Beta blockers exposure and traumatic brain injury: a literature review

TIMOTHY Y. TRAN, B.A., IRIE E. DUNNE, B.A., AND JOHN W. GERMAN, M.D.

Division of Neurosurgery, Department of Surgery Albany Medical College Albany, New York

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

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.^{28,45} Although treatment guidelines are now applied effectively to the treatment of these patients, their prognosis remains poor.²⁰

A significant proportion of TBIs result in death attributable to nonneurologic organ dysfunction secondary to the initial traumatic insult.²³ Zygun et al.⁵² 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.^{7,8} 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.^{3,9,21,38,39} 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.^{7,17,27,49–51} 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 SAH⁴⁷ and noncerebral insults such as burn injuries.^{2,19} Epinephrine and norepinephrine levels have been observed to increase several fold in patients with TBIs compared with controls.^{17,27,49–51} 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,^{7,17,50,51} while other investigators have not found such a correlation.²⁷ 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-

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.

Table 1: Catecholamine surge after TBI in humans*

Authors, Year	No. of Patients	Normal Levels†	Post-TBI Levels†	Comments
Clifton et al., 1981	30	—	—	plasma NE in TBI patients was negatively correlated w/ GCS score ($r = -0.49$, $p < 0.001$).
Woolf et al., 1983	17	NE = 164 ± 50 ; E = 20 ± 6 ; DA = 35 ± 9	NE = 593 ± 59 ; E = 125 ± 14 ; DA = 34.1 ± 4.7	plasma NE & E were significantly elevated compared w/ catecholamine values in healthy volunteers ($p < 0.001$).
Hamill et al., 1987	33	NE <392; E <78; DA <105	GCS Score 3–4 NE = 1686 ± 416 ; E = 430 ± 172 ; DA = 236 ± 110 GCS Score 8–11 NE = 477 ± 89 ; E = 76 ± 15 ; DA = 26 ± 4	NE may have prognostic value: among patients w/ GCS scores 3–4, those who improved to GCS Score >11 at 1 week postinjury had only slightly elevated NE (544 ± 89); those who died or remained unchanged had markedly elevated NE (2176 ± 531).
Woolf et al., 1987	61	NE <447; E <71; DA <91	GCS Score 3–4 NE = 1502 ± 265 ; E = 400 ± 108 ; DA = 190 ± 69 GCS Score 8–11 NE = 413 ± 47 ; E = 102 ± 14 ; DA = 64 ± 20	patients w/ most severe brain injury (GCS Scores 3–4) had NE & E 4–5 $\times$ normal level; patient NE w/ GCS scores of 3–4 was predictive of outcome.
Woolf et al., 1988	24	NE = 1.79 ± 0.15 pmol/ml; E = 0.23 ± 0.04 pmol/ml; DA = 0.90 ± 0.47 pmol/ml	NE = 5.80 ± 1.40 pmol/ml; E = 1.26 ± 0.32 pmol/ml; DA = 1.04 ± 0.37 pmol/ml	GCS score was inversely proportional to degree of NE & E increase ($r = -0.41$, $p < 0.0001$ & $r = -0.37$, $p < 0.0002$)
Mautes et al., 2001	29	plasma NE = 185–275; CSF NE = 40–120	—	95% of TBI patients w/ NE Tx exhibited elevated plasma NE 14 days postinjury, while 60% of patients w/o Tx had increased plasma NE.

* CSF = cerebrospinal fluid; DA = dopamine; E = epinephrine; NE = norepinephrine; — = values not provided.

† Catecholamine levels given in pg/ml except where otherwise noted.

mune systems,^{2,8,12,13,23,25,28,29,35,41,47,48,50,52} the effects of the catecholamine surge and hyperadrenergic state on the brain are less clear. Adrenergic receptors have been identified in the brain^{1,22} and cerebral vasculature, but there is little clinical evidence of the effects of the catecholamine surge on the brain itself. Bryan⁶ 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 3 main sources of the catecholamines that may stimulate the cerebral beta adrenergic receptors: systemic, from the adrenal medulla; 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 ef-

ficacy in the treatment of cardiovascular disease. More recently the clinical indication and application of beta blockers has expanded significantly.^{2,19,26,29,46,47} Since the introduction of propranolol, other agents have been developed and several different beta blockers are available clinically. These agents can be classified into 3 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 stroke work, limits 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.^{6,35,40} 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

Beta blocker exposure in TBI

TABLE 2: Use of beta blockers after TBI in humans*

Authors, Year	Inclusion Criteria	No. of Patients		No. of Patients Who Died (%)		p Value
		BB(–)	BB(+)	BB(–)	BB(+)	
Arbabi et al., 2007†	GCS <13	511	94	—	—	—
Cotton et al., 2007	head AIS ≥3 30< LOS <4	246	174	27 (11)	9 (5.2)	0.03
Riordin et al., 2007	head AIS ≥5	308	138	135 (44)	29 (21)	<0.001
Salim et al., 2008	head AIS ≥3	329	91	118 (36)	22 (24)	0.0363
Inaba et al., 2008	blunt head injury w/ ICU admission	953	203	199 (21)	34 (17)	0.183

* All evidence in these studies was Level III. BB(–) = not exposed to beta blockers; BB(+) = exposed to beta blockers; ICU = intensive care unit; LOS = length of stay.

† Study includes patients with other traumatic injuries. These numbers reflect only TBIs. Data on TBI mortality rate were not provided.

burn victims.¹⁹ 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.^{4,11,14–16,32–35,42,44} Authors of recent retrospective reviews who have suggested a benefit of beta blockers in patients after TBI will then be reviewed.^{3,9,21,38,39} 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 euvoemia 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,³⁶ 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,³⁰ the Lund group has used hemodynamic⁴ and microdialysis⁴² 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^{11,32,33} and children⁴⁴ treated with Lund therapy. Eker and colleagues¹¹ 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, Naredi et al.^{32,33} indicate a similar incidence of low mortality and good outcomes. Naredi et al.³² 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 authors³³ 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-

sults is controversial due to the nonrandomized nature of the studies and the use of historical controls. No doubt using a patient group from 1982–1986 as a control for comparison with data obtained in patients over the period 1989–1994 weakens the results of Eker et al.¹¹ It has been noted that between those time frames, the general quality of care improved,¹⁴ and the use of decompressive craniectomies increased.³⁷ The lack of a control group in the studies conducted by Naredi et al.^{32,33} compromises their ability to demonstrate that Lund therapy provides a significant survival advantage. Thus, Lund therapy, while promising and apparently based on physiological principles, 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 colleagues³ 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 tachyarrhythmias. 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.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.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 ≥ 4 ; OR = 0.3, $p = 0.001$), and also among those with severe TBI (GCS score ≤ 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,⁵ and elevated cardiac troponin I levels have been observed in acute nontraumatic cerebral insults such as SAH, stroke, and intracerebral hemorrhage,^{10,18,31} and may reflect a more significant catecholamine surge.

Salim et al.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.⁴³ The administration of propranolol following acute myocardial infarction has been associated with the restoration of parasympathetic tone and diminished sympathetic activity.²⁴

Riordin et al.³⁸ therefore sought to determine whether

Beta blocker exposure in TBI

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.³⁹ 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.

References

1. Alexander RW, Davis JN, Lefkowitz RJ: Direct identification and characterisation of beta-adrenergic receptors in rat brain. **Nature** **258**:437–440, 1975
2. Arbabi S, Ahrns KS, Wahl WL, Hemmila MR, Wang SC, Brandt MM, et al: Beta-blocker use is associated with improved outcomes in adult burn patients. **J Trauma** **56**:265–271, 2004
3. Arbabi S, Campion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, et al: Beta-blocker use is associated with improved outcomes in adult trauma patients. **J Trauma** **62**:56–52, 2007
4. Asgeirsson B, Grände PO, Nordström CH, Berntman L, Messeter K, Ryding E: Effects of hypotensive treatment with alpha 2-agonist and beta 1-antagonist on cerebral haemodynamics in severely head injured patients. **Acta Anaesthesiol Scand** **39**:347–351, 1995
5. Babuin L, Jaffe AS: Troponin: the biomarker of choice for the detection of cardiac injury. **CMAJ** **173**:1191–1202, 2005
6. Bryan RM: Cerebral blood flow and energy metabolism during stress. **Am J Physiol** **259**:H269–H280, 1990
7. Clifton GL, Ziegler MG, Grossman RG: Circulating catecholamines and sympathetic activity after head injury. **Neurosurgery** **8**:10–14, 1981
8. Clifton GL, Robertson CS, Kyper K, Taylor AA, Dhenkne RD, Grossmann RG: Cardiovascular response to severe head injury. **J Neurosurg** **59**:447–454, 1983
9. Cotton BA, Snodgrass KB, Fleming SB, Carpenter RO, Kemp CD, Arbogast PG, et al: Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. **J Trauma** **62**:26–33, 2007
10. Di Angelantonio E, Fiorelli M, Toni D, Sacchetti ML, Lorenzano S, Falcou A, et al: Prognostic significance of admission levels of troponin I in patients with acute ischaemic stroke. **J Neurol Neurosurg Psychiatry** **76**:76–81, 2005
11. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH: Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. **Crit Care Med** **26**:1881–1886, 1998
12. Friese RS, Barber R, McBride D, Bender J, Gentilello LM: Could beta blockade improve outcome after injury by modulating inflammatory profiles? **J Trauma** **64**:1061–1068, 2008
13. Gebhard F, Pfetsch H, Steinbach G, Strecker W, Kinzl L, Bruckner UB: Is interleukin 6 an early marker of injury severity following major trauma in humans? **Arch Surg** **135**:291–295, 2000
14. Gisvold SE: The Lund concept for treatment of head injuries—faith or science? **Acta Anaesthesiol Scand** **45**:399–401, 2001
15. Grande PO: The effects of dihydroergotamine in patients with head injury and raised intracranial pressure. **Intensive Care Med** **15**:523–527, 1989
16. Grande PO, Asgeirsson B, Nordstrom CH: Volume-targeted therapy of increased intracranial pressure: the Lund concept unifies surgical and non-surgical treatments. **Acta Anaesthesiol Scand** **46**:929–941, 2002
17. Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M: Catecholamines predict outcome in traumatic brain injury. **Ann Neurol** **21**:438–443, 1987

18. Hays A, Diringner MN: Elevated troponin levels are associated with higher mortality following intracerebral hemorrhage. **Neurology** **66**:1330–1334, 2006
19. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR: Reversal of catabolism by beta-blockade after severe burns. **N Engl J Med** **345**:1223–1229, 2001
20. Hesdorffer DC, Ghajar J: Marked improvement in adherence to traumatic brain injury guidelines in United States trauma center. **J Trauma** **63**:841–847, 2007
21. Inaba K, Teixeira PG, David JS, Chan LS, Salim A, Brown C, et al: Beta-blockers in isolated blunt head injury. **J Am Coll Surg** **206**:432–438, 2008
22. Joyce JN, Lexow N, Kim SJ, Artymyshyn R, Senzon S, Lawrence D, et al: Distribution of beta-adrenergic receptor subtypes in human post-mortem brain: alterations in limbic regions of schizophrenics. **Synapse** **10**:228–246, 1992
23. Kraus J, Conroy C, Cox P, Ramstein K, Fife D: Survival times and case fatality rates of brain-injured persons. **J Neurosurg** **63**:537–543, 1985
24. Lampert R, Ickovics JR, Viscoli CJ, Horwitz RI, Lee FA: Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. **Am J Cardiol** **91**:137–142, 2003
25. Maier B, Lefering R, Lehnert M, Laurer HL, Steudel WI, Neugebauer EA, et al: Early versus late onset of multiple organ failure is associated with differing patterns of plasma cytokine biomarker expression and outcome after severe trauma. **Shock** **28**:668–674, 2007
26. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after non-cardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. **N Engl J Med** **335**:1713–1720, 1996
27. Mautes AEM, Muller M, Cortbus F, Schwerdtfeger K, Maier B, Holanda M, et al: Alterations of norepinephrine levels in plasma and CSF of patients after traumatic brain injury in relation to disruption of the blood-brain barrier. **Acta Neurochir (Wien)** **143**:51–58, 2001
28. Morganti-Kossmann MC, Satgunaseelan L, Bye N, Kossmann T: Modulation of immune response by head injury. **Injury** **38**:1392–1400, 2007
29. Morel DR, Forster A, Suter PM: Evaluation of I.V. labetalol for treatment of posttraumatic hyperdynamic state. **Intensive Care Med** **10**:133–137, 1984
30. Moss E: Cerebral blood flow during induced hypotension. **Br J Anaesth** **74**:635–637, 1995
31. Naidech AM, Kreiter KT, Janjua N, Ostapkovich ND, Parra A, Commichau C, et al: Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. **Circulation** **112**:2851–2856, 2005
32. Naredi S, Eden E, Zall S, Stephensen H, Rydenhag B: A standardized neurosurgical neurointensive therapy directed toward vasogenic edema after severe traumatic brain injury: clinical results. **Intensive Care Med** **24**:446–451, 1998
33. Naredi S, Olivecrona M, Lindgren C, Ostlund AL, Grande PO, Koskinen LO: An outcome study of severe traumatic head injury using the “Lund therapy” with low-dose prostacyclin. **Acta Anaesthesiol Scand** **45**:402–406, 2001
34. Nilsson F, Nilsson T, Edvinsson L, Bjorkman S, Nordstrom CH: Effects of dihydroergotamine and sumatriptan on isolated human cerebral and peripheral arteries and veins. **Acta Anaesthesiol Scand** **41**:1257–1262, 1997
35. Nordstrom CH, Messeter K, Sundbarg G, Schalen W, Werner M, Ryding E: Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. **J Neurosurg** **68**:424–431, 1988
36. Payen D, Quintin L, Plaisance P, Chiron B, Lhoste F: Head injury: clonidine decreases plasma catecholamines. **Crit Care Med** **18**:392–395, 1990
37. Polin RS, Shaffrey ME, Bogaev CA, Tisdale N, Germanson T, Bocchicchio B, et al: Decompressive bifrontal craniectomy in the treatment of severe refractory posttraumatic cerebral edema. **Neurosurgery** **41**:84–92, 1997
38. Riordan WP Jr, Cotton BA, Norris PR, Waitman LR, Jenkins JM, Morris JA Jr: Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling. **J Trauma** **63**:503–510, 2007
39. Salim A, Hadjizacharia P, Brown C, Inaba K, Teixeira PG, Chan L, et al: Significance of troponin elevation after severe traumatic brain injury. **J Trauma** **64**:46–52, 2008
40. Schmalbruch IK, Linde R, Paulson OB, Madsen PL: Activation-induced resetting of cerebral metabolism and flow is abolished by beta-adrenergic blockade with propranolol. **Stroke** **33**:251–255, 2002
41. Seekamp A, Jochum M, Ziegler M, van Griensven M, Martin M, Regel G: Cytokines and adhesion molecules in elective and accidental trauma-related ischemia/reperfusion. **J Trauma** **44**:874–882, 1998
42. Stahl N, Ungerstedt U, Nordstrom CH: Brain energy metabolism during controlled reduction of cerebral perfusion pressure in severe head injuries. **Intensive Care Med** **27**:1215–1223, 2001
43. Su CF, Kuo TB, Kuo JS, Lai HY, Chen HI: Sympathetic and parasympathetic activities evaluated by heart-rate variability in head injury of various severities. **Clin Neurophysiol** **116**:1273–1279, 2005
44. Wahlstrom MR, Olivecrona M, Koskinen LO, Rydenhag B, Naredi S: Severe traumatic brain injury in pediatric patients: treatment and outcome using an intracranial pressure targeted therapy—the Lund concept. **Intensive Care Med** **31**:832–839, 2005
45. World Health Organization, Peden M (ed): **World Report on Road Traffic Injury Prevention**. Geneva: World Health Organization, 2004 (http://www.paho.org/English/DD/PUB/Summary_World_report_Road_safety.pdf) [Accessed 3 September 2008]
46. Wallace A, Layug B, Tateo I, Li J, Hollenberg M, Browner W, et al: Prophylactic atenolol reduces postoperative myocardial ischemia. McSPI Research Group. **Anesthesiology** **88**:7–17, 1998
47. Walter P, Neil-Dwyer G, Cruickshank JM: Beneficial effects of adrenergic blockade in patients with subarachnoid haemorrhage. **BMJ** **284**:1661–1664, 1982
48. Woiciechowsky C, Schoning B, Cobanov J, Lanksch WR, Volk HD, Docke WD: Early IL-6 plasma concentrations correlate with severity of brain injury and pneumonia in brain-injured patients. **J Trauma** **52**:339–345, 2002
49. Woolf PD, Akowuah ES, Lee L, Kelly M, Feibel J: Evaluation of the dopamine response to stress in man. **J Clin Endocrinol Metab** **56**:246–250, 1983
50. Woolf PD, Hamill RW, Lee LA, Cox C, McDonald JV: The predictive value of catecholamines in assessing outcome in traumatic brain injury. **J Neurosurg** **66**:875–882, 1987
51. Woolf PD, Hamill RW, Lee LA, McDonald JV: Free and total catecholamines in critical illness. **Am J Physiol** **254**: E87–E291, 1988
52. Zygun DA, Kortbeek JB, Fick GH, Laupland KB, Doig CJ: Non-neurologic organ dysfunction in severe traumatic brain injury. **Crit Care Med** **33**:654–660, 2005

Manuscript submitted June 14, 2008.

Accepted August 28, 2008.

Address correspondence to: John W. German, M.D., Division of Neurosurgery, Department of Surgery, Albany Medical College, 47 New Scotland Avenue, Albany, New York 12108. email: jwgerman@hotmail.com.