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Skeletal muscle microcirculatory abnormalities are associated with exercise intolerance, ventilatory inefficiency, and impaired autonomic control in heart failure

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cardiopulmonary exercise testing;
heart rate recovery;
near-infrared spectroscopy;
oxygen kinetics;
vascular occlusion technique

BACKGROUND: Several skeletal muscle abnormalities have been identified in patients with chronic heart failure (CHF), including endothelial dysfunction. We hypothesized that skeletal muscle microcirculation, assessed by near-infrared spectroscopy (NIRS), is impaired in CHF patients and is associated with disease severity.

METHODS: Eighty-three stable patients with mild–moderate CHF (72 males, mean age 54 ± 14 years, body mass index 26.7 ± 3.4 kg/m^2) and 8 healthy subjects, matched for age, gender and body mass index, underwent NIRS with the vascular occlusion technique and cardiopulmonary exercise testing (CPET) evaluation on the same day. Tissue oxygen saturation (StO_2, %), defined as the percentage of hemoglobin saturation in the microvasculature compartments, was measured in the thenar muscle by NIRS before, during and after 3-minute occlusion of the brachial artery. Measurements included StO_2, oxygen consumption rate (OCR, %/min) and reperfusion rate (RR, %/min). All subjects underwent a symptom-limited CPET on a cycle ergometer. Measurements included VO_2 at peak exercise (VO_2peak, ml/kg/min) and anaerobic threshold (VO_2AT, ml/kg/min), VE/VCO_2 slope, chronotropic reserve (CR, %) and heart rate recovery (HRR_1, bpm).

RESULTS: CHF patients had significantly lower StO_2 (75 ± 8.2 vs 80.3 ± 6, $p < 0.05$), lower OCR (32.3 ± 10.4 vs 37.7 ± 5.5, $p < 0.05$) and lower RR (10 ± 2.8 vs 15.7 ± 6.3, $p < 0.05$) compared with healthy controls. CHF patients with RR ≥9.5 had a significantly greater VO_2peak ($p < 0.001$), VO_2AT ($p < 0.01$), CR ($p = 0.01$) and HRR_1 ($p = 0.01$), and lower VE/VCO_2 slope ($p = 0.001$), compared to those with RR <9.5. In a multivariate analysis, RR was identified as an independent predictor of VO_2peak, VE/VCO_2 slope and HRR_1.

CONCLUSIONS: Peripheral muscle microcirculation, as assessed by NIRS, is significantly impaired in CHF patients and is associated with disease severity.

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Patients with chronic heart failure (CHF) present several skeletal muscle function abnormalities that seem to play a central role in the pathophysiology of exercise intolerance that occurs in CHF.[1]

Levels of several inflammatory cytokines, endothelin and von Willebrand factor are elevated in CHF, indicating an inflammatory status and a significant endothelial dysfunction with decreased vascular reactivity and peripheral vascular dysfunction.[2,3] As shown previously, impaired endothelial function is associated with exercise intolerance,

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disease severity and increased incidence of hospitalization, cardiac transplantation and mortality.[3–5]

An indirect evaluation of peripheral microcirculation can be performed by near-infrared spectroscopy (NIRS), a simple, reproducible technique that monitors regional tissue oxygen saturation (StO_2) continuously and non-invasively.[6] The information obtained from StO_2 measurements can be further enriched by applying the vascular occlusion technique.[7–9] This technique allows evaluation of peripheral tissue oxygen utilization and restoration, which depends mainly on integrity and functionality of the vascular endothelium.

We hypothesized that CHF patients present significant peripheral microcirculation abnormalities that are related to CHF disease severity.

The main purposes of the present study were to: (1) examine peripheral microcirculation by NIRS in CHF patients; and (2) clarify whether peripheral microcirculation is associated with disease severity as assessed by cardiopulmonary exercise testing (CPET) prognostic parameters.

Methods

Study population

The study group consisted of 83 patents with stable CHF (72 males; mean age 54 ± 14 years, body mass index 26.7 ± 3.4 kg/m^2) with a left ventricular ejection fraction (LVEF) ≤45%. All patients were on a stable optimal medical regimen for at least 3 months. They were referred to our laboratory from the heart failure clinic of our institution to perform a symptom-limited cardiopulmonary exercise test (CPET), as part of heart failure evaluation. Exclusion criteria from the study were moderate to severe chronic obstructive pulmonary disease, body mass index (BMI) >30 kg/m^2 and any acute inflammatory disease. Patients were also excluded from the study if there was any contraindication for CPET according to the American Thoracic Society/American College of Chest Physicians Statement on CPET.[10] A control group, consisting of 8 apparently healthy subjects matched for age, gender and BMI (7 males, mean age 54 ± 9 years, BMI 27.9 ± 3.6 kg/m^2), was also included in the study. Baseline demographic data and clinical characteristics of all patients and healthy subjects are presented in Table 1. Informed consent was obtained from all patients, as approved by the human study committee of our institution.

Table 1 Baseline Characteristics in Patients With CHF and Controls

Characteristics	CHF (N = 83)	Controls (N = 8)	p[a]
Age, years	54 ± 14	54 ± 9	NS
Gender, (M/F)	72/11	7/1	NS
BMI (kg/m^2)	26.7 ± 3.4	27.9 ± 3.6	NS
NYHA class	(27 I/38 II/18 III)	—	
LVEF (%)	31 ± 11	—	
CHF etiology			
Non-ischemic	40		
Ischemic	43		
Arterial hypertension	28 (34%)	—	
Diabetes	17 (21%)	—	
Dyslipidemia	30 (36%)	—	
Smoke	64 (77%)	—	
Medical treatment			
ACE inhibitors	76 (92%)	—	
Beta-blockers	74 (89%)	—	
Furosemide	68 (82%)	—	
Spironolactone	36 (43%)	—	
Amiodarone	28 (34%)	—	
Digitalis	16 (19%)	—	
Nitrates	10 (12%)	—	
Statins	30 (36%)	—	
Anti-platelets	37 (45%)	—	
Anti-coagulants	18 (22%)	—	

Continuous variables values are presented as mean ± SD. ACE, angiotensin-converting enzyme; CHF, chronic heart failure; BMI, body mass index; LVEF, left ventricular ejection fraction; NS, not a statistically significant difference; NYHA, New York Heart Association.

[a]Patients with chronic heart failure (CHF) vs healthy subjects.

Study design

All CHF patients and healthy subjects were initially evaluated by NIRS and the 3-minute vascular occlusion technique (VOT). All measurements were applied under the same conditions (in a seated position, having been at rest for at least 15 minutes, in the morning, and not having a meal for at least 8 hours). After the NIRS evaluation, all study participants underwent an incremental symptom-limited CPET on a cycle ergometer.

NIRS measurements

The application of NIRS in humans has been validated[11] and the physiologic aspects of NIRS have been described elsewhere.[6–9] In our study, tissue oxygen saturation (StO_2) was measured by NIRS analysis (Inspectra; Hutchinson Technology, Hutchinson, MN) of the thenar muscle. Consequently, the VOT was performed to provide more information on tissue oxygenation and vascular reactivity, as described previously.[7–9] The StO_2 (%) was monitored continuously throughout the NIRS evaluation. No muscle contractions in the upper limbs were allowed during measurements. StO_2 curves were analyzed offline by Inspectra, version 4.01 (Hutchinson). The first-degree slope of the desaturation of hemoglobin (during stagnant limb ischemia) and of the StO_2 increase (after the release of the brachial artery occlusion) was used to extrapolate the oxygen consumption rate (OCR, %/min) and reperfusion rate (RR, %/min), respectively. The peak StO_2 after the cuff release was also measured (StO_2peak).

Cardiopulmonary exercise testing

All subjects performed a symptom-limited CPET on an electromagnetically braked cycle ergometer (Ergolin 800; Sensor Medics, Anaheim, CA). The work rate increment was estimated using the Hansen et al equation to attain a test duration of 8 to 12 minutes, as shown in our previous studies.[12] Gas exchange was assessed while the patient was breathing through a low-resistance valve with the nose clamped, using a metabolic cart (Vmax 229; Sensormedics, Yorba Linda, CA). Measurements were recorded for 2 minutes at rest, for 3 minutes of unloaded pedaling before exercise, during exercise, and for the first 5 minutes of recovery. Peripheral oxygen saturation was measured continuously by pulse oximetry.