In modern, industrialized countries TBI is the leading cause of death and disability in children and young adults, and over the next 2 decades the global public health burden is expected to increase. Although treatment guidelines are now applied effectively to the treatment of these patients, their prognosis remains poor. A significant proportion of TBIs result in death attributable to nonneurologic organ dysfunction secondary to the initial traumatic insult. Zygun et al. observed nonneurologic organ dysfunction in 89% of patients, with respiratory and cardiovascular failure as the most commonly associated disorders in 23 and 18%, respectively. Some authors have speculated that the hyperadrenergic state frequently observed after TBI is a prominent contributor to these extracranial injuries. Thus, it may be useful to explore the efficacy of treatments that attenuate the effects of sympathetic hyperactivity, as these may provide survival benefits to patients with TBI.

Recently, the authors of several retrospective studies have sought to determine whether beta blockers can provide a benefit in patients with TBIs. In the present study, the rationale and evidence in support of the use of beta blockers in patients with TBI is summarized. We have tried to limit the current discussion to that of the human condition, and invoke animal studies only when necessary to provide additional pertinent information for this literature review.

Traumatic Brain Injury and the Catecholamine Surge

The evidence for a significant catecholamine surge following TBI is summarized in Table 1. For decades it has been known that brain injury is associated with a significant catecholamine surge. It should be noted that this phenomenon is not unique to TBI and has also been observed after other intracranial processes such as SAH and noncerebral insults such as burn injuries. Epinephrine and norepinephrine levels have been observed to increase several fold in patients with TBIs compared with controls. The initial surge is followed by a hyperadrenergic state lasting a variable time period after the initial trauma. Some authors have noted a correlation between the increase in catecholamine levels, the severity of the TBI, and clinical outcome, while other investigators have not found such a correlation. Whether the initial catecholamine surge is detrimental or beneficial to the patient who has sustained a TBI is currently unknown. Certainly from an evolutionary medicine point of view maintenance of cerebral blood flow and metabolism would seem to afford a survival advantage.

Although clinically relevant systemic effects of the catecholamine surge following systemic trauma and traumatic and nontraumatic brain injury have been described in relation to the cardiac, pulmonary, endocrine, and im-

**Beta blockers exposure and traumatic brain injury:**

*a literature review*

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Traumatic brain injury (TBI) continues to carry a significant public health burden and is anticipated to worsen worldwide over the next century. Recently the authors of several articles have suggested that exposure to beta blockers may improve mortality rates following TBI. The exact mechanism through which beta blockers mediate this effect is unknown. In this paper, the authors review the literature regarding the safety of beta blockers in patients with TBI. The findings of several recent retrospective cohort studies are examined and implications for future investigation are discussed. Future questions to be addressed include: the specific indications for the use of beta blockers in patients with TBI, the optimal type and dose of beta blocker given, the end point of beta blocker therapy, and the safety of beta blockers in cases of severe TBIs. (DOI: 10.3171/FOC.2008.25.10.E8)

**Key Words:** adrenergic receptor • beta blocker • brain injury • catecholamine • trauma

**Abbreviations used in this paper:** AIS = abbreviated injury scale; BBB = blood-brain barrier; GCS = Glasgow Coma Scale; HRV = heart rate variability; MABP = mean arterial blood pressure; OR = odds ratio; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.
Bryan reviewed the effects of catecholamine surge on the brain itself. The effects of the catecholamine surge and hyperadrenergic state on the brain are less clear. Adrenergic receptors have been identified in the brain and cerebral vasculature, but there is little clinical evidence of the effects of the catecholamine surge on the brain itself. Bryan reviewed the effects of stress (but not specifically that of TBI) on cerebral blood flow and energy metabolism. He emphasized the role of beta adrenergic receptors within the brain as a key mediator of stress effects on cerebral blood flow and energy metabolism. He also emphasized that there are three main sources of the catecholamines that may stimulate the cerebral beta adrenergic receptors: systemic, from the superior cervical ganglia; central, from the locus ceruleus; and sympathetic, from the superior cervical ganglia. Whether the survival advantage after TBI incurred by exposure to beta blockers is systemically or centrally mediated is currently unknown. As some beta blockers readily cross the BBB while others do not, the cerebral effects may or may not have clinical implications for future trial design.

**Beta Blockers**

Beta blockers were first described and developed in the 1950s. Nobel laureate Sir James W. Black introduced propranolol as the first clinically useful beta blocker for the treatment of angina. Currently, beta blockers are commonly prescribed agents familiar to all physicians with well-known side effect profiles and a proven record of efficacy in the treatment of cardiovascular disease. More recently the clinical indication and application of beta blockers has expanded significantly. Since the introduction of propranolol, other agents have been developed and several different beta blockers are available clinically. These agents can be classified into three generations: 1) first generation or nonselective, 2) second generation or selective, and 3) third generation or specialized. Again we emphasize that some beta blockers readily cross the BBB while others do not, and the cerebral effects may or may not have clinical implications for future trial design.

The possible mechanisms through which beta blockers improve survival remain purely speculative but include systemic, predominantly cardiac, and cerebral effects. Hypothetically, the cardioprotective effects are mediated through a reduction in heart rate, stroke volume, and MABP, which lowers myocardial oxygen demand, and thus lowers the risk of myocardial infarction. As cardiac dysfunction is relatively common after TBI, this may represent a significant opportunity through which clinical outcome can be improved. Hypothetically, the neuroprotective effects of beta blockers may be mediated through decreased cerebral blood flow and decreased glucose and oxygen consumption, thus reducing cerebral metabolism. Again this potential benefit remains purely speculative. Finally, a slowing of the catecholamine-induced catabolic state has been demonstrated with the use of beta blockers in

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**Table 1: Catecholamine surge after TBI in humans**

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>No. of Patients</th>
<th>Normal Levels†</th>
<th>Post-TBI Levels†</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clifton et al., 1981</td>
<td>30</td>
<td>—</td>
<td>—</td>
<td>plasma NE in TBI patients was negatively correlated w/GCS score (r = −0.49, p &lt;0.001).</td>
</tr>
<tr>
<td>Woolf et al., 1983</td>
<td>17</td>
<td>NE = 164 ± 50; E = 20 ± 6; DA = 35 ± 9</td>
<td>NE = 593 ± 59; E = 125 ± 14; DA = 34.1 ± 4.7</td>
<td>plasma NE &amp; E were significantly elevated compared w/catecholamine values in healthy volunteers (p&lt;0.001).</td>
</tr>
<tr>
<td>Hamill et al., 1987</td>
<td>33</td>
<td>NE &lt;392; E &lt;78; DA &lt;105</td>
<td>GCS Score 3–4 NE = 1686 ± 416; E = 430 ± 172; DA = 236 ± 110</td>
<td>NE may have prognostic value: among patients w/GCS scores 3–4, those who improved to GCS Score &gt;11 at 1 week postinjury had only slightly elevated NE (544 ± 89); those who died or remained unchanged had markedly elevated NE (2176 ± 531).</td>
</tr>
<tr>
<td>Woolf et al., 1987</td>
<td>61</td>
<td>NE &lt;447; E &lt;71; DA &lt;91</td>
<td>GCS Score 3–4 NE = 1502 ± 265; E = 400 ± 108; DA = 190 ± 69</td>
<td>patients w/most severe brain injury (GCS Scores 3–4) had NE &amp; E 4–5 × normal level; patient NE w/GCS scores of 3–4 was predictive of outcome.</td>
</tr>
<tr>
<td>Woolf et al., 1988</td>
<td>24</td>
<td>NE = 1.79 ± 0.15 pmol/ml; E = 0.23 ± 0.04 pmol/ml; DA = 0.90 ± 0.47 pmol/ml</td>
<td>GCS Score 8–11 NE = 413 ± 47; E = 102 ± 14; DA = 64 ± 20</td>
<td>GCS score was inversely proportional to degree of NE &amp; E increase (r = −0.41, p &lt;0.001) &amp; r = −0.37, p &lt;0.0002)</td>
</tr>
<tr>
<td>Mautes et al., 2001</td>
<td>29</td>
<td>plasma NE = 185–275; CSF NE = 40–120</td>
<td>—</td>
<td>95% of TBI patients w/NE Tx exhibited elevated plasma NE 14 days postinjury, while 60% of patients w/Tx had increased plasma NE.</td>
</tr>
</tbody>
</table>

* CFS = cerebrospinal fluid; DA = dopamine; E = epinephrine; NE = norepinephrine; — = values not provided.
† Catecholamine levels given in pg/ml except where otherwise noted.
burn victims. As hypermetabolism has been associated with brain injury this may represent an additional avenue of efficacy.

Although the specific effects of beta blockers following TBI are currently unknown, there are implications for trial design as both the systemic effects—especially myocardial ischemia and cardiac arrhythmia—and the central effects—especially intracranial pressure and brain oxygenation—must be monitored.

Use of Beta Blockers After TBI

Because beta blockers have been advocated by the Lund group, we will briefly review their work here. Authors of recent retrospective reviews who have suggested a benefit of beta blockers in patients after TBI will then be reviewed. These later studies are summarized in Table 2.

Lund Therapy

The group from Lund, Sweden, have developed and advocated the use of a management protocol for the treatment of TBI based on volume-targeted therapy principles. The basis for this protocol is the optimization of fluid flow across the BBB to reduce cerebral edema. Measures advocated by the Lund group to achieve this goal include: 1) stress reduction with adequate sedation and catecholamine blockade; 2) maintenance of euvolemia through the use of erythrocyte transfusion and maintenance of a normal albumin level; 3) preservation of cerebral perfusion pressure (60–70 mm Hg for adults and 40–55 mm Hg for children and adolescents); 4) avoidance of cerebrospinal drainage; 5) use of early nutrition; and 6) use of mechanical ventilation to promote normal oxygenation and ventilation.

In part the protocol advocated by the group from Lund emphasizes the use of metoprolol, a selective beta1-antagonist, and clonidine, an alpha2-agonist, which are used to limit the posttraumatic hyperadrenergic stress response. These investigators advocate the use of these agents to limit the formation of cerebral edema. Clonidine mediates systemic vasodilation and inhibits the release of central catecholamine, and metoprolol reduces myocardial contractility, lowers cardiac output, and lowers MABP. Combined, these drugs can be used to lower MABP, hypothetically reducing capillary hydrostatic pressure to the point where fluid filtration halts and reabsorption can occur. Although this induced reduction in MABP may lower cerebral perfusion pressure, the Lund group has used hemodynamic and microdialysis data to suggest that this effect is well tolerated by patients with brain injuries.

Clinical studies indicate that the volume-targeted Lund therapy may reduce the mortality rate following TBI. To date, several studies have been performed that indicate improved survival in adults and children treated with Lund therapy. Eker and colleagues conducted a prospective, nonrandomized trial in which 53 patients with severe brain injuries (GCS score ≤ 8) with intracranial hypertension (intracranial pressure ≥ 25 mm Hg) were treated according to the principles of the Lund therapy. Compared with a historical control group, consisting of 38 patients meeting the same selection criteria but treated with conventional principles, mortality was reduced from 47 to 8% (p < 0.001).

In 2 additional studies in adults with TBI who underwent treatment according to the Lund therapy, Nareid et al. and Nareid et al. indicate a similar incidence of low mortality and good outcomes. Nareid et al. reported the results from 38 Lund therapy–treated patients with a 13% mortality rate. Of the 33 surviving patients, 27 (71%) were noted to have had a good recovery or moderate disability. In another study, these same authors report that only 1 of 31 patients who underwent treatment with Lund therapy died, and 22 experienced a good recovery or only moderate disability.

It should be noted that the significance of these re-
The studies conducted by Naredi et al.\textsuperscript{32,33} comprised of patients with TBI without significant adverse effects. Agents clonidine and metoprolol can be applied to a group appears to have shown that the adrenergic blocking outcome can be elucidated. Despite these criticisms this principle, will require a more comprehensive prospective, randomized clinical trial before the true effects on outcome can be elucidated. Despite these criticisms this group appears to have shown that the adrenergic blocking agents clonidine and metoprolol can be applied to a group of patients with TBI without significant adverse effects.

Retrospective Cohort Studies

Arbabi and colleagues\textsuperscript{1} published a retrospective cohort study examining the effect of beta blocker exposure on outcome in a group of 4117 trauma patients, of whom 303 received beta blockers. Forty-five percent of the patients taking beta blockers had been prescribed these agents preinjury. These patients were older and had a higher incidence of hypertension, cardiac disease, renal disease, and diabetes. The remainder of the patients exposed to beta blockers received these agents for treatment of blunt aortic injury and for medical complications identified in the course of their hospitalization such as hypertension and tachyarrythmias. This latter group of patients was noted to be more severely injured and have lower GCS scores. After adjusting for confounding factors patients exposed to beta blockers were found to have a lower risk of death. This effect was greatest among patients with clinically significant TBI (GCS score < 13).

Cotton et al.\textsuperscript{9} published a retrospective cohort study that examined the effects of beta blocker exposure in 420 patients with TBI. Inclusion criteria included a length of stay between 4 and 30 days and an AIS score > 3. The 174 patients exposed to beta blockers, despite being older, more severely injured, having a higher rate of concomitant respiratory and infectious complications, and having a longer average length of stay, demonstrated a mortality rate less than half that of patients who were not exposed to beta blockers (5.1 vs 10.8%, \( p = 0.036 \)). Adjusting for the potential confounders described above, the relative risk of death between the patients exposed to beta blockers and those who were not was 0.29. With a specific focus on patients with TBI, the study by Cotton et al. also demonstrates a reduction in mortality rates for patients exposed to beta blockers.

Inaba et al.\textsuperscript{21} published a larger retrospective cohort study that also examined the effect of beta blocker exposure on deaths in 1156 patients with TBI. Patients with major associated systemic injuries and those believed to have a nonsurvivable brain injury were excluded. The 203 patients exposed to beta blockers were older, more severely injured, more likely to have sustained a skull fracture, and more likely to undergo a decompressive craniectomy. After adjusting for confounding factors, the authors reported that exposure to beta blockers was independently associated with a reduction in mortality rates (OR = 0.54, \( p < 0.01 \)). Following stratification of the patient population by age and injury severity, the authors found that beta blocker exposure provided a significant survival advantage among elderly patients (older than 55 years) with severe head injuries (AIS score \( \geq 4; \) OR = 0.3, \( p = 0.001 \)), and also among those with severe TBI (GCS score \( \leq 8; \) OR = 0.43, \( p = 0.01 \)). These results suggest that elderly patients with severe TBI could achieve a significant survival advantage with beta blocker treatment.

Although the above studies suggest that exposure to beta blockers may improve survival in patients sustaining a TBI they do not clarify the specific indications for beta blockers in patients with TBI. The authors of 2 other studies have tried to address this issue by evaluating biochemical and physiological data to predict subsets of patients with brain injuries who may benefit most from beta blocker exposure. A specific population that may benefit the most from beta blocker exposure is the subset of patients with brain injuries who exhibit elevated cardiac troponin I levels. Cardiac troponin I has been used as a biochemical marker of myocardial injury,\textsuperscript{7} and elevated cardiac troponin I levels have been observed in acute nontraumatic cerebral insults such as SAH, stroke, and intracerebral hemorrhage,\textsuperscript{10,18,31} and may reflect a more significant catecholamine surge.

Salim et al.\textsuperscript{39} undertook a retrospective cohort study of 420 patients with TBI, of whom 173 were noted to have elevated cardiac troponin I levels identified either on admission (in 125 patients) or during hospitalization (in 48). Patients who demonstrated elevated cardiac troponin I levels had a lower GCS score, were more severely injured, and had a higher mortality rate. When all the patients were analyzed, those exposed to a beta blocker were significantly less likely to die compared to those who were not (24.2 vs 35.9%, \( p = 0.0363 \)). In the whole group analysis, however, the effect of beta blocker exposure was not shown to independently reduce the mortality rate (OR = 0.59, \( p = 0.09 \)).

Subgroup analysis confirmed that in patients with an elevated cardiac troponin I level, beta blocker exposure did independently protect against death. Conversely, in patients with a normal cardiac troponin I level, beta blocker exposure did not independently reduce the risk of death. These findings suggest that cardiac troponin I levels may be used as a biochemical marker to predict which patients with TBI will benefit from exposure to beta blockers.

A physiological indicator for beta blockade may be the presence of decreased HRV. The severity of brain injury has been associated with an increase in sympathetic activity and a reduction in parasympathetic tone, an autonomic imbalance that reduces HRV and presumably increases the likelihood of myocardial ischemic injury due to increased metabolic demand.\textsuperscript{43} The administration of propanolol following acute myocardial infarction has been associated with the restoration of parasympathetic tone and diminished sympathetic activity.\textsuperscript{24}
Beta blocker exposure provided a survival advantage in patients with TBI and reduced HRV. The authors examined 446 patients with TBIs with head AIS scores ≥ 5, of whom 138 received beta blockers. These authors reported that overall patients exposed to beta blockers had a significantly lower mortality rate than those who were not exposed (21 vs 44%, p < 0.001). Also, while this finding did not reach statistical significance due to inadequate power, there was a notable trend suggesting that beta blocker exposure within the first 24 hours in patients with reduced HRV conveyed a notable reduction in mortality (25 vs 60%, p = 0.67).

Taken together, these retrospective studies provide consistent evidence to suggest that beta blocker exposure following TBI conveys a survival advantage. A double-blind, multicenter, prospective randomized trial will be needed to answer this issue definitely. Prior to designing such a trial, several questions must be addressed as outlined below. Some of these questions may be more efficiently addressed through the use of animal models of TBI.

Concluding Thoughts

Before embarking on such a trial, several basic questions must be answered. Some of these concerns are outlined briefly below:

**What are the Best Indications for Beta Blockers in Patients with TBI?** As Salim et al.9 and Riordin et al.38 have suggested, the indications for beta blocker use in patients with TBIs have yet to be defined. Will all such patients benefit from beta blockers, or just a subset of patients?

**Which Beta Blocker?** Currently, there is no evidence to suggest which beta blocker is the safest or most efficacious to use in patients with TBIs. Although the selective beta blocker metoprolol has been advocated by the Lund group,4,11,14–16,32–35,42,44 a prospective randomized trial published in 1982 suggested a benefit of the nonselective beta blocker propranolol in patients with aneurysmal SAH.47 Some beta blockers pass through the BBB and others do not—will this be of clinical importance?

**Exposure or Beta Blockade?** A central limitation to the studies we have discussed is the lack of knowledge regarding the physiological end point of treatment. While many of the patients may be exposed to beta blockers, it is currently unknown whether the physiological effect of the drug was necessary or even achieved. Whether physiological titration of the chosen beta blocker will be necessary to achieve optimal efficacy is presently unknown.

**When Should Beta Blockers Be Started?** Based on our current understanding of the effect of hypotension on brain injury, many physicians will have real concerns about potentially exposing a poorly resuscitated patient with brain injuries to the known secondary insult of hypotension. However, Riordin et al.38 have suggested that early exposure to beta blockers may be required.

Conclusions

There is mounting evidence from retrospective cohort studies to suggest that beta blocker exposure in patients who have sustained a TBI limits the mortality rate. Despite these findings, there are multiple unresolved issues that must be addressed prior to embarking on a multicenter, prospective trial of beta blockers in patients with TBI.

Disclosure

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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