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Heart failure and movement-induced hemodynamics: Partitioning the impact of central and peripheral dysfunction

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ABSTRACT

Background: The complex pathophysiology of heart failure (HF) creates a challenging paradigm to differentiate the role of central and peripheral hemodynamic dysfunction during conventional exercise. Adopting a novel reductionist approach with potential clinical relevance, we studied the central and peripheral contributors to both continuous and single passive leg movement (PLM)-induced hyperemia in 14 HF patients with reduced ejection fraction (HFrEF) and 13 controls.
Methods: Heart rate (HR), stroke volume (SV), cardiac output (CO), mean arterial pressure (MAP), and femoral artery blood flow (FBF) were recorded during PLM.
Results: The FBF response (area under the curve; AUC) to 60 s of continuous PLM was attenuated in the HFrEF (25 ± 15 ml AUC) compared to controls (199 ± 34 ml AUC) as were peak changes from baseline for FBF, leg vascular conductance (LVC), CO, and HR. During single PLM, increases in CO and HR were smaller and no longer different between groups, supporting the use of this modality to assess groups with disparate central hemodynamics. Interestingly, single PLM-induced hyperemia, likely predominantly driven by flow-mediated vasodilation due to minimal vessel deformation, was essentially nonexistent in the HFrEF (−9 ± 10 ml AUC) in contrast to the controls (43 ± 25 ml AUC).
Conclusions: These data fail to support a HFrEF-associated exaggeration in the mechanoreceptor driven component of the exercise pressor response. In fact, by exhibiting limited central hemodynamic responses compared to the controls, the observed attenuation in movement-induced FBF in HFrEF appears largely due to peripheral vascular dysfunction, particularly flow-mediated vasodilation.

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1. Introduction

Heart failure (HF) is primarily characterized by the inability of the heart to adequately support the requirement for blood flow and oxygen delivery both at rest and during exercise [1–3]. However, as the pathophysiology of HF is complex, the exact mechanisms responsible for the attenuated peripheral hemodynamic responses, first reported by Zelis et al. [4,5], are difficult to identify. Passive leg movement (PLM), typically achieved by the continuous movement of the knee joint through a 90° range of motion [6], elicits an increase in limb blood flow and vascular conductance without the increase in metabolism associated with active exercise. Previous work by our group [7] and others [8] has suggested that PLM also offers insight into nitric oxide (NO) bioavailability and endothelial-dependent vasodilation, likely due to the deformation of the vascular bed [9]. In concert with this peripheral vasodilation, mechanoreceptors result in an increase in heart rate (HR) and CO [10,11] in an attempt to maintain perfusion pressure [12].

Therefore, PLM has been proposed as a novel reductionist model that can isolate the muscle mechanoreceptors from central command and group IV metabosensitive afferents [13] and a method for determining NO bioavailability that might be easily adopted by clinicians [7]. Interestingly, a modification of this method in which only a single PLM is performed limits the mechanoreceptor response and subsequently the central hemodynamic effects of PLM. As single PLM employs a minimal physical stimulus, the movement-induced hyperemia likely relies more on flow-mediated vasodilation and less on the mechanical deformation and muscle pump than continuous PLM and is facilitated less by increases in HR and CO. These two variants of PLM may allow for a better

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understanding of both the central and peripheral factors controlling movement-induced hyperemia in HF.

As PLM directly interrogates the leg, which plays a major role in human locomotion and exercise capacity, this mode of assessment is very specific to the challenges faced by patients with HF. Consequently, using both continuous and single PLM this study sought to determine the central and peripheral contributors to movement-induced hyperemia in HF patients with reduced ejection fraction (HFrEF). Specifically, we hypothesized that 1) due to an exaggerated mechanoreceptor sensitivity, patients with HFrEF will exhibit exaggerated HR, CO, and mean arterial pressure (MAP) responses to continuous PLM compared to controls, 2) despite this augmented central hemodynamic response, continuous PLM-induced hyperemia, as measured by femoral blood flow (FBF), will be attenuated in HFrEF compared to controls due to limited peripheral vascular function, and 3) the presence of vascular dysfunction in HFrEF, will be supported by an attenuated FBF in this group compared to controls in response to single PLM, which will diminish the impact of any central hemodynamic differences.

2. Methods

2.1. Subjects

Fourteen patients with HFrEF (New York Heart Association Class II and III) and thirteen healthy age-matched controls were recruited either by word of mouth or in the HF clinics at the University of Utah and the Salt Lake City VA Medical Center. The protocol was approved by these institutions and written informed consent was obtained from all participants. The healthy controls were normotensive (<140/90), and free of overt cardiovascular disease, as determined by health history questionnaire. Exclusion criteria for the healthy controls included a diagnosis of cardiovascular disease, diabetes mellitus, hypercholesterolemia, and hypertension. Inclusion criteria for the patients with HF included New York Heart Association classification of II and III and an ejection fraction of <35%. All of the HFrEF patients were considered to be on optimal medical therapy by their physicians. Subjects were nonsmokers, did not have any lower limb orthopedic problems, did not have peripheral arterial disease, did not suffer from any type of neuropathy, and did not participate in any form of regular exercise. Subjects reported to the laboratory for testing in a fasted state, and without caffeine or alcohol use for 12 and 24 h, respectively. Additionally, subjects had not performed any vigorous activity within the past 24 h.

2.2. Continuous and single passive leg movement (PLM) protocols

Subjects rested supine for approximately 20 min prior to the start of data collection and remained in this position throughout the entire protocol. The continuous PLM protocol consisted of a 60 s baseline data acquisition followed by a one minute bout of passive leg extension. Passive exercise was achieved by a member of the research team moving the subject's lower leg through a range of motion, defined by 90 and 180° knee joint angles, at a rate of 1 Hz (throughout the protocol the control leg remained fully extended and supported). Real time feedback to the investigator was provided by a digital goniometer to ensure a consistent range of motion and a metronome was used to maintain the cadence. Prior to the start and throughout the protocol subjects were encouraged to remain passive and resist any urge to assist with leg movement. To avoid a startle reflex and active resistance to the passive movement, subjects were made aware that passive movement would take place sometime in the next minute, but, to minimize the chance of an anticipatory response, they were not informed exactly when this movement would initiate.

To further examine the role of limb movement and minimize differences in the central hemodynamic responses between the groups, single PLM was performed on a subset of subjects (controls n = 8, HFrEF n = 7). The single PLM testing protocol was performed as described above with the exception that only a single PLM was implemented from the 180° to 90° and back to the 180° knee joint angle in 1 s and measurements were then made for the following minute.

2.3. Measurements

2.3.1. Arterial blood flow and blood velocity measurements and analyses

Measurements of arterial blood velocity and vessel diameter were performed during the PLM protocols, with a Logic 7 ultrasound system (General Electric Medical Systems, Milwaukee, WI, USA). The Logic 7 was equipped with linear array transducer operating at an imaging frequency of 14 MHz. Vessel diameter was determined at a perpendicular angle along the central axis of the scanned area. Second-by-second anterograde and retrograde blood velocities were obtained using the same transducer with a Doppler frequency of 5 MHz. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insonation angle of 60° or less. The sample volume was maximized according to vessel size and was centered within the vessel based on real-time ultrasound visualization. Arterial diameter was measured, and mean velocity values (angle-corrected, and intensity weighted area under the curve) were then automatically calculated using commercially available software (Logic 7). Using arterial diameter and V_{mean}, second-by-second blood flow in the femoral arteries was calculated as: Blood flow = $V_{mean}\pi(\text{vessel diameter}/2)^2 \times 60$, where blood flow is in milliliters per minute.

2.3.2. Central hemodynamic variables

HR, stroke volume (SV), CO, and MAP signals from the Finometer (Finapres Medical Systems BV, Amsterdam, The Netherlands) were simultaneously acquired (200 Hz) using commercially available data acquisition software (AcqKnowledge, Biopac Systems). SV was calculated using the Modelflow method, which includes age, gender, height and weight in its algorithm (Beatscope version 1.1; Finapres Medical Systems BV, Amsterdam, The Netherlands) [14]. CO was then calculated as the product of HR and SV. This methodology has been documented to accurately track CO during a variety of experimental protocols including exercise [15–19] and in patients with both hypertension and vascular disease [20]. Leg vascular conductance (LVC) was calculated as leg blood flow/MAP.

2.3.3. Data acquisition

Throughout the protocol HR, SV, CO, MAP, electrocardiography and knee joint angle signals underwent A/D conversion and were simultaneously acquired (200 Hz) using the data acquisition software (AcqKnowledge, Biopac Systems). In addition, this data acquisition software also acquired (10,000 Hz) the audio anterograde and retrograde signals from the Doppler ultrasound system to serve as a qualitative indicator of blood velocity changes and to ensure accurate temporal alignment of blood velocity measurements obtained from these systems and the other signals collected (i.e. finometer and goniometer) [6].

2.4. Statistical analyses

Statistics were performed using commercially available software (SPSS 17.0, Chicago, IL). As both central and peripheral responses were transient, only data from the first 60 s of passive movement were compared and prior to analysis all second-by-second data were smoothed using a rolling 3 second average. A 2 × 2 (intervention and group) repeated-measures analysis of variance was used to determine whether maximal relative changes and peaks in CO, HR, SV, MAP, FBF, and LVC differed between groups and intervention. Tukey's honestly significant difference test was used for post hoc analysis when a significant main effect was identified. Statistical significance was established with $\alpha \leq 0.05$. All data are expressed as mean ± standard error (SE).

3. Results

3.1. Subject characteristics

The patients with HFrEF and the healthy controls were well matched for age and other physical characteristics that were assessed (Table 1). The disease specific characteristics and medications of the patients with HFrEF are displayed in Table 2. It should be noted that although all the HFrEF patients had implanted cardioverter/defibrillators, none were being actively paced during the study.

Table 1
Subject characteristics.

	Controls	HFrEF
Subjects (n)	13	14
Age (yrs)	63 ± 2	62 ± 1
Weight (kg)	83 ± 3	89 ± 5
Height (cm)	178 ± 2	176 ± 2
Body mass index (kg/m^2)	26 ± 1	28 ± 1
Systolic blood pressure (mm Hg)	124 ± 5	112 ± 3*
Diastolic blood pressure (mm Hg)	73 ± 2	72 ± 2
Glucose (mg/dL)	88 ± 3	107 ± 6*
Cholesterol (mg/dL)	184 ± 10	152 ± 13*
HDL (mg/dL)	48 ± 3	42 ± 2*
LDL (mg/dL)	119 ± 10	99 ± 10
Triglycerides (mg/dL)	99 ± 14	118 ± 20
Hemoglobin (g/dL)	15 ± 1	14 ± 1
Hematocrit (%)	44 ± 1	43 ± 2
RBC (M/uL)	5.0 ± 0.2	4.8 ± 0.2
WBC (K uL)	5.6 ± 0.4	6.8 ± 0.5

Mean ± SE; HDL: high density lipoprotein; LDL: low density lipoprotein; RBC: red blood cells; WBC: white blood cells.
* Significantly different from controls.