

ORIGINAL WORK



# Cerebral Perfusion Pressure Directed-Therapy Modulates Cardiac Dysfunction After Traumatic Brain Injury to Influence Cerebral Autoregulation in Pigs

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## Abstract

**Background:** Traumatic brain injury (TBI) is an important contributor to morbidity and mortality. Low cerebral perfusion pressure (CPP, mean arterial pressure [MAP] minus intracranial pressure) after TBI is associated with cerebral ischemia, impaired cerebral autoregulation, and poor outcomes. Normalization of CPP and limitation of cerebral autoregulation impairment is a key therapeutic goal. However, some vasoactive agents used to elevate MAP such as phenylephrine (Phe) improve outcome in females but not male piglets after TBI while dopamine (DA) does so in both sexes. Clinical evidence has implicated neurological injuries as a cause of cardiac dysfunction, and we recently described cardiac dysfunction after TBI. Cardiac dysfunction may, in turn, influence brain health. One mechanism of myocyte injury may involve catecholamine excess. We therefore tested the hypothesis that TBI caused cardiac dysfunction and catecholamine excess which may reciprocally be modulated by vasoactive agent choice to normalize CPP and prevent impairment of cerebral autoregulation after injury.

**Methods:** TBI was produced in anesthetized pigs equipped with a closed cranial window, and Phe or DA administered to normalize CPP.

**Results:** Plasma cardiac enzymes troponin and creatine kinase and catecholamines epinephrine and norepinephrine were elevated by TBI, such release potentiated by Phe in males but blocked in female piglets and blocked in both sexes after DA. Cerebral autoregulation was impaired after TBI, worsened by Phe in males but protected in females and males treated with DA. Papaverine-induced dilation was unchanged by fluid percussion brain injury, DA, and Phe.

**Conclusions:** These data indicate that pressor choice in elevation of CPP is important in limiting cardiac dysfunction and suggest that DA protects cerebral autoregulation in both sexes via reduction of cardiac biomarkers of injury and catecholamines released after TBI.

**Keywords:** Cerebral autoregulation, Traumatic brain injury, Creatine kinase, Catecholamines

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## Introduction

Traumatic brain injury (TBI) is an important contributor to morbidity and mortality in pediatric trauma, and boys have worse outcome than girls [1]. Cerebral autoregulation is a homeostatic mechanism that is designed to maintain cerebral blood flow (CBF) to meet the brain's high metabolic demands, but this process may often be impaired after TBI [1]. CBF then becomes pressure passive and can result in secondary cerebral hypoperfusion in the presence of hypotension, leading to poor patient outcome [2]. Low cerebral perfusion pressure (CPP, mean arterial pressure [MAP] minus intracranial pressure [ICP]) after TBI is associated with cerebral ischemia, impaired cerebral autoregulation, and poor outcomes. Normalization of CPP and limitation of cerebral autoregulation impairment is a key therapeutic goal. However, vasoactive agents used to elevate MAP to increase CPP after TBI have not sufficiently been compared regarding effect on autoregulation after TBI. In fact, we have observed that ability of some vasoactive agents to prevent impairment of cerebral autoregulation after TBI is sex-dependent. For example, while phenylephrine (Phe) prevented impairment of autoregulation in females it aggravated such impairment in male piglets after fluid percussion brain injury (FPI) due to block of the deleterious mediator extracellular signal-related kinase (ERK) mitogen-activated protein kinase (MAPK) in the former and potentiation of upregulation in the latter [3]. Dopamine (DA) protected cerebral autoregulation after piglet TBI in both sexes due to equivalent blockade of ERK MAPK [4, 5].

Medical evidence has implicated neurological injuries, particularly subarachnoid hemorrhage (SAH), as a cause of cardiac dysfunction [6–8]. Despite the frequency with which TBI affects the general population, its potential impact on cardiac function has received little attention [9]. In clinical work, we were the first to describe cardiac dysfunction after TBI, which lasted for up to 2 weeks after TBI [10–13]. Cardiac biochemical markers of injury (troponin, creatine kinase) were observed to be elevated and associated with abnormal echocardiography [10].

One theory explaining the pathogenesis of TBI-induced cardiac dysfunction involves a catecholamine-induced effect secondary to ischemia, elevated ICP, and damage to the insular cortex and hypothalamus [14]. This results in a catecholamine storm which is clinically manifested by tachycardia, increased vascular resistance, and cardiac dysfunction. The mechanism of myocyte injury involves catecholamine excess, elevated intracellular calcium, and reperfusion injury. Elevated catecholamine levels decrease the viability of myocytes through cAMP-mediated calcium overload. The end result of the catecholamine storm is mitochondrial dysfunction and cell death.

Heart–brain interactions can also occur wherein the primary injury to the brain is driven by the heart. Low cardiac output and systemic hypotension may decrease CBF. Since TBI, an entity in which hypotension has been exquisitely linked to poor outcomes [15], is associated with cardiac dysfunction [10], a vicious cycle of TBI affecting heart function to affect neurologic outcome may occur. The management of cardiac dysfunction in the TBI population may be especially important because it may have a role in preventing secondary brain injury from hypotensive episodes. In TBI, cerebral perfusion is largely affected by impaired cerebral autoregulation [16], which in the context of the neurovascular unit (NVU), affects neuronal cell integrity. We have prior observed that FPI in the newborn pig causes neuronal cell necrosis in CA1 and CA 3 hippocampus, an important brain area for learning and memory [17], giving functional significance to FPI-induced altered NVU function. We propose that treatment with vasoactive agents to normalize CPP may differentially affect cardiac function.

While we have clear evidence that Phe only protects cerebral autoregulation in female newborn pigs while DA protects in both sexes after TBI due to differential block of ERK MAPK upregulation [5], an alternative explanation may be found in differential prevention of cardiac dysfunction after TBI by Phe vs DA. We, therefore, hypothesize that both post traumatic cerebral autoregulation and cardiac biomarkers of injury are sex-dependently altered by Phe and DA.

## Materials and Methods

### Closed Cranial Window Technique and TBI

Yorkshire newborn (1–5 days, 1.0–1.4 kg) of either sex was studied. This protocol (805388) was approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. The anesthetic regimen consisted of pre-medication with dexmedetomidine (20 µg/kg im), induction with isoflurane (2–3%), isoflurane taper to 0% after start of total intravenous anesthesia (TIVA) with fentanyl (200 µg/kg/h), midazolam (1 mg/kg/h), dexmedetomidine (2 µg/kg/h), and propofol (2–10 mg/kg/h). Maintenance of TIVA lasted for the balance of the surgical and experimental portions of the pig preparation. A catheter was inserted into a femoral artery to monitor blood pressure and to sample blood gas tensions and pH. The trachea was cannulated, and the animals were ventilated with room air. A heating pad was used to maintain the animals at 37°–39 °C, monitored rectally. A cranial window was placed in the parietal skull of these anesthetized animals. The closed cranial window technique for measuring pial artery diameter has been previously described [3, 4]. An Integra Camino monitor was used to measure ICP.

The method used to induce lateral FPI has been described previously [3, 4]. A device designed by the Medical College of Virginia was used. A small opening was made in the parietal skull contralateral to the cranial window. A metal shaft was sealed into the opening on top of intact dura and fluid coupled to the brain injury device. The intensity of the injury was moderate (1.9–2.2 atm) with a constant duration of 19–23 ms.

### Protocol

Pial small arteries (resting diameter, 120–160  $\mu\text{m}$ ) were examined to determine the effects of FPI. Typically, 2–3 ml of artificial CSF was flushed through the window over a 30 s period, and excess CSF was allowed to run off through one of the needle ports.

Forty pigs were randomized to one of each experimental intervention group (all  $n=5$  male and  $n=5$  female): (1) sham control (craniotomy but no injury), (2) FPI, (3) FPI post-treated with Phe, and (4) FPI post-treated with DA. CPP was targeted (55–60 mm Hg for newborn pigs per 2012 Pediatric Guidelines) to determine the dose of the iv infusion (typically 0.8–1.2  $\mu\text{g}/\text{kg}/\text{min}$  iv) of Phe or DA, and vasoactive drug treatment is started when CPP decreases below 45 mm Hg. These animals were already being given an infusion of saline (to accommodate for loss during ventilation), and in prior studies, an infusion of saline did not make a significant difference in support of CPP over the prolonged time period of the protocol (4 h post FPI) [3, 4].

Cerebral autoregulation was tested via two techniques. The first quantified the transient hyperemic response ratio (THRR) [17]. In the second, hypotension was used as the stimulus and was produced by the rapid withdrawal of either 5–8 or 10–15 ml blood/Kg, yielding moderate or severe hypotension (decreases in MAP of 25 and 45%, respectively). Such decreases in blood pressure were maintained constant for 10 min by titration of additional blood withdrawal or blood reinfusion. The vehicle for all agents was 0.9% saline. In sham control animals, responses to THRR, hypotension (moderate, severe), and papaverine ( $10^{-8}$ ,  $10^{-6}$  M) were obtained initially and then again 4 h later. In drug post-treated animals, drugs were administered after FPI and responses to THRR, hypotension, and papaverine obtained at 4 h post insult. The order of agonist administration was randomized within animal groups. A wait period of 20 min occurred between each set of stimuli in order to allow pial artery diameter to return to control value.

### Longitudinal TBI Studies

In a subset of animals ( $n=5$  males and  $n=5$  females), pigs were intubated, anesthetized with isoflurane (1–3%), and underwent a short procedure in a sterile surgical

suite. The scalp was reflected, a craniotomy produced (dura intact), the brain injury adapter placed in the hole, and FPI produced. The animals were sutured closed and allowed to recover. At 8 days post FPI, the above acute surgical procedure (cranial window placement for pial artery diameter measurement) was performed. Vascular responses to cerebral autoregulation and papaverine were obtained, and plasma samples were drawn for later enzyme-linked immunosorbent assay (ELISA) analysis of troponin and epinephrine (EPI).

### ELISA

Commercially available ELISA Kits were used to quantify plasma troponin I (Enzo), creatine kinase (CKMB, Abcam), and catecholamines norepinephrine (NE) and EPI (Eagle Bioscience).

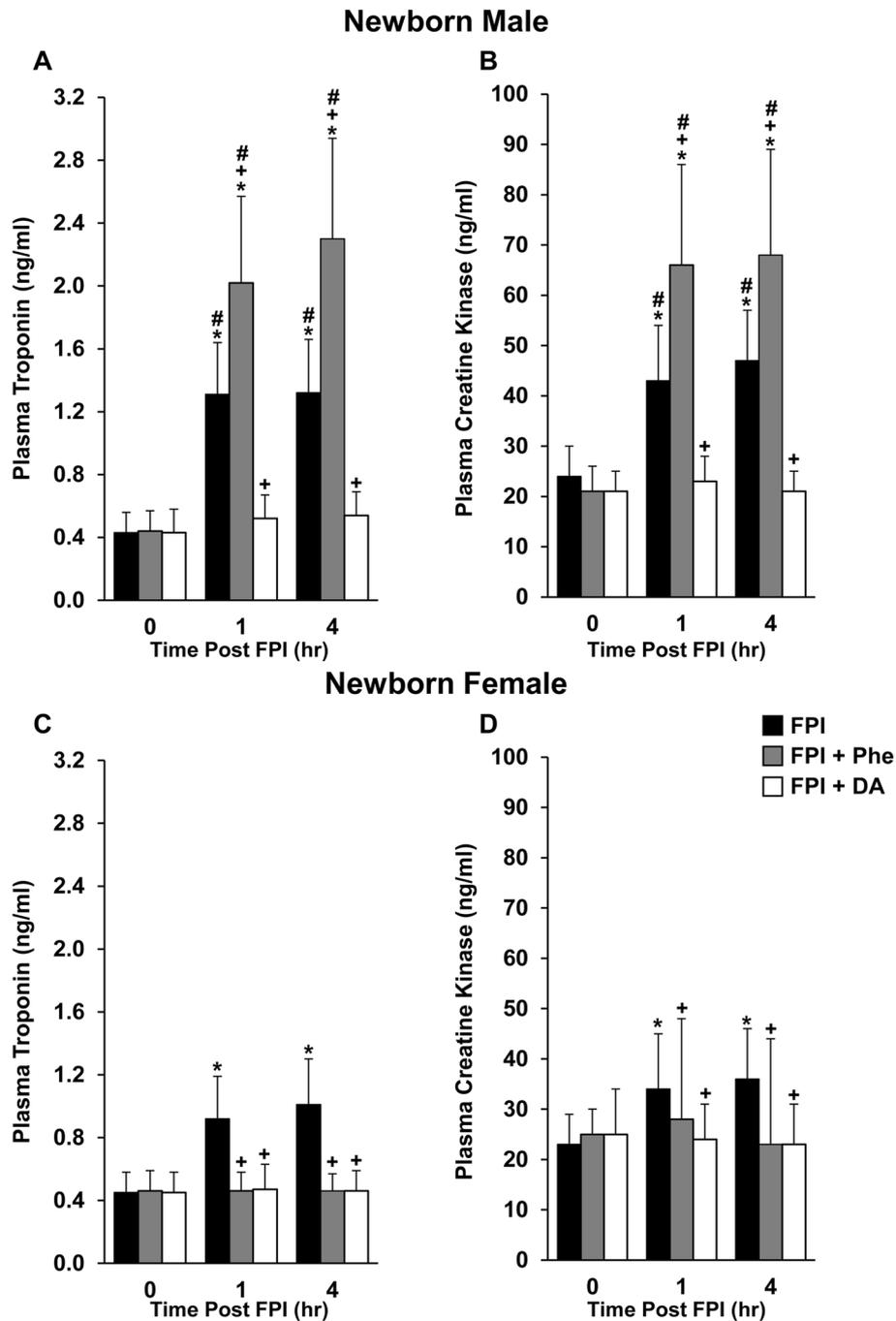
### Statistical Analysis

Order of administration of stimuli was randomized, and investigators were blinded to study group. We obtained responses to vasoactive stimuli, repetitively (time control), in sham pigs to minimize the possibility of a false positive in our studies. Papaverine served as an internal control in that dilation was unchanged after FPI due to it not being dependent on signaling pathways used to elicit vasodilation during hypotension. Pial artery diameter, plasma troponin, creatine kinase, NE, and EPI were analyzed using analysis of variance (ANOVA) for repeated measures. If the value was significant, the data were then analyzed by Fishers protected least significant difference test. Sample size was determined by power analysis such that  $n$  level of  $P<0.05$  would yield a power of at least 0.85 in all statistical tests for change in pial artery diameter and biochemical mediator level, as shown previously [2–4, 17]. There were five replicates for each experimental intervention. Values are represented as mean  $\pm$  standard deviation of the absolute value or as percent changes from control value. Endpoint was a limitation of negative outcome (eg impairment of cerebral autoregulation).

## Results

### FPI Produces Cardiac Dysfunction in Male and Female Piglets Which is Modulated by Phe and DA

Plasma biomarkers of cardiac injury such as troponin (sham control  $0.50 \pm 0.02$  ng/ml) and creatine kinase (sham control  $24 \pm 3$  ng/ml) were elevated within 1 h of injury, and these levels remained elevated for 4 h in acute study animals (Fig. 1), but troponin was markedly elevated at 8 days post injury in animals studied longitudinally ( $0.50 \pm 0.03$  and  $20 \pm 3$  ng/ml for sham and 8 days post FPI,  $n=5$ ), supportive of myocardial damage and not a low grade myocarditis. The increase in plasma troponin and creatine kinase was significantly



**Fig. 1** Influence of FPI on plasma troponin (ng/ml) and creatine kinase (ng/ml) in male and female newborn pigs as a function of time (h) after FPI, FPI + Phe, and FPI + DA,  $n=5$  shown as mean  $\pm$  standard deviation of the mean. \* $p < 0.05$  compared to 0 time + $p < 0.05$  compared to corresponding FPI alone value # $p < 0.05$  compared to female value

greater in males compared to females (Fig. 1;  $0.50 \pm 0.03$  and  $20 \pm 3$  ng/ml vs  $0.52 \pm 0.03$  and  $13 \pm 2$  ng/ml for sham and 8 days post FPI in males and females,  $n=5$ ).

Phe-potentiated increased plasma troponin and creatine kinase associated with FPI (Fig. 1). In contrast, DA

blocked elevations in troponin and creatine kinase after injury (Fig. 1).

#### **FPI Elevates Plasma NE and EPI in Male and Female Piglets Which is Modulated by Phe and DA**

Plasma levels for NE and EPI were elevated within 1 h of injury, and these levels remained elevated for 4 h (Fig. 1), but EPI was markedly elevated at 8 days post injury in animals studied longitudinally ( $32 \pm 5$  and  $112 \pm 13$  ng/ml for sham and 8 days post FPI,  $n=5$ ), supportive of a catecholamine storm hypothesis (14) and explaining the pathogenesis of brain injury-induced cardiac dysfunction. Increases in NE and EPI were significantly greater in males compared to females (Fig. 2;  $32 \pm 5$  and  $112 \pm 13$  vs  $34 \pm 5$  and  $91 \pm 10$  ng/ml for sham and 8 days post FPI,  $n=5$ ). Phe-potentiated increased plasma levels of NE and EPI associated with FPI (Fig. 2). In contrast, DA blocked elevations in NE and EPI after injury (Fig. 2).

#### **FPI Impairs Cerebral Autoregulation in Male and Female Piglets Which is Modulated by Phe and DA**

Cerebral autoregulation, as judged by the THRR and pial artery dilation during acute hypotension, was blunted after FPI, which was reversed to vasoconstriction by Phe infusion in the newborn male at 4 h post FPI (Figs. 3, 4). THRR and pial artery dilation were blunted by FPI in the newborn female, but such decreases were less than in the newborn male at 4 h post FPI (Figs. 3, 4). Phe administration protected cerebral autoregulation in the newborn female compared to the newborn male (Figs. 3, 4). The degree to which cerebral autoregulation was either impaired by FPI, further impaired by Phe in the male or protected by DA in the male and female was statistically correlated with degree to which plasma biomarkers of cardiac injury were changed by these conditions. For example, the plasma concentrations of troponin and creatine kinase were increased by FPI in males and females ( $p < 0.05$ ), further increased over the latter levels by Phe and associated with further impairment of cerebral autoregulation in the male ( $p < 0.05$ ), but levels were blunted by Phe and associated with protection of cerebral autoregulation by Phe in the female ( $p < 0.05$ ) (Figs. 1, 3, 4). Papaverine-induced pial artery dilation was unchanged by FPI, Phe, and DA (Fig. 5), indicating that effects of TBI, Phe, and DA were not an epiphenomenon, but specific to signaling pathways activated by TBI. In longitudinal studies, cerebral autoregulation as judged by THRR and pial artery dilation during hypotension continued to be impaired at 8 days post FPI ( $13 \pm 1$  and  $23 \pm 1$  vs  $2 \pm 1$  and  $4 \pm 1\%$  increase in pial artery diameter during moderate and severe hypotension in sham and 8 days post FPI male piglets,  $n=5$ ). Papaverine-induced pial artery vasodilation was unchanged at 8 days post FPI

compared to sham control conditions. These data indicate that cerebral autoregulation impairment associated with cardiac dysfunction and elevated catecholamines is prolonged in nature after FPI. ICP was more significantly elevated more in newborn males compared to females after FPI ( $3 \pm 1$  and  $17 \pm 1$  vs  $2 \pm 1$  and  $13 \pm 1$  mm Hg). Phe and DA reduced ICP in males and females after FPI to roughly the same degree ( $10 \pm 2$  and  $9 \pm 2$  for Phe and DA in males,  $8 \pm 1$  and  $7 \pm 2$  mm Hg for Phe and DA in females), similar to that observed previously [3, 4].

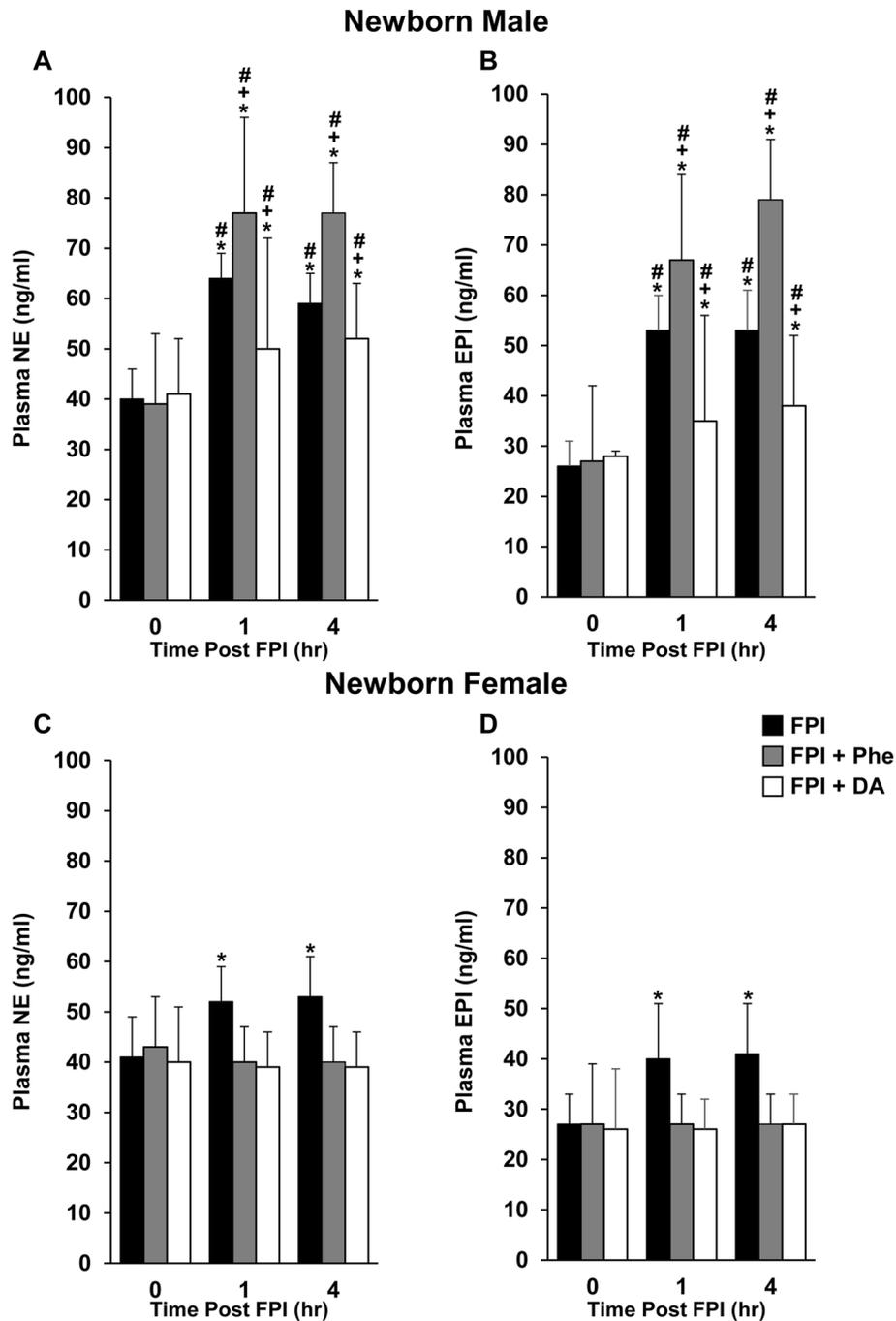
#### **Physiological Values**

Blood chemistry values were collected before and after all experiments. There were no statistically significant differences in pH,  $p\text{CO}_2$ , or  $p\text{O}_2$  values between sham control and FPI animals. MAP was similar in newborn males and females prior to FPI ( $66 \pm 9$  and  $68 \pm 10$  mm Hg), decreased to a similar amount after FPI in both sexes ( $48 \pm 6$  and  $49 \pm 7$  mm Hg) and was normalized to a similar degree by Phe and DA ( $67 \pm 10$  and  $66 \pm 11$  mm Hg for males and females treated with Phe;  $66 \pm 10$  and  $67 \pm 11$  mm Hg for males and females treated with DA). Heart rate did not differ between males and females under sham and FPI conditions, and heart rate increased to a similar degree in males and females when treated with Phe and DA after FPI.

#### **Discussion**

A key new finding of translational relevance in this study is that FPI is associated with elevations of plasma biomarkers of cardiac injury such as troponin and creatine kinase as a function of sex, with increases being greater in males compared to females. Such elevations of cardiac enzymes were prolonged, lasting at least 8 days post FPI and associated with an equally prolonged sex-dependent impairment of cerebral autoregulation. These observations indicate that TBI is associated with a sex-dependent cardiac dysfunction. A study design limitation, however, is that other more direct indices of cardiac function, such as determination of left ventricular ejection fraction via ultrasound, were not considered.

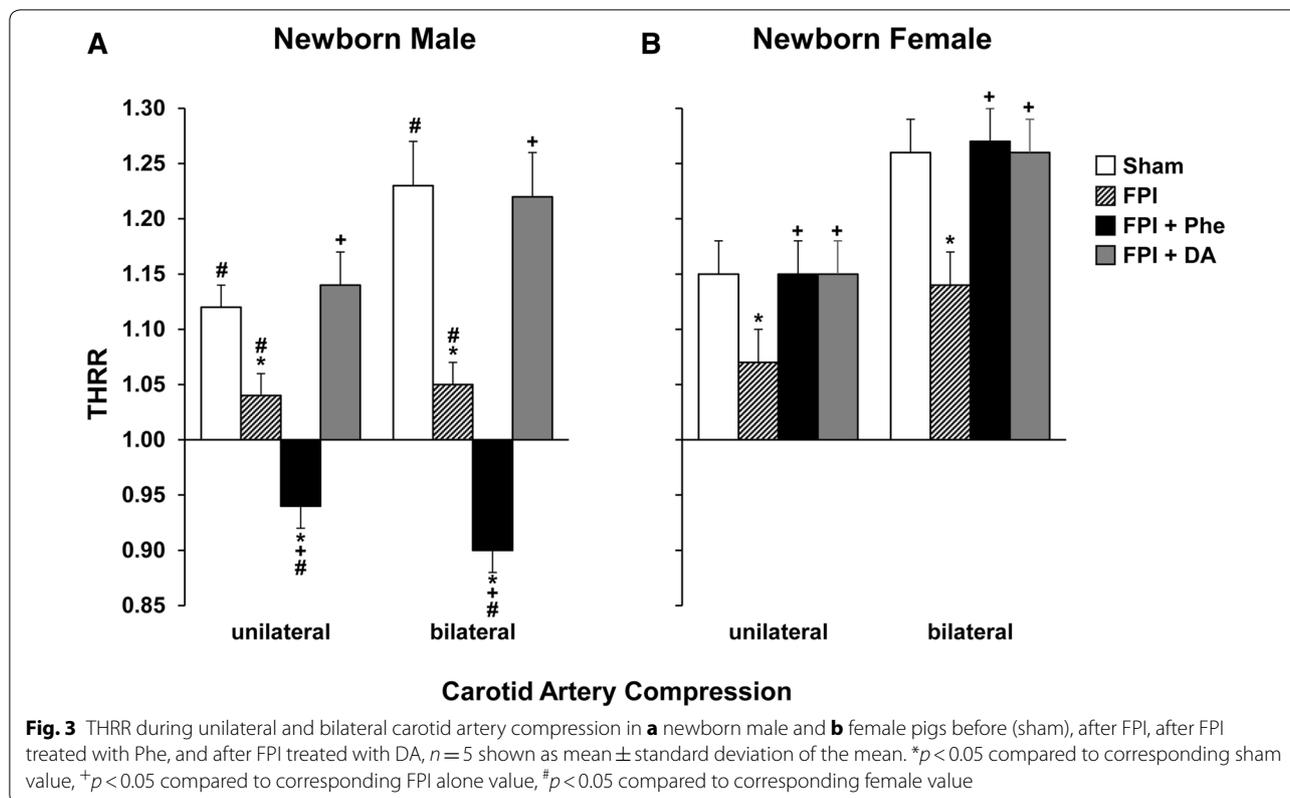
Limitation of cerebral autoregulation impairment is a key therapeutic goal. The typical critical care pathway used as a therapeutic intervention is to administer a vasoactive agent that will elevate MAP and thereby normalize CPP. However, we have observed that ability of some vasoactive agents to prevent impairment of cerebral autoregulation after TBI is sex-dependent. For example, while Phe prevented impairment of autoregulation in females it aggravated such impairment in male piglets after TBI [3]. In contrast, DA prevented impairment of cerebral autoregulation in both sexes [4]. Interestingly, in this study, we observed a correlation between level of



**Fig. 2** Influence of FPI on plasma NE and EPI (ng/ml) concentrations as a function of time (h) in newborn male and female pigs after FPI, FPI + Phe, and FPI + DA,  $n = 5$  shown as mean  $\pm$  standard deviation of the mean. \* $p < 0.05$  compared to 0 time + $p < 0.05$  compared to corresponding FPI alone value # $p < 0.05$  compared to female value

cardiac enzyme concentration and degree of impairment of autoregulation after TBI. For example, troponin and creatine kinase are elevated more in males compared to females (Fig. 1), which is correlated with greater impairment of cerebral autoregulation in males compared to

females after TBI (Figs. 3, 4). When troponin and creatine kinase elevations are blocked with Phe in the female, there is protection of cerebral autoregulation. In males, however, Phe further increases troponin and creatine kinase and cerebral autoregulation is further

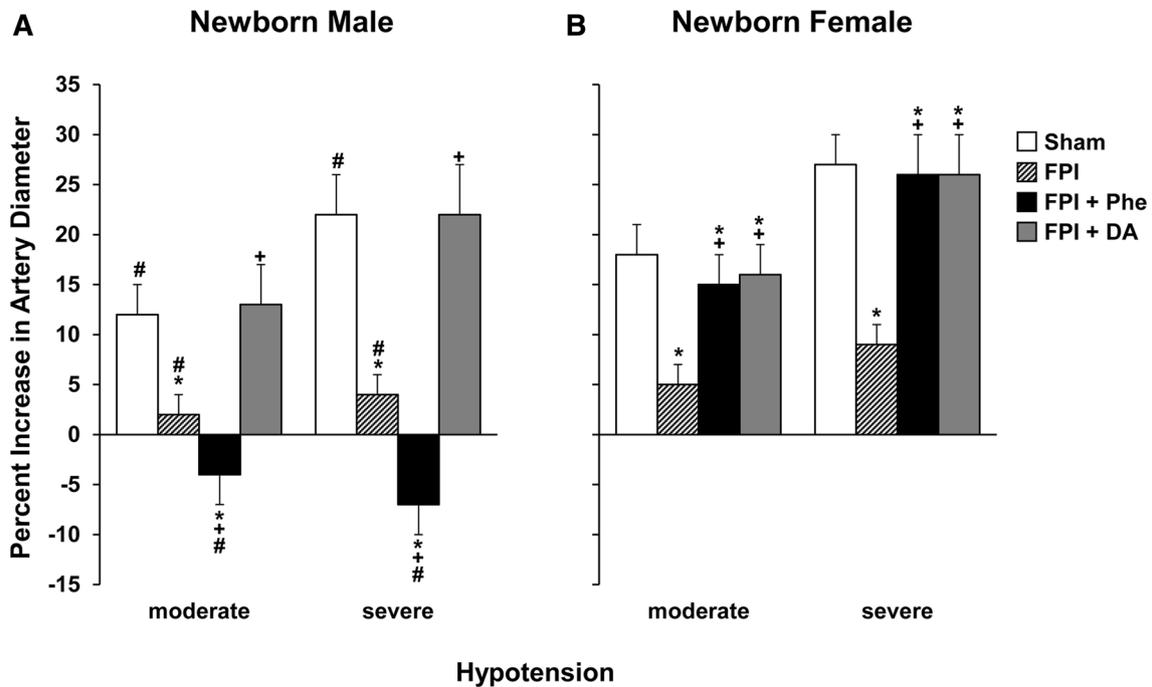


impaired. In this case, pial artery dilation during hypotension is converted from the small impaired pial artery dilator to a vasoconstrictor by Phe (Fig. 4). However, DA blocked elevations in these enzymes and there is complete protection of cerebral autoregulation. Therefore, a second key new finding in the present study is that Phe aggravated the observed increase in plasma troponin and creatine kinase in the male but not the female while DA blocked increases in cardiac enzymes in both sexes, serving as a potential explanation for the prior observed sex dependency of some vasoactive agents in improvement of outcome after TBI. A limitation to the present study is that the dose of Phe required to reach the CPP target was not rigorously studied as a function of sex. Nonetheless, it is interesting to note that it was observed that the dose required to reach the CPP target was lower in males compared to females in the setting of TBI.

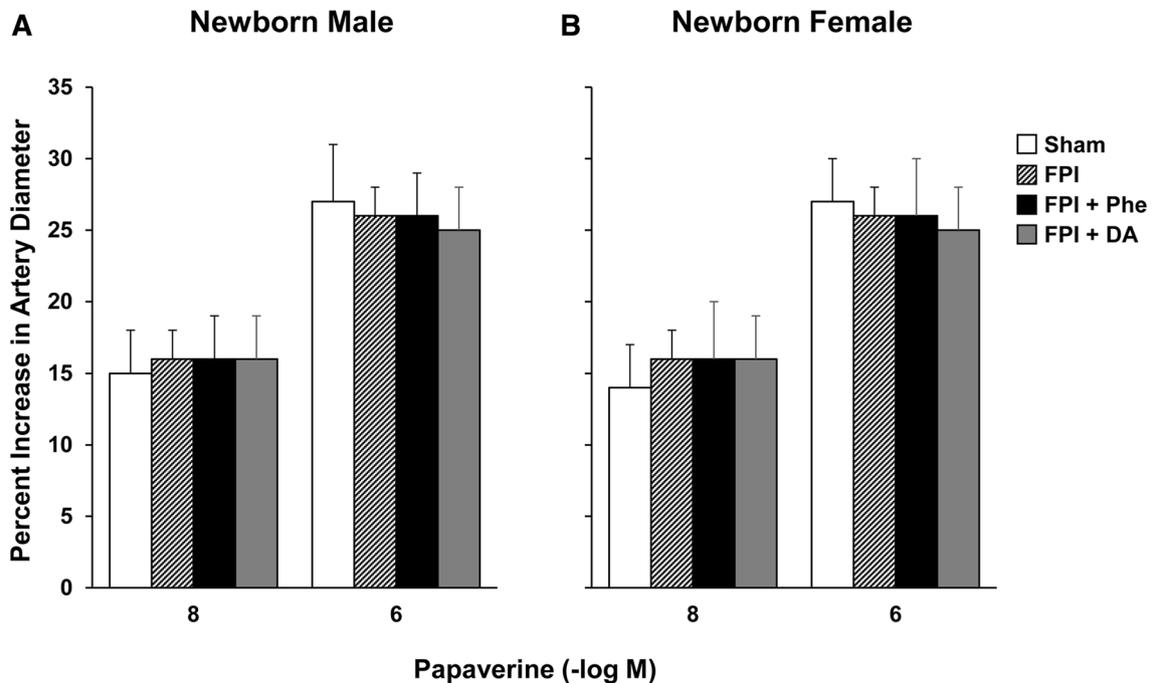
Medical evidence has implicated neurological injuries, particularly SAH, as a cause of cardiac dysfunction [6–8]. Despite the frequency with which TBI affects the general population, its potential impact on cardiac function has received little attention [9]. In clinical work, we were the first to describe cardiac dysfunction after TBI, which lasted for up to 2 weeks [7, 10–13]. Cardiac enzymes (troponin, creatine kinase) were observed to be elevated and associated with abnormal

echocardiography [10]. Results of the present study extend these clinical observations in two ways: (1) degree of cardiac enzyme elevation after TBI is sex-dependent and (2) vasoactive agents used to elevate MAP and improve brain outcome differentially modulate cardiac enzyme release in a sex-dependent manner after TBI.

Three main theories explaining the pathogenesis of brain injury-induced cardiac dysfunction include multi-vessel coronary spasm causing ischemia, microvascular dysfunction, and the catecholamine hypothesis [18]. The prevailing theory involves a catecholamine-induced effect secondary to ischemia, elevated ICP, and damage to the insular cortex and hypothalamus [14]. This results in a catecholamine storm which is clinically manifested by tachycardia, increased vascular resistance, and cardiac dysfunction. Early systolic dysfunction following TBI has been observed [19], and these patients have a distinctive hemodynamic profile with early hypertension and tachycardia, followed by a decrease in blood pressure over the first day after TBI [20]. This profile suggests an early maladaptive catecholamine excess state as a potential underlying mechanism of TBI-induced systolic dysfunction [20]. Injury to the myocardium secondary to catecholamine release results and is aggravated by dysregulated endocrine function and neuroinflammation [8, 13].



**Fig. 4** Influence of FPI on pial artery diameter during hypotension (moderate, severe) in **a** newborn male and **b** newborn female pigs. Conditions are before (sham control), after FPI, after FPI treated with Phe, and after FPI treated with DA,  $n=5$  shown as mean  $\pm$  standard deviation of the mean. Baseline artery diameter was  $140 \pm 16$   $\mu\text{m}$  prior to hypotension before (sham) FPI,  $115 \pm 14$   $\mu\text{m}$  after FPI,  $138 \pm 18$   $\mu\text{m}$  after FPI treated with Phe, and  $141 \pm 20$   $\mu\text{m}$  after FPI treated with DA,  $n=5$ . \* $p < 0.05$  compared to corresponding sham value, † $p < 0.05$  compared to corresponding FPI alone value, # $p < 0.05$  compared to corresponding female value



**Fig. 5** Influence of papaverine ( $10^{-8}$ ,  $10^{-6}$  M) on pial artery diameter in **a** newborn male and **b** newborn female pigs. Conditions are before (sham control), after FPI, after FPI treated with Phe, and after FPI treated with DA,  $n=5$  shown as mean  $\pm$  standard deviation of the mean

The mechanism of myocyte injury involves catecholamine excess, elevated intracellular calcium, and reperfusion injury. Elevated catecholamine levels decrease the viability of myocytes through cAMP-mediated calcium overload. The end result of the catecholamine storm is mitochondrial dysfunction and cell death with the resulting histologic feature of contraction band necrosis [7]. There has been growing interest into the secondary role of the inflammatory cascade in brain–heart interactions. Neurologic injury can trigger a neuroinflammatory response, including release of cytokines from the brain into the systemic circulation associated with cardiac dysfunction after TBI [21]. The activation of the sympathetic nervous system can also lead to unchecked myocardial inflammation, resulting in myocardial cell death and cardiac dysfunction [22].

Cardiac dysfunction resulting from TBI leads to decreased cardiac output, hypotension, and decreased CBF thereby predisposing to the possibility that such cardiac injury may reciprocally contribute to further neurologic injury [7]. A third key new finding in the present study is that the catecholamine excess associated with cardiac dysfunction is prolonged (at least 8 days post FPI) and can be modulated by vasoactive agents administered in treatment of TBI and that this modulation is sex-dependent. In particular, Phe blocked elevations of NE and EPI in plasma in females but potentiated such elevations in males after FPI. In contrast, DA blocked elevations of catecholamine levels in plasma after FPI in both sexes. These data suggest that administration of drugs intended to improve outcome of the brain after TBI may have secondary, perhaps unintended, effects on the heart. Such secondary heart effects may either summate the beneficial or exacerbate the deleterious effects of such drug therapy given in treatment of the brain.

Prior studies had been directed at mechanism(s) involved in impairment of cerebral autoregulation and brain histopathology after FPI and their modulation by therapeutic intervention with Phe and DA [23]. We have used an established porcine model of FPI that mimics TBI to corroborate clinical observations regarding cerebral autoregulation and hypotension after TBI [23]. Like humans, piglets have gyrencephalic brains, are sensitive to FPI, and newborn 1–5 day old pigs mimic young children [24]. Cerebral autoregulation is impaired to a greater extent in males and newborns compared to female and juvenile pigs, which parallels that observed clinically [2, 23].

Mechanistically, impairment of cerebral autoregulation after FPI involves the sequential release of endothelin-1 (ET-1) and activated oxygen via protein kinase C, and cyclooxygenase-2-dependent pathways which upregulates the amount of phosphorylated (activated) ERK

MAPK to impair K channel function and dilator systems dependent on intact K channels, such as autoregulation [23]. Prior unrelated studies indicated an association between upregulation of ERK MAPK with increased CSF IL-6 after FPI [17]. More recently, we have observed that increased CSF IL-6 contributed to impairment of cerebral autoregulation and histopathology after FPI [25]. Phe blocks upregulation of ET-1, release of activated oxygen, ERK MAPK phosphorylation, and impairment of K channel function to result in prevention of impairment of cerebral autoregulation and histopathology in the female but aggravates these indices of outcome in the male after FPI via augmented activation of these deleterious signaling pathway sequence [23]. DA, on the other hand, prevents impairment of cerebral autoregulation and brain histopathology via block of the deleterious signaling cascade equivalently in male and female pigs after FPI [23]. Future studies will investigate relationships between neuroinflammatory mediators, cardiac dysfunction, and catecholamines in the setting of TBI. Presently, we speculate that the block of cardiac release of troponin and creatine kinase by Phe in the female and by DA in both the male and the female after FPI limits the feed-forward cycle of cardiac dysfunction producing further brain injury. Conversely, the augmentation of cardiac release of troponin and creatine kinase by Phe in the male after FPI similarly augments brain injury as seen with cerebral autoregulation as the index of outcome. Since neuroinflammatory mediators can be released centrally after TBI to cause cardiac dysfunction, we further speculate that the heart can in a feed-forward manner cause additional brain injury via central release of IL-6, whose release can then be differentially modulated by Phe and DA in males and females to either improve or aggravate negative outcome in the setting of TBI. Therefore, brain–heart cross-talk in the setting of TBI and its secondary sex-dependent manipulation by administration of vasoactive drugs should be considered by clinicians when therapeutically intervening in treatment of TBI.

## Conclusions

These data indicate that pressor choice in elevation of CPP is important in limiting cardiac dysfunction and suggest that DA protects cerebral autoregulation in both sexes via reduction of biomarkers of cardiac injury and catecholamines released after TBI.

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### Author Contributions

WA designed the study, participated in pig TBI experiments, analyzed and interpreted the data, and wrote the manuscript. MV designed the study, interpreted the data, and wrote the manuscript.

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### Conflicts of interest

All authors have no conflict of interest to declare.

### Ethical Approval

This protocol (805388) was approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania.

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### References

- Freeman SS, Udomphorn Y, Armstead WM, Fisk DM, Vavilala MS. Young age as a risk factor for impaired cerebral autoregulation after moderate-severe pediatric brain injury. *Anesthesiology*. 2008;108:588–95.
- Chaiwat O, Sharma D, Udomphorn Y, Armstead WM, Vavilala MS. Cerebral hemodynamic predictors of poor 6 month Glasgow Outcome Score in severe pediatric traumatic brain injury. *J Neurotrauma*. 2009;26:657–63.
- Armstead WM, Kiessling JW, Kofke WA, Vavilala MS. Impaired cerebral blood flow autoregulation during post traumatic arterial hypotension after fluid percussion brain injury is prevented by phenylephrine in female but exacerbated in male piglets by ERK MAPK upregulation. *Crit Care Med*. 2010;38:1868–74.
- Armstead WM, Riley J, Vavilala MS. Dopamine prevents impairment of autoregulation after TBI in the newborn pig through inhibition of upregulation of ET-1 and ERK MAPK. *Pediatr Crit Care Med*. 2013;14:e103–11.
- Armstead WM. Cerebral blood flow autoregulation and dysregulation. *Anesthesiol Clin*. 2016;34:465–77.
- Kono T, Morita H, Kuroiwa T, Onaka H, Takatsuka H, Fujiwara A. Left ventricular wall motion abnormalities in patients with subarachnoid hemorrhage: neurogenic stunned myocardium. *J Am Coll Cardiol*. 1994;24:636–40.
- Krishnamoorthy V, Mackensen GB, Gibbons EF, Vavilala MS. Cardiac dysfunction after neurologic injury. What do we know and Where are we going? *Chest*. 2016;149:1325–31.
- Mashaly HA, Provencio JJ. Inflammation as a link between brain injury and heart damage: the model of subarachnoid hemorrhage. *Cleveland Clin J Med*. 2008;75:526–30.
- Bahloul M, Chaari AN, Kallel H, Khabir A, Ayadi A, Charfeddine H, Hergafi L, Chaaari AD, Ben Chelly HE, Hamida C, Rekik N, Bouazizz M. Neurogenic pulmonary edema due to traumatic brain injury: evidence of cardiac dysfunction. *Am J Crit Care*. 2006;15:462–70.
- Prathep S, Sharma D, Hallman M, Joffe A, Krishnamoorthy V, Mackensen BG, Vavilala MS. Preliminary report on cardiac dysfunction after isolate traumatic brain injury. *Crit Care Med*. 2014;42:142–7.
- Krishnamoorthy V, Prathep S, Sharma D, Fujita Y, Armstead W, Vavilala MS. Cardiac dysfunction following brain death after severe pediatric traumatic brain injury: a preliminary study of 32 children. *Int J Crit Illn Inj Sci*. 2015;5:103–7.
- Krishnamoorthy V, Borbely X, Rowhani-Rahbar A, Souter MJ, Gibbons E, Vavilala MS. Cardiac dysfunction following brain death in children: prevalence, normalization, and transplantation. *Pediatr Crit Care Med*. 2015;16:e107–12.
- Krishnamoorthy V, Prathep S, Sharma D, Gibbons E, Vavilala MS. Association between electrocardiographic findings and cardiac dysfunction in adult isolated traumatic brain injury. *Indian J Crit Care Med*. 2014;18:570–4.
- Samuels MA. The brain-heart connection. *Circulation*. 2007;116:77–84.
- Pick J, Chesnut RM, Marshall LF, et al. Extracranial complications of severe head injury. *J Neurosurg*. 1992;77:901–7.
- Vavilala MS, Tontisirin N, Armstead W, Zimmerman JZ, Chesnut R, Lam AM. Hemispheric differences in cerebral autoregulation in children with moderate and severe traumatic brain injury. *Neurocrit Care*. 2008;9:45–54.
- Armstead WM, Riley J, Vavilala MS. Norepinephrine protects autoregulation and reduces hippocampal necrosis after traumatic brain injury via block of ERK MAPK and IL-6 in juvenile pigs. *J Neurotrauma*. 2016;33:1761–7.
- Lee VH, Oh JK, Si Mulvagh, Wijdicks EF. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2006;5:243–9.
- Krishnamoorthy V, Rowhani-Rahbar A, Gibbons EF, Rivara FP, Temkin NR, Pontius C, Luk K, Graves M, Lozier D, Chaikittisilpa N, Kiatchai T, Vavilala MS. Early systolic dysfunction following traumatic brain injury: a cohort study. *Crit Care Med*. 2017;45:1028–36.
- Krishnamoorthy V, Rowhani-Rahbar A, Chaikittisilpa N, Gibbons EF, Rivara FP, Temkin NR, Quistberg A, Vavilala MS. Association of early hemodynamic profile and the development of systolic dysfunction following traumatic brain injury. *Neurocrit Care*. 2017;26:379–87.
- Chaikittisilpa N, Krishnamoorthy V, Lele A, Qui Q, Vavilala MS. Characterizing the relationship between systemic inflammatory response syndrome and early cardiac dysfunction in traumatic brain injury. *J Neuro Res*. 2018;96:661–70.
- Nguyen H, Zaroff JG. Neurogenic stunned myocardium. *Curr Neurol Neurosci Rep*. 2009;9:486–91.
- Armstead WM. Cerebral blood flow autoregulation and dysautoregulation. In: Kofke WA, editor "Advances in neuroscience in anesthesia and critical care" issue of anesthesiology clinics, vol. 34. Elsevier; 2016. p. 465–477.
- Dobbing J. The later development of the brain and its vulnerability. In: Davis JA, Dobbing J, editors. *Scientific foundations of pediatrics*. London: Heineman Medical; 1981. p. 744–59.
- Curvello V, Pastor P, Hekierski H, Armstead WM. Inhaled nitric oxide protects cerebral autoregulation and reduces hippocampal necrosis after traumatic brain injury through inhibition of ET-1, ERK MAPK, and IL-6 upregulation in pigs. *Neurocrit Care*. 2018;10:15. <https://doi.org/10.1007/s12028-018-0638-1>.