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Hypertension after Severe Traumatic Brain Injury: Friend or Foe?

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Abstract

Traumatic brain injury (TBI) is a major public health problem, with severe TBI contributing to a large number of deaths and disability worldwide. Early hypotension has been linked with poor outcomes following severe TBI, and guidelines suggest early and aggressive management of hypotension after TBI. Despite these recommendations, no guidelines exist for the management of hypertension after severe TBI, although observational data suggests that early hypertension is also associated with an increased risk of mortality after severe TBI. The purpose of this review is to discuss the underlying pathophysiology of hypertension after TBI, provide an overview of the current clinical data on early hypertension after TBI, and discuss future research that should test the benefits and harms of treating high blood pressure in TBI patients.

Introduction

Traumatic brain injury (TBI) is a major public health problem. In the United States alone, over 5 million Americans live with disabilities secondary to TBI¹, and with lifetime costs per case estimated at close to \$400,000 in 2007². Severe TBI, representing the greatest level of injury, has been associated with several extracranial complications, which can adversely affect outcomes³. Among these complications, hypotension is common and well recognized⁴, and has been independently associated with high mortality and poor functional outcomes^{5,6}. Based on these findings, major guidelines, including those of the Brain Trauma Foundation, recommend maintaining a systolic blood pressure greater than 90mmHg after a severe TBI⁷. Despite these data and a compelling physiologic rationale to maintain adequate blood pressure to support cerebral perfusion pressure (CPP) in the face of impaired cerebral autoregulation^{8,9}, recent data suggest that arterial hypertension after TBI is also associated with poor outcomes^{10,11}. Yet, unlike for arterial hypotension there are no recommendations regarding prevention or treatment of arterial hypertension after severe TBI.

In this brief review, we will discuss the current data surrounding arterial hypertension following TBI. We used a strategy that employed a search in PubMed in September 2015

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using the keywords “traumatic brain injury” or “TBI,” and “hypotension,” “hypertension,” or “blood pressure.” We further searched through reference lists to review related articles. Our goal is to provide brief review of the current data surrounding arterial hypertension after TBI, physiologic underpinnings, and discuss the current data on the impact of hypertension on outcomes after TBI. Lastly, we suggest a framework for future research into this important topic.

Catecholamine Excess after Traumatic Brain Injury

Available evidence suggests that the mechanisms involved in high systemic blood pressure after TBI center around a catecholamine excess state. Severe injury to the brain parenchyma triggers pathways of catecholamine release through regional injury to the brain, elevation in intracranial pressure (ICP), and activation of the lower brain and hypothalamic neuroendocrine pathways¹². Regional injury involving insular and subcortical brain regions have been associated with increased sympathoadrenal tone, catecholamine release, and autonomic dysfunction in diverse neurologic insults, including subarachnoid hemorrhage (SAH) and stroke^{13,14}. Initial injury to the brain often also increases ICP through local mass effect and diffuse cerebral edema – this increase in ICP results in a complex interaction with the neuroendocrine response by activating the autonomic system, with further release of catecholamines¹⁴. The end result of this systemic catecholamine release is often an increase in arterial blood pressure.

The initial catecholamine response and resulting systemic hypertension may be protective to a point, by maintaining CPP in the setting of impaired cerebral autoregulation after TBI¹⁵. Yet, catecholamine-induced hypertension may also cause secondary brain damage by aggravation of vasogenic edema and intracranial hypertension, potentially as a result of increased hydrostatic capillary pressure in the brain^{16,17}. Furthermore, preclinical studies and clinical studies in other brain injury paradigms, such as SAH, suggest an elevated catecholamine response to injury with significant end-organ cardiac effects. For example, animal studies in SAH have demonstrated a high myocardial sensitivity to catecholamines¹⁸ and correlated catecholamine excess with high degrees of myocardial injury¹⁹; interestingly, pretreatment with either adrenalectomy or propranolol seemed to mitigate this effect²⁰. In addition, clinical studies of stress cardiomyopathy following SAH also show a strong association of catecholamine excess with cardiac dysfunction^{21,22}.

In addition to the physiologic consequences of catecholamine excess, preclinical studies suggest direct neurotoxicity of catecholamines²³; while most of these studies are not in the context of TBI, they are still relevant in demonstrating the contribution of a hyperadrenergic state to poor neurologic outcomes after acute brain injury. Furthermore, attenuation of the catecholamine response has been associated with improved neurologic outcomes in both preclinical and clinical studies. For example, animal and human studies investigating interruption of adrenergic pathways with beta-blockers have demonstrated favorable properties on the cerebral circulation and preservation of cerebral blood flow^{24,25}. From a clinical standpoint, treatment of humans with SAH with beta and alpha-adrenergic antagonists has been associated with improvements in neurologic outcomes²⁶. In the TBI literature, a growing body of observational literature has demonstrated an improvement in

outcomes with early exposure to beta-blockers^{27,28}. Overall, the improvements in clinical outcomes associated with attenuation of the catecholamine response highlight the central role that elevated catecholamines play following neurologic injury.

Elevated catecholamine levels within 48 hours of injury have been shown to be prognostic of poor outcome after TBI^{29,30}. In TBI patients, elevated plasma norepinephrine and epinephrine levels can predict poor Glasgow Coma Score at 1 week, greater ventilator days and length of stay, as well as worsened survival³¹. Similar to SAH, the catecholamine-excess state after injury may also be responsible for severe non-neurologic organ dysfunction, including neurogenic stunned myocardium^{32,33} and neurogenic pulmonary edema^{34,35}. Furthermore, non-neurologic organ dysfunction is common after TBI and independently contributes to worse outcome after TBI^{36,37}. Thus, while a catecholamine excess state (and consequent hypertension) may initially be protective following injury, dysregulated catecholamine excess appears to be associated with poor physiological and patient level outcomes. Because these associations are based on observational studies, further data is necessary to understand whether catecholamine excess is simply a biomarker for severity of TBI, or if it is causally related to poor outcomes.

Impact of Hypertension Following Traumatic Brain Injury

The pathophysiologic impact of hypertension on neurophysiologic mechanisms after TBI is complex, and involves the interplay between systemic blood pressure and cerebral edema, ICP, and cerebral autoregulation³⁸. In the non-injured brain, cerebrovascular autoregulatory mechanisms maintain a constant cerebral blood flow, despite large changes in systemic blood pressure. The relationship between systemic blood pressure and ICP is illustrated by the development of plateau waves in the setting of intact autoregulation³⁹. In the first phase, when systemic blood pressure is reduced, autoregulatory vasodilatation, which aims to maintain cerebral blood flow, leads to an increase in ICP; thus, CPP initially decreases. In the second phase, as ICP continues to rise, a point is reached where CPP falls below the ischemic threshold, and systemic blood pressure then increases to re-establish normal CPP. In the final phase, autoregulatory vasoconstriction stabilizes the balance between systemic blood pressure and CPP. In the injured brain, these autoregulatory mechanisms are often impaired, and large increases in systemic blood pressure are directly referred to the cerebral capillaries, resulting in breakdown of the blood-brain barrier, worsened cerebral edema, and increased ICP⁴⁰. With absence of autoregulatory vasoconstriction, increases in systemic blood pressure may cause increased regional cerebral blood flow and transudation of fluid across the disrupted blood-brain barrier, thus resulting in cerebral edema⁴¹⁻⁴⁴. Furthermore, increased cerebral edema and elevated ICP may impair cerebral perfusion and result in cerebral ischemia⁴⁵.

In addition to the physiologic considerations outlined above, several observational studies in the TBI literature have demonstrated an association between early hypertension and poor outcomes (Table 1). In the adult population, a consistent “U-shaped” relationship with mortality has been noted, with patients with both admission hypotension (generally defined as a systolic blood pressure [SBP] < 90 mmHg) and hypertension (depending on study, defined as an SBP > 150, SBP ≥ 140, or SBP > 160 mmHg) being at higher risk for in-

hospital mortality. While the association of hypertension and worse outcomes in adult patients may simply be due to a greater burden of comorbidities, the data on high blood pressure and outcomes in children (who are generally free of comorbidities) is consistent with the adult data. Furthermore, this U-shaped relationship between early blood pressure and mortality has been observed in multiple neurologic injury paradigms, including ischemic stroke and hemorrhagic stroke⁴⁶. Limitations of these studies include their retrospective design, lack of granular details on patient management, and lack of data on long-term and functional outcomes. Thus, future research should focus on high-quality prospective studies to define appropriate early blood pressure thresholds following TBI.

Should Hypertension after Traumatic Brain Injury be Treated?

While preclinical and clinical studies suggest deleterious neurophysiologic effects of catecholamine excess and consequent hypertension early after injury, current guidelines do not address the optimal treatment goals in hypertensive patients following TBI. In other neurologic hemorrhage paradigms, data suggest that early blood pressure reduction is likely safe and may possibly be of benefit. In the INTERACT2 trial⁴⁷, which randomized patients with intracerebral hemorrhage within 6 hours to a goal SBP < 140 mmHg versus a goal SBP < 180 mmHg, investigators found no differences in mortality, although a prespecified ordinal analysis of modified Rankin scores suggested improved functional outcomes in the group with lower blood pressure goals. In the ATACH2 trial⁴⁸, which achieved greater and faster blood pressure reduction in patients with intracerebral hemorrhage compared to the INTERACT2 trial, investigators found no difference in mortality or disability between groups randomized to a SBP goal of 110-139 mmHg versus a SBP goal of 140-179 mmHg. While well-conducted RCTs of systemic blood pressure lowering have not been conducted in the TBI population, a strategy of blood pressure reduction with alpha- and beta-antagonists in an effort to reduce cerebral transcapillary water exchange, reduce cerebral edema, and improve ICP control (the “Lund” concept⁴⁵) has been reported since 1996 in several centers throughout Sweden, with several non-randomized studies reporting improved outcomes^{16,49}. Due to methodologically limited evidence to support this practice following TBI, this strategy remains controversial.

As mentioned earlier, there is some data suggesting that catecholamine reduction may be beneficial in TBI, potentially due to their modulating effect of the maladaptive catecholamine-excess state following severe TBI. A meta-analysis of 4 observational cohort studies evaluating beta-blockers in the setting of TBI was recently published by Alali et al. showed that beta-blockers exposure was associated with in-hospital mortality reduction (OR 0.35; 95% CI 0.27-0.45)²⁷. Mosheni, et al. demonstrated that non-exposure to beta-blockers in isolated TBI patients was associated with a 5-fold increase of mortality compared to patients exposed to beta-blockers, regardless of type or dose of beta-blocker (adjusted OR 5.0, 95% CI 2.7 – 8.5)²⁸. Zangbar, et al. conducted a retrospective propensity-matched cohort study evaluating patients exposed to metoprolol after TBI compared to patients with no beta-blocker exposure (n=356), and determined that metoprolol exposure was associated with a survival advantage (p=0.01) independent of heart rate⁵⁰. A recent small prospective observational study (n=38) in moderate to severe TBI patients concluded that low-dose

propranolol administration within 12 hours of ICU admission was associated with a reduced ICU and hospital length of stay, but not mortality⁵¹.

Recent advances in multimodal brain monitoring may help to develop personalized blood pressure targets following TBI. Multimodal brain monitoring includes a variety of invasive and non-invasive monitors of cerebral hemodynamics, including ICP, CPP, brain tissue oxygenation, brain temperature, cerebral blood flow, and markers of cerebral autoregulation. Rather than using a single value to guide brain resuscitation, the use of multimodal brain monitoring has been suggested as a way to optimize CPP, cerebral blood flow, and brain oxygenation⁵². In addition, brain hemodynamic goals may require revision based on the status of an individual's cerebral autoregulatory capacity, as autoregulation is not abolished in all cases of TBI, and regional differences in autoregulation impairment may exist⁴⁵. While formal autoregulation testing may be cumbersome, continuous monitors of autoregulation have recently been developed from commonly collected bedside parameters, including blood pressure and ICP data. For example, the pressure reactivity index, which incorporates analytic software to analyze the moving correlation of mean arterial pressure and ICP⁵³, has been demonstrated to be associated with clinical outcomes after TBI⁵⁴, as well as to assist in defining optimal CPP targets in these patients⁵⁵. With the availability of continuous data on systemic blood pressure, cerebral perfusion, brain oxygenation, and cerebral autoregulation, it is possible to individually tailor hemodynamic management following TBI. Thus, future studies should closely evaluate these neurophysiologic outcomes in the context of treatment for injury-induced hypertension.

While clinical guidelines have focused on systolic blood pressure targets following TBI, maintenance of CPP as an endpoint may be a more important variable in early hemodynamic management. While it would be intuitive to think that maintenance of a supraphysiologic CPP may improve outcomes following TBI, therapies directed at maintenance of elevated CPP have been associated with side effects of high vasopressor doses and a higher incidence of the acute respiratory distress syndrome⁵⁶. Furthermore, it is the mean arterial pressure, rather than systolic blood pressure, that is used to calculate CPP, thus creating paradoxical systolic blood pressure and mean arterial pressure goals in certain clinical situations. Use of multimodal monitoring, including the consideration of CPP in the broader setting of systemic pressure, cerebral autoregulation, brain oxygenation, and cardiac function may further help to individualize optimal CPP goals in TBI patients, as well as to help stratify patients that will and will not benefit from higher CPP targets.

Currently, there is no consensus as to whether hypertension in TBI patients should be aggressively treated, what the particular treatment threshold is, or the benefit of particular pharmacologic strategies to achieve blood pressure goals in TBI. This leaves clinicians to decide on a case-by-case basis what blood pressure level to consider as "hypertension" in TBI and whether the potential ischemic risks of lowering blood pressure outweigh the benefits of prevention of hemorrhage. For example, there is no formal strategy to consider the risk of intracranial hemorrhage, cerebral edema, or intracranial hypertension against potential benefits of cerebral perfusion, providing collateral cerebral blood flow or autoregulation status in deciding blood pressure targets. Furthermore, the relationship between hypertension and poor outcomes in these studies may not have captured the

relationship between cerebral perfusion and outcomes, independent of high ICP. Therefore, the concepts of multimodal brain monitoring, cerebral autoregulation, and optimization of ICP and cerebral perfusion, as discussed above, may all play a pivotal role in the decision of whether or not to treat systemic hypertension following TBI.

Conclusion

While the association of early hypotension and poor outcomes following TBI has been established, with management priorities outlined in clinical practice guidelines, recent evidence suggests early hypertension following TBI patients may also be harmful. The mechanistic underpinning of elevated blood pressure following TBI is likely related to a catecholamine excess state, and observational clinical studies have shown potential benefit of catecholamine reduction in these patients. However, questions regarding treatment of early hypertension in TBI patients remain unanswered, and future research should focus on the benefit and harm of treating high blood pressure in TBI patients, appropriate blood pressure targets, and the use multimodal brain monitoring to personalize blood pressure management following TBI.

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Table 1
Summary of the articles that have demonstrated the relationship between elevated blood pressure and poor outcomes in adult and pediatric brain injury patients

<i>Adult Studies</i>		
	Population	Result
<i>Butcher et al, 2007</i> ⁴⁰	6,801 moderate to severe TBI patients from IMPACT database	<ul style="list-style-type: none"> U-shaped relationship between admission blood pressure and outcomes Admission SBP > 150mmHg was associated with worse 6-month Glasgow Outcome Scale (GOS) (adjusted OR 1.30, 95% CI 1.08-1.57)
<i>Zafar et al, 2011</i> ⁵	7,238 isolated moderate to severe blunt TBI patients from National Trauma Data Bank	<ul style="list-style-type: none"> Greater odds of in-hospital mortality associated with an emergency department SBP > 140mmHg (adjusted OR 1.6, 96% CI 1.32-1.96)
<i>Ley et al, 2011</i> ¹¹	14,382 blunt trauma patients (2,601 had moderate to severe TBI) from The Los Angeles County Trauma System Database	<ul style="list-style-type: none"> An admission SBP > 160mmHg was a significant predictor of in-hospital mortality in TBI patients (adjusted OR 1.59, 95% CI 1.10 – 2.29)
<i>Sellmann et al, 2012</i> ⁶⁷	23,500 trauma patients with ISS > 9 (11,252 had TBI) from German Society for Trauma Surgery (DGU)	<ul style="list-style-type: none"> TBI patients with a pre-hospital SBP > 160mmHg had a greater odds of in-hospital mortality compared to normotensive patients (adjusted OR 1.9, 95% CI 1.4 – 1.6)
<i>Fuller et al, 2014</i> ⁶⁸	5,057 TBI patients (Head AIS > 2) from European trauma registry	<ul style="list-style-type: none"> U-shaped relationship between admission SBP and mortality Greater mortality with SBP > 140 but the relationship was attenuated after covariate adjustment The effect remained statistically significant in SBP 190-199 [OR 1.8 (95% CI 1.0 – 3.2)] and SBP > 200mmHg [OR 2.0 (95% CI 1.2 – 3.3)]
<i>Barmparas et al, 2014</i> ⁹	315,242 TBI patients (Head AIS > 3) from National Trauma Data Bank	<ul style="list-style-type: none"> Pre-hospital SBP of 160-180mmHg conferred a greater odds of mortality compared to normotensive patients (adjusted OR 1.97, 95% CI 1.76 – 2.21)
<i>Pediatric Studies</i>		
<i>Kanter et al, 1985</i> ⁶⁰	42 children with multiple causes of acute brain injuries	<ul style="list-style-type: none"> Patients who had a highest intensive care unit (ICU) SBP that exceeded 95th percentile by more than 20mmHg had more severe neurologic deficits or hospital mortality compared to patients who did not (56% vs. 13%, p=0.03)
<i>Vavilala et al, 2003</i> ⁶¹	172 severe TBI children	<ul style="list-style-type: none"> Age-appropriate systolic blood pressure (AASBP) may be a more sensitive predictor of outcome at hospital discharge Patients with SBP > 90mmHg and AASBP < 75th percentile had a higher odds for a poor outcome compared with patients with SBP > 90mmHg and AASBP > 75th percentile (OR 3.5, 95% CI 1.7-7.3) A trend toward greater mortality at AASBP 90-94th percentile and AASBP > 95th percentile (not statistically significant)