Cardiac Structure and Function in Well-Healed Burn Survivors

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Long-term burn survivors have reduced aerobic capacity, placing them at increased risk for cardiovascular disease, morbidity, and mortality. However, the exact mechanism contributing to a reduced aerobic capacity remains incompletely understood, but may be related to adverse cardiovascular remodeling. Therefore, it was hypothesized that well-healed burn survivors would exhibit adverse left ventricular (LV) remodeling and impaired LV function. To test this hypothesis, 22 well-healed moderately burned individuals (age: 41 ± 14 years; BMI: 27.7 ± 5.4 kg/m²; male/female: 12/10; extent of burn: 37 ± 12 %BSA), 11 well-healed severely burned individuals (age: 43 ± 12 years; BMI: 29.5 ± 5.8 kg/m²; male/female: 8/3; extent of burn: 73 ± 11 %BSA), and 12 healthy, age-matched controls (age: 34 ± 9 years; BMI: 28.6 ± 5.2 kg/m²; male/female: 5/7) were enrolled in the study. All subjects were sedentary, performing less than 30 minutes of aerobic exercise per day, 3 days per week. LV morphology and function were assessed via cardiac magnetic resonance imaging. In contrast to the hypothesis, neither the presence nor severity of burn injury adversely affected LV morphology or function, when compared with equally sedentary nonburned controls. However, of note, LV mass of all three groups was in the lowest 5th percentile compared with normative values. Finally, group differences in LV morphology were largely explained by differences in aerobic capacity. Taken together, these data suggest a prior burn injury itself does not result in pathological remodeling of the LV and support a role for aerobic exercise training to improve cardiac function.

Every year, ~150,000 patients are treated in emergency rooms in the United States with burn-related injuries, with 40,000 to 70,000 of those being hospitalized for an extended period of time.¹ The American Burn Association reports that ~16 percent of hospitalized patients have burns covering 20 percent or more of their body surface area (BSA).¹ This equates to between 6400 and 11,200 individuals per year experiencing severe burns covering 20 percent or more of their BSA. Military conflicts are also a significant source of burn-related injuries, given that 5% to 20% of all battlefield injuries are burn related.^{2–4} Twenty years ago, burns covering half of a person's BSA were fatal, but currently patients with up to 90% BSA burned are surviving. Thus, more individuals are living with severe burn injuries than ever before. However, the long-term physiological consequences of these injuries are under-studied and thus remain unclear.

Our group recently showed that ~75 percent of well-healed burn survivors (beyond 1.5 years postinjury and without any open wounds), having 17% to 75% of their BSA grafted, had a maximal oxygen uptake ($\text{VO}_{2\text{max}}$, a measure of aerobic capacity) in the lowest 20th percentile rankings, relative to sex and age-adjusted nonburned individuals.⁵ These data corroborate previous work in pediatric burn survivors (age: 19 ± 5 years) studied 12 $\pm$ 4 years postinjury, showing impaired $\text{VO}_{2\text{max}}$ compared with healthy age-matched controls.⁶ These findings are important because reductions in $\text{VO}_{2\text{max}}$ are strongly associated with cardiovascular-specific, as well as all-cause morbidity and mortality.⁷ Epidemiological studies have, indeed, documented greater cardiovascular disease risk in long-term adult and pediatric burn survivors.^{8,9} The exact mechanism(s) driving the impairment in aerobic capacity, however, remains poorly understood.

Burn trauma induces a hypermetabolic and hyperinflammatory state that is characterized by muscle protein catabolism, immune dysfunction, and organ failure.^{10–15} In animal models of acute burn injuries, cardiac function is also severely compromised immediately postinjury^{14,15}; however, these findings have yet to be translated to well-healed human patients. To address this knowledge gap, we performed cardiac magnetic resonance imaging (MRI) in a cohort of well-healed burn injury survivors, to assess left ventricular (LV) morphology and function. To extend our prior observations, we also included a group of healthy controls, matched for physical activity level, for direct comparisons of aerobic capacity and LV morphology/function. We hypothesized that burn injury survivors would demonstrate evidence of cardiac atrophy and impaired global LV systolic function compared with controls,

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and that these adverse adaptations would be directly related to the percentage of BSA burned.

METHODS

Study Participants

Twenty-two individuals (age: 41 ± 14 years; BMI: 27.7 ± 5.4 kg/m²; male/female: 12/10) with moderate well-healed burn injuries covering between 20% and 55% of their BSA (mean: 37 ± 12 %BSA), 11 individuals (age: 43 ± 12 years; BMI: 29.5 ± 5.8 kg/m²; male/female: 8/3) with severe, well-healed burn injuries covering between 55% and 90% of their BSA (mean: 73 ± 11 %BSA), and 12 healthy, age-matched controls (age: 34 ± 9 years; BMI: 28.6 ± 5.2 kg/m²; male/female: 5/7) participated in the study. Participants were ≥ 18 months postinjury, had no contraindications to the MRI, and were sedentary at the time of study (defined as performing less than 30 minutes of physical activity 3 times per week). Participants with any cardiovascular, metabolic, or neurological diseases were excluded from the study. Participants refrained from alcohol, caffeine, and exercise for 24 hours before laboratory visits and were at least 4 hours postprandial. All participants performed two graded maximal exercise tests (separated by a minimum of 48 hours), and LV morphology and function was assessed by cardiac MRI and echocardiography on differing days. Study procedures and informed consent documents were approved by the University of Texas Southwestern Medical Center and the Texas Health Presbyterian Hospital Dallas Institutional Review Boards and conformed to the latest version of the *Declaration of Helsinki*.

Anthropometric Data and Medical History

Before enrollment, participant's height, mass, and medical history (including current medication use) were recorded to ensure that they met the inclusion criteria stated above. Areas of skin having sustained severe burns were determined using previously defined methods.¹⁶ Following a period of supine rest, heart rate was monitored via electrocardiogram (Solar 8000i, GE Healthcare, Milwaukee, WI) interfaced with a cardiometer (CWE, Ardmore, PA) and blood pressure was assessed using a commercially available automated sphygmomanometer (Tango+, SunTech Medical, Raleigh, NC).

Graded Cardiopulmonary Exercise Test

Two stepwise graded maximal exercise tests were performed with participants in the upright position on a commercially available cycle ergometer (Lode Excalibur Sport, Lode, Groningen, Netherlands). Participants began cycling at a consistent cadence, at an exercise intensity of 40–50 W, which increased by 20–40 W every 1–2 minutes thereafter until volitional exhaustion. During this test, ventilatory data and expiratory gases were measured using a commercially available gas analysis system (Parvo TrueOne 2400, Parvo Medics, East Sandy, UT), in addition to ECG monitoring (Solar 8000i, GE Healthcare, Milwaukee, WI). Peak power output and maximal heart rate were recorded at the point of volitional fatigue, whereas $\dot{V}O_{2\max}$ was calculated as the highest 30-second average achieved during the test. The highest $\dot{V}O_{2\max}$ of the two performed tests was used for these analyses.

LV Morphology by Cardiac MRI

All cardiac structural measures were assessed by electrocardiogram-gated cardiac MRI cine images (1.5T Avanto, Siemens Healthcare, Erlangen, Germany or 3T Achieva, Philips Medical Systems, Best, Netherlands). A series of 10 to 12 multiphase steady-state free precession cine images were acquired perpendicular to the long axis of the LV from base to apex (short-axis) taken at end-expiration. Four-chamber and 2-chamber parasternal long-axis images were collected using the same multiphase gradient-echo cine images taken at end-expiration. Native T1 images were also calculated using a mid-ventricular short axis slice using a vendor provided MOLLI 5(3)3 pulse sequence (Philips Medical Systems, Best, Netherlands). Image acquisition settings were kept constant throughout the whole study. All cardiac MRI data were analyzed offline by an experienced observer using commercially available analysis software (CVI42, version 5.6.8, Circle Cardiovascular Imaging, Calgary, AB). For calculation of LV mass and volumes, epicardial and endocardial borders of each slice were traced manually at end-diastole and end-systole. LV stroke volume and ejection fraction were calculated from standard formulae. LV concentricity was calculated by dividing LV mass index by LV end-diastolic volume. Quantification of native T1 was performed on the septum for all subjects, using the same commercially available analysis software.

LV Diastolic Function by Echocardiography

LV diastolic function was assessed by transthoracic echocardiograms obtained using an iE33 echocardiograph (Philips Medical Systems, Andover, MA) with participants in the supine position. Pulse-wave Doppler images were collected using a sample volume of 2.0 mm placed at the tips of the mitral valve leaflets, followed by pulse-wave tissue Doppler images of the septal and lateral wall using a 5.0-mm sample volume. A minimum of 3 consecutive cardiac cycles were collected for each image and were stored offline for post hoc analysis using a commercially available analysis software (Xcelera version R4.1L1, Philips, Philips Medical Systems, Netherlands). Peak early (E) and late (A) trans-mitral inflow velocities and the E wave deceleration time were determined from the pulse-wave Doppler images, whereas the tissue Doppler images were used to determine septal and lateral wall early (e') and late (a') diastolic tissue velocities. The average e' and a' from both the septal and lateral walls were considered for statistical evaluation. The ratios between early and late mitral inflow velocities (E to A) and tissue velocities (e'/a'), along with the ratio between early mitral inflow velocity and early tissue velocity (E/e') were subsequently calculated. All images were evaluated offline by an experienced sonographer who was blinded to the study design, participants, and groups.

Statistical Analysis

All dependent variables, apart from peak power output and absolute $\dot{V}O_{2\max}$, were normally distributed and homoscedastic, as tested by the Shapiro–Wilk test. Cross-sectional comparisons between all three groups were assessed by one-way analysis of variance (ANOVA) for normally distributed variables and Kruskal–Wallis for nonparametric variables, with post hoc Tukey's tests performed following significant

group main effects. Correlations between dependent variables were assessed by Pearson's and Spearman's correlations where appropriate. To account for differences in sex among the three study groups, relationships between dependent variables were adjusted accordingly. Strong correlations were considered when $r > 0.5$, whereas moderate correlations were considered when $r > 0.3$. All statistical analyses were performed using SPSS (version 24 IBM SPSS Statistics, Armonk, NY). All data are expressed as means $\pm$ SD unless otherwise stated, and statistical significance was accepted at $P \leq .05$.

RESULTS

Participant characteristics, burn history, and medical history are detailed in Table 1. As typical with burn survivors, participants were taking more medications than that of controls. There was no difference in the time postburn injury between the moderate and severe burn participants (17.6 ± 12.3 vs 15.7 ± 11.1 years, moderate vs severe; $P > .05$), nor was there a difference between all three groups in age, height, mass, BMI, or BSA.

Table 1. Participant characteristics, medical history hemodynamics, and echocardiography-derived diastolic parameters for moderate and severely burned individuals and healthy age-matched control participants

	Control (n = 12)	Moderate burn (n = 22)	Severe burn (n = 11)
Patient demographics			
Age (yr)	34 $\pm$ 9	41 $\pm$ 14	43 $\pm$ 12
Sex (male/female)	5/7	12/10	8/3
Height (cm)	170.3 $\pm$ 9.0	169.7 $\pm$ 9.1	172.8 $\pm$ 9.0
Body mass (kg)	82.9 $\pm$ 16.8	80.2 $\pm$ 19.4	87.5 $\pm$ 15.1
Body mass index (kg/m ²)	28.6 $\pm$ 5.2	27.7 $\pm$ 5.4	29.5 $\pm$ 5.8
Fat-free mass (kg)	53.9 $\pm$ 10.0	56.7 $\pm$ 17.2	51.1 $\pm$ 15.0
Body surface area (m ²)	1.94 $\pm$ 0.21	1.91 $\pm$ 0.24	2.01 $\pm$ 0.17
Medications, n (%)			
Hypertension	1 (8)	3 (14)	2 (18)
Hypercholesterolemia	1 (8)	1 (5)	1 (9)
Hypothyroidism	1 (8)	2 (9)	1 (9)
Stimulants	2 (17)	0 (0)	0 (0)
Anti-histamine	0 (0)	2 (9)	2 (18)
Penicillin	0 (0)	2 (9)	0 (0)
Pain killers	0 (0)	3 (14)	3 (27)
Anti-inflammatory	0 (0)	2 (9)	3 (27)
Medical marijuana	0 (0)	3 (14)	1 (9)
Sedatives	0 (0)	3 (14)	2 (18)
Burn injury			
Total BSA injured (%)	—	37 $\pm$ 12 [‡]	73 $\pm$ 11
Duration postinjury (yr)	—	17.6 $\pm$ 12.3	15.7 $\pm$ 11.1
Hemodynamics and cardiopulmonary exercise test			
Heart rate (bpm)	61 $\pm$ 9	62 $\pm$ 12	58 $\pm$ 9
Systolic BP (mmHg)	116 $\pm$ 12	120 $\pm$ 11	121 $\pm$ 9
Diastolic BP (mmHg)	74 $\pm$ 8	76 $\pm$ 13	77 $\pm$ 8
Mean arterial BP (mmHg)	88 $\pm$ 8	91 $\pm$ 11	91 $\pm$ 7
Absolute VO _{2max} (L/min)	2.71 $\pm$ 0.85	2.13 $\pm$ 0.52*	2.41 $\pm$ 0.36
Relative VO _{2max} (ml/kg/min)	33.8 $\pm$ 11.2	27.5 $\pm$ 7.1	27.7 $\pm$ 5.3
Maximal heart rate (bpm)	187 $\pm$ 10	178 $\pm$ 17	170 $\pm$ 11*
Maximal RER	1.26 $\pm$ 0.12	1.23 $\pm$ 0.11	1.18 $\pm$ 0.12
Echocardiography diastolic parameters			
E Velocity (cm/s)	71.3 $\pm$ 12.5	76.8 $\pm$ 14.6	73.2 $\pm$ 15.0
A Velocity (cm/s)	48.7 $\pm$ 16.7	47.9 $\pm$ 12.4	50.9 $\pm$ 12.3
Deceleration time (ms)	198 $\pm$ 42	199 $\pm$ 45	208 $\pm$ 34
E/A ratio	1.56 $\pm$ 0.43	1.72 $\pm$ 0.58	1.48 $\pm$ 0.32
e' Velocity (cm/s)	12.0 $\pm$ 2.7	11.6 $\pm$ 2.3	12.0 $\pm$ 1.72
a' Velocity (cm/s)	9.1 $\pm$ 2.3	8.8 $\pm$ 2.4	10.2 $\pm$ 4.8
e'/a' Ratio	1.44 $\pm$ 0.63	1.44 $\pm$ 0.65	1.31 $\pm$ 0.40
E/e' Ratio	6.27 $\pm$ 2.14	6.80 $\pm$ 1.66	6.18 $\pm$ 1.27

BP, blood pressure; VO_{2max}, maximal whole-body oxygen consumption; RER, respiratory exchange ratio; E Velocity, early diastolic mitral inflow velocity; A Velocity, late diastolic mitral inflow velocity; e' Velocity, early diastolic tissue velocity; a' Velocity, late diastolic tissue velocity.

*Indicates significantly different from control individuals

‡Indicates significantly different from severely burned individuals.

Figure 1. Differences in left ventricular (LV) morphology and function between nonburned controls (black bars), moderately burned (open bars), and severely burned individuals (gray bars). Despite a similar ejection fraction, moderately burned individuals had a lower end-diastolic volume (EDV), stroke volume, and cardiac output compared with the severely burned group. LV ejection fraction and concentricity were not different between the groups, suggesting no pathological remodeling in either patient groups. *Significant difference compared with severe group $P < .05$ by one-way ANOVA. See [Supplementary Material](#) for cardiac responses indexed to body surface area.

LV end-diastolic volume, stroke volume, and cardiac output were lowest in the moderately burned individuals, with no differences between the control group and severely burned group (Figure 1). No other group differences in LV morphology or function (including indices of diastolic function; see Table 1) were observed between groups. Moreover, no further group differences were observed in LV morphology after indexing to BSA, or in native myocardial T1 time (see [Supplementary Material](#)). Finally, moderately burned individuals did present with significantly lower absolute $\text{VO}_{2\text{max}}$ compared with the control group; however, no other group differences were observed for absolute or relative $\text{VO}_{2\text{max}}$.

To help explain these seemingly dichotomous results between the moderate and severe burn groups, we evaluated the relationship between aerobic capacity and LV morphology

(Figures 2 and 3). Interestingly, absolute $\text{VO}_{2\text{max}}$ was strongly related to LV end-diastolic volume, end-systolic volume, stroke volume, and LV mass (all $P < .05$ and $r > 0.50$, Figure 3), whereas cardiac output and LV concentricity index were moderately related to absolute $\text{VO}_{2\text{max}}$ (all $P < .05$ and $r > 0.30$, Table 2). Only stroke volume was moderately related to severity of burn injury ($r = .35$, $P = .05$).

DISCUSSION

Burn injury represents a severe cardiometabolic challenge, leading to a hypercatabolic, hyperinflammatory state that is characterized by muscle protein catabolism, immune dysfunction, and organ failure.^{10,17–22} Here, we sought to evaluate, for the first

Figure 2. Relationship between absolute maximal whole-body oxygen consumption ($\text{VO}_{2\text{max}}$) and (A) left ventricular mass and (B) end-diastolic volume (EDV) in controls, moderately burned, and severely burned participants after controlling for sex differences between groups. Greater $\text{VO}_{2\text{max}}$ was associated with a greater LV mass and EDV, evidence of physiological eccentric adaptation.

Figure 3. Relationships between the extent of the burn injury (graded by body surface area; %BSA Burned) and (A) end-diastolic volume (EDV), (B) stroke volume, and (C) left ventricular mass in both moderate and severely burned individuals. Severity of burn injury was positively associated with increases in stroke volume. These relationships can be almost entirely explained by maximal aerobic capacity (VO_{2max}) as absolute VO_{2max} was also related to (D) EDV, (E) stroke volume, and (F) left ventricular mass in both moderate and severely burned individuals. Data shown are from correlation analysis adjusted for group differences in sex.

time, cardiac morphology and function in well-healed burn survivors. In contrast to our hypothesis, while we observed modest differences in cardiac morphology between burn survivors and healthy controls, these differences were largely explained by aerobic fitness. Indeed, lower aerobic fitness was associated with reduced end-diastolic volume and LV mass, regardless of group categorization or the degree of burn injury.

Table 2. Relationships between absolute VO_{2max} and left ventricular structural and functional parameters in moderately burned, severely burned, and control individuals combined before and after adjusting for sex

	Nonadjusted		Adjusted for sex	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
LV mass (g)	.75	<.001	.61	<.001
EDV (ml)	.67	<.001	.60	<.001
ESV (ml)	.69	<.001	.58	<.001
Stroke volume (ml)	.53	<.001	.49	<.001
Ejection fraction (%)	-.14	.36	-.01	.99
Cardiac output (l/min)	.38	.01	.37	.02
LV concentricity (g/ml)	.31	.04	.23	.88

LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume.

Evidence from animal models of acute burn injuries suggests that cardiac function is severely compromised leading to impaired function and overall remodeling. For example, cardiac myocyte contractile function (via the Langendorff method) is impaired in many animal models of acute burn injury.^{15,23,24} This underlying impairment in systolic contractile function is caused in part by reduced LV contractility,^{25,26} resulting in an attenuated cardiac output and stroke volume.²³ These preclinical data have been supported by at least one other study, which found LV ejection fraction to be reduced in a pediatric population of burn survivors ~12 years postinjury.⁶ Cardiac diastolic function has also been suggested to be impaired in well-healed pediatric burn survivors and that such impairments may be related to elevated levels of myocardial fibrosis.⁶ However, results from the current investigation do not support these observations, as we found no difference in LV ejection fraction, diastolic function, or tissue characteristics between groups. Although it remains unclear why the preclinical data are so different from our current observations, we speculate that it relates to the timing of postburn observations (days/weeks vs >decade). Indeed, the preclinical studies often focus on the acute postburn injury period, when sympathetic nerve activity is elevated, along with marked catabolism and systemic inflammation.¹⁰⁻¹⁵ Why our findings differ from the above mentioned pediatric clinical study remains equivocal, as these patients were also studied many years postburn.

However, our study cohort was significantly older, and ejection fraction was assessed using different imaging modalities.

The most striking finding of this investigation was the divergent LV morphological changes observed between the moderate and severely burned individuals. Indeed, our data suggest a reduction end-diastolic volume (ie, cardiac size) in the moderately burned individuals compared with healthy controls. In contrast, the severely burned individuals studied herein remained similar to controls. The reason for this observation remains unclear. That LV concentricity was similar between all three groups does not support pathological remodeling. Based on our data, aerobic capacity is the primary explanation, as aerobic capacity was significantly impaired in the moderately burned individuals compared with controls, and that aerobic capacity was significantly correlated with end-diastolic volume and LV mass, independent of burn injury. Interestingly, LV mass of all three groups was in the lowest 5th percentile compared with normative values from a large population-based trial (Multi-Ethnic Study of Atherosclerosis, $n = 6814$).²⁷ We interpret this finding to further support the hypothesis that the changes in LV morphology found in this study are likely driven by aerobic fitness, perhaps associated with a sedentary lifestyle.

To our surprise, the severely burned individuals had some of the highest aerobic fitness levels among any of the participants. Although we do not believe that burn injury promotes aerobic fitness, it is likely that this observation is driven by selection bias. Indeed, the participants who enrolled in this study were part of a larger trial designed to evaluate the effects of 6 months of exercise training on aerobic capacity in long-term burn survivors. The level of commitment for such a trial, and the overall appeal to enroll, is likely to attract participants with exercise tendencies. Moreover, participants with various “exclusion” comorbidities, related to their burn injuries or not, were prohibited from enrolling in the study. Thus, the enrolled participants were relatively healthy and were willing to commit to an extensive exercise training regimen and therefore were unlikely to reflect the actual diversity of burn survivors. Finally, although the participants did not participate in regular aerobic exercise at the time of enrollment, we cannot control for any differences in preburn injury exercise levels, or activity level during the initial years following the burn injury, which may carry over to the observed assessments.

We previously reported that aerobic fitness is markedly reduced in burn survivors, such that ~75 percent of burn survivors had a VO_{2max} in the lowest 20th percentile for their age and sex.⁵ The present data both confirm and extend this prior observation, showing lower than expected fitness levels for the given age, and sex of the participants compared with previously published normative data.^{28,29} Moreover, it is noteworthy that when the low level of physical activity in the control group is matched to that of burn participants, the control group had the highest mean VO_{2max} relative to the two burned groups. However, these findings should be confirmed in a larger cohort of well-healed burn survivors. Consistent with our LV morphology data, we interpret this finding to reflect a non-pathological impairment in aerobic capacity. The implication of this finding supports, and even emphasizes, the important role of exercise rehabilitation in burn survivors. This concept is further supported by prior investigations in children with burn injuries who showed increases in skeletal muscle mass and aerobic capacity with in-hospital exercise training.^{30,31}

Study Limitations

We recognize the limitations surrounding this cross-sectional study. Longitudinal research evaluating cardiac morphology and function throughout the recovery period is indeed warranted. The sample size of this investigation is also relatively low, limiting the translation of the present results to the greater burn population at large. Nevertheless, this proof-of-concept study does provide significant insight and helps us to address an important question in the field. Importantly, the results herein strongly encourage future work evaluating the impact of cardiac rehabilitation in this population as a way to normalize the long-term cardiovascular impact of burn-injury.

CONCLUSION

Taken together, these data are the first to evaluate cardiac morphology and function in well-healed adult burn survivors. We observed modest differences in cardiac morphology between burn survivors and healthy controls; however, these differences were almost entirely explained by aerobic fitness. Indeed, lower aerobic fitness was associated with reduced end-diastolic volume and LV mass, regardless of group categorization or the extent of burn injury. These data strongly support the importance of aerobic exercise in the burn survivor as a means to maintain (and improve) cardiac health.

SUPPLEMENTARY DATA

Supplementary data is available at *Journal of Burn Care & Research* online.

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- Conversations with burn experts discussing active issues in our field

<https://academic.oup.com/jbcr/pages/podcasts>