

BETA-BLOCKER USE IN THE ACUTELY INJURED PATIENT

Traumatic Brain Injury

A hyper-adrenergic state has long been demonstrated in those patients with severe TBI, as well as non-traumatic sub-arachnoid hemorrhage. This sympathetic hyperactivity may present anywhere along the continuum; from a mild and apparently benign SIRS state to the disruptive and difficult to control paroxysmal sympathetic storms (PSS). The most severe form of the hyper-adrenergic states, PSS, presents with paroxysmal sympathetic system activation and adrenal release of catecholamines. These PSS events, with their associated tachycardia, hypertension, tachypnea, mydriasis, and diaphoresis, often resemble those of pheochromocytoma and hyperthyroid storms (earning them the nickname “brain storms”). Several investigators have evaluated the post-TBI state (with regards to the plasma and urinary correlates of a hyper-adrenergic phenomenon) and noted a greater than 7-fold increase in norepinephrine, epinephrine, and their urine excreted metabolites. Elevations appear to correlate with significant increases in sympathetic hyperactivity and are most pronounced during the first week following injury.

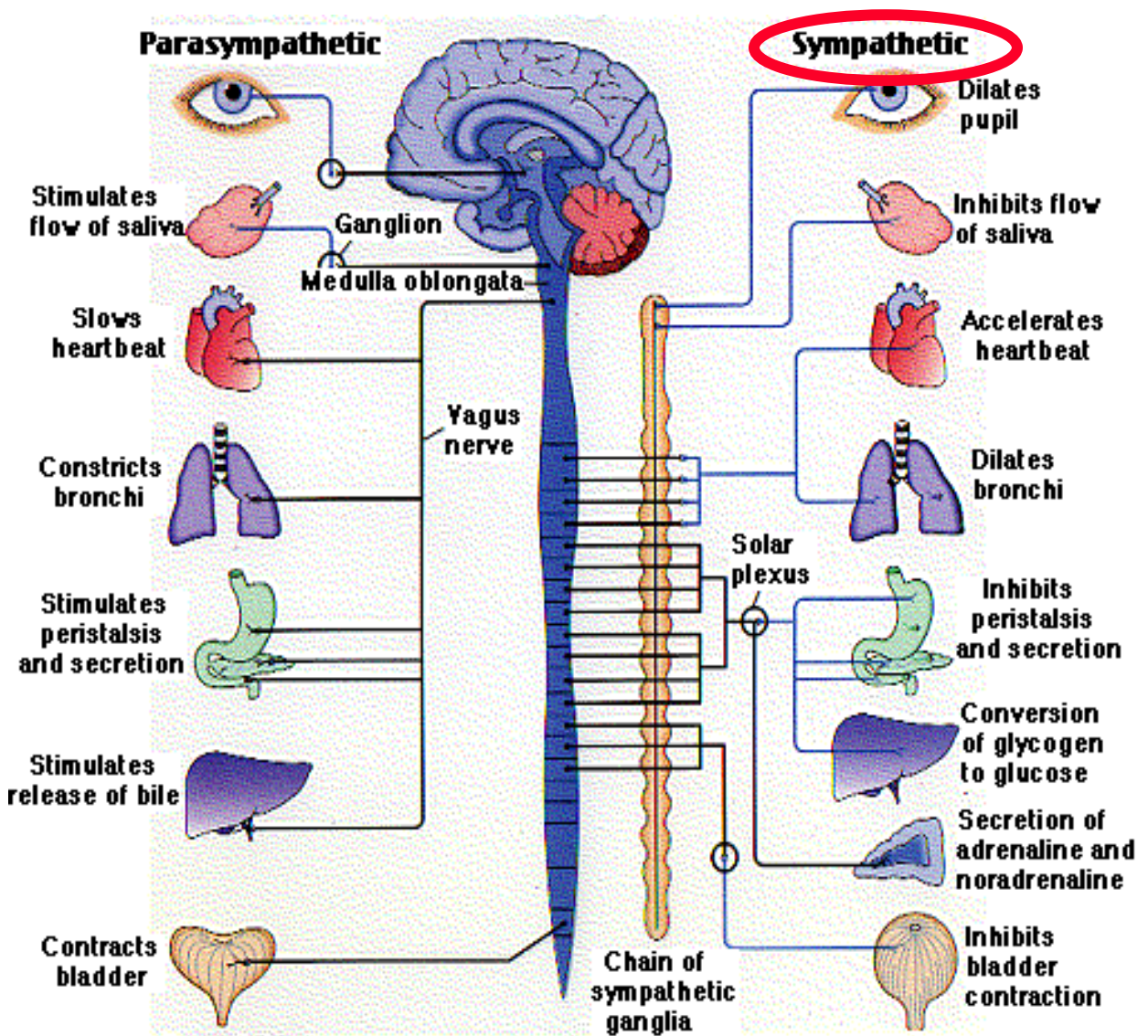
Beginning in the late 1970's and continuing throughout the 1980's, Neil-Dwyer and colleagues published several studies on the hyper-adrenergic state following intra-cranial hemorrhage. Although the majority of these related to patients with nontraumatic SAH, the group later published findings in the TBI population as well. The authors noted that in both groups, patients with a clinically and/or biochemically significant hyper-adrenergic state appeared to have an increased morbidity and mortality. Mechanism involved

included a severe hyper-metabolic state, myocardial ischemia/infarction, and pulmonary dysfunction. In addition, the authors noted (as did Woolf and colleagues almost a decade later) that other severely injured patients without TBI lacked the catecholamine surge and were noted to have better survival rates. More importantly, this group of investigators demonstrated that administration of beta-blockers (BB) in patients with severe TBI could attenuate the hyper-adrenergic response, thereby decreasing cardiac complications and improving neurological recovery.

Despite extensive research and advances in the critical care arena, mortality following severe TBI has remained unacceptably high. Poor outcomes are generally attributed to the severity of the primary brain injury and little (if any) real progress has been made on improving survival. In 1998, however, Eker and colleagues proposed that poor outcomes from severe TBI were not a consequence of the primary insult that that could not be prevented, but rather a failure to utilize less “traditional” therapeutic approaches. By treating intra-cranial hypertension with a multi-drug regimen, including scheduled intravenous metoprolol and clonidine, the authors noted a reduction in arterial inflow pressure. Through the use of this protocol, the Lund group demonstrated a significant reduction in mortality and improvement in Glasgow Outcome Scale at six months ($p < 0.001$).

By investigating and treating the extra-cranial manifestations (or non-neurological organ dysfunction) of severe TBI, these previously overlooked and harmful secondary insults

become potential avenues for improving survival in this population. We recently demonstrated that exposure to beta-blockers in patients with severe TBI was associated with a significant reduction in mortality (adjusted RR 0.29). This reduction in mortality is even more impressive when considering that the BB (+) group was older, more severely injured, had higher respiratory and infectious complications, and had a lower predicted survival.



Early cardiac uncoupling (reduction in HRV) in patients with severe TBI has been shown by several studies to be associated with a marked increase in mortality. We recently noted that the percentage of time spent in such an “uncoupled” state allowed stratification of mortality risk. Several authors have recently noted an improvement in survival in patients with TBI who were exposed to beta-blockers during their initial hospitalization. We noted that in the most severe forms of TBI ($AIS \geq 5$) beta-blocker exposure was associated with improved survival. Although this benefit lost statistical significance when those dying in the first 24 hours were excluded, this population was older and more severely injured. Therefore, as a group we would have expected to observe a higher mortality when compared to a younger, less injured cohort who were not exposed to beta-blockers. In addition, we feel that we have identified a particular group of severe TBI patients who may benefit from beta-blockers. Patients who spend greater than 5% of the first 24 hours uncoupled, appear to receive the greatest survival benefit from beta-blocker exposure. The present study further supports a call for a multi-institutional, randomized trial to investigate the effect of beta-blockers on survival in patients with severe TBI, as well as identifying those most likely to benefit and therapeutic end-points for these medications.

WHICH TBI PATIENTS GET BB?

All TBI patients with:

1) intra-cranial hemorrhage by CTH,

AND

2) persistent hyper-adrenergic state with paroxysmal tachycardia, tachypnea and hypertension; may also demonstrate diaphoresis, mydriasis, agitation

WHICH BB TO USE AND HOW MUCH?

1. Propranolol and labetalol are lipophilic, penetrate BBB, and exhibit central & peripheral actions.
2. Initiate propranolol @ 10 mg PT/PO q8
3. If no gut access, use labetalol 10-20 mg I.V. q4
4. Utilize labetalol 10-40mg I.V. q2 prn

WHEN TO START AND HOW LONG TO CONTINUE?

1. Initiate after 24-48 h, adequate resuscitation.
2. Rule out sepsis, missed injuries, un-addressed pain prior to initiating BB
3. Continue for at least 14 days. May wean as HR remains <100.

HOW TO TITRATE BB?

1. Consider titration to a mean HR < 90bpm and/or improvement in symptom severity/frequency

2. May also titrate for a return of CVRD to less than 5%

Geriatric trauma

Numerous studies have documented the beneficial effects of peri-operative beta blockade in patients undergoing non-cardiac surgery. In addition to a significant reduction in preoperative cardiac mortality, decreases in long-term overall mortality, long-term cardiac mortality, postoperative myocardial infarction, and postoperative myocardial ischemia have been demonstrated in patients receiving beta-blockade in the peri-operative period. The current ACC/AHA guidelines recommend peri-operative beta blockade as a Class I recommendation for patients who required use of beta blockers in the recent past for control of angina, arrhythmia, or hypertension, and high-risk patients with findings of ischemia on preoperative testing undergoing vascular surgery.

WHICH TRAUMA PATIENTS GET BB?

The most recent iteration of the *American College of Surgeons Resources for Optimal Care of the Injured Patient* identifies the use of beta-blockers in patients with (1) prehospital use of BB, (2) known coronary artery disease, or (3) age greater than 65 years should be standard of care. The College has placed this under the standards for Patient Safety Practices along with DVT prophylaxis and peri-operative antibiotics.

WHICH BB TO USE AND HOW MUCH?

1. If patient is on home BB, this medication should be restarted initially at ½ dose and then titrated to full dose as tolerated.

2. If not on BB at home, but patient meets indications, metoprolol should be utilized.

Start at 12.5-25 mg PO/PT q 12h. Titrate to HR <80 bpm as BP tolerates.

3. If metoprolol proves ineffective, propranolol can be utilized. Initiate @ 10 mg PT/PO q 8h.

4. If no gut access, use labetalol 10-20 mg I.V. q 4h or metoprolol 5-10 mg I.V. q 4h

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