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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 seconds 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).

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DISCLOSURES

There are no conflicts of interest to report.

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.

Keywords

passive exercise; blood flow; exercise pressor response; afferents; mechanoreflex

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 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 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.

METHODS

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 hours, respectively. Additionally, subjects had not performed any vigorous activity within the past 24 hours.

Continuous and Single Passive Leg Movement (PLM) Protocols

Subjects rested supine for approximately 20 minutes prior to the start of data collection and remained in this position throughout the entire protocol. The continuous PLM protocol consisted of a 60 second 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 one second and measurements were then made for the following minute.

Measurements

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 antegrade 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: $\text{Blood flow} = V_{\text{mean}} \pi (\text{vessel diameter}/2)^2 \times 60$, where blood flow is in milliliters per minute.

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.

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 antegrade 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].

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 seconds 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 $\alpha = 0.05$. All data are expressed as mean $\pm$ standard error (SE).

RESULTS

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.

Hemodynamic Responses to Continuous Passive Leg Movement

The FBF and LVC responses to continuous PLM are illustrated in Figure 1. Baseline FBF was significantly lower in the patients with HFrEF (209 ± 12 ml/min) compared to the controls (295 ± 38 ml/min). Following the onset of continuous PLM, the maximum blood flow achieved in the passively moved leg increased significantly above baseline in both the patients with HFrEF (378 ± 24 ml/min, 85 %) and controls (775 ± 77 ml/min, 202 %), although the response was attenuated in the patients with HFrEF. The transient increase in FBF as a result of continuous PLM, as assessed by the area under the curve (AUC) during 60 seconds of movement, resulted in a significantly smaller hyperemic response in the patients with HFrEF (25 ± 15 ml AUC) compared to the controls (199 ± 34 ml AUC) (Figure 1B).

Baseline mean arterial pressure (MAP) was significantly lower in the patients with HFrEF (80 ± 3 mmHg) compared to controls (91 ± 3 mmHg) (Figure 2). Despite the differences in MAP, peak LVC following continuous PLM was still significantly attenuated in the patients with HFrEF (4.9 ± 0.4 ml/min/mmHg, 87 %) compared to the controls (8.6 ± 0.8 ml/min/mmHg, 185%) (Figure 1C). Similarly, the LVC AUC was also significantly reduced in the patients with HFrEF compared to the controls (Figure 1D).

The central hemodynamic responses to continuous PLM over time are illustrated in Figure 2. Baseline HR was significantly higher in the patients with HFrEF (66 ± 4 beats/min) compared to the controls (56 ± 2 beats/min) with no significant baseline differences in SV or CO. However, with the initiation of continuous PLM, the patients with HFrEF displayed a significantly attenuated change in HR (Peak: 66 ± 3 beats/min, 3%) and CO (Peak: 5.9 ± 0.4 L/min, 8%) compared to the controls (Peak HR: 63 ± 2 beats/min, 13%; and Peak CO: 6.8 ± 0.7 L/min, 17%). There was no significant difference in the SV and MAP peak responses between groups.

Hemodynamic Responses to Single Passive Leg Movement

In the subset of subjects that performed single PLM, baseline FBF was significantly lower in the patients with HFrEF (237 ± 23 ml/min) compared to the controls (336 ± 42 ml/min) (Figure 3A). During single PLM, FBF increased significantly above baseline in both the patients with HFrEF (Peak: 362 ± 43 ml/min, 54 %) and the controls (Peak: 569 ± 77 ml/

min, 73%), but this response was significantly attenuated in the HFrEF group. The transient response in FBF, as assessed by AUC, resulted in a significantly lower and essentially unchanged single PLM-induced hyperemic response in the patients with HFrEF (-9 ± 10 ml AUC) compared to the controls (43 ± 25 ml AUC) (Figure 3B).

There was a significantly lower baseline MAP in the patients with HFrEF (78 ± 3 mmHg) compared to the controls (93 ± 5 mmHg) and no difference in either group in response to the single PLM (Figure 4). Peak change in LVC from baseline following single PLM was lower in the patients with HFrEF (4.8 ± 0.6 ml/min/mmHg, 60 %) compared to the controls (6.6 ± 0.8 ml/min/mmHg, 86%), but was not significantly different. However, LVC AUC was significantly blunted in the HFrEF patients (Figure 3C).

Baseline HR was significantly higher in the patients with HFrEF (67 ± 2 beats/min) than in the controls (60 ± 3 beats/min). However, at the start of single PLM there was not a significant increase above baseline in either group (Figure 4A). With single PLM, peak SV was significantly increased above baseline in both the patients with HFrEF (96 ± 10 ml, 6%) and the controls (120 ± 14 ml, 8%), but the group responses were not different from each other (Figure 4B). There was a relatively small SV driven, increase in CO, but this was again not different between groups (Figure 4C).

DISCUSSION

Utilizing PLM, a novel reductionist model that provides insight into peripheral vascular function and can isolate the group III mechanoreceptors, we sought to partition the central and peripheral contributors to movement-induced hyperemia in patients with HFrEF. There are several key findings from this study, with the first being; there was no evidence of an exaggerated mechanoreceptor driven component of the exercise pressor reflex during continuous PLM in optimally medicated patients with HFrEF. In fact, the HR and CO responses to continuous PLM in patients with HFrEF were attenuated compared to controls. Concomitantly, the patients exhibited a diminished movement-induced FBF that could not be attributed to these central hemodynamic differences because the MAP response to continuous PLM in both groups was similar. With single PLM, central hemodynamic responses were similar between the patients and controls, and the evidence of peripheral vascular dysfunction not only remained, but became more evident. In combination, these findings highlight the lack of an exaggerated mechanically-induced contribution to the exercise pressor reflex in medicated patients with HFrEF and, despite exhibiting central hemodynamic dysfunction, the attenuated FBF in HFrEF appears largely due to peripheral vascular dysfunction. Consequently, these findings additionally suggest that PLM can be used as a novel *in vivo* method with which to determine endothelium-dependent peripheral vascular function in both health and disease.

Mechanoreceptors and HFrEF

One of the compensatory mechanisms for a failing heart is increased sympathetic nerve activity at both rest and during exercise. This has been proposed to be due, at least in part, to exaggerated afferent signaling from sensitized group III mechanoreceptors in the skeletal muscle [21] and documented in both animal models of HF [22] and in patients with HF [23].

During exercise, these sensitized mechanoreceptors are thought to contribute to a greater than normal peripheral neural reflex, known as the exercise pressor reflex [24]. PLM targets the group III mechanoreceptors and eliminates exercise-induced metabolism. Therefore, we hypothesized that HR and MAP responses in patients with HFrEF would be exaggerated during PLM. However, even at rest the patients with HFrEF in the current study had a significantly lower MAP (80 ± 3 mmHg) compared to the controls (91 ± 3 mmHg) and this attenuation in pressure continued throughout continuous PLM (Figure 2D). Interestingly, there was no difference in the maximal MAP response elicited by continuous PLM (% change from baseline) between the groups. Considering that PLM specifically isolates the group III mechanoreceptors, thought to be sensitized in HF, the similar MAP response to the initiation of continuous PLM, was somewhat surprising. However, this finding actually further supports previous work by Middlekauf et al. [25] and our own group [26] that was unable to reveal any evidence of an exaggerated exercise pressor reflex during passive arm exercise and active handgrip exercise, respectively, in patients with HFrEF. It is acknowledged that the lower baseline MAP and the lack of an exaggerated exercise pressor reflex could be attributed to the patient's pharmacological therapies, but this approach was chosen to minimize risk and study these patients with their disease pharmacologically controlled.

Peripheral vascular dysfunction in patients with HFrEF

Although HF is clearly a pathology that affects central hemodynamics, there are also peripheral abnormalities associated with this disease that include alterations in skeletal muscle [3, 27], increased sympathetic nerve activity [22, 28], and peripheral vascular dysfunction [29], all of which have been proposed to contribute to a reduction in both limb blood flow and exercise capacity. Indeed, although upon initiation of continuous PLM there was a significant increase in FBF in both groups (Figure 1), as hypothesized, the FBF response was consistently attenuated in the patients compared to controls. This attenuation was clearly evident in the peak FBF response, percent change from baseline, and AUC.

Previous work by our group [7] and others [8] has revealed that the continuous PLM model offers insight into NO bioavailability and endothelial-dependent vasodilation. Specifically, by using an intra-arterial infusion of N^G-monomethyl-L-arginine to inhibit NO synthase, the hyperemic and vasodilatory response to continuous PLM was reduced by approximately 80% [7]. In the current study, both continuous and single PLM assessments resulted in significantly attenuated FBF in the patients with HFrEF compared to controls. Thus, these findings suggest that the attenuation in FBF following PLM in the patients with HFrEF could be due to compromised NO-dependent vasodilation. Although diminished endothelial function is a likely explanation for the decreased FBF in the patients with HFrEF, there is also a possibility that the globally increased vasoconstriction associated with sensitized group III mechanoreceptors in this patient population [21, 23] may have played a role. However, it should be noted that the single PLM model, which greatly reduces the stimulation of the group III mechanoreceptors as evidenced by the lack of a HR response in either subject group, also revealed that the FBF response in the HFrEF was still greatly attenuated. In combination, these data are consistent with the fact that impaired endothelium-dependent vasodilation has long been associated with many cardiovascular

diseases, including HF [30, 31], but extends these findings to movement-induced hyperemia, uncomplicated by changes in metabolism. Utilization of the single PLM removed the influence of the persistent mechanical stimulus associated with continuous movement of the leg. Thus, the FBF response to single PLM is likely to be predominantly a result of flow-mediated vasodilation. Although, continuous PLM FBF in the patients with HFrEF was reduced compared to the controls, the attenuation in HFrEF patient FBF during the single PLM model was of a greater magnitude. This far greater reduction in flow-mediated vasodilation, isolated by the single PLM approach, in patients with HFrEF compared to the combination of vasodilatory stimuli induced by the continuous mechanical deformation may be of great significance in terms of the impact of HF on the peripheral vascular response to exercise. Additionally, these data suggest that both single and continuous PLM can be used as a novel *in vivo* method with which to determine endothelium-dependent peripheral vascular function in both health and disease.

Central hemodynamics and FBF in patients with HFrEF

It is well accepted that activities of daily living and exercise capacity are limited in patients with HF and this diminished physical function is often attributed to the failing cardiac pump and the associated changes in central hemodynamics. Indeed, exercise capacity is heavily dependent upon the ability of the heart to increase CO to effectively maintain blood pressure and support blood flow and oxygen delivery to the working muscles. In patients with HF the ability to increase both SV and HR tends to be reduced. SV is typically reduced at rest and then fails to increase appropriately during exercise as the dilated left ventricle is already at or near maximal volume and is therefore unable to further increase preload and ejection fraction [3, 32]. As a compensatory mechanism, resting HR is often higher in patients with HF and consequently the heart rate reserve is attenuated, contributing to a blunted CO response during exercise [32]. In the current subjects, baseline HR was indeed significantly higher in the HFrEF patients and the increase in HR upon initiation of continuous PLM was attenuated compared to the controls (Figure 2). This attenuated HR response to continuous PLM also resulted in a significant attenuation in peak CO in the patients with HFrEF.

It could be surmised that the attenuated FBF in response to continuous PLM observed in the patients with HFrEF was due to the disease related reductions in HR and CO. However, importantly, despite differences in the CO response, PLM-induced changes in MAP were similar between groups and, as described by Ohm's law, subsequent differences in FBF must have been the consequence of vascular resistance. Thus, it appears that the documented central hemodynamic differences did not contribute to the reduced PLM-induced FBF in the HFrEF. To further address potential concerns about the different PLM-induced central hemodynamics in the patients and controls, single PLM was also performed in a subset of both groups. By design, single PLM did not result in a significant increase in HR above baseline in either the HFrEF patients or the control group (Figure 4A). There was also no difference between the groups in terms of SV and therefore the CO response, which was attenuated compared to the continuous PLM trials. Despite the similar central hemodynamic responses (HR, SV, and CO) to single PLM in both groups, the patients with HFrEF still exhibited a greatly attenuated response compared to the controls both in terms of peak FBF response (HFrEF: 362 ± 43 ml/min; Control: 569 ± 77 ml/min) and FBF AUC (HFrEF: -9

± 7 ml; Control: 43 ± 25 ml). These data support the use of single PLM as means by which to reduce the impact of differing central hemodynamics responses on the peripheral hyperemic response and suggest that the attenuated FBF exhibited by the patients with HFrEF is, indeed, largely due to peripheral vascular dysfunction.

Experimental Considerations

We acknowledge several experimental considerations that may be perceived as limitations to this study. First, although vascular function is recognized to be attenuated in both non-ischemic and ischemic HFrEF patients compared with controls, the relatively small sample size resulted in the inability to make comparisons between etiologies. Additionally, as we chose not to remove these HFrEF patients from their current medications, we cannot rule out the possibility of a pharmacological effect on the hemodynamic responses assessed herein. Also, due to a need to maintain patient safety, the investigators were not blinded to the health status of the subjects (HFrEF vs Controls). Finally, although NO has been previously documented to play a large role in the PLM response [7, 8], this study does not provide direct evidence of this and therefore other vasodilators may have mediated the responses reported here.

Conclusion

In response to continuous PLM there was no evidence of an exaggerated mechanoreceptor driven component of the exercise pressor reflex in patients with HFrEF. In fact, the HR and CO response to continuous PLM was attenuated. A similar MAP response with both continuous and single PLM, which normalized central hemodynamics, revealed that the attenuated FBF in patients with HFrEF is a consequence of peripheral vascular function. These data further support the need to focus on the periphery when targeting exercise intolerance and disease progression in patients with HF and document PLM as a novel tool for assessing peripheral vascular function in both health and disease.

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Highlights

- Use novel reductionist approach to isolate contributors to movement-induced hyperemia
- No evidence of exaggerated exercise pressor reflex in HFrEF
- Attenuated movement-induced leg blood flow is partially due to vascular dysfunction
- Passive leg movement is novel tool in assessing vascular function in health & disease
- Supports the need to focus on the periphery when targeting exercise intolerance

Figure 1.

Peripheral hemodynamic responses to continuous PLM in controls and patients with HFrEF. Data are presented as mean $\pm$ SE for femoral blood flow (A), femoral blood flow area under the curve (AUC) (B), leg vascular conductance (C), and leg vascular conductance AUC (D). The transition from baseline to movement occurs at 0 on the axis.

Figure 2.

Central hemodynamic responses to continuous PLM in controls and patients with HFrEF. Data are presented as mean $\pm$ SE for heart rate (A), stroke volume (B), cardiac output (C), and mean arterial pressure (D) across time. Note: These figures are presented to illustrate the general trends. As the analyses were performed on data from individuals who exhibited varying response kinetics, averaging removes some of the information in the original individual recordings. Therefore, maximum change is represented in the upper corner of each figure.

Figure 3.

Peripheral hemodynamic responses to single PLM in controls and patients with HFrEF. Data are presented as mean $\pm$ SE of femoral blood flow (A), femoral blood flow area under the curve (AUC) (B), leg vascular conductance (C), and leg vascular conductance AUC (D). The transition from baseline to movement occurs at 0 on the axis.

Figure 4.

Central hemodynamic responses to single PLM in controls and patients with HFrEF. Data are presented as mean $\pm$ SE of heart rate (A), stroke volume (B), cardiac output (C), and mean arterial pressure (D) across time. Note: These time plots are presented to illustrate the general trends. As the analyses were performed on data from individuals who exhibited varying response kinetics, averaging removes some of the information in the original individual recordings. Therefore, maximum change is represented in the upper corner of each figure.

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 (mmHg)	124±5	112±3 [*]
Diastolic blood pressure (mmHg)	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 bloodcells.

^{*} Significantly different from controls.

Table 2

HFrEF characteristics and medications

Disease specific characteristics:	HFrEF
Diagnoses:	
Ischemic cardiomyopathy	11/14
Non-ischemic cardiomyopathy	3/14
Left Ventricular Ejection fraction (%)	24±2
NYHA Class E	10/14
NYHA Class III	4/14
HFrEF Duration (yrs)	7±2
History of Hypertension	8/14
History of Hypercholesterolemia	9/14
Diabetic	5/14
B-type Natriuretic Peptide (pg mL)	595±234
Medications:	
Beta-blocker	13/14
ACE-Inhibitor	9/14
Angiotensin Receptor Blocker	3/14
Statin	11/14
Diuretic	11/14
Calcium channel-blocker	0/14
Alpha-blocker	0/14
Oral Hypoglycemic agent	2/14
Insulin	2/14

Mean±SE or expressed as the fraction of all subjects where appropriate.