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Review Article

Translational approach towards determining the role of cerebral autoregulation in outcome after traumatic brain injury

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ABSTRACT

Cerebral autoregulation is impaired after traumatic brain injury (TBI), contributing to poor outcome. In the context of the neurovascular unit, cerebral autoregulation contributes to neuronal cell integrity and clinically Glasgow Coma Scale is correlated to intactness of autoregulation after TBI. Cerebral Perfusion Pressure (CPP) is often normalized by use of vasoactive agents to increase mean arterial pressure (MAP) and thereby limit impairment of cerebral autoregulation and neurological deficits. However, current vasoactive agent choice used to elevate MAP to increase CPP after TBI is variable. Vasoactive agents, such as phenylephrine, dopamine, norepinephrine, and epinephrine, clinically have not sufficiently been compared regarding effect on CPP, autoregulation, and survival after TBI. The cerebral effects of these clinically commonly used vasoactive agents are incompletely understood. This review will describe translational studies using a more human like animal model (the pig) of TBI to identify better therapeutic strategies to improve outcome post injury. These studies also investigated the role of age and sex in outcome and mechanism(s) involved in improvement of outcome in the setting of TBI. Additionally, this review considers use of inhaled nitric oxide as a novel neuroprotective strategy in treatment of TBI.

1. The definition of bidirectional translational research as the focus for this review

Recent clinical trials in traumatic brain injury (TBI) have been unable to demonstrate therapeutic effects even when there appears to be good evidence for efficacy in one or more preclinical models. Translational work has been primarily focused on outcomes of efficacy that correlate with degree of injury in the animal models but do not mimic practical clinical measures of the underlying pathology that could facilitate stratification for clinical trial design. For example, despite animal studies documenting impaired cerebral autoregulation and poor outcomes, cerebral autoregulation testing is not routinely performed in the care of children with severe TBI. The ability to closely monitor background intensive care unit therapies in basic science animal TBI models may be helpful in identifying novel therapeutic strategies to improve outcome. Basic science insights into mechanism may, in turn inform design of newer therapeutic strategies to improve outcome after TBI. Bidirectional translational research is defined as the bedside observation informing the study design of the basic science preclinical animal model, which, in turn, generates data that informs the attainment of better mechanistic data in TBI patients.

2. Cerebral autoregulation and traumatic brain injury

Cerebral autoregulation is a homeostatic process that regulates and maintains cerebral blood flow (CBF) constant across a range of blood pressures in order to meet the brain's high metabolic demands. The original conceptualization was proposed by Lassen (1959) as a triphasic curve consisting of the lower limit, the plateau and the upper limit. This homeostatic mechanism ensures that as mean arterial pressure (MAP) or cerebral perfusion pressure (CPP) increases, resistance increases (vasoconstriction) in the small cerebral arteries. CPP is defined as MAP minus intracranial pressure (ICP). Conversely, this process maintains constant CBF by decreasing cerebrovascular resistance or vasodilation when MAP or CPP decreases. However, given that the lower limit of cerebral autoregulation frequently influences clinical management, it

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should be noted that this value has been challenged as being too low (Drummond, 1997). One clinical study documented well developed cerebral autoregulatory mechanisms in infants with no difference in the lower limit of autoregulation between children and adolescents, suggesting a larger difference between resting MAP and lower limit of autoregulation with increasing age (Vavilala, 2003).

TBI is the leading form of pediatric trauma and boys of all ages and children under 4 years have worse outcomes than girls and older children (Langlois et al., 2005; Newacheck et al., 2004; Chaiwat et al., 2009). Cerebral autoregulation is often impaired after TBI (Armstead, 2016). CBF then becomes pressure passive and can result in secondary cerebral hypoperfusion in the presence of hypotension, leading to poor patient outcome (Chaiwat et al., 2009). Low CPP is associated with low CBF. In the context of the neurovascular unit, low CBF is thought to contribute to neuronal cell necrosis (Armstead, 2016; Armstead et al., 2016a, 2016b). Importantly, the degree of autoregulatory impairment is associated with Glasgow Coma Scale value after TBI (Freeman et al., 2008), indicating the functional significance of loss of this physiological control mechanism with higher TBI severity.

TBI in humans is characterized by a vast spectrum of evolving neuropathology, which span varying degrees of hemorrhage, brain swelling, contusions, diffuse axonal injury, and ischemia. Compared to children without TBI, children with TBI have lower middle cerebral artery velocity (Vavilala et al. 2004) and cerebral hypoperfusion (CBF $<$ 25 ml/100 g/min) is the dominant derangement (Adelson et al., 1997). Cerebral hypoperfusion is associated with cerebral ischemia and poor outcome (Coles et al., 2004; Skippen et al., 1997; Sharples et al., 1995). Young children with TBI and $<$ 4 years of age are more at risk of impaired cerebral autoregulation than older children and after moderate -severe TBI, boys also have more impairment of autoregulation compared to girls after adjusting for injury severity (Freeman et al., 2008). Small studies indicate that after TBI, some patients have hypoperfusion while others have normal to elevated middle cerebral artery flow velocities when autoregulation is impaired, when mean arterial pressure is either low or high respectively (Vavilala et al., 2008). Hemispheric differences have also been observed within patients (Vavilala et al., 2008). Changes in perfusion and autoregulation have also been observed during the first 10 days in children with TBI (Lele et al., 2018), suggesting temporal alterations in cerebral autoregulation.

If cerebral autoregulation is impaired, lower blood pressure may result in diminished CPP and CBF. After TBI, ICP is often increased, which further decreases CPP, leading to more cerebral vasodilation if autoregulation is intact but this is often not known. Therefore, there is uncertainty as to whether it would be useful to empirically increase MAP to prevent cerebral ischemia as a means to protect cerebral autoregulation, since theoretically, augmenting MAP in the hyperemic brain could result in cerebral hemorrhage (Mandera et al., 2002; Bruce et al., 1981; Aldrich et al., 1992). We examined the relationship between cerebral hemodynamic predictors during the first 72 h after injury, including cerebral autoregulation, and long-term outcome after severe, Glasgow Coma Scale (GCS) score $<$ 9, pediatric TBI. Ten (28%) of the 36 children examined had poor outcome. Independent risk factors for poor 6-month GCS were impaired cerebral autoregulation and hypotension (systolic blood pressure $<$ 5th percentile). In this study, both impaired cerebral autoregulation and systolic blood pressure $<$ 5th percentile were independent risk factors for poor 6-month GCS, suggesting a causal role for impaired autoregulation, independent of hypotension on outcome. A recent clinical study documented impaired cerebral autoregulation even in complex mild TBI, associated with the presence of headache and during the first five days after TBI (Vavilala et al., 2018b).

3. Neuromonitoring of TBI

Considerable amounts of data estimating CBF in healthy children and in children with TBI have been obtained using transcranial Doppler ultrasonography (Vavilala et al., 2018a). Transcranial Doppler ultrasonography is commonly used to estimate CBF because it is non-invasive and operable at the bedside. Transcranial Doppler ultrasonography measures cerebral blood flow velocity. Although it does not directly measure CBF, transcranial Doppler monitored changes in cerebral blood flow velocity generally correlate well with changes in CBF (Fisher and Truemper, 1999; Giller et al., 1998). However, it has been noted that transcranial Doppler pulsatility index is not a reliable indicator of ICP in children with severe TBI, thereby limiting its ability provide accurate information on CPP (Fugaji et al., 2009).

Assessment of cerebral autoregulation can be accomplished via either static or dynamic means. In the static method, only steady state relationships between CBF and MAP are considered without taking into account the time course of changes in these two parameters. Determination of a steady state relationship can be accomplished through administration of drugs which change MAP, yielding two values of CBF and their difference in relation to the MAP change being indicative of autoregulation (Lassen, 1974).

In the dynamic method, assessment is based on determination of dynamic changes of CBF in response to dynamic changes in MAP. Several approaches are used to assess dynamic cerebral autoregulation via CBF recovery time. In the first, which uses the thigh cuff method (Aaslid et al., 1989), regulation is defined by the slope of cerebral vascular resistance (CVR) recovery, where CVR = CPP/CBF; the steeper the slope of CVR, the better is the autoregulation (Tiecks et al., 1995). In a second method, the CBF recovery after the cuff release is quantified as an autoregulation index, calculated as a second-order differential equation relating changes in CBF and MAP (Tiecks et al., 1995).

A third approach considers study of CBF response to slow oscillations in MAP induced by head up tilting, paced breathing or thigh-cuff inflation (Reinhard et al., 2006; Diehl et al., 1995; Aaslid et al., 2007). Transfer function analysis is then done using beat-to-beat MAP measurements as input and CBF as output (Zhang et al., 1998). The time delay of phase difference between MAP and CBF as a function of frequency can be used to determine the degree of intactness of autoregulation. Since the thigh cuff inflation/deflation technique presents problems in the TBI patient, where manipulation of MAP would occur at a time when the injured brain may be least able to tolerate it, this approach is viewed as being preferable in the setting of TBI. The pressure reactivity index is one such measure of dynamic auotoregulation that uses this approach. The pressure reactivity index is defined as the moving Pearson's correlation coefficient between MAP and ICP (Czosnyka et al., 1997) and derives from the notion that in the normal brain, in low compliance states such as are frequently seen after TBI, increases in MAP will lead to constriction of the cerebral blood vessels in order to maintain constant flow. This results in a decrease in ICP due to a decrease in intracranial blood volume. Pressure reactivity index values range from -1 (perfectly intact autoregulation) to $+1$ (complete absence of autoregulation). Studies in both adults and children have demonstrated a strong relationship between pressure reactivity index and outcome, with values $>$ 0.2 associated with high morbidity and mortality (Czosnyka et al., 1997; Steiner et al., 2002; Zweifel et al., 2008; Sorrentino et al., 2012; Rhee et al., 2018). The pressure reactivity index has been shown to vary with cerebral perfusion pressure, making it is a promising target for clinical therapeutics aimed at improving autoregulation and outcome but this largely remains a research tool.

The optimal MAP and optimal CPP are thought to be in the center of the autoregulatory plateau and represent the pressures where vascular responsiveness is most robust. Preliminary data suggest that multimodal neuromonitoring may benefit provision of adequate CPP which in turn may be desired when cerebral autoregulation is impaired (Young et al., 2016). Several studies have suggested that a larger difference between actual time-averaged CPP and optimal CPP is associated with a greater risk of poor outcome (Depreitere et al., 2014;

Needham et al., 2017), though this has recently been contested (Kramer et al., 2019). While it appears clear that there is an association between optimal CPP and global outcome in the setting of TBI, some of the limitations to these studies relate to use of a single site and/or low numbers of enrolled patients. Additional randomized larger studies will be needed to further clarify the significance of the optimal CPP. Nonetheless, the importance of maintaining the optimal CPP can be appreciated by the clinical observation that time is an important factor in the relationship between CPP and cerebral autoregulation; eg that in the presence of compromised autoregulation, the brain's capacity to tolerate an otherwise "safe" CPP is diminished (Guiza et al., 2017).

4. Clinical observations inform basic science modeling of TBI

Current 2019 Pediatric Guidelines recommend maintaining CPP above 40 mmHg (Kochanek et al., 2019), noting that an age-related continuum for the optimal CPP is between 40 and 65 mmHg. The lower limit of autoregulation does not appear to increase with age, meaning that the mathematical difference between resting MAP and lower limit of autoregulation increases with age since MAP increases with age (Vavilala et al., 2002). Therefore, young children may be more at risk of cerebral ischemia with MAP or CPP below the lower limit of autoregulation. Since mathematically CPP = MAP – ICP, when ICP is elevated as in TBI, CPP can be normalized through elevation of MAP. However, vasoactive agents clinically used to elevate MAP, such as dopamine, phenylephrine, norepinephrine, and epinephrine (Ishikawa et al., 2009; Sookplung et al., 2011; Steiner et al., 2004) have not sufficiently been compared regarding effect on CPP, CBF, autoregulation, and survival after TBI, and clinically, current vasoactive agent use is variable. Additionally, the cerebral effects of these clinically commonly used vasoactive agents are not well characterized. Consequently, there are no recommendations regarding preferred choice of vasoactive agents in pediatric TBI. For this reason, we decided to rigorously investigate the cerebral effects of vasoactive agents in our preclinical model of TBI.

5. Preclinical models of pediatric TBI

There have been a number of studies that have characterized the effects of TBI using immature animals (Babikian et al., 2010; Robertson et al., 2001). Many have used rodent basic science mimics of TBI. To some degree all of these studies have the disadvantage of not permitting repeated measurements of systemic physiological variables and regional CBF because of the small size of the subjects. Additionally, rodents have a lissencephalic brain containing more grey than white matter. In contrast, piglets have a gyrencepahalic brain that contains substantial white matter similar to humans, which is more sensitive to ischemic damage than grey matter. Several neuroprotectants identified in preclinical stroke and TBI studies in rodents have yielded disappointing results when entered into clinical trials. We speculate that one major reason for this failure may be that these drugs preferentially protect grey matter and therefore appear as most promising in rodent models. Previous studies of TBI in pigs have focused on lesion volume and edema rather than cerebral hemodynamics (Grate et al., 2003; Duhaime et al., 2000a, 2003). The one previous study of age related effects on CBF (Duhaime et al., 2000b) involved a model of focal injury (cortical contusion) and not diffuse or mixed focal/diffuse as in FPI, which is thought to more closely simulate pediatric TBI (Adelson, 1999; Gennarelli, 1994). More recent studies in piglets used nonimpact head rotation as the injury model, but only used carotid artery blood flow as an indirect index of cerebral hemodynamics (Clevenger et al., 2015).

6. Preclinical experimental approach using pigs to identify vasoactive agents that improve outcome after pediatric TBI

Little is known about how age at time of injury and sex influence cerebral autoregulation and responsiveness to vasoactive agents. Thus, in earlier studies in our lab we used male and female newborn (1–5 day old) and juvenile (3–4 week old) pigs, which correspond to the human ages of < 4 and > 4 yrs. of age (Dobbing, 1981) to characterize the effects of TBI. These studies were designed to correspond with human studies demonstrating age and sex dependency in TBI effects (Freeman et al., 2008). Indeed, it was observed that cerebral autoregulation was impaired to a greater extent and for a longer time duration in newborn compared to juvenile pigs after FPI of equivalent intensity (Armstead and Kurth, 1994; Armstead, 2016). Similarly, autoregulation was impaired to a greater extent in male compared to female pigs after FPI (Armstead et al., 2010a).

Vasoactive agents were administered to elevate MAP with intent of normalizing CPP using an approach that typically is used clinically. In particular, the vasoactive agent infusion was begun once CPP dropped below 45 mmHg and the dose was increased until the target CPP was reached.

The abilities of 4 commonly used vasoactive agents to improve two indices of outcome, autoregulation and hippocampal cell necrosis, were investigated in pigs. Phenylephrine potentiated impairment of cerebral autoregulation in newborn males, but prevented impairment of cerebral autoregulation and histopathology in newborn females and older males and females after TBI (Table 1) (Armstead et al., 2010a; Curvello et al., 2017a). Norepinephrine yielded a similar outcome to phenylephrine, but phenylephrine augmented impairment while impairment was the same as vehicle after TBI with NE (Table 1) (Armstead et al., 2016a, 2016b). Outcome was protected in young males and females and older females, but not older males after epinephrine (Table 1) (Armstead et al., 2017). In contrast, dopamine prevented impairment of autoregulation and histopathology after TBI in both ages and sexes (Table 1) (Armstead et al., 2013; Curvello et al., 2017b). These data indicate that the clinical impact is significant in that autoregulation therapy and particularly CPP optimal therapy is robustly affected by the choice of vasoactive drug.

These studies advance the field in several ways. First, these studies indicate that there are sex and age dependent differences in ability to improve outcome when using drugs to achieve an equivalent CPP post injury. To mimic the clinical situation, CPP was targeted (55–60 and 65–70 mmHg for young and older pigs per 2012 Pediatric Guidelines) to determine the dose of the intravenous infusion of the particular vasoactive agent.

A second advance recognizes that targeting a given CPP is not

Table 1
Age and sex dependent effects of vasoactive agents on outcome after TBI. As adapted from Armstead and Vavilala, 2019.

Vasoactive agent	Outcome after TBI			
	Newborn		Juvenile	
	Male	Female	Male	Female
EPI	Protection Modulation of JNK MAPK	Protection	No Protection	Protection
NE	No Protection Modulation of IL-6 via ERK MAPK	Protection	Protection	Protection
Phe	Potentiated Impairment Modulation of ERK MAPK	Protection	Protection	Protection
DA	Protection Modulation of ERK MAPK	Protection	Protection	Protection

EPI = epinephrine, NE = norepinephrine, Phe = phenylephrine, DA = dopamine, extracellular signal-related kinase = ERK, and c-Jun N-terminal kinase = JNK, mitogen activated protein kinase = MAPK, interleukin = IL This table illustrates the age and sex dependent effects of various vasoactive agents on two aspects of outcome (cerebral autoregulation and hippocampal histopathology) in the setting of TBI and the mechanism by which this outcome will be affected.

sufficient and considers the use of cerebral autoregulation to individualize blood pressure management after TBI (Curvello et al., 2017b). Indeed, it has been observed that the degree of intactness of autoregulation is associated with GCS in pediatric TBI patients (Freemen at al 2008). While there are number of brain areas involved in learning and memory, the hippocampus is thought to be a key area. Damage to the hippocampus was quantified by H + E stain of dying neuronal cells. A correlate to GCS in a preclinical model, therefore, is the degree of neuronal cell death in the CA1 and CA3 hippocampus after TBI. These data advance the field in that they support manipulation of cerebral autoregulation via targeted use of vasoactive agents in the setting of TBI as a means to improve cognitive outcome. Therefore, a therapeutic paradigm which singly focuses on elevation of MAP after TBI is somewhat simplistic.

Recent studies have contributed to a third advance in the field: the mechanism whereby vasoactive choice determines outcome as a function of age and sex after TBI. The advancement of knowledge is that administration of a series of vasoactive agents may all accomplish the same goal of normalization of CPP but yet produce very different outcomes because diverse signaling pathways are modulated.

Relaxation of blood vessels can be mediated by several mechanisms, including cGMP, cAMP, and K^+ channels (Faraci and Heistad, 1998). Activation of K channels increases K^+ efflux, causing hyperpolarization of vascular smooth muscle and vasodilation. Pharmacological studies using selective activators and inhibitors have provided evidence that K^+ channels, especially ATP sensitive and calcium sensitive channels, regulate cerebrovascular tone (Faraci and Heistad, 1998).

Vasodilation can be used as an index of the intactness of K channel function after TBI (Faraci and Heistad, 1998). Pial artery dilation during hypotension is due to activation of ATP and calcium sensitive K channels (Armstead, 1999), giving functional significance to intactness of K channel function. Since pial artery dilation in response to ATP and calcium sensitive K channel agonists is blunted more in the male than the female after FPI (Armstead et al., 2011), sex dependent greater reductions in CBF and impairment of cerebral autoregulation in the male compared to the female may relate to more aggravated impairment of K channel function in that sex. It was observed that the peptide adrenomedullin (ADM), which activates ATP sensitive K channels, is upregulated in the female but not the male after FPI, while exogenous adrenomedullin administration prevents impairment of autoregulation in both sexes (Armstead and Vavilala, 2007). These data indicate that the presence of an endogenous neuroprotectant in the female contributes to differential sex dependent outcome post insult.

Mitogen activated protein kinase (MAPK) is an important signaling pathway and exists in at least three isoforms, p38, extracellular signal-related kinase (ERK), and c-Jun N-terminal kinase (JNK). The phosphorylated (activated) JNK and ERK isoforms are increased in concentration after TBI and contribute to reduced CBF, impaired cerebral autoregulation, and histopathology after TBI (Armstead et al., 2010a, 2016b). Cerebral autoregulation is impaired more in males compared to females and in the younger compared to the older pig after TBI, owing to greater upregulation of phosphorylated ERK and JNK (Armstead et al., 2010a; 2016). Phenylephrine blocked phosphorylation of ERK MAPK in young female and older male and female pigs after TBI, but augmented upregulation in young males (Table 1), resulting in augmented impairment of cerebral autoregulation in young males and protection of cerebral autoregulation in all other groups after TBI (Armstead et al., 2010a; Curvello et al., 2017a). Epinephrine blocked phosphorylation of JNK in young male, young female, and older female but not older male pigs after TBI (Table 1), causing impairment of autoregulation. On the other hand, norepinephrine blocked phosphorylation of ERK MAPK in young female and older male and female pigs after TBI, but not in young males (Table 1), resulting in impairment of cerebral autoregulation in young males and protection in all other groups (Armstead et al., 2016a, 2016b). Interleukin-6 (IL-6) concentration was elevated after TBI and contributed to increased phosphorylation of ERK (Table 1) (Armstead et al., 2016b). DA blocked phosphorylation of ERK after TBI in both sexes and ages (Table 1), yielding protection of cerebral autoregulation after TBI in both sexes and age groups (Armstead et al., 2013; Curvello et al., 2017b).

Brain concentration of adrenomedullin is increased after TBI (Robertson et al., 2001) and achieves protection through blockade of the upregulation of the ERK isoform of MAPK after injury (Armstead, 2016; Armstead and Vavilala, 2014). Endothelin-1 (ET-1) contributes to blunted K channel agonist mediated dilation after FPI via release of activated oxygen which can then activate ERK (Armstead and Vavilala, 2014). Because more phosphorylated ERK MAPK is released after TBI in the male compared to the female, there is greater impairment of autoregulation and ATP and calcium sensitive K channel agonist-mediated cerebrovasodilation post injury in males compared to females (Armstead et al., 2011).

Of the vasoactive agents investigated, including phenylephrine, epinephrine, and norepinephrine, dopamine is the only one demonstrated to improve outcome after TBI in both sexes and ages. These data suggest that dopamine should be considered as a first line treatment to protect cerebral autoregulation and promote cerebral outcomes in pediatric TBI irrespective of age and sex.

There are, however, some experimental caveats that should be considered. Vasoactive agents may have direct effects on brain independent of effects on CBF and cerebral autoregulation. For example, vasoactive agents may have effects on pericytes, shunt flow and/or effects at the capillary level. Further, vasoactive agent associated effects in the hippocampus may reflect direct neurotoxic events and/or influence on secondary ischemic episodes. These and other phenomena may likely play key roles in determining ultimate outcome.

7. Inhaled nitric oxide improves outcome in preclinical experimental TBI

An alternative strategy to normalize CPP could involve administration of a cerebrovasodilator to elevate CBF. Recently, it was observed that inhaled NO (iNO) prevented impairment of cerebral autoregulation and neuronal cell necrosis in hippocampal regions CA1 and CA3 after FPI in both male and female newborn and juvenile pigs (Hekierski et al., 2018). The fact that outcome was improved regardless of sex and age is significant clinically since the above discussion centered on the need for use of a single vasoactive agent to elevate MAP and normalize CPP in treatment of pediatric TBI. Somewhat surprisingly, though, statistically significant pial artery dilation, which reflects an increase in CBF, and an increase in calculated CPP were not consistently observed with iNO (Hekierski et al., 2018). Nonetheless, it was observed that reductions in blood flow in the hippocampus associated with FPI were blocked by iNO (Hekierski et al., 2018), supportive of the neurovascular unit concept and neuroprotection via improved CBF. Importantly, iNO did not produce a confounding drop in MAP. In prior experiments conducted in pigs, administration of the direct NO releaser sodium nitroprusside did not protect cerebral autoregulation after FPI (Armstead et al., 2010b). SNP did elevate CPP and CBF, but only during normotension but not during hypotension when autoregulation was tested after FPI (Armstead et al., 2010b). In these studies, SNP was administered systemically where it decreased MAP, which might have caused an unwanted reduction in CPP.

Results of this study also extend the observations of others regarding the potential of iNO to be neuroprotective in CNS pathology such as TBI and stroke (Terpolilli et al., 2012, 2013). iNO was observed to improve CBF, reduce ICP, brain edema formation, and blood brain barrier (BBB) disruption, while improving neurological function in an adult murine TBI model of focal injury, controlled cortical impact (Terpolilli et al., 2013). However, use of a large animal model more similar to the human (the pig) and an injury model (fluid percussion brain injury), which is mixed focal/diffuse in the present study better mimics the human condition, where the primary injury seen in the young adult population

is diffuse. Second, role of age and sex was not considered in the work of Terpolilli (2013). The latter is important to investigate since iNO has been observed to limit histopathology in males but not females after neonatal murine cerebral hypoxia/ischemia (Zhu et al., 2013).

Additional studies were designed to investigate the mechanism whereby iNO improved outcome after FPI in the pig. First, iNO had a protective effect on the NVU, perhaps via what we have historically termed the permissive effect of NO. In this concept, the mere presence of NO, in a dose that has no discernable biological effect (on pial artery diameter for example) is all that is needed to permit vascular responses dependent on intact NO functioning, such as cerebral autoregulation, to occur (Faraci and Heistad, 1998; Armstead et al., 1989). The concept that iNO is a permissive factor and improves outcome after TBI without consistent frank increases in CBF and CPP is a unique element to that study. Cerebral autoregulation, itself, is dependent on a number of factors to mediate the vascular response, including prostaglandins, cAMP, and cGMP dependent signaling, all of which are dependent on NO (Faraci and Heistad, 1998).

In other studies, it was observed that that fluid percussion brain injury was associated with elevations of CSF ET-1, the ERK isoform of MAPK, and IL-6 and that blockade of their upregulation by iNO was associated with protection of cerebral autoregulation and prevention of histopathology due to brain injury (Fig. 1) (Curvello et al., 2018), thereby providing a mechanism for iNO mediated protection after FPI. In prior experiments conducted in pigs, intravenous administration of the direct NO releaser sodium nitroprusside did not block upregulation of ERK in the brain (Armstead et al., 2010b), providing an explanation as to why it was not protective after fluid percussion brain injury.

It is increasingly recognized that overproduction of pro-inflammatory cytokines is an important factor contributor to mortality in numerous pathologies, including TBI. Interestingly, IL-6 appears to have both a deleterious and a beneficial role in a number of neurologic conditions (Sordillo et al., 2016). IL-6 plays a key role in induction of nerve growth factor by astrocytes and thus functions in the repair of the injured brain (Kossman et al., 1996). Similarly, elevated levels of IL-6 were found in survivors compared to those who died after severe TBI (Winter et al., 2004). On the other hand, others have suggested that IL-6 has harmful effects after TBI. For example, motor coordination deficits in mice after mild TBI could be prevented by IL-6 blockade (Yang et al., 2013). Similarly, an anti-IL-6 antibody increased functional spinal cord recovery in mice after injury (Nakamura et al., 2005). However, little work has been done to investigate the effects of IL-6 blockers in humans after TBI. In fact, many view IL-6 as more of a marker of injury after TBI (Nwachuku et al., 2016). Our recent studies address this question in that we observed that FPI was associated with an elevation of CSF IL-6 concentration while an IL-6 antagonist, LMT-28, prevented impairment of cerebral autoregulation and brain histopathology (Curvello et al., 2018). Prior unrelated studies indicated an association between upregulation of ERK MAPK with increased CSF IL-6 after FPI (Armstead et al., 2016b). Since iNO blocked upregulation of IL-6 after fluid percussion brain injury (Curvello et al., 2018), it was postulated that iNO achieves brain protection via block of the sequential release of ET-1, ERK MAPK, and IL-6 (Fig. 1). Since cerebral autoregulation impairment and brain histopathology results from blockade of K channel function after TBI (Armstead and Vavilala, 2014), it is speculated that iNO ultimately achieves brain protection after TBI via block of impairment of K channel function (Pastor et al., 2019) (Fig. 1). However, a caveat to these studies is that the time window for study is short (within 6 h of FPI). Future studies will be needed to determine if iNO has capability to yield enduring protection.

8. Conclusions

This review has identified gaps between specific efficacy and practical clinical measures. Specific examples are that typical clinical care does not include consideration of cerebral autoregulation status, use of transcranial Doppler or other measures of cerebral perfusion, determination of the lower limit of cerebral autoregulation, evaluation of hemispheric differences in cerebral function, or consideration of sex in the use of vasoactive agents.

Key points in this review follow. 1. CPP is monitored at a bedside and manipulated with various vasoactive agents. If CPP is not maintained, the serious neuropathological perturbations lead to irreversible brain damage. Information regarding how CPP is measured, the pros and cons of various methods, and the current gaps in clinical knowledge are presented. 2. What is known about endothelial molecular pathways altered after TBI and how vasoactive agents affect them. 3. Current Guidelines do not specify the choice of vasoactive agent(s). Hence, the pick is random. 4. Bidirectional translational research is defined as the bedside observation informing the study design of the basic science preclinical animal model, which, in turn, generates data that informs the attainment of better clinical outcome in TBI patients. 5. Using this approach, it was concluded that age and sex are factors which should be considered in choice of the vasoactive agent, including both physiologic perturbations, data about cell death and potential molecular mechanisms explaining these changes. 6. Finally, recent finding using iNO were described and the conclusion reached that iNO may be an additional agent to augment CPP after TBI.

This review has identified gaps in our knowledge and next questions to be answered. For example, iNO improves outcome irrespective of sex and/or age and hence may be prove to be a better therapeutic intervention. Since iNO administration does not require neurocritical care unit specialized instrumentation as part of its administration, it can be administered after injury, speeding the time towards ability to treat. Other areas for future investigation may include angiogenesis, repair/reshaping of the neurovascular unit, and whether the latter areas differ

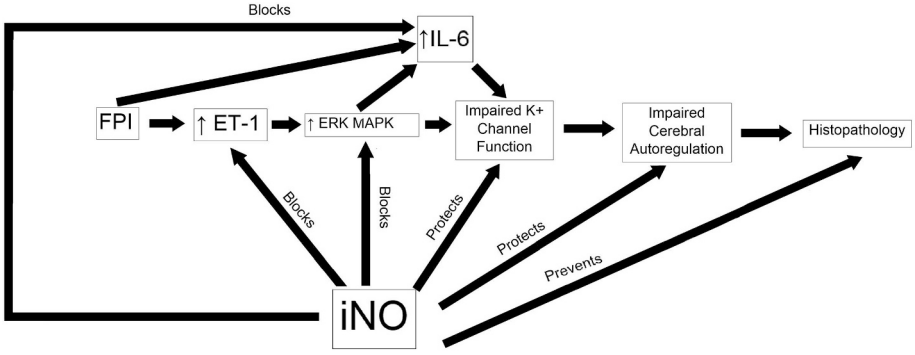

Fig. 1. Mechanistic figure illustrating signaling pathways and their modulation by iNO to achieve neuroprotection after TBI. Fluid percussion brain injury (FPI) causes the sequential release of endothelin −1 (ET-1) and the ERK isoform of mitogen activated protein kinase (MAPK) to impair cerebral autoregulation. In the context of the neurovascular unit, cerebral hemodynamics influences neuronal cell integrity. Thus, impaired cerebral autoregulation is thought to result in brain histopathology. FPI also appears to directly increase the CSF concentration of interleukin −6 (IL-6) or indirectly via activation of ERK MAPK, which in turn can impair cerebral autoregulation. Administration of iNO may improve outcome (prevent impairment of cerebral autoregulation and histopathology) via block of upregulation of IL-6 ET-1, and ERK MAPK.
As adapted from Pastor et al., 2019.

substantially in the pediatric compared to the adult injured brain. Finally, future studies should consider whether short term improved outcome with a given therapeutic approach can achieve enduring protection.

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