

Effect of Internal Jugular Vein Compression on Intracranial Hemorrhage in a Porcine Controlled Cortical Impact Model

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Abstract

Internal jugular vein (IJV) compression has been shown to reduce axonal injury in pre-clinical traumatic brain injury (TBI) models and clinical concussion studies. However, this novel approach to prophylactically mitigating TBI through venous congestion raises concerns of increasing the propensity for hemorrhage and hemorrhagic propagation. This study aims to test the safety of IJV compression in a large animal controlled cortical impact (CCI) injury model and the resultant effects on hemorrhage. Twelve swine were randomized to placement of a bilateral IJV compression collar (CCI+collar) or control/no collar (CCI) prior to CCI injury. A histological grading of the extent of hemorrhage, both subarachnoid (SAH) and intraparenchymal (IPH), was conducted in a blinded manner by two neuropathologists. Other various measures of TBI histology were also analyzed including: β -amyloid precursor protein (β -APP) expression, presence of degenerating neurons, extent of cerebral edema, and inflammatory infiltrates. Euthanized 5 h after injury, the CCI+collar animals exhibited a significant reduction in total SAH ($p=0.024-0.026$) and IPH scores ($p=0.03-0.05$) compared with the CCI animals. There was no statistically significant difference in scoring for the other markers of TBI (β -APP, neuronal degeneration, cerebral edema, or inflammatory infiltration). In conclusion, IJV compression was shown to reduce hemorrhage (SAH and IPH) in the porcine CCI model when applied prior to injury. These results suggest the role of IJV compression for mitigation of not only axonal, but also hemorrhagic injury following TBI.

Key words: animal studies; CCI; head trauma; SAH; TBI

Introduction

AN ESTIMATED 1,600,000–3,800,000 sports-related concussions occur annually.¹ Despite improved technology, safety measures, and protective equipment, there are no current measures that alter the rotational/angular force that is applied directly to the brain during a concussive injury.

A concussion is caused by acceleration of the head leading to relative motion of the brain parenchyma and intracranial fluids within the skull.² This motion in concert with the viscoelastic nature of the brain causes macroscopic injury from stretching and tearing of bridging and intraparenchymal blood vessels, parenchymal contusions with the brain forcefully deforming and colliding with the skull, and importantly, microscopic injury from the strain and resultant secondary injury of axonal fibers. A novel approach to the prevention of traumatic brain injury (TBI) is through

decreasing brain compliance, previously referred to as “brain turgor,” and “slosh” mitigation (slosh is the dynamics of fluids within moving containers).^{3–5} Internal jugular vein (IJV) compression and engorgement of the cranial venous system enlarges the brain and increases brain turgor (makes it stiffer) through changes in vascular dynamics and cerebrospinal fluid (CSF) absorption.^{3,6–11} This reduces relative motion, or slosh, between the brain and the skull and diminishes deformation of the brain. Two previous animal studies have shown a striking reduction in axonal injury through pre-injury application of a customized cervical collar introducing IJV compression.^{4,5} More recently, two clinical studies have demonstrated a significant reduction in subconcussive microstructural axonal injury on diffusion tensor imaging in high school players who wore a collar-like device during a season of play.^{12,13}

Although sports concussive injuries are not commonly associated with hemorrhagic lesions, they are still possible. On average,

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six deaths occur annually in American football because of brain injury, most commonly from subdural hemorrhage.^{14,15} Therefore, this therapy would not be appropriate if there was an increased potential for or propagation of hemorrhagic injury in the presence of venous congestion. The purpose of this study is to assess whether there is increased risk of hemorrhage following IJV compression in response to a standard controlled cortical impact (CCI) TBI in a swine model.

Methods

Animals

Fourteen Yorkshire female swine (2 practice and 12 study animals) were housed in the hospital animal facility with appropriate feed. The custom-made IJV compression collar was assessed with ultrasound in the two practice animals and was noted to show narrowing of the IJV, but without occlusion or compromise of the adjacent carotid arteries. The entirety of the experimental protocol was approved by the NorthShore Evanston Institutional Animal Care and Use Committee (EH14-390).

Anesthesia

On the day of surgery, the subject was sedated with midazolam 0.1–0.5 mg/kg IM for placement of an 18-20G IV catheter. Anesthesia, propofol 16–22 mg/kg IV, and analgesia, buprenorphine 0.01 mg/kg IM, was then given prior to intubation. The subject was intubated and subsequently maintained on inhaled isoflurane (1–3%), paralytic, and ventilator support with goal of: respiratory rate 12–15 breaths per minute, ventilator pressure of 18–22 cm H₂O, tidal volume of 5–10 mL/kg, and end tidal CO₂ of 40–50 mm Hg. The animal was paralyzed with pancuronium, 0.05 mg/kg IV, 0.6–5 µg/kg/min continuous IV infusion to maintain complete peripheral nerve twitch suppression. Throughout the surgery, the pig received maintenance IV fluids. A femoral artery catheter was placed for continuous monitoring of blood pressure and blood gas sampling prior to initiation of the surgical procedure. The animals were also maintained in normal physiological state with continuous rectal temperature (temp), pulse oximetry, and heart rate (HR) (telemetry) monitoring. Each physiological parameter was recorded every 15 min pre- and post-injury for comparison.

Experimental protocol

Our CCI protocol was modeled from the study by Manley and coworkers.¹⁶ The CCI large animal model was chosen because we felt that it best tested our hypothesis by providing a direct, focal hemorrhagic lesion.¹⁷ Following successful anesthetization and intubation, the swine was rotated to the prone position and the head was placed into a modified animal stereotactic frame to prevent movement at the time of impact. A cranial perforator drill and Kerrison rongeurs were used to make an 18 mm burr hole 7 mm anterior to the coronal suture and 3 mm lateral to the midline on the right side of the skull (Fig. 1). The dura was exposed carefully as to not cause an iatrogenic durotomy. An Integra[®] Camino[®] pressure transducer was then placed parasagittally 5 mm caudally to the coronal suture on the left side of the skull. This location was chosen so that the pathological sections surrounding the CCI impact lesion did not involve the area where the transducer was placed. Intracranial pressure (ICP) was observed for proper insertion with adequate waveform.

At this point, each swine was randomized to have no collar or collar application. For the animals with collar application, the custom-made collar (Fig. 2) was used to slowly compress the IJV until the ICP was noted to rise by 1 mm Hg. The HR and parameters of oxygenation were monitored.

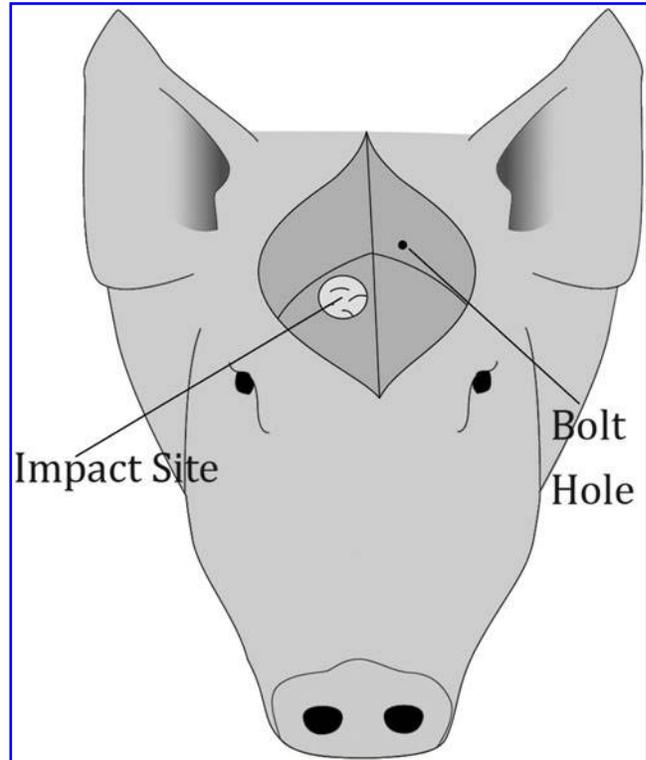


FIG. 1. Location of craniectomy for controlled cortical impact (CCI) and intracranial pressure (ICP) wire placement.

The CCI was made with placement of a 15 mm cylindrical piston indenter directly onto the surface of the dura. The Leica Impact One[™] CCI device was then set to a velocity of 3.5 m/sec to a depth of 9 mm with a 400 ms dwell. Following injury, the collar was immediately removed from the animals that received intervention. It was noted which animal had durotomy following impact. The craniotomy was subsequently covered with bone wax to form a

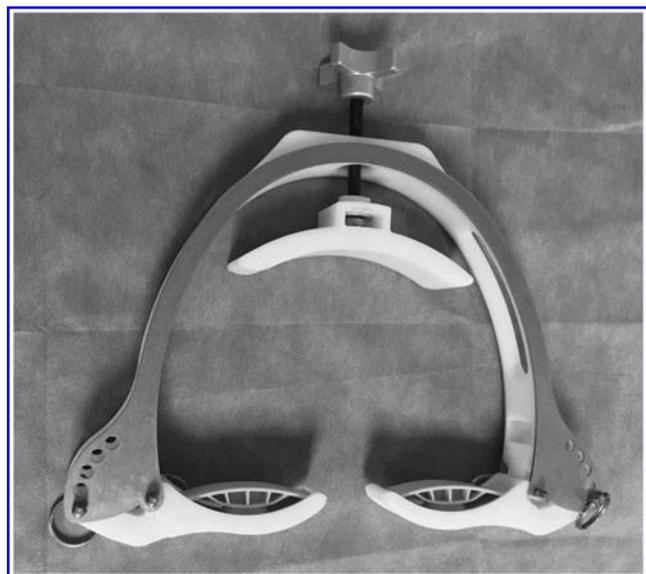


FIG. 2. Custom made internal jugular vein (IJV) compression collar. Note the C-shaped collar with open medial portion to prevent tracheal compression.

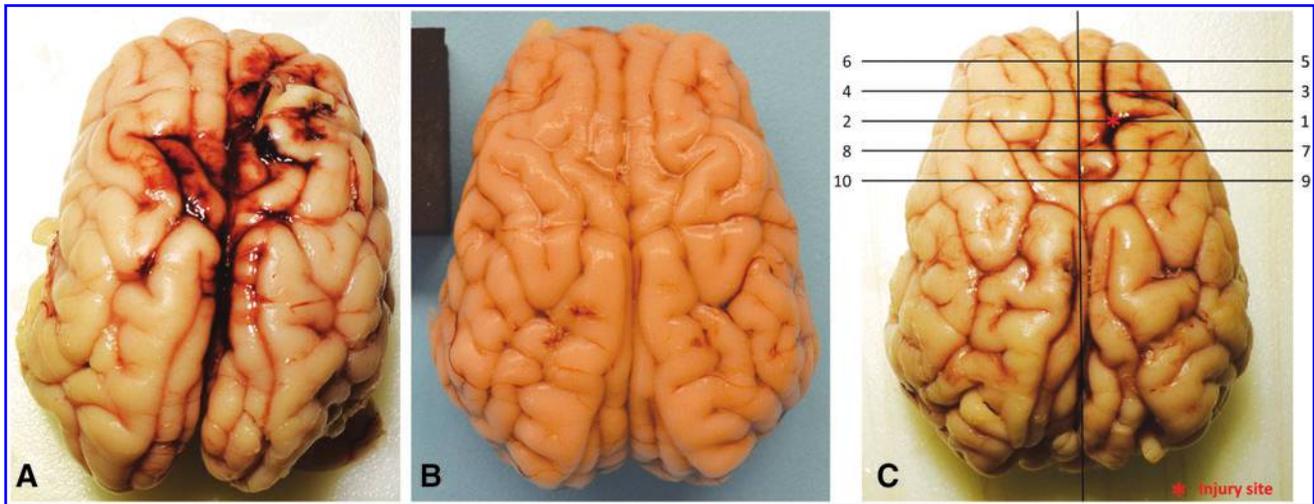


FIG. 3. Representative hemorrhage from whole brain gross pathology of (A) controlled cortical impact (CCI) and (B) CCI+collar swine brain. (C) Depiction of anatomical sectioning (10 total plus sections from bilateral thalami) in relation to CCI injury site. Color image is available online at www.liebertpub.com/neu

seal. Each animal was maintained under general anesthesia and mechanical ventilation for 5 h prior to euthanasia, allowing time for development of hemorrhage.

Tissue Preparation and Histological Grading

After euthanasia, the brain was subsequently removed through a large craniectomy and post-fixed in 10% formalin for 10 days. The brain was then sectioned from 10 predefined locations plus sections from the left and right thalami, and stained by hematoxylin and eosin (Fig. 3C: at injury site, 5 and 10 mm in front and behind the lesion, contralateral corresponding location, and bilateral thalami). Contralateral sections were taken because of the superficial spread of subarachnoid hemorrhage (SAH) from the CCI site to the adjacent hemisphere in multiple animals. Because of a more diffuse superficial hemorrhage (nonspherical in nature) seen grossly on a subset of animals, the standardized approach to volumetric measurements of injury was not feasible.^{17–20} For this reason, we developed a histological grading system for SAH. All locations were scored as: 0 for no subarachnoid hemorrhage seen, 1 for SAH confined to the subarachnoid space, and 2 for SAH in the subarachnoid space with extension into the underlying interstitial tissue. Scores in increments of 0.5 were assigned to those that were intermediate between each degree of SAH. Other markers of TBI pathology, specifically β -amyloid precursor protein (APP) (use of rabbit anti-APP [1:100], Novex Life Technologies #512700), neuronal degeneration/atrophy, cerebral edema, intraparenchymal hemorrhage, and inflammatory infiltration were scored as: 0-not present, 1-mild, 2-moderate, and 3-severe.

All pathological slides were analyzed during one viewing session and scored in a blinded manner by two neuropathologists (J.L. and S.A.) on two separate days. Each neuropathologist's scores from all 12 sections were then totaled to provide a semiquantitative measure of overall hemorrhage for each animal.

Statistical analysis

We determined a total n of 12 through the use of Mead's resource equation, taking into account that the expected standard deviations and expected differences between two groups were unknown at the time of experiment.²¹

Continuous variables were reported as mean \pm standard deviation. The normality assumption for continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were

compared between collar and no collar groups by a two sample t test or Wilcoxon rank-sum test as appropriate. Repeated measures ANOVA was used to compare the pre- and post-injury changes between groups (specifically ICP values). Intraclass correlation (ICC) concordance correlation coefficient was determined between the two pathological graders to assess for inter-rater agreement. ICC was found to be poor to moderate between the two graders (ICC for SAH: 0.474, ICC for intraparenchymal hemorrhage [IPH]: 0.718). One grader showed a tendency to rate all slides with slightly more hemorrhage than did the other pathologist. For this reason, an average score is not feasible between the two graders, and statistical analysis was performed on each separate score. Lastly, to alleviate

TABLE 1. PHYSIOLOGICAL PARAMETERS BETWEEN THE CCI AND CCI+COLLAR SWINE

	CCI (n=6, mean \pm SD)	CCI+collar (n=6, mean \pm SD)
Age at surgery (days)	75 \pm 0.9	75.5 \pm 1.6
Weight (kg)	31.6 \pm 5.4	31.4 \pm 3.8
Presence of durotomy	3/6	1/6
Total anesthesia time (min)	438.8 \pm 74	452 \pm 28
MAP (pre-injury)	66.4 \pm 8.0	65.3 \pm 9.0
MAP (post-injury)	67.1 \pm 9.4	62.0 \pm 12.3
HR (pre-injury)	92.4 \pm 7.3	95.9 \pm 6.7
HR (post-injury)	107.3 \pm 7.8	100 \pm 10.1
Temp °C (pre-injury)	36.8 \pm 1.0	36.9 \pm 1.1
Temp °C (post-injury)	37.7 \pm 1.0	37.1 \pm 1.0
ICP (mm Hg) (pre-injury)	7.0 \pm 3.1	3.6 \pm 3.8
		(pre-collar)
		5.6 \pm 3.1
		(after collar application)
ICP (mm Hg) (post-injury)	10.5 \pm 1.6	6.6 \pm 3.2
pCO ₂ (mm Hg)	39.1 \pm 4.4	40.1 \pm 6.8
pO ₂ (mm Hg)	389.2 \pm 58.9	418.3 \pm 68.4
Hb (g/dL)	8.5 \pm 0.3	8.8 \pm 1.1
Hct (%)	26.3 \pm 0.9	27.2 \pm 3.4
Na (mmol/L)	140 \pm 2.0	143 \pm 5.0
Glucose (mg/dL)	69.2 \pm 41.4	50.8 \pm 15.7

CCI, controlled cortical impact; MAP, mean arterial pressure; HR, heart rate; ICP, intracranial pressure; Hb, hemoglobin; Hct, hematocrit; Na, sodium.

the bias of the small sample *t* test, the bootstrapping hypothesis test was performed on the 2000 random samples selected via resampling from the original data. The bootstrapping *p* values were calculated and presented in the tables. Statistical analyses were performed on SAS 9.3 (Cary, NC) Windows platform. *P* < 0.05 was considered as statistically significant.

Results

Physiological parameters

The 12 animals were on average 31.5 ± 4.4 kg and 75.2 ± 1.3 days old at time of injury. Pre-injury and post-injury mean arterial blood pressure (MAP), temp, and HR were found to not have any statistical difference between the collared and control animals. Prior to CCI, all animals were tested for arterial $p\text{CO}_2$ and $p\text{O}_2$, venous hemoglobin (Hb), hematocrit (Hct), sodium (Na), and glucose levels. There was no statistical difference between these laboratory studies in the collared and control animals (Table 1). Prior to collar application, the baseline ICP for the CCI animals was slightly higher than for the CCI+collar animals but not significant. As expected, collar application caused an increase in ICP of 1–2 mm Hg in the collared animals.

TABLE 2. HISTOLOGICAL SCORING OF SUBARACHNOID HEMORRHAGE (SAH) AND INTRAPARENCHYMAL HEMORRHAGE (IPH) BETWEEN THE CONTROLLED CORTICAL IMPACT (CCI) AND CCI+COLLAR SWINE

Neuropathologist	Histological score	CCI (n=6, mean±SD)	CCI+collar (n=6, mean±SD)	p value
1	SAH	7.13±2.2	3.58±2.2	0.029
2	SAH	12.0±3.0	7.2±3.0	0.024
1	IPH	3.0±1.3	0.67±1.2	0.017
2	IPH	2.5±0.9	1.0±1.2	0.050

The post- injury ICP seen in the control animals was significantly higher but because of the increased pre-injury baseline, the overall mean change between groups was similar (*p*=0.13). Because of the mild superficial nature of the injury and early time point for euthanasia, we did not expect any substantial increases in ICP. There was also a non-statistically significant increase in durotomy following injury in the uncollared versus the collared animals.

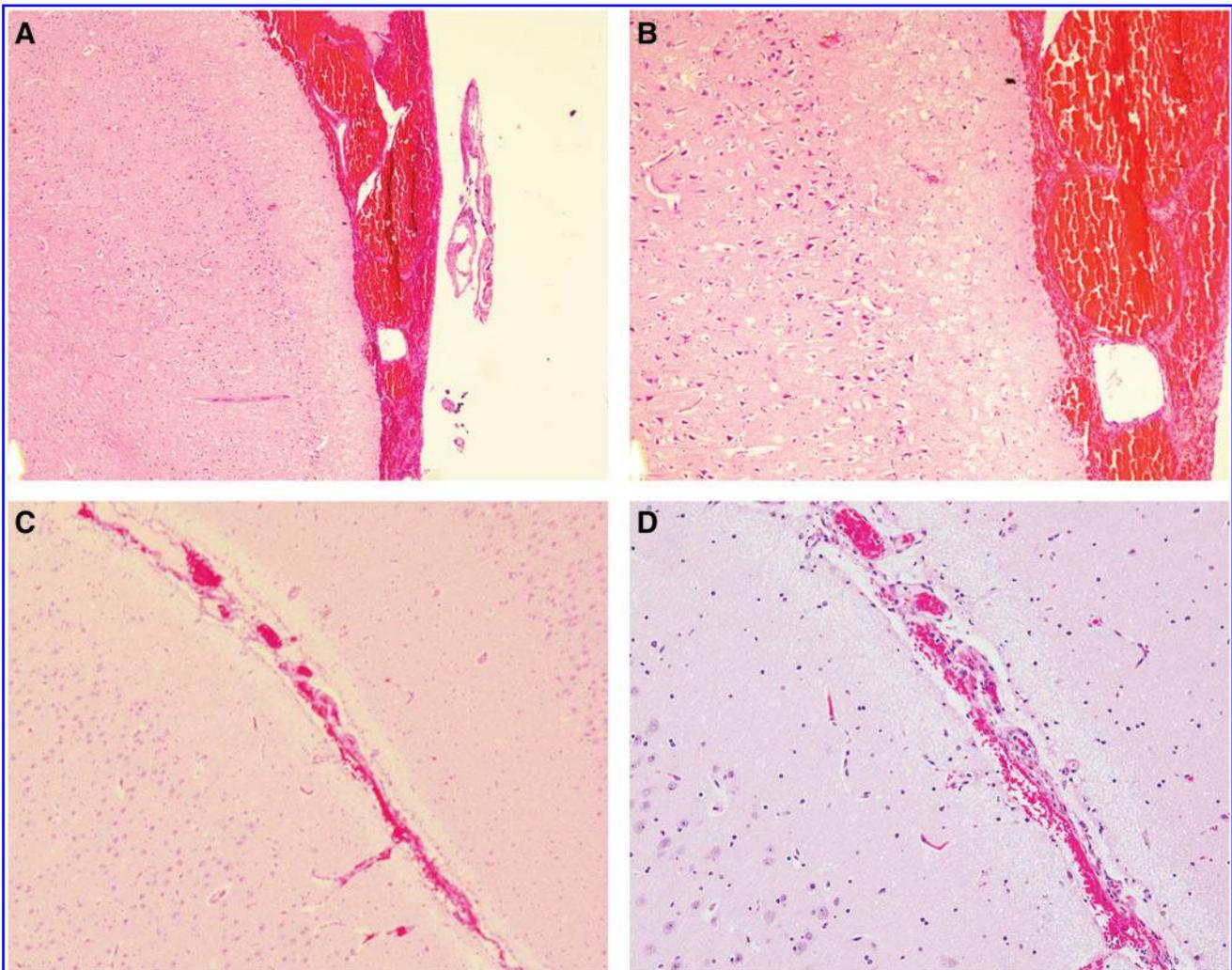


FIG. 4. Representative subarachnoid hemorrhage from pathological section of a controlled cortical impact (CCI) (A, 40× and B, 100× magnifications) and CCI+collar swine brain (C, 100× and D, 200× magnifications). Note the hallmark histological signs of injury (neuronal atrophy and cerebral edema) at the higher magnification in CCI animals. Color image is available online at www.liebertpub.com/neu

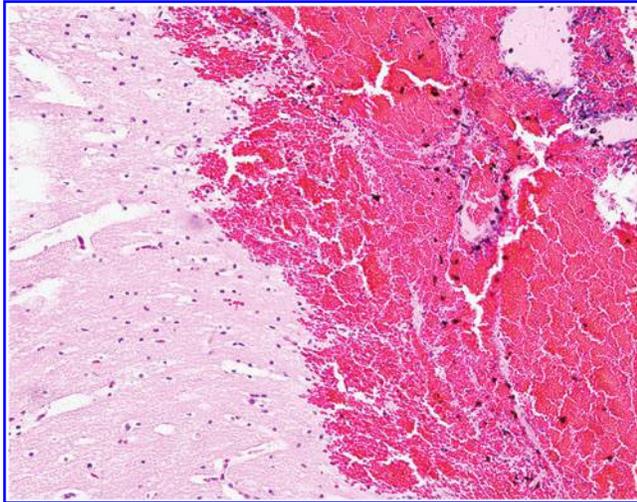


FIG. 5. Grade 2 subarachnoid hemorrhage (hemorrhage in the subarachnoid space with extension into the underlying interstitial tissue). This pathological slide was obtained from a controlled cortical impact (CCI) animal (200 \times). Color image is available online at www.liebertpub.com/neu

Histological grading

The CCI+collar animals were noted to have a decreased SAH score when compared with the CCI animals (first grader: CCI+collar 3.42 ± 2.0 vs. CCI: 7.13 ± 2.2 , $p=0.026$; second grader: CCI+collar 7.17 ± 3.0 vs. CCI 12.0 ± 3.0 , $p=0.024$) (Table 2 and Figs. 3–5). A statistically significant difference was also seen in another scoring metric for hemorrhage, the presence of IPH. The CCI+collar animals were found to have a decreased IPH score compared with the control group score (first grader: CCI+collar 0.67 ± 1.2 vs. CCI 3.0 ± 1.3 , $p=0.03$; second grader: CCI+collar 1.0 ± 1.2 vs. CCI 2.5 ± 0.9 , $p=0.05$) (Table 2). There were no significant differences between the additional markers for TBI (amyloid precursor protein Table 3): CCI+collar 2.9 ± 2.1 vs. CCI 5.8 ± 4.1 , $p=0.17$, degenerative/shrunken neurons: CCI+collar 3.2 ± 3.1 vs. CCI 3.8 ± 2.2 , $p=0.7$, cerebral edema: CCI+collar 3.4 ± 2.5 vs. CCI 3.3 ± 1.9 , $p=1.0$, and inflammatory infiltration: CCI+collar 3.8 ± 8.2 vs. CCI 5.0 ± 7.0 , $p=0.8$) (Table 3). There was a trend toward a decreased APP score in the CCI+collar animals compared with the CCI animals; however, this was not statistically significant. This may be because of either the small sample size or the limitations of the injury model.

TABLE 3. HISTOLOGICAL SCORING OF RESPONSE TO INJURY BETWEEN THE CCI AND CCI+COLLAR SWINE

	CCI (n=6, mean \pm SD)	CCI+collar (n=6, mean \pm SD)	p value
APP score	5.8 ± 4.1	2.9 ± 2.1	ns
Neuronal atrophy score	3.8 ± 2.2	3.2 ± 3.1	ns
Cerebral edema score	3.3 ± 1.9	3.4 ± 2.5	ns
Inflammatory infiltrates score	5.0 ± 7.0	3.8 ± 8.2	ns
Presence of microglial nodules	1/6	2/6	ns
Presence of meningitis	2/6	1/6	ns
Presence of infarct	1/6	2/6	ns

CCI, controlled cortical impact; APP, amyloid precursor protein

Other notable histological findings, which were not used in a scoring metric, were the presence of focal early tissue infarct (CCI: 1/6 vs. CCI+collar: 2/6), microglial nodules (CCI: 1/6 vs. CCI+collar: 2/6), and leptomeningeal inflammatory infiltration (CCI: 2/6 vs. CCI+collar: 1/6). The presence of leptomeningeal inflammatory infiltrates was presumed to be a robust inflammatory response from the TBI or the presence of foreign material (ICP wire) and not a pre-existing infection within the animals. At no point during the swines' presurgical or surgical course did they exhibit signs of meningitis (decreased feeding, low activity level, failure to gain weight, fevers, hemodynamic instability). An inflammatory response was also noted by Manley and coworkers in their study, but without any further details.¹⁶

Discussion

Depending on the severity of force, acceleration of the cranium may lead to the inexorable movement of the viscoelastic brain within the skull leading to microstructural injury and/or hemorrhagic lesions. IJV compression and, presumably its effect on brain turgor, size, and resultant slosh mitigation, has been shown in pre-clinical and clinical studies to significantly reduce microstructural axonal damage from concussive impacts and acceleration forces.^{12,13,22,23} This appealing approach as a prophylactic measure to TBI can only be considered for therapeutic use if mild venous congestion is shown to not intensify hemorrhagic injury. In this experiment, we have demonstrated that IJV compression prior to injury did not increase the propensity for hemorrhagic extension; and more significantly, actually reduced hemorrhage (both SAH and IPH) in the porcine CCI model. This novel prophylaxis through venous engorgement is intriguing in its capacity to address the multiple different mechanisms of TBI on microscopic (diffuse axonal injury) and macroscopic (hemorrhage) levels that lead to morbidity and mortality.^{4,5,12,13}

Because of the absence of acceleration injury in the CCI model, our results suggest a mechanism elucidated by IJV compression in addition to slosh mitigation through venous structural alterations. A quantitative mathematical model of the complex venous network is a substantial technical challenge, and is beyond the scope of this article; however, studies of simpler geometries and loading conditions have reported that increased internal pressure, volume, and diameter increases load bearing capacity in cylindrical fluid-filled vessels.^{23–25} It is possible that an analogous effect explains our findings, that the compliant venous system prompts only mild engorgement following IJV compression, staying far from its critical point of iatrogenic rupture;²⁶ however, now with the added protective benefits of increasing resistance to external deformation, that is, turgor, through altered internal vessel properties.

Presumably, mild IJV compression is tolerated by the venous system because of its compliant nature and collateral drainage. In studies looking at dural sinus or superior vena cava occlusion, the low pressure/compliant system allowed further filling in the bridging/cortical/parenchymal veins and anastomotic channels.^{2,27,28} These properties permit larger increases in volume with a nonlinear effect on pressure.^{3,29} Also, IJV compression does not lead to deleterious cerebral venous outflow obstruction because the cerebral venous drainage in the recumbent adult and swine is dependent on both the IJV and Batson's epidural venous plexus.^{27,30} Considered part of the cerebrospinal venous system, the valveless, large capacitance vertebral venous plexus allows bidirectional flow that plays an important role in the regulation of cerebral venous outflow and ICP.³¹ The biomechanical properties

of the venous system described earlier are theorized and require further research to elucidate this presumed advantageous physiological alteration and effect on hemorrhage reduction.

The limitations of the CCI model are noted (need for craniectomy, superficial impact with minimal acceleration type injury); however, it was chosen because we felt that it best tested our hypothesis concerning propensity for hemorrhagic brain injury in the setting of venous congestion in a large animal model. Also, the gyrencephalic nature of our porcine model is felt to be superior to the previous lissencephalic rodent experiments and is believed to be more applicable to human TBI. Further experimental work and clinical application of strategies to reduce brain motion are needed to better define the exciting possibilities of cerebral protection by internal means, rather than the historical external protection by helmets.

Conclusion

IJV compression prior to injury was demonstrated to not increase the risk of hemorrhagic injury when applied in the porcine CCI model. The previously published work in slosh mitigation, in concert with this current study, suggests the feasibility that IJV compression may be an efficacious and safe approach to concussion prophylaxis. An even more fascinating finding of this study was that mild venous congestion actually had a protective effect against both SAH and IPH. Although IJV compression was originally conceived as a method to reduce concussive injury through reduced brain movement or slosh, the results of the present experiment raise the question of whether severe or lethal brain injury from acceleration-deceleration forces or “major slosh” and resultant intracranial hemorrhage would also be positively affected by elevation of cerebral venous volume through mild IJV compression prior to injury.

Acknowledgments

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Author Disclosure Statement

Julian Bailes holds stock in Q30 Sports Science, LLC based on the original patent for IJV compression, and David Smith is a consultant to Q30 Sports Science, LLC. The other authors have nothing to disclose. The views expressed in this article are those of the authors and do not reflect the official policy or position of the US Army, Department of Defense, or the US government.

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