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Impaired skeletal muscle vasodilation during exercise in heart failure with preserved ejection fraction

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ABSTRACT

Background: Exercise intolerance is a hallmark symptom of heart failure patients with preserved ejection fraction (HFpEF), which may be related to an impaired ability to appropriately increase blood flow to the exercising muscle.
Methods: We evaluated leg blood flow (LBF, ultrasound Doppler), heart rate (HR), stroke volume (SV), cardiac output (CO), and mean arterial blood pressure (MAP, photoplethysmography) during dynamic, single leg knee-extensor (KE) exercise in HFpEF patients ($n = 21$; 68 ± 2 yrs) and healthy controls ($n = 20$; 71 ± 2 yrs).
Results: HFpEF patients exhibited a marked attrition during KE exercise, with only 60% able to complete the exercise protocol. In participants who completed all exercise intensities (0–5–10–15 W; HFpEF, $n = 13$; Controls, $n = 16$), LBF was not different at 0 W and 5 W, but was 15–25% lower in HFpEF compared to controls at 10 W and 15 W ($P < 0.001$). Likewise, leg vascular conductance (LVC), an index of vasodilation, was not different at 0 W and 5 W, but was 15–20% lower in HFpEF compared to controls at 10 W and 15 W ($P < 0.05$). In contrast to these peripheral deficits, exercise-induced changes in central variables (HR, SV, CO), as well as MAP, were similar between groups.
Conclusions: These data reveal a marked reduction in LBF and LVC in HFpEF patients during exercise that cannot be attributed to a disease-related alteration in central hemodynamics, suggesting that impaired vasodilation in the exercising skeletal muscle vasculature may play a key role in the exercise intolerance associated with this patient population.

1. Introduction

In the U.S. alone, heart failure (HF) afflicts over 5 million people [1] and places a considerable burden on the health care system, at a cost exceeding $30 billion annually [2]. Although HF has traditionally been associated with reduced ejection fraction (HFrEF), greater than one-half of HF patients actually exhibit normal or "preserved" ejection fraction (HFpEF) [3,4]. Interestingly, the prognosis for HFpEF patients is similar to that of HFrEF, [3,5], but in contrast to HFrEF, there is no optimal treatment strategy for HFpEF patients [6,7], and there have been no improvement in clinical outcomes in this cohort over the past two decades [5]. Given that the prevalence of HFpEF continues to rise at a rate of 1% per year relative to HFrEF [5], this represents an ever-increasing public health issue.

Severe exercise intolerance is a hallmark symptom of HF, and previous studies have documented similar magnitudes of exercise intolerance in HFpEF and HFrEF [8]; however, unlike HFrEF, the mechanisms underlying exercise intolerance in HFpEF have not been thoroughly investigated [9]. Clearly, cardiac abnormalities including increased left ventricular stiffness and the associated elevation in chamber filling pressures [10,11] may contribute to the symptoms of exercise intolerance in HFpEF [12], particularly during whole body dynamic exercise [13]. However, a growing number of studies have reported minimal impairments in central hemodynamics during exercise in HFpEF, implicating peripheral, non-cardiac mechanisms as important contributors to exercise intolerance in this cohort [14–16]. Indeed, there is emerging evidence supportive of disease-related changes in skeletal muscle fiber type composition and resultant alterations in muscle function in HFpEF patients [14,15], in line with the proposed systemic nature of HFpEF pathophysiology. In addition, exercise training studies have reported improvements in peak O_2 consumption in the absence of changes in central hemodynamics in HFpEF [17,18], further illustrating the extent to which non-cardiac mechanisms may contribute to exercise intolerance in this cohort.

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Considering this evidence of peripheral dysfunction in HFpEF, it is somewhat surprising how few studies to date have examined disease-related changes in the regulation of skeletal muscle blood flow during exercise. Puntawangkoon et al. [19] observed a reduction in superficial femoral artery blood flow upon cessation of supine cycling exercise in HFpEF patients compared to controls despite similar flow in the ascending and descending aorta, suggesting impaired distribution of cardiac output (CO) in the HFpEF group. More recently, Borlaug et al. [20] reported an impaired reduction in systemic vascular resistance during submaximal cycling exercise in HFpEF patients compared to hypertensive control patients, suggesting a disease-related change in "vasodilatory reserve". However, to our knowledge, no studies to date have attempted direct measurements of blood flow in the exercising muscle of HFpEF patients.

Also noteworthy is the fact that each of these previous studies [19,20] utilized cycle ergometry exercise, a modality that induces significant cardiopulmonary stress and therefore makes difficult the task of isolating central and peripheral contributions to perfusion of the exercising limbs. This limitation may be overcome through use of knee-extensor (KE) exercise, a small muscle mass model that does not provoke significant cardiopulmonary stress [21]. While members of our group [22–24] and others [25,26] have utilized KE exercise to examine the regional regulation of exercising leg blood flow in HFrEF, this exercise model has not been employed to examine peripheral hemodynamics in the HFpEF patient population. In view of the well-defined relationship between blood flow, O_2 uptake, and exercise capacity [27,28], disease-related changes in the regulation of skeletal muscle blood flow may be an important contributor to exercise intolerance in this patient group.

Therefore, using the small muscle mass KE exercise paradigm, we sought to evaluate exercise-induced changes in central and peripheral hemodynamics in HFpEF patients compared to healthy controls. We hypothesized that exercise-induced increases in cardiac output would be similar between groups, but that vasodilation in the active skeletal muscle would be attenuated in HFpEF patients compared to controls. If proven correct, such findings could have significant implications for our understanding of exercise intolerance in this growing patient population.

2. Methods

2.1. Participants

HFpEF patients were recruited from the HF clinics at the University of Utah and the Salt Lake City Veterans Affairs Medical Center (VAMC), and healthy controls were recruited from the greater Salt Lake City community. Patient inclusion criteria were consistent with the TOPCAT trial [29], which is as follows; (1) HF defined by the presence of ≥1 symptom at the time of screening (paroxysmal nocturnal dyspnea, orthopnea, dyspnea on exertion) and 1 sign (edema, elevation in jugular venous distention) in the previous 12 months; (2) LVEF ≥45%; (3) controlled systolic blood pressure; and (4) either ≥1 hospitalization in the previous 12 months for which HF was a major component of hospitalization, or B-type natriuretic peptide (BNP) in the previous 60 days ≥100 pg/mL. Exclusion criteria for the HFpEF group included significant valvular heart disease, acute atrial fibrillation, body mass index (BMI) >45, and any orthopedic limitations that would prevent performance of KE exercise. For the control group, participants were not taking any prescription medications and were free of overt cardiovascular disease, as indicated by a health history. All participants were non-smokers. All procedures were approved by The University of Utah and the Salt Lake City VAMC Institutional Review Boards, and studies were performed at the VA Salt Lake City Geriatric Research, Education, and Clinical Center in the Utah Vascular Research Laboratory.

2.2. Protocols

On the experimental day, participants reported to the laboratory approximately 8 h postprandial, and a fasting glucose and lipid panel was performed on blood drawn from an antecubital vein in all participants using standard methods. Data collection took place in a thermoneutral environment with participants in the semi-recumbent position (~60° reclined). A subset of patients ($n = 10$) returned to the laboratory within two weeks of the experimental day for 6-min walk (6MW) test [30] and gait speed [31] assessments to characterize functional capacity. The 6MW has been shown to predict survival and peak O_2 consumption in heart failure patients [30], and gait speed is associated with survival in aged humans [31].

2.2.1. Knee-extensor exercise

The KE exercise paradigm utilized in this investigation has been described previously in detail [21,32,33]. Briefly, participants sat in a semi-recumbent position on an adjustable chair in front of a modified cycle ergometer (model 828E; Monark Exercise AB, Vansbro, Sweden). A custom made metal boot, connected by a metal bar to the crank arm of the ergometer, held the subject's foot and lower leg, enabling participants to turn the crank of the ergometer by extending their leg. Resistance was applied directly to the flywheel to elicit incremental work rates [0 (i.e. unweighted), 5, 10, and 15 W, 1 Hz]. Participants exercised for 3 min at each level, and each exercise bout was separated by a 3 min recovery period.

2.3. Measurements

2.3.1. Ultrasound Doppler

Blood velocity and vessel diameter of the common femoral artery were determined in the exercising leg using a Logiq 7 ultrasound Doppler system (GE Medical Systems, Milwaukee, WI). The artery was insonated 2 to 3 cm proximal to the bifurcation of the superficial and deep branches. Blood velocity was collected at a Doppler frequency of 5 MHz in high-pulsed repetition frequency mode (2 to 25 kHz). Sample volume was optimized in relation to vessel diameter and centered within the vessel. Vessel diameter was obtained during end diastole (corresponding to an R wave documented by the simultaneous ECG signal; Logic 7) using the same transducer at an imaging frequency ranging from 9 to 14 MHz. An angle of insonation of ≤60 degrees [34] was achieved for all measurements. Commercially available software (Logic 7) was used to calculate arterial diameter as well as angle-corrected, time-averaged, and intensity-weighted mean blood velocity (V_{mean}). LBF was calculated with the formula: LBF (ml/min) = ($V_{mean} \times \pi$ (vessel diameter/2)$^2 \times 60$) and leg vascular conductance (LVC) was calculated as: LVC (ml/min/mm Hg) = LBF/mean arterial pressure (MAP).

2.3.2. Central cardiovascular variables

Heart Rate (HR) was monitored continuously from a standard three-lead ECG recorded in duplicate on the data acquisition device (Biopac, Goleta, CA, U.S.A.) and the Logiq 7. HR and beat-to-beat arterial blood pressure was determined non-invasively using photoplethysmography (Finapres Medical Systems BV, Amsterdam, The Netherlands). Using the arterial waveform, SV was calculated using the Modelflow method (Beatscope version 1.1; Finapres Medical Systems BV, Amsterdam, The Netherlands) [35], which has been documented to accurately track SV during a variety of experimental protocols, including exercise [36–39]. In heart disease patients, this methodology has been shown to accurately track changes in cardiac output in <95% of cases when compared to the conventional thermodilution technique [40]. MAP was calculated as: MAP (mm Hg) = diastolic arterial pressure + (pulse pressure · 0.33). CO was calculated as: CO (L/min) = SV × HR. Using the Du Bois formula, body surface area (BSA) was calculated as: BSA = $0.007184 \times$ Weight (W)$^{0.425} \times$ Height (H)$^{0.725}$. Using BSA, stroke index