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CHANGES IN CARDIAC PHYSIOLOGY AFTER SEVERE BURN INJURY

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Abstract

Objective—Cardiac stress, mediated by increased catecholamines, is the hallmark of severe burn injury typified by marked tachycardia, increased myocardial oxygen consumption, and increased cardiac output. It remains one of the main determinants of survival in large burns. It is currently unknown for how long cardiac stress persists after a severe injury. Therefore, the aim of this study was to determine the extent and duration of cardiac stress after a severe burn. To determine persistence of cardiac alteration we determined cardiac parameters of all surviving patients with burns ≥ 40% total body surface area (TBSA) from 1998 to 2008.

Methods—One-hundred ninety-four patients were included in this study. Heart Rate (HR), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), cardiac index (CI), and ejection fractions (EF) were measured at regular intervals from admission up to two years after injury. Rate pressure product (RPP) was calculated as a correlate of myocardial oxygen consumption. All values were compared to normal non-burned children to validate our findings. Statistical analysis was performed using log transformed ANOVA with Bonferroni correction, and Student's t-test where applicable.

Results—Heart rate, cardiac output, cardiac index and RPP remained significantly elevated in burned children for up to two years when compared to normal ranges ($p<0.05$) indicating vastly increased cardiac stress. Ejection fraction was within normal limits for two years.

Conclusions—Cardiac stress persists for at least 2 years post burn and we suggest that attenuation of these detrimental responses may improve long-term morbidity.

Keywords

catecholamines; cardiac output; hemodynamics; heart rate

INTRODUCTION

Severe thermal injury, which is defined as burns greater than or equal to over 40% of total body surface area (TBSA), is complicated by a profound hypermetabolic response directly proportional to the size of the original injury.[1] Poorer outcomes from severe burn injury are associated with increased mortality rates, increased rates of infections, and cardiac dysfunction.[2-4] Cardiac stress is the hallmark of the acute phase response after severe burn injury and the severity of which determines post-burn outcomes. Cardiac stress is

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propagated by the 10- to 20-fold surge of plasma catecholamines – the mediator of the post-burn hypermetabolic response.[2, 5, 6]

The initial response to severe burn injury or early shock state is characterized by a decrease in cardiac output and metabolic rate.[7] The reduction in cardiac output is partially due to hypovolemia and reduced venous return.[8, 9] The initial phase involves both right and left heart failure and depression in contractility, thought to be mediated by circulating vasoconstrictors.[10, 11] The upregulation of catecholamines and other catabolic agents, such as glucagon, and cortisol, induce a hyperdynamic cardiovascular response, and increased oxygen consumption.[12] This is further confounded by massive volume loss post burn. Both hypovolemic shock and major tissue trauma which typify severe burn injury lead to marked tachycardia, increased myocardial oxygen demand, and decreased contractility.[13] This response is unparalleled to any other forms of injury. While derangements in pulmonary and systemic physiology are known and well described in the literature[12], the full extent and duration of these derangements has not been fully evaluated. While during the acute hospitalization, cardiac stress may lead to increases in mortality[14, 15]; a prolonged derangement can lead to an increase in morbidity in pediatric burn patients. Thus, the aim of this study was to investigate the extent and duration of cardiac stress after severe burn injury.

METHODS

Patients

One-hundred ninety-four patients that suffered burns ≥ 40% TBSA, that received no experimental anabolic drugs or beta-blocking agents during the acute hospitalization or long term were studied up to two years post-burn. In addition, none of these patients received more than ten days of any inotropic agents. Inclusion criteria included all patients who had consented to an Institutional Review Board (IRB)-approved experimental protocol between 1998 and 2007 and were admitted to our burn unit at the Shriners Burn Institute of Galveston, Texas. All patients were reported to be healthy without heart or respiratory disease before injury. All required at least one surgical intervention to be included in this study. After the patient or the patient's parents consented to the study, patients were randomized to receive standard of care (control). The patients randomized to control during the acute intensive care unit (ICU) or long term did not receive any research medications during their ICU hospitalization or once discharged, respectively.

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 was 1500 kcal/m^2 body surface + 1500 kcal/m^2 area as previously published.[16] The nutritional route of choice in our patient population was enteral nutrition. Therefore, almost all patients received nutrition via a duodenal (Dobhoff) or nasogastric tube.

Patient demographics (age, date of burn and admission, sex, burn size and depth of burn) and concomitant injuries, such as inhalation injury, morbidity, and mortality were recorded.

Cardiac Function

Resting heart rate (HR), and mean arterial pressure (MAP) were measured continuously throughout acute hospitalization by continuous cardiac monitoring in the ICU, and at various intervals after discharge (6 months, 9 months, 12 months, 18 months, and 24 months post-

burn). Daily averages were calculated and the means compared to accepted nomograms for normal, non-burned children.[17,18] Heart rate was presented as percent of normal values in order to compare the heart rate for all ages in all patients.

M-Mode echocardiograms were used to determine resting cardiac output (CO), cardiac index (CI), stroke volume (SV), and left ventricular ejection fraction (EF). None of the patients suffered from other concomitant diseases affecting cardiac function, such as diabetes mellitus, coronary artery disease, hypertension, or hyperthyroidism. Cardiac output was adjusted for body surface area (BSA) and expressed as an index. All cardiac ultrasound measurements were made with the Sonosite Titan echocardiogram, with a 3.5 MHz transducer. Three measurements were performed and averaged for data analysis and recordings were performed with the subjects in a supine position and breathing freely according to the American Society of Echocardiography recommendations.[2,13,14] Cardiac output, stroke volume, and heart rate were normalized for age by comparing to non-burned children, age-matched children in published nomograms and expressed as percent of normal values.[17,18] CO, SV, and CI were measured weekly during the acute hospitalization and at various intervals after discharge (6 months, 9 months, 12 months, 18 months, and 24 months post-burn).

Calculations

Rate pressure products (RPP) are an estimate of the energy expenditure of the heart and correlate with myocardial oxygen consumption. RPP results were compared to previously published data[19-23] and are calculated by:

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

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

$$\mathrm{SV} \times \mathrm{MAP} \times \mathrm{HR}\ (\text{milliliters per min} \times \mathrm{mmHg} \times \mathrm{bpm})$$

Both RPP and CW were measured at regular weekly intervals during the acute hospitalization and at various intervals after discharge (6 months, 9 months, 12 months, 18 months, and 24 months post-burn).

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 had to sign a written informed consent form. Data are expressed as percentage, means ± SD or SEM, where appropriate. Statistical analysis was performed by Student's t-test, or log transformed ANOVA followed by Bonferroni correction. Significance was accepted at $p<0.05$.

RESULTS

Demographics

One-hundred ninety-four patients, severely burned children with burns, encompassing over 40% of their TBSA were included in the present study. Burn patients were on average 8 ± 5 (standard deviation) years of age, 40% were females and 60% were males. Patients suffered from a severe burn injury encompassing 60% TBSA, and third-degree burns of over 47%

TBSA. Twenty-one non-burned volunteers were 14 ± 3 (standard deviation) years of age, 33% were females and 67% were males. There was no significant difference in age between the two groups.

Heart Rate

Heart rate was profoundly elevated post-burn (Figure 1). The average heart rate on admission was 170 ± 4% of normal values and peaked by week four at 181 ± 7% (Figure 1). By discharge, average heart rate decreased to 155 ± 3% of normal values. While heart rate decreased over time, it was still 125 ± 5% of normal values two years post-burn (Figure 1). Healthy, non-burned volunteers had an average heart rate of 99 ± 4% of normal when compared to published nomograms. Compared to these normal, non-burned children, the heart rate of burned children was significantly elevated for two years post-burn ($p<0.001$).

Cardiac Output

Cardiac output was elevated throughout the study period (Figure 2). During the acute hospitalization, cardiac output was 157 ± 7% of normal values on admission and decreased minimally to 144 ± 5% of normal values by discharge (Figure 2). Cardiac output decreased to 130-140% of normal values only after two years post-burn (Figure 2). Healthy, non-burned volunteers had an average cardiac output of 93 ± 9% of normal value when compared to published nomograms. Compared to these normal, non-burned children, cardiac output of burned children was significantly elevated for two years post-burn ($p<0.04$).

Cardiac Index

Cardiac output was adjusted for BSA and expressed as an index. Cardiac index was elevated throughout the study period (Figure 3). Cardiac index approached 6 L/min/m^2 BSA during the acute hospitalization (Figure 3). Cardiac index decreased to 5 L/min/m^2 BSA after discharge and remained stable until two years after the initial insult. The normal range in the literature for children is about 3.0-4.5 L/min/m^2 BSA.[17,18] Healthy, non-burned volunteers had an average cardiac index of 3.1 ± 0.5 L/min/m^2 BSA. Compared to normal, non-burned children, cardiac index was significantly elevated throughout the study period ($p<0.03$).

Stroke Volume (not pictured)

During the acute hospitalization, SV was less than 100% of normal values. It increased to 110% of predicted compared to age-matched non-burned children by one year after discharge until to two years post-burn. Compared to normal, non-burned children, stroke volume was not significantly different.

Mean Arterial Pressure (not pictured)

The MAP for these children did not significantly change over time. MAP remained around 80 mmHg from admission to two years post-burn. Compared to normal, non-burned children, these mean arterial pressures were not significantly different.

Rate Pressures Product

Myocardial oxygen consumption was significantly elevated for two years post-burn (Figure 4). Rate pressure product was significantly higher than normal values throughout the study period compared to accepted published values (Figure 4).[23] After discharge, and up to two years post-burn these values decreased significantly ($p<0.001$) but were still significantly higher than normal, non-burned volunteers ($p<0.001$) (Figure 4).

Cardiac Work (not pictured)

Cardiac work was elevated until two years after injury.

Ejection Fraction

Ejection fraction was preserved throughout the study period (Figure 5). The average ejection fraction on admission was 69 ± 2%. By week 4, average ejection fraction decreased to 61 ± 7%, but still indicating preserved cardiac function. The normal range in the literature for children is ≥50%.[17, 18] Healthy, non-burned volunteers had an average ejection fraction of 57 ± 5%. While ejection fraction was significantly elevated compared to the non-burned volunteers during the first two weeks of hospitalization ($p<0.05$), all values are within normal limits.

DISCUSSION

Severe burn injury is complicated by a surge of plasma catecholamines that mediate the profound hypermetabolic response suffered by severely burned patients. The elevated levels of plasma catecholamines instigate cardiac stress post-burn. Plasma catecholamine levels are elevated months to years post-burn, but the derangements in cardiac physiology last up to at least two-years after injury.[2, 5, 24] The affects of a sustained release of large amounts of circulating catecholamines may be detrimental to the myocardium.[25] The trauma alone requires increased oxygen delivery and tissue perfusion due to increased metabolic needs.[25] This leads to an upregulation of the sympathetic nervous system.[25, 26] When these needs are not met, shock ensues. Increased catecholamines increase myocardial oxygen delivery, myocardial oxygen consumption and cause focal degeneration of the myocardium, and hypertrophy. In excess, they cause cardiac deficiency, local myocardial hypoxia, and cardiac death.[27] Thus, prolonged exposure to catecholamine levels 10-fold higher than normal is cause for clinical concern. They have been implicated in cardiomyopathies, myocarditis, pathological myocardial lesions and necrosis after prolonged exposure.[28, 29]

The average daily heart rate was elevated in our patients up to two years post burn. Heart rate was elevated despite any afforded resuscitative efforts. While our data are up to two years post injury, heart rate of severely burned children was still 120% of predicted compared to normal values for children. This demonstrates tremendous work done by the heart up to two years after the initial insult, compromising the heart's ability to delivery oxygen efficiently.[30] The optimal cardiac index, output and other parameters have not been determined for our patient population to adequately and appropriately provide the metabolic needs for these patients. Thus, supraphysiologic values may be necessary.[31] The increased need for oxygen delivery required by the burn injury requires an increase in either cardiac output or arterial oxygen content. When the arterial oxygen content is optimized, cardiac output must then be increased to increase oxygen delivery. This increase in cardiac output is partially mediated by the increase in both heart rate and contractility[30] – mediated by circulating catecholamines.[5] While this can lead to increased morbidity and possibly mortality long term for severely burned pediatric patients, it is currently unknown if and or how extensive damage may become.

However, despite how elevated the cardiac response is for two years, it appears to be a blunted response when compared to normal sympathetic stimulation seen in normal healthy patients with catecholamine levels 10-fold higher than normal.[5] This could be due to derangements in the regulation and coupling of beta-adrenergic receptors post burn or physiologic derangements in the autonomic nervous system in response to this major trauma.[25, 30] In fact, patients had preserved ejection fraction throughout the study period indicating preserved cardiac function. In addition, we did not see the initial decrease in

cardiac output seen in early shock in our patients, even with patients admitted day of burn. This could be due to the fact that most of our patients are admitted after some resuscitative efforts have been initiated at outside facilities.

Despite continued elevated heart rate, stroke volume increased up two years after initial injury. This explains the sustained increased cardiac output as there was no decrease in SV to compensate over time for the increased heart rate. This could all represent a sign of chronic cardiac stress, as there is a prolonged increase in circulating catecholamines but decreased sensitivity to these signals and a derangement in physiologic response.[32] High levels of catecholamines with suboptimal responses have been documented and implicated in patients with chronic cardiac failure and decreased cardiac reserve.[32] While we have not shown chronic cardiac failure in our patient population, the data demonstrate chronic cardiac stress. Correlates of myocardial oxygen consumption, RPP, remained elevated for two years post-burn. There was a significant decrease nine months after the initial injury, however, this correlate was still elevated above normal published values. One limitation of our study is that there are no documented normal values for our mostly Hispanic population for RPP. Based on published values from Gillum[23], we took one of the highest recorded ranges for normal children of different ethnicities, and still our patients far exceed those values.

The long-term ramifications of the cardiac stress seen post burn is still unknown. Initially, it was thought that these derangements would subside shortly after the acute hospitalization or the initial resuscitation. More recent research has shown that these responses may last months after the initial insult.[33-35] We demonstrated here, a significant increase in cardiac work up to two years after the initial injury. This may be to a detriment to our pediatric burn patients by increasing cardiovascular complications in the future. Our group has now embarked on a study looking at metabolism, growth, and cardiac function up to ten years after injury to investigate long term affects of severe thermal injury. There is evidence that patients with heart failure with preserved ejection fractions have similar mortality risks and complications as those with depressed ejection fractions.[36] These findings support the use of an anti-catabolic agent to attenuate the effects of increased catecholamines, beta-adrenergic regulation, and the need for cardiovascular protection.

Our group has ongoing studies with the use of propranolol, a non-selective beta-receptor antagonist post-burn. We have shown significant improvements in hypermetabolism, the post-burn inflammatory response and cardiac stress. [25, 37, 38]

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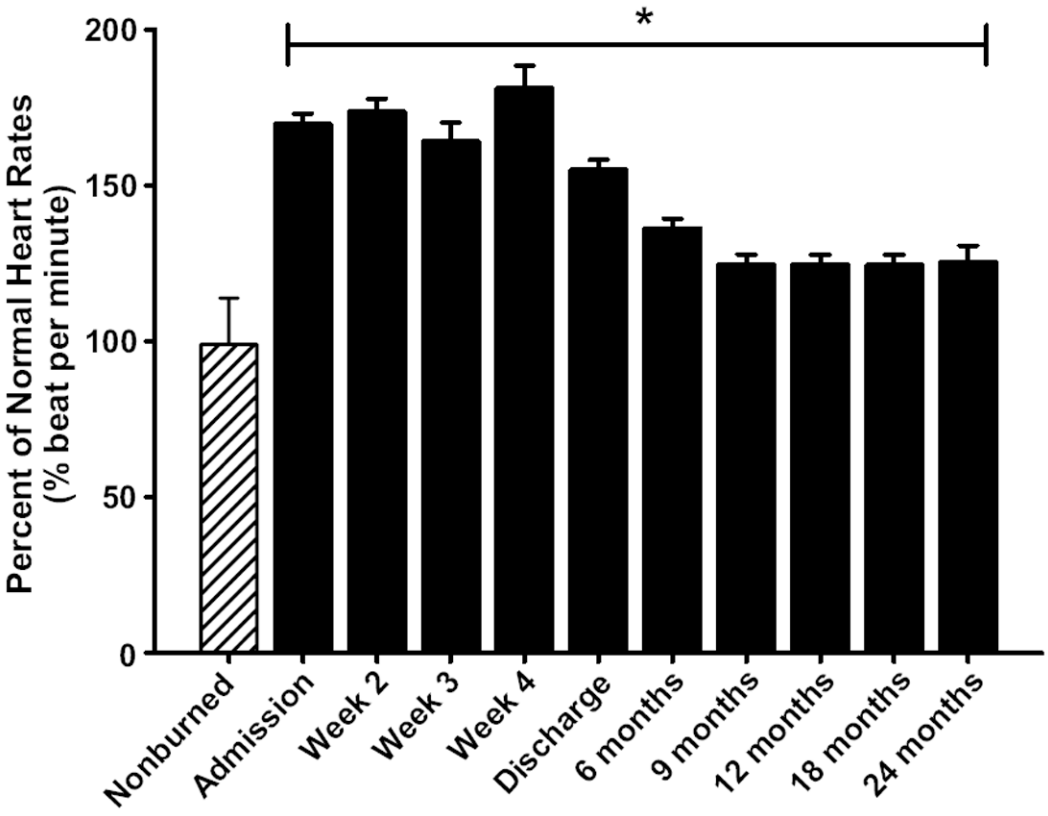

Figure 1.

Average heart rate for pediatric burn patients compared to non-burned volunteers, normalized for age by comparing to published nomograms.[17, 18] Heart rates are significantly higher than normal for two years post-burn. Data is plotted as average ± standard error of the mean (SEM). * Denotes statistical significance of $p<0.05$.

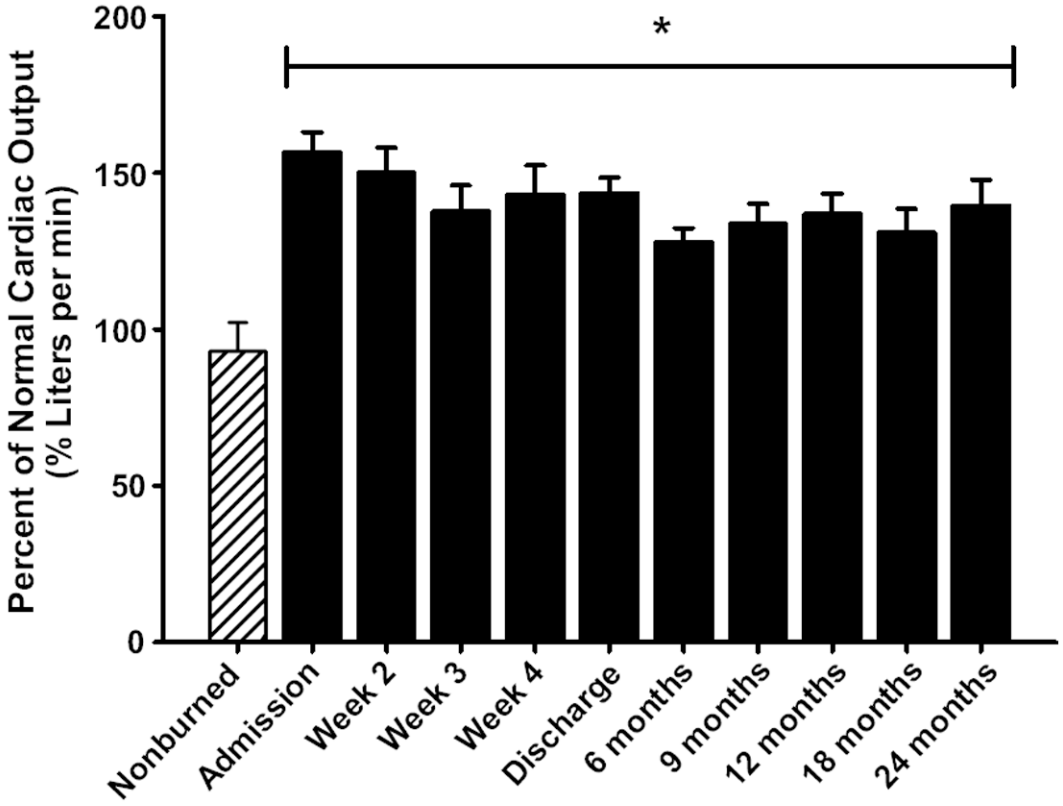

Figure 2.

Average cardiac output for pediatric burn patients compared to non-burned volunteers, normalized for age by comparing to published nomograms.[17,18] Cardiac outputs are significantly higher than normal for two years post-burn. Data is plotted as average ± standard error of the mean (SEM). * Denotes statistical significance of $p<0.05$.

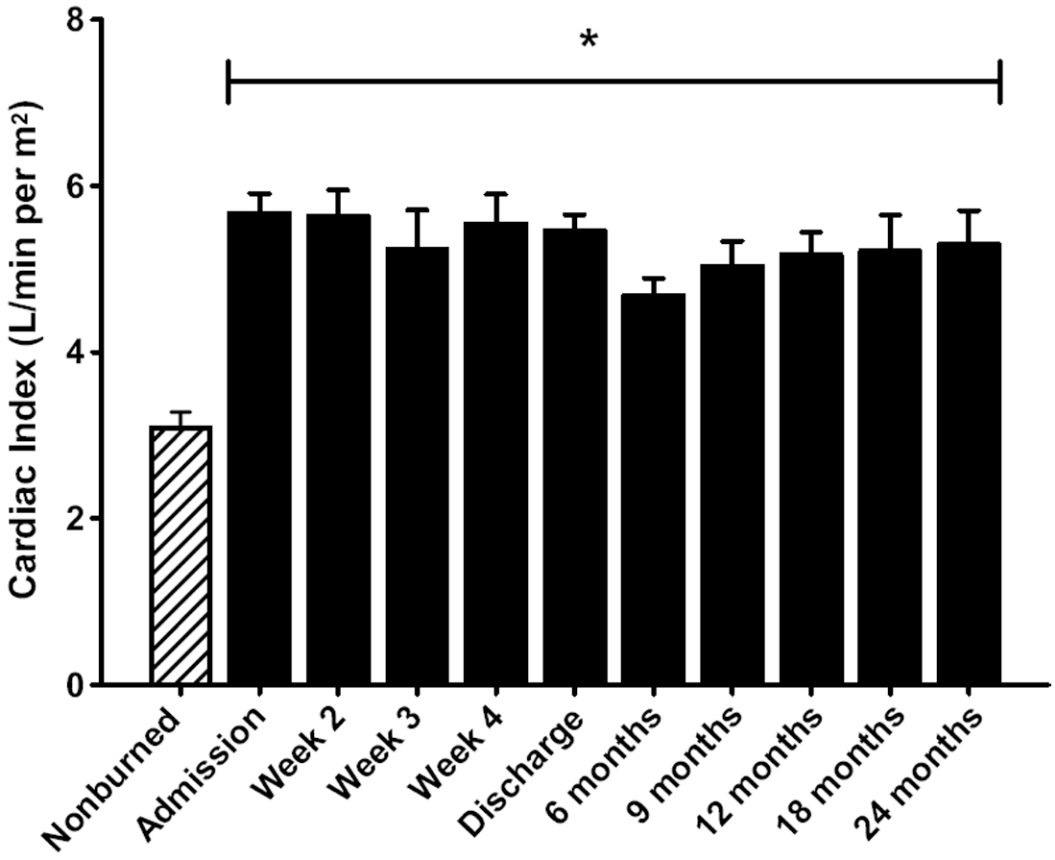

Figure 3.
Average cardiac index for pediatric burn patients compared to non-burned volunteers. Cardiac indices are significantly higher than normal for two years post-burn. Data is plotted as average ± standard error of the mean (SEM). * Denotes statistical significance of $p<0.05$.

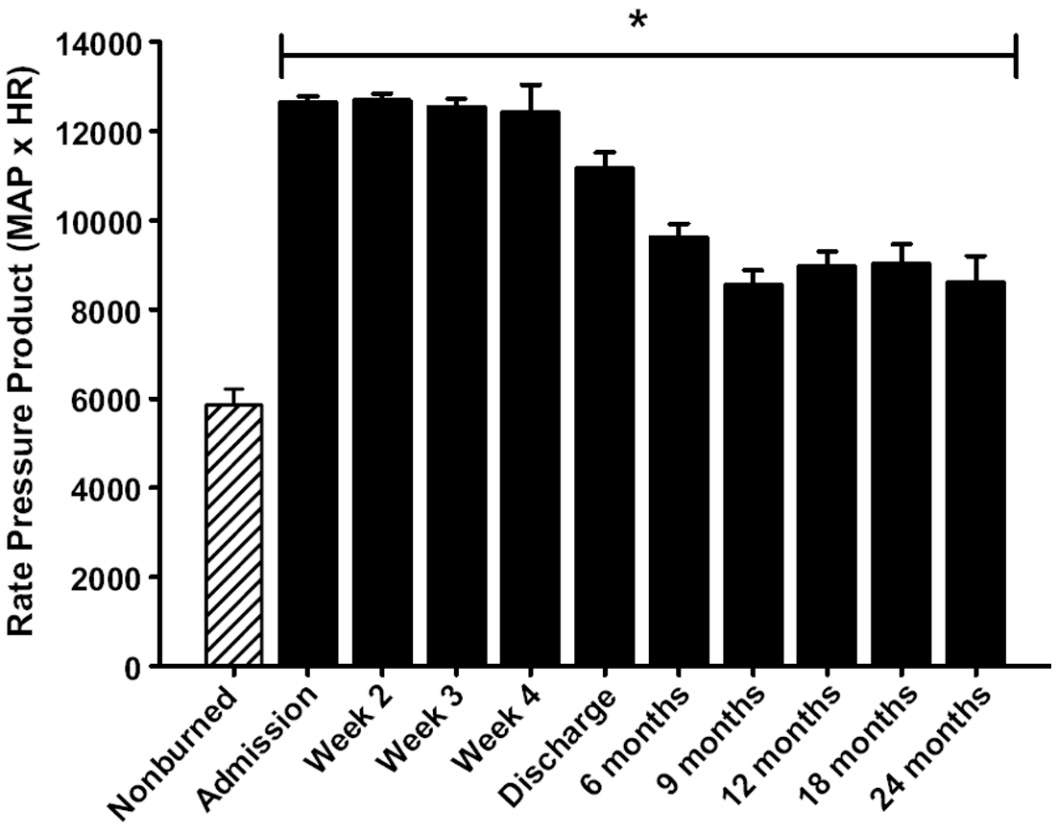

Figure 4.
Average rate pressure product for pediatric burn patients compared to non-burned volunteers. Myocardial oxygen consumption is significantly higher than normal for two years post-burn. Data is plotted as average ± standard error of the mean (SEM). * Denotes statistical significance of $p<0.05$.

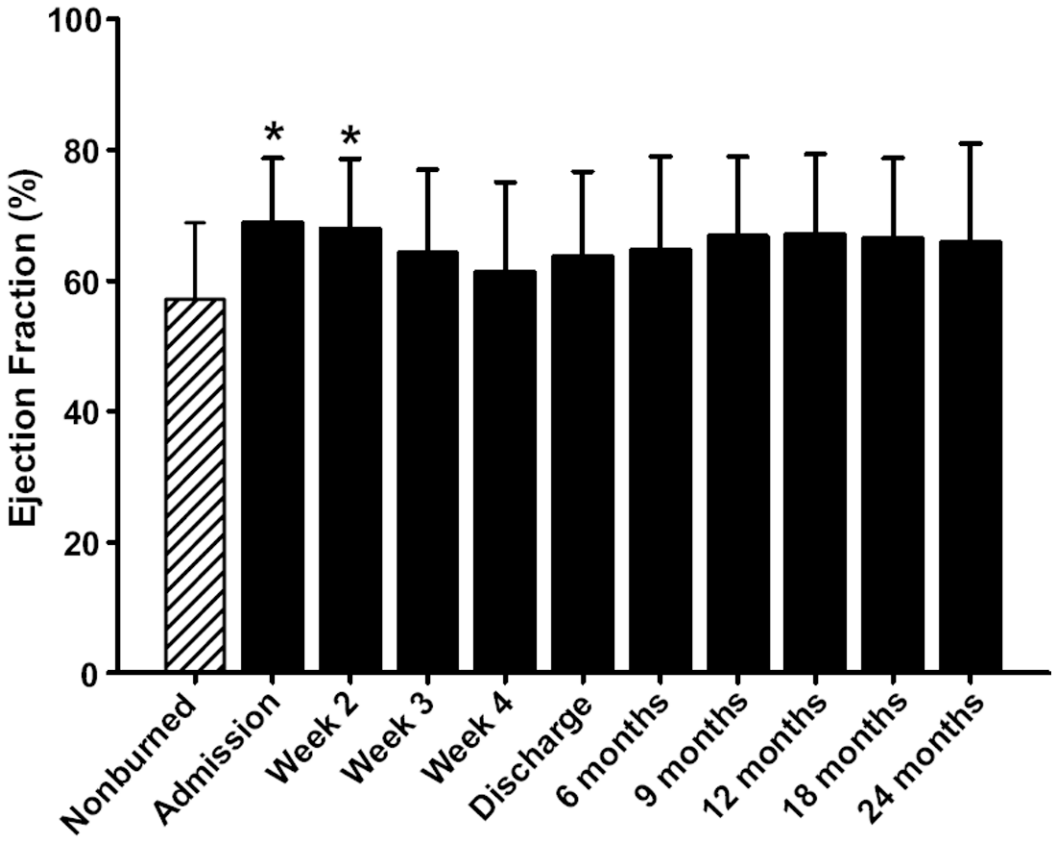

Figure 5.
Average ejection fraction for pediatric burn patients compared to non-burned volunteers. Ejection fraction was significantly elevated on admission and the second week of hospitalization compared to non-burned volunteers, but still within normal limits.[17,18] Data is plotted as average ± standard error of the mean (SEM). * Denotes statistical significance of $p<0.05$.