Resting β-Adrenergic Blockade Does Not Alter Exercise Thermoregulation in Children With Burn Injury: A Randomized Control Trial

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The objective of this study was to test the hypothesis that propranolol, a commonly prescribed β-blocker to burned children, in combination with exercise-heat stress, increases the risk of heat illness and exercise intolerance. In a randomized double-blind study, propranolol was given to 10 burned children, and placebo was given to 10 additional burned children (matched for TBSA burned; mean ± SD, 62 ± 13%), while nonburned children served as healthy controls. All groups were matched for age and body morphology (11.2 ± 3.0 years; 146 ± 19 cm; 45 ± 18 kg; 1.3 ± 0.4 m^2). All children exercised in hot conditions (34.3 ± 1.0°C; 26 ± 2% relative humidity) at 75% of their peak aerobic capacity. At the end of exercise, none of the groups differed for final or change from baseline intestinal temperature (38.0 ± 0.5°C; 0.02 ± 0.01Δ°C·min^{-1}), unburned (37.0 ± 0.6°C) and burned skin temperatures (36.9 ± 0.7°C; nonburn group excluded), heat loss (21 ± 18 W m^{-2}), whole-body thermal conductance (118 ± 113 W m^{-2}), or physiological strain index (5.6 ± 1). However, burn children exercised less than nonburn group (21.2 ± 8.6 vs 30 ± 0.0 min; $P < .001$) and had a lower calculated exercise tolerance index (1.0 ± 0.0 vs 6.7 ± 4.3; $P < .01$). Burned children had lower peak heart rates than nonburned children (173 ± 13 vs 189 ± 7 bpm; $P < .01$), with greater relative cardiac work rates at the end of exercise (97 ± 10 vs 85 ± 11% peak heart rate; $P < .01$). Resting β-adrenergic blockade does not affect internal body temperature of burned children exercising at similar relative intensities as nonburn children in the heat. Independent of propranolol, a suppressed cardiac function may be associated to exercise intolerance in children with severe burn injury. (J Burn Care Res 2018;39:402–412)

Burn trauma induces prolonged activation of the sympathetic nervous system, causing an increase in catecholamines and energy expenditure (20–100% above normal)[1,2] that impairs cardiac function and disrupts whole-body metabolism.[3–5] Propranolol, a nonselective β-adrenergic blocking agent, sometimes is given to burn patients for decreasing metabolic rate[1,6] and cardiac work.[5,7,8] Burn patients also have severe muscle catabolism and weakness, which are worsened by prolonged physical inactivity.[5] However, early exercise rehabilitation immediately after hospital discharge restores lean body mass and exercise capacity while improving quality of life.[9–12]

Currently, there is no consensus on the safety of physical activity under hot conditions in severely burned children at discharge and in combination with propranolol treatments. Exercise-heat stress causes an increase in heart rate (i.e., cardiovascular drift). In nonburned adults, β-adrenergic blockade under thermal neutral and hot conditions prevents an elevation of heart rate and stroke volume.[13,14] Additionally, β-adrenergic blocking drugs have been found to reduce peripheral leg blood flow, while increasing vascular resistance in burned adult

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patients at rest.[15] Given that temperature regulation is disrupted from inadequate core-skin insulation (removal of epidermis, dermis, and subcutaneous tissue), propranolol treatment may increase the risk for heat-related injury by impairing thermoregulation during exercise-heat stress and suppressing cardiac function. Additionally, we have recently shown that cardiac output during submaximal exercise is impaired in severely burned children compared with age-matched nonburned children under thermal neutral conditions.[16] Therefore, we designed a study in burned children to determine whether propranolol affects thermoregulatory capacity. Our objectives were 2-fold: determine whether β-blockade at rest 1) impairs temperature regulation during exercise-heat stress and 2) impairs exercise tolerance in children with burn injury. We hypothesized that burned children would have similar skin and internal thermal responses as age- and body-matched controls and that β-blockade would decrease exercise tolerance.

METHODS

Ethical Approval

All experiments were approved by the Institutional Review Board of the University of Texas Medical Branch and were conducted in accordance with the Declaration of Helsinki. Thirty-two children participated in this study. Before subjects participated in the study, informed consent was obtained from parents or legal guardians, and child assent was obtained, as applicable.

Experimental Design

For this double-blinded randomized control trial, after admittance, patients were given propranolol or placebo. Propranolol was given once patients were fluid stabilized, which was by 24 to 72 hours from admission. Within 48 hours of admission to our institution, pediatric patients undergo standard of care treatment involving total burn excision. Wounds were covered with available autograft and remaining open wounds covered with homograft. Total fluid resuscitation was administered within 24 hours of admission and according to the Galveston formula (5,000 mL/m^2 TBSA burned plus 2,000 mL/m^2 TBSA lactated Ringer solution). All patients received the same nutritional support during the first week, which was calculated as 1500 kcal/m^2 body surface plus 1500 kcal/m^2 area burned feed through enteral duodenal or nasogastric route.[17] During the remainder of acute stay, intake was modified to 1.4 times weekly measured resting energy expenditure. Patients were discharged once wounds were 95% healed. Once discharged from acute hospital care, patients were then randomized to complete an exercise heat tolerance test that was performed under thermal hot and neutral conditions. A healthy, nonburned age- and body size-matched group also completed the treadmill exercise heat tolerance test. However, for ethical reasons, we did not give propranolol to the cohort of nonburned healthy children. Before the main study, an aerobic capacity test (peak VO_2) and body composition (dual-energy x-ray absorptiometry) scan were administered. Within 1 week of preliminary assessments, after instrumentation, burned subjects and healthy nonburned controls rested in a thermal neutral environment for 20 minutes. They then entered a hot environment and exercised at 75% of their peak VO_2 for a maximal time of 30 minutes or until they could not continue. During exercise, intestinal temperature, temperature of burned and unburned skin, heart rate, and subjective assessment of strain were continuously measured. All individuals also completed exercise testing under thermal neutral conditions for a comparison of measures on exercise tolerance and total exercise time completed for up to 30 minutes. Based on our previous studies,[18,19] at a similar exercise intensity, to detect a change in internal temperatures between burned and nonburned children of at least 0.70°C within a group and between groups during exercise at similar time points, (SD of 0.50 and alpha = 0.05), we projected a requirement for a sample size of 12 children per group to attain a power of 80%.

Subjects

Thirty-two children participated in this study. Before subjects participated in the study, informed consent was obtained from parents or legal guardians, and child assent was obtained, as applicable. Twenty pediatric burn patients, 12.1 ± 3.6 years old, with ≥ 50% TBSA burns, were enrolled in the study. At admission, TBSA burned was documented in Lund and Browder charts and adjusted accordingly upon demarcation of third-degree burns. All burn patients at our institution surviving a burn of > 30% or more were solicited for involvement of this study. Twelve reference nonburned healthy children, 9.7 ± 1.2 years old, were also enrolled and matched for age and recruited from the local community through publically posted flyers and word of mouth. Subject characteristics are presented in Table 1. Race for all children was white, while ethnic background was Hispanic or Latino (88%) or Caucasian, non-Hispanic (22%). We calculated body mass index (BMI), BMI percentile, and BSA

Table 1. Subjects' physical and exercise characteristics*

	Burned		Nonburned	
Characteristics	**Placebo**	**Propranolol**	**Control**	***P*-value**
n (Male/female)	10 (10/0)	10 (10/0)	12 (8/4)	—
Age (yr)	11.9 ± 4.1	12.3 ± 3.3	9.7 ± 1.2	.10
Time of testing (months postburn)	5.4 ± 3	3.5 ± 1	—	.08
Body morphology				
Height (cm)	145.2 ± 22	146.6 ± 16	145.1 ± 22	.96
Weight (kg)	44.2 ± 26	41.7 ± 14	43.7 ± 14	.78
BSA (m^{-2})	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.2	.90
BSA nonburn (m^{-2})	0.55 ± 0.3†	0.44 ± 0.2†	1.4 ± 0.2	**< .0001**
BMI ($kg \cdot m^{-2}$)	19.5 ± 7	18.8 ± 3	22.6 ± 6	.59
BMI (%ntile)	51.9 ± 32	54.8 ± 30	81.2 ± 26	.24
TBSA burn (%)	58 ± 14	67 ± 11	—	.54
TBSA third-degree burn (%)	46 ± 23	55 ± 19	—	.34
Total body fat (%)	23.5 ± 7†	21.6 ± 6†	30.7 ± 7	**.008**
Peak exercise				
Peak VO_2 ($L \cdot min^{-1}$)	1.1 ± 0.8	0.9 ± 0.5	1.5 ± 0.3	.08
Peak VO_2 ($mL \cdot O_2 \cdot kg\ min^{-1}$)	24.1 ± 7†	22.2 ± 7†	32.0 ± 6	**< .0001**
Peak HR ($beat \cdot min^{-1}$)	174 ± 15†	173 ± 12†	189 ± 7	**.006**
Submaximal exercise				
75% peak VO_2 ($L \cdot min^{-1}$)	0.8 ± 0.6†	0.7 ± 0.3	1.1 ± 0.2	.08
Heat production ($W \cdot m^{-2}$)	142 ± 61	128 ± 45†	203 ± 23	**< .001**
Heat production ($W \cdot kg^{-1}$)	4.4 ± 1†	4.1 ± 1†	6.0 ± 1	**< .001**

BMI, body mass index; BMI %ile, body mass index percentile for age; HR, heart rate; VO_2, volume of oxygen.

*Data reported as mean ± SD.

†Statistically different from nonburned healthy controls, $P<.05$.

and found no differences. BMI was calculated by dividing weight in kilograms by the square of height in meters. BMI percentile was computed according to the normative values for children provided by the centers for disease control and prevention (CDC),[20] and BSA (m^2) was calculated according to DuBois and DuBois.

β-Adrenergic Blockade and Placebo Administration

Burned children were randomly assigned to receive propranolol (tablet form; N = 10) or placebo (N = 10). Propranolol or placebo was started within 72 hours of admission to the intensive care unit (ICU) and continued while at the time of testing. Propranolol dosage was titrated to decrease heart rate by 20 ± 5% by the physicians and nurses who routinely examined the patients' heart rate (see Table 1 for resting heart rates). The usual dose was 2 to 4 mg/kg/day (3.6 ± 1 mg/ kg/day; n = 4 regular formulation; n = 6 long-acting formulation), which allowed for a target heart rate of 88 ± 13 bpm before the exercise study day. Exercise heat tolerance testing was started after hospital discharge when burn wounds were 95% healed.

Peak Aerobic Exercise Capacity Test

Aerobic exercise capacity (peak VO_2) was determined by a modified Bruce protocol maximal treadmill exercise test performed to volitional exhaustion. Respiratory gasses were analyzed using breath-by-breath data using an automated MedGraphics CardiO2 metabolic cart (St. Paul, MN) after O_2 and CO_2 gas and air flow were calibrated using known gasses and a 3-L syringe. Speed and angle of elevation started at 1.7 mph and 0%, respectively. Thereafter, the speed and level of incline were increased every 3 minutes. Subjects were constantly encouraged to complete 3-minute stages, and the test was terminated once peak volitional effort was achieved. Because no validated, universally accepted criteria exist in children for the determination of peak VO_2,[21] we used similar standards as adults,[22] with the test considered maximal once subjects signaled to stop exercise and at least 3 of the following criteria were met: a respiratory exchange ratio of ≥ 1.05, a leveling off in VO_2 with increasing workloads (less than 2 $mL \cdot kg \cdot min^{-1}$), volitional fatigue, exercise final heart rate of 190 bpm or greater, or a final test time between 8 and 15 minutes. Similar criteria have been used by others in children.[21] All groups met the criteria of 3 of the aforementioned list. For all exercise

tests, burned children wore comfortable, loose clothing (shorts, t-shirt, and running shoes), and pressure garments, which were issued as the standard of care to reduce scar formation.

Exercise-Heat Tolerance Test

Within the same week of preliminary testing, subjects completed a 30-minute treadmill exercise tolerance test under heated and neutral environmental conditions at a predetermined workload of 75% of their peak VO_2. Before the exercise tolerance test, all participants swallowed an ingestible temperature capsule (MiniMitter, Seattle, WA) with a minimum of 5 hours before exercise testing for the measurement of internal body temperature (intestinal temperature) via telemetry. Skin temperature was assessed using a Mon-A-Therm Model 6510 temperature monitoring system (Mallinckrodt Co., Mexico). Temperature probes were placed on unburned, ungrafted (nonburned) skin as well as on healed burn sites that had previously been fascially excised and grafted (burned skin). Site placement was determined via patient chart review. Heart rate was measured using a Polar heart rate monitor (Polar Electro, Kempele, Finland). No food or drinks were allowed within 1 hour of testing. All fans and ventilation outlets were turned off during each exercise session, and an intestinal temperature measurement greater than 39.0°C was chosen for test termination to ensure the safety of all children.

Subjects were exposed to ambient room conditions that were thermal neutral (22.8 ± 0.3°C dry bulb temperature [Tdb], 43 ± 3% relative humidity [R*h*]) and hot (34.3 ± 1.0°C Tdb, 26 ± 2% R*h*). A comprehensive list of environmental parameters that we[23] and others have used were calculated as described elsewhere.[24,25] The thermal neutral condition was significantly different from the hot condition with regard to dry bulb temperature, relative humidity, mean radiant temperature (T*r*: 31.1 ± 0.05 vs 29.3 ± 0.11°C; $P < 0.05$), the radiative heat transfer coefficient (H_r: 6.03 ± 0.01 vs 5.95 ± 0.01 $W \cdot m^{-2} \cdot K$; $P < 0.05$), partial water vapor pressure in ambient air (P_a: 12.8 ± 0.9 vs 10.7 ± 0.03 mmHg; $P < 0.05$), and dew point (T_{dp}: 9.5 ± 1 vs 12.0 ± 0.3°C; $P < 0.05$). No difference was detected between groups in any hot or neutral parameter.

Thermal Calculations

The dimension of each equation was expressed as watts normalized to BSA ($W \cdot m^{-2}$). The rate of metabolic heat production during exercise was estimated by indirect calorimetry by subtracting external work (W) from metabolic energy expenditure (M) and dividing by BSA (m^2). The rate of external work (watts) was calculated from the following standard formula: W = body mass in kg × 9.81 × (speed in mph × 0.44704) × (% grade/100). Metabolic energy expenditure (M) was calculated using the following equation: $M\ (W \cdot m^{-2}) = (((EE \times VO_2 \times t)/(t \times 60))/m^2)$. Tissue and whole body conductance was measured using the heat transfer between the internal body and the skin and the ambient environment.[26,27] Tissue thermal conductance ($W \cdot m^{-2} \cdot °C^{-1}$) was calculated as: $K = M - E_{res}/$ Tint - T_{sk} (burned and unburned skin temperature). Whole-body thermal conductance ($W \cdot kg^{-2} \cdot °C^{-1}$) took into account the internal body temperature (Tint) and ambient environmental temperature (T_a) and was calculated as follows: M/(Tint$_a$ - ambient temperature in °C). Heat loss was calculated as Q (W) = m × c × ΔT, where m = mass (kg^{-1}), c = specific heat of tissues (0.83 $kcal \cdot kg^{-1}$), and ΔT = internal temperature change (baseline - final).[28] Because matching exercise intensity relative to peak VO_2 results in different metabolic heat productions, we calculated the matching of metabolic heat production that would predict internal temperatures by dividing the rate of change of internal body temperature (start - end intestinal temperature/completed exercise time; Δ°C/min) and dividing that value by the their metabolic heat production at 75% peak VO_2, then multiplied that value by 150 and 250 W; example for predicting matching 150 W of exercise heat production ($[\Delta°C/min \div H_{prod}] \times 150$ W). These data estimate what the internal temperatures would have been if matched for exercise heat production.

Physiological Strain and Exercise Tolerance Indices

The physiological strain index is determined from the increase in core temperature and heart rate from baseline to some end time.[29] It is a validated measurement indicating heat strain (0–2 = no strain and 8–10 = very high strain) and is commonly used as an indicator of heat stress during exercising under thermoneutral conditions and hyperthermia (36.5–39.5°C). It can be calculated using the following formula: $5 \times ([Tint - Tint0] \times [39.5 - Tint0]^{-1}) + 5 \times ([HRt - HR0] \times [peakHR - HR0]^{-1})$, where Tint (intestinal temperature) and HRt (heart rate) are simultaneously measured during the exposure and Tint0 and HR0 are the initial measurements. The total time of completed exercise of the 30 minutes was used as an indicator of exercise tolerance. Additionally, we developed an objective index to quantify subjective responses at the end of the exercise. All subjects were asked questions on their symptoms at the end of exercise, and answers were coded (with a number) as follows: feeling hot (1), fatigue (2), nausea or dizziness (3), observed crying (4), and could not

complete the 30 minutes of exercise (5). The calculated exercise tolerance index included the summation of all symptoms. Additionally, relative heart rate during the exercise tolerance test was determined from peak heart rate values of the peak VO_2 test.

Data and Statistical Analyses

Subjects' physical and exercise characteristics were analyzed using a factorial 1-way analysis of variance that assessed differences among groups (propranolol/placebo/control). Temperatures of burned skin, unburned skin, and intestines were each analyzed separately using a repeated measures factorial analysis of variance design that assessed the interaction and main effects of group (propranolol/placebo/control) across time (minutes). For only the change (Δ) in temperature analysis (in Figure 1), because most of the burned children could not complete the 30 minutes of exercise, the full 30 minutes of temperature values were determined using the rate of change of temperature (preexercise minus end of exercise temperature divided by total time exercise; Δ°C/min). The calculated exercise tolerance index and completed exercise time were analyzed using a factorial 2-way analysis that assessed interactions and main effects for groups (propranolol/placebo/control) and environmental temperatures (34/22°C). The physiological strain and relative heart rate were also analyzed with a factorial 1-way analysis for interaction and main effects for group and time (rest to the end of exercise). Data were analyzed using SPSS Statistics (Version 23, IBM Corp., Armonk, NY), with significance set at $P < .05$. For each analysis, where appropriate, significant interactions were found, post hoc Bonferroni comparisons were made with appropriate Greenhouse-Geisser corrections for violations of sphericity. Figures were created with GraphPad Prism (6, GraphPad Software, Inc., La Jolla, CA). All data were reported as mean ± SD.

RESULTS

Subject Physical and Exercise Characteristics Matching

Subject physical and exercise characteristics are presented in Table 1. There was no difference between the placebo and propranolol group in the time of exercise testing after burn injury (4.4±2.5 months). Age and body morphology (height, weight, and BMI) was matched among the 3 groups. However, BMI-for-age percentile was lower in burned children than in the aged-matched nonburned children ($P = .04$). Burned children groups had less relative body fat than nonburned controls ($P = .008$). TBSA burn and third-degree burn were matched between placebo and propranolol groups. Children with burn injury had similar absolute peak VO_2 and at 75% submaximal exercise values. However, they had relative values that were 27.6% less than nonburned healthy controls ($P < .0001$). Additionally, peak HR values for the burned groups were attenuated by 8% compared with nonburned controls ($P < .01$). The calculated exercise heat production was likewise reduced (by 33%) during submaximal exercise ($P < .001$).

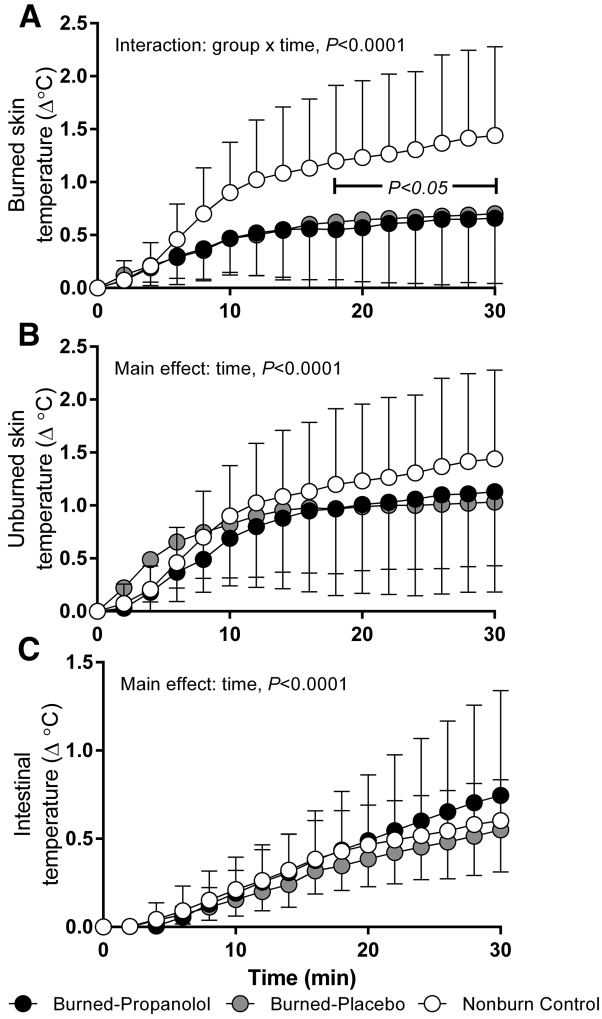

Figure 1. Effect of exercise-heat stress on skin and internal temperature (34°C) in burned children treated with propranolol (black circle, n = 10) or placebo (gray circle, n = 10) and in nonburned healthy controls (white circle, n = 12).

β-Adrenergic Blockade Does Not Alter the Thermal Response to Heat Stress Induced by Exercise at Relative Work Rates

Preexercise temperatures and heart rate under thermal neutral conditions as well as thermal responses

to exercise under hot conditions (postexercise) are found in Table 2. No differences were detected between placebo or propranolol groups in preexercise intestinal or skin temperature. Propranolol reduced resting heart rate to levels similar to those in nonburned children, while heart rate in the placebo group was elevated at rest ($P < .01$). Similarly, at the end of exercise, no differences were observed for final temperatures for each group. Final absolute heart rate was not different among groups at the end of exercise.

The change in intestinal, burned, and unburned skin temperatures over the course of 30 minutes of exercise are reported in Figure 1. Propranolol did not affect the temperature of burned skin; however, the temperature response of burned skin (placebo and propranolol) differed from that of skin from healthy nonburned children (interaction for group × time, $P < .0001$). For unburned skin, the temperature response to exercise-heat stress did not differ among the propranolol, placebo, or nonburned groups. Intestinal temperature rose in a similar fashion among groups (main effect for time, $P < .0001$).

As shown in Table 2, the rate of change for intestinal temperature was similar among groups. Heat loss similarly did not differ between groups. Additionally, at the end of exercise, heat exchange in burned skin was similar between groups, as seen by whole-body thermal conductance and tissue thermal conductance. However, tissue thermal conductance was lower in burned skin (both propranolol and placebo) than in healthy nonburned skin ($P < .001$).

β-Adrenergic Blockade Does Not Improve Exercise Tolerance Under Hot or Neutral Conditions in Burned Children

No differences in the exercise tolerance index were detected between the propranolol and placebo groups (Figure 2A). However, these burned groups had lessened exercise tolerance than the nonburned group (main effect for group, $P < .01$). Additionally, under thermal neutral conditions, burned children still had a lower exercise tolerance than nonburned children (main effect for temperature, $P < .01$). Analysis of exercise time under hot and neutral conditions revealed that burned children exercised for 30% less time under hot conditions than nonburned children (interaction for group × temperature, $P < .01$; Figure 2B).

Children With Burn Injury Exercise at Greater Relative Peak Heart Rates With Similar Physiological Strain During Exercise-Heat Stress That Are Not Altered by β-Adrenergic Blockade Compared With Nonburned Children

The physiological strain at rest and at the end of exercise was not affected by propranolol and was similar among all groups (Figure 3A; main effect for time,

Table 2. Thermal response to exercise heat stress

	Burned		Nonburned	
Response Variable	**Placebo**	**Propranolol**	**Control**	***P*-value**
Preexercise				
Intestinal temperature (°C)	37.7 ± 0.4	37.5 ± 0.5	37.4 ± 0.2	.16
Local burned skin temperature (°C)	36.0 ± 0.8	36.5 ± 0.2*	35.3 ± 1.0	**.003**
Local unburned skin temperature (°C)	36.0 ± 0.6	36.0 ± 0.8	35.3 ± 1.0	.06
Heart rate (beats/min)	109 ± 26*†	88 ± 13	82 ± 11	**.003**
End of exercise				
Intestinal temperature (°C)	38.0 ± 0.5	38.1 ± 0.5	37.9 ± 0.2	.51
Local burned skin temperature (°C)	36.7 ± 0.7	37.2 ± 1.0	36.7 ± 0.4	.28
Local unburned skin temperature (°C)	37.1 ± 0.5	37.1 ± 0.8	36.7 ± 0.4	.18
Heart rate (beats/min)	169 ± 22	166 ± 17	159 ± 17	.42
Peak heart rate (%)	97 ± 10*	96 ± 8*	85 ± 11	< **.008**
Total exercise time (min)	20.0 ± 9*	22.3 ± 9*	30.0 ± 0	< **.001**
Heat exchange at end of exercise				
Intestinal temperature rate of change (°C·min^{-1})	0.020 ± 0.010	0.025 ± 0.020	0.018 ± 0.010	.47
Heat loss (W·m^{-2})	15.6 ± 17	23.5 ± 23	22.1 ± 13	.57
Body thermal conductance (W·m^{-2})	109.5 ± 80	155.5 ± 184	92.9 ± 30	.43
Tissue conductance of burned skin (W·m^{-2})	135.5 ± 56	151.9 ± 137	196.2 ± 33	.24
Tissue conductance of unburned skin (W·m^{-2})	148.8 ± 56*	114.1 ± 41*	196.2 ± 33	< **.001**

*Statistically different from nonburned healthy controls.
†Statistically different from propranolol group.

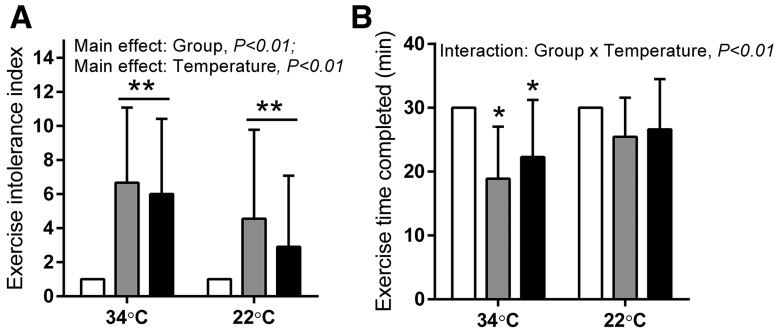

Figure 2. Calculated exercise tolerance index (A) and completed exercise time (B) under warm (34°C) and neutral (22°C) conditions in burned children treated with propranolol (black bar, n = 10) or placebo (gray bar, n = 10) and in nonburned healthy controls (white bar, n = 12). **P* < .05 and ***P* < .01 vs nonburned group.

P < .01). During preexercise resting heat stress, only the placebo group had greater relative peak heart rate than the nonburned group. At the end of exercise, relative peak heart rate was 16% greater in both the placebo and propranolol groups than in the nonburned group (*P* < .05; main effect of group; main effect of time, *P* < .0001).

When Exercise Heat Production Is Matched, Burned Children May Have Greater Heat Gain During Exercise

The estimated rate of change of internal body temperature at a fixed rate of low and moderate exercise heat production are calculated in Figure 4A and 4B, respectively. Heat gain in burned children was estimated to increase by 143% at 150 W/m^2 and 250 W/m^2 (*P* < .01 for both).

DISCUSSION

We undertook this study to test the hypothesis that propranolol does not affect skin and internal thermal responses but does contribute to exercise tolerance. The results show that burned children receiving propranolol as part of their long-term rehabilitation experience similar heat gain (intestinal temperature) as burned children receiving placebo and healthy nonburned children when exercising at a similar relative intensity in the heat. In addition, propranolol does not affect temperature changes in the healed burned skin and unburned skin. Likewise, propranolol did not affect exercise tolerance, as both placebo and propranolol groups had similar exercise tolerance indices and completed exercise times. These data suggest that, under the current testing conditions, propranolol does not cause an abnormal rise in internal temperatures or significant changes in skin temperature in burned children during exercise at relative intensities.

Previous reports on the effects of propranolol during exercise in the heat have been conflicting. Gordon et al[30] reported that nonburned adults have no significant changes in rectal or skin temperature following propranolol administration but have a significant increase in sweat rate. Similarly, Freund et al[31] reported no changes in rectal temperature and increased sweat rate but a decrease in mean skin temperature and blood flow during exercise in the heat. Crandall et al[32] reported no significant effects of propranolol on skin blood flow during whole-body passive heating. Although β-adrenergic blockade

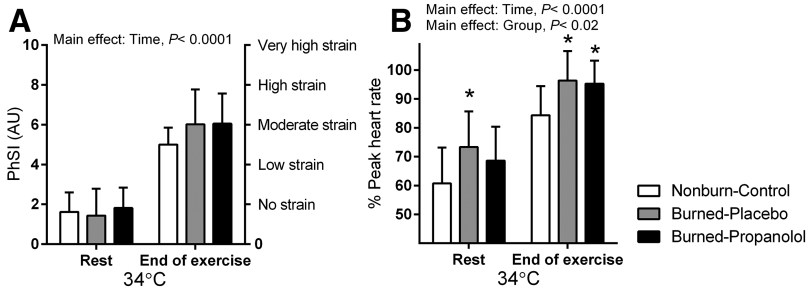

Figure 3. Calculated PhSI (A) and relative peak heart rate (B) at rest and at the end of exercise under warm (34°C) conditions in burned children treated with propranolol (black bar, n = 10) or placebo (gray bar, n = 10) and in nonburned healthy controls (white bar, n = 12). **P* < .05 vs nonburned children group. PhSI, physiological strain index.

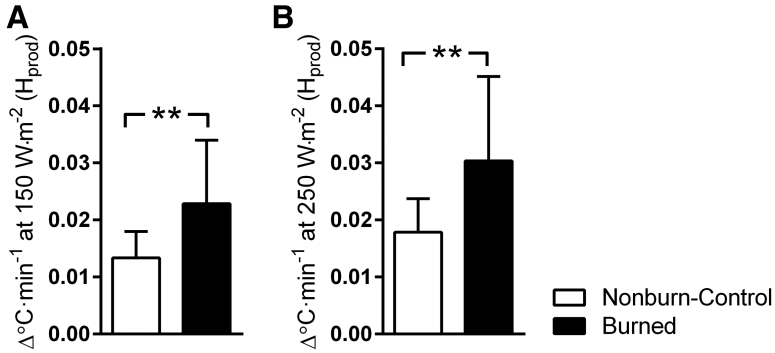

Figure 4. Estimated rate of change of internal body temperature while matching heat production at 150 $W \cdot m^{-2}$ (A) and 250 $W \cdot m^{-2}$ (B) in burned children (black bar, n = 20) and nonburned healthy controls (white bar, n = 12). $^{**}P \leq .01$.

is widely used in clinical practice, knowledge of the effects of β-blockade on the thermoregulatory response to exercise in burned children is limited. In this study, we show that propranolol does not affect thermal responses when exercising at similar relative exercise intensities. As in our previous studies, burned children were not any more likely to reach exertional hyperthermia than age- and body size-matched nonburned subjects exercising at the same relative intensity.[18,19]

We found that the rate of change for internal temperature and final postexercise internal temperatures and unburned skin temperatures did not differ between burned and nonburned healthy children. However, this was likely because, at 75% of their peak VO_2, burned children generate 33% less metabolic heat than age- and body size-matched nonburned children. When we calculated the low- and moderate-matched heat production and estimated what internal temperature would have been, we found that the rate of change of internal body temperature may increase 143% more in burned children than nonburned healthy children. This would suggest that, after 30 minutes of low-heat-producing exercise (150 W), the final body temperature would be 38.7°C for burned children and 38.3°C for nonburned children. At moderate heat-producing exercise (250 W), it would be 39.2°C in burned children and 38.6°C in nonburned children. Regardless of disparities between thermoregulation, it seems that burned children do not reach exertional hyperthermia, which is similar to our previous findings; however, children with severe burn injury display signs of exercise intolerance.[18,19]

Propranolol did not affect the temperature response of burned and unburned skin. However, because baseline values for burned skin were 1.0°C higher at rest than those of nonburned healthy children, the change appeared to be attenuated. These data are similar to our findings from previous work on skin blood flow perfusion, which showed that there are profound elevations in cutaneous blood flow perfusion in burned skin of children at rest.[23] This is likely due to inadequate core-skin insulation after burn injury and adjustments for maintaining thermal homeostasis. Notably, we have previously found that propranolol reduces skin blood flow only under hot conditions, and in this study, skin temperature for the propranolol group was significantly greater than that of nonburned healthy controls. This may suggest that when matching exercise heat production, burned children taking propranolol may have an increased risk for heat-related injury due to an increase in skin temperatures during exercise, but this requires further study as both propranolol and placebo groups had similar exercise heat production and ending internal temperatures.

Exercise-heat stress causes profound cardiovascular stress. Cardiac output increases to meet the metabolic demand of active muscles, and blood is redistributed and sent to the skin where heat produced as a result of exercise can be lost to the ambient environment. Exercise-heat stress generally causes an increase in heart rate (i.e., cardiovascular drift) and a reduction in stroke volume. In nonburned adults, β-adrenergic blockade under thermal neutral and hot conditions prevents an elevation of heart rate and stroke volume.[13,14] Propranolol is used clinically to reduce cardiac strain in burned patients[33] and is part of the standard of care at our institute. Additionally, propranolol is continued up to 1 year postdischarge, thus these important questions have clinical relevance. In this study, propranolol returned resting heart rate to levels seen in nonburned healthy children. However, we found that the placebo and propranolol groups had similar heart rate values at the end of exercise, suggesting that propranolol did not affect

final heart rate response. Additionally, peak heart rate values were not affected, as both the placebo and propranolol groups had similar values at the end of their peak VO_2 test. This suggests that propranolol beta-blocked at rest but exercise stress may have overcame the block during peak exertion. In addition, something may be different with children with severe burn injury that are in a hyperadrenergic state. These results are in agreement to previous work that found attenuated cardiac output during submaximal exercise.[16] Notably, patients with severe burn injury show similar symptoms of heart failure and coronary artery disease, such as exercise intolerance, and resting cardiac dysfunction.[34,35] In adults with coronary artery disease, Marshall et al[36] (1980) found that during exercise propranolol (160 mg/d) did not affect exercise left ventricular performance, whereas in healthy controls, it produced a negative inotropoic effect. Thus, in our children with severe burn injury, the amount of propranolol given to block at rest may have had similar negligible heart rate blocking responses at peak exercise due to cardiac dysfunction and/or reduced β-adrenergic responsiveness similar to that found in heart failure patients.[37,38] Additionally, we found that relative heart rate (expressed as percentage of peak heart rate) for the burned group was 10% greater than that for the nonburned healthy group. In fact, the prescribed 75% of peak VO_2 was near maximal for their cardiac function at the end of exercise, which may have contributed to the reduced exercise tolerance.

Beyond 5 years postburn, adults have a reduced peak VO_2 and time to fatigue compared with nonburned healthy adults[39] and published norms.[40] In addition, some have reported that burned patients have limited exercise endurance due to abnormal lung function at 2 to 3 years postburn.[41,42] We have recently found that, immediately after hospital discharge, burned children have impaired cardiovascular response to submaximal exercise[16] and exercise aerobic capacity values that are in the very poor (< 25 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)-to-poor (25–31 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$) range relative to nonburned children.[9,43] In the current study, submaximal exercise was typically terminated because a child refused to continue. Many of the children who did complete the exercise session commented on an overall feeling of being "too hot" but were able to push through and finish the test. This pattern held true for burned children regardless of whether they were administered propranolol or placebo. Because symptoms of exercise tolerance were found in burned children during exercise under both thermal neutral and hot conditions, cardiac dysfunction may play a role, though this requires further study. Both burned children and nonburned healthy controls had similar calculated physiological strain at rest and at the end of exercise-heat stress. However, burned children had a shorter exercise time than nonburned controls under hot conditions but not under thermal neutral conditions, suggesting that heat stress may exacerbate the exercise tolerance symptoms.

A limitation worth mentioning is the relatively low number of patients in our study. Further work should look at a larger cohort of burn children. Additionally, exercise intensity was matched as a relative percentage of peak VO_2, and this presents a challenge when interpreting thermal physiology data. A mechanistic approach would have been to match exercise heat production between groups. Nevertheless, this approach has strengths, given that it has real-world applicability because rehabilitation exercise is commonly prescribed as a relative percentage of peak work rate and not absolute work rate. Notably when humans are given the opportunity to choose exercise intensity, they self-pace at similar relative intensities in hyperthermic conditions.[44]

With the many long-term risk factors that are associated with burn trauma, our results demonstrate that children with burn injury can exercise in hot conditions and burn injury, though the well-being and hydration status should still be monitored during outdoor play or exercise. However, burn injury should not discourage the medical community from promoting outdoor physical activity after burn injury, as exercise is important for restoring lean body mass, exercise capacity, and quality of life.[9–12]

CONCLUSION

In summary, we have found that propranolol does not cause hyperthermia in children with burn injury exercising at similar relative intensities as nonburned counterparts. Further understanding of the cardiac dysfunction during exercise will offer insight for cardiovascular rehabilitation medicine in burned children.

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