Published in final edited form as:

Shock. 2016 October ; 46(4): 341–351. doi:10.1097/SHK.0000000000000636.

β -blockade Use for Traumatic Injuries and Immunomodulation: A review of proposed mechanisms and clinical evidence

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Abstract

Sympathetic nervous system activation and catecholamine release are important events following injury and infection. The nature and timing of different pathophysiologic insults have significant effects on adrenergic pathways, inflammatory mediators, and the host response. Beta adrenergic receptor blockers (β -blockers) are commonly used for treatment of cardiovascular disease but recent data suggests that the metabolic and immunomodulatory effects of β -blockers can expand their use. β -blocker therapy can reduce sympathetic activation and hypermetabolism as well as modify glucose homeostasis and cytokine expression. It is the purpose of this review to examine either the biologic basis for proposed mechanisms or to describe current available clinical evidence for the use of β -blockers in traumatic brain injury (TBI), spinal cord injury (SCI), hemorrhagic shock, acute traumatic coagulopathy, erythropoietic dysfunction, metabolic dysfunction, pulmonary dysfunction, burns, immunomodulation, and sepsis.

Keywords

Beta blockade; beta blocker; propranolol; metoprolol; trauma; injury; catecholamines; immunosuppression

Introduction

The physiologic concept that β adrenergic receptor blocker (β -blocker) therapy can decrease tissue oxygen consumption and hypermetabolism has led several investigators to research the role of β -blockers following traumatic injury. Increased sympathetic activity and exaggerated catecholamine release may be triggered by traumatic brain injury (TBI), autonomic dysfunction associated with spinal cord injury (SCI), hemorrhagic shock, burns, infection, tissue hypoperfusion, hypoxia, and direct tissue injury. The intensity and duration of catecholamines released as part of the host response to injury can influence the activation of the acute inflammatory response.⁽¹⁾ Catecholamines are an integral part of the neuro-endocrine-immune/inflammatory network.⁽¹⁾ Not only do stress and inflammation have key roles following injury, but these responses also change over the course of critical illness in those that survive their initial insult. Therefore, it is a complicated process to consider the

potential contributions of β -blockers in modulating the stress response, the inflammatory response, hypermetabolism, and host protective immunity. This review provides an overview of the β adrenergic receptor and the pharmacology of β -blockers. Subsequently, it discusses both animal and existing clinical studies regarding β -blocker use in TBI, SCI, hemorrhagic shock, acute traumatic coagulopathy, erythropoietic dysfunction, metabolic dysfunction, pulmonary dysfunction, burns, immunomodulation, and sepsis.

β adrenergic receptors and their pharmacology

β adrenergic receptors are G-protein coupled receptors of three types (β -1, β -2, and β -3), all of which activate adenylate cyclase which then increases cyclic adenosine monophosphate, activating protein kinase A.⁽²⁾ The β adrenergic receptor itself can be phosphorylated by protein kinase A, which leads to its internalization and downregulation.⁽³⁾ Each receptor is activated by epinephrine (EPI) and norepinephrine (NE).⁽²⁾ Plasma EPI levels primarily reflect adrenal medullary release, whereas circulating NE represents spillover from sympathetic neuron terminals, and both can function as neurotransmitters.⁽⁴⁾ While EPI and NE have nearly equal potency for β -1 receptors, NE has up to 100-fold selectivity for β -2 receptors and EPI has greater potency for β -3 receptors.⁽²⁾ β -1 receptors are concentrated in cardiomyocytes, β -2 receptors predominate in blood vessels and airway smooth muscle tissues, and each receptor is found in every major organ system.⁽³⁾ β -1 stimulation increases chronotropy and inotropy in cardiomyocytes, whereas β -2 stimulation causes smooth muscle dilation in blood vessels and airways.⁽²⁾ β -3 receptor functions include lipolysis in white adipose tissue, thermogenesis in brown adipose tissue, and modulation of hematopoietic progenitor cell (HPC) mobilization.⁽²⁻⁵⁾

β -blockers are characterized by their variable selectivity among receptor subtypes (Table 1).⁽⁶⁾ Some β -blockers also inhibit α -1 adrenergic receptors, and therefore potentiate vasodilation.⁽⁶⁾ Commonly prescribed β -blockers include: (1) nonselective β -blockers that antagonize both β -1 and β -2 receptors, (2) β -1 selective antagonists, and (3) α -1 and nonselective β -blockers. β -2 and β -3 blockade may be accomplished with experimental selective antagonists or with non-selective β -blockers.⁽⁵⁾ Experimental β -3 antagonists include L-748337, which has been shown to inhibit nitric-oxide mediated cellular proliferation,⁽⁷⁾ and SR 59230A hydrochloride, which has been used to investigate brown adipose tissue thermogenesis and colonic motility in rodent models.⁽⁸⁾

There are several potential adverse effects of β -blockers. β -blockade may compromise cardiovascular function and the compensatory response by decreasing blood pressure and heart rate.⁽⁹⁾ These effects are particularly deleterious in the context of hemorrhagic shock,⁽¹⁰⁾ limiting the clinical application of β -blockers for patients with severe bleeding. In addition, because β -2 stimulation potentiates smooth muscle dilation in the airways,⁽²⁾ blockade of these receptors may result in bronchoconstriction. This phenomenon may unmask or exacerbate the effects of asthma.⁽¹¹⁾ Patients with diabetes and those at increased risk for developing diabetes may be adversely affected by long term β -blocker use due to the propensity of these medications to blunt insulin sensitivity.⁽¹²⁾ Finally, chronic β -blockade has been associated with increased incidence of sexual dysfunction, though the causal mechanism remains unclear.⁽¹³⁾

Traumatic brain injury

Plasma NE and urine catecholamines are significantly elevated following TBI and correlate with the severity of neurologic deficit.^(14, 15) This catecholamine surge affects brain inflammatory markers and increases both cardiac and cerebral oxygen demands. β -blockade's mechanism of action in TBI is not yet fully understood, but there are preclinical studies demonstrating that it affects both inflammatory and oxygenation pathways. In microglial cells, β adrenergic stimulation attenuates lipopolysaccharide (LPS)-induced inflammatory cytokine production, and nonselective β -blockers reverse this effect.^(16, 17) In stroke patients, propranolol decreases cerebral oxygen consumption, carbon dioxide production, and glucose consumption.^(18, 19) Similarly, mice that receive propranolol have improved neurologic recovery one hour after TBI, better grip test scoring, and significantly less brain edema on histological analysis.⁽²⁰⁾ Propranolol has also been shown to improve cerebral oxidative phosphorylation and lipid synthesis.^(19, 21) In animal studies, β -blockers have been shown to improve cerebral perfusion by 152% and decrease cerebral hypoxia by 24%.⁽¹⁸⁾ Propranolol given after TBI has been shown to improve oxygen delivery to the brain via increased cerebral perfusion on both immunohistochemical analysis and by micro-positron emission tomography analysis compared to TBI in mice not receiving β -blockade.⁽²⁰⁾

β -blockers have displayed promising results in animal studies, case series, retrospective reviews, cohort studies, one randomized trial, and a meta-analysis.^(22–30) β -blocker administration following acute TBI is associated with lower in-hospital mortality (Table 2). Safety data in one study revealed no increase in adverse events.⁽²⁵⁾ The beneficial effects of β -blockers for severe TBI may be due to improved cerebral autoregulation. The Lund protocol, which includes the use of metoprolol, is thought to decrease vasogenic edema.⁽³¹⁾ Cotton et al.⁽²⁴⁾ excluded early deaths but demonstrated a survival advantage for β -blockers in TBI. Those receiving β -blockers had a lower mortality than the non- β -blocker group (5.1% vs 10.8%). Schroeppel et al.⁽³⁰⁾ demonstrated a smaller survival advantage after excluding deaths within the first 24 hours. β -blockers do not appear to significantly decrease heart rate variability or blood pressure among patients with TBI, though overall effects on cardiac output have not been directly measured in this patient population.^(25, 27, 28) Currently, there is evidence to suggest a benefit of β -blockers following TBI but there is a lack of well-designed controlled trials to address important functional outcomes, quality of life, and long-term mortality in TBI patients. In addition, there is a lack of uniformity on which β -blocker should be given. Future prospective studies should detail appropriate dosing, ideal agent, and the population of TBI patients most likely to benefit.

Spinal cord injury

Autonomic dysfunction often accompanies spinal cord injury.⁽³²⁾ Following T5–T6 blunt spinal cord injury (SCI), rats have been shown to exhibit neurogenic shock for three minutes after injury with mean arterial pressure (MAP) decrease by 78% and mean heart rate decrease by 63%.⁽³³⁾ Both heart rate and MAP returned to basal values within 20 minutes, demonstrating the transient nature of autonomic dysfunction following SCI in this model.⁽³³⁾ Rats receiving propranolol before injury did not experience the dramatic decrease in heart

rate that was observed among injured rats that did not receive propranolol.⁽³³⁾ The propranolol group also had fewer increases and decreases in blood pressure.⁽³³⁾

In addition, β -blockers may prevent or reduce the severity of secondary insult following SCI. Rodents receiving metoprolol immediately after T7–T10 blunt SCI have been shown to have lower spinal cord myeloperoxidase levels, indicating decreased neutrophil activity.⁽³⁴⁾ In a rabbit model of spinal cord ischemia and reperfusion, selective β -1 blockade with nebivolol beginning two days prior to injury improved motor deficit scores compared to animals not receiving β -blockers.⁽³⁵⁾ Nebivolol may be protective in spinal cord ischemia via free radical scavenging and antioxidant activity, independent of β -blockade effects.⁽³⁵⁾ Propranolol has similarly been shown to restore axonal function after SCI by suppressing glial scar formation and astrocyte hypertrophy.⁽³⁶⁾ β -blockers may have several potential clinical applications in spinal cord injury: blunting early autonomic imbalances, decreasing post-injury inflammation, and minimizing ischemia-reperfusion injury. All of these findings must be interpreted in the context that β -blockers were administered prior to traumatic injury in these preclinical studies. So additional animal studies examining the use of β -blockers after spinal cord injury are warranted.

Hemorrhagic shock

Hypotension decreases aortic arch and carotid sinus baroreceptor stimulation, triggering increased sympathetic tone and hypercatecholaminemia.⁽¹⁾ β -blockers suppress the hyperdynamic cardiovascular response to hypotension, limiting clinical application in hemorrhagic shock. Taniguchi et al.⁽¹⁰⁾ demonstrated that oral administration of the α -1, β -1, and β -2 antagonist carvedilol prior to hemorrhagic shock increased mortality and exacerbated the inflammatory response in a rodent model. The authors noted that a dose-response relationship analysis was not performed.⁽¹⁰⁾ Despite these findings, β -blockers have been shown to be useful for investigating hemorrhagic shock pathophysiology. The observation that blood lactate levels rise in the absence of a hypoxic insult triggered investigation of pertinent metabolic pathways, leading to several important findings.⁽³⁷⁾ Propranolol and phenoxybenzamine administration prior to hemorrhagic shock does not affect skeletal muscle perfusion, but lowers plasma lactate levels during hemorrhage and after resuscitation.^(38, 39) Propranolol alone blocks EPI-stimulated muscle lactate production, but increases plasma EPI and lactate levels.⁽³⁸⁾ Plasma EPI stimulates aerobic glycolysis in skeletal muscle, resulting in lacticemia despite adequate tissue perfusion.⁽³⁸⁾ Muscle lactate, muscle glucose-6-phosphate, and Na^+ - K^+ -ATPase pump activity each follow the same trend, supporting the hypothesis that EPI-stimulated aerobic glycolysis contributes to skeletal muscle glycolysis in shock, increasing plasma lactate levels.⁽³⁹⁾ β -2 receptor regulation is important in this metabolic pathway.⁽⁴⁰⁾ Although β -blockers may be clinically detrimental in hemorrhagic shock, they have been invaluable in accurately describing lactate production during shock.

Acute traumatic coagulopathy

Severe traumatic injury often leads to acute traumatic coagulopathy (ATC) that is characterized by hypocoagulability and hyperfibrinolysis.⁽⁴¹⁾ Principle processes responsible

for ATC include tissue hypoperfusion, post-traumatic inflammation, and activation of the neurohumoral system.⁽⁴²⁾ ATC may be induced by the circulating catecholamine surge that is associated with severe trauma, hemorrhage, and endothelial damage.⁽⁴³⁾ ATC is an independent risk factor for increased transfusion requirements, multiple organ failure, and mortality.⁽⁴⁴⁾

Rodents subjected to laparotomy and hemorrhagic shock were compared to another group pretreated with chemical sympathectomy to evaluate autonomic function in ATC and its influence on endothelial and coagulation activation.⁽⁴⁵⁾ Chemical sympathectomy suppressed tissue type plasminogen activator, plasmin-antiplasmin complex, soluble thrombomodulin, and syndecan-1.⁽⁴⁵⁾ Reduction of sympathetic activation with chemical sympathectomy yielded antifibrinolytic and endothelial protective effects in rats with ATC.⁽⁴⁵⁾ Similarly, in a rodent laparotomy, hemorrhagic shock, and femur fracture model, rodents pre-treated with propranolol had decreased sympathetic tone, decreased fibrinolytic marker levels, and decreased tumor necrosis factor (TNF)- α and interleukin (IL)-6 without significant effects on fibrinogen or mortality.⁽⁴²⁾ β -blockers had an endothelial protective effect by reducing soluble thrombomodulin and syndecan-1 levels.⁽⁴²⁾ β -blockers were shown to be protective against inflammation, glycocalyx shedding, hyperfibrinolysis, and endothelial damage.⁽⁴²⁾

Of note, ATC patients may present with hemorrhagic shock,⁽⁴⁶⁾ which is a contraindication to β -blocker therapy as discussed in the previous section. In addition, β -blockers decrease platelet aggregation, potentially limiting their clinical application for patients with ATC.⁽⁴⁷⁾ Finally, fibrinolytic pathways appeared to shut down in over half of all severely injured patients in one study.⁽⁴⁶⁾ For these patients, anti-fibrinolytic therapy may be harmful.⁽⁴⁸⁾ The net effect of β -blocker therapy on coagulation is not yet completely understood. Despite limitations in clinical pharmacologic management of ATC, experimental studies have shown that rodent models may effectively emulate human ATC pathophysiology, and have established a foundation on which further research may fully elucidate mechanisms and best practices for management of ATC.

Erythropoietic Dysfunction

Anemia affects 95% of patients who remain critically ill for three or more days, and is associated with longer lengths of stay, increased incidence of organ failure, and increased mortality.^(49, 50) Patients who require blood transfusion within 24 hours of severe traumatic injury are at increased risk for persistent anemia.⁽⁵¹⁾ Management typically involves red blood cell transfusion which is associated with immune suppression, infectious complications, and increased mortality.^(51, 52) Studies examining treatment alternatives to blood transfusion have not been successful. In a large multicenter prospective randomized trial, IV iron supplementation in trauma patients was not found to significantly affect hemoglobin (Hb) concentration or transfusion rates.⁽⁵³⁾ Similarly, in critically ill patients, erythropoietin- α administration increased Hb concentration at 29 days (1.6 vs. 1.2 g/dl), but did not decrease transfusion rates, and was associated with increased incidence of thrombotic events.⁽⁵⁴⁾

There are both animal and human data to suggest that post-injury anemia is related to erythropoietic dysfunction at the level of the bone marrow.^(55–58) NE has dose dependent effects on bone marrow progenitor cell growth.⁽⁵⁷⁾ Adding NE at supraphysiologic concentrations to normal human bone marrow *in vitro* decreases bone marrow hematopoietic progenitor cell (HPC) growth by more than 95%.⁽⁵⁹⁾ Similarly, supraphysiologic NE infusions suppress erythroid blast forming unit (BFU-E) colony growth and erythroid colony forming unit (CFU-E) growth *in vivo* in a dose dependent fashion.⁽⁶⁰⁾ EPI also suppresses bone marrow CFU-E growth, but with less potency than NE.⁽⁵⁷⁾ High NE levels promote HPC egress from the bone marrow via G-CSF-induced CXCL12 (SDF-1) downregulation.^(61, 62) Mesenchymal stem cells (MSCs) express β adrenergic receptors and are critical for maintaining hematopoietic stem cell pluripotency and facilitating orderly differentiation.^(63, 64) Although NE has been shown to inhibit MSC chondrogenesis,⁽⁶⁵⁾ the effects of β -blockers on MSC modulation of erythropoiesis have not yet been reported. In addition, post-injury inflammation has been shown to increase hepcidin, thereby decreasing intestinal iron absorption and reducing the amount of substrate available for erythropoiesis.⁽⁶⁶⁾ Therefore, catecholamine effects on the bone marrow, modulation of MSCs, and systemic inflammation may each play important roles in the pathophysiology of persistent injury-associated anemia.

Critically ill trauma patients have significantly elevated urine NE levels for nearly two weeks after traumatic injury.⁽⁵⁷⁾ This hypercatecholaminemia is associated with a persistent injury-associated anemia.⁽⁵⁶⁾ Persistent injury-associated anemia lasts for more than one week after traumatic injury and occurs out of proportion to blood loss. This condition is characterized by low reticulocyte counts despite adequate iron stores and erythropoietin levels, implicating pathophysiologic bone marrow dysfunction.^(58, 67) A rat model of combined lung contusion, hemorrhagic shock, and chronic stress-induced anemia (Hb 11.1 vs. 13.3 g/dl in controls) seven days after initial injury and was associated with excessive HPC egress and decreased bone marrow cellularity (Figure 1).⁽⁶⁸⁾

Since it was determined that NE played a substantial role in bone marrow dysfunction, subsequent studies have concentrated on the effects of β -blockade on bone marrow function. Using the aforementioned lung injury rodent model, the use of propranolol before lung injury reversed bone marrow HPC growth suppression (Figure 1). To determine which β adrenergic receptors were involved in this bone marrow protection, additional studies with selective β -1, β -2, and β -3 blockers given prior to lung injury demonstrated that bone marrow protection was mediated through β -2 and β -3 receptors.⁽⁵⁾ Propranolol therapy was then tested in the hemorrhagic shock rodent model. Results mirrored what was found in the lung injury rodent model. Propranolol protected bone marrow HPC growth whether it was administered prior to or immediately after hemorrhagic shock.⁽⁵⁵⁾ In a combined lung contusion and hemorrhagic shock model, propranolol was administered immediately after resuscitation and was given daily for seven days. Daily propranolol use was associated with a significant increase in bone marrow HPC growth, restoration of Hb, and reduced HPC mobilization into the peripheral blood.⁽⁶⁹⁾ Propranolol administration in these studies was not associated with increased mortality or significant changes in blood pressure, but effective propranolol dosing did correlate with a 20% decrease in heart rate.⁽⁵⁵⁾ Dose studies demonstrated that the safe range of intraperitoneal propranolol injections in rats was

between 0.5 mg/kg to 20 mg/kg. Daily treatments of 5 and 10 mg/kg of propranolol provided significant bone marrow protection by preserving bone marrow cellularity and also preventing prolonged bone marrow HPC growth suppression.⁽⁵⁵⁾ Lower doses of propranolol did not sufficiently provide bone marrow protection.⁽⁵⁵⁾

A clinical translational study has verified some of the rodent findings.⁽⁵⁶⁾ In a pilot trial, severely injured patients were randomized to receive propranolol after resuscitation was complete (serum lactate ≤ 4 mg/dl) or to a no β -blocker therapy as a control group.⁽⁵⁶⁾ Those randomized to receive propranolol had propranolol doses titrated to decrease initial HR by 10–20%.⁽⁵⁶⁾ The β -blocker treatment group had reduced HPC mobilization, increased reticulocyte counts, and a non-significant trend toward increased Hb levels.⁽⁵⁶⁾ There is abundant preclinical data suggesting the beneficial effects of β -blocker therapy for erythropoietic dysfunction after traumatic injury but only one clinical trial. Thus, a large, prospective, randomized trial investigating the role of β -blockers in post-injury bone marrow protection is warranted.

Metabolic dysfunction

Increased protein catabolism and hyperglycemia is partly mediated by β -2 adrenergic signaling.⁽⁷⁰⁾ EPI induces insulin resistance and enhances hepatic glucose production.⁽⁷¹⁾ Propranolol has been shown to reduce plasma glucose concentrations by decreasing endogenous glucose production.⁽⁷²⁾ Propranolol also improves nitrogen balance, suggesting reduced muscle proteolysis.⁽⁷³⁾ Herndon et al. have shown that propranolol treatment in children attenuates resting energy expenditure and reverses muscle catabolism. In contrast, these effects are not seen with selective β -1 blockade and have not been shown in adults.⁽⁷⁴⁾

In severely injured patients, obesity (body mass index ≥ 30 kg/m²) is associated with increased incidence of sepsis, Acute Respiratory Distress Syndrome (ARDS), renal failure, and multiple organ failure as well as increased hospital length of stay, longer duration of mechanical ventilation, and increased mortality.^(75, 76) Serum glucose ≥ 200 mg/dl within 24 hours of injury is a risk factor for multiple organ failure and mortality in trauma patients with hemorrhagic shock, and is associated with worse neurologic outcomes in head injury patients.^(77, 78) These scenarios were combined in an experiment involving obese Zucker rats with insulin resistance subjected to extremity fracture.^(79, 80) Although basal glucose levels were not significantly different between obese and lean Zucker rats, obese rats had increased glucose levels within ten minutes of injury and persisting throughout the six hour experiment.⁽⁸⁰⁾ Post-injury hyperglycemia in obese rats was suppressed with selective β -2 blockade.⁽⁸⁰⁾ Post-injury hyperglycemia was caused by impaired glucose uptake and alleviated by hepatic β -2 receptor blockade.⁽⁸⁰⁾ These results are consistent with propranolol's capacity to decrease free fatty acid oxidation and lipolysis, redirecting fuel utilization toward glucose oxidation.⁽⁷²⁾ Animal studies have demonstrated a benefit for propranolol use in reducing post-injury hyperglycemia but further study examining the potential long term benefits, reduced infection, and improved metabolism have not been studied. The design of a future randomized controlled trial may consider investigating the metabolic changes as well.

Pulmonary Dysfunction

The inflammatory state after trauma and hemorrhagic shock leads to gut and pulmonary dysfunction.⁽⁸¹⁾ Pulmonary dysfunction is manifested by increased neutrophil infiltration, histologic changes, and changes in pulmonary function.⁽⁸²⁾ In a rodent model of lung contusion and hemorrhagic shock with and without propranolol administration, lung injury scores were significantly attenuated three hours after injury in the propranolol treatment group.⁽⁸³⁾ Baranski et al. hypothesized that the improvement in lung injury scores was related to either the systemic effects of propranolol or a reduction in gut permeability.⁽⁸³⁾

ARDS is characterized by acute onset, hypoxia with $\text{PaO}_2/\text{FiO}_2$ ratio <300 mm Hg, diffuse infiltrates on chest X-ray, and the absence of cardiac failure.⁽⁸⁴⁾ Trauma, hemorrhage, burns, and sepsis often precipitate this condition. Mortality for ARDS remains between 27–45%.⁽⁸⁵⁾ Pathophysiologic mechanisms include immunoregulatory cytokine dysfunction and intrapulmonary leukocyte activation preceding systemic inflammation.^(86, 87) Pulmonary denervation studies in dogs have established the role of the autonomic nervous system in ARDS models.⁽⁸⁸⁾ The effects of β -blockers in ARDS depend upon the etiology of pulmonary insult. A murine model delineated essential differences between α and β adrenergic stimulation.⁽⁸⁶⁾ Animals subjected to hemorrhagic shock activated nuclear factor kappa (NF- κ B) and cyclic adenosine monophosphate response element binding protein, thereby promoting inflammatory cytokine gene expression including IL-1 and TNF- α .⁽⁸⁶⁾ Mice that received β -blockers prior to hemorrhage had significantly elevated mRNA levels of lung mononuclear IL-1 and TNF- α as compared to controls.⁽⁸⁶⁾ Conversely, mice receiving α adrenergic blockade prior to hemorrhage had decreased lung levels of IL-1 and TNF- α .⁽⁸⁶⁾ These findings are consistent with overall effects of α and β stimulation on inflammatory cytokine profiles summarized in Figure 2.

When pulmonary injury was induced by a septic insult, selective β -1 blockade protected against lung injury and decreased lung tissue expression of the inflammatory protein high-mobility group box 1.⁽⁸⁹⁾ More recently, increased $\text{PaO}_2/\text{FiO}_2$ ratios were observed three hours after administration of esmolol in a pig model of endotoxic shock.⁽⁹⁰⁾ This result was consistent with overall findings of immunomodulatory β -blocker effects in numerous experimental sepsis models.⁽⁹¹⁾ Differential effects of β -blockade depending on ARDS etiology may be due to variations in the control of different inflammatory cytokine gene expression.⁽⁹²⁾ Experimental data show that high pulmonary vascular flow is important in the development of ARDS, so logically selective β -1 blockade would reduce lung damage but randomized controlled trials are needed before the use of selective β -1 blockade in ARDS can be routinely advocated.⁽⁹¹⁾

Burns and wound healing

Burn injuries induce significant hypercatecholaminemia in children and adults.^(93, 94) There have been several studies in burn patients demonstrating that propranolol improves wound healing, decreases cardiac work, and reduces metabolic demands without causing significant arterial hypotension or metabolic dysregulation.^(95–97) Rodent models have provided the pathophysiologic basis for these clinical advances. Stress response pathways, including p38

MAPK, JNK, and NF- κ B, are activated by scald burn injury and have been effectively blocked with propranolol.⁽⁹³⁾ In mice subjected to full thickness scald injury and wound sepsis with *Pseudomonas aeruginosa* inoculation, adrenergic stimulation modulated CD59⁺ monocyte progenitor maturation, decreased β adrenergic receptor cell surface density, and increased receptor affinity in a process which was reversed by selective β -2 receptor blockade.⁽⁹⁸⁾

In a full thickness burn rat model, daily propranolol administration corrected stress-induced insulin receptor dysregulation.⁽⁹⁹⁾ In addition, β -blocker treatment resulted in enhanced wound healing at the macroscopic level, and at the microscopic level there was improved epithelialization, collagen deposition, and angiogenesis, as well as decreased protease activity.⁽¹⁰⁰⁾ β -blocker treatment also conferred wound healing advantages in the absence of comorbid metabolic dysfunction. In a partial thickness excisional wound model, rabbits were allocated to receive no treatment or propranolol infusion during a seven hour period of infusion with isotope tracers D-[U-¹³C₆]glucose, L-[ring-¹³C₆]phenylalanine, L-[1-¹³C]leucine, and L-[1,2-¹³C₂]leucine.⁽¹⁰¹⁾ Tracer analysis demonstrated that wound DNA fractional synthetic rates were similar, but protein fractional synthetic rates were greater in the propranolol group.⁽¹⁰¹⁾ Local effects of β -blockade may also be due in part to the presence of β adrenergic receptors on MSCs and endothelial cells.⁽¹⁰²⁾ β -2 receptor blockade increases migration and proliferation of keratinocytes during wound epithelialization, accelerating epidermal barrier repair.⁽¹⁰²⁾ NE-depleted mice have increased wound angiogenesis,⁽¹⁰³⁾ and rats treated with propranolol demonstrate increased wound blood vessel density.⁽¹⁰⁴⁾ Likewise, among human burn patients, propranolol use resulted in faster donor site healing times.⁽⁹⁵⁾

Immunomodulation after trauma

Following traumatic injury there is a complex interaction between the neuroendocrine and the immune systems. The β adrenergic system is a well-known modulator of the immune system, and circulating catecholamines have immunomodulatory properties.⁽¹⁰⁵⁾ β adrenergic stimulation has diverse effects on natural killer (NK) cells, CD14⁺ monocytes, T lymphocytes, and B lymphocytes.^(105, 106) Lymphoid tissues containing these cells are innervated by the sympathetic nervous system, where NE functions as a neurotransmitter.⁽³⁾ Catecholamines have also been shown to down-regulate the synthesis of pro-inflammatory cytokines such as TNF-alpha, IL-6 and IL-1 and upregulate synthesis of anti-inflammatory cytokines.⁽³⁾ The pattern of cytokine production and the polarization of T-cell populations in sepsis may depend on the T-helper type 1 (Th1) and Th2 balance. Th1 cells are presumed to promote cellular immunity while Th2 cells promote the humoral response. β -2 adrenergic stimulation suppresses Th1 cell polarization, shifting the immune response away from cellular immunity in favor of humoral immunity.⁽³⁾ Although the precise mechanisms have not been elucidated, the apparent lack of β -2 adrenergic receptors on Th2 cells may partially explain this phenomenon.⁽¹⁰⁷⁾

Circulating catecholamines after trauma and hemorrhagic shock have been shown to reduce hepatic β adrenergic receptor binding capacity.⁽¹⁰⁸⁾ In a hemorrhagic shock model, mice were pretreated with either propranolol or metoprolol, and both agents significantly reduced

the number of circulating natural killer cells and CD8⁺ lymphocytes.⁽¹⁰⁵⁾ These effects may be due in part to catecholamine-induced changes in adhesion molecule and chemoattractant receptor expression.^(109, 110) The clinical effects of immunosuppression must be considered in the context of several factors relating to the nature of the physiologic insult, as discussed in the sepsis section.

In a retrospective review of 663 critically ill trauma patients, those receiving β -blockers within thirty days of ICU admission had significantly lower in-hospital mortality compared to patients with similar ISS scores not receiving β -blockers (11% vs. 19%).⁽¹¹¹⁾ In a large retrospective review of 4,117 trauma patients who received β -blockers during their hospital stay (60% received β -blockers for hypertension, 20% for heart rate control, and 45% were on chronic β -blockers), the β -blocker cohort all-cause mortality odds ratio was 0.3 after adjusting for age, Glasgow Coma Scale, and Injury Severity Score.⁽²²⁾ These improved outcomes with β -blockers could be due to decreased myocardial oxygen demand,⁽¹⁰⁾ improved myocardial oxygen utilization,⁽¹¹²⁾ and/or immunomodulation of hypercatecholaminemia.⁽¹⁰⁵⁾ A prospective controlled trial enrolled 42 critically ill trauma patients and allocated β -blocker naïve subjects to initiate β -blocker therapy 24 hours after resuscitation and hemodynamic normalization.⁽¹¹³⁾ Metoprolol was given unless resuscitation requirements were ≥ 2 liters, in which case short-acting esmolol was initiated and then converted to longer-acting metoprolol after 24 hours of hemodynamic stability. Mean daily heart rate was lower in the β -blocker group and mean daily systolic blood pressure was not significantly affected. Baseline and hospital day one plasma IL-6 levels did not differ between groups. On hospital day four, serum IL-6 levels were lower in the β -blocker group. In addition to relating post-injury β -blocker use to IL-6 levels, this study also demonstrated that β -blockade was safe for a small cohort of critically ill trauma patients.⁽¹¹³⁾ To summarize, β -1 and β -2 adrenergic receptors seem to exert opposite actions on the immune system, but more investigation is required to understand if β -blockers of selective β -blockade can offer advantages in immune function.

Sepsis

Interactions between adrenergic pathways and host protective immunity are complex. Catecholamines and β -adrenergic stimulation have exhibited net anti-inflammatory effects in animal and human sepsis models, primarily by reducing pro-inflammatory cytokine mRNA levels.^(1, 114–119) Diminished immunosuppressive effects in prolonged septic shock may indicate that catecholamine-induced immunosuppression depends upon the duration of catecholamine exposure.⁽¹²⁰⁾ Immune cell apoptosis has also been proposed as a mechanism for immunosuppression in sepsis.⁽¹²¹⁾ Septic humans exhibit significant lymphocyte apoptosis within one day of septic insult, and lymphocyte recovery appears to correlate with improved clinical outcomes.⁽¹²²⁾ Although hypercatecholaminemia has been shown to contribute to pro-apoptotic molecular up-regulation and β -blockade may prevent post-hemorrhage splenocyte apoptosis; the role of hypercatecholaminemia in sepsis-induced leukocyte apoptosis remains unclear.^(105, 123) Finally, NE has been shown to decrease T cell production of the chemokine CCL3, which regulates leukocyte recruitment to sites of infection.⁽¹²⁴⁾ This effect was abrogated by propranolol in a murine thermal injury model.⁽¹²⁴⁾

In contrast to hypercatecholaminemia-mediated immunosuppression, the septic insult itself causes a pro-inflammatory mediator surge.^(125, 126) Reports of different cytokine profile responses to catecholamine challenge and septic insult may be due to variable catecholamine concentrations, timing of interventions, and differential α and β adrenergic stimulation. Exogenous alpha adrenergic stimulation can have either immunoenhancing or immunosuppressive effects on IgM production *in vitro*, depending on drug concentration.⁽¹²⁷⁾ In one experiment, an 18 hour delay between EPI administration and LPS challenge was chosen to facilitate a pro-inflammatory environment prior to septic challenge, because simultaneous EPI and LPS administration has been shown to have an anti-inflammatory effect.⁽¹²⁵⁾ In addition, alpha adrenergic stimulation increases TNF-alpha expression in murine peritoneal macrophages in a process that is reversed with alpha adrenergic blockade but augmented by β adrenergic blockade.^(128, 129) Conversely, β adrenergic stimulation decreases TNF-alpha expression in a process that is reversed by β blockers but not alpha adrenergic blockade.^(128, 129) Similarly, β adrenergic stimulation inhibits TNF- α expression in human monocytes, an effect that is prevented by β -blockers but not alpha adrenergic blockade.⁽¹³⁰⁾ Individual studies investigating interactions among catecholamines, adrenergic receptors, and cytokines are listed in Table 3.

The predominant effects of pathologic insults and β -blocker treatment on inflammation are summarized in Figure 2. Effects of catecholamine concentrations, timing of pathophysiologic events, and differential alpha and β adrenergic stimulation must be considered within context. Too much or too little inflammation may be detrimental, and adrenergic receptor blockade can facilitate either condition. In addition, the effects of β -blockade on infectious outcomes following the systemic inflammatory response syndrome (SIRS)⁽¹³¹⁾ and the compensatory anti-inflammatory response syndrome (CARS)⁽¹³²⁾ are unknown. Although it remains plausible that restitution of T cell CCL3 production with β -blockers may augment adaptive immunity and thereby abrogate CARS, this hypothesis has not been tested in the clinical setting. However, several beneficial effects of β -blockers in sepsis have been described, including restoration of normal cellular metabolism, improved glucose regulation, and improved cardiac function.⁽⁹¹⁾ Notably, epidemiologic data suggested that critically ill septic patients with chronic β -blocker prescriptions had lower 28 day mortality than sensitivity and pair-matched controls (17.7% vs. 22.1%).⁽¹³³⁾ The first randomized controlled trial was performed by Morelli et al.⁽¹³⁴⁾ Continuous esmolol infusion in septic shock patients requiring NE was associated with a significant reduction in NE and fluid requirements and a decreased 28 day mortality.⁽¹³⁴⁾ Large clinical trials evaluating the potential benefits of β -blockers in sepsis are warranted. More data is needed to fully describe the complex relationships among sepsis, the inflammatory response, catecholamines, and adrenergic receptors.

Future Directions

Initial sympathetic activation after injury is beneficial but persistent severe overactivation is likely detrimental. Therefore, β -blocker therapy and tight regulation of β adrenergic receptors may provide unique advantages in managing several injuries and physiologic insults (Table 4). However, more preclinical research is needed to continue to elucidate mechanisms of action, cellular targets, safety, and clinical efficacy of β -blockers. In

addition, more research is needed to determine which patients would benefit most from this therapy. In all prospective studies, the timing, dosing, and which β -blocker therapy have yet to be answered. Once these objectives are met, level I evidence regarding β -blockade after TBI and models in which β -blockers are administered after SCI would be beneficial. Valuable knowledge will be gained by additional preclinical studies examining mechanisms by which β -blockers could confer protection against ATC and studies clarifying therapeutic strategies and clinical endpoints for post-injury hypermetabolism and glucose dysregulation among patients with obesity and pre-existing metabolic dysfunction. A large, prospective, randomized trial investigating the role of β -blockers in post-injury bone marrow protection is warranted. Research should continue to further elucidate the complex relationships among trauma, the inflammatory response, sepsis, catecholamines, and β adrenergic receptors with attention to catecholamine concentrations, timing of pathophysiologic events, and differential β adrenergic receptor effects.

Acknowledgments

This research was supported by the National Institutes of Health. AMM was supported by NIH NIGMS grant R01 GM105893-01A1. TJL was supported by a training grant in burn and trauma research T32 GM-08431. This work was also supported by grants R01 GM40586-24 and R01 GM-081923-06 awarded by the NIGMS. PAE was supported by P30 AG028740 from the National Institute on Aging and by the NIH NIGMS grant R01 GM113945-01. Finally, AMM LLM and PAE were all supported by P50 GM111152-01 (NIGMS).

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Figure 1.

Pathophysiology of persistent injury-associated anemia after severe trauma Lung contusion immediately followed by hemorrhagic shock with a mean arterial pressure of 30–35 mm Hg for 45 minutes along with chronic restraint stress for two hours daily until sacrifice on day seven creates a persistent hypercatecholamine state. Nonselective β -blocker, propranolol, was administered 10 minutes after HS and daily after CS. (LC: lung contusion, HS: hemorrhagic shock, CS: chronic stress, HPC: hematopoietic progenitor cell, BM: bone marrow)

Figure 2.

The predominant effects of pathologic insults and β -blockers on inflammatory cytokines (EPI: epinephrine, NE: norepinephrine).

Table 1

Properties of β -blockers. Time to peak and half-life are based on clinical pharmacokinetics. Use of L-748,337 and SR 59230A have been reported only in experimental studies.

Medication	Selectivity	Time to peak	Half-life	Other effects
Propranolol	nonselective	1–1.5 hr	3–5 hr	membrane stabilizer, ↓ portal pressure
Nadolol	nonselective	3–4 hr	20–24 hr	↓ portal pressure
Pindolol	nonselective	1 hr	3–4 hr	↓ atrioventricular nodal conduction
Timolol	nonselective	1–2 hr	3–4 hr	↓ sympathetic outflow
Metoprolol	β_1 antagonist	0.3–2 hr	3–4 hr	
Esmolol	β_1 antagonist	2–10 min	10 min	
Bisoprolol	β_1 antagonist	2–4 hr	9–12 hr	
Atenolol	β_1 antagonist	2–4 hr	6–7 hr	
Acebutolol	β_1 antagonist	2–4 hr	4–13 hr	membrane stabilizer, sympathomimetic
Nebivolol	β_1 antagonist	1.5–4 hr	10–19 hr	potentiates nitric oxide
Carvedilol	α_1 -1, β_1 , β_2 antagonist	1–5 hr	6–10 hr	α_1 -1 blockade, membrane stabilization
Labetalol	α_1 -1, β_1 , β_2 antagonist	1–2 hr	6–8 hr	
L-748,337	β_3 antagonist	NA	NA	↓ nitric oxide mediated cell proliferation
SR 59230A	β_3 antagonist	NA	NA	

Table 2

β-blocker use in TBI patients

Study	Design	n	Sample population	β-blocker	Outcome
Arbabi ⁽²³⁾	Retrospective	524	subgroup: admission GCS < 14	not specified	scheduled BB associated with ↓mortality
Cotton ⁽²⁴⁾	Retrospective	420	hAIS 3, no major neck injury, HLOS 4–30d	β1, non-selective	BB for 2d associated with ↓mortality
Cruikshank ⁽²⁵⁾	Prospective	114	Primary diagnosis acute TBI	β1	BB x 7days associated with ↓SVT, ST/T EKG changes
Glass ⁽²⁶⁾	Retrospective	419	hAIS > 3, HLOS > 3d	β1, non-selective	BB for 2d associated with delay in ↓ Hb
Inaba ⁽²⁷⁾	Retrospective	1156	hAIS < 6, no major associated injury	not specified	BB associated with ↓mortality, especially for age 55
Murry ⁽²⁸⁾	Prospective	38	hAIS 4–5, no non-survivable injuries	non-selective	BB for 2d associated with ↓ICU/HLOS, no ↓HR, SBP
Riordan ⁽²⁹⁾	Retrospective	446	hAIS 5, no major neck injury	β1, non-selective	BB exposure associated with ↓mortality
Schroeppel ⁽³⁰⁾	Retrospective	2601	all blunt TBI, mean ISS 26	β1, non-selective	2 doses BB associated with ↓mortality

GCS: Glasgow Coma Scale, BB: β-blocker, hAIS: head Abbreviated Injury Score, HLOS: hospital length of stay, Hb: hemoglobin, ICU: intensive care unit, HR: heart rate, SBP: systolic blood pressure, TBI: traumatic brain injury, ISS: Injury Severity Score.

Table 3

Effects of adrenergic stimulation and septic insult on pro- and anti-inflammatory cytokines

Study	Design	Findings
Bergmann ⁽¹²⁰⁾	Human in vitro	EPI + LPS → ↓ plasma TNF-α and IL-6, ↑ IL-10, early effects > late effects
Deng ⁽¹¹⁴⁾	Mouse in vitro	EPI + LPS → ↓ splenic macrophage IL-6 and TNF-α, ↑ IL-10
Rough ⁽¹²⁵⁾	Mouse in vitro	EPI + LPS → ↑ RAW 264.7 TNF-α expression, reversed with β-2 blockade
	Mouse in vivo	T/H + LPS → ↑ splenic macrophage IL-6 and TNF-α, reversed with β-2 blockade
Sekut ⁽¹¹⁷⁾	Human in vitro	β stimulation + LPS → ↓ THP-1 TNF-α, reversed with β-2 blockade
	Mouse in vivo	β stimulation + LPS → ↓ serum TNF-α, reversed with non-selective β blockade
Severn ⁽¹³⁰⁾	Human in vitro	β stimulation + LPS → ↓ serum TNF-α, reversed with non-selective β blockade
	Human in vitro	β stimulation + LPS → ↓ THP-1 TNF-α, reversed with non-selective β blockade
Spengler ⁽¹²⁸⁾	Mouse in vitro	α stimulation + LPS → ↑ peritoneal macrophage TNF-α, reversed with α-2 blockade
Spengler ⁽¹²⁹⁾	Mouse in vitro	β stimulation + LPS → ↓ peritoneal macrophage TNF-α, augmented with α-2 blockade, reversed with non-selective β blockade
van der Poll ⁽¹¹⁸⁾	Human in vivo	EPI + LPS (<i>Escherichia coli</i> 0113) → ↓ plasma TNF-α
	Human in vitro	EPI + LPS (<i>Escherichia coli</i> 0127) → ↓ plasma TNF-α, ↑ IL-10
Wilson ⁽¹²⁶⁾	Rat in vivo	CLP → ↑ lung /plasma TNF-α expression, ↓ with non-selective β blockade

EPI: epinephrine, LPS: lipopolysaccharide, TNF: tumor necrosis factor, IL: interleukin, RAW 264.7: murine leukemic cell line, T/H: trauma and hemorrhage, THP-1: human leukemic monocyte cell line, CLP: cecal ligation and puncture.

Table 4

Proposed mechanisms for beneficial effects of β -blockers.

Injury/Insult	B blockade	Proposed Mechanism	Result
Traumatic brain injury	non-selective	↓NE-induced cytokine production	↓brain edema, ↑oxygenation
Spinal cord injury	non-selective	blunting autonomic dysfunction	hemodynamic stability
	β -1 blockade	↓PMN activation and oxidative stress	↑motor function
Acute traumatic coagulopathy	non-selective	blunting hyperadrenergic response	↓fibrinolysis, inflammation
Post-injury hyperglycemia	non-selective	↓FA oxidation and lipolysis	↑glucose oxidation
	β -2 blockade	hepatic β -2 receptor blockade	normoglycemia
Post-injury anemia	β -2,3 blockade	↓NE-induced bone marrow dysfunction	↓HPC egress, ↑HPC growth, Hb
Burns/wounds	non-selective	block p38 MAPK/JNK/NF- κ B pathway	↑wound healing
Infection/sepsis	non-selective	↓ NE-induced immune cell apoptosis	↓immunosuppression
	β -2 blockade	↓EPI-induced splenic macrophage priming	↓inflammation

NE: norepinephrine, PMN: neutrophil, FA: fatty acid, HPC: hematopoietic progenitor cell, Hb: hemoglobin, MAPK: mitogen-activated protein kinase, JNK: c-Jun N-terminal kinase, NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells, EPI: epinephrine