IMPAIRED SKELETAL MUSCLE MITOCHONDRIAL AND VASCULAR FUNCTION IN PEOPLE WITH HEART FAILURE

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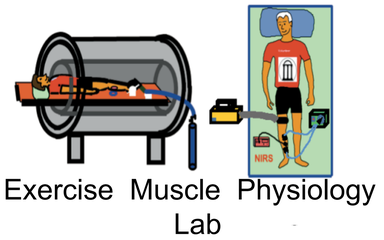

Abstract

Heart failure (HF) has been associated with skeletal muscle dysfunction not explained by reduced cardiac output. **PURPOSE:** To compare skeletal muscle mitochondrial capacity and O_2 delivery in people with and without HF using near-infrared spectroscopy (NIRS). **METHODS:** Participants (aged 45-70 years old) had HF and implanted cardioverter-defibrillators (ICDs) (n = 14) or were age-match controls without HF (n = 25). The NIRS device was placed over the wrist flexor muscles. Mitochondrial capacity was obtained by performing repeated arterial occlusions to measure recovery kinetics of O_2 consumption following a brief bout of forearm exercise. Halftime of reactive hyperemia was measured following an arterial occlusion to complete desaturation. **RESULTS:** The recovery time constant was slower in HF (HF: 1.2 ± 0.3 s; Control: 1.5 ± 0.2 s, p <0.0001). Reactive hyperemia was slower in the HF group (HF: 24.6 ± 3.6 s; Control: 19.3 ± 7.9 s, p = 0.001). **CONCLUSION:** HF was associated with a 22% reduction in mitochondrial capacity and 25% slower O_2 delivery compared to age-matched controls. These impairments were in non-locomotor muscles, suggesting a general effect of HF rather than changes in activity patterns of the muscle.

Introduction

HF is a complex clinical condition characterized by functional or structural alterations to the heart resulting in inadequate oxygenated blood delivery to all the body's organs. This condition is widespread affecting over 6 million adults in the United States alone. Interestingly, HF patients suffer functional and exertional intolerances irrespective of their cardiac output. Evidence has suggested that these impairments are due not only to cardiac dysfunction, but to peripheral abnormalities in the skeletal muscle as well. Peripheral impairments seen in HF could be due to physical inactivity, inadequate oxygenated blood delivery, or reduced oxidative metabolism in skeletal muscle. Mitochondrial dysfunction has been associated with skeletal muscle myopathies in HF, but the exact role that mitochondria play is still not clearly understood.

Purpose:

- **To compare mitochondrial capacity in people with and without heart failure**
- **To compare oxygen reperfusion in people with and without heart failure**

Hypotheses

- **People with HF will have impaired mitochondrial capacity**
- **People with HF will have impaired O_2 reperfusion**

	Heart Failure	Control
N	14	25
Age (yrs)	63.4 ± 6.2	61.1 ± 5.1
Height (cm)	180.1 ± 8.9	167.5 ± 8.4
Weight (kg)	95.5 ± 11.9	77.5 ± 19.1
ATT (cm)		
Non-Dominant	0.71 ± 0.3	0.79 ± 0.3
Dominant	0.65 ± 0.2	0.82 ± 0.4
Ejection Fraction (%)	27.45 ± 5.6	N/A

Methods

Participants

Fourteen participants with HF (11 male, 3 female) and twenty-five participants without HF (6 male, 18 female) were enrolled in this study. The study was conducted with the approval of the Institutional Review Board at the University of Georgia (Athens, GA), and each subject gave written, informed consent before testing.

Experimental Setup and Protocols

Each subject was placed supine on a padded table with their arm fully extended perpendicular to their body. The NIRS measurements were collected using a continuous wave NIRS device (Oxymon, Artinis Medical Systems BV, The Netherlands). The NIRS probe was placed on the subject's forearm. A blood pressure cuff (Hokanson SC12D, Bellevue, WA) was placed on the upper arm, proximal to the probe, above the elbow. The cuff was attached to a rapid inflation system (Hokanson E20 Cuff Inflator, Bellevue, WA) powered by a 10-gallon commercially available air compressor (California Air Tools 210DLV, San Diego, CA). After each test was completed, B-mode ultrasound (LOGIQ e; GE HealthCare, USA) was used to measure the adipose tissue thickness (ATT) under the NIRS probe.

Mitochondrial Capacity

To measure mitochondrial capacity, short duration exercise (7-10 seconds of wrist curls) was used to increase mVO_2. After a short bout of exercise, a series of 18-20 occlusions were made (duration = 3-10 sec) to characterize the recovery of post-exercise oxygen consumption. An example of a typical NIRS mitochondrial test is shown in Figure 2.

O_2 Reperfusion

The blood pressure cuff was inflated for 2-5 minutes until the O_2 saturation reached 0%. The cuff was released and the time to half the magnitude of the peak O_2 hyperemia was measured.

Data Analysis

The NIRS tests were analyzed using custom-written routines in Matlab v. 7.13.0.564 (Mathworks, Natick, MA).

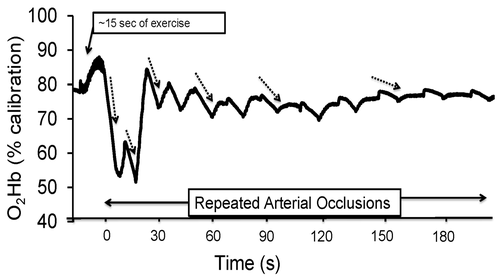

Figure 1: *Representative example of the O_2Hb signal during repeated arterial occlusions. Slopes of signal become less steep over time illustrating the recovery of O_2 consumption after exercise.*

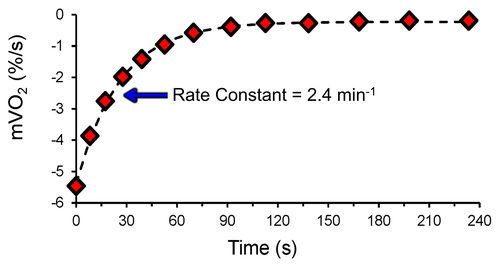

Figure 2: *A monoexponential curve fitted to the measurements of oxygen consumption in Figure 1. The resulting rate constant is directly proportional to mitochondrial capacity.*

Results

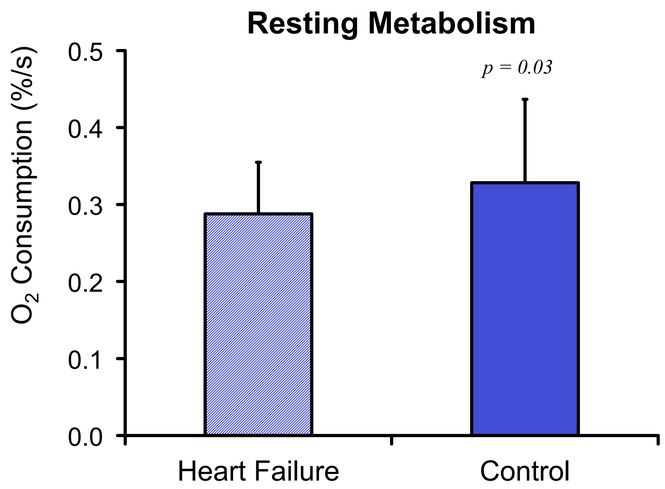

Figure 3: *Resting O_2 consumption of people with and without HF. People with HF had slightly reduced O_2 consumption at rest (p =0.047). Mean (SD)*

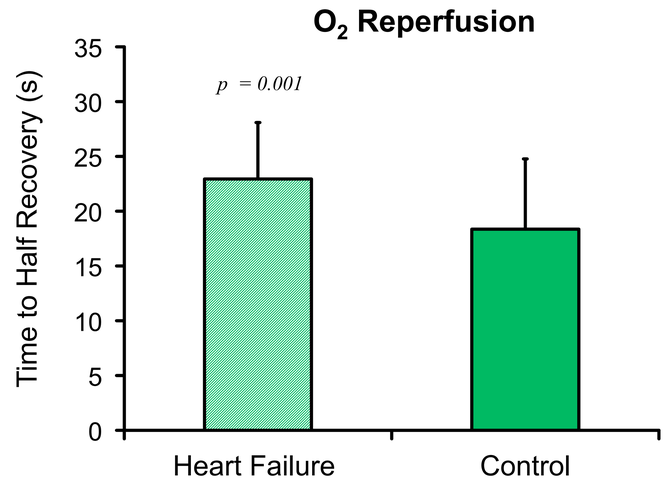

Figure 5: *Time to half peak O_2 hyperemia following 3-5 min arterial occlusion. People with HF had a slower reperfusion rate, indicating impaired vascular function. (p=0.001).Mean (SD)*

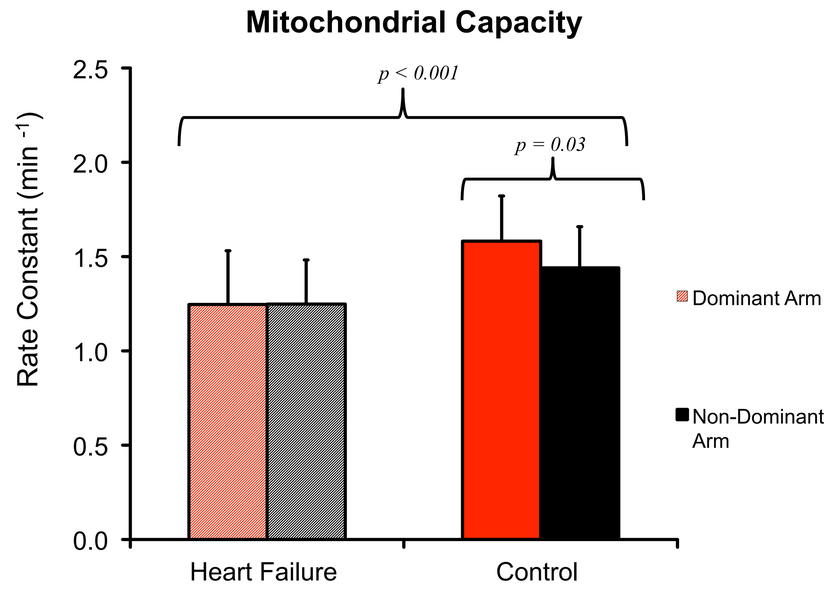

Figure 4: *Mitochondrial capacity of people with and without HF. People with HF had impaired mitochondrial capacity. People without HF showed better mitochondrial capacity in their dominant arm compared to their non-dominant arm. People with HF showed a lack of mitochondrial plasticity, as no difference was found between their arms. Mean (SD)*

	Heart Failure	Control	Difference
Mitochondrial Capacity (min^{-1})			
Non-dominant Arm	1.3 ± 0.2	1.4 ± 0.2	7%
Dominant Arm	1.3 ± 0.3	1.6 ± 0.2	21%
Combined Arms	1.2 ± 0.3	1.5 ± 0.2	22%
Resting O2 Consumption (%/s)	0.29 ± 0.1	0.33 ± 0.1	13%
Time to Half Recovery (s)	24.9 ± 3.6	19.3 ± 7.9	25%

Summary

- **People with HF had reduced mitochondrial capacity**
- **People with HF had reduced oxygen delivery**
- **People with HF had reduced resting O_2 consumption**

Conclusions

- **People with HF had reductions in metabolic rate and reperfusion, consistent with literature.**
- **The reduced mitochondrial capacity in HF might be a result of impaired plasticity of mitochondrial capacity**
- **Future studies should look into the link between medications and mitochondrial impairment**