Published in final edited form as:

Surgery. 2011 February ; 149(2): 231–239. doi:10.1016/j.surg.2010.05.015.

PROPRANOLOL DECREASES CARDIAC WORK IN A DOSE-DEPENDENT MANNER IN SEVERELY BURNED CHILDREN

Felicia N Williams^{†,‡}, David N Herndon^{*,†,‡}, Gabriela A Kulp[†], and Marc G Jeschke^{*,†}

* Department of Surgery, The University of Texas Medical Branch, Galveston, TX

† Shriners Hospitals for Children, Galveston, TX

Abstract

Background—Severe burn is followed by profound cardiac stress. Propranolol, a non selective β_1 , β_2 -receptor antagonist, decreases cardiac stress, but little is known about the dose necessary to cause optimal effect. Thus, the aim of this study was to determine in a large prospective randomized controlled trial the dose of propranolol that would decrease heart rate at least 15% of admission heart rate and improve cardiac function. Four-hundred six patients with burns >30% total body surface area (TBSA) were enrolled and randomized to receive standard care (controls, n=235) or standard care plus propranolol (n=171).

Methods—Dose-response and drug kinetics of propranolol were performed. Heart rate and mean arterial pressure were measured continuously. Cardiac output (CO), cardiac index (CI), stroke volume (SV), rate pressure product, and cardiac work (CW) were determined at regular intervals. Statistical analysis was performed using ANOVA with Tukey and Bonferroni corrections and Student's t-test when applicable. Significance was accepted at $p < 0.05$.

Results—Propranolol given initially at 1 mg/kg/day decreased heart rate by 15% compared to control patients but was increased to 4 mg/kg/day within the first 10 days to sustain treatment benefits ($p < 0.05$). Propranolol decreased CO, rate pressure product, and CW without deleterious effects on mean arterial pressure. The effective plasma drug concentrations were achieved in 30 minutes, and the half-life was 4 hours.

Conclusions—The data suggest that propranolol is an efficacious modulator of the post-burn cardiac response when given at a dose of 4 mg/kg/day, which decreases and sustains heart rate 15% below admission heart rate.

Keywords

cardiac work; beta-blockade; pediatric burns; propranolol; tachycardia; hypermetabolism

Address correspondence to: Marc G. Jeschke, MD, PhD, Shriners Hospitals for Children, 815 Market St, Galveston, TX 77550, Telephone: (409) 392-4978, FAX: (409) 770-6919, majeschk@utmb.edu or mcjeschke@hotmail.com.

[‡]Authors contributed equally to the work presented in this manuscript.

Authors have no disclosures to declare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Severe thermal injury is characterized by a profound hypermetabolic response directly proportional to the original injury that persists up to two years post burn¹. Pediatric burn patients show dramatic increases in resting energy expenditure, resting heart rate, cardiac output (CO) and cardiac work (CW) that may lead to physiologic exhaustion if left untreated^{2, 3}. Furthermore, there are profound decreases in lean body mass, bone mineral content, bone mineral density, and nutritional deficiencies that can lead to impaired growth over time^{1, 4–6}. These derangements are manifestations of the increased levels of plasma catecholamines post-burn^{7, 8}. Plasma catecholamine levels increase 10- to 20-fold post burn, and increases persist up to 12 months post injury^{7, 8}. This pattern leads to a hyper-adrenergic response to the burn injury propagating the cardiac and metabolic derangements in severely burned patients.^{9, 10} Our group hypothesized that this effect is a detrimental, catecholamine-driven response and blocking this response at the receptor level would attenuate burn-induced changes¹¹. Propranolol, a non-selective β_1 , β_2 -receptor antagonist, attenuates the effects of endogenous catecholamines, thus decreasing CW when given during the acute hospitalization of pediatric burn patients¹¹. Propranolol mitigates the degree and extent of hypermetabolism, hyper-catabolism, and immune dysfunction experienced by these patients.^{12, 13} Clinically, propranolol decreases tachycardia and decreases myocardial oxygen consumption of pediatric burn patients^{11, 14, 15}. When given to decrease resting heart rate 15–20% of admission heart rate, propranolol increases lean body mass and decreases resting energy expenditure over time compared to children receiving standard care¹¹.

Despite the efficacy of propranolol, little is known about the dose of propranolol necessary to cause this decrease in resting heart rates of pediatric burn patients. In addition, the pharmacokinetics of propranolol in this severely injured population is essentially unknown. Thus, the aim of this study was to determine in a large prospective randomized controlled trial the dose of propranolol per kg body weight that would elucidate the appropriate attenuation of CW during the acute hospitalization and the associated dose kinetics of the drug.

PATIENTS AND METHODS

Four-hundred six patients with burns over 30% total body surface area (TBSA) who consented to an IRB-approved experimental protocol between 1998 and 2007 and were admitted to our burn unit and required at least one operative intervention were included in this study. All patients who were enrolled into the study were randomized to receive standard care (controls, n=235) or standard care plus propranolol (n=171). Both groups were similar in age, TBSA, and time from burn to hospital hospitalization. After the patient or the patient's legal guardian consented to the study, patients were randomized to receive standard of care with propranolol to decrease heart rate by 15–20% or just standard of care. Propranolol was administered enterally, via a feeding tube every six hours throughout the entire acute hospital stay. Propranolol dose was initiated at 1 mg/kg/day and titrated to decrease heart rate by 15%–20% of admission heart rate. Propranolol was given once patients were fluid stabilized, which was by 24–72 hours from admission.

Within 48 hours of admission, all patients underwent total burn wound excision, and the wounds were covered with available autograft. Any remaining open areas were covered with homograft. After the first operative procedure, it took 5–10 days until the donor site healed, and patients were then taken back to the operation theater. This procedure was repeated until all open wound areas were covered with autologous skin. All patients underwent the same nutritional treatment. The caloric daily intake requirement was calculated as 1500 kcal/m²

body surface + 1500 kcal/m² area burned, as published previously¹⁶. The enteral route was preferred in our patient population. Therefore, almost all patients received nutrition via a duodenal or nasogastric tube.

Patient demographics (age, date of burn and admission, sex, burn size and depth of burn) morbidity, and mortality were recorded. Wound healing was evaluated from time of donor site healing and thus time between operative interventions.

Cardiac Function

Heart rate (HR), and mean arterial pressure (MAP) were measured continuously throughout acute hospitalization by continuous cardiac monitoring in the intensive care unit (ICU) using arterial lines. Daily averages were calculated and the means compared to accepted, published nomograms for normal, non-burned children^{17, 18}. Heart rate was graphed as percent of normal in order to compare heart rate.

M-Mode echocardiograms were used to determine resting CO, cardiac index (CI), and stroke volume (SV). CO was adjusted for body surface area and expressed as an index. CO, SV, and CI were measured weekly during the acute hospitalization. In patients with chest burns, or prohibitive burn wound dressings, measurements were collected once wounds were covered appropriately without risk of shearing. CO and SV were normalized for age by comparing to accepted, published nomograms for non-burned, age-matched children^{17, 18}. All cardiac ultrasonographic measurements were made with the Sonosite Titan echocardiogram, with a 3.5 MHz transducer by an experienced echocardiographer. M-mode tracings were obtained at the level of the tips of the mitral leaflets in the parasternal long axis position, and measurements were performed according to the recommendations of the American Society of Echocardiography¹⁹. Left ventricular volumes were determined at end diastole and end systole and used to calculate SV, CO, and CI. Three measurements were performed and averaged for data analysis; recordings were performed with the subjects in a supine position and breathing freely⁷. The echocardiography operator was blinded to treatment group.

Calculations

Rate pressure product (RPP) is used to estimate myocardial oxygen consumption. It is a correlate of myocardial oxygen consumption¹⁵. RPP is calculated by:

$$\text{MAP} \times \text{HR} (\text{mmHg} \times \text{beats per minute [bpm]})$$

CW is the work done by the heart per minute to pump blood through the ventricles. CW is calculated by:

$$\text{SV} \times \text{MAP} \times \text{HR} (\text{mL per beat} \times \text{mmHg} \times \text{bpm})$$

RPP was measured daily, and CW was measured at regular weekly intervals during the acute hospitalization.

Drug Kinetics

On the third day of propranolol treatment, a baseline blood concentration for propranolol was obtained. With the next dose of propranolol, subsequent blood drug levels were obtained at 15 minutes (mins), 30 mins, 1 hour (hr), 2 hours (hrs), 4 hrs, and 6 hrs. The 6-hour level served as the baseline for the second dose of drug for that day. Blood drug levels

were again obtained. The propranolol levels were analyzed by an original high performance liquid chromatography method (HPLC) developed at this institution: extraction on Oasis (hydrophilic lipophilic balance) HLB cartridge (condition with 1 mL Methanol and 1 mL water; load 200 μ L of serum in 800 μ L of acidic solution; wash with 50% Methanol in water, pH=2.9, elute with Methanol pH=10.9; evaporate to dry and reconstitute in 50% Methanol/water); Haisil C18 column, 5 μ m, 250 $\times$ 4.5; mobile phase 22% Acetonitrile in water, first to pH=11.2 with Triethylamine, then to pH=3 with Phosphoric acid; UV detection at 220 nm; flow rate 0.7 ml/min.

Ethics and Statistics

The study was reviewed and approved by the Institutional Review Board of the University of Texas Medical Branch, Galveston, Texas. Prior to the study, each subject, parent or child's legal guardian signed a written, informed consent form. Data are expressed as percentage, means $\pm$ standard deviation (SD) or standard error of the mean (SEM), where appropriate. Statistical analysis was performed by One-way and Two-way ANOVA followed by Tukey and Bonferroni correction and Student's t-test where appropriate. Significance was accepted at $p < 0.05$. This study's clinical trial was registered at www.clinicaltrials.gov under the identifier number NCT00239668.

RESULTS

Demographics

Four-hundred six patients with burns encompassing over 30% of their TBSA were included in the present study. Twenty patients were excluded from the control group leaving 215 patients randomized to standard of care. Forty-six patients were excluded from the propranolol group leaving 125 patients. Patient demographics are included in Table 1. Propranolol treated patients were randomized to receive standard of care plus propranolol at an initial dose of 1 mg/kg body weight per day. Patients randomized to control were on average 8 years of age. Patients randomized to receive propranolol were on average 7 years of age. Both groups suffered from a severe burn injury with 55% TBSA ($\pm$ 15% SD for the propranolol patients and $\pm$ 17% for control), and third-degree burns of over 40% TBSA ($\pm$ 22% SD for the propranolol patients and $\pm$ 25% for control). There were no significant differences in duration of stay in the ICU, or sex distribution.

Heart Rate

Heart rate presented as percent of normal for both groups increased profoundly post-burn (Fig. 1A). There were no differences in heart rate between groups before propranolol treatment was initiated (Fig. 1A). The average percent predicted heart rate on admission for control patients was 173 ± 4 (SEM) beat per minute (bpm), while the average heart rate for propranolol patients was 166 ± 1 bpm (Fig. 1A). There was a decrease in heart rate for the propranolol patients by day two of treatment compared to heart rates prior to treatment, which was sustained throughout treatment course ($p < 0.001$) (Fig. 1A and B). For controls, heart rate did not decrease throughout the study period compared to admission heart rate ($p > 0.05$). Propranolol patients had a 15% decrease in percent of normal heart rate due to treatment during the study period ($p < 0.001$). Compared to control patients, propranolol-treated patients had a decrease in percent of normal heart rate by 18% ($p < 0.001$) (Fig. 1A and B).

Propranolol administered within the first week after hospital admission was initiated at a starting dose of 1 mg/kg body weight per day (mg/kg/day). This dose was sufficient to decrease heart rates 10–15% of admission heart rates and between groups ($p < 0.001$). The dose of propranolol had to be increased to 4 mg/kg/day to achieve and maintain a decrease

in heart rate of 15% compared to controls and compared to heart rate before treatment (Fig. 1B).

Rate Pressure Product

There were no significant differences in rate pressure product, which is associated with and a correlate of myocardial oxygen consumption, between the groups before propranolol treatment. With treatment, there was a decrease in RPP, suggesting that myocardial oxygen consumption was decreased ($p<0.001$) (Fig. 1C).

Sex

To further validate these findings, we stratified the data for sex, age, and TBSA burns. During the study period, female control patients had an average heart rate of 172 ± 1 bpm, while propranolol-treated females averaged 146 ± 1 bpm after propranolol was initiated ($p<0.001$) (Fig. 2A). Male control patients averaged 171 ± 1 bpm, while propranolol-treated male patients average 152 ± 1 bpm ($p<0.001$) (Fig. 2B). Before treatment, there were no significant differences between male and female patients. After treatment with propranolol, both males and females showed a significant decrease in heart rate (Fig. 2A and B). Both males and females required an average of 4 mg/kg/day to maintain significant decreases in heart rate during the acute hospitalization. There were no differences between dose requirements.

Age

Patients were separated into three age groups: 0–3 years (propranolol [n=48] versus control [n=65]), 4–10 years (propranolol [n=49] versus control [n=83]), and 11–18 years (propranolol [n=28] versus control [n=67]). All three groups showed a decrease in heart rate with propranolol treatment ($p<0.05$) (Fig. 3A–C). All groups required an increase in propranolol dosing to 4 mg/kg by day 20 to maintain decreases in heart rate during the acute hospitalization.

TBSA

Patients were separated into three groups based on burn size suffered: 30–60% TBSA (propranolol [n=80] versus control [n=139]), 60–80% TBSA (propranolol [n=33] versus control [n=58]), and >80% TBSA (propranolol [n=12] versus control [n=18]). All three groups showed decreases in heart rate with propranolol treatment ($p<0.001$) (Fig. 4A–C). The smaller burns required 4 mg/kg/day (Fig. 4A). Burns encompassing 60–80% TBSA required doses 4–6 mg/kg/day to maintain a decreased heart rate (Fig. 4B). The largest burns required 4 mg/kg/day (Fig. 4C).

CO, CI, SV

During this study period, there were no differences between groups in CO, CI, or SV before treatment with propranolol was initiated. By week two, there was a decrease in percent of normal CO in the propranolol patients compared to control patients and was sustained through the study period ($135\% \pm 5\%$ versus $158\% \pm 8\%$), respectively ($p<0.05$). There was no decrease in CI. With treatment, the measured SV for propranolol patients was greater than control patients ($112\% \pm 8\%$ compared to age-matched non-burned children for propranolol versus $94\% \pm 5\%$ for control patients) ($p<0.02$).

CW

There were no significant differences in CW between groups before propranolol treatment. With treatment, there was a decrease in CW for the propranolol-treated patients compared to

control patients (337186 ± 22837 ml/beat $\times$ mmHg $\times$ bpm versus 476372 ± 42379 ml/beat $\times$ mmHg $\times$ bpm) ($p < 0.004$).

Drug Kinetics

The effective plasma drug concentration for therapeutic propranolol is 50 nanograms per ml (ng/ml) ²⁰. Peak levels are reached at 1 to 3 hrs after administration ^{21, 22}. Pediatric burn patients receiving propranolol reached acceptable peak concentration levels by 30 mins to 1 hr and trough levels by hour two (a representative patient presented in Figure 5). Actual heart rate decreased 10% (139 at baseline to 125 at 1 hour) at 1 hour after dosing (Fig. 5). The half-life for this drug is between 4 to 6 hours.

DISCUSSION

The post-burn hypermetabolic response is propagated by the uncontrolled surge of catecholamines ⁸. Clinically, patients have hyperdynamic physiology. Initially, there is an “ebb” phase demonstrated by a decrease in CO with an increase in myocardial oxygen consumption and demand ². This ebb is followed by a “flow” phase, in which CO can increase up to 200% of normal CO accompanied by an increase in myocardial oxygen consumption ¹⁵. Heart rate also increased up to 200% of normal despite resuscitative efforts. Increased heart rate results in a shortened ventricular filling time and thus results in a decrease in SV ^{15, 23}. To further complicate this clinical profile is the third and final stage of the hypermetabolic response post-burn – physiologic exhaustion ³. If clinicians are not able to fully resuscitate the patient to attenuate the “flow” phase, these patients become even more physiologically deranged – increasing morbidity and mortality. We have shown that the clinical course for pediatric patients with large burns is often confounded by cardiac complications. ^{24, 25} Therefore, cardiac function is one of the main determinants of outcome from severe burn injury ²⁶.

Propranolol, a non-selective, beta-adrenergic receptor antagonist may decrease mortality (unpublished data) in our patient population. A non-selective beta-antagonist permits an unbalanced action of catecholamines on the peripheral vascular bed with no vasodilating action to counterbalance the effects of the catecholamines on peripheral α -adrenergic receptors. Propranolol decreases the effects of plasma catecholamines that propagate the hypermetabolic response ^{11, 14}. By decreasing the deleterious effects, propranolol mitigates the degree and extent of the hypermetabolic response. We have shown that by decreasing heart rates by 15–20% of admission heart rates, we decrease cardiac work and RPP, which may indicate a decrease in myocardial oxygen consumption. Over time, by decreasing these physiologic demands, patients avoid further proteolysis, lipolysis, and muscle breakdown for energy requirements ¹¹. The patients have increased lean body mass over time and increased bone mineral content and density ¹¹. Specifically, propranolol has been shown to improve net-muscle protein balance via improving the efficiency of protein synthesis ¹¹. In fact, in our study in 2001, the net balance of protein synthesis and protein breakdown achieved anabolic levels in patients that received propranolol treatment ¹¹. While the normal physiologic state post severe burn is one of profound proteolysis, and increases in resting energy expenditure, propranolol treatment accelerated protein synthesis, and decreased resting energy expenditure ¹¹. This physiologic change is attributed to an increase in the intracellular recycling of free amino acids ¹¹. While metabolic rates are not shown in this study, patients that received propranolol treatment had no significant increases in metabolic rate compared to control patients that had a statistically significant increase in metabolic rate during the study period.

Patients with burns encompassing 80%–100% TBSA demonstrated a lot of variability in dosing during the acute hospitalization than the other size burns. This finding may be multi-

factorial in nature. These patients are the most critical patients. Both their status and response to treatment were tenuous during the acute hospitalization. Larger burns, in general, had more trips to the operating room and had longer resuscitation times on average. This likely attributed to the delay in increasing dose of propranolol.

Drug kinetic studies were performed on 50 patients in our hospital. Tests were performed to determine appropriate time and dosing. Data suggest that patients often fail to meet appropriate drug levels and thus need increasing doses. In addition, the data suggest that patients are so hypermetabolic that they reach peak levels much sooner than expected, and further tests need to be done to determine if these patients require shorter dosing frequencies. Propranolol is absorbed completely after oral administration and distributed widely throughout tissues, with peak plasma levels achieved 1 to 3 hours after administration^{18, 21, 22, 27}. It has variable bioavailability with extensive first-pass metabolism. Any hepatic dysfunction or impairment will alter bioavailability^{27, 28}. It is well-established that pediatric burned patients may have hepatic dysfunction during the acute phase post-burn⁷. Plasma concentrations can vary quite widely due to genetic differences or constitutional factors, such as age and environmental factors²⁸. The main metabolite after oral administration of the drug, 4-hydroxypropranolol, is also pharmacologically active and may be more potent than the parent compound^{27, 28}. This factor may explain the decrease in heart rate even when plasma concentration appears to be low.

One limitation of this study was M-mode echocardiography to determine CO and SV. Patients that had severe chest burns or prohibitive dressings had to have measurements taken at later time points, although within the study period. In addition, more invasive methods often show that M-mode echocardiograms may underestimate cardiac measurements, especially with confounding factors of pulmonary edema and fluid overload²⁹. Another limitation of our study is that there is a discrepancy in the number of patients in each arm of the study. At our institution, there are many prospective randomized controlled trials at our institution that require a control group. We use the same controls for the studies, thus, there is a larger control group compared to the many different drug arms of the studies. In addition, there were a number of patients that were excluded from the study that some may feel represent a bias. Those that were excluded, were excluded for the following reasons: burns <30% TBSA, receiving other anabolic agents, futility on admission, withdrew after consent obtained by family, or never received propranolol (that were randomized to receive propranolol). Those that need further explanation are patients that received other agents. Six patients received propranolol + oxandrolone or intensive insulin and were excluded. Another group were the 4 patients whose care was deemed futile due to the severity of injury, or significant anoxic brain injury. One family withdrew after consent was signed, so that patient's data was removed. The last group was the group that never received propranolol treatment. This group did not receive treatment due to physician error (failure to write the order), nursing error (failure to administer drug) or the patient received the drug only during the rehabilitative period and not during the acute hospitalization. We do not feel that these patients represent a significant bias.

Conclusions

When propranolol is given at 1 mg/kg/day, we saw a beneficial decrease in heart rates 10% lower than admission heart rates. Over the first 10 days, patients need that dose increased to 4 mg/kg/day due to either tachyphylaxis or the sustained "flow" phase of the hypermetabolic response. We did not see any clinically important hypotension in our pediatric patients randomized to propranolol treatment as indicated by a decrease in MAP to less than 60 mmHg. This lack of drug-induced hypotension may be related to the fact that these patients are so hyperdynamic that they can tolerate treatment. In addition, patients are fully

resuscitated before beginning treatment, which may have prevented any untoward cardiac events. If a patient had any clinically important decreases in respiratory rate, bronchospasm or hypotension, one propranolol dose was held and re-initiated with the next scheduled dose. While we did not have any patients that had a history of asthma included in this study, they would have been excluded due to the risk of bronchospasm with beta-blockade. We need further evidence to see the safety of starting the dose at 4 mg/kg/day and to determine whether decreasing heart rates further would lead to detrimental effects on CO, cardiac work, and myocardial oxygen consumption. For severely burned adult patients, oral propranolol at a standard dose of 20 mg every 6 hours is given and increased as needed. Our current findings, however have led us to embark on a multi-center trial using propranolol at a dose of 4 mg/kg in the acute hospitalization to decrease cardiac stress post-burn.

Acknowledgments

This work is supported by grants from Shriners Hospitals for Children (8660, 8490, 8640, 8760, and 9145), grants from the National Institutes of Health (NIH) (T32GM08256, P50GM60338, R01-GM56687, R01-HD049471), grants from National Institute on Disability and Rehabilitation Research (NIDRR) (H133A020102, H133A70019), National Institute of General Medical Sciences (NIGMS) (U54 GM62119), and the American Surgical Association.

References

1. Reiss E, Pearson E, Artz CP. The metabolic response to burns. *J Clin Invest* 1956;35:62–77. [PubMed: 13278402]
2. Cuthbertson DP, Angeles Valero Zanuy MA, Leon Sanz ML. Post-shock metabolic response. 1942. *Nutr Hosp* 2001;16:176–82. [PubMed: 11708288]
3. Selye H. Stress and the general adaptation syndrome. *Br Med J* 1950;1:1383–92. [PubMed: 15426759]
4. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. *Arch Surg* 1990;125:392–5. [PubMed: 2306187]
5. Wilmore DW. Pathophysiology of the hypermetabolic response to burn injury. *J Trauma* 1990;30:S4–6. [PubMed: 2254989]
6. Yu YM, Tompkins RG, Ryan CM, Young VR. The metabolic basis of the increase of the increase in energy expenditure in severely burned patients. *JPEN J Parenter Enteral Nutr* 1999;23:160–8. [PubMed: 10338224]
7. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman OE, Norbury WB, et al. Pathophysiologic response to severe burn injury. *Ann Surg* 2008;248:387–401. [PubMed: 18791359]
8. Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg* 1974;180:653–69. [PubMed: 4412350]
9. Bernardin G, Kisoka RL, Delporte C, Robberecht P, Vincent JL. Impairment of beta-adrenergic signaling in healthy peripheral blood mononuclear cells exposed to serum from patients with septic shock: involvement of the inhibitory pathway of adenylyl cyclase stimulation. *Shock* 2003;19:108–12. [PubMed: 12578116]
10. Maass DL, Hybki DP, White J, Horton JW. The time course of cardiac NF-kappaB activation and TNF-alpha secretion by cardiac myocytes after burn injury: contribution to burn-related cardiac contractile dysfunction. *Shock* 2002;17:293–9. [PubMed: 11954829]
11. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001;345:1223–9. [PubMed: 11680441]
12. Novotny NM, Lahm T, Markel TA, Crisostomo PR, Wang M, Wang Y, et al. beta-Blockers in sepsis: reexamining the evidence. *Shock* 2009;31:113–9. [PubMed: 18636043]
13. Oberbeck R, van Griensven M, Nickel E, Tschernig T, Wittwer T, Pape HC. Influence of beta-adrenoceptor antagonists on hemorrhage-induced cellular immune suppression. *Shock* 2002;18:331–5. [PubMed: 12392276]
14. Baron PW, Barrow RE, Pierre EJ, Herndon DN. Prolonged use of propranolol safely decreases cardiac work in burned children. *J Burn Care Rehabil* 1997;18:223–7. [PubMed: 9169945]

15. Minifee PK, Barrow RE, Abston S, Desai M, Herndon DN. Improved myocardial oxygen utilization following propranolol infusion in adolescents with postburn hypermetabolism. *J Pediatr Surg* 1989;24:806–10. discussion 10–1. [PubMed: 2769550]
16. Hart DW, Wolf SE, Zhang XJ, Chinkes DL, Buffalo MC, Matin SI, et al. Efficacy of a high-carbohydrate diet in catabolic illness. *Crit Care Med* 2001;29:1318–24. [PubMed: 11445678]
17. Hazinski, MF. Cardiovascular disorders. In: Hazinski, MF., editor. *Nursing Care of the Critically Ill Child*. 2. St. Louis: Mosby-Year Book; 1992. p. 117-394.
18. Rudolph, AM. The fetal circulation and postnatal adaptation. In: Rudolph, AM., editor. *Congenital Diseases of the Heart: Clinical-Physiological Considerations*. 2. Armonk, NY: Futura Publishing Company; 2001. p. 3-44.
19. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072–83. [PubMed: 709763]
20. Carmona MJ, Malbouisson LM, Pereira VA, Bertoline MA, Omosako CE, Le Bihan KB, et al. Cardiopulmonary bypass alters the pharmacokinetics of propranolol in patients undergoing cardiac surgery. *Braz J Med Biol Res* 2005;38:713–21. [PubMed: 15917952]
21. Frishman W, Jacob H, Eisenberg E, Ribner H. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 8. Self-poisoning with beta-adrenoceptor blocking agents: recognition and management. *Am Heart J* 1979;98:798–811. [PubMed: 40429]
22. Frishman W, Silverman R, Strom J, Elkayam U, Sonnenblick E. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 4. Adverse effects. Choosing a beta-adrenoreceptor blocker. *Am Heart J* 1979;98:256–62. [PubMed: 36744]
23. Jones, S.; Muthu, K.; Shankar, R.; Gamelli, R. Significance of the adrenal and sympathetic response to burn injury. In: Herndon, DN., editor. *Total Burn Care*. 3. Philadelphia: Saunders Elsevier; 2007. p. 343-60.
24. Horton JW, Maass DL, White DJ, Sanders B, Murphy J. Effects of burn serum on myocardial inflammation and function. *Shock* 2004;22:438–45. [PubMed: 15489636]
25. Jeschke MG, Mlcak RP, Finnerty CC, Norbury WB, Gauglitz GG, Kulp GA, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care* 2007;11:R90. [PubMed: 17716366]
26. Pereira C, Murphy K, Herndon D. Outcome measures in burn care. Is mortality dead? *Burns* 2004;30:761–71. [PubMed: 15555787]
27. Shand DG. Pharmacokinetics of propranolol: a review. *Postgrad Med J* 1976;52 (Suppl 4):22–5. [PubMed: 787953]
28. Routledge PA, Shand DG. Clinical pharmacokinetics of propranolol. *Clin Pharmacokinet* 1979;4:73–90. [PubMed: 378502]
29. Mathews L, Singh RK. Cardiac output monitoring. *Ann Card Anaesth* 2008;11:56–68. [PubMed: 18182765]

Figure 1.

(A) Average percent predicted daily heart rates for control versus propranolol patients during the first 20 days post-burn or days of treatment with propranolol. Heart rates decreased with treatment * $p < 0.05$.

(B) Average percent predicted daily heart rates for control versus propranolol patients during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * $p < 0.05$.

(C) Average daily rate pressure product of control patients versus propranolol patients during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day * $p < 0.05$.

Figure 2.

(A) Average percent predicted daily heart rates of female control versus female propranolol patients during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * $p < 0.05$.

(B) Average percent predicted daily heart rates of male control versus male propranolol patients during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * $p < 0.05$.

Figure 3.

(A) Average percent predicted daily heart rates of control patients aged 0–3 years versus propranolol patients aged 0–3 years during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * $p < 0.05$.

(B) Average percent predicted daily heart rates of control patients aged 4–10 years versus propranolol patients aged 4–10 years during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * $p < 0.05$.

(C) Average percent predicted daily heart rates of control patients aged 11–18 years versus propranolol patients aged 11–18 years during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * $p < 0.05$.

Figure 4.

(A) Average percent predicted daily heart rates of control patients with 30–60% total body surface area versus propranolol patients with 30–60% total body surface area during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4 mg/kg/day to maintain 10–15% decrease in heart rates * p<0.05.

(B) Average percent predicted daily heart rates of control patients with 60–80% total body surface area versus propranolol patients with 60–80% total body surface area during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required 4–6 mg/kg/day to maintain 10–15% decrease in heart rates * p<0.05.

(C) Average percent predicted daily heart rates of control patients with >80% total body surface area versus propranolol patients with >80% total body surface area during the first 20 days post-burn or days of treatment with propranolol with daily dose of propranolol in mg/kg/day. Patients required over 4 mg/kg/day to maintain 10–15% decrease in heart rates * p<0.05.

Figure 5.

Plasma drug concentration of propranolol in ng/ml of one representative pediatric burn patient and time blood obtained with heart rate at time of blood draw. There was a decrease of 10% in actual measured heart rate at one hour.

Table 1

Demographics

	Propranolol	Control	P Value
<i>n</i>	125	215	N/A
Age (years)	7 ± 5	8 ± 5	0.08
TBSA (%)	55 ± 15	55 ± 15	0.80
TBSA 3rd (%)	42 ± 22	40 ± 24	0.82
Duration of stay (days)	30 ± 20	26 ± 20	0.39
Sex (M:F)	89:36	128:87	N/A

Data presented as average ± standard deviation, percentage or ratio.