional recovery if the animal were to return to a baseline resting MAP of 86-123 mm Hg for the ensuing 12 weeks. Given that there was, however, increased hemorrhage in the vasopressor-treated animals, the question of whether this brief period of vasopressor support impacted long term recovery in the pigs would be interesting to test in the future. One additional limitation to consider is that we did not evaluate potential drug-drug interactions between the vasopressors and various

anaesthetics, analgesics, and hypnotics, and so the potential influence that such interactions might have on spinal cord tissue hemodynamics is unknown.

This is a preclinical investigation of local tissue hemodynamics in response to clinically utilized vasopressor, and our data indicate that there is an advantage to using norepinephrine over phenylephrine. We acknowledge that ultimately, a human study would be desirable to determine whether neurologic outcomes were improved on norepinephrine versus phenylephrine. Such a comparative study would suffer the same challenges that plague ongoing clinical trials of neuroprotective agents for acute SCI in terms of patient recruitment, stratification of injury severity, and variability in neurologic recovery. While clearly desirable, the undertaking of a clinical trial in acute SCI to compare norepinephrine versus phenylephrine would be a non-trivial matter that would take considerable time and resources. In the absence of such clinical data, given our preclinical results demonstrating a differential (and advantageous) response with norepinephrine versus phenylephrine, physicians who are relatively agnostic about the choice of vasopressor (or who simply adhere to institutional preference) may be encouraged to utilize norepinephrine in the setting of acute traumatic SCI.

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References

1. Tator, C.H. and Fehlings, M.G. (1991). Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. Journal of neurosurgery 75, 15-26.

2. Martirosyan, N.L., Feuerstein, J.S., Theodore, N., Cavalcanti, D.D., Spetzler, R.F. and Preul, M.C. (2011). Blood supply and vascular reactivity of the spinal cord under normal and pathological conditions. Journal of neurosurgery. Spine 15, 238-251.

3. Levi, L., Wolf, A. and Belzberg, H. (1993). Hemodynamic parameters in patients with acute cervical cord trauma: description, intervention, and prediction of outcome. Neurosurgery 33, 1007-1016; discussion 1016-1007.

4. Vale, F.L., Burns, J., Jackson, A.B. and Hadley, M.N. (1997). Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. Journal of neurosurgery 87, 239-246.

5. Ryken, T.C., Hurlbert, R.J., Hadley, M.N., Aarabi, B., Dhall, S.S., Gelb, D.E., Rozzelle, C.J., Theodore, N. and Walters, B.C. (2013). The acute cardiopulmonary management of patients with cervical spinal cord injuries. Neurosurgery 72 Suppl 2, 84-92.

6. Hawryluk, G., Whetstone, W., Saigal, R., Ferguson, A., Talbott, J., Bresnahan, J., Dhall, S., Pan, J., Beattie, M. and Manley, G. (2015). Mean Arterial Blood Pressure Correlates with Neurological Recovery after Human Spinal Cord Injury: Analysis of High Frequency Physiologic Data. Journal of neurotrauma 32, 1958-1967.

7. Catapano, J.S., John Hawryluk, G.W., Whetstone, W., Saigal, R., Ferguson, A., Talbott, J., Bresnahan, J., Dhall, S., Pan, J., Beattie, M. and Manley, G. (2016). Higher Mean Arterial Pressure Values Correlate with Neurologic Improvement in Patients with Initially Complete Spinal Cord Injuries. World neurosurgery 96, 72-79.

8. Yue, J.K., Tsolinas, R., Burke, J.F., Deng, H., Upadhyayula, P.S., Robinson, C.K., Lee, Y.M., Chan, A.K., Winkler, E.A. and Dhall, S.S. (2017). Vasopressor support in managing acute spinal cord injury: a knowledge update. Journal of neurosurgical sciences.

9. Muzevich, K.M. and Voils, S.A. (2009). Role of vasopressor administration in patients

with acute neurologic injury. Neurocritical care 11, 112-119.

10. Bangash, M.N., Kong, M.L. and Pearse, R.M. (2012). Use of inotropes and vasopressor agents in critically ill patients. British journal of pharmacology 165, 2015-2033.

11. Wei, E.P., Raper, A.J., Kontos, H.A. and Patterson, J.L., Jr. (1975). Determinants of response of pial arteries to norepinephrine and sympathetic nerve stimulation. Stroke 6, 654-658.

12. Ract, C. and Vigue, B. (2001). Comparison of the cerebral effects of dopamine and norepinephrine in severely head-injured patients. Intensive care medicine 27, 101-106.

13. Di Gennaro, J.L., Mack, C.D., Malakouti, A., Zimmerman, J.J., Armstead, W. and Vavilala, M.S. (2010). Use and effect of vasopressors after pediatric traumatic brain injury. Developmental neuroscience 32, 420-430.

14. Sookplung, P., Siriussawakul, A., Malakouti, A., Sharma, D., Wang, J., Souter, M.J., Chesnut, R.M. and Vavilala, M.S. (2011). Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. Neurocritical care 15, 46-54.

15. Inoue, T., Manley, G.T., Patel, N. and Whetstone, W.D. (2014). Medical and surgical management after spinal cord injury: vasopressor usage, early surgerys, and complications. Journal of neurotrauma 31, 284-291.

16. Lee, J.H., Jones, C.F., Okon, E.B., Anderson, L., Tigchelaar, S., Kooner, P., Godbey, T., Chua, B., Gray, G., Hildebrandt, R., Cripton, P., Tetzlaff, W. and Kwon, B.K. (2013). A novel porcine model of traumatic thoracic spinal cord injury. Journal of neurotrauma 30, 142-159.

17. Streijger, F., Lee, J.H., Manouchehri, N., Melnyk, A.D., Chak, J., Tigchelaar, S., So, K., Okon, E.B., Jiang, S., Kinsler, R., Barazanji, K., Cripton, P.A. and Kwon, B.K. (2016). Responses of the Acutely Injured Spinal Cord to Vibration that Simulates Transport in Helicopters or Mine-Resistant Ambush-Protected Vehicles. Journal of neurotrauma 33, 2217-2226.

18. Rabchevsky, A.G., Fugaccia, I., Sullivan, P.G. and Scheff, S.W. (2001). Cyclosporin A treatment following spinal cord injury to the rat: behavioral effects and stereological assessment of tissue sparing. Journal of neurotrauma 18, 513-522.

19. Pfister, D., Strebel, S.P. and Steiner, L.A. (2008). Effects of catecholamines on cerebral blood vessels in patients with traumatic brain injury. European journal of anaesthesiology. Supplement 42, 98-103.

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20. Kroppenstedt, S.N., Sakowitz, O.W., Thomale, U.W., Unterberg, A.W. and Stover, J.F. (2002). Influence of norepinephrine and dopamine on cortical perfusion, EEG activity, extracellular glutamate, and brain edema in rats after controlled cortical impact injury. Journal of neurotrauma 19, 1421-1432.

21. Kroppenstedt, S.N., Sakowitz, O.W., Thomale, U.W., Unterberg, A.W. and Stover, J.F. (2002). Norepinephrine is superior to dopamine in increasing cortical perfusion following controlled cortical impact injury in rats. Acta neurochirurgica. Supplement 81, 225-227.

22. Kroppenstedt, S.N., Kern, M., Thomale, U.W., Schneider, G.H., Lanksch, W.R. and Unterberg, A.W. (1999). Effect of cerebral perfusion pressure on contusion volume following impact injury. Journal of neurosurgery 90, 520-526.

23. Friess, S.H., Bruins, B., Kilbaugh, T.J., Smith, C. and Margulies, S.S. (2015). Differing effects when using phenylephrine and norepinephrine to augment cerebral blood flow after traumatic brain injury in the immature brain. Journal of neurotrauma 32, 237-243.

24. Steiner, L.A., Johnston, A.J., Czosnyka, M., Chatfield, D.A., Salvador, R., Coles, J.P., Gupta, A.K., Pickard, J.D. and Menon, D.K. (2004). Direct comparison of cerebrovascular effects of norepinephrine and dopamine in head-injured patients. Critical care medicine 32, 1049-1054.

25. Johnston, A.J., Steiner, L.A., Chatfield, D.A., Coles, J.P., Hutchinson, P.J., Al-Rawi, P.G., Menon, D.K. and Gupta, A.K. (2004). Effect of cerebral perfusion pressure augmentation with dopamine and norepinephrine on global and focal brain oxygenation after traumatic brain injury. Intensive care medicine 30, 791-797.

26. Roy, B., McCullough, L.D., Dhar, R., Grady, J., Wang, Y.B. and Brown, R.J. (2017). Comparison of Initial Vasopressors Used for Delayed Cerebral Ischemia after Aneurysmal Subarachnoid Hemorrhage. Cerebrovascular diseases 43, 266-271.

27. Furlan, J.C., Noonan, V., Cadotte, D.W. and Fehlings, M.G. (2011). Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: an evidence-based examination of pre-clinical and clinical studies. Journal of neurotrauma 28, 1371-1399.

28. Friess, S.H., Smith, C., Kilbaugh, T.J., Frangos, S.G., Ralston, J., Helfaer, M.A. and Margulies, S.S. (2012). Early cerebral perfusion pressure augmentation with phenylephrine after traumatic brain injury may be neuroprotective in a pediatric swine model. Critical care medicine 40, 2400-2406.

29. Dudkiewicz, M. and Proctor, K.G. (2008). Tissue oxygenation during management of cerebral perfusion pressure with phenylephrine or vasopressin. Critical care medicine 36, 2641-2650.

30. Malhotra, A.K., Schweitzer, J.B., Fox, J.L., Fabian, T.C. and Proctor, K.G. (2003). Cerebral perfusion pressure directed therapy following traumatic brain injury and hypotension in swine. Journal of neurotrauma 20, 827-839.

31. Cherian, L., Chacko, G., Goodman, J.C. and Robertson, C.S. (1999). Cerebral hemodynamic effects of phenylephrine and L-arginine after cortical impact injury. Critical care medicine 27, 2512-2517.

32. Sahuquillo, J., Amoros, S., Santos, A., Poca, M.A., Panzardo, H., Dominguez, L. and Pedraza, S. (2000). Does an increase in cerebral perfusion pressure always mean a better oxygenated brain? A study in head-injured patients. Acta neurochirurgica. Supplement 76, 457-462.

33. Brassard, P., Seifert, T., Wissenberg, M., Jensen, P.M., Hansen, C.K. and Secher, N.H. (2010). Phenylephrine decreases frontal lobe oxygenation at rest but not during moderately intense exercise. Journal of applied physiology 108, 1472-1478.

34. Nissen, P., Brassard, P., Jorgensen, T.B. and Secher, N.H. (2010). Phenylephrine but not ephedrine reduces frontal lobe oxygenation following anesthesia-induced hypotension. Neurocritical care 12, 17-23.

35. Lucas, S.J., Tzeng, Y.C., Galvin, S.D., Thomas, K.N., Ogoh, S. and Ainslie, P.N. (2010). Influence of changes in blood pressure on cerebral perfusion and oxygenation. Hypertension 55, 698-705.

36. Meng, L., Cannesson, M., Alexander, B.S., Yu, Z., Kain, Z.N., Cerussi, A.E., Tromberg, B.J. and Mantulin, W.W. (2011). Effect of phenylephrine and ephedrine bolus treatment on cerebral oxygenation in anaesthetized patients. British journal of anaesthesia 107, 209-217.

37. Tark, B.E., Messe, S.R., Balucani, C. and Levine, S.R. (2014). Intracerebral hemorrhage associated with oral phenylephrine use: a case report and review of the literature. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 23, 2296-2300.

38. Koyama, K., Mito, T., Takashima, S. and Suzuki, S. (1990). Effects of phenylephrine and dopamine on cerebral blood flow, blood volume, and oxygenation in young rabbits.

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Pediatric neurology 6, 87-90.

39. Goddard, J., Lewis, R.M., Armstrong, D.L. and Zeller, R.S. (1980). Moderate, rapidly induced hypertension as a cause of intraventricular hemorrhage in the newborn beagle model. The Journal of pediatrics 96, 1057-1060.

40. Soubeyrand, M., Dubory, A., Laemmel, E., Court, C., Vicaut, E. and Duranteau, J. (2014). Effect of norepinephrine on spinal cord blood flow and parenchymal hemorrhage size in acute-phase experimental spinal cord injury. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 23, 658-665.

41. Saadoun, S. and Papadopoulos, M.C. (2016). Spinal cord injury: is monitoring from the injury site the future? Critical care 20, 308.

42. Strauch, J.T., Lauten, A., Zhang, N., Wahlers, T. and Griepp, R.B. (2007). Anatomy of spinal cord blood supply in the pig. The Annals of thoracic surgery 83, 2130-2134.

43. Schomberg, D.T., Miranpuri, G.S., Chopra, A., Patel, K., Meudt, J.J., Tellez, A., Resnick, D.K. and Shanmuganayagam, D. (2017). Translational Relevance of Swine Models of Spinal Cord Injury. Journal of neurotrauma 34, 541-551.

44. Schomberg, D.T., Tellez, A., Meudt, J.J., Brady, D.A., Dillon, K.N., Arowolo, F.K., Wicks, J., Rousselle, S.D. and Shanmuganayagam, D. (2016). Miniature Swine for Preclinical Modeling of Complexities of Human Disease for Translational Scientific Discovery and Accelerated Development of Therapies and Medical Devices. Toxicologic pathology 44, 299-314.

45. Swindle, M.M.S., A.C. (2015). Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques. CRC Press, Taylor & Francis Group.

46. Bouchard, G.F.B., L.D.; Liu, J.; Shoemake, C.; Brocksmith, D.; Trickey, J.; Teel, A.; (2015). Miniature Swine Book of Normal Data. Sinclair Research LLC: USA.

47. Gianotti, G.C.B., W.K.; Meyer, F.S.; Carregaro, A.B.; Contesini, E.A. (2014). Cardiorespiratory Dynamics of Sedated Pigs Submitted to DiFerent Inspired Oxygen Fractions under Controlled Mechanical Ventilation. Acta Scientiae Veterinariae 42, 6.

48. Hannon, J.P.B., C.A.; Wade, C.E. (1989). Normal Phsyiological Values for Conscious Pigs Used in Biomedical Research. In: *Institute Report*. Research, D.o.M.T. (ed). United States Department of Defense: San Francisco.

Table 1. Impact parameters across the experimental groups. There were no differences of injury parameters across groups (Dunn multiple comparison test), indicating the contusion injury was consistent throughout the study with regards to force, displacement and velocity (p>0.05). Data presented as mean ± SEM.

Parameters	**Group 1**	**Group 2**	**Group 3**
	controls	PE	NE
N	4	9	9
Body weight (Kg)	29.1 ± 2.7	31.1 ± 1.6	29.9 ± 1.3
Max Force (Kdynes)	2737 ± 191	3477 ± 205	3441 ± 177
Displacement (mm)	3.0 ± 0.2	3.2 ± 0.1	3.1 ± 0.1
Impact Velocity (mm/s)	1621 ± 41	1723 ± 18	1717 ± 16

SCI: spinal cord injury; PE: phenylephrine; NE: norepinephrine

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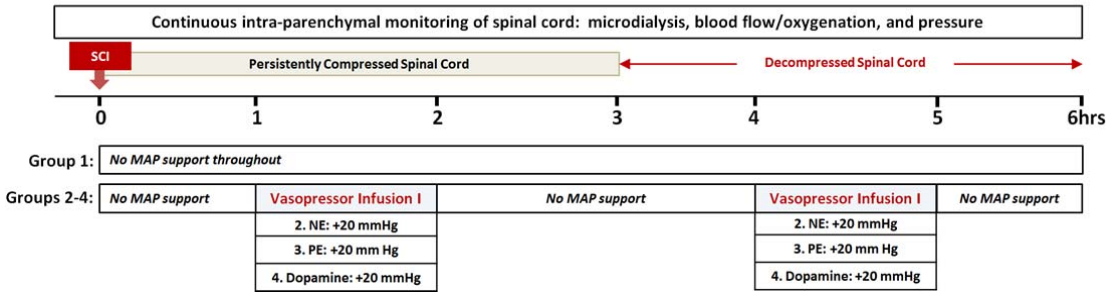

Figure 1. Experimental Design. Following the contusion SCI injury at T10, there was 3 hours of sustained compression, followed by 3 hours of decompression. We augmented MAP by 20 mm Hg following SCI with either norepinephrine, phenylephrine, or dopamine; a control group had no MAP augmentation. Vasopressors were administered for 1 hour during sustained compression and after decompression. We will assess intraparenchymal SCBF, oxygenation, and concentrations of glucose, lactate, pyruvate, glutamate, and glycerol before, during, and after vasopressor administration. NE: norephinephrine, PO_2: partial pressure of oxygen, PE: phenylephrine, SCBF: spinal cord blood flow, SCI: spinal cord injury.

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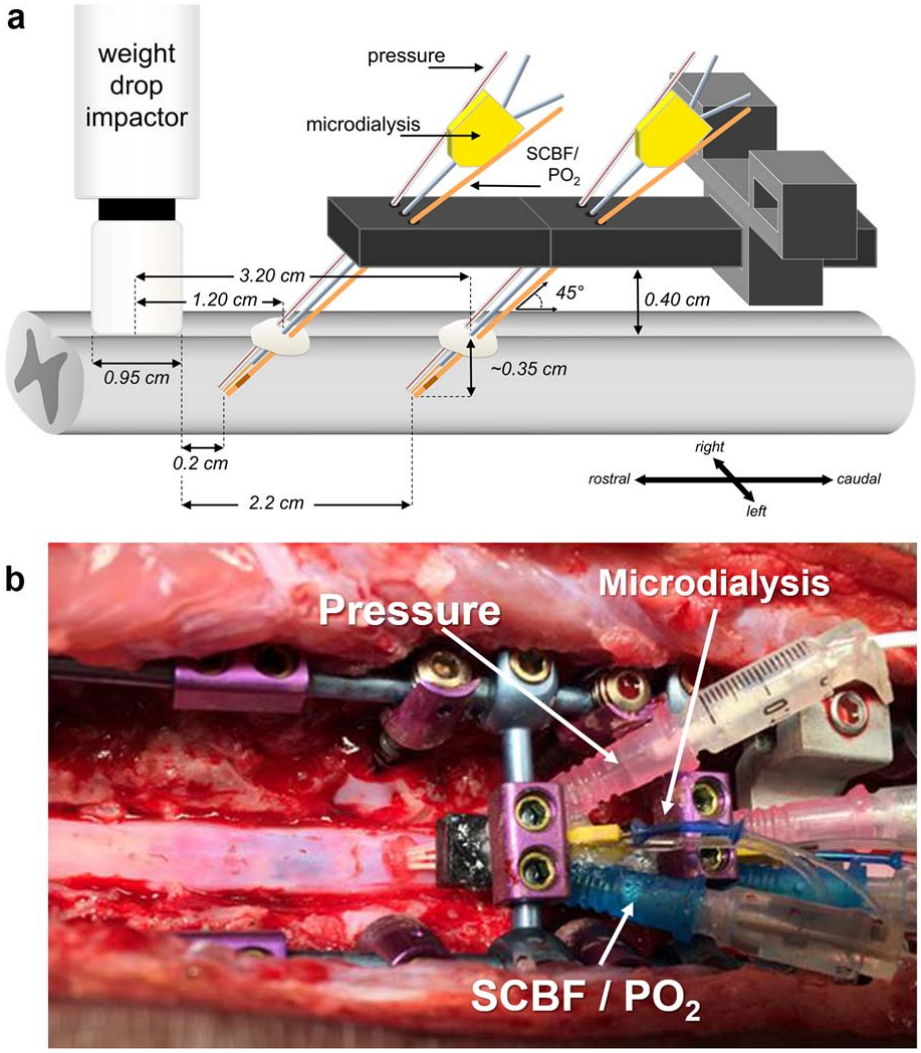

Figure 2. Intraparenchymal monitoring set-up for inserting and securing SCBF/PO_2, pressure and microdialysis probes within the spinal cord. (a) Schematic drawing and (b) surgical set-up illustrating the fixation device, which is secured rigidly via the pedicle screw/rod construct to the spinal column. The device has three independently drilled channels through which the SCBF/ PO_2 (left), pressure (right) and microdialysis (middle) probes are inserted. The final location of the sensor tips are approximately 0.2 cm and 2.2 cm away from the edge of the impactor. * Spinal cord injury hemorrhage.

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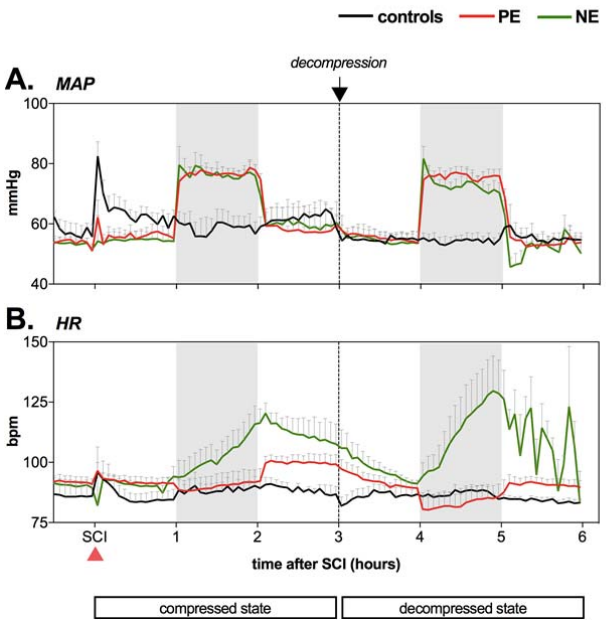

Figure 3. Usage of PE and NE after SCI to augment MAP by 20 mmHg. Animals were distributed into three groups: 1) NE group, 2) PE group, and 3) controls. All three groups received a T10 contusion injury followed by 3 hours of compression [0-3 hpi] and then 3 hours of post-decompression [3-6 hpi]. Decompresion is shown by the vertical dashed line. (**A**) During each 3-hour period, the NE and PE group received a 1-hour infusion of NE (4 mg in 250 ml of 0.9% saline/1.25% dextrose) or PE (1 ml in 250 ml of 0.9% saline/1.25 % dextrose) respectively to raise MAP 20 mmHg above pre-SCI levels (i.e. target MAP: of 75-85 mmHg; see grey shading). (**B**) Raising MAP with NE by 20 mmHg significantly increased HR over time, while PE showed a tendency to decrease HR. Data is expressed as mean ± SEM. HPI: hours post-injury; HR: heart rate; MAP: mean arterial pressure; NE; norepinephrine; PE: phenylephrine; SCI: spinal cord injury.

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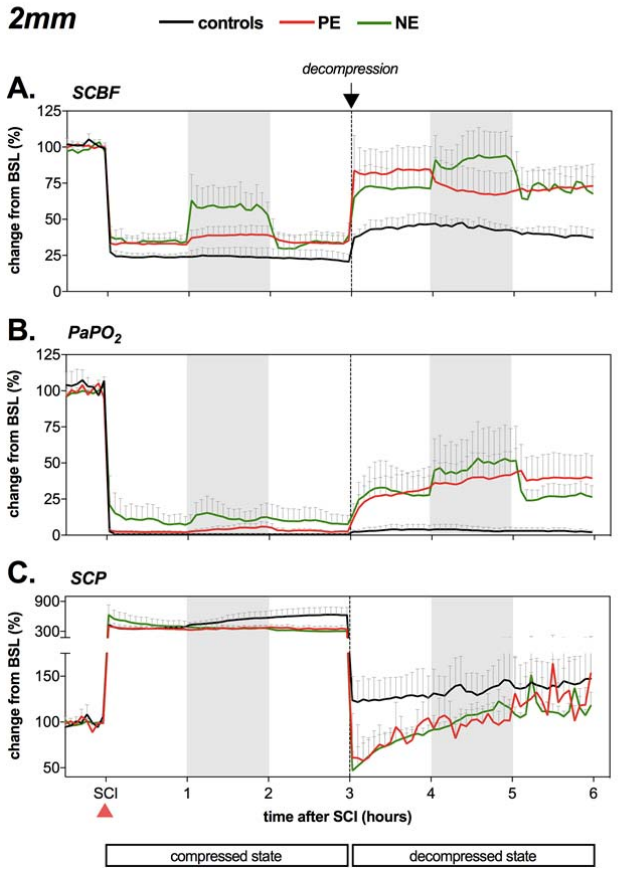

Figure 4. Effect of NE and PE infusion after SCI on blood flow, partial pressure of oxygen and pressure in the penumbra (2-mm). The percentage change (%Δ) is calculated using an average of 30 minutes of baseline before SCI. (**A**) Spinal cord blood flow (SCBF), (**B**) partial pressure of oxygen (PO_2) and (**C**) pressure responses of 1-hour of vasopressor infusion (grey shading) during the compressed [0-3 hpi] and decompressed [3-6 hpi] state of the spinal cord. Decompresion time is shown by the vertical dashed line. The NE vasopressor group demonstrated a partial recovery of SCBF and PO_2 during MAP increase of 20 mmHg during compression as well decompression. In the decompressed state PE infusion resulted in a drop of SCBF. Data is expressed as mean ± SEM. HPI: hours post-injury; NE; norepinephrine; PE: phenylephrine; SCI: spinal cord injury.

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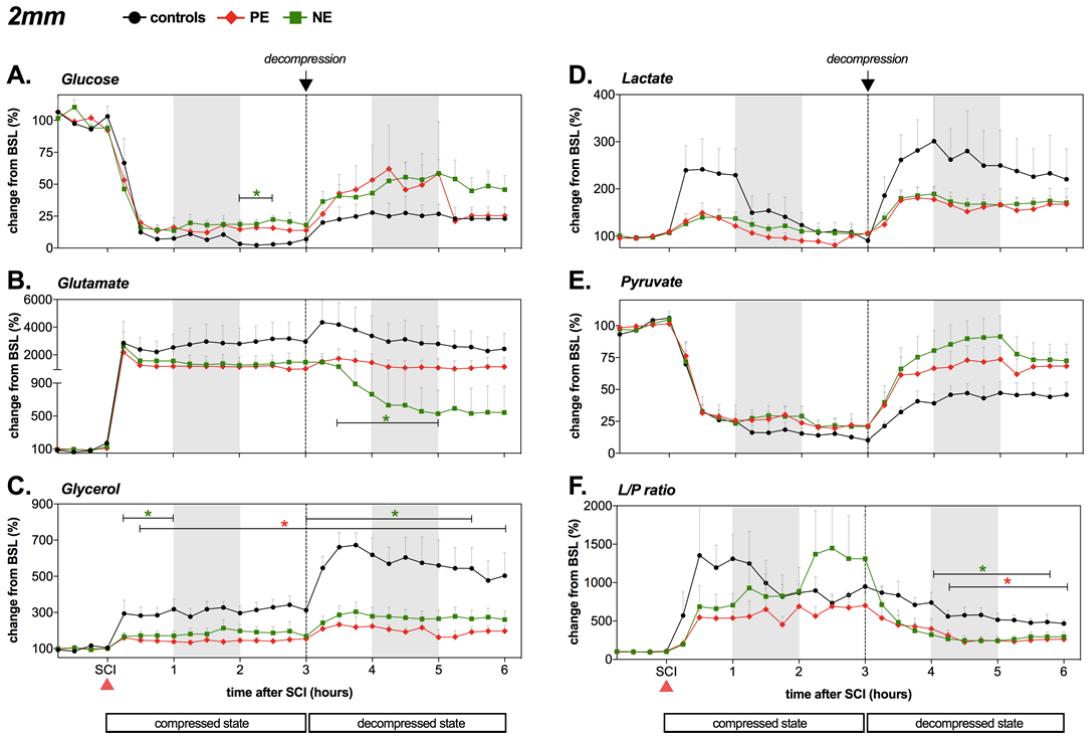

Figure 5. Effect of PE and NE infusion after SCI on microdialysis markers of cellular distress and energy metabolism (2-mm). The percentage change (%Δ) is calculated using an average of 60 minutes of baseline before SCI. (**A**) Glucose (B) glutamate (**C**) glycerol, (**D**) Lactate, (**E**) Pyruvate and (**F**) L/P ratio responses of 1-hour of vasopressor infusion (grey shading) during the compressed [0-3 hpi] and decompressed [3-6 hpi] state of the spinal cord. Decompresion time is shown by the vertical dashed line. Compared to the SCI-control group, glutamate values in the NE group were significantly ($p<0.05$) lower 0.5 hours after decompression and during the second NE infusion. For both the PE and NE group, the L/P ratio values were significantly lower 1.0 hour after decompression and onwards compared to control animals. Between the PE and NE groups, the response in L/P ratio was not significantly different at any time. Data is expressed as mean ± SEM. HPI: hours post-injury; NE; norepinephrine; PE: phenylephrine; SCI: spinal cord injury.

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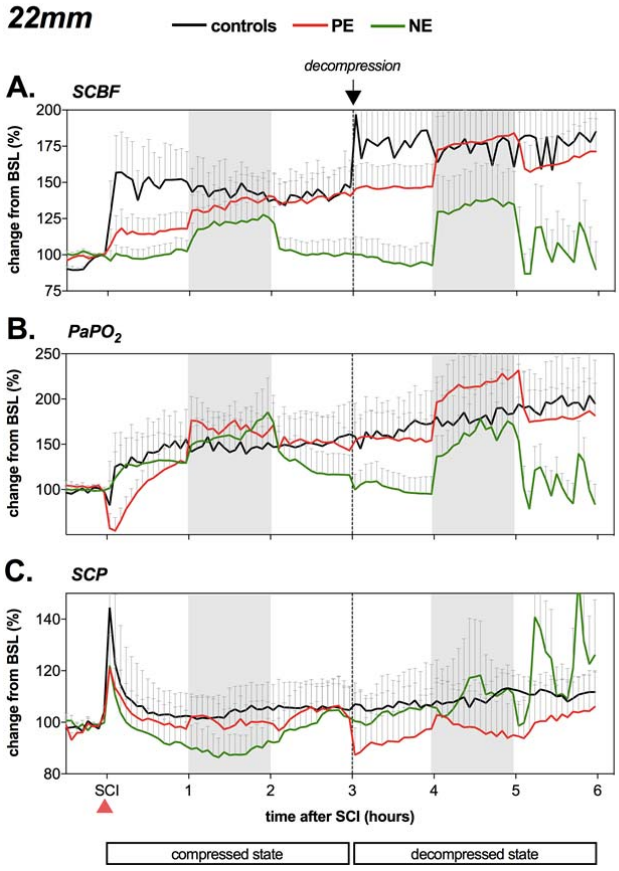

Figure 6. Effect of NE and PE infusion after SCI on blood flow, partial pressure of oxygen and pressure in the penumbra (22-mm). The percentage change (%Δ) is calculated using an average of 30 minutes of baseline before SCI. (**A**) Spinal cord blood flow (SCBF), (**B**) partial pressure of oxygen (PO_2) and (**C**) pressure responses during 1-hour of vasopressor infusion (grey shading) during the compressed [0-3 hpi] and decompressed [3-6 hpi] state of the spinal cord. Decompresion time is shown by the vertical dashed line. Both vasopressors increased SCBF and PO_2 above pre-injury levels. Notably, SCBF continued to rise in the PE group even after infusion was ceased. Data is expressed as mean ± SEM. HPI: hours post-injury; NE; norepinephrine; PE: phenylephrine; SCI: spinal cord injury.

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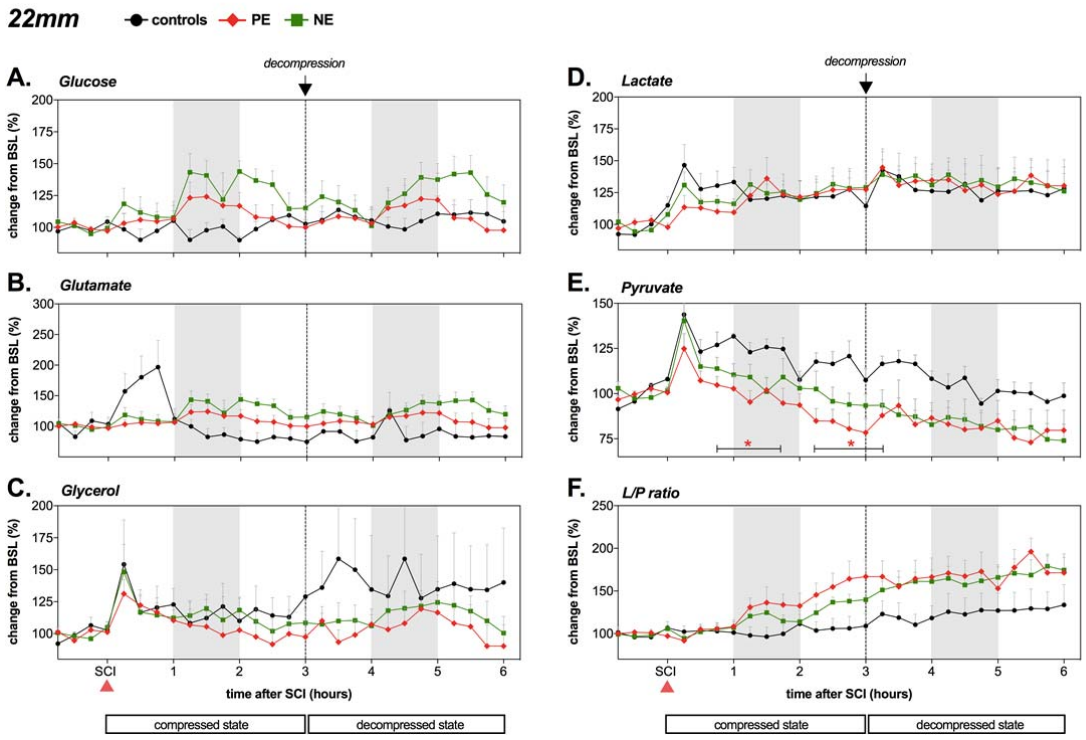

Figure 7. Effect of PE and NE infusion after SCI on microdialysis markers of cellular distress and energy metabolism (22-mm). The percentage change (%Δ) is calculated using an average of 60 minutes of baseline before SCI. (**A**) Glucose (B) glutamate (**C**) glycerol, (**D**) Lactate, (**E**) Pyruvate and (**F**) L/P ratio responses of 1-hour of vasopressor infusion (grey shading) during the compressed [0-3 hpi] and decompressed [3-6 hpi] state of the spinal cord. Decompresion time is shown by the vertical dashed line. The SCI-induced metabolic responses at the 22-mm position were far less pronounced compared to the 2-mm position. Between the experimental groups no significant differences were observed. Data is expressed as mean ± SEM. HPI: hours post-injury; NE; norepinephrine; PE: phenylephrine; SCI: spinal cord injury.

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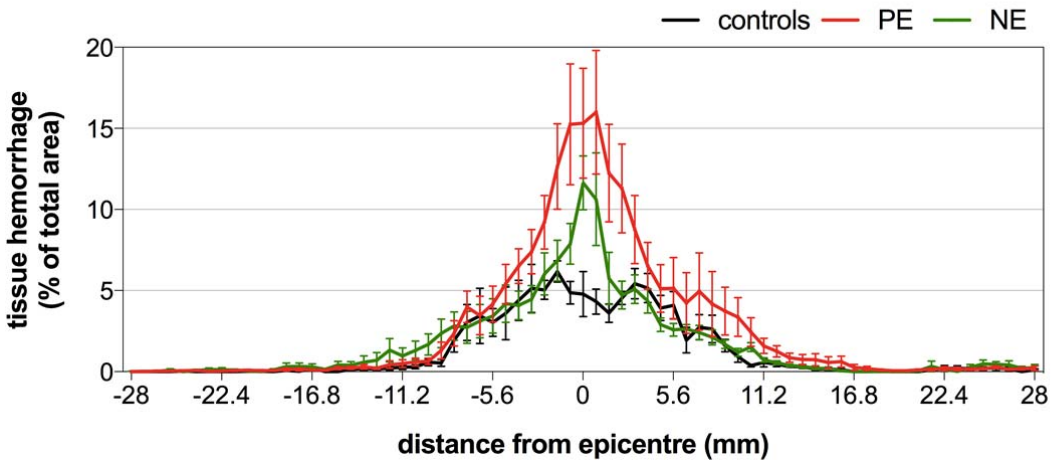

Figure 8. Effect of PE and NE infusion after SCI on spinal cord *hemorrhage*. Area measurements of hemorrhage were taken from axial sections of spinal cord tissue 800 μm apart, and represented here as the percentage (%) of each axial section measured. The PE group had significantly more hemorrhage than control animals ($p<0.05$) through the wider zone of injury (±16.8 mm) and also in the central zone immediately around the epicenter (±2.8 mm). The difference between NE and control was not statistically significant in either the wider or central zone of injury. Data is expressed as mean ± SEM.