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β -adrenergic blockade does not impair the skin blood flow sensitivity to local heating in burned and non-burned skin under neutral and hot environments in children

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Abstract

Objective—Tested the hypothesis that propranolol, a drug given to burn patients to reduce hypermetabolism/cardiac stress, may inhibit heat dissipation by changing the sensitivity of skin blood flow (SkBF) to local heating under neutral and hot conditions.

Methods—In a randomized double-blind study, a placebo was given to 8 burned children while propranolol was given to 13 burned children with similar characteristics (mean $\pm$ SD: 11.9 $\pm$ 3y, 147 $\pm$ 20cm, 45 $\pm$ 23kg, 56 $\pm$ 12% TBSA). Non-burned children (n=13, 11.4 $\pm$ 3y, 152 $\pm$ 15cm, 52 $\pm$ 13kg) served as healthy controls. A progressive local heating protocol characterized SkBF responses in burned and unburned skin and non-burned control skin under the two environmental conditions (23°C and 34°C) via laser-Doppler flowmetry.

Results—Resting SkBF was greater in burned and unburned skin compared to the non-burned control (main effect: skin, $P < 0.0001$; 57 $\pm$ 32 burned; 38 $\pm$ 36 unburned vs 9 $\pm$ 8 control %SkBF_{max}). No difference was found for maximal SkBF capacity to local heating between groups. Additionally, dose response curves for the sensitivity of SkBF to local heating were not different among burned or unburned skin, and non-burned control skin (EC₅₀, $P > 0.05$) under either condition.

Conclusion—Therapeutic propranolol does not negatively affect SkBF under neutral or hot environmental conditions and further compromise temperature regulation in burned children.

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COMPETING INTEREST

The authors have no competing financial interests to declare.

AUTHORS' CONTRIBUTIONS

S.J.M. and O.E.S. designed the study. S.J.M. performed experiments. E.R. analyzed data and drafted the manuscript. E.R., S.J.M., D.N.H., R.P.M., O.E.S., edited and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Keywords

microcirculation; skin blood flow perfusion; laser Doppler flowmetry; burn injury; pediatrics; temperature regulation

INTRODUCTION

Each year, nearly half a million Americans are affected by burn trauma, with approximately 40,000 hospitalizations and 3,400 deaths occurring annually [23]. Globally, it is estimated that 265,000 deaths occur yearly. Major advancements in the understanding of burn care over the last 50 years have led to improved survival rates, shorter hospital stays, and decreased morbidity and mortality rates [44]. These include resuscitation protocols, early intervention and wound closure, support for the hypermetabolic response, infection control, early enteral nutrition, and intensive glucose control. Burn trauma causes a profound activation of the sympathetic autonomic nervous system that induces the classic flight-or-fight response. While this mechanism is beneficial under acute stress, prolonged overactivation of the adrenergic system is thought to be detrimental to cardiac physiology and whole-body metabolism [31,41,47]. Hypermetabolic stress following burn trauma induces an immunometabolic reaction coupled with a sympathetic response that increases catecholamines and energy expenditure (20–100% above normal) [29,56] as well as heat production, most likely mediated through the browning of subcutaneous white adipose tissue [42,55]. The hypermetabolic stress response elevates cardiac stress as reported by an increase in resting cardiac output, resting heart rate, rate pressure product, and stroke volume. The β adrenergic blocker, propranolol, improves systemic burn care by blocking the action of the catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline) at both β_1 - and β_2 -adrenergic receptors. By these mechanisms, propranolol has been found to reduce resting energy expenditure and cardiac function, diminish blood loss [27,39], improve wound healing [2], and attenuate muscle wasting [14].

By blocking β_2 receptors in blood vessels, propranolol reduces skin blood flow in healthy and hypertensive adults [38] and decreases peripheral leg blood flow, while increasing vascular resistance in adult burned patients [25]. In healthy adults, the administration of propranolol during exercise under heat stress was found to decrease sweating [32] as well as forearm and maximal forearm blood flow [19,45]. Thermal homeostasis is disrupted in burn patients due to the inability of burned skin to control heat loss [4,56,57] coupled with an attenuated or absent sweat rate response post-burn in the grafted skin [13,35,54]. Thus, propranolol may further impair temperature regulation by reducing blood flow in burned and unburned skin and reducing the dissipation of heat under hot conditions. If this is the case, propranolol may increase the risk of heat-related illness in burned patients.

It is currently unknown whether propranolol affects skin blood flow during passive or exercise heat stress in burned children, which may be susceptible to hyperthermia due to a reduced capacity to temperature regulate. Therefore, our objective of this project was to determine if propranolol administration affects burned children's skin in response to local heating and hot environmental conditions. We hypothesized that propranolol therapy would

inhibit heat dissipation in burned and non-burned healthy skin by decreasing skin blood flow while in a resting state under thermal neutral and hot conditions.

MATERIALS AND METHODS

Ethical Approval

All experiments were approved by the Institutional Review Board of the University of Texas Medical Branch and were in accordance with the *Declaration of Helsinki*. A combined 34 children participated in this study. Prior to participation in the study, informed consent was obtained from parents or legal guardians, and assent was obtained from children.

Subjects

Twenty-one burned (11.9 ± 3 y, 147 ± 20 cm, 45 ± 23 kg, $56 \pm 12\%$ total body surface area [TBSA] burn) and 13 non-burned healthy children (11.4 ± 3 y, 152 ± 15 cm, 52 ± 13 kg) completed all study assessments. Subject characteristics are presented in Table 1. The race for all participants were White. The ethnic background for all were 89% Hispanic or Latino and the remaining were White, non-Hispanic. Three body mass indices were used: body mass index (BMI), BMI percentile (BMI%ile), and body surface area (BSA). BMI ($\text{kg}\cdot\text{m}^{-2}$) was calculated by weight in kilograms divided by the square of height in meters, BMI (%ile) was computed according to the normative values for children provided by the CDC [8] and BSA (m^2) was calculated according to DuBois and DuBois [15]. Subjects were matched for age, height, weight, BSA, and BMI ($P > 0.05$). Total body surface area and third-degree burn were likewise matched between placebo and propranolol groups ($P > 0.05$). However, peak aerobic exercise capacity was 32% less in burned children compared to the non-burn healthy children ($P = 0.01$). BMI percentile values were significantly less (-39%) in the burned children compared to non-burned healthy children ($P < 0.05$).

Peak aerobic exercise capacity test

Aerobic exercise capacity ($\text{VO}_{2\text{peak}}$) 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-liter syringe. Speed and angle of elevation started at 1.7 miles per hour 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. Notably, no validated, universally accepted criteria exist in children for the determination of peak VO_2 [46]. Therefore, using similar standards as adults [28], the test was deemed to be maximal once subjects signaled to stop exercise and at least three of the following met criteria: a respiratory exchange ratio (RER) of ≥ 1.05 , a leveling off in VO_2 with increasing workloads (less than $2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), volitional fatigue, exercise final heart rate of 190 bpm or greater, or a final test time between 8 to 12 min. Similar criteria have been used by others in children [46,52].

Skin blood flow perfusion

For the purpose of probe placement, skin was defined as the following: 1) burned skin as the burned, fascially excised skin of the burned child (burned skin); 2) unburned skin as the unaffected healthy skin, also from the burned child (unburned skin); and 3) non-burned skin as the healthy skin of the control healthy non-burned child (non-burned healthy control skin). Skin blood flow was determined using a laser-Doppler flowmetry probe (Perimed, Stockholm, Sweden) housed in a customized Peltier thermoelectric heat controlled plate that permitted the control of local skin temperature while simultaneously measuring skin blood flow. Burn patients' medical charts were reviewed to determine sites for probe placement on the burned, fascially excised skin and unburned skin. Skin blood flow (SkBF) perfusion was measured on the right and left forearms for all children. The dose-response protocol entailed a 2-minute steady state resting measurement that started at 36°C and progressively increased in local skin heating 1°C every two minutes up to 42°C. Each child was informed of the importance of remaining very still and not moving during testing. If the child moved during the measurement and caused a spike in perfusion, the 2-minute interval was restarted to ensure that steady state was achieved and that increases in perfusion were not the result of movement artifact. Pressure garments were not worn during the measurement of SkBF.

β-adrenergic blockade and placebo administration

Thirteen burned children received propranolol (tablet form), and 8 burned children received a placebo. Thirteen non-burned children served as healthy controls. Propranolol dosage was titrated to decrease heart rate by 20±5% by the physicians and nurses who routinely examined the patients' heart rate. Baseline heart rate during hospitalization was 131±12 bpm (range 96–120bpm). The usual dose was 2–4 mg/kg/24 hours which allowed for a target heart rate with propranolol at 106±10bpm (range 96–120bpm). The time chosen to start the examination of SkBF was at hospital discharge when burn wounds were 95% healed. Propranolol or placebo was started within 72 hours of admission to the ICU. This ranged from 28–125 days and had a mean of 73 ± 36 days. Administration of propranolol or placebo was randomly assigned.

Environmental conditions

Subjects were exposed to thermal neutral ($23\pm2^{\circ}\text{C}$ T_{db} , $43\pm4\%$ R_h) and hot ($34\pm1^{\circ}\text{C}$ T_{db} , $26\pm2\%$ R_h) ambient room conditions. A comprehensive list of environmental parameters that may have affected heat dissipation and commonly used by others were calculated [17,20,36]. Mean radiant temperature (T_r , °C) is defined as the uniform surface temperature of an imaginary black enclosure with which human exchanges the same heat by radiation as in the actual environment and calculated as $T_r(^{\circ}\text{C}) = ((1 + (0.222 \times (v_a^{0.5}))) \times (T_g - T_{db})) + T_{db}$ where v_a = air velocity ($0.5 \text{ m}\cdot\text{s}^{-1}$), T_g = black globe temperature (°C) and T_{db} = dry bulb temperature. The radiative heat transfer coefficient characterizes the transfer of thermal energy in terms of heat flow and temperature difference between two participating media and is calculated as $H_r(\text{W}\cdot\text{m}^{-2}\cdot\text{K}^{-1}) = 4 \cdot E \cdot \sigma \cdot A_r A_d ((273.2 + (T_r/2))^3)$, where E = emissivity of the skin surface (0.98), s = Stefan-Boltzmann constant ($5.67 \times 10^{-8} \text{ W}\cdot\text{m}^{-2}\cdot\text{K}^{-4}$), and $A_r A_d$ = ratio of the area of the body exposed to radiation versus the total body surface area (0.70 for seated posture). The physical properties of moist air were determined from partial

water vapor pressure in ambient air (mmHg) calculated as $P_a = (461.5 \text{ J/kg K}) \cdot T_{db}$. Relative humidity (R_h) is ratio of the water vapor pressure to the vapor pressure of saturated air at the same temperature, expressed as a percentage, and dew point (T_{dp}) was used as an index of air moisture and defined as the temperature to which air would cool. Dew point was calculated from algorithms based on Magnus's form equation [1]. No differences ($P > 0.05$) within environmental condition were observed for any parameter for each group.

General Experimental Protocol

The experiment was a randomized double-blind design, in which a placebo or propranolol was given under two environmental conditions. Burned subjects and non-burned healthy controls rested in a thermal neutral and hot environmental conditions (randomized). After instrumentation, a dose-response local heating SkBF perfusion protocol was performed in burned (healed, fascially excised burned grafted skin) and unburned ungrafted skin of burned and non-burned healthy children with measurements for all children being performed on the right and left forearms.

Data and statistical analyses

Subject characteristics were analyzed using a 3-way factorial ANOVA design that assessed the interaction and main effects of skin blood flow of skin (burn/non-burn/control) and drug (propranolol/placebo/control) across two environmental conditions (neutral/hot). The analysis used absolute perfusion arbitrary units and relative defined as a percentage to maximal SkBF at 42°C (%SkBF_{max}). We defined 100% SkBF_{max} as the absolute perfusion unit at the end of the local heating perturbation at 42°C. Incremental area under the curve was analyzed by a trapezoidal model (%SkBF × °C). Dose-response curves used absolute SkBF perfusion units for each local heating dosage (from 36°C to 42°C) and were normalized and each perfusion unit at each °C dose was log transformed for the log-dose response analysis. The EC₅₀ indicated the concentration of the local temperature dose that gave a half-maximal response. For each analysis, where appropriate significant interactions were found, *post hoc* Hom-Sidak comparisons were made with appropriate Greenhouse-Geisser corrections for violations of sphericity. The relationship between AUC and the surface area of burned and third-degree burns were analyzed using Pearson product correlation. Data were analyzed using GraphPad Prism (6, GraphPad Software, Inc., La Jolla, CA, USA) with significance set at $P < 0.05$. All data were reported as mean ± SD.

RESULTS

Propranolol affects resting absolute skin blood flow in burned skin only during hot conditions but does not affect the maximal capacity for skin blood flow perfusion under thermal neutral and hot conditions

Resting and maximal absolute values (arbitrary units, AU) for SkBF perfusion during neutral and hot conditions in the placebo and propranolol groups are shown for burned (Figure 1A, 1B) and unburned skin (Figure 1C, 1D) each of which compared to the corresponding values for non-burned healthy child's (control) skin. Under neutral conditions, resting burned skin had 84–86% higher SkBF perfusion than non-burned healthy control skin ($P < 0.001$), and this was not affected by propranolol. However, under hot conditions, burned skin in the

propranolol group had resting SkBF that was 45% lower than that in the placebo group (Interaction, propranolol $\times$ environmental temperature, $P<0.01$) and that was similar to SkBF in non-burned healthy control skin (burned: 49 ± 46 vs control: 29 ± 12 , AU, $P>0.05$). SkBF in unburned skin was not affected by propranolol (Figure 1C). During the hot conditions, SkBF perfusion in placebo and propranolol unburned skin increased to a similar degree as SkBF perfusion in non-burned healthy control skin (main effect of temperature, $P<0.001$). Maximal SkBF perfusion at a local skin temperature of 42°C in the burned (Figure 1B) and unburned skin (Figure 1D) of burned children was not affected by either propranolol or environmental condition.

The relative change in skin blood flow perfusion to the progressive local heating differs between the burned and non-burned skin under neutral and hot and conditions compared to non-burned skin

Figure 2 shows the effect of only the neutral and hot environmental conditions (only with the placebo) on SkBF responses to progressive local heating between the burned and unburned skin compared to the non-burned healthy control skin (normalized as a percentage of maximal blood flow; %SkBF_{max}) for each local temperature. Burned skin was significantly elevated (AUC; +79%, $P<0.001$) above non-burned controls during neutral conditions (interaction, skin $\times$ temperature, $P<0.0001$). Under the hot condition, the burned skin was significantly increased to a greater extent than unburned skin and non-burned healthy control skin (AUC; +33%, $P<0.05$).

Propranolol does not affect blood flow perfusion in burned and unburned skin under neutral and hot conditions

Figure 3 represents the effect of propranolol on %SkBF_{max} response to the progressive local heating in burned (Figure 3A) and unburned skin (Figure 3B) that were each compared to non-burned healthy children skin (control). Burned skin %SkBF_{max} were similar between placebo and propranolol for each local temperature during neutral and hot conditions (Figure 3A). However, AUC for the burned skin was +43% greater than non-burned control skin ($P<0.001$) under neutral conditions. AUC between placebo and propranolol was different (AUC +25%, $P<0.01$) during the hot conditions. However, these seem to have been influenced by the initial resting SkBF values that propranolol affected (see Figure 1). Propranolol or environmental condition did not affect the unburned skin and shows similar relative dose-responses compared to control non-burned healthy children skin (Figure 3B; AUC, $P>0.05$).

Sensitivity to local heating is similar among burned and unburned skin of burned children and non-burned control skin

Dose-response analysis showed that the sensitivity of SkBF to local heating did not differ between either unburned (Figure 4A) or burned skin (Figure 4B) and non-burned healthy control skin under thermal neutral and hot conditions. Additionally, the local heating dosage that elicited the half-maximal response (EC₅₀) was not different for each comparison. These data differ from the previous analysis due to the normalization of baseline and maximal SkBF perfusion units.

Absolute body surface area of third-degree total burns strongly correlates with the local heating dose-response

The relationship between body surface area burned and the AUC for the SkBF dose-response to local heating for the placebo group under neutral conditions is shown in Figure 5. In burned skin, the greater burned body surface area was associated with a lower perfusion response to progressive local heating and when the third-degree burn was used, the correlations improved with a reduced variability. No correlations were found for the BSA of unburned skin and perfusion response.

DISCUSSION

The aim of this study was to test the hypothesis that the blood flow response to local heating in burned and unburned skin of burned children is altered under and neutral and hot conditions when propranolol is administered. Contrary to our hypothesis, these results suggest that propranolol therapy does not affect the maximal capacity of skin blood flow or the sensitivity to local heating under thermal neutral or warm environments. However, we did observe that propranolol reduced resting absolute and relative SkBF perfusion under hot conditions in burned skin. Independent of resting differences, the sensitivity of the skin to increase perfusion to local heating did not differ between burned or unburned burned children's skin and non-burned healthy control skin. Additionally, to our knowledge, these data show for the first time in burned children that the resting burned and unburned SkBF perfusion are profoundly increased compared to non-burned healthy control skin; likely in response to the severity of the burn and hypermetabolic response.

Body temperature is determined by a complex balance between heat production and heat loss. The noradrenergic vasoconstrictor system and sympathetic active vasodilator system are under sympathetic neural control, which regulates heat exchange with the environment. During exercise and passive heat stress, 80% to 90% of the sympathetic vasodilator system controls cutaneous circulation and sweating to assist in the transfer of internal body heat to the skin and the environment [9,24,51]. However, adjustments for maintaining thermal homeostasis after burn injury may differ than non-burned healthy population due to the inadequate core-skin insulation. For example, it has been reported that burn patients have a shifted upward internal body temperature set-point that is mediated by sympathetic and catecholamine activity, which stimulate heat production and substrate mobilization. The shifted internal body temperature set-point is maintained in spite of the damaged skin's poor ability to regulate internal body temperature through an increase in energy expenditure. Under cool conditions, depending on degree burned, heat dissipation increases due to the removal of the epidermis, dermis, and subcutaneous tissue, prompting an increase in energy expenditure. In this context, metabolic rates and catecholamines are found to be reduced in warm conditions (32–35°C) when ambient temperature matches internal body temperature (minimizing heat exchange) while being elevated in neutral cool environments (22°C; increasing the gradient heat exchange) [4,30,56,57]. Our finding related to resting skin blood flow are in agreement with this as we found that in a neutral environment, skin blood flow in both burned and unburned skin are significantly elevated by 40–60% of maximal capacity compared to non-burned healthy children skin, which is at about 10% SkBF_{max} (Figure 1).

Thus, the profound increase in SkBF in burned children compared to non-burned healthy children (control) may be due to the continuous dissipation of heat from the burned skin in conjunction with the hypermetabolic response. However, it is hard to precisely explain this as the higher SkBF response from the damaged skin may be initiating the hypermetabolic response that may ultimately be defending core body temperature. This concept is currently not well defined and has not been studied mechanistically in burn patients. Interestingly, these elevated values are similar to those seen after passive heating (increase 1°C above baseline) in non-burned healthy adults utilizing single and integrative laser Doppler and laser Doppler imaging methods (~60%SkBF_{max}) [6]. In our study groups, under hot conditions, resting and maximal SkBF was increased in the unburned skin (figure 1C, 1D) to a similar extent and control non-burned healthy children (main effects for condition, $P = 0.02$). Notably, under hot conditions, when propranolol was administered, resting blood flow perfusion in burned skin was attenuated compared to placebo. However, no differences were found with placebo burned skin (Figure 1A), and we can only speculate that adrenergic blockade in combination with increased ambient temperatures (passive whole body heating) affected local receptors on vessels near the burned skin. Burn patients exhibit systemic β -adrenergic desensitization [37] and it has been reported that keratinocytes and immune cells control blood flow in an extensive countercurrent loop system of the damaged skin [10]. In addition, β -adrenergic blockers improve wound healing through keratinocytes that synthesize endogenous epinephrine [48,49].

Davis et al. (2007) report that in adults with burn injuries, cutaneous vasodilation and sweating in response to heat stress is severely impaired in well-healed grafted skin compared to adjacent undamaged skin [12,13]. We found similar responses in children during a progressive local heating perturbation (Figure 2, AUC; +79% greater than unburned skin). It has been suggested that grafted skin does not have functional sweat glands and that, compared to nongrafted skin, has impaired endothelial-dependent cutaneous vasodilator responses to an endothelial-dependent vasodilator (acetylcholine) and an endothelial-independent nitric oxide donor (sodium nitroprusside) during local microdialysis administration [12] and during whole-body heating [13]. However, because we found no differences between the burned and unburned skin in their maximal capacity to perfuse blood in response to local heating, it is likely that the increase in skin blood flow occurred through direct, local heating-induced vasodilation via local sensory nerves and not through endothelial-dependent mechanisms.

During the progressive local heating protocol, we found that propranolol did not affect the relative skin blood flow response to each increase in local temperature in the unburned skin under thermal neutral or hot conditions. Unburned skin responded the same as control non-burned healthy control skin (Figure 3B). Crandall et al. (1997) reported that during skin microdialysis infusion propranolol inhibits skin blood flow but does not contribute to vasodilation in response to whole-body heating in healthy adults [11]. Additionally, Wilson et al. (2002) reported that α -adrenergic receptors become desensitized during whole-body heating in healthy adults [58]. Burned skin in the propranolol group did not differ during thermal neutral and local heating; however, AUC under hot conditions was significantly attenuated during progressive local heating perturbations. However, this difference may have been due to the initial reduction seen with propranolol under resting conditions prior to local

heating. Further support for propranolol not affecting SkBF were the dose-response analysis with normalized baseline and maximal values (Figure 4) which showed no difference in EC_{50} among burned or unburned, and non-burned control skin. These data suggest that the sensitivity of the SkBF response to progressive local heating is similar among burned, unburned, and non-burned healthy control skin.

The major differences were seen during rest. While the data had high variability, this may be due to the severity of burn injury in the children. We found that the AUC (%SkBF_{max} to local heating) was strongly correlated with the absolute BSA burned. When the surface of third-degree burns was used, the relationship strengthened and variation was minimized (Figure 4). For example, one subject with a BSA of 1.04 m⁻² third-degree burn had a 363 AUC %SkBF_{max} response, while another with a 0.22 m⁻² third-degree burn had a 722 AUC %SkBF_{max} response. This shows that, because baseline SkBF perfusion is closer to maximal capacity in those with greater absolute third-degree burns, the response to local heating is limited due to their baseline upward shift. No correlations were found between BSA of unburned skin and the perfusion response, suggesting that the hypermetabolic response to the severity of burns is associated with skin blood flow perfusion at rest. Additionally, when we analyzed the relative percentage of BSA and AUC %SkBF_{max} responses, no significant correlations were found. This is in agreement with others' work showing a strong relationship between the hypermetabolic response to burn injury and increased heat loss at rest [4,7,18,56,57]. Our data on the correlative relationship between skin blood flow AUC and surface with third-degree burn may be clinically useful for characterizing the severity of the hypermetabolic response in burn patients, though this warrants further study. Notably, Henane et al. (1981) reported a strong relationship between metabolism and total heat loss (E, Evaporative + R, Radiation + C, Convection) using partitioned calorimetry parameters. Additionally, it was reported that R + C accounted for 60–80% of the increased metabolic heat production in burn patients [5,26].

Several studies have reported that when propranolol is given to healthy adults during exercise under heat stress, there are decreases in sweating [32], resting and maximal forearm blood flow [11,19,45] and resting metabolic rate [3,40]. However, Crandall et al (1997) found that in healthy adults, propranolol given during whole-body heating did not affect SkBF. We cannot confirm that propranolol does not affect healthy children similarly from our study and due to an ethical limitation, we did not give propranolol to the cohort of non-burned healthy children (control).

In conclusion, the results of this study demonstrated that therapeutic propranolol does not negatively affect skin blood flow in response to progressive local heating under thermal neutral or warm environmental conditions, which can further compromise temperature regulation in burned children. Thus, propranolol administration in our group of burned children is likely safe in regards to not affecting skin blood flow perfusion under hot conditions. Propranolol in combination with ambient whole-body heating did reduce local skin blood flow during resting conditions in burned skin. However, this may be viewed as beneficial if the hypermetabolic strain was reduced. Additionally, mechanisms underlying skin blood flow, sweat rate, and the responses to more stringent environmental conditions require further investigation to fully determine the capacities of burned and unburned skin.

In addition, the skin's ability to regulate temperature under rest and exercise, and interactions with drugs during heat stress in children require further study. Importantly, changes in blood pressure, which propranolol may have affected, would have altered vascular conductance, and this requires further understanding.

PERSPECTIVE

While others have furthered the understanding of temperature regulation in burned adults during passive heating [12,13,18,26,54,57,58] and exercise heat stress [21,22,43,53,54], none have studied heat exchange at rest in burned children and only a few (work from our laboratory, [33,34]) have investigated exercise heat stress in burned children. To our knowledge, this is the first study characterizing skin blood flow responses to local heating in burned and non-burned children. Prepubescent non-burned healthy children do not sweat as much as adults during heat stress. In addition, morphologic differences coupled with their rapid growth and development during puberty, which alters hormones and metabolism [16,50], may result in temperature regulation and heat exchange during rest and exercise that is different from what is seen in adult burns, and this requires further understanding. From a clinical perspective, understanding these mechanisms that are influenced by BSA burned, initial heat production at rest and during exercise, and environmental conditions, in conjunction with drugs that improve the hypermetabolic state, can have important safety implications for rehabilitation exercise medicine in burned children.

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Abbreviations used

AUC	Area under the curve
BMI	Body mass index
BMI%ile	Body mass index percentile
D_{pt}	Dew point
EC₅₀	Concentration that gave a half-maximal response
H_r	Radiative heat transfer coefficient
P_a	Partial water vapor pressure in ambient air
R_h	Relative humidity

SkBF	Skin blood flow perfusion
%SkBF_{max}	Percentage of maximal skin blood flow perfusion
TBSA	Total body surface area burned
T_{db}	Dry bulb temperature
T_r	Mean radiant temperature
VO_{2peak}	Peak oxygen uptake

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Figure 1.

Absolute resting (A, C) and maximal (B, D) skin blood flow perfusion (SkBF, arbitrary units) of burned (A, B) and unburned (C, D) skin of burned children under thermal neutral and hot conditions with placebo (white circle), propranolol (black circle) and compared to non-burned healthy children (control, black/white box). All data presented as $\pm$ SD. Burned placebo $n=8$, burned propranolol $n=13$, non-burned controls $n=13$. *, indicates significantly different compared to control non-burned children; +, indicates significant difference compared to neutral condition. Dashed line indicates control means.

Figure 2.

Comparison of skin blood flow (as a percentage of maximal skin blood flow, %SkBF_{max}) responses between burned (black circle/bar) and unburned skin (white circle/bar) of burned children and non-burned healthy children (control: black/white box/diagonal bar) skin during the progressive local skin heating under thermal neutral (A) and hot (B) environmental conditions with placebo. The associated area under the curve are located to the right of each. All data presented as $\pm$ SD. *, indicates significantly different than control non-burned healthy children in the dosage/%SkBF graphs; +, indicates significantly different than unburned skin. Burned and unburned placebo $n = 8$, non-burned controls $n = 13$.

Figure 3.

Comparison of skin blood flow (as a percentage of maximal skin blood flow, %SkBF_{max}) responses for burned (A) and unburned skin (B) of burned children during the progressive local skin heating under for placebo (white circle/bar) and propranolol (black circle/bar) under neutral and hot conditions. Each were compared to non-burn healthy children's skin (control: black/white box, diagonal bars). The area under the curves for the dose response of progressive local skin temperature on skin blood are located below of each. All data presented as $\pm$ SD. Burned placebo n = 8, burned propranolol n = 13, non-burned healthy controls n = 13. * indicates significantly different than control non-burned children in the dosage/%SkBF graphs.

A Unburned skin compared to nonburned children skin

B Burned skin compared to nonburned children skin

Figure 4.

The dose-response curves on the sensitivity of progressive local heating on changes on skin blood flow perfusion in unburned skin (A) and burned skin (B) under thermal neutral and hot conditions with placebo (white circle) or propranolol (black circle) compared to non-burned healthy children (controls, white box) under similar environmental conditions. Dotted line indicates the half maximal response to the dose effect observed (EC_{50}). Burned placebo $n = 8$, burned propranolol $n = 13$, non-burned controls $n = 13$.

Figure 5.

The relationship between the area under the curve progressive SkBF dose-response and absolute body surface area of burned (black circle), 3rd degree burned (grey circle), and unburned (black star) during the placebo administration (n=8) under a thermal neutral environmental condition. Dotted lines indicate 95% confidence band.

Table 1Subject characteristics (mean $\pm$ SD).

	Burned		Non-burned
	Placebo	Propranolol	Control
Number of subjects (male/female)	8 (7/1)	13 (12 /1)	13 (9/4)
Age (y)	11.5 $\pm$ 4	12.2 $\pm$ 3	11.4 $\pm$ 3
Height (cm)	144.4 $\pm$ 19	147.0 $\pm$ 15	152 $\pm$ 15
Weight (kg)	42.5 $\pm$ 27	41.9 $\pm$ 15	52 $\pm$ 13
BSA (m ⁻²)	1.3 $\pm$ 0.4	1.3 $\pm$ 0.3	1.5 $\pm$ 0.3
BMI (kg·m ⁻²)	19.1 $\pm$ 7	18.8 $\pm$ 3	22.4 $\pm$ 4
BMI (%tile)	*44.0 $\pm$ 34	*48.6 $\pm$ 32	76.2 $\pm$ 30
TBSA burn (%)	57.1 $\pm$ 12	65.6 $\pm$ 12	-
TBSA 3 rd -degree burn (%)	47.3 $\pm$ 18	55.3 $\pm$ 18	-
VO ₂ peak (mLO ₂ ·kg·min ⁻¹)	*24.3 $\pm$ 18	*22.0 $\pm$ 7	34.1 $\pm$ 9

BSA, Body surface area; BMI, body mass index; BMI %ile, body mass index percentile for age; TBSA, percent total body surface area burn.

* Statistically different from non-burned healthy control ($P < 0.05$).

Table 2

Ambient environmental conditions.

	Environmental			Neutral			Hot		
	Temperature			Burned			Burned		
	Main effects	Placebo	Propranolol	Non-burned	Control	Non-burned	Placebo	Propranolol	Control
T_{db} (°C)	*	*22.4±1.3	*22.4±1.8	*23.7±1.9			34.6±2.0	33.8±0.9	34.5±0.7
T_r (°C)	*	*31.2±0.2	*31.2±0.3	*31.0±0.3			29.3±0.3	29.4. ±0.1	29.3±0.1
H_r (W·m ⁻² ·K)	*	*6.04±0.01	*6.04±0.01	*6.03±0.01			5.95±0.02	5.96±0.01	5.95±0.01
P_a (mmHg)	*	*12.3±0.4	*12.9±2.2	*13.3±1.4			10.7±0.7	10.5±0.6	10.9±0.6
R_h (%)	*	*41.4±1.4	*43.2±7.4	*44.3±4.4			25.4±2.1	26.1±2.0	26.0±1.4
D_{pt} (°C)	*	*8.6±1.2	*9.0±3.8	*10.8±2.1			11.9±1.1	11.6±0.8	12.2±0.9

T_{db} , dry bulb temperature; T_r , mean radiant temperature; H_r , radiative heat transfer coefficient; P_a , partial water vapor pressure in ambient air; R_h , relative humidity; D_{pt} , dew point.

*, indicated main effect for condition, $P<0.0001$. No differences were found between placebo, propranolol, and control within each thermal neutral or hot condition, $P \geq 0.47$.

*, Indicates statistically different from hot condition ($P \leq 0.01$).