Published in final edited form as:
Adv Surg. 2013 ; 47: 177–197.

Is propranolol of benefit in pediatric burn patients?

Celeste C. Finnerty, PhD^{*,†,#,**} and David N. Herndon, MD, FACS^{*,†}

^{*}Shriners Hospitals for Children—Galveston

[†]Department of Surgery,, University of Texas Medical Branch

[#]Institute for Translational Sciences, University of Texas Medical Branch

^{**}Sealy Center for Molecular Medicine, University of Texas Medical Branch

Keywords

propranolol; burns; beta-blockade; hypermetabolic response; pediatric; catabolism; cardiac stress; safety

Introduction

Severe burn injuries result in metabolic and physiological derangements that persist throughout the acute and rehabilitative stages.¹⁻³ This hypermetabolic response is driven by supraphysiologic elevations in stress hormones, catecholamines, and inflammatory mediators.^{2,3} Increased peripheral lipolysis,⁴ increased muscle wasting,⁵ elevated resting energy expenditure,⁶ and suppressed immune function⁷ characterize the post burn hypermetabolic response. Although the initial catecholamine-induced response is protective and supportive of survival,⁸ the prolonged stress response can be detrimental and either impedes recovery or leads to organ failure and death.⁵ In addition to increasing skeletal muscle catabolism, elevated catecholamine levels also cause elevations in peripheral lipolysis, resting energy expenditure, and cardiac stress in severely burned patients.⁹ The actions of catecholamines on the cardiovascular system are largely mediated by the alpha- (α -) and beta- (β -) adrenergic receptors. To mitigate the effects of chronically elevated catecholamine levels on the hypermetabolic response following burn injury, blockade of the β -1 and β -2 adrenoreceptors has been achieved with the non-selective β 1,2-adrenoreceptor antagonist propranolol.⁹⁻¹⁷ Despite the notion that blocking the stress response would negatively impact hemodynamic and metabolic responsiveness,^{9,10} studies have demonstrated that blockade of catecholamine signaling improves pediatric burn patient outcomes.⁹⁻¹⁹ Reductions in cardiac work and cardiac stress are accompanied by decreased lipolysis, catabolism, and hepatic steatosis, with concurrent increases in skeletal muscle protein anabolism. Few adverse events have been associated with propranolol use.¹³⁻¹⁵

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Contact Information and Correspondence: David N. Herndon, MD, Shriners Hospitals for Children—Galveston, 815 Market Street, Galveston, TX 77550; Tel: (409) 770-6744; Fax (409) 770-6919; dherndon@utmb.edu; Celeste C Finnerty, PhD, Shriners Hospitals for Children—Galveston, 815 Market Street, Galveston, TX 77550; Tel: (409) 770-6567; Fax (409) 770-6919; ccfinner@utmb.edu.

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Disclosure: The authors declare no conflicts of interest.

Propranolol administration to massively burned patients may be a standard of care for the pharmacological amelioration of the hypermetabolic response in the not-so-distant future.

The hypermetabolic response to burn injury

The extensive hypermetabolic response following a severe burn injury affects many organ systems and persists for up to two years following the injury.^{2, 20} The chances of survival are improved by this adaptive response, enabling increased metabolic demands to be met through stepped-up mobilization of energy substrates by tissue catabolism.⁸ With current nutritional support regimens meeting the metabolic requirements of the severely burned patient, however, this stress response results in excess tissue catabolism that negatively impacts patient outcome.⁸ Following injury, metabolic activity and tissue perfusion immediately decrease during the early 'ebb' phase which lasts for 2 to 3 days.²¹ This is soon followed by a long-lasting 'flow' phase which is defined by hypercatabolism and hyperdynamic circulation. Medical support of the flow phase is necessary in order to avoid physiological exhaustion and death.^{1, 5, 22} In severely burned children, the hallmarks of this hypermetabolic response include increased metabolic rates, hyperdynamic circulation, lipolysis, catabolism of muscle and bone, hepatic steatosis, infections, insulin resistance, and growth retardation.^{2, 4, 20, 22-28}

Substrates supporting increased metabolic demands are released by catabolism of tissue fuel stores.^{5, 29} Lipolysis, glycolysis, and proteolysis lead to excess free substrate that then must be used, eliminated, or stored. In response to elevated catecholamine levels, fatty acids and triglycerides are released into the plasma by lipolysis.^{4, 9} Free fatty acids not used for fuel are typically deposited in the liver or in peripheral muscle, leading to dysfunction in these tissues. Proteolysis releases amino acids which are either used to build new proteins or, more frequently, catabolized and eliminated, creating a negative nitrogen balance.^{5, 20} Protein loss and subsequent negative nitrogen balance are proportional to the injury severity and the metabolic response. Extensive reduction of lean body mass through the hypercatabolic response has detrimental effects on survival and recovery. Following reductions of up to 10% of lean body mass, immune dysfunction occurs. Wound healing is impaired with losses of up to 20% of lean body mass. Pressure sores and pneumonia risk increase with lean body mass losses of up to 30%. With losses of lean body mass equal to or in excess of 40%, death is almost certain.³⁰ Nitrogen loss in excess of 20-25 g/m² of total body surface area per day induces catabolism associated mortality.^{5, 31} In pediatric burn patients who survive, protein catabolism significantly retards growth as well.³² Circumvention or mitigation of the hypermetabolic response is necessary to reduce tissue catabolism.⁵

The 10- fold elevation of plasma catecholamines following a burn injury induces hyperdynamic, metabolic, catabolic, and inflammatory responses that persist for several years.² Chronic elevation of epinephrine and nor-epinephrine continues for ~2 months and a year post-injury, respectively.^{2, 33} Although systemically elevated in the plasma, heightened elimination of urinary catecholamines accompanies elevated plasma catecholamine levels, demonstrating depletion of catecholamine reserves.^{9, 34} Severe catecholamine depletion is associated with development of sepsis and death. Attenuation of the post-burn catecholamine surge may improve patient outcomes.

Effect of burn-injury on cardiac function

Elevated plasma catecholamines contribute to post-burn cardiac stress.^{3, 9} During the 'ebb' phase, reduced cardiac output is caused by hypovolemia and decreased venous return. Circulating endogenous vasoconstrictors and inflammatory signals worsen cardiac output by decreasing preload along with depressed myocardial contractility. Surges in catecholamines,

cortisol, and glucagon during the subsequent 'flow' phase lead to a hyperdynamic cardiovascular state characterized by tachycardia, local myocardial hypoxia, and increased myocardial oxygen consumption. Burn-induced increases in resting heart rate, cardiac output, cardiac work, and resting energy expenditure can lead to physiologic exhaustion unless steps are taken to attenuate this response.^{28, 35} Significant cardiac morbidity and mortality can occur as a result of chronically elevated catecholamine levels that stimulate prolonged cardiac stress.^{36, 37}

We have shown that in severely burned children compared to normal, age-matched, non-burned children, pathological elevations in average heart rates, rate pressure product, cardiac index, and cardiac output persist for at least two years, $p < 0.05$.²⁸ Burn injury did not affect stroke volume or mean arterial pressure, and the ejection fraction was only elevated for the first 2 weeks following burn before returning to normal levels. Reduced cardiac efficiency was suggested by the increase in rate pressure product, a correlate of myocardial oxygen consumption. Prolonged increases in cardiac work typically decrease the efficiency of oxygen delivery by the heart.³⁸ Compensatory increases in arterial oxygen content and cardiac output are therefore required to ensure adequate oxygen delivery. Although cardiac function appeared to be preserved, as indicated by normal ejection fraction despite chronic catecholamine stimulation, it is unknown whether this prolonged increase in work eventually results in cardiac failure in these patients. Persistently elevated catecholamine levels, resulting in sympathetic overstimulation and cardiac failure, indicate that the cardiovascular response may also exceed the metabolic demands of the patients. Although elevations of epinephrine and norepinephrine are typically associated with increased heart rate and stroke volume, this was not the case in children with massive burn injuries. The lack of increase in stroke volume may represent derangements in the β -adrenergic receptor signaling pathways, resulting in decreased tissue sensitivity to chronically elevated levels of catecholamines.^{38, 39}

Beta-blockade in severely burned adults

The ability of catecholamines to initiate and propagate the hypermetabolic response was demonstrated by Wilmore and colleagues in 1974.⁹ By administering α - and β -adrenoreceptor blocking agents, the role of the β -adrenergic receptor in potentiating post burn elevations of metabolic rate, blood pressure, pulse, and free fatty acid levels was demonstrated. The participation of the α -adrenergic receptor in these burn-induced responses was ruled out as well. The administration of catecholamines to non-burned volunteers demonstrated that epinephrine infusion was sufficient to induce a partial hypermetabolic response as characterized by nitrogen loss, increased respiration and metabolism, and altered levels of blood glucose, free fatty acids, glucagon, and growth hormone. The role of catecholamines in initiating the hypermetabolic response was clearly established. These early studies suggested the possibility of pharmacologically reducing the hypermetabolic response to burn injury with β -blockade.

Administration of propranolol to reduce the hypermetabolic response in severely burned children

Over the past 25 years, the mitigation of the effects of chronically elevated catecholamines through β -adrenergic receptor blockade has been established as an effective strategy for reducing post-burn hypercatabolism and cardiac stress.^{10-12, 14-19} Propranolol, a non-selective β -1, β -2 adrenergic receptor antagonist is commonly used to reduce tachycardia and hypertension by preventing catecholamine binding to β -adrenoreceptors. Furthermore, propranolol has been used to treat myriad pediatric conditions with few serious adverse events.¹⁴ From the initial study to determine whether propranolol administration would

jeopardize metabolic and hemodynamic stability,¹⁰ to the recent demonstration of the long-term safety and efficacy of propranolol administration,¹⁴ we have demonstrated that propranolol administration to decrease heart rate by 15-20% improves outcomes in children with large burn injuries.

In order to elucidate whether deleterious effects resulted from blunting the catecholamine-induced response to burn injury, β -blockade was initiated for short periods during early experiments. Following demonstration of safety and efficacy with each evaluation, the duration of propranolol administration was slowly extended from several days to the entirety of the first post-burn year. The chapter is divided into two sections: 1) acute administration during the initial ICU admission and 2) long-term administration which was initiated within several days of admission and continued throughout the first year following burn injury. In all of the evaluations presented here, the control and propranolol-treated cohorts were similar, with no differences in age, burn size, time to admission, and other demographic and clinical evaluations performed prior to propranolol administration.

PROPRANOLOL ADMINISTRATION DURING ACUTE HOSPITALIZATION

Hemodynamic and metabolic stability

The effects of propranolol on hemodynamic and metabolic responsiveness were studied in 40 severely burned children.¹⁰ Twenty-two control and 18 propranolol treated subjects were studied. For 5 days, propranolol was administered at a dose of 2 mg/kg/day. We hypothesized that propranolol would reduce myocardial work, lipolysis, and tremulousness without negatively impacting cardiac output, metabolic rate, or protein breakdown. When administered during the hyperdynamic 'flow' phase, propranolol significantly decreased heart rate, left ventricular work, and the rate pressure product, $p < 0.05$. Differences in basal resting energy expenditure, PAO_2/FiO_2 ratios, arterial-venous blood oxygen content differences, or oxygen consumption were not found. Adequate oxygen delivery and cardiac output were maintained, and oxygen consumption was not increased following propranolol treatment. Metabolic rate was not affected during this short 5 day infusion protocol either. Tremulousness, agitation, and anxiety were also reduced in those patients treated with propranolol. This study was the first to show that heart rate could be safely reduced by the chronic infusion of propranolol for 5 days in severely burned children without jeopardizing hemodynamic stability.

Cardiac work

Administration of propranolol was then extended to determine whether the positive effects on cardiac work continued with extended administration.¹⁹ Twenty two patients were studied. Propranolol was administered every 8 hours for 10 days to reduce heart rate by 10 to 20%. With longer duration of therapy, a sustained decrease in heart rate was observed along with a decrease in the rate pressure product. Cardiac stress was also reduced following propranolol treatment, as indicated by decreased myocardial oxygen consumption. Tachyphylaxis did not result following longer administration of propranolol. Because the majority of children who die as a result of massive burn injuries exhibit myocardial damage (e.g. subendocardial ischemia or focal myocardial necrosis), reduction in cardiac stress decreased burn-induced morbidity. This study confirmed that longer administration of propranolol could be used to safely reduce cardiac complications.

Propranolol administration was then extended for the duration of the acute hospitalization period and cardiac function was again assessed.¹³ Of the 406 severely burned children enrolled, 235 were randomized to control and 171 were randomized to propranolol therapy. Propranolol was initiated within 24-72 hours of admission and given to decrease heart rate by ~20%. Within two days of the initiation of propranolol treatment, significant reductions

in resting heart rates occurred ($p<0.001$; Figure 1) This decrease was noted throughout the study period until the time of discharge. In comparison to predicted heart rates for age, the percent of predicted heart rate in the propranolol cohort decreased by 15% compared to the 18% decrease in control patients, $p<0.001$. Significant reductions in rate pressure product and myocardial oxygen consumption throughout the study period were attributed to propranolol administration, $p<0.001$. Differences were not found in an age- or sex-dependent manner. By the 20th post-burn day, an increase in propranolol dose to 4mg/kg/day was necessary in order to maintain the reduction in heart rate. Cardiac index was not altered with propranolol administration. Significantly greater stroke volumes were found in the propranolol cohort: 112% $\pm$ 8% compared to 94% $\pm$ 5% in controls, $p<0.02$.

These findings demonstrate that administration of propranolol improves cardiac physiology for the duration of acute hospitalization. In the immediate post-burn period, cardiac output is decreased while myocardial oxygen consumption increases. When hyperdynamic circulation develops, heart rates increase greatly, leading to less time for ventricular filling and reduced stroke volumes. Cardiac output and myocardial oxygen typically increase during this phase. Propranolol administration during the hyperdynamic phase decreased myocardial oxygen consumption. Cardiac stress was further reduced by decreasing heart rate and stroke volumes. By decreasing these parameters, cardiac morbidity and the likelihood of physiological exhaustion is greatly decreased. These beneficial effects of propranolol on cardiac parameters demonstrated clinical utility for reducing cardiac stress in severely burned patients.

Fat metabolism

The reduction of free fatty acids in propranolol treated adults suggested an effect of propranolol on reducing the availability of the primary energy substrate that fuels hypermetabolism. We determined whether lipolysis was mediated via the β_1 - or the β_2 -adrenergic receptor.⁴⁰ Patients were either administered the β_1 -selective antagonist metoprolol or the non-specific $\beta_{1,2}$ antagonist propranolol during 8 hour intervals for five days. Initial dosing with 2mg/kg/day of each drug was titrated to reduce baseline heart rate by 20%. Both metoprolol and propranolol significantly reduced cardiac work in severely burned children. Lipolysis, however, was only decreased by propranolol administration, demonstrating β_2 selective mediation of peripheral lipolysis.

Prior work showed that increased peripheral lipolysis induces greater fatty acid reesterification to triacylglycerols in the liver.⁴ In light of the reduction of lipolysis that accompanied propranolol administration, whether propranolol subsequently reduced the incidence of fatty infiltration of the liver was determined next.

Using stable isotope methods, the effects of propranolol on hepatic fat accumulation were determined by measuring the metabolism of splanchnic fatty acid and very low density lipoprotein-triacylglycerol (VLDL-TG).¹⁶ Fatty acid uptake, oxidation, and secretion in VLDL-TGs across the splanchnic bed were quantitated with and without propranolol treatment. Fatty acid availability and hepatic triacylglycerol storage were greatly reduced with propranolol treatment, $p<0.05$. These results demonstrated that hepatic steatosis was reduced following propranolol treatment.

Subsequent studies demonstrated that the percent increase in liver size over expected normal values was also significantly reduced with propranolol treatment.¹⁷ The majority of control patients (80%) had increases in liver size of 100% or more. Of the propranolol treated patients, 86% experienced either a decrease or no change in liver size. Lipolysis was assessed by measuring plasma triglyceride levels and determining body composition. Plasma triglyceride levels were significantly reduced in patients receiving propranolol. Lipolysis

was significantly greater in the control cohort as apparent by reduced peripheral and truncal fat mass. These studies showed that propranolol decreased lipolysis, availability of free fatty acids for accumulation in the liver, and subsequent development of hepatic steatosis.

Gene expression in adipose tissue from control and propranolol treated patients was assessed in order to determine potential mechanisms behind lipolysis reduction. Biopsies of adipose tissue were taken from control and propranolol-treated patients at two time-points corresponding to 1) the second surgery and 2) 5 days later. The expression of 147 genes was affected by propranolol treatment; of those, 10 genes involved in lipid metabolism were reduced with propranolol treatment (TABLE 1). These results indicate that propranolol reduced peripheral lipolysis by decreasing lipid metabolism down-stream of the β_2 adrenoreceptor. Reduction in lipolysis led to decreased concentrations of circulating triglycerides and subsequent reduction of liver size and steatosis.

Muscle protein catabolism

Decreases in cardiac work, resting energy expenditure, and lipolysis in severely burned children treated with propranolol indicated an overall reduction of the hypermetabolic response. This led to the hypothesis that skeletal muscle catabolism would also be reduced with propranolol administration to reduce heart rate by 15 to 20%. Patients were randomized to either the control or propranolol cohort.¹² After two weeks of propranolol administration, a significant reduction in oxygen consumption and resting energy expenditure was found, confirming results. Stable isotope studies revealed an astounding improvement in the net skeletal muscle protein balance that was the result of a reduction in burn-induced proteolysis with an unexpected increase in muscle anabolism following propranolol administration (Figure 2). Body composition studies showed retention of both fat and fat-free mass in patients treated with propranolol, thereby validating the stable isotope study findings.

Elucidation of the mechanisms associated with reduction of skeletal muscle catabolism and the concurrent increase in muscle accretion was achieved by studying gene expression in muscle tissue biopsies from patients in each cohort.⁴¹ A significant up-regulation of 13 genes related to muscle metabolism was reported in patients treated with propranolol (TABLE 2). In these same patients, expression of 5 genes related to insulin resistance and gluconeogenesis was decreased. The restoration of metabolic functions in the skeletal muscle by improving cellular transport, prompting mRNA translation, protein export, and down-regulation of inflammatory processes may be behind the reduction of catabolism and improved anabolism in skeletal muscle from patients treated with propranolol.

Infections and inflammation

Following reports of increased inflammation and infectious episodes associated with propranolol administration in the critically ill,^{42, 43} we examined immune function in children with massive burns randomized to control or propranolol treatment.¹⁵ End points included assessments of systemic cytokine expression, infectious episodes, and incidence of sepsis. Differences in the incidence of sepsis or other infections did not exist between the control or propranolol cohorts. At a single time point, minor alterations in TNF and IL-1 β concentrations were found with propranolol treatment. Whether these changes have biological importance is unlikely given the small alterations at single time points. These results indicated that propranolol did not suppress immune function or induce inflammation in severely burned children.

Amelioration of the hypermetabolic response in the acute setting

Taken together, the results of studies performed during the acute hospitalization period demonstrated that propranolol can be administered safely to severely burned children in

order to reduce the post-burn hypermetabolic response. Propranolol administration led to reductions in heart rate, cardiac work, lipolysis, hepatic steatosis, and skeletal muscle breakdown, and increased creation of skeletal muscle. The lack of impact on immune function further supports the use of propranolol during acute hospitalization.

ADMINISTRATION OF PROPRANOLOL FOR ONE YEAR POST-BURN

Characterization of the pathophysiological response to burn injury has shown that burn-induced hypermetabolic response lasts for at least 1 to 2 years after the injury.^{2, 5} We therefore extended β -blockade with propranolol for a full year post burn.^{3, 9, 14} The recent publication of the interim analysis of this ongoing clinical trial demonstrated continued safety and efficacy of long-term propranolol administration to reduce the hypermetabolic response in severely burned children. Endpoints included cardiac function, resting energy expenditure, and body composition.

Patient Population

In this randomized controlled trial, 179 patients were enrolled, with 89 randomized to control (the standard of care treatment group) and 90 patients randomized to receive propranolol administration (~4 mg/kg/d) to reduce heart rate by 15%. Propranolol treatment was initiated within 3 $\pm$ 2 days of admission. The patient groups were similar with respect to age, burn severity, incidence of inhalation injury, length of stay, and mortality.

Cardiac Function

The percent of predicted heart rate was calculated to determine the effect of β -blockade with propranolol on cardiac function.^{44, 45} During hospitalization, continuous measurements were recorded. Following discharge, patients recorded their heart rates four times per day. Measurements were also conducted at each follow-up visit (3, 6, 9, and 12 months post burn). At the time of acute admission, heart rates were elevated ~1.7 fold above normal-for-age values in the control and propranolol cohorts (respectively 169 $\pm$ 34% predicted, and 163 $\pm$ 33% predicted; $p=0.19$) (Figure 3a). Myocardial oxygen consumption was measured by calculating the rate pressure product (heart rate $\times$ mean arterial pressure).⁴⁵ At the time of admission, both groups had rate pressure products increased by ~1.6 fold (control: 11,009 $\pm$ 280 bpm; propranolol, 11,435 $\pm$ 304 bpm $\times$ mmHg, $p=0.66$). Following initiation of propranolol administration, the percent of the predicted heart rate was significantly decreased during the first post-burn week and remained so for the duration of the study. At one year post-burn, the percent of the predicted heart rates in the control cohort compared to the propranolol cohort remained significantly elevated (119 $\pm$ 2% and 110 $\pm$ 2%, respectively, $p=0.01$). Decreases in the rate pressure product of approximately 15% were apparent in the propranolol group from 2 weeks until 6 months post burn (Figure 3b). Mean arterial pressure recordings during the acute hospitalization period were used to determine the incidence of hypotension (MAP<65mm Hg). Hypotension was not found in either cohort. Although subtle decreases in mean arterial pressure were noted in propranolol-treated patients 2 weeks, 4 weeks, and 2 months post-burn, the decreases were not significant following adjustments for multiple testing.

Hypermetabolism

As reported in our earlier studies, at the time of admission, all patients were hypermetabolic with elevated basal metabolic rates predicted with the Harris-Benedict equation.^{46, 47} The percent of predicted resting energy expenditure was significantly decreased with propranolol treatment that extended from the 2nd post-burn week until 6 months post burn ($p<0.001$; Figure 3c)

Body Composition

Dual-image x-ray absorptiometry was used to measure body composition, including central mass, central fat mass, peripheral lean body mass, total bone mineral content, and total lumbar mineral content. Total body mass increased in both groups from the time of discharge until the 12 month time point. Although nutritional intake was similar between the groups, the control group exhibited significantly higher accretion of central mass. In the propranolol-treated group, as early as 3 months post-burn, there was a 17% decrease central mass. These differences remained significantly different throughout the study period, $p < 0.001$. The propranolol-treated group had significantly lower central fat mass, with a 23% maximal decrease 12 months post-burn. Peripheral lean body mass increased 11% in the propranolol-treated group compared to the control cohort 6 months post-burn. Lean body mass was also preserved with propranolol treatment at 3, 6, 9, and 12 months ($p = 0.02$). Furthermore, by six months post-burn, treatment with propranolol decreased the likelihood of losing more than 5% of total bone mineral content / total body mass ($p = 0.01$). This effect persisted throughout the end of the study (Figure 4a-c).

Adverse Events

Incidences of the following adverse events were collected prospectively: bradycardia, hypotension, hypoglycemia, respiratory arrest, cardiac arrhythmia, and death. There were five deaths in the placebo group. In the propranolol-treated group, we reported few incidences of bradycardia ($n=2$), hypotension ($n=0$), hypoglycemia ($n=1$), respiratory compromise ($n=2$), cardiac arrhythmia ($n=1$), or death ($n = 4$). Propranolol administration was halted following the adverse event and then re-initiated at a reduced dose. Sepsis, confirmed by autopsy, was the cause of death for the five control patients and four propranolol-treated patients.

Prolonged attenuation of the hypermetabolic response with the long-term administration of propranolol in severely burned children

This ongoing randomized controlled study was designed to test the efficacy of propranolol in reducing the hypermetabolic response in children with burns over 30% or more of the total body surface area. Propranolol was administered at an approximate dose of 4mg/kg/d beginning 96 hours post-burn and ending one year later. This interim analysis showed that in severely burned children, the 4mg/kg/d dose of propranolol was well tolerated with few related adverse events. Significant reductions in heart rate, cardiac work, resting energy expenditure, lipolysis, and catabolism of lean body mass and bone were found during the majority of the treatment period. We also found that although these aspects of the hypermetabolic response were attenuated with propranolol treatment, the measured parameters were not returned to normal levels by the time that administration was discontinued. This suggests that larger doses of propranolol, possibly administered for longer periods of time, may achieve even greater improvements in this patient population.

The long-term implications of the persistent post-burn hypermetabolic response on cardiovascular morbidity and metabolism are unknown. Continued evaluations of these patients well into the next decades will be necessary to determine the effects of prolonged episodes of tachycardia and increased cardiac work, and to evaluate whether the reductions in heart rate with propranolol administration reduce this morbidity. The long-term effects of reducing resting energy expenditure and body composition will be evaluated as the children achieve full growth by measuring height and weight velocities, growth, strength, and final stature. Body composition studies showed an overall decrease in the central deposition of fat, and an increase in lean body mass, with propranolol treatment. This decrease is likely to be related to the earlier findings of Wolfe and Herndon showing that peripheral lipolysis and subsequent development of hepatic steatosis are prevented with propranolol.

administration.^{16, 40} By reducing peripheral lipolysis, the release of free fatty acids is decreased, leading to possible increases in insulin sensitivity. Lean body mass was increased in propranolol-treated patients. The low incidences of associated adverse events along with marked reduction in cardiac stress and the hypermetabolic response shows that propranolol can be safely administered to severely burned children.

Summary

In severely burned children, propagation of the catecholamine-induced hypermetabolic response can be reduced by propranolol administration. The degree of mitigation of the deleterious effects of burn injury is dependent on the dose of propranolol and duration of administration. By achieving a decrease of resting heart rate by 15-20%, cardiac work is significantly reduced over time. Proteolysis and lipolysis are similarly reduced, due to the decrease in resting energy expenditure and potentiation of catecholamine signaling. Instead of the typical net proteolysis that occurs following a severe burn injury, skeletal muscle protein synthesis is increased. These beneficial results (summarized in Table 3) were attained safely and largely without adverse events. The results of this study suggest that additional studies with larger participant numbers will show beneficial results in terms of growth, cardiac physiology, and the attenuation of the metabolic syndrome. We are currently conducting two multi-center trials to test the administration of propranolol in severely burned children. The first is a multi-center study to determine the safety of acute administration of propranolol in severely burned adults. The second study is to confirm the results of a single study trial testing the safety and efficacy of propranolol administration for a full-year post-injury in severely burned children. We anticipate that the findings of our trial are generalizable to patients with different types of surgical stress that are in similar hypermetabolic states.

METHODS

Administration and safety guidelines

Propranolol can be safely administered to patients in the ICU and in the outpatient setting with appropriate exclusion of ineligible patients, upward titration of the dose following initiation of therapy, and constant monitoring for adverse events.

Patients were excluded based on pre-existing conditions which may complicate the evaluation of endpoints (pre-existing conditions including HIV, AIDS, a 5 year history of malignancy, diabetes); those with conditions which may be worsened by β -blockade (asthma); and those deemed clinically futile at admission due to the severity of their injuries.

Propranolol administration can begin within 24 to 72 hours following admission, after fluid is stabilized. Although earlier studies utilized intravenous administration of propranolol, we now give propranolol by nasogastric tube unless oral feeds cannot be tolerated. Propranolol is escalated from an initial dose of 1mg/kg/day to ~4 mg/kg/day to achieve an ~20% decrease in resting heart rate in the following manner. Propranolol is given at a dose of 0.3 – 1.0 per mg per kilogram of bodyweight every four to six hours to achieve a total dose of ~2 mg/kg/day. The dose was then titrated to achieve a decrease of 20% below the average heart rate recorded for the patient during the 24 hours prior to propranolol administration. Monitoring of heart rate and blood pressure was continuous while the patient was in the ICU. A dose of propranolol was held, or decreased, when the mean blood pressure was below 65 mm Hg. Therapy was reinitiated with incremental increases of propranolol doses until the study goal of an approximate decrease of 20% of basal heart rate was re-established.

Kinetic studies of propranolol plasma drug concentrations in severely burned children showed that peak concentrations were achieved in our patients within 30 minutes to 1 hour following administration.¹³ Trough levels were attained by the second hour following administration. Propranolol's half-life is between 4 and 6 hours. We are currently determining whether this reduced half life in pediatric burn patients is accompanied by retention of higher levels metabolites in the circulation.

At discharge, patients older than 6 years of age were switched to the exentab formulation, enabling once-daily administration of propranolol. Children under 6 years of age remained on liquid formulation given 4 times daily. At the time of discharge, patients were issued a blood pressure cuff and a diary for continued monitoring. Following discharge, patients recorded heart rates and blood pressures four times per day. When heart rates were less than 60 beats per minute or blood pressure was under the normal values for age, patients were instructed to contact the physicians for instructions. Heart rate logs and pill audits were logged with each return to clinic.

Potential side effects associated with propranolol administration include bradycardia, hypotension, cardiac arrhythmia, hypoglycemia, respiratory arrest, and death. Over the course of administering propranolol to more than 300 patients, we have recorded few adverse events. In all cases, administration of propranolol was halted and then reinitiated as described above.

Enrollment and Ethics

Assessments were performed at admission, during the acute hospital stay, at the time of discharge, and at 3, 6, 9, and 12 months post-burn. A written informed consent form, approved by the Institutional Review Board of the University of Texas Medical Branch (Galveston, TX), was signed by the legal guardian prior to enrollment in the study. In children older than 7 years of age, assent was obtained prior the study start.

Standard Burn Care

The Galveston formula, a total of $5,000 \text{ mL/m}^2$ TBSA burned + $2,000 \text{ mL/m}^2$ TBSA lactated Ringer's solution, was used to determine the volume of fluid administered for fluid resuscitation during the first 24 hours. Within 48 hours of admission, all patients underwent burn wound excision and coverage with autograft or allograft. Bed rest for the first 4 days was followed by ambulation on each subsequent day until the following surgery. Patients underwent excision and grafting procedures every 6 to 7 days until 95% healing was achieved for all burned sites.

Enteral nutrition was administered to all patients via a nasogastric or nasoduodenal tube; Vivonex TEN® enteral nutrition provides 6% fat, 15% protein, and 82% carbohydrate. Daily intake for the first week post-injury was calculated as: $1,500 \text{ kcal/m}^2 \text{ TBSA} + 1,500 \text{ kcal/m}^2 \text{ TBSA burned}$. From the first post-burn week through the time of discharge from the acute unit, daily intake was calculated as 1.4 times the weekly measured resting energy expenditure (see Indirect Calorimetry below for more details). Retinol binding protein, pre-albumin, and albumin measurements were performed on all hospitalized patients to check nutritional status. Following hospital discharge, Boost® (Nestle Health Care Nutrition, Nestlé S.A., Vevey, Switzerland) was consumed three times daily to supplement the patients' dietary intake with 41 grams of carbohydrate, 10 grams of protein, and 4 grams of fat per serving. Once the staff nutritionist confirmed that the patients' regular diet supplied 1.4 times the resting energy expenditure in order to meet patient's caloric requirements, Boost was discontinued. Caretakers were interviewed in order to assess dietary intake daily.

when patients returned to the tub room, weekly while residing in the community, and at time points >6 months post burn when the patients returned for clinical care.

ASSESSMENTS

Cardiac and Blood Pressure Measurements

Blood pressures and resting heart rates were measured and recorded using non-invasive cuff measurements or continuous arterial monitoring; measurements were continuous while the patients were in-hospital. At all follow-up visits, measurements were recorded once. Patients and families were trained to use the blood pressure cuffs that were issued to them. Heart rates and blood pressures were then measured and recorded four times per day following discharge throughout the duration of the study. If the patient's heart rate fell below 60 bpm or the blood pressure was below the normal for age, patients and caretakers were instructed to call the study nurse or physician. The percent of predicted heart rate values were calculated by comparing burn patient heart rates and normograms from age-matched, healthy non-burned children.^{44, 45} The formula for calculating the percent of predicted heart rate used was: actual heart rate / age adjusted norm. The rate pressure product was calculated using the formula: mean arterial pressure $\times$ heart rate.⁴⁵

A pediatrician reviewed the caretakers' heart rate and blood pressure diaries on a routine basis. The propranolol dose was titrated to achieve a systolic blood pressure and pulse within 15% of the mean values for the age-matched non-burned normal patient cohort. If heart rates ranging from 70 beats per minute (teenagers) to 90 beats per minute (younger children) or systolic blood pressures from 90 mmHg (teenagers) to 80 mmHg (younger children) were recorded, then the next dose of propranolol was administered to the patients. If these parameters were not met, however, the propranolol dose was held and patients were assessed at the time when the following dose was to be administered. When administration of propranolol was missed several times within a week because of heart rate or blood pressure, the dose was then adjusted to ensure that heart rates and blood pressures were in the correct range with treatment.

Indirect Calorimetry

The resting energy expenditures were measured on resting patients between 12 AM and 5 AM on a weekly basis during the hospitalization period using a Sensor-Medics Vmax 29 metabolic cart (Yorba Linda, CA). Each minute, an analysis was performed on inspired and expired gas. When both oxygen consumption and carbon dioxide production reached and maintained a steady state for 5 min, the values were recorded. Normal values, predicted using the Harris-Benedict equation and body mass index, were compared to the measured values.^{26, 48, 49}

Body Composition

Body composition was determined using dual energy x-ray absorptiometry (DEXA) (QDR-4500W Hologic, Waltham, MA); peripheral lean body mass (PLBM), central fat, central mass, total lumbar bone mineral content (TLBMC), and total bone mineral content (TBMC), were measured. Daily calibrations using a spinal phantom in the single-beam, lateral, and anteroposterior modes were performed in order to minimize systemic deviations. Correct identification of bone, lean mass, air, and fat was ensured using a tissue bar phantom to calibrate the individual pixels in the image.²⁷ Prior to measurement, intravenous fluids and enteral feedings were discontinued for the duration of the exam and then reinitiated afterward. Results were expressed as percent change from patient baseline (determined within 3 ± 2 weeks post burn). At each time point, bone loss was calculated as the percent change from baseline. Patients were then stratified based on a loss of more than 5% in total

body bone mineral content less head per total body mass (TBMC/TBM) and TLBMC as determined by DEXA. The proportion of patients randomized to placebo or propranolol in each strata was recorded and the likelihood (odds ratios $\pm$ 95% CI) of presenting a clinically significant bone loss of at least 5% in both of these parameters was estimated.

Measurement of Hormones

Blood and urine were obtained at admission, during the acute hospitalization period at regular intervals, and at follow-up visits. Using serum separator tubes, blood was collected and centrifuged (1,320 rpm, 10 min). Serum was decanted and stored at -80°C for later analyses. HPLC and ELISA techniques were used to determine serum levels of parathyroid hormone (PTH), IGF-I, IGFBP-3, osteocalcin, testosterone, albumin, and total protein, as described elsewhere.^{27, 48, 49} Measurement of urinary catecholamine levels was performed as described elsewhere.^{27, 48, 49}

Stable Isotope Studies—Infusion of stable isotopes was performed by the Metabolic Core Facility at the Shriners Hospitals for Children – Galveston by previously published methods.^{4, 10, 12, 16, 20, 41}

Gene Expression Studies—Messenger RNA was isolated from tissue biopsy samples and then sent to the Genomic Core at the University of Texas Medical Branch for processing. Gene expression was elucidated using Affymetrix Human Genome U95 microarrays. Data was analyzed as previously published.^{17, 41}

Acknowledgments

The authors thank Deborah Benjamin, Wes Benjamin, Maria Cantu, Mario Celis, Tabatha Elliot, Kathryn Epperson, Eric Henry, Holly Goode, Kara Hougen, Joanna Huddleston, Mary Kelly, Xuyang Liang, Maria Magno, Liz Montemayor, Marc Nicolai, Sylvia Ojeda, Maricela Pantoja, Cathy Reed, Lisa Richardson, Lucile Robles, Pam Stevens, Sierra Tinney, Judith Underbrink, Becky Whitlock, the nutrition department, and the respiratory therapy team for their assistance in obtaining the study measurements. Finally, we thank Kasie Cole-Edwards for editing and proofreading the manuscript. This study is registered at clinicaltrials.gov, NCT00675714.

Funding: This study was supported by grants from Shriners Hospitals for Children (84080, 71001, 71008, 8660, 8760, 8740, 8507 and 9145), National Institutes of Health (R01 GM56687, T32 GM008256, P50 GM60338), the National Institute for Disabilities and Rehabilitation Research (H133A070026 and H133A70019), CCF is an Institute for Translational Sciences Career Development Scholar supported, in part, by NIH (KL2RR029875 and UL1RR029876). This study is registered at clinicaltrials.gov, NCT00675714.

Abbreviations and Acronyms

α	alpha
AIDS	acquired immune deficiency syndrome
B	beta
bpm	beats per minute
ELISA	enzyme-linked immunosorbent assay
FFA	free fatty acids
Hg	mercury
HPLC	high-pressure liquid chromatography
HIV	human immunodeficiency virus
ICU	intensive care unit

IGF	insulin-like growth factor
IGFBP	insulin-like growth factor binding protein
IL	Interleukin
REE	resting energy expenditure
RNA	ribonucleic acid
TBSA	total body surface area
TNF	tumor necrosis factor
VLDL-TG	very low density lipoprotein – triacylglycerol

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Key Points

1. In severely burned children, propagation of the catecholamine-induced hypermetabolic response can be reduced by propranolol administration.
2. The degree of mitigation of the deleterious effects of burn injury is dependent on the dose of propranolol and duration of administration.
3. By achieving a decrease of resting heart rate by 15-20%, cardiac work is significantly reduced over time.
4. Proteolysis and lipolysis are similarly reduced, due to the decrease in resting energy expenditure and potentiation of catecholamine signaling. Instead of the typical net proteolysis that occurs following a severe burn injury, skeletal muscle protein synthesis is increased.

FIGURE 1.

Heart rate in the acute phase is decreased with propranolol treatment

From:Williams, FN et al. *Surgery*. 2011 Feb;149(2):231-9.

FIGURE 2.

Reduction in skeletal muscle catabolism accompanies an increase in skeletal muscle anabolism

FROM: DAVID N. HERNDON, DN ET AL. N ENGL J MED 2001; 345:1223-1229

FIGURE 3.

REDUCTION IN CARDIAC WORK AND METABOLIC INDICES: (A) PERCENT PREDICTED HEART RATE. (B) RATE PRESSURE PRODUCT. (C) RESTING ENERGY EXPENDITURE (REE), expressed as the percentage of energy expenditure predicted by the HARRIS BENEDICT EQUATION. IN A-C, DATA ARE SHOWN AS THE LOESS-SMOOTHED TREND WITH SHADING INDICATING SEM. From: Herndon DN, et al. *Ann Surg.* 2012 Sep;256(3):402-11.

FIGURE 4.

Effect of propranolol on body composition. (a) Percent change in central mass, (b) percent change in truncal fat, and (c) percent change in peripheral lean mass. In a-c, data are expressed as percent change from patient baseline and are shown as the Loess-smoothed trend with shading indicating SEM. *Significant difference at $P < 0.05$. From: Herndon DN, et al. *Ann Surg.* 2012 Sep;256(3):402-11.

Table 1
Fat metabolism-related genes differentially expressed between control and propranolol-treated patients

Molecule Name	Entrez Gene ID for Human	Molecule Name	fold change
ACAA2	10449	acetyl-CoA acyltransferase 2	−6.7
ACACA	31	Acetyl-CoA carboxylase 1	−5.5
APOC1	341	apolipoprotein C1	−5.5
FADS1	3992	linoleoyl-CoA desaturase	−5.9
GPR137B	7107	g-protein coupled receptor 137B	−4.5
GPX4	2879	glutathione peroxidase	−3.2
HADH	3033	hydroxylacyl-CoA dehydrogenase	−5.4
ME1	4199	malic enzyme 1	−4.8
SCD	6319	stearoyl-CoA desaturase	−10.5
SCP2	6342	propanoyl-CoA C-acyltransferase	−3

Table 2
Muscle metabolism-related genes differentially expressed between control and propranolol-treated patients

Molecule Name	Entrez Gene ID for Human	Molecule Name	fold change
BCL6	604	B-cell CLL lymphoma 6	-1.7
BLCAP	10904	bladder cancer associated protein	1.6
CD164	8763	CD164	1.6
DYNC1LI2	1783	dynein	2.5
FAM127A	8933	family with sequence similarity 127, member A	1.8
FBP2	8789	fructose-1,6-bisphosphatase 2	-2.9
GADD45G	10912	growth arrest and DNA damage inducible, gamma	2.6
HSPA5	3309	heat shock 70 kDa protein 5	2.2
MAP3K5	4217	mitogen-activated protein kinase kinase kinase 5	2.1
MDH1	4190	malate dehydrogenase	1.5
MYL4	4635	Myosin light chain 4	-1.8
TNIP1	10318	TNFAIP3 interacting protein	2.1
VEGFA	7422	vascular endothelial growth factor	-1.5

Table 3

Results of β_1 and β_2 Adrenergic Receptor mediated signaling following a burn injury, without and with β -blockade

	Cardiac Effects	Metabolism	Muscle Protein	Fat Metabolism
Burn Injury	-Increased HR -Increased hyperdynamic circulation -Increased cardiac work	Increased REE	Degradation increased Synthesis decreased Decreased LBM	Increased lipolysis Increased circulating TGs, FFAs Increased hepatic steatosis
Burn + Propranolol	-Decreased HR -Decreased hyperdynamic circulation -Decreased cardiac work	Decreased REE	Degradation decreased Synthesis increased Increased LBM	Decreased lipolysis Decreased circulating TGs, FFAs Decreased hepatic steatosis