

# Adrenergic modulation of erythropoiesis following trauma

by Alicia M. Mohr

of functional oxygen metabolism. Following TBI, hyperglycolysis may occur within hours of the injury, resulting in acidosis and cell death and, in animal models, acute elevations in Glu have been shown to last for seven to nine days following TBI. Therefore, Glu, an excitatory amino acid, has been implicated in exacerbating primary TBI and its effect may last for more than one week following the injury. MRS can track the changes in Glu concentration and its influence on brain injury severity. In addition to the study of Glu, reductions in NAA have been correlated with brain injury in both animals and humans. NAA is found only in the central nervous system and is the second most abundant compound in the brain (only Glu is more abundant). Because NAA is thought to be related to catabolic activity and axonal repair, its relationship to brain injury has been widely studied. Animal studies have shown NAA reductions following TBI as early as one hour post injury and examination of metabolism in humans has revealed that NAA depression may continue for months prior to metabolic rebound. The Cho peak has also been shown to be elevated in cases of local tissue breakdown or repair or in the case of tissue inflammation for weeks following injury. Thus, decline in NAA and elevations in Cho are considered reliable markers at the level of the brain substrate representative of TBI. Therefore measuring NAA, Cho, and Glu following TBI provides investigators with the unique opportunity to monitor acute changes at the brain level that coincide with behavioral changes observed during recovery.

While MRS has shown great promise in predicting brain injury severity and patient outcome, the exact protocols for using MRS with TBI remain undetermined. The purpose of this research is to examine three critical areas: 1.) when in the post-injury time period MRS data should be acquired (e.g., within one week of injury, within one month of injury) for gathering optimal predictive data; 2.) how metabolites should be measured (i.e., absolute concentrations or changes in concentration over time); and 3.) brain locations best suited for MRS data acquisition (i.e., acquisition near lesion sites or acquisition at sites remote from probable brain lesion).

In humans, MRS has now been applied to the study of both acute and chronic TBI and there is evidence of significant correlation with injury severity and cognitive outcome. This research will provide further insight into the uses of MRS and the treatment of traumatic brain injury.

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In research conducted in the Division of Trauma at UMDNJ-University Hospital's trauma center, I have pursued a separate line of investigation on erythropoietic dysfunction following severe injury. Erythropoiesis and the formation of red blood cells is a complex process involving bone marrow stem cells, progenitor cells, and stromal cells. Severe traumatic injury is a stress state, commonly associated with a "fight or flight response." During this time, the stress hormones epinephrine and norepinephrine are released and bind to adrenergic receptors. It is the impact of this stress or "adrenergic state" on erythropoiesis and its subsequent dysfunction that is the focus of my research.

Persistent anemia is a common occurrence in critically injured patients and multiple transfusions are frequently needed. Anemia has associated adverse effects and the safety of transfusions is uncertain. An understanding of the pathophysiology of anemia in the intensive care unit (ICU) patient facilitates selection of an optimal treatment strategy. Adrenergic modulation of erythropoiesis is known to occur under normal conditions and typically red blood cell growth is enhanced. Yet, following traumatic injury, red blood cell growth is suppressed and the presence of anemia is persistent. Adrenergic

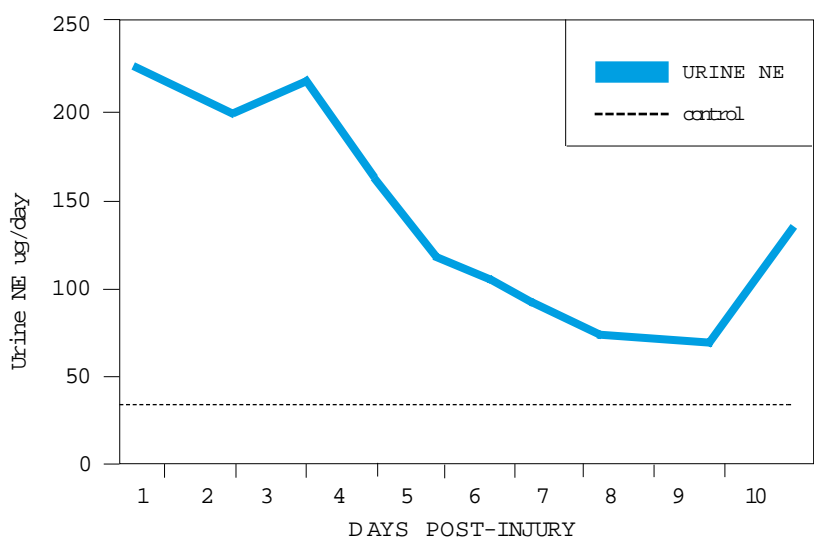


Figure 1. Mean urine norepinephrine levels (ug/day) are significantly increased in critically ill patients compared to normal controls from the date of admission up to day 10 post injury.

stimulation is known to accompany traumatic injury but there is no information on its effects on bone marrow during trauma. We hypothesize that since adrenergic stimulation occurs with trauma, the anemia associated with injury may be related to the cells' altered ability to proliferate and differentiate into red blood cells. This response is due to either the magnitude or the persistence of adrenergic stimulation that occurs with injury. If true, an investigation of the contributions of bone marrow stroma and the mediators involved in altered erythropoiesis after injury, as well as the use of adrenergic antagonists, may produce important advances in trauma care by suggesting a clinical approach to anemia that could diminish its current morbidity.

My work regarding the adrenergic modulation of erythropoiesis following trauma is an extension of the research that I began in the laboratory of David Livingston, MD. That research provided the groundwork and background for my current studies. Knowing that persistent anemia follows

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severe injury, and that the defect lies in the bone marrow rather than in peripheral blood, allows us to analyze the specific impact of the stress state on bone marrow erythropoiesis. My initial studies have focused on hormonally replicat-

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ing *in vitro* the stress state using normal bone marrow. We are also expanding our study to include trauma patients admitted to the Surgical Trauma ICU at UMDNJ-University Hospital.

In one of our studies, we have demonstrated that urine norepinephrine levels from critically injured patients are significantly elevated as compared to a control group (Figure 1). The initial elevation of norepinephrine immediately following injury is six times that of normal levels. This super-stimulated state lasts for seven to 10 days following severe injury. Epinephrine levels are also elevated but return to baseline levels more quickly.

Adrenergic agonists, epinephrine, norepinephrine and isoproterenol, were added to bone marrow cultures *in vitro* to assess their effect on erythropoietic progenitors, specifically erythroid burst forming units (BFU-E) and erythroid colony forming units (CFU-E). These adrenergic agonists induced proliferation of BFU-E and CFU-E, which were grown in the presence of bone marrow stroma. All three adrenergic agents exerted their highest stimulatory effect at lower doses. At the highest concentration, most colony numbers dropped considerably, suggesting that the adrenergic effect is dose-related. In our studies, BFU-E colonies had a significantly higher response than did CFU-E to adrenergic agonists. This differential effect to catecholamine stimulation may be a hierarchical response resulting from the adrenergic effect on the terminal maturation at the

BFU-E stage, which precedes CFU-E in the erythropoietic maturation scheme. To determine if the bone marrow stroma is essential for this proliferative process associated with adrenergic stimulation, bone marrow stroma was

depleted. When these same adrenergic agonists are added to bone marrow cultures of BFU-E and CFU-E lacking bone marrow stroma, the proliferative

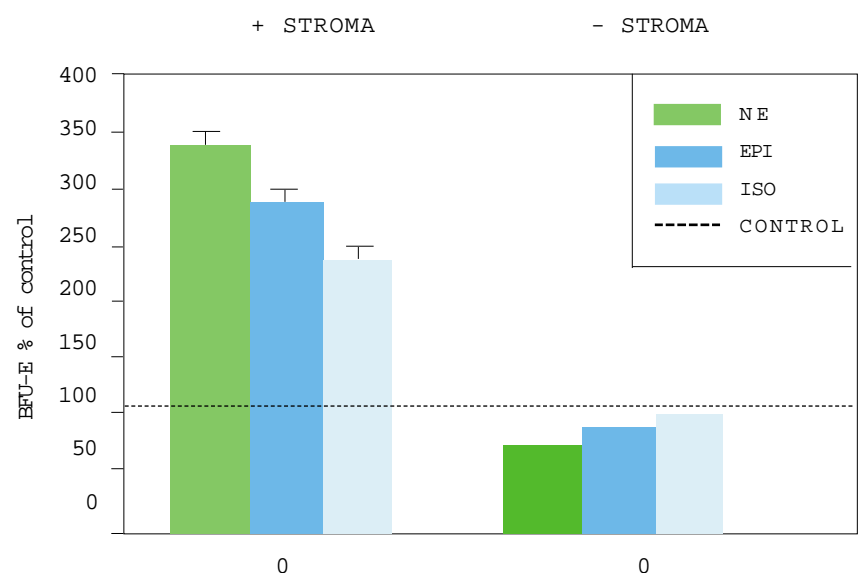



Figure 2. BFU-E colonies grown with the addition of norepinephrine, epinephrine, isoproterenol in cultures with the presence of stroma (+ stroma) vs. stroma-depleted bone marrow (- stroma).

effect is abrogated (Figure 2).

Thus far, we have shown that there is a significant and persistent hypercatecholamine state after severe injury. Our *in vitro* analyses support the notion that erythropoiesis is also modulated by the adrenergic system. Our research discovered a dichotomy. On one hand there is a hypercatecholamine period after severe injury that is characterized by overt bone marrow dysfunction, seen as anemia and leucopenia. Yet, on the other hand, our data shows that the addition of adrenergic agents to erythroid precursors *in vitro* leads to an overwhelming pro-erythropoietic stimulus. Future studies will focus on the mechanisms that account for the paradox of adrenergic stimulation observed in trauma patients as opposed to the *in vitro* effects on bone marrow cultures. There may be a direct correlation between the magnitude and duration of the stress response seen following injury and resultant erythropoietic dysfunction. Perhaps with the use of adrenergic antagonists, the adrenergic modulation of erythropoiesis may be altered.

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# Preventing inflammatory complications of shock and trauma

by **Carl J. Hauser**

**T**rauma causes more than 140,000 deaths per year in the U.S. and is the leading cause of death between birth and age 45. From birth to age 36, death from trauma exceeds all other causes of death combined. More than 50,000 preventable deaths occur per year when trauma, hemorrhage, sepsis or shock triggers the systemic inflammatory response syndrome, or SIRS. SIRS, however, is simply a convenient clinical descriptor. In fact, after injury, the organism is exposed to a wide variety of non-specific initiators of inflammation such as ischemia/reperfusion, molecular “danger signals,” and non-apoptotic cell death. These events can lead to a complex and sometimes massive activation of innate immunity. Circulating neutrophils (polymorphonuclear leukocytes) are the dominant effector cells of the innate immune response to injury. Thus after injury, when ischemia, reperfusion, sepsis or other insults activate neutrophils, the result can be an immune attack on vital organs. This is most commonly clinically manifested as the acute respiratory distress syndrome or as multiple organ failure.

During the last seven years my laboratory has focused on the translational biology of neutrophil inflammation after injury. I began by studying a group of G-protein coupled (GPC) white blood cell chemoattractants called chemokines. Chemokines were known to exist in high concentration in clinical plasma samples of injured patients. The concentrations of chemokines in

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