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Transpulmonary thermodilution for hemodynamic measurements in severely burned children

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ABSTRACT

Introduction: Monitoring of hemodynamic and volumetric parameters after severe burns is of critical importance. Pulmonary artery catheters, however, have been associated with many risks. Our aim was to show the feasibility of continuous monitoring with minimally invasive transpulmonary thermodilution in severely burned pediatric patients.

Methods: This prospective cohort study was conducted in patients with severe burns over 40% total body surface area (TBSA), admitted within 96 hours after burn injury. Transpulmonary thermodilution measurements were performed using the PiCCO system (Pulsion Medical Systems, Munich, Germany). Cardiac index (CI), intrathoracic blood volume index (ITBVI), extravascular lung water index (EVLWI), and systemic vascular resistance index (SVRI) were recorded twice daily. Statistical analysis was performed using one-way repeated measures ANOVA with post-hoc Bonferroni test for intra-and inter-group comparisons.

Results: Seventy-nine patients with a mean age of 9±5 years and a mean TBSA burn of 64±20% were studied. CI significantly increased compared to levels at admission and was highest three weeks post burn. ITBVI increased significantly starting eight days post-burn. SVRI continuously decreased early in the perioperative burn period. EVLWI increased significantly starting at nine days post-burn. Young (0-5 years old) children had a significantly increased EVLWI and decreased ITBVI when compared to older (12-18 years old) children. EVLWI was significantly higher in patients that did not survive burn injury.

Conclusions: Continuous PiCCO measurements were performed for the first time in a large cohort of severely burned pediatric patients. The results suggest that hyperdynamic circulation begins within the first week after burn injury and continues throughout their entire ICU stay.

INTRODUCTION

Large burns of greater than one-third of the total body surface area (TBSA) result in a massive inflammatory response, which in turn causes severe and unique hemodynamic and cardiovascular challenges. Early excision of necrotic tissue and prompt coverage has tempered the post-burn hypermetabolic response, decreased excess fluid loss, and ultimately led to improved survival [1-3]. Still, continued hemodynamic support with appropriate fluid resuscitation and administration of cardiovascular agents, is needed in the early post-burn period to oppose hypervolemia, alterations in afterload and myocardial depression [4-7], which can accelerate organ dysfunction [8].

Invasive hemodynamic monitoring via pulmonary artery catheter (PAC) permits the direct and continuous measurement of central venous pressure, pulmonary capillary occlusion pressure, cardiac output, systemic vascular resistance, and oxygen delivery and consumption. However, the PAC is highly invasive and associated with substantial risks that often outweigh its benefits [9]. In order to overcome the disadvantages of the PAC, less invasive techniques have been developed. The PiCCO catheter (Pulsion Medical Systems, Munich, Germany) combines advanced hemodynamic monitoring and volumetric measures without the necessity of a right heart catheterization. It utilizes transpulmonary thermodilution (TPTD), in which a cold saline bolus is injected into the central venous circulation and the subsequent change in blood temperature is measured by a thermistor-tipped arterial catheter, allowing for the determination of cardiac output (CO) [10-12]. Additionally, TPTD estimates global end-diastolic volume and intrathoracic blood volume (ITBVI), indicators of cardiac preload, and extravascular lung water (EVLWI), an index of pulmonary edema [13]. The use of TPTD goal-directed therapy based on ITBVI and EVLWI measurements in critically ill patients has been studied in various prospective trials and showed promising results [14]. Only one prospective randomized study to compare goal-directed therapy guided by TPTD measurements with standard care (Baxter formula) in burn shock management has been performed in adult burn patients [11].

At the Shriners Hospitals for Children in Galveston, TPTD has been the standard of care hemodynamic monitor for children with severe burns over 40% TBSA. The goals of this study were to report the hemodynamic and volumetric status in severely burned children within the first three weeks post burn, to identify differences in hemodynamic parameters between different age groups, and to identify differences in hemodynamic parameters between survivors and non-survivors.

MATERIALS AND METHODS

Severely burned children admitted to the Shriners Hospitals for Children, Galveston, Texas, between December 2005 and March 2008, were considered for this study. Permission for conducting the study was obtained from the Institutional Review Board at the University of Texas Medical Branch, Galveston, Texas (Protocol # 08-289). Informed written consent was obtained in all cases. The following inclusion criteria were used:

Burn size equals or exceeds 40% TBSA and at least 30% TBSA full thickness burn;

Patients are admitted within 120 hours of injury; Patients are not septic at admission.

Exclusion criteria included any kind of cardiopulmonary illness.

All patients were weighed on admission and calculation of all indexed values was based on the initial burn size and body surface area of the individual patient. Analgesia and sedation was performed according to our routine guidelines. In case mechanical ventilation was required, initial ventilator settings included a pressure-controlled mode of ventilation, frequency of 10-15 breaths/min, inspiration/expiration time of 1:2, and initial positive end-expiratory pressure (PEEP) of 4 cm H_2O. PEEP was adjusted according to the pulmonary function and oxygenation levels of the patient. All patients underwent staged early excision and grafting with autografts, allografts, or both, between 48 and 72 hours post burn, and in approximately weekly intervals thereafter. Expanded autograft (meshed 1:4) with allograft overlay was applied to as much area as was possible to cover. The rest of the wound area was covered with unexpanded fresh allograft (meshed 1:1.5). Donor sites were re-cropped when healed, and allograft surgically excised and consecutively replaced with autograft skin.

Demographics

Mortality rates, length of ICU stay, cumulative length of hospital stay based on 95% healing of grafts, total number of procedures performed during acute admission, and total operating room (OR) time were recorded. Weights were measured within 5 days of admission and at discharge using standard clinical scales. The clinical scales were calibrated monthly.

PiCCO measurements

All patients had central venous (inferior or superior vena cava) and arterial (brachial, radial, or femoral artery) access placed upon initial admission. TPTD measurements were performed using the Pulsiocath 3 or 4 F thermistor-tipped catheter (Pulsion Medical Systems, Munich, Germany). Cardiac index, intrathoracic blood volume index and extravascular lung water index was determined using an injection of 10 mL cooled saline solution (0–6°C) into the central venous catheter. Systemic vascular resistance was calculated based on measured cardiac output, mean arterial and central venous pressures. Injections were manual and not coordinated with the respiratory cycle. Measurements were performed at least twice daily. Each procedure consisted of three injections via the venous access and all saline boluses were administered within a maximum time span of 10 minutes. Results were calculated as the mean of these three consecutive measurements. Heart rate, mean arterial pressures (MAP), and central venous pressure (CVP) was calculated from aforementioned variables or recorded directly by the hardware at the same time-points as the thermal bolus injections. Data were recorded and exported to a personal computer with the PICCO-VoLEF-WIN software (version 4.0, Pulsion Medical Systems) combined with the Pulsion PICCOPlus device (PC 8100, software version V6.0, Pulsion Medical Systems).

Statistics

For inter-individual comparison, all flow-related or volume-related variables were normalized to body surface area. Continuous values were compared using the Student's t-test or the Mann-Whitney test, depending on their distributional properties. To test the influence of time on the hemodynamic and volumetric variables, a two-way analysis of variance to determine the statistical significance of the change over time of each of the variables and the influence of treatment was performed. When difference was detected, post hoc analysis was performed using the Bonferroni test. Differences in proportions such as mortality rate, infection rates, and incidence of sepsis were compared using the chi-square test. In all cases, p-values <0.05 were considered as statistically significant.

RESULTS

Between December 2005 and September 2008, seventy-nine acutely burned children were enrolled into the study. Demographics of the groups are listed in Table 1 (for the complete cohort), Table 2 (for different age groups), and Table 3 (for survivors and non-survivors).

Complete cohort

In the complete cohort of severely burned children, MAP remained relatively unchanged with a mean value of 85 mmHg, central venous pressure increased after the initial loading phase and then gradually declined during the remainder of the measurement period, and heart rates remained elevated with tachycardia during the entire acute ICU stay (data not shown). Cardiac index was significantly increased compared to admission values after the second day of admission, and, overall, continuously increased during the entire measurement period (Figure 1). Intrathoracic blood volume index and EVLWI showed similar patterns: a gradual increase over the entire measurement period, reaching significance when compared to day 0 or day 1 at 8 or 9 days post-burn, respectively (Figure 2A and B). Systemic vascular resistance index demonstrated a continuous decrease during the measurement period, also reaching significance after nine days post-burn when compared to the first day post-burn (Figure 3).

Age Groups

Patients were divided into three age groups (Table 2). Heart rate was significantly increased in the youngest compared to the oldest age group until 10 days post-burn (Figure 4A). No significant differences in cardiac index measurements were observed between age groups after day 1 post-burn (Figure 4B). Systemic vascular resistance index, initially, was significantly lower in the youngest age group compared to both older patient groups. This difference, however, was not sustained after the end of the volume loading phase on day 2 post-burn (Figure

4C). Central venous pressure in the youngest patient group as compared to older children showed increased values throughout the measurement period. The differences, however, reached significance levels only sporadically (Figure 4D). Intrathoracic blood volume index and EVLWI showed an opposing pattern in the youngest versus the oldest patient group: a significant increase in ITBVI was observed in the oldest patient group compared to the youngest group (Figure 5A), while EVLWI displayed significantly higher values in the youngest patient group compared with the older patient throughout most of the measurement period (Figure 5B).

Survivors vs. Non-Survivors

Patients were sub-divided into those who survived and those who died during the acute stay (Table 3). Mean arterial pressure, preload and afterload parameters showed no significant differences between the groups (Figure 6A-D). On the other-hand, EVLWI was significantly higher in the non-survivors compared to the survivors (Figure 7).

Complications

One child developed an arterial embolism in the left leg approximately one week after arterial catheter placement. However, since the patient also suffered from a coagulopathy it is not clear whether the catheter placement or the coagulopathy caused the embolism.

DISCUSSION

Early excision and debridement of burn-injured tissues, coupled with prompt coverage, is an integral part of burn management [1-3]. An adequate fluid resuscitation in the first 24 to 48 hours post-burn, in order to overcome hypovolemia and restore hemodynamic and cardiovascular function, remains a pivotal part of acute burn care [15]. Formulas for the calculation of resuscitation fluid requirements (Parkland, Brooke, and Galveston Formulas) have been established; the needs of the individual patient are addressed based on constant reassessment of urinary output and volume status [8]. For the first time in a large cohort of severely burned children, hemodynamic and volumetric parameters were assessed for the first three weeks of ICU stay. Patterns of hemodynamic measurements were established using the PiCCO catheter, a novel technology based on transpulmonary thermodilution.

In the phase of early resuscitation after a severe burn, it is paramount to promptly restore vascular volume and to preserve tissue perfusion but minimize tissue edema [16]. The primary goal of therapy is to replace the massive intravascular volume loss due to the pathophysiological response of thermal injury. Resuscitation formulas, such as Evans, Brooke, and Parkland, have been developed over the last decades as initial guides for the volume replacement therapy in order to preserve adequate organ perfusion [15]. After the first 72 hours post burn, fluid management needs to be frequently re-evaluated in order to avoid hypovolemia, hypervolemia, and edema or organ dysfunction. Clinical monitoring of burn shock resuscitation and general fluid management has traditionally relied on the clinical assessment of cardiovascular status, urine output, and biochemical parameters as indicators of vital organ perfusion. Heart rate, blood pressure, central venous pressure, electrocardiographic recordings, and baseline laboratory measurements (complete blood count, electrolytes, glucose, albumin, and base deficit [17]) are the primary modalities for monitoring the volumetric and cardiovascular status in any patient. Fluid balance during burn shock resuscitation is typically monitored by measuring hourly urine output via an indwelling bladder catheter. A general recommendation during the early post-burn period is to administer volume support to produce a urinary output between 30 and 50 mL/h in adults [18] and between 1.0 – 1.5 mL/kg/h in patients weighing less than 30 kg [19]. It has been demonstrated, however, that over-resuscitation is associated with adverse outcome and increased mortality in burn patients [19].

Invasive hemodynamic monitoring has been used in intensive care settings for the past three decades. The advent of pulmonary artery catheterization permitted the direct measurement of central venous pressure, pulmonary capillary wedge pressure, cardiac output, systemic vascular resistance, oxygen delivery, and oxygen consumption. PAC-guided therapy has been studied most extensively in trauma and critically ill adult surgical patients. Although controversial, some suggest that hemodynamic data derived from the PAC are beneficial to ascertain cardiovascular performance in certain situations, e.g. in patients with inadequate noninvasive monitoring, or when endpoints of resuscitation cannot be clearly defined [20]. PAC-guided monitoring with resuscitation to hyperdynamic endpoints decreased ICU stay, ventilator days, and incidence of organ failures when compared to patients resuscitated to normal hemodynamic values [21, 22]. In burn patients, studies with the use of PAC for goal-directed burn shock resuscitation have shown a benefit of more aggressive resuscitation to hyperdynamic endpoints, with decreased mortality and ICU stay [23]. However, the general practicability, risk-benefit ratio, and lack of mortality reduction when using PAC have been widely criticized. In the last decade, its use in the United States has decreased significantly [9]. So far, no prospective study with the use of goal-directed PAC therapy has been conducted in a pediatric burn population.

The PiCCO catheter was developed in Germany by Ulrich Pfeiffer in the 1980s [24]. Briefly, it represents a combination of two techniques for advanced hemodynamic and volumetric management without the necessity of a right heart catheterization. Firstly, it utilizes transpulmonary thermodilution, where a cold saline bolus is injected into the central venous circulation, and the subsequent change in blood temperature is picked up by a thermistor-tipped arterial catheter [25]. The cardiac output is calculated by means of the Stewart-Hamilton-equation, derived from the area of the transpulmonary thermodilution curve. Stroke volume variation and systemic vascular resistance are derived from the arterial pulse contour. Intrathoracic blood volume and extravascular lung water are derived from the mean transit time and cardiac output, and the down slope time of the thermodilution curve, respectively. Limitations of this technology include the presence of an intra-cardiac right-left-shunt [25]. In our patient cohort, there was no evidence of intra-cardiac shunts (data not shown).

There is limited information on goal-directed therapy using TPTD measurements in burn injured patients. Holm et al. [11] used TPTD goal-directed therapy for the initial resuscitation of burn shock in adult burn patients, comparing it to controls that were resuscitated according to the Baxter formula. TPTD-directed resuscitation was associated with increased fluid requirements compared to controls during the first 48 hours following burn. One conclusion might be that TPTD results in a more aggressive fluid infusion, which could be detrimental. However, TPTD was shown to reduce the incidence of hypovolemia compared to the Baxter formula and EVLWI was not different [11]. So far, there have been no randomized clinical trials have been performed using TPTD-guided therapy of acute burn shock in severely burned pediatric patients. Furthermore, there have been no reports on the continuous use of TPTD for hemodynamic and cardiovascular monitoring in burn patients during their entire ICU stay.

In the present study, the PiCCO catheter was used to measure critical hemodynamic and volumetric parameters over time following severe burn injury in pediatric patients. We sought to determine the influence of age on the hemodynamic response to burn injury, and how information obtained by the PiCCO catheter could be used as a predictive tool for determining mortality.

With regards to the entire patient cohort, cardiac output continuously increased over the entire study period. This hypermetabolic circulation has been shown to persist for more than two years post burn [26]. The product of increased heart rate and decreased systemic vascular resistance results in the flow phase post burn, which has been demonstrated to have a major impact on the outcome of burn patients.

We were able to demonstrate significant differences between our youngest patients with a mean age of 3 years, and the oldest group with a mean age of 15 years. The youngest patient group showed markedly elevated lung water (up to 25 mL/kg in some cases) compared to the older patients. Our results agree with Schiffmann et al. [27] who demonstrated that critically ill infants had mean EVLWI of over 27 mL/kg. These authors speculated that increased EVLWI was related to the severity of the underlying disease. However, they also acknowledge that since normal values of EVLWI are not defined for infants, apart from singular case reports [28], the underlying cause remains unclear.

The effect of an increase in EVLWI on mortality is well established in ICU patients [29]. Furthermore, protocols using EVLWI as a monitor to guide volume and other cardiovascular support have been shown to decrease length of ICU stay [30] and mortality when employing a fluid restriction approach. [29]. In general, fluid restriction therapy in ICU patients with acute lung injury improves lung function and shortens the duration of mechanical ventilation [31]. The key finding in our large cohort of severely burned children is consistent with Eisenberg et al. [29] who showed that increased EVLWI is associated with mortality. It remains to be determined if goal directed approaches using EVLWI as a primary endpoint to direct fluid support in severely burn injured children will indeed have an influence on mortality. The use of a normalized and validated morbidity score, such as the pediatric logistic organ dysfunction (PELOD) score [32, 33], to support an interpretation of organ failure, is another way to determine how the use of the PiCCO catheter can be used as a predictor of morbidity and mortality. A prospective study is currently underway at our institution to determine the effects of the use of transpulmonary thermodilution on clinical outcomes, including organ function.

CONCLUSIONS

Burn patients show an impairment of ventricular compliance consistent with experimental models of burn injury [34-38], and this impairment is more pronounced in the youngest patient group. After the initial volume loading, ongoing fluid replacement schemes may not be adequate for the very young patient (under 3 years), as seen in this study with the measurements of extravascular lung water. Overall, TPTD measurement is a rapid, safe and easy-to-install method for minimally invasive hemodynamic monitoring. The obtained cardiac output, preload and afterload variables have been validated in multiple studies [12, 39-42]. Compared to the pulmonary artery catheter, the PiCCO methodology may represent a superior method to direct fluid therapy support, since intrathoracic blood volume is a more sensitive and specific indicator of cardiac preload than pulmonary artery occlusion pressure or central venous pressure [42]. This is likely due to the higher preload specificity of volume versus pressure.

KEY MESSAGES

- Key volumetric and hemodynamic parameters, such as cardiac output, intrathoracic blood volume, extravascular lung water, and systemic vascular resistance can be measured in severely burned pediatric patients with the transpulmonary thermodilution technique, which is less invasive than pulmonary artery catheter techniques.
- Severely burned children up to five years old have significantly increased lung water and significantly decreased intrathoracic blood volume compared to those between 12 and 18 years of age, which underscores the importance of tightly controlled fluid management in the burned child.
- The hyperdynamic state in a burned patient begins within the first week after burn injury and continues throughout their entire ICU stay.

ABBREVIATIONS

CI, Cardiac Index; CVP, Central Venous Pressure; EVLWI, Extravascular Lung Water Index; ICU, Intensive Care Unit; ITBVI, Intrathoracic Blood Volume Index; MAP, Mean Arterial Pressure; OR, Operating Room; PAC, Pulmonary Artery Catheter; PEEP, Positive End-Expiratory Pressure; SVRI, Systemic Vascular Resistance Index; TBSA, Total Body Surface Area; TPTD, Transpulmonary Thermodilution.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

LKB participated in the design of the study, collected the data, and drafted the manuscript. DNH conceived of the study, participated in its design and coordination, and manuscript preparation. JFB collected data and participated in the manuscript preparation. MK participated in the manuscript preparation and data analysis. JOL, SPF and MGJ participated in data collection, study design, and manuscript preparation. DNH and MGJ did study coordination. All authors read and approved the final manuscript.

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Table 1. Entire Cohort Demographics

n	79
Age [years]	9.2 (9.3)
TBSA Burn [%]	64.0 (35.0)
TBSA Full Thickness Burn [%]	50.0 (45.5)
Type of Burn	
• Flame	70%
• Scald	25%
• Other	5%
M:F Ratio	2.3:1
Length of Stay [days]	28.6 (23.6)
Survivors	80%

Data presented as median (interquartile range). TBSA = Total body surface area.

Table 2. Age Group Demographics

Age Group	0 – 4.9 years	5 – 11.9 years	12 – 18 years	p-value
Patients (n)	21	31	27	ns
Age (years)	3 (2)	8 (4)	15 (3)	<0.05
Burn to Admission (hours)	44 (36)	29 (45)	42 (67)	ns
% TBSA Burn	64 (41)	61 (31)	73 (32)	ns
% TBSA 3rd-degree burn	60 (43)	48 (33)	53 (51)	ns
Male: Female Ratio	2:1	5.3:1	1.3:1	ns
Length of Stay (days)	29 (25)	28 (22)	31 (23)	ns

Data presented as median (interquartile range). TBSA = Total body surface area.

Table 3. Survivors vs. Non-Survivors Demographics

Group	Survivors	Non-Survivors	p-value
Patients (n)	64	15	
Age (years)	8 (9)	12 (8)	ns
Burn to Admission (hours)	33 (31)	61 (71)	ns
% TBSA Burn	58 (30)	87 (11)	<0.001
% TBSA 3rd-degree burn	46 (41)	81 (16)	<0.001
Male: Female Ratio	1.7:1	1.5:1	ns
Length of Stay (days)	28 (19)	33 (39)	ns

Data presented as median (interquartile range). TBSA = Total body surface area.

FIGURE LEGENDS

Figure 1. Cardiac Index in the entire patient cohort between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean.* $p<0.05$ vs. day 0. † $p<0.05$ vs. day 1.

Figure 2. (A) Intrathoracic Blood Volume and (B) Extravascular Lung Water in the entire patient cohort between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean.* $p<0.05$ vs. day 0. † $p<0.05$ vs. day 1.

Figure 3. Systemic Vascular Resistance in the entire patient cohort between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean.* $p<0.05$ vs. day 0. † $p<0.05$ vs. day 1.

Figure 4. (A) Heart Rate, (B) Cardiac Index, (C) Systemic Vascular Resistance, and (D) Central Venous Pressure measurements in three different age groups between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean.* $p<0.05$ youngest (0-4.9 years) vs. oldest (12-18 years) age group.

Figure 5. (A) Intrathoracic Blood Volume and (B) Extravascular Lung Water in three different age groups between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean. * $p<0.05$ youngest (0-4.9 years) vs. oldest (12-18 years) age group.

Figure 6. (A) Central Venous Pressure, (B) ITBVI, (C) Cardiac Index and (D) SVRI measurements in survivors vs. non-survivors between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean. * $p<0.05$ survivors vs. non-survivors.

Figure 7. Extravascular lung water in survivors vs. non-survivors survivors between burn (day 0) and day 21 post-burn. Data expressed as means ± standard error of mean. * $p<0.05$ survivors vs. non-survivors.

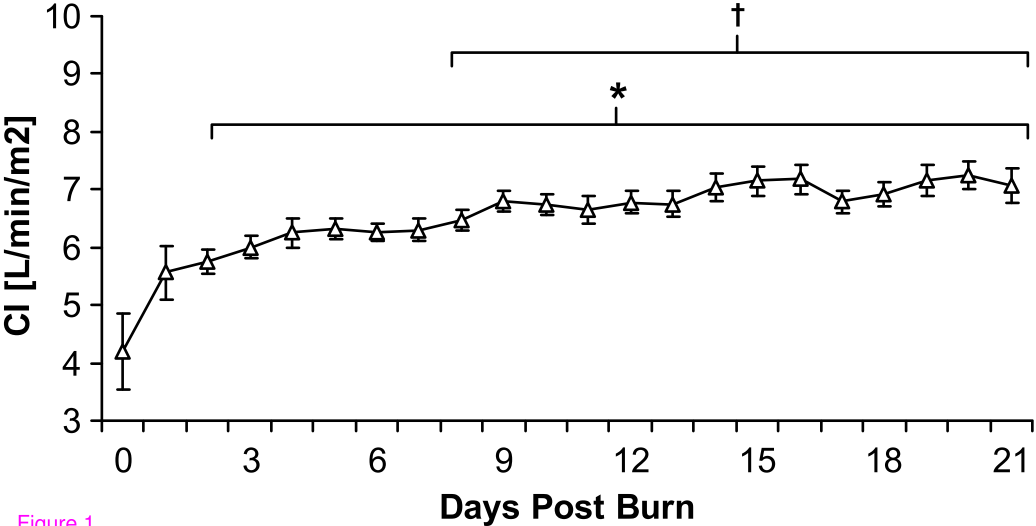


Figure 1

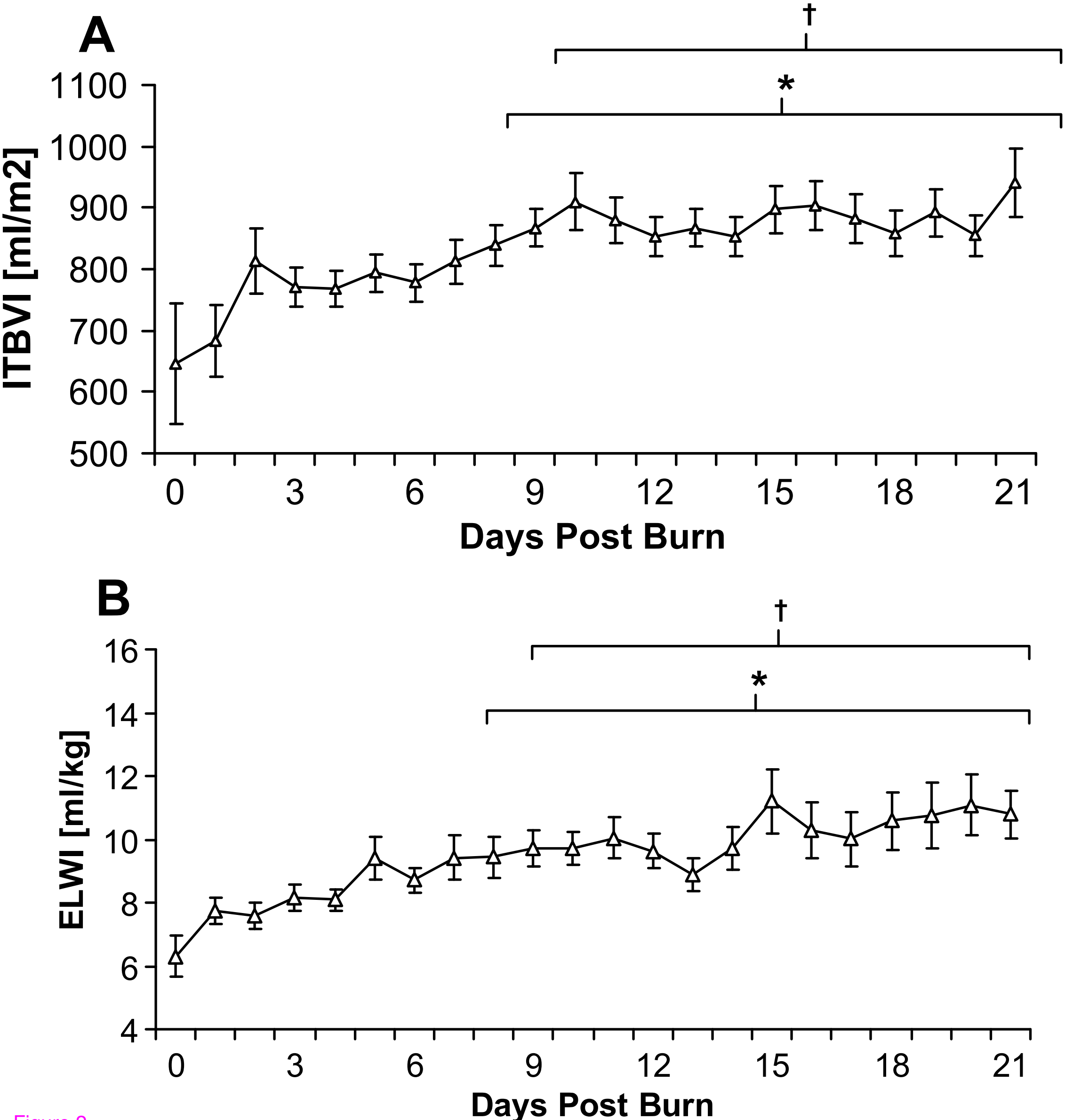
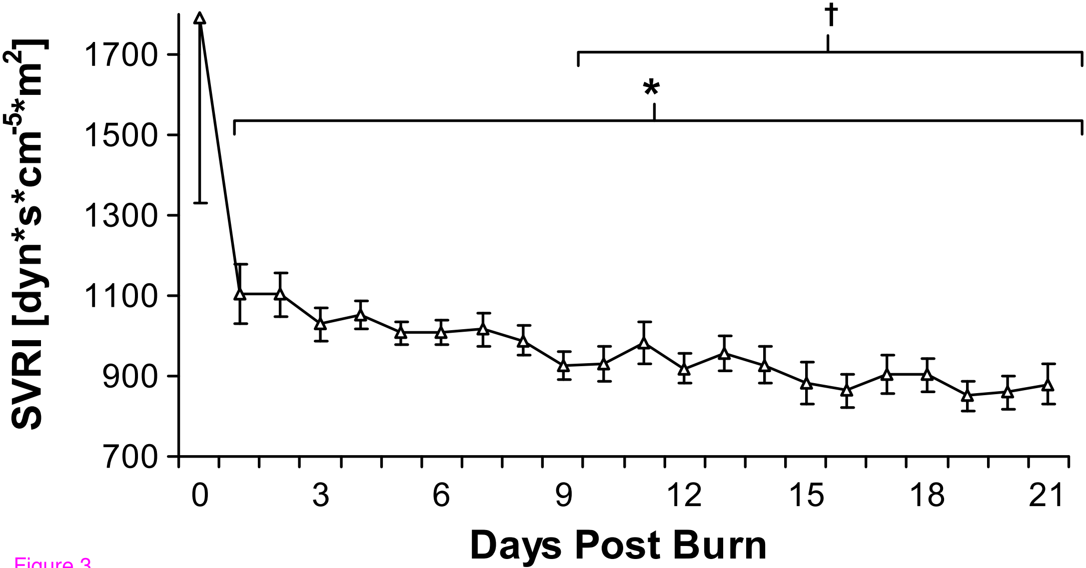

A
†
*
ITBVI [ml/m2]
1100
1000
900
800
700
600
500
0
3
6
9
12
15
18
21
Days Post Burn
B
†
*
ELWI [ml/kg]
16
14
12
10
8
6
4
0
3
6
9
12
15
18
21
Days Post Burn

Figure 2



SVRI [dyn*s*cm-5*m2]
1700
1500
1300
1100
900
700
0
3
6
9
12
15
18
21
Days Post Burn
*
†

Figure 3

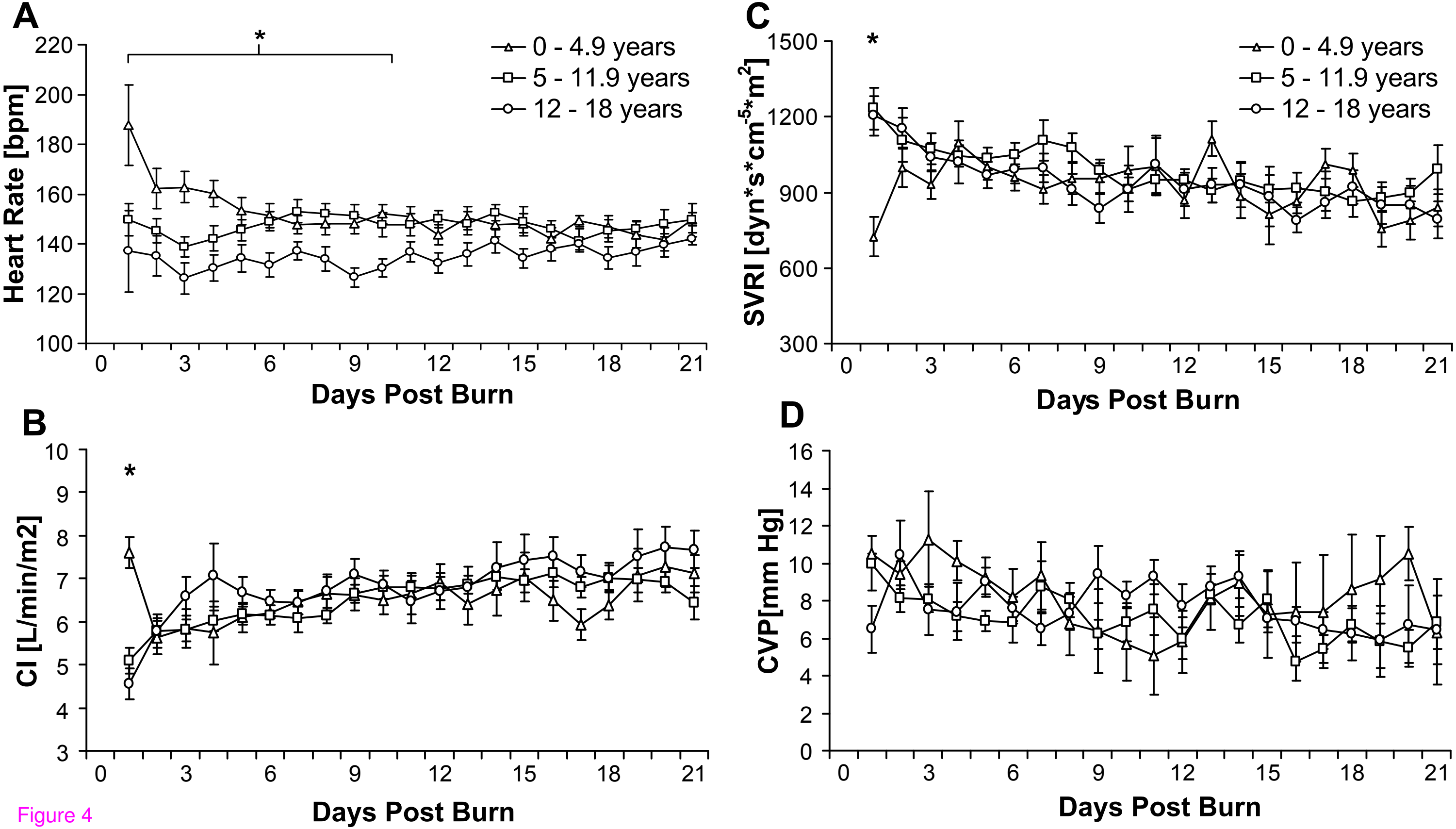
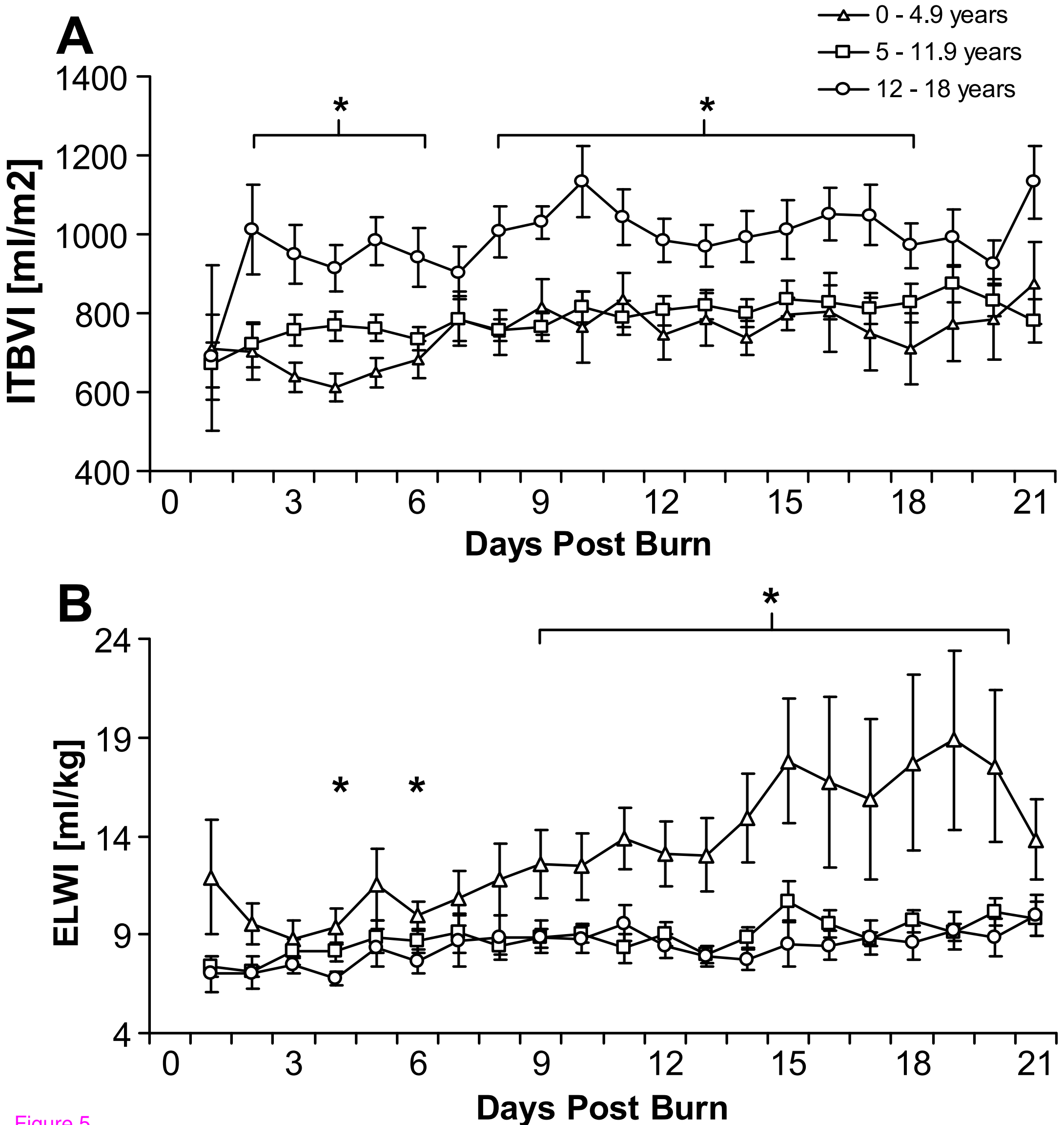
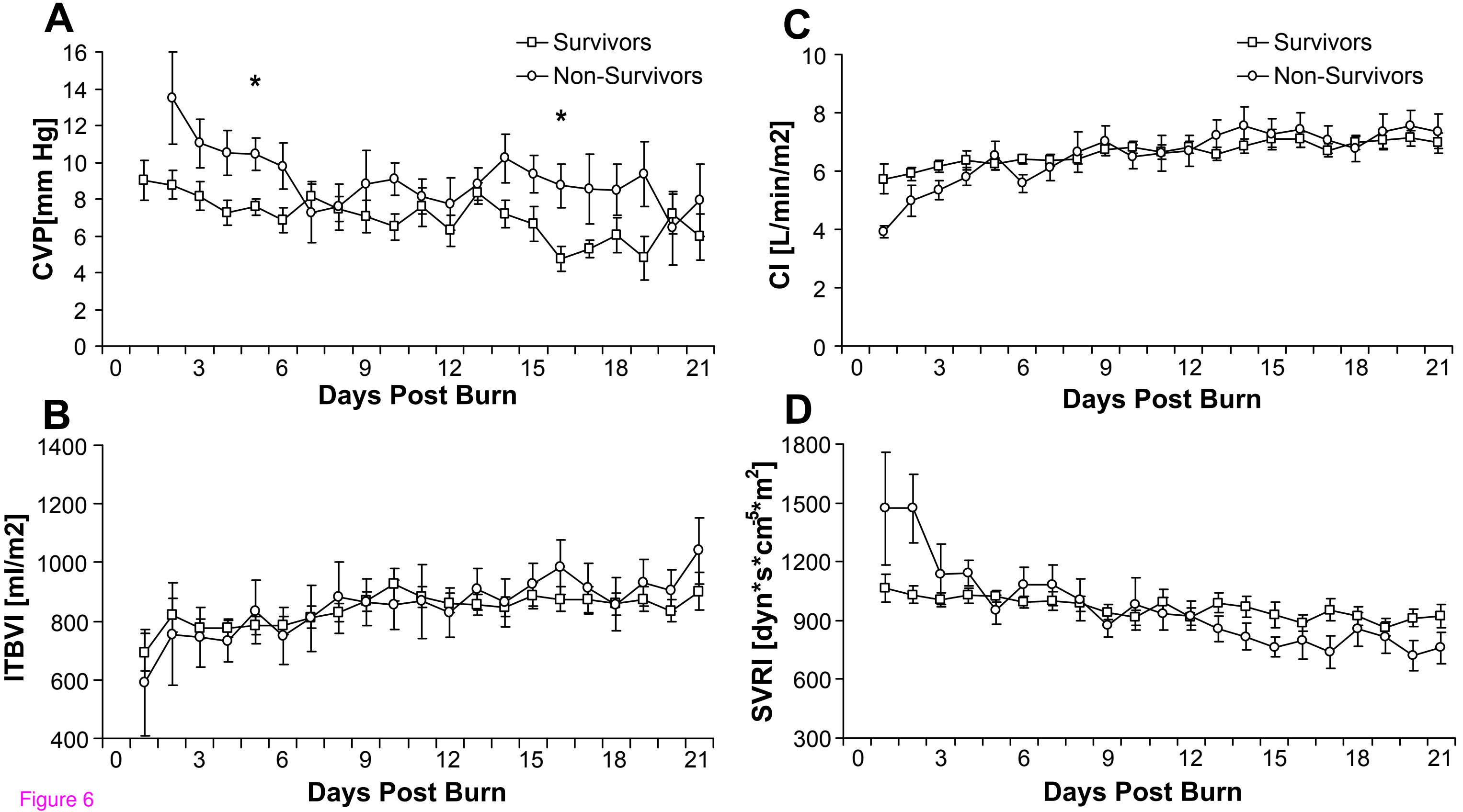

A
Heart Rate [bpm]
Days Post Burn
0 - 4.9 years
5 - 11.9 years
12 - 18 years
B
CI [L/min/m2]
Days Post Burn
C
SVRI [dyn*s*cm^-5*m^2]
Days Post Burn
D
CVP[mm Hg]
Days Post Burn

Figure 4



A
0 - 4.9 years
5 - 11.9 years
12 - 18 years
1400
1200
1000
800
600
400
ITBVI [ml/m2]
*
*
0
3
6
9
12
15
18
21
Days Post Burn
B
24
19
14
9
4
ELWI [ml/kg]
*
*
*
0
3
6
9
12
15
18
21
Days Post Burn

Figure 5



A
Survivors
Non-Survivors
*
*
CVP[mm Hg]
16
14
12
10
8
6
4
2
0
0
3
6
9
12
15
18
21
Days Post Burn
B
ITBVI [ml/m2]
1400
1200
1000
800
600
400
0
3
6
9
12
15
18
21
Days Post Burn
C
Survivors
Non-Survivors
CI [L/min/m2]
10
8
6
4
2
0
0
3
6
9
12
15
18
21
Days Post Burn
D
SVRI [dyn*s*cm^{-5}*m^2]
1800
1500
1200
900
600
300
0
3
6
9
12
15
18
21
Days Post Burn

Figure 6

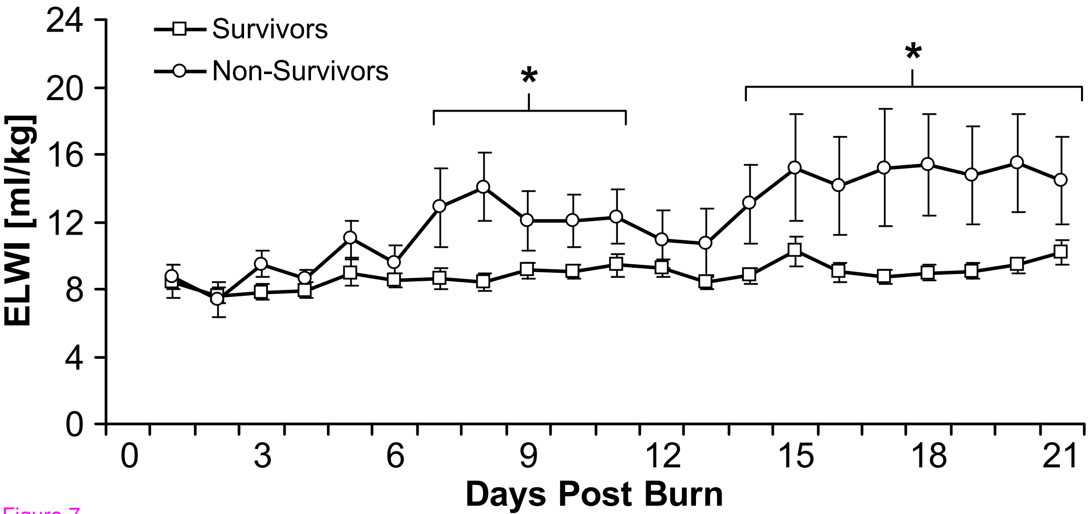

Survivors
Non-Survivors
*
*
ELWI [ml/kg]
24
20
16
12
8
4
0
0
3
6
9
12
15
18
21
Days Post Burn

Figure 7