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Early Cerebral Perfusion Pressure Augmentation with Phenylephrine after Traumatic Brain Injury may be Neuroprotective in a Pediatric Swine Model

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Abstract

Objective—Cerebral perfusion pressure (CPP) less than 40 mm Hg following pediatric traumatic brain injury (TBI) has been associated with increased mortality independent of age, and current guidelines recommend maintaining CPP between 40–60 mm Hg. Although adult TBI studies have observed an increased risk of complications associated with targeting a CPP > 70, we hypothesize that targeting a CPP of 70 mm Hg with the use of phenylephrine early after injury in the immature brain will be neuroprotective.

Design—Animals were randomly assigned to injury with CPP = 70 mm Hg (CPP70) or CPP = 40 mm Hg (CPP40). Diffuse TBI was produced by a single rapid rotation of the head in the axial plane. Cerebral microdialysis, brain tissue oxygen, intracranial pressure, and cerebral blood flow (CBF) were measured 30 min – 6 h post-injury. One hour after injury, CPP was manipulated with the vasoconstrictor phenylephrine. Animals were euthanized 6 h post-TBI, brains fixed, and stained to assess regions of cell injury and axonal dysfunction.

Setting—University center.

Subject—21 four week-old female swine.

Measurements and Main Results—Augmentation of CPP to 70 mm Hg resulted in no change in axonal dysfunction, but significantly smaller cell injury volumes at 6 hours post injury compared to CPP40 (1.1% vs. 7.4%, p < 0.05). Microdialysis lactate/pyruvate ratios were improved at CPP70 compared to CPP40. CBF was higher in the CPP70 group but did not reach statistical significance. Phenylephrine was well tolerated and there were no observed increases in serum lactate or intracranial pressure in either group.

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Work was performed at the University of Pennsylvania.

Conclusions—Targeting a CPP of 70 mm Hg resulted in a greater reduction in metabolic crisis and cell injury volumes compared to a CPP of 40 mm Hg in an immature swine model. Early aggressive CPP augmentation to a CPP of 70 mm Hg in pediatric TBI before severe intracranial hypertension has the potential to be neuroprotective, and further investigations are needed.

Keywords

pediatric head injury; cerebral perfusion pressure; phenylephrine; neuroprotection; swine; cerebral blood flow

INTRODUCTION

Early post-traumatic brain injury (TBI) cerebral hypoperfusion may greatly contribute to secondary brain injury, and therefore morbidity and mortality (1). Low cerebral blood flow (CBF) states have been demonstrated in children by xenon CT scans following TBI within 24 hours of the initial injury, but by 48 hours these patients had normal or supernormal blood flows (1). More recently, a retrospective study of children with severe TBI observed that poorer outcomes were correlated with early low CBF (2). A retrospective study of 146 pediatric TBI patients observed a strong association of poor outcome at discharge with hypotension within the first 6 hours of injury (3). The window for treatment of hypoperfusion appears to be early after pediatric TBI, and may be of relatively short duration in children.

Currently, pediatric cerebral perfusion pressure (CPP) thresholds used in the ICU environment (40–60 mmHg) have been extrapolated from adult experimental and clinical TBI and stroke studies (4–5). Chambers *et al.*, have published much needed age-specific pediatric thresholds for critical CPP, below which cerebral ischemia occurs with unfavorable neurologic outcomes and increased mortality (6–8). These studies identified inadequate CPP levels but did not identify an "optimal treatment" CPP, and therefore assumed that these CPP levels were equivalent to brain injury insult thresholds. Use of currently accepted pediatric CPP guidelines (CPP > 40 mm Hg) does not ensure adequate oxygen delivery to brain tissue (9–10). This raises the question: is a CPP > 40 mm Hg in the pediatric TBI patient high enough, and should this target CPP be modulated over time with a higher CPP set early after injury? Mild induced hypertension after ischemic stroke has shown promise in animal models but remains controversial in the clinical setting (11–12). Adult TBI studies have observed an increased risk of adult respiratory distress syndrome associated with targeting a CPP > 70 mm Hg, but it is unclear how applicable this is to the early resuscitation of the head-injured child (13–14).

Initial stabilization of the pediatric TBI patient may occur in limited resource environments where complex invasive intracranial monitoring may not be available. Early stabilization of cerebrovascular hemodynamics with a vasopressor, such as phenylephrine, and targeting a higher mean arterial pressure (MAP) or CPP may reduce brain injury and improve long-term outcomes. We have previously developed a novel critical care model of pediatric closed head injury that utilizes a large animal model to enable full clinical modalities used in neuro-intensive care (15). In this study, we tested the hypothesis that targeting a higher CPP (70 vs. 40 mm Hg) with the use of phenylephrine early after TBI in our immature swine model would be neuroprotective.

MATERIAL AND METHODS

Animal Preparation

All protocols were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. Four week-old female piglets whose brain development, myelination, and cerebrovascular responses correspond to the human toddler were studied (16–17). Piglets were anesthetized with an intramuscular injection of ketamine (20mg/kg) and xylazine (2 mg/kg) followed by inhaled 4% isoflurane. Vitals signs including heart rate, blood pressure, respiratory rate, end-tidal CO_2, pulse oximetry, and rectal temperature were monitored continuously and recorded every 15 minutes. Rectal temperature was maintained between 37.5 – 38.5 °C using a heating pad.

Piglets were orally intubated and mechanically ventilated (positive end expiratory pressure of 5 mm Hg, tidal volume 10–12 mL/kg). Femoral artery and venous catheters were placed for continuous MAP monitoring, arterial blood gas sampling, and intravenous (IV) fluid administration. Animals were administered 50 mcg/kg fentanyl IV, followed by a fentanyl infusion (50 mcg/kg/hr) and normal saline (4 mL/kg/hr) (18). Following initiation of the fentanyl infusion, isoflurane was reduced to 0.5–1%. Mechanical ventilation was adjusted to maintain end-tidal CO_2 between 35–40 mm Hg and fraction of inspired oxygen was maintained between 28–30%. Pre- and post-injury arterial blood gas samples were obtained hourly (Nova Biomedical, Waltham, MA) until euthanasia 6 hours after injury.

Non-impact rotational brain injury

Animals were randomized to either a goal CPP of 70 mm Hg (CPP70, N = 10), or 40 mm Hg (CPP40, N = 11). Animals experienced rapid axial head rotations without impact (angle rotation 90° over 10–12 msec) as described previously (19–21). Immediately prior to injury, isoflurane was discontinued. Angular velocity was measured using an angular rate sensor (ATA, Albuquerque, NM) attached to the linkage sidearm. After injury, mechanical ventilation was continued and latency to return of pinch reflex following injury was recorded and isoflurane 0.5–1% was resumed. The animal was removed from the bite-plate and placed in the prone position.

Neuromonitoring

After injury, four burr holes were prepared for placement of fiber-optic intracranial pressure monitor, brain tissue oxygen monitor, and microdialysis probe. The fiber-optic intracranial pressure probe (Integra, Plainsboro, NJ), was secured with a single lumen bolt. The Licox catheter system (Integra, Plainsboro, NJ) was placed to measure brain tissue oxygenation ($PbtO_2$). The brain tissue oxygen probe was inserted to a depth of 1.5 cm, secured with bone wax, and allowed to equilibrate for 30 minutes before values were recorded. A hyperoxia test was performed to confirm proper catheter placement. Data for intracranial pressure and $PbtO_2$ were recorded every 15 minutes until sacrifice.

A microdialysis probe (PAS 12, 4mm length, CMA, North Chelmsford, MA) was placed on the opposite side of the skull from the $PbtO_2$ catheter into subcortical white matter. Immediately after insertion, the probe was infused with sterile 0.9% NaCl at a rate of 1 μL/min. Dialysate samples were collected every 30 minutes until sacrifice and stored at −80 C and analyzed for lactate and pyruvate using a CMA600 analyzer (CMA, North Chelmsford, MA).

A CBF thermal diffusion probe (Hemedex, Cambridge, MA) was inserted to a depth of 1.5 cm in half of the animals in each group (CPP70 N = 5, CPP40 N = 6) and data was recorded every 15 minutes until sacrifice. A separate group of injured animals (INJ, N=5) and

instrumented shams (SHAM, N=4) underwent CBF monitoring as reference groups for CBF values without CPP modulation.

Cerebral Perfusion Modulation

There is limited data on the comparative effectiveness of commonly used vasopressors in adult and pediatric TBI. Phenylephrine has been reported to be the most commonly used vasopressor for CPP modulation after TBI in both adult and pediatric retrospective studies and was chosen for these studies (22–23). Due to the lack of data supporting or refuting targeting a CPP of 70 mm Hg in children or immature animals early after TBI, we designed our study to compare the accepted limits of the therapeutic range (40 mm Hg – 70 mm Hg). One hour after injury, phenylephrine infusions were initiated and titrated to goal CPP (either 40 or 70 mm Hg) until euthanasia 6 hours after injury.

Histology

At 6 hours post-injury, animals were sacrificed via an overdose of pentobarbital. Brains were perfusion-fixed, and two 6 μm sections were cut from every 3 mm block. Sections were stained with Hematoxylin and Eosin (H&E), or with the immunohistochemical markers for axonal injury beta-amyloid precursor protein (β-APP) (Chemicron 22C11 used at dilution of 1:5000) and counterstained with Meyer's hematoxylin. Areas of cell injury on H&E staining were identified by changes in staining intensity, and characterized by cell shrinkage and cytoplasmic eosinophilia (24). Regions of β–APP reactivity and cell injury were noted by a blinded neuropathologist and the locations of white matter damage and cell injury were traced in each slice using our previously described procedure to determine total area (15). Total and injured areas were multiplied by section thickness to determine total and injured brain volumes.

Statistical Analysis

Physiological, arterial blood gas, and neuromonitoring parameter (ICP, $PbtO_2$, microdialysis, CBF) data were analyzed across groups, and time using repeated measures ANOVA tests and Tukey-Kramer tests were used for post hoc analysis with significance defined as $P < 0.05$. Six hour values for LPR and $PbtO_2$ were compared to previously reported historical controls for injured and sham animals with ANOVA tests. Dunnett's tests were employed to determine statistical significance of physiological data and intracranial monitoring values pre-and post-administration of phenylephrine. Neuropathology comparisons between groups were analyzed using Student's t-test. All values are expressed as mean ± the standard error of the mean. A post-hoc power analysis was performed. Based on our previous results in injured animals, to detect a 3% difference in injury volumes with 80% power, a total of 20 animals (10 in each group) would be required (15).

RESULTS

Injury and Physiological Data

Angular peak velocity was similar between the two groups (CPP70, 171.7 ± 3.3 rad/s vs. CPP40 170.2 ± 2.1 rad/s, p = 0.77). Average unconscious time (return of pinch reflex) was also similar between the two groups (CPP70, 15.4 ± 2.5 min vs. CPP40 15.7 ± 1.9 min, p = 0.81). Physiological and arterial blood gas data for CPP40 and CPP70 are shown in Table 1 and 2 respectively. MAP was significantly higher in CPP70 after initiation of phenylephrine one hour after injury, but there were no observed increases in arterial lactate levels due to phenylephrine administration (Table 2). Of note, we observed a baseline metabolic alkalosis in our animals (consistent with previous reports) and adjusted our goal $PaCO_2$ to 40–45 mm Hg (25). Phenylephrine dosing requirements for CPP70 were significantly higher compared

to CPP40 (Table 3), but no significant changes in ICP were noted in either group after the initiation of phenylephrine (Figure 1). CPP was significantly higher for CPP70 compared to CPP40, and goal CPP was achieved and maintained in both groups (Figure 2).

Intracranial Monitoring

In order to assess temporal responses to CPP modulation, we measured $PbtO_2$, microdialysate lactate pyruvate ratios (LPR) as a measure of cellular metabolism, and CBF. $PbtO_2$ was higher for CPP70 compared to CPP40 after the initiation of phenylephrine but did not reach statistical significance (Figure 3). $PbtO_2$ responded to CPP modulation and was significantly higher during the post-injury interval of 2–6 hours compared to initial values measured within 1 hour of injury in CPP70, and during the post-injury interval of 3.5–5 hours in CPP40 (Figure 3).

After initiation of phenylephrine, CPP70 had significantly lower LPR compared to CPP40 $p < 0.05$ (Figure 4). CPP modulation to 70 mm Hg resulted in significantly lower LPR levels during the post-injury interval 2–6 hours compared to initial values measured within 1 hour of injury. There was no correlation between serum and microdialysate lactate levels.

Repeated measures ANOVA analysis of CBF revealed significant group, time, and group*time effects (Figure 5) ($p < 0.05$). Subsequent Tukey-Kramer analysis demonstrated CBF for CPP70 was significantly higher compared to INJ ($p < 0.05$). CPP40 CBF was lower than CPP70 after phenylephrine initiation but did not reach statistical significance. Dunnett's test for CPP70 demonstrated significantly higher CBF during the post-injury interval 1.5–6 hours compared to initial post-injury values. Similarly, CP40 CBF was higher during post-injury interval 3–5 hours compared to initial post-injury values.

Neuropathology

Neuropathology revealed regions of injury predominantly in the frontal and parietal lobes. Traumatic axonal injury volumes at 6 hours post injury as determined by β-APP immunohistochemistry were not different between the 2 groups (Figure 6). Cell injury volumes determined by H&E were significantly larger in CPP40 compared to CPP70 (Figure 6). Regions of cell injury were predominantly observed in cortical regions of the frontal lobes.

DISCUSSION

In the present study, the objective was to use our previously described clinically relevant large animal model of pediatric neurocritical care to evaluate early CPP augmentation with phenylephrine following non-impact inertial head injury (15). Our immature swine model has the advantage of similar brain structure and development as the pediatric brain, and the brain size can accommodate neuromonitoring equipment utilized in the pediatric intensive care unit. Since there is currently no data supporting or refuting utilizing a CPP of 70 mm Hg in children or immature animals early after TBI, we chose to compare the accepted limits of the therapeutic range (40 mm Hg – 70 mm Hg).

Physiologic effects of phenylephrine

Phenylephrine infusions were successfully titrated to reach goal CPP. The larger dosing of phenylephrine required to achieve the higher CPP was well tolerated without signs of systemic tissue hypoperfusion (arterial lactate levels, Table 2), although animals were only exposed to phenylephrine for 5 hours. Heart rates of animals in both groups gradually increased over the 6 hour observation period, which we believe is due to the known tachycardia associated with fentanyl infusions in immature swine and not attributable to

phenylephrine (26). Previous studies in adult swine reported worsening pulmonary edema with phenylephrine administration for CPP support (27), but we did not observe any changes in PaO_2 or FiO_2 requirements. Peak MAPs achieved in the CPP70 group were within the normal range of awake immature swine (25). Phenylephrine requirements to maintain goal CPP were higher than typically observed in children but lower than reported in adult swine models of TBI and hemorrhagic shock (28–29). These differences may be due to our use of volatile anesthetics, the age of the animals, and/or variations in pharmacodynamics of phenylephrine across species.

Early phenylephrine titration to higher CPP reduces cell injury

Our model tests whether early relative hypoperfusion contributes to the severity of secondary brain injury *before* significant intracranial hypertension is observed. In our model, animals had only mild intracranial hypertension in the early hours after injury; however we observed significant areas of cell injury on H&E examination. Manipulation of CPP from 40 to 70 mm Hg resulted in significantly lower cell injury volumes, but there were no differences in traumatic axonal injury volumes as assessed by β-APP immunohistochemistry. We hypothesize that these areas of cell injury we observed and reported previously result from decreased perfusion and metabolic crisis in specific cortical regions (15), correlating well with the regions affected in children with TBI undergoing long term follow-up (30).

CPP augmentation with phenylephrine improves PbtO$_2$ following non-impact inertial head injury

Phenylephrine infusions significantly improved $PbtO_2$ in both groups. There are several possible explanations for the lack of significant difference between the two groups. $PbtO_2$ is a small regional measurement, and in our model, probes were inserted to a depth of 1.5 cm into the subcortical white matter of the frontal lobe. In these regions we observed no difference in axonal injury by β-APP immunohistochemistry between groups. However, differences in injury volumes between the groups were observed on H&E examination in regions closer to the brain surface away from the region of $PbtO_2$ detection in our model. Increased $PbtO_2$ in regions of injury may represent an improvement in oxygen delivery, lower oxygen utilization due to altered cellular metabolism, or a combination of both. The fidelity of $PbtO_2$ monitoring is probably insufficient to be used as a single marker to detect or describe all the effects of early CPP modulation on the reduction of secondary brain injury.

CPP augmentation to 70 mm Hg early after injury improves brain cellular metabolism

Cellular metabolism as measured by cerebral microdialysis LPR was significantly improved in CPP70 compared to CPP40. This would suggest an increase in substrate delivery with aggressive CPP augmentation. Microdialysis sampling can create concentration gradients which extends the region of brain tissue being measured several millimeters out from the probe site (31). This is much further than $PbtO_2$, which may explain the lack of statistical significance of our $PbtO_2$ measurements between the two groups. Our findings of improvement in LPR with CPP augmentation are contrary to findings observed in the pericontusional tissue of adult head injured patients (32), but the pathophysiology and response to rises in mean arterial pressure may differ in a non-impact diffuse injury model.

Phenylephrine improves CBF following non-impact head injury

Previous TBI studies in swine and humans have demonstrated improvement in $PbtO_2$ after CPP augmentation but have not directly measured CBF (29, 33). Utilizing a thermal diffusion probe placed in the subcortical white matter, we were able to record repeated

measurements of quantitative CBF over time. Along with improvement in $PbtO_2$ and cellular metabolism, we observed significant increases in quantitative CBF. These increases in CBF were not associated with increases in ICP, which has been previously reported in a rat model (34). Targeting a CPP of 70 mm Hg resulted in higher CBF with values approaching CBF levels in anesthetized uninjured animals. It should be noted that the observed average $PaCO_2$ was slightly higher than current recommended guidelines, which may alter CBF, although there were no statistical differences in $PaCO_2$ between the groups. We conclude CPP augmentation with phenylephrine *early* after TBI in an immature swine model increases CBF, correcting hypoperfusion, reducing cellular metabolic crisis, improving $PbtO_2$, and results in a reduction in cell injury volumes.

Limitations of the study

There are several limitations to our experimental design which must be considered when translating our results to the care of the pediatric patient with TBI. First, our model of non-impact inertial head injury does not encompass the complete heterogeneity of pediatric TBI, specifically focal contusions. The pathophysiology and responses to CPP augmentation in uninjured, peri-contusional, and "core" contusion brain tissue may differ to what we have observed in our diffuse injury model. Second, the effects of volatile anesthetics on cerebral autoregulation and neuroprotection are well described, and may influence phenylephrine's effects on CBF and cell injury volumes (35–36). We are currently developing an anesthetic plan for our model which avoids inhaled anesthetics and mimics sedation typically utilized in the pediatric intensive care unit. Third, although we did not observe changes in arterial oxygenation, ICP, or serum lactate with phenylephrine administration, brain and lung water content were not measured. Increases in lung water content after phenylephrine administration for CPP augmentation have been reported in adult swine (27). It is unclear if immature swine have different phenylephrine pharmacodynamics and toxicity tolerances. Fourth, the observation period was only a total of 6 hours after injury, limiting our outcome measures to multi-modal intracranial monitoring and acute neuropathology and lacking neurobehavioral functional outcomes. In future studies we plan to develop longer survival times and apply our previously developed neurobehavioral outcome measures (19, 37). Pediatric TBI patients may need vasopressor support for several days after injury, and it is still unclear whether CPP augmentation with vasopressors and target CPP should change as the injury evolves over time. Fifth, we chose a relatively short delay in administration of phenylephrine after injury, and further investigations are needed to examine the length of the therapeutic window. Sixth, we only utilized female swine in our study. Sex-dependent differences in the response of CBF autoregulation to phenylephrine administration after TBI have been reported in swine, and our results may not be generalizable to male swine (38–39). Future studies to examine the role of sex in our non-impact head injury model are planned. Seventh, there are a multitude of approaches to the augmentation of CPP; including different vasopressors, colloid and crystalloid administration, and hyperosmolar therapy. We chose phenylephrine since it is a commonly used vasopressor in pediatric TBI (23). Future studies will evaluate other means of CPP augmentation. Finally, we chose to study only two target CPP levels, a CPP of 40 and 70 mm Hg which are at or beyond the extremes of current guideline recommendations (40). It is possible that a CPP between these two groups may effectively reduce metabolic crisis, improve CBF, and reduce cell injury, with less risk of systemic side effects.

CONCLUSION

In our swine model of pediatric closed head injury we observe early derangements in CBF, $PbtO_2$, cellular metabolism, and acute neuropathology. Early administration of phenylephrine improved cerebral metabolism, CBF and $PbtO_2$. Targeting a CPP of 70 mm

Hg resulted in a greater reduction in metabolic crisis and cell injury volumes compared to a CPP of 40 mm Hg, but did not result in statistically significant differences in CBF and $PbtO_2$ in a swine model of pediatric TBI. Early aggressive CPP augmentation to a CPP of 70 mm Hg in pediatric TBI before severe intracranial hypertension may be neuroprotective, and further investigations are needed.

Acknowledgments

REFERENCES

1. Adelson PD, Clyde B, Kochanek PM, et al. Cerebrovascular response in infants and young children following severe traumatic brain injury: A preliminary report. Pediatric Neurosurgery. 1997; 26:200–207. [PubMed: 9436831]

2. Adelson PD, Srinivas R, Chang Y, et al. Cerebrovascular response in children following severe traumatic brain injury. Childs Nerv Syst. 2011; 27(9):1465–1476. [PubMed: 21559825]

3. Samant, UBt; Mack, CD.; Koepsell, T., et al. Time of hypotension and discharge outcome in children with severe traumatic brain injury. J Neurotrauma. 2008; 25(5):495–502. [PubMed: 18419252]

4. Cunningham AS, Salvador R, Coles JP, et al. Physiological thresholds for irreversible tissue damage in contusional regions following traumatic brain injury. Brain. 2005; 128:1931–1942. [PubMed: 15888537]

5. Jackson S, Piper IR. A study of the effects of using different cerebral perfusion pressure (CPP) thresholds to quantify CPP "secondary insults" in children. Acta Neurochir Suppl. 2000; 76:453–456. [PubMed: 11450066]

6. Chambers IR, Jones PA, Lo TY, et al. Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury. J Neurol Neurosurg Psychiatry. 2006; 77(2):234–240. [PubMed: 16103043]

7. Chambers IR, Stobbart L, Jones PA, et al. Age-related differences in intracranial pressure and cerebral perfusion pressure in the first 6 hours of monitoring after children's head injury: association with outcome. Childs Nerv Syst. 2005; 21(3):195–199. [PubMed: 15580513]

8. Chambers IR, Kirkham FJ. What is the optimal cerebral perfusion pressure in children suffering from traumatic coma? Neurosurg Focus. 2003; 15(6):E3. [PubMed: 15305839]

9. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg. 2005; 103:805–811. [PubMed: 16304983]

10. Stiefel MF, Udoetuk JD, Storm PB, et al. Brain tissue oxygen monitoring in pediatric patients with severe traumatic brain injury. J Neurosurg. 2006; 105(4 Suppl):281–286. [PubMed: 17328278]

11. Llinas RH. Ischemic stroke and ICU care. Semin Neurol. 2008; 28(5):645–656. [PubMed: 19115171]

12. Broderick JP, Hacke W. Treatment of acute ischemic stroke: Part II: neuroprotection and medical management. Circulation. 2002; 106(13):1736–1740. [PubMed: 12270871]

13. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. Crit Care Med. 1999; 27(10):2086–2095. [PubMed: 10548187]

14. Contant CF, Valadka AB, Gopinath SP, et al. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. J Neurosurg. 2001; 95(4):560–568. [PubMed: 11596949]

15. Friess SH, Ralston J, Eucker SA, et al. Neurocritical care monitoring correlates with neuropathology in a Swine model of pediatric traumatic brain injury. Neurosurgery. 2011; 69(5): 1139–1147. [PubMed: 21670716]

16. Duhaime AC, Margulies SS, Durham SR, et al. Maturation-dependent response of the piglet brain to scaled cortical impact. J Neurosurg. 2000; 93(3):455–462. [PubMed: 10969944]

17. Winter JD, Dorner S, Lukovic J, et al. Noninvasive MRI measures of microstructural and cerebrovascular changes during normal swine brain development. Pediatr Res. 2011; 69(5 Pt 1): 418–424. [PubMed: 21258264]

18. Swindle, MM. Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques. Boca Raton: CRC Press; 2007.

19. Friess SH, Ichord RN, Owens K, et al. Neurobehavioral functional deficits following closed head injury in the neonatal pig. Exp Neurol. 2007; 204(1):234–243. [PubMed: 17174304]

20. Raghupathi R, Margulies SS. Traumatic axonal injury after closed head injury in the neonatal pig. J Neurotrauma. 2002; 19:843–853. [PubMed: 12184854]

21. Raghupathi R, Mehr MF, Helfaer MA, et al. Traumatic axonal injury is exacerbated following repetitive closed head injury in the neonatal pig. J Neurotrauma. 2004; 21(3):307–316. [PubMed: 15115605]

22. Sookplung P, Siriussawakul A, Malakouti A, et al. Vasopressor use and effect on blood pressure after severe adult traumatic brain injury. Neurocrit Care. 2011; 15(1):46–54. [PubMed: 20878264]

23. Di Gennaro JL, Mack CD, Malakouti A, et al. Use and effect of vasopressors after pediatric traumatic brain injury. Dev Neurosci. 2010; 32(5–6):420–430. [PubMed: 21124016]

24. Eucker SA, Smith C, Ralston J, et al. Physiological and histopathological responses following closed rotational head injury depend on direction of head motion. Exp Neurol. 2010

25. Hannon JP, Bossone CA, Wade CE. Normal physiological values for conscious pigs used in biomedical research. Lab Anim Sci. 1990; 40(3):293–298. [PubMed: 2162986]

26. Rajan V, Beharry KD, Williams P, et al. Pharmacodynamic effects and pharmacokinetic profile of continuous infusion fentanyl in newborn piglets. Biol Neonate. 1998; 74(1):39–47. [PubMed: 9657668]

27. Malhotra AK, Schweitzer JB, Fox JL, et al. Cerebral perfusion pressure directed therapy following traumatic brain injury and hypotension in swine. J Neurotrauma. 2003; 20(9):827–839. [PubMed: 14577861]

28. Armstead WM, Kiessling W, Riley J, et al. Phenylephrine Infusion Prevents Impairment of ATP and Calcium Sensitive K Channel Mediated Cerebrovasodilation After Brain Injury in Female But Aggravates Impairment in Male Piglets Through Modulation of ERK MAPK Upregulation. J Neurotrauma. 2010

29. Dudkiewicz M, Proctor KG. Tissue oxygenation during management of cerebral perfusion pressure with phenylephrine or vasopressin. Crit Care Med. 2008; 36(9):2641–2650. [PubMed: 18679110]

30. Slawik H, Salmond CH, Taylor-Tavares JV, et al. Frontal cerebral vulnerability and executive deficits from raised intracranial pressure in child traumatic brain injury. J Neurotrauma. 2009; 26(11):1891–1903. [PubMed: 19929215]

31. Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. J Neurotrauma. 2005; 22(1):3–41. [PubMed: 15665601]

32. Nordstrom CH. Assessment of critical thresholds for cerebral perfusion pressure by performing bedside monitoring of cerebral energy metabolism. Neurosurg Focus. 2003; 15(6):E5. [PubMed: 15305841]

33. Johnston AJ, Steiner LA, Coles JP, et al. Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. Crit Care Med. 2005; 33(1):189–195. discussion 255-187. [PubMed: 15644668]

34. Cherian L, Chacko G, Goodman JC, et al. Cerebral hemodynamic effects of phenylephrine and L-arginine after cortical impact injury. Crit Care Med. 1999; 27(11):2512–2517. [PubMed: 10579273]

35. De Cosmo G, Cancelli I, Adduci A, et al. Changes in hemodynamics during isoflurane and propofol anesthesia: a comparison study. Neurol Res. 2005; 27(4):433–435. [PubMed: 15949243]

36. Bedforth NM, Girling KJ, Skinner HJ, et al. Effects of desflurane on cerebral autoregulation. Br J Anaesth. 2001; 87(2):193–197. [PubMed: 11493488]

37. Friess SH, Ichord RN, Ralston J, et al. Repeated traumatic brain injury affects composite cognitive function in piglets. J Neurotrauma. 2009

38. Armstead WM, Kiessling JW, Kofke WA, et al. Impaired cerebral blood flow autoregulation during posttraumatic arterial hypotension after fluid percussion brain injury is prevented by phenylephrine in female but exacerbated in male piglets by extracellular signal-related kinase mitogen-activated protein kinase upregulation. Crit Care Med. 2010; 38(9):1868–1874. [PubMed: 20562700]

39. Armstead WM, Kiessling JW, Kofke WA, et al. SNP improves cerebral hemodynamics during normotension but fails to prevent sex dependent impaired cerebral autoregulation during hypotension after brain injury. Brain Res. 2010; 1330:142–150. [PubMed: 20298682]

40. Kochanek PM, Carney N, Adelson PD, et al. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents--second edition. Pediatr Crit Care Med. 2012; 13(Suppl 1):S1–S82. [PubMed: 22217782]
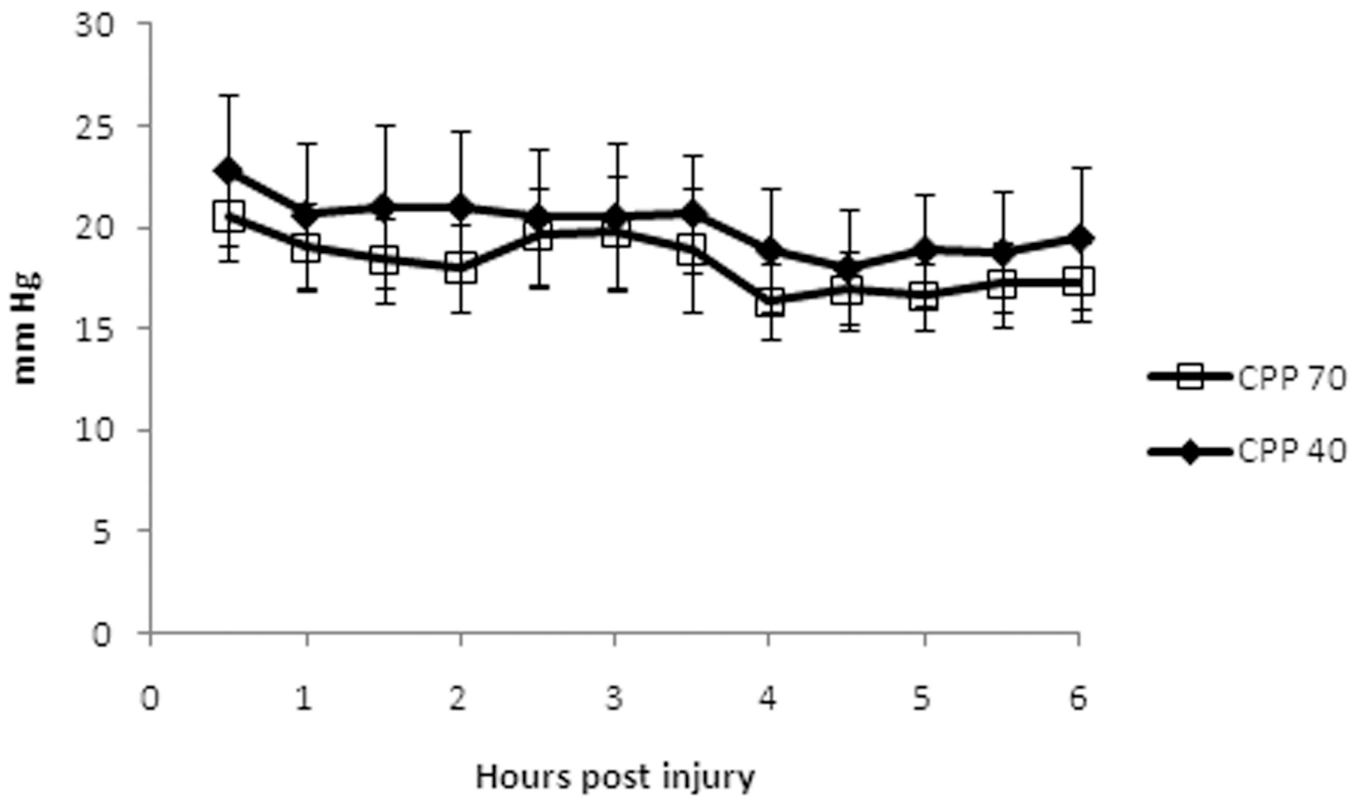
Figure 1.
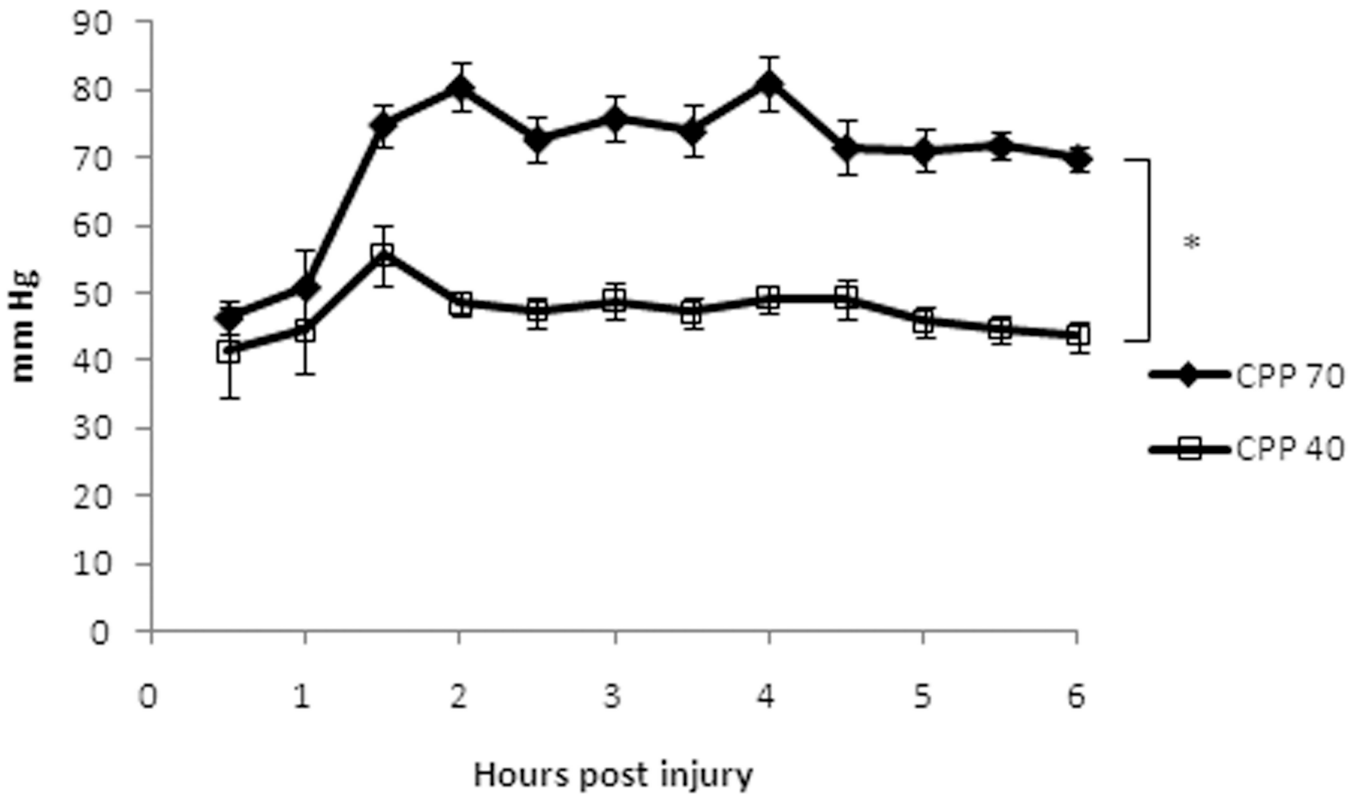Intracranial pressure over time. Phenylephrine was initiated at 1 hour post injury.

Figure 2.
Cerebral pressure over time. Phenylephrine was initiated at 1 hour post injury. (*$P < 0.05$).
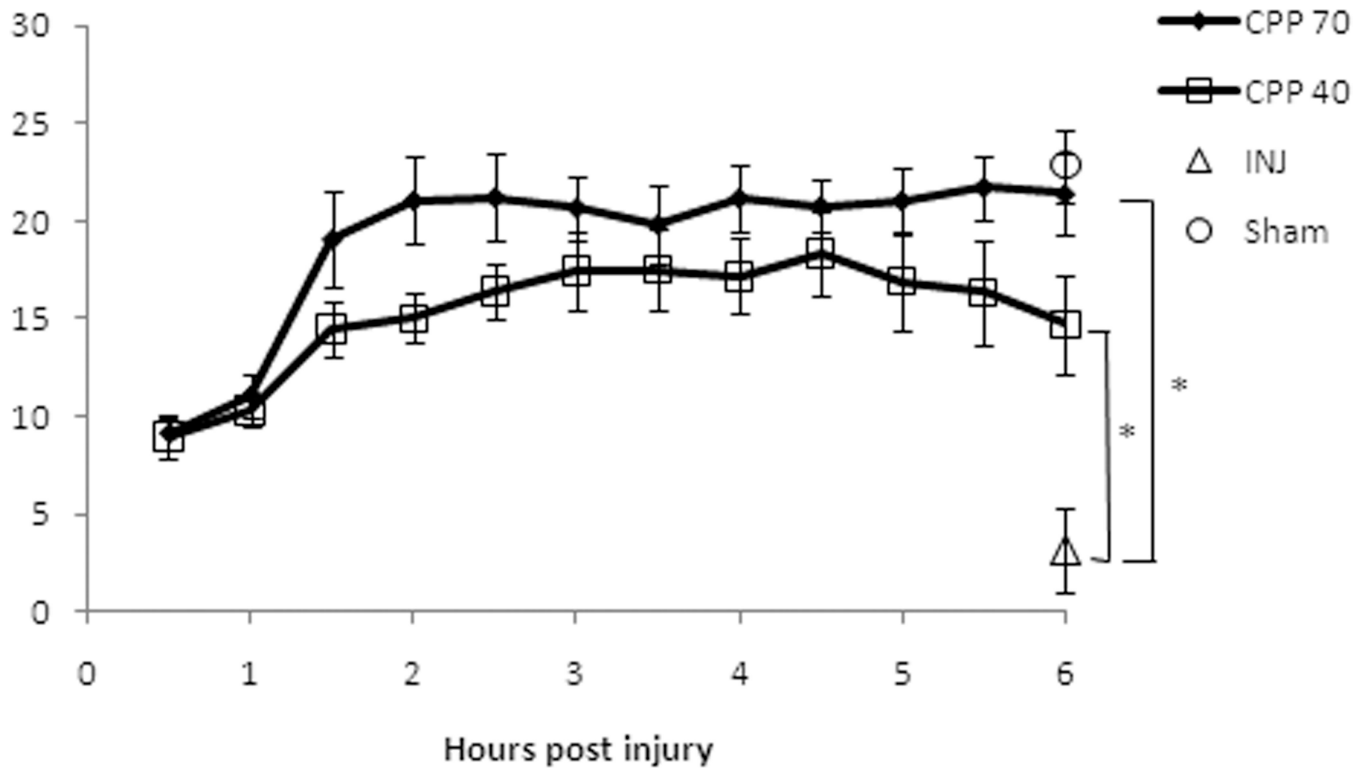
Figure 3.
Brain tissue oxygenation (PbtO$_2$) over time. (* *P* < 0.05 for overall group means). INJ, injured animals without phenylephrine support; Sham, instrumented uninjured shams previously reported (15).

Figure 4.
Lactate-pyruvate ratio (LPR) over time. (* *P* < 0.05 for overall group means). INJ, injured animals without phenylephrine support; Sham, instrumented uninjured shams previously reported (15).
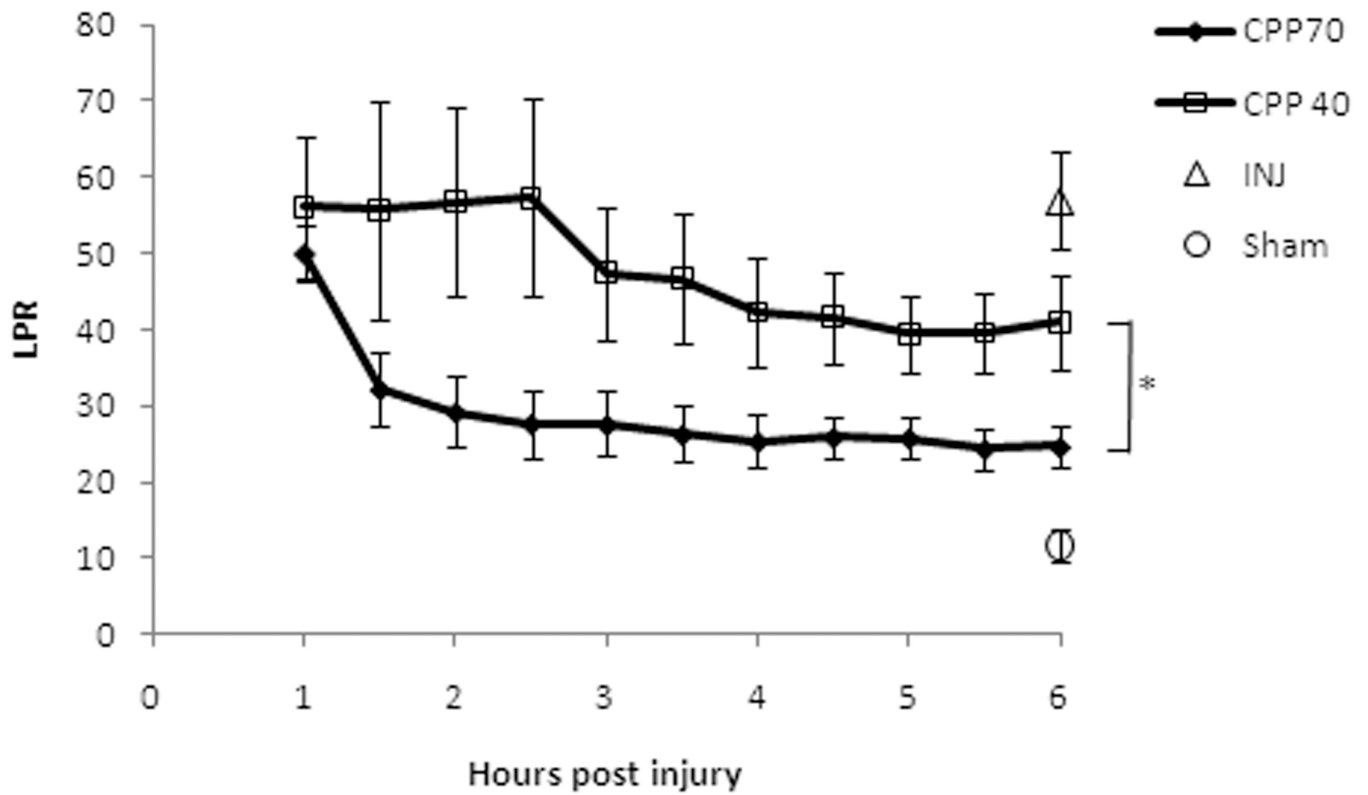
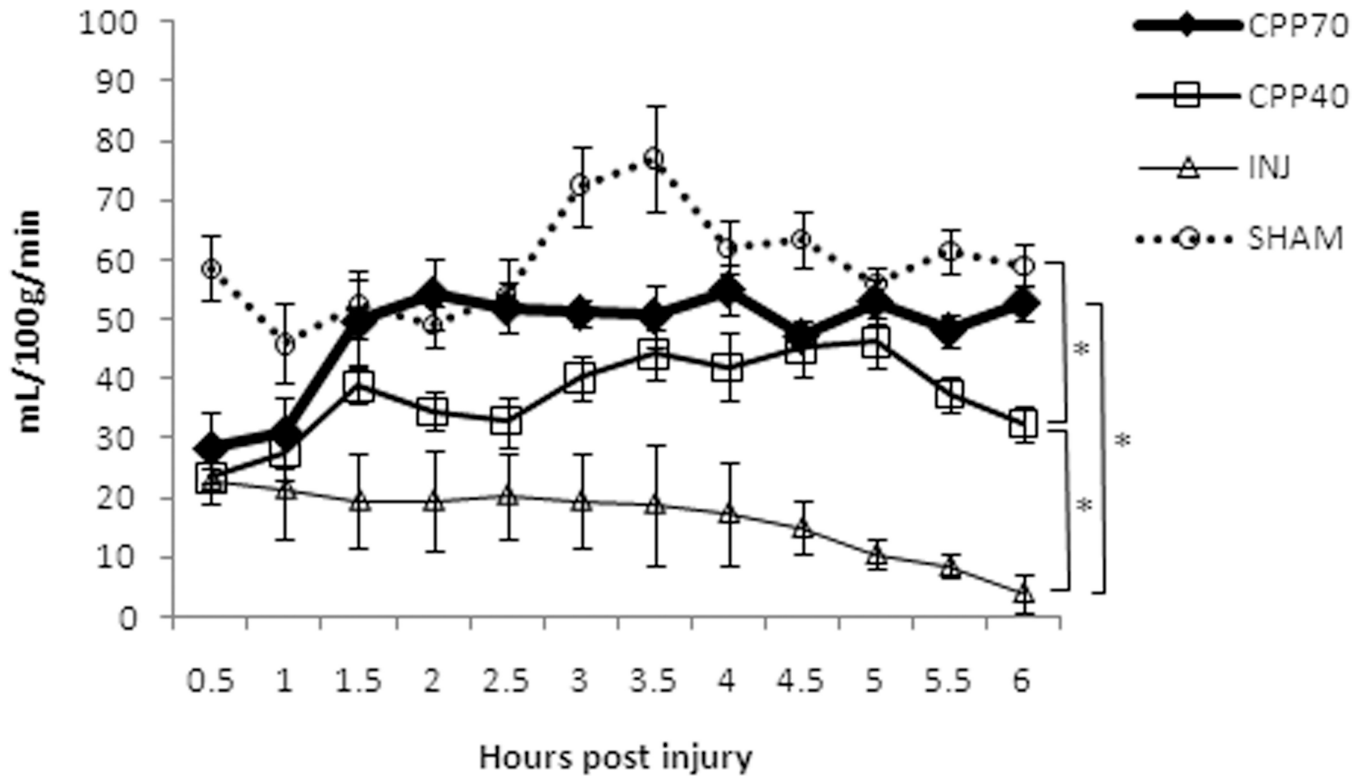**Figure 5.**
Cerebral blood flow (CBF) over time. Two additional groups of animals were analyzed, injured animals without CPP modulation (INJ, N=5) and instrumented shams (SHAM, N=4). (*$P < 0.05$ at 6 hours post injury).
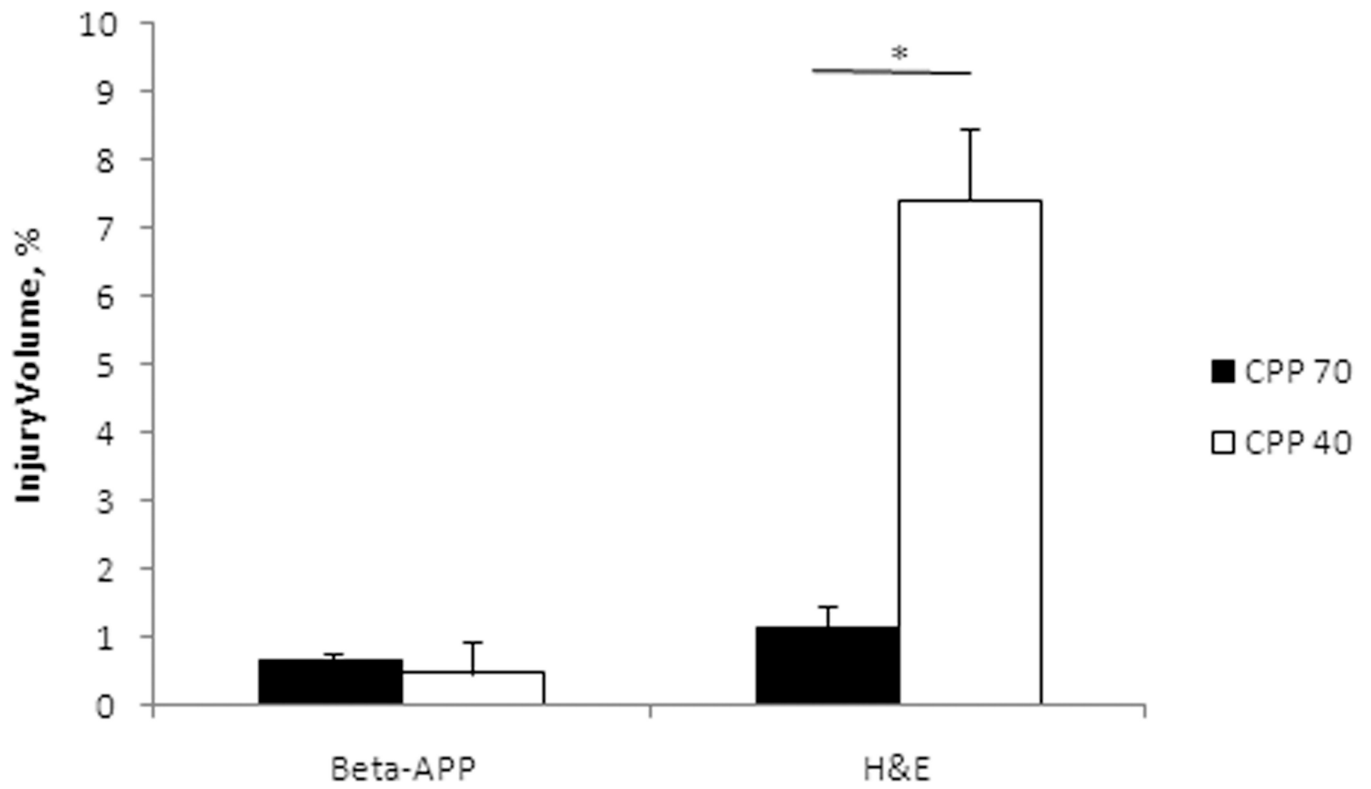
Figure 6.
Traumatic axonal injury volumes determined by β-APP immunohistochemistry and cell
injury volumes determined by H&E at 6 hours post injury. (*P < 0.05).

Table 1

Physiological Data

Physiological data pre-injury, 1 hour, 3 hours, and 6 hours post-injury.

Parameter	CPP 40	CPP 70
Heart Rate (beats/min)		
Baseline	108 ± 12	106 ± 10
1 hour	115 ± 11	100 ± 12
3 hour	120 ± 9	103 ± 13
6 hour	136 ± 12	136 ± 11
MAP (mm Hg)		
Baseline	69 ± 8	68 ± 9
1 hour	66 ± 12	73 ± 6
3 hour	70 ± 9	93 ± 5 *
6 hour	62 ± 11	87 ± 4 *
Temperature (°C)		
Baseline	36.4 ± 0.5	36.4 ± 0.5
1 hour	36.8 ± 0.4	36.8 ± 0.6
3 hour	37.2 ± 0.6	37.6 ± 0.6
6 hour	37.2 ± 0.6	37.6 ± 0.5

(MAP) mean arterial pressure.

*
denotes statistically significant difference compared to CPP 40, $P < 0.001$ with Tukey-Kramer post-hoc analysis. ± standard deviation

Table 2

Arterial Blood Gas Values

Arterial blood gas data pre-injury, 1 hour, 3 hours and 6 hours post-injury.

Parameter	CPP 40	CPP 70
pH		
Baseline	7.55 ± 0.03	7.54 ± 0.05
1 hour	7.51 ± 0.05	7.46 ± 0.05
3 hour	7.48 ± 0.05	7.49 ± 0.03
6 hour	7.51 ± 0.06	7.51 ± 0.03
$PaCO_2$ (torr)		
Baseline	43.8 ± 2.1	44.8 ± 4.1
1 hour	46.1 ± 4.5	51.3 ± 2.4
3 hour	48.7 ± 3.1	47.1 ± 3.5
6 hour	45.2 ± 2.9	47.7 ± 3.3
PaO_2 (torr)		
Baseline	143.5 ± 17.1	140.1 ± 19.3
1 hour	138.1 ± 10.6	134.0 ± 15.1
3 hour	129.6 ± 12.3	134.2 ± 13.4
6 hour	132.5 ± 14.8	131.4 ± 15.2
Lactate (mmol/L)		
Baseline	1.0 ± 0.3	1.0 ± 0.3
1 hour	1.6 ± 0.3	1.3 ± 0.2
3 hour	1.0 ± 0.2	0.9 ± 0.1
6 hour	1.2 ± 0.3	0.9 ± 0.2
Sodium (mmol/L)		
Baseline	138.9 ± 4.1	141.1 ± 3.5
1 hour	138.5 ± 3.6	141.1 ± 3.9
3 hour	140.2 ± 3.4	139.7 ± 2.3
6 hour	137.6 ± 2.3	138.4 ± 2.5
Glucose (mg/dL)		
Baseline	77 ± 6	82 ± 10
1 hour	120 ± 10	130 ± 16
3 hour	109 ± 12	116 ± 17
6 hour	82 ± 4	84 ± 5

± standard deviation.

Table 3

Phenylephrine dosing and cerebral hemodynamics, 2, 4, and 6 hours post-injury.

Parameter	CPP 40	CPP 70
Phenylephrine (mcg/kg/min)		
2 hour	0.5 ± 0.3	2.3 ± 1.5[*]
4 hour	0.6 ± 0.4	2.9 ± 1.3[*]
6 hour	0.5 ± 0.2	3.3 ± 0.9[*]
ICP (mm Hg)		
1 hour	20 ± 3	20 ± 4
2 hour	20 ± 4	19 ± 4
4 hour	20 ± 5	18 ± 4
6 hour	19 ± 4	18 ± 3
CPP (mm Hg)		
1 hour	44 ± 6	45 ± 6
2 hour	48 ± 4	75 ± 4[*]
4 hour	49 ± 5	79 ± 5[*]
6 hour	47 ± 4	71 ± 4[*]

(ICP) intracranial pressure, (CPP) cerebral perfusion pressure.

[*] denotes statistically significant difference compared to CPP 40, $P < 0.01$ with Tukey-Kramer post-hoc analysis. ± standard deviation