Sympathetic Hyperactivity After Traumatic Brain Injury and the Role of Beta-Blocker Therapy

Daiithi S. Heffernan, MD, Kenji Inaba, MD, Saman Arbabi, MD, MPH, and Bryan A. Cotton, MD, MPH

Head injury remains the leading cause of death among trauma patients and accounts for one-third of all trauma mortalities. Of these, 75% will die within the first 3 days. In patients who survive beyond this period, however, the underlying causes of death are the result of non-neurologic organ dysfunction (NNOD) manifest primarily through respiratory failure and cardiovascular dysfunction. Recent literature has demonstrated an association between neurologic trauma and the development of NNOD, which appears to be a result of sympathetic hyperactivity.

Historically, several terms have been used to describe this phenomenon, including sympathetic storms, brainstorming, acute hypothalamic instability, and diencephalic seizures. However, paroxysmal sympathetic storms (PSS) best describes this complication after severe brain injury, because it is a syndrome of intermittent agitation, diaphoresis, hyperthermia, hypertension, tachycardia, tachypnea, and extensor posturing.

The first description of PSS was by Penfield in 1929 wherein a 41-year-old man with sympathetic hyperactivity was described. The ensuing postmortem examination on this patient revealed a tumor involving the foramen of Monro. Following this, the author collected a series of patients who had suffered traumatic brain injury (TBI) and described the manifestation of symptoms very similar to this initial individual.

Following this, the frequency of publications describing sympathetic hyperactivity after TBI began to increase. Rossitch and Bullard detailed the cases of nine individuals suspected of autonomic dysfunction syndrome. These patients presented with signs of sympathetic discharge and extensor posturing after severe closed head injury and acute hydrocephalus. Examining the responses to medications, it was proposed that TBI was somehow inducing alterations in the opiate and dopaminergic pathways. With our advancing understanding of the pathophysiology of PSS and extravascular manifestations of TBI, many investigators have focused on the potential for beta-adrenergic blocking medications. Despite this, sympathetic hyperactivity after TBI remains poorly recognized with likely undertreatment of a condition with high morbidity and mortality.

PATHOPHYSIOLOGY

The full etiology and pathophysiology of PSS is as yet still being defined and understood. However, it is believed that after TBI, excessive activation of the sympathetic system occurs. This leads to end organ or effector organ activation among which is adrenal release of catecholamines. Both central and peripheral catecholamine release leads to the clinical manifestations of tachycardia, hypertension, diaphoresis, tachypnea, and mydriasis. There also appears to be a loss of inhibition of central sympathoexcitatory regions. As evidence mounts, it is becoming more apparent that there is little evidence to support PSS as being of epileptogenic origins, with it more likely to be a function of cerebral disconnection.

Disconnection theories state that dysautonomia occurs due to loss of higher control over one or more excitatory centers. Conventional disconnection theories suggest that when pathways from the cerebral cortex to the midbrain are injured, cortical regulation of the upper brain stem and diencephalic regions (which are the central excitatory foci driving the paroxysms) is lost. Another disconnection theory, the excitatory:inhibitory ratio (EIR) model, suggests that damage to the brain stem and diencephalic centers release the excitatory spinal cord processes from their inhibitory effects. In essence, the spinal cord is responsible for modulating both the afferent stimuli from the periphery as well as the efferent centrally originating signals. As brain activity and brain stem output increases, the spinal cord acts to modulate the EIR, thus protecting the end organ. When the brain stem EIR is overwhelmed by excess brain activity, as seen in TBI, then the neighboring spinal EIR is also overwhelmed, losing its protective effect, and is unable to inhibit or balance large volumes of catecholamine surges to the peripheral organs. This is manifested by end-organ dysautonomia of multiple end organs, such as smooth muscle (rigidity) or cardiac muscle (tachycardia). An overlap condition occurs when both sympathetic overactivity (hyperthermia, tachycardia, hypertension, tachypnea, and sweating) and...
motor overactivity (rigidity, spasticity, and dystonias) are manifested simultaneously.11

Models of subarachnoid hemorrhage (SAH) have revealed multiple hypothalamic lesions, and clinically hypothalamic dysfunction is a noted feature of the recovery phase after PSS and TBI. In patients with TBI, postmortem evaluations have demonstrated that 70% of deaths have hypothalamic lesions.13 In PSS, dysfunction occurs within the autonomic centers in the diencephalon (thalamus or hypothalamus) or their connections to cortical, subcortical, or brain stem loci that mediate autonomic function. Initial postulations suggested a release phenomenon in which loss of cortical and subcortical control of basic functions occurs, including blood pressure and temperature regulation.14 This was further expanded to describe a mechanism involving activation (or loss of inhibition) of central sympathoexcitatory regions such as the paraventricular hypothalamic nucleus, lateral periaqueductal gray substance, lateral parabrachial nucleus, or rostral ventricular medulla.15 The subsequent release of adrenomedullary catecholamines during PSS episodes may lead to hypertension, tachycardia, and tachypnea.16,17

Conversely, it must be recognized that other potential sources of catecholamines namely from the adrenal medulla, and from the superior cervical ganglia, may be activated by injury completely independent of central activity. Release from the ganglia or from the adrenal medulla could lead to the released catecholamines circulating centrally back to the cerebral cortex resulting in PSS. Hoftnagl et al. followed plasma epinephrine and norepinephrine (NE) levels in patients after severe closed head injury and noted fluctuating levels with the varying phases of recovery after TBI. This spillover from the neurologic system leads to a threefold increase in plasma levels of NE. This finding lasts at least 10 days but has been reported to take up to 6 months for normalization of NE levels.18 Patients who had normalization of their NE levels had persistently elevated NE levels, up to seven times normal. Plasma NE levels at 48 hours after the TBI were found to mimic the dysfunction seen with conditions such as pheochromocytoma crises, malignant hyperthermia, or a thyroid storm, all of which should be considered.7–10 PSS is diagnosed in the setting of (1) severe brain injury, (2) temperature ≥38.5°C, (3) heart rate ≥130 beats per minute, (4) respiratory rate ≥30 breaths per minute, (5) agitation, (6) diaphoresis, and (7) dystonia (rigidity or decerebrate posturing) (Table 1). Although not all these signs are necessary for a diagnosis, these events typically occur for at least 3 days. During the first week after TBI, this increase in sympathetic activity has actually been correlated with a five- to sevenfold increases in plasma NE and epinephrine levels.21 However, neither plasma nor urinary catecholamine levels should be routinely obtained (nor are they required) to make the diagnosis of PSS. Computed tomography (CT) scan may initially reveal diffuse axonal injury or a specific brain injury; however, there are no specific findings of PSS itself on CT scan. Magnetic resonance imaging may reveal intraventricular hemorrhage or ventriculomegaly. PSS is not associated with seizures, and thus an Electroencephalography (EEG) is not necessary for the diagnosis.

### CONSEQUENCES OF PSS EPISODES

Occurrence of PSS after TBI may contribute to increased morbidity and mortality. PSS has been associated with hypermetabolism, myocardial necrosis, pulmonary hypertension, and pulmonary edema. Injured patients without TBI do not display a catecholamine surge and have a better survival.19

In patients with PSS, the ECG changes are secondary to an autonomic imbalance, the most common of which is sinus tachycardia.22,23 Bradycardia, ST segment changes, and fatal ventricular dysrhythmia occur in up to 5% of all patients with PSS.24 Furthermore, the sympathetic hyperactivity that occurs after TBI has ongoing deleterious effects on the myocardium, which may lead to ventricular hypokinesis.25,26 This has been shown as a 50% reduction in left ventricular function by either transthoracic echocardiography or scintigraphy. The myocardial necrosis that is seen in PSS patients is similar to that seen in patients with pheochromocytoma. Myocardial necrosis is usually found in patients with premortem ECG disturbances and/or elevated cardiac enzymes.27–29 Indeed, such necrosis is a common autopsy finding in patients with severe TBI.30,31

After the catecholamine surge in PSS, the pulmonary circulation becomes acutely overloaded, which is exacerbated by disruptions in the capillary endothelium and basement membrane.32 Mistaking the diagnosis and attempting to unload the pulmonary vasculature with diuretics worsen the condition.33

### MAKING THE DIAGNOSIS

Essentially, clinical features predominate the initial steps in making the diagnosis. A high index of suspicion should be maintained. It is essential that, in these complex critically ill patients, one needs to be cognizant of the need to assess for and rule out other causes of these clinical features, such as infection, poorly controlled pain, or pulmonary embolism.

In many respects, the biochemical presentation seems to mimic the dysfunction seen with conditions such as pheochromocytoma crises, malignant hyperthermia, or a thyroid crisis. However, there are other important differences. In pheochromocytoma crises, the catecholamine surge is sustained, whereas in this situation, the plasma catecholamines increase acutely for at least 3 days. It is also important to note that the catecholamines during PSS episodes may lead to hypertension, tachycardia, and tachypnea.16,17 Conversely, it must be recognized that other potential sources of catecholamines namely from the adrenal medulla, and from the superior cervical ganglia, may be activated by injury completely independent of central activity. Release from the ganglia or from the adrenal medulla could lead to the released catecholamines circulating centrally back to the cerebral cortex resulting in PSS. Hoftnagl et al. followed plasma epinephrine and norepinephrine (NE) levels in patients after severe closed head injury and noted fluctuating levels with the varying phases of recovery after TBI. This spillover from the neurologic system leads to a threefold increase in plasma levels of NE. This finding lasts at least 10 days but has been reported to take up to 6 months for normalization of NE levels.18 Patients who had normalization of their NE levels had persistently elevated NE levels, up to seven times normal. Plasma NE levels at 48 hours after the TBI were found to mimic the dysfunction seen with conditions such as pheochromocytoma crises, malignant hyperthermia, or a thyroid storm, all of which should be considered.7–10 PSS is diagnosed in the setting of (1) severe brain injury, (2) temperature ≥38.5°C, (3) heart rate ≥130 beats per minute, (4) respiratory rate ≥30 breaths per minute, (5) agitation, (6) diaphoresis, and (7) dystonia (rigidity or decerebrate posturing) (Table 1). Although not all these signs are necessary for a diagnosis, these events typically occur for at least 3 days. During the first week after TBI, this increase in sympathetic activity has actually been correlated with a five- to sevenfold increases in plasma NE and epinephrine levels.21 However, neither plasma nor urinary catecholamine levels should be routinely obtained (nor are they required) to make the diagnosis of PSS. Computed tomography (CT) scan may initially reveal diffuse axonal injury or a specific brain injury; however, there are no specific findings of PSS itself on CT scan. Magnetic resonance imaging may reveal intraventricular hemorrhage or ventriculomegaly. PSS is not associated with seizures, and thus an Electroencephalography (EEG) is not necessary for the diagnosis.

### CONSEQUENCES OF PSS EPISODES

Occurrence of PSS after TBI may contribute to increased morbidity and mortality. PSS has been associated with hypermetabolism, myocardial necrosis, pulmonary hypertension, and pulmonary edema. Injured patients without TBI do not display a catecholamine surge and have a better survival.19

In patients with PSS, the ECG changes are secondary to an autonomic imbalance, the most common of which is sinus tachycardia.22,23 Bradycardia, ST segment changes, and fatal ventricular dysrhythmia occur in up to 5% of all patients with PSS.24 Furthermore, the sympathetic hyperactivity that occurs after TBI has ongoing deleterious effects on the myocardium, which may lead to ventricular hypokinesis.25,26 This has been shown as a 50% reduction in left ventricular function by either transthoracic echocardiography or scintigraphy. The myocardial necrosis that is seen in PSS patients is similar to that seen in patients with pheochromocytoma. Myocardial necrosis is usually found in patients with premortem ECG disturbances and/or elevated cardiac enzymes.27–29 Indeed, such necrosis is a common autopsy finding in patients with severe TBI.30,31

After the catecholamine surge in PSS, the pulmonary circulation becomes acutely overloaded, which is exacerbated by disruptions in the capillary endothelium and basement membrane.32 Mistaking the diagnosis and attempting to unload the pulmonary vasculature with diuretics worsen the condition.33

### MAKING THE DIAGNOSIS

Essentially, clinical features predominate the initial steps in making the diagnosis. A high index of suspicion should be maintained. It is essential that, in these complex critically ill patients, one needs to be cognizant of the need to assess for and rule out other causes of these clinical features, such as infection, poorly controlled pain, or pulmonary embolism.

In many respects, the biochemical presentation seems to mimic the dysfunction seen with conditions such as pheochromocytoma crises, malignant hyperthermia, or a thyroid crisis. However, there are other important differences.
PSS are associated with significant increases in cerebral blood volume that result in increased intracranial pressure. NE initially maintains the blood-brain barrier, but over time, sustained levels lead to a leaky blood-brain barrier, thus inducing cerebral edema.34 The sustained levels of NE worsens cerebral ischemia and necrosis.21

TBI is notable for increases in metabolic demands. Superimposed on this, the extra metabolic demands during PSS events are considerable and notable for profound catabolism. The energy expenditure of these patients is increased by up to 75%.35,36 This hypermetabolic state is marked by a resistance to nutritional support and ensuing weight loss, which further complicates the outcome of these patients.37 Propranolol administration has been associated with a decrease in energy expenditure of between 5%36 and 18%.38 Catecholamines are noted to induce interleukin (IL)-10 release from monocytes. Patients with PSS have higher levels of IL-10 and severely depressed monocyte IL-12-DR expression, 62% of whom developed severe infections.39 Further adrenergic stimulation inhibits tumor necrosis factor (TNF)-α and IL-6 production from splenic macrophages in a sepsis model.40

ANIMAL MODELS INCORPORATING BETABLACKERS AND INTRACRANIAL INJURY

Increasing data from animal models seem to support retrospective and observational data in humans of the potential benefit of beta-blocker use in patients with TBI. While there remains considerable work to be undertaken, collectively, the data infer better functional outcomes and lower cerebral edema after treatment with beta-blockers. Administration of propranolol to a murine model of blunt head injury led to a 152% improvement in cerebral perfusion and a 24% reduction in cerebral hypoxia.41 The authors propose therefore that adrenergic-mediated cerebral vasoconstriction is a mechanism contributing to the secondary events after TBI. Lui demonstrated a protective effect of propranolol after blunt trauma, including better neurologic recovery, better grip test scoring, and reduced brain edema.42 It was postulated that the effects were a result of propranolol on the vasomotor centers in the hypothalamus.

Recently, McLean et al.43 evaluated the effect of beta-agonist on preserving cardiac function after lethal injuries. The authors randomly assigned swine to sham, lethal head injury or lethal head injury with esmolol infusion. The infusion was initiated 30 minutes before lethal head injury and then continued for 45 minutes. Compared with controls, those who received beta-receptor antagonist maintained baseline systolic function, diastolic function, and oxygen delivery at 6 hours after brain death. The authors concluded that beta-blockers preserve cardiac function by preventing beta-adrenergic receptor desensitization and hypothesized that their use in potential donors might increase the number of organs available for transplantation.

Akin to the inflammatory cascade that follows a major trauma and systemic inflammatory response syndrome, in septic patients, it is often noted that considerable morbidity and mortality may be attributable to the profound and dramatic immune and inflammatory response to insulting event. Insight into the immune and inflammatory modulating properties of beta-blockers may potentially be gleaned from review of the vagal input into the immune response after sepsis.

In experimental models of sepsis, it has been shown that cytokine production may be controlled by efferent vagal nerve input via an inflammatory reflex.44,45 This efferent pathway has been termed the “Cholinergic Anti-Inflammatory Pathway.”46 Stimulation of this pathway significantly suppressed systemic levels of TNF-α. Specifically, it has been shown that modulation of this pathway is via innate immune cells expressing the nicotinic acetylcholine receptor subunit alpha-7 (α-7nAChR).47 Furthermore, animals deficient in Chrnα, the gene which encodes the α-7nAChR, produce an exaggerated cytokine response to endotoxemia. Intriguingly, peripheral cells, such as macrophages, are known to express the α-7nAChR, and as such their cytokine expression may be controlled via vagal nerve activity.

Stimulation of the vagus nerve significantly downregulates the production of IL-1, IL-6, IL-8, and TNF but intriguingly does not affect the production of the anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGF-β). Thereby, this potentially acts as a centrally controlled brake on the immune and inflammatory response to a variety of infectious and traumatic insults.

Although it is understood that this vagal control of the inflammatory response is under central control, there is still little known about the exact mechanisms. However, it is believed that muscarinic receptors (specifically the M1-subtype), which are widely disturbed in the brain, play a key role. Muscarine injected into the cerebral ventricles inhibited endotoxemia-induced serum TNF in a dose-dependent fashion.48 Furthermore, activation of these central muscarinic receptors significantly increased heart rate variability. These effects were not observed after direct peripheral muscarinic receptor activation.

During hypoxia, glomus cells depolarize and release dopamine and noradrenaline, thereby causing depolarization of nearby sensory fibers of the vagus nerve, which propagate to the brain stem.49,50 It was further shown that this central arc may be mediated by IL-1 binding to the glomus cells adjacent to the vagus nerve.

Further evidence of the potential role of the beta-adrenergic system in relation to cerebral injury may be gained from review of the literature pertaining to cerebral ischemia reperfusion.51 Mice lacking the beta-2 adrenergic receptor were shown to have significantly decreased brain infarct volume after cerebral artery occlusion and reperfusion. Although the exact mechanism is unclear, it is further believed to be mediated via the anti-apoptotic heat shock protein 72 (Hsp72). This would be consistent with the findings that in the penumbra surrounding a stroke, significant features of apoptosis are noted.52,53 Furthermore, it has been shown that administration of carvedilol after ischemia-reperfusion significantly decreases the volume of infarcted tissues by at least 40% coupled with decreased TNF-α, IL-1β, and cerebral apoptosis.54 Although these are indeed very different physiologic insults, they provide intriguing background insights.
into possible similar explanations seen in the survival benefit with sympathetic system manipulation.

TREATMENT OPTIONS

Before engaging in the treatment of PSS, it is critical to assess for and treat any potential underlying disorders, specifically hypovolemia, infection, or electrolyte disturbance. Following this, the goals of treatment are to (1) eliminate the cause; (2) decrease the frequency of events; and (3) decrease the intensity of events. It is also important to realize that many of the currently used medications for agitation, such as benzodiazepines, can have dramatic deleterious cognitive and emotional side effects on such patients.

Alpha-2 Agonists

It was postulated that the long standing overactivity of the sympathetic system may lead to end-organ damage and dysfunction, which thus led to the consideration of beta-blockers and adrenergic neuron blocking drugs in TBI recovery. Centrally acting agents such as clonidine and dexmedetomidine have also been used for PSS. It is postulated that because these agents act centrally, they have a neuroprotective effect. Clonidine has been shown to decrease the sympathetic activity and improved outcomes in a rat model of incomplete cerebral ischemia. Clinically, clonidine decreases cerebral vasconstriction and improved outcomes in patients with traumatic brain lesions.

Beta-Adrenergic Antagonists

One of the early considerations for the use of beta-blockers for head injury came with the publication on a volume-targeted therapy principle (Lund Therapy) that aimed to achieve and maintain normovolemia within the brain. It was postulated that opening of the blood-brain barrier led to brain edema. Thus, effective treatment of brain edema would include reduction of hydrostatic capillary pressure and preservation of normal colloid osmotic pressure. Eleven patients with severe head injury were administered anti-hypertensive therapy (beta-1-antagonist, metoprolol, and alpha-2-agonist, clonidine) and a potential precapillary vasoconstrictor (dihydroergotamine). Nine of the 11 patients survived with excellent neurologic outcomes. The authors concluded that therapy should focus on extravascular rather than intracellular edema with agents such as beta-blockers. The group further advanced the concept when they contended that brain edema, and hence secondary brain injury, should be controlled with anti-hypertensive therapy aimed at reducing cerebral perfusion. The investigators argued that this would lead to normovolemia via lowering cerebral blood flow to normal levels, offering better efficacy in reducing the interstitial tissue volume.

Much of the early work on the role of beta-blockers came through their application in patients with nontraumatic SAH. Walter et al. randomized SAH patients to either conventional management or the addition of propranolol. There was a trend toward less neurologic deficit at the end of the study period of 4 weeks. However, there was a clear survival benefit seen in the treatment group at 1 year. Neil-Dwyer et al. undertook a placebo-controlled randomized trial of propranolol and phenotamoline for patients presenting with SAH. Notably, patients receiving placebo displayed ECG changes of ST segment depression and T-wave inversion compared with normal ECG in patients receiving the study drug combination. The authors further assessed the myocardium in the patients who died after SAH and found focal necrotic lesions on the hearts of those who received placebo and none in the patients taking propranolol. Their postulation was that given the predominance of beta-receptors located on the heart that beta-blockers would blunt the end-organ damage from the sympathetic storm induced by the intracranial bleed.

Some of the earliest clinical work on the effect of beta-blockade in a stress response to injury was undertaken by Herndon et al. in their work with burn patients. The group has shown a significant catecholamine surge associated with burns, both in adults and in children. Burn-related sympathetic activity leads to stress cascade activation, with increased secretion of cytokines and activation of the mitogen-activated protein kinase (MAPK), JNK, and NFKappaB pathways, which are all believed to lead to end-organ dysfunction and immunosuppression. Modulation of these pathways via catecholamine manipulations leads to wound macrophage alterations and wound healing abnormalities. Administration of beta-blockers to patients with severe burns has been associated with decreased resting energy expenditure, improved the net muscle-protein balance, dampening of the hypermetabolic response, improved bone metabolism and immune deficiency, and decreased peripheral lipolysis. Furthermore, it has been shown that beta-blockade decreases postburn muscle proteolysis and improves the physical sequelae of severe burns. Extrapolating from this data, it is therefore to be noted that in the correctly selected patient, beta-blocker administration offers many beneficial effects to counter the immune and inflammatory dysfunction that accompanies a major trauma such as a severe burn. Although a different physiologic entity, it does highlight the impact of physiologic exhaustion seen in severe trauma and burns. These findings coupled with a better understanding of the sympathetic hyperactivity seen with intracranial trauma led many to speculate about the application of beta-blockers in TBI.

In light of increased appreciation for the consequences of a hyperadrenergic state after intracranial pathology (organ dysfunction and death), studies in the 1970s addressed possible associations with beta-blocker use and improved mortality. Easton et al. outlined the treatment of six patients with sympathetic hyperactivity, detailing long-term symptomatic relief. Propranolol use in patients with severe closed head injury has been noted to be associated with a reduction in metabolic expenditure of between 5% and 18%. This may be attributable to the effect of beta-blockers on heart rate, because 10% of resting energy expenditure can be attributed to tachycardia.

Two of the earliest double-blind randomized controlled trials with beta-blockers demonstrated decreased episodes of and decreased intensity of PSS. Propranolol, which is more lipophilic than most beta-blockers and has better blood-brain barrier penetration, was used predominantly in early studies. Thus, this allows better central as well as peripheral activity. Brooke et al. enrolled 21 patients with severe closed head injury. Significant reductions in the episodes and intensity of
agitation were noted, associated with decreased need for chemical or physical restraints. Greendyke et al. demonstrated reductions in assaultive behavior in 10 patients with organic brain disease who were previously refractory to conventional medications. Direct cardioprotective effects of beta-blockers involve preventing myocardial necrosis and decreasing the acute myocardial infarction rate. Cruickshank et al. demonstrated reductions in supraventricular tachycardia, ST changes, and less necrotic lesions.

If patients survive the initial trauma and head injury, many will develop NNOD and some will eventually die as a result of these extracranial manifestations. Among these, respiratory and cardiovascular dysfunction are the most common. In a study of 209 consecutive patients with severe head injury, the onset of NNOD was independently associated with hospital mortality (odds ratio 1.63) and independently associated with dichotomized Glasgow Outcome Score with an odds ratio for worse outcome of 1.53. An investigation by Kemp et al. in patients with severe head injury (Abbreviated Injury Scale [AIS] ≥3) confirmed this finding. Two-thirds of deaths in their study were attributable to NNOD, and only one-third died from neurologic causes alone. Twenty-five percent of patients died exclusively from non-neurologic causes, the most common being cardiovascular (36% of patients) and respiratory (34% of patients) causes.3

Following the understanding of factors contributing to mortality in TBI, it was postulated that blocking the hyperadrenergic state would improve mortality (Table 2). Cotton et al. undertook a review of 420 severe head injury patients defined by head AIS of ≥3 and stratified them by beta-blocker exposure during their hospital stay. In the 174 patients with beta-blocker exposure, a 71% reduction in the odds of mortality was noted, despite higher rates of respiratory failure (70% vs. 47%; p < 0.001) and higher infectious complications (38% vs. 21%; p < 0.001). This was even more remarkable given the fact the beta-blocker exposed group was older, more severely injured, and had lower predicted survival.

Arbabi et al. described a cohort of 4,117 patients of whom 303 had beta-blocker exposure during their hospital course. Just under half of this group had beta-blockers pre-trauma. Again, the beta-blocker group was older and had a higher incidence of comorbidities such as hypertension, cardiac disease, and diabetes. The predominant indications for beta-blocker use, other than restarting home medication, were for the treatment of blunt aortic injury, hypertension, and heart rate control. After adjusting for confounding factors, patients exposed to beta-blockers had an odds ratio of death of 0.3 (p < 0.001), an effect most pronounced among patients with significant TBI (GCS score <12).

Inaba et al. evaluated the effects of beta-blockers on 1,156 isolated head injuries. The investigators excluded patients with AIS of ≥4 in any part other than head, and they excluded patients with AIS of 6 head. Eighteen percent of these patients received beta-blockers during their intensive care unit stay. Similar to the findings of Arbabi et al. and Cotton et al., patients who received beta-blockers were older, more severely injured, more likely to have sustained a skull fracture, and were more likely to have undergone craniotomy. The authors reported that exposure to beta-blockers was independently associated with a reduction in mortality rates (OR = 0.54, p < 0.01). After stratifying for age and severity of head injury, it was shown that beta-blocker use in older patients (age 55 years or older) with head AIS ≥4 had the greatest benefit on mortality (28% versus 60%; p = 0.001).

Neideen et al. reviewed beta-blocker use in all geriatric trauma patients. Of the 1,479 admitted patients, 273 patients were taking beta-blockers before the trauma. Overall, there was no difference in mortality between beta-blocker versus no beta-blockers pretrauma (14.7% vs. 13.4%; p = 0.5). Within the groups, the use of warfarin pre-trauma had the greatest negative impact on mortality. In patients without head injury, pretrauma beta-blocker use was associated with a significant increase in mortality (odds ratio 2.14). In patients with head injury, the pretrauma use of beta-blockers was not associated with this increased mortality. A limitation of this study was a lack of description of whether these patients had beta-blockers restarted during their hospital course.

Cardiovascular events constitute a predominant NNOD in TBI, clinically manifesting as a tachycardia. With progression of TBI, it is believed that patients experience a reduction in the normal heart rate variability (HRV). HRV is the magnitude of variance (SD) in integer heart rate noted at 5-minute intervals. A critical reduction in HRV is described as cardiac uncoupling, which is generally defined as variability that has fallen to 0.3 to 0.6 beats per minute range. It has been shown that increasing severity of TBI, as reflected by

| TABLE 2. Retrospective Studies Linking the Association Between Beta-Blocker Use in Patients With Traumatic Brain Injury and Improved Survival |
|---|---|---|---|---|---|---|
| **Authors** | **Inclusion Criteria** | **BB (%) Patients (n)** | **BB (+) Patients (n)** | **Mortality in BB (%) Patients, n (%)** | **Mortality in BB (+) Patients, n (%)** | **p** |
| Arbabi et al. | GCS <13 | 511 | 94 | 163 (32) | 17 (18) | <0.001 |
| Cotton et al. | Head AIS ≥3 | 246 | 174 | 27 (11) | 9 (5.2) | 0.03 |
| Riordan et al. | Head AIS ≥5 | 308 | 138 | 135 (44) | 29 (21) | <0.001 |
| Salim et al. | Head AIS >3 | 329 | 91 | 118 (36) | 22 (24) | 0.03 |
| Inaba et al. | CHI with ICU admission | 953 | 203 | 199 (21) | 34 (17) | 0.01 |
| Neideen et al. | Any pretrauma beta-blocker use | 463 | 105 | 161 (13.4) | 40 (14.7%) | 0.558 |

AIS, Abbreviated Injury Scale; BB, beta-blocker; CHI: Closed Head Injury; GCS: Glasgow Coma Scale.

All the studies denote similar improvements in mortality associated with beta-blockers, despite these patients being older and, in general, more severely injured.

1606 © 2010 Lippincott Williams & Wilkins
decreasing GCS score, correlate with decreasing HRV.\textsuperscript{77} Furthermore, cardiac uncoupling in trauma patients has been shown to adversely affect outcomes,\textsuperscript{78} notably in head-injured patients.\textsuperscript{79,80} Lowensohn et al.\textsuperscript{81} observed a reduction in the normal cyclic changes in heart rate in patients with severe head injury and noted a rapid decline in HRV with rising intracranial pressures, and the affect of autonomic dysfunction on HRV and outcomes has been characterized by multiple studies. Neurologic recovery from brain injury is associated with the restoration of normal HRV.\textsuperscript{82,83} Riordan et al.\textsuperscript{84} examined the association of beta-blocker exposure and cardiac uncoupling in the most severely head-injured patients (AIS $\geq 5$). Although the numbers were too small to achieve statistical significance, the data showed a trend toward improved survival in patients with early (<24 hours) cardiac uncoupling who received beta-blockers. However, in patients with the highest degrees of cardiac uncoupling (>20% in the first 24 hours), there was a dramatic and significant reduction in mortality for patients who received beta-blockers (80% vs. 39%; $p = 0.001$). The same group detailed that the finding of early loss of HRV, within 24 hours, expanded to a larger population of all trauma victims and not just head injuries. Herein, early loss of HRV was strongly correlated with two- to sixfold increased risk of dying.\textsuperscript{85} Within this larger group, the association was strongest in patients with TBI.

When applying the principles of HRV and cardiac uncoupling to the broader TBI population, it appears that achieving heart rate reduction impacts mortality. Snodgrass et al.\textsuperscript{86} noted that achieving a heart rate of 90 beats per minute or less significantly decreases mortality from 7% to less than 2%. Thus, it might be proposed that a heart rate of 90 beats per minute might be a target to achieve. Another well-described marker of the cardiac dysfunction that occurs after TBI and nontraumatic SAH is an elevation of cardiac troponin I. Elevated troponin I levels have been shown to occur in patients with acute nontraumatic cerebral insults such as stroke and intracranial hemorrhage.\textsuperscript{87,88} This may be a consequence of a more pronounced sympathetic storm. Salim et al.\textsuperscript{89} described the prognostic significance of elevated troponin in 125 patients from a cohort of 420 patients with severe TBI. Patients with TBI and an elevated troponin had a lower GCS (7.5 vs. 8.7, $p < 0.05$), higher Injury Severity Score (27.4 vs. 24.8, $p < 0.01$), and increased mortality (44% vs. 29%, $p < 0.05$). Beta-blocker exposure was associated with a significant reduction in mortality (OR = 0.38; $p = 0.03$) in TBI patients with an elevated troponin.

In essence, available retrospective and observational data strongly implies a protective effect of beta-blockers in patients with TBI. Taking all available data together, there is a lack of uniformity on which beta-blocker was used. Although propranolol has the best blood-brain barrier penetration, the effects noted seem to be independent of the specific beta-blocker used. This observation would speak to the end-organ protection, especially cardiac, afforded by beta-blockers. Decreasing cerebral metabolism via reduction in cerebral blood flow and reduction in cerebral consumption of oxygen and glucose may indeed mechanistically explain the central neuroprotection of beta-blockers. Future studies should address, first, whether exposure to beta-blockers impacts mortality in patients with severe TBI. If so, then whether this benefit is only observed in patients in whom there is sympathetic hyperactivity present or if benefit is seen only in those who achieve a target heart rate will need to be determined. Clearly, a prospective multicenter randomized control trial would best address many of the issues and concerns arising from these retrospective studies.

While it appears that TBI patients as a group benefit from beta-blockade therapy, it remains unclear via which pathway and specific mechanism this beneficial effect is mediated. However, the hyperadrenergic pathway offers a biologically plausible mechanism and possible therapeutic goal. This may offer the clinician specific targets such as heart rate and blood pressure control to target during therapy. We would offer a word of caution that until a randomized controlled trial can confirm the large number of retrospective data, we would recommend only treating patients who have been appropriately resuscitated and who manifest evidence of sympathetic hyperactivity.

**CONCLUSION**

TBI remains the leading cause of death in trauma victims. Excluding nonsurvivable head injuries, the cause of death is often due to NNOD, especially cardiac manifestations. PSS is driven by hypothalamic disturbances or an imbalance of the EIR within the brain stem. Blocking of the hyperadrenergic response with beta-blockers has been shown to be associated with significant improvements in mortality, most notably in older and more severely injured patients. Many questions remain unanswered, particularly dosing, timing, targeting to a specific effect, and whether there is a difference between beta-blockers.

It appears clear that beta-blockers should play a significant role in future management of TBI and PSS. We look forward to future prospective trials that clarify the appropriate dosing, ideal agent, and the population most likely to benefit from the use of beta-receptor antagonists.

**REFERENCES**


