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Metaboreceptor Activation in Heart Failure with Reduced Ejection Fraction: Linking Cardiac and Peripheral Vascular Hemodynamics

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Abstract

This study sought to evaluate the muscle metaboreflex in heart failure patients with reduced ejection fraction (HFrEF), with an emphasis on the interaction between cardiac and peripheral vascular hemodynamics across multiple levels of metaboreceptor activation. In 23 HFrEF patients (63 ± 2 yrs) and 15 healthy controls (64 ± 3 yrs), we examined changes in mean arterial pressure (MAP), cardiac output (CO), systemic vascular conductance (SVC), effective arterial elastance (Ea), stroke work (SW), and forearm deoxyhemoglobin concentration during metaboreceptor activation elicited by post-exercise circulatory occlusion (PECO) following three levels of static-intermittent handgrip exercise (15, 30, and 45% maximal voluntary contraction (MVC)). Across workloads, the metaboreflex-induced increase in deoxyhemoglobin and MAP were similar between groups. However, in controls, the pressor response was driven by changes in CO (Δ495 ± 155, Δ564 ± 156, Δ666 ± 217 ml/min), while this change was accomplished by intensity-dependent reductions in SVC in patients with HFrEF (Δ−4.9 ± 1.5, Δ−9.1 ± 1.9, Δ−12.7 ± 1.8 ml/min/mmHg). This differential response contributed to the exaggerated increases in Ea in HFrEF compared to controls, coupled with a blunted response in SW in the HFrEF patients. Together, these findings indicate a preserved role of the metaboreflex-induced pressor response in HFrEF, but suggest that this response is governed by changes in the peripheral circulation. The net effect of this response appears to be maladaptive, as it places a substantial hemodynamic load on

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the left ventricle that may exacerbate left ventricular systolic dysfunction and contribute to exercise intolerance in this patient population.

Keywords

Heart Failure; Metaboreflex; Exercise; Arterial Blood Pressure

Introduction

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome which is commonly linked to exercise intolerance (Wilson *et al.*, 1983; Sullivan & Hawthorne, 1995). While there are many contributing factors to exercise intolerance in this patient population, maladaptation of skeletal muscle has been increasingly recognized, with specific interest focused on the muscle metaboreflex. Activation of this reflex pathway is mediated by metabolically-sensitive group IV afferent fibers (metaboreceptors) originating in skeletal muscle, which increase efferent sympathetic nervous system activity in an effort to augment perfusion of the exercising skeletal muscle through increases in arterial blood pressure (ABP) (O'Leary & Augustyniak, 1998; Crisafulli *et al.*, 2007; Amann *et al.*, 2011). Whether the metaboreflex is altered in HFrEF patients remains an ongoing topic of debate (Middlekauff & Sinoway, 2007; Piepoli & Coats, 2007), with evidence for both similar (Sterns *et al.*, 1991; Carrington *et al.*, 2001; Notarius *et al.*, 2001; Kon *et al.*, 2004) and exaggerated (Piepoli *et al.*, 1996; Shoemaker *et al.*, 1998; Silber *et al.*, 1998; Piepoli *et al.*, 1999; Piepoli & Coats, 2007) reflex increases in mean arterial blood pressure (MAP) during metaboreflex activation. These disparate findings suggest that significant uncertainty remains regarding disease-related changes in the muscle metaboreflex in HFrEF patients, as well as the contribution of this reflex to the cardiovascular response to exercise.

Beyond the simple determination of the pressor response, further insight into the importance of metaboreceptor activation in patients with HFrEF may be gained by considering the relative contribution of changes in cardiac (i.e. cardiac output, CO) and peripheral vascular (i.e. systemic vascular conductance, SVC) hemodynamics to the increase in MAP in these patients. Interestingly, in an animal model of systolic heart failure (HF), the contribution of these factors to the overall metaboreflex-induced pressor response have been documented to be solely due to a reduction in SVC across exercise intensities (Hammond *et al.*, 2000). This is vastly different than the response observed in healthy animals, where the metaboreflex-induced increase in MAP is predominantly due to an increase in CO at low to moderate exercise intensities, with a shift towards a reliance on SVC to increase MAP only during high intensity efforts, when the ability to increase CO was compromised (Augustyniak *et al.*, 2001). In humans, only one study to date has examined cardiac and peripheral vascular contributions to the metaboreflex in HFrEF. In this study, Crisafulli *et al.* (2007) reported a metaboreflex-induced increase in MAP which was predominantly driven by an increase in CO in healthy individuals and by a reduction in SVC in patients with HFrEF, suggesting a greater role of the peripheral vasculature in governing the pressor response. However, this study only included one level of metaboreceptor activation, leaving uncertainty regarding the

differential nature of the response that has been demonstrated in an animal model of systolic HF (Hammond *et al.*, 2000).

Whether the metaboreflex-mediated increase in MAP is achieved by cardiac or peripheral vascular mechanisms may be of functional significance in HFrEF patients, as this reflex may further stress cardiac muscle through a substantial increase in afterload. Indeed, SVC, a measure of systemic vascular tone, represents the non-pulsatile component of arterial afterload (Yin & Avolio, 1987; Kass & Kelly, 1992), and considering that patients with HFrEF are known to be afterload-sensitive (Asanoi *et al.*, 1989; Kameyama *et al.*, 1991; Schwartzenberg *et al.*, 2012a), these patients can experience severe impairments in left ventricular systolic function when arterial afterload is increased (Kameyama *et al.*, 1991). Thus, while the metaboreflex response is typically viewed as an effective way to increase perfusion of the exercising muscle by increasing perfusion pressure in healthy individuals, this reflex may, in fact, exacerbate existing left ventricular systolic dysfunction in HFrEF patients if metaboreceptor activation results in a marked reduction in SVC.

Thus, this study aimed to use post-exercise circulatory occlusion (PECO) following static-intermittent handgrip exercise across a range of exercise intensities to comprehensively investigate the interaction between cardiac and peripheral vascular responses to metaboreceptor activation in HFrEF. We hypothesized that, compared to controls,: 1) HFrEF patients would exhibit similar increases in MAP across all levels of metaboreceptor activation, 2) HFrEF patients would exhibit a greater dependence on reductions in SVC than increases in CO to achieve the metaboreflex-induced pressor response, and 3) HFrEF patients would exhibit a greater increase in effective arterial elastance (Ea) and an attenuated increase in functional left ventricular systolic work in response to metaboreceptor activation.

Methods

Ethical Approval

Protocol approval and written informed consent were obtained according to University of Utah and Salt Lake City Veterans Affairs Medical Center Institutional Review Board requirements (IRB #40212, approved 06/16/2010), in compliance with clause 35 of the Declaration of Helsinki.

Subjects

23 NYHA class II-III HFrEF patients (22 males, 1 female) and 15 healthy controls (14 males, 1 female) of similar age were recruited either by word of mouth or in the HF clinics at the University of Utah Health Sciences Center and the Salt Lake City VA Medical Center. All subjects were nonsmokers, and controls were not taking any prescription medication and were free of overt cardiovascular disease, as indicated by a health history questionnaire. All studies were performed in a thermoneutral environment, with subjects reporting to the laboratory fasted, and not having performed any exercise within 24 hours of the study.

Handgrip Exercise and Metaboreceptor Activation

Subjects were instrumented with a Finometer (Finapres Medical Systems, Amsterdam, The Netherlands) on the non-exercising arm, a 3-lead ECG (Biopac, Goleta, CA, U.S.A.) to measure heart rate, and a pneumatic blood pressure cuff distal to the antecubital fossa on the exercising arm to isolate the metaboreflex following exercise. Subjects remained in the supine position for the duration of the protocol. After ~20 minutes of rest, baseline measurements were taken over the course of 1 minute. Each subject's maximal voluntary contraction (MVC) was then established by taking the highest value recorded of three maximal contractions using a handgrip dynamometer (TSD121C, Biopac Systems, Goleta, CA). Static-intermittent handgrip exercise was performed at three intensities based on each subject's MVC (15, 30, and 45% of MVC). The subjects squeezed the dynamometer to the sound of a metronome (1 Hz) and real-time force output was displayed on a computer monitor so that subjects could evaluate their effort and make corrections when necessary. Each bout of handgrip exercise lasted 3 minutes, and was followed by 2 minutes of PECO to isolate the metaboreflex, with measurements taken during the final minute. Forearm ischemia was achieved through the inflation of the pneumatic blood pressure cuff on the exercising arm to suprasystolic pressures (>250 mmHg) 5 seconds prior to cessation of exercise. A 5 minute recovery period was given after each period of metaboreceptor activation to allow cardiovascular variables to return to resting values. If cardiovascular variables did not return to resting values after 5 minutes, additional rest was given.

Measurements

Hemodynamic Variables—Stroke volume (SV), heart rate (HR), CO, and ABP were determined non-invasively (Finapres Medical Systems BV, Amsterdam, The Netherlands). SV was calculated using the Modelflow method which includes age, sex, height, and weight in its algorithm (Beatscope version 1.1; Finapres Medical Systems BV, Amsterdam, The Netherlands) (Bogert & van Lieshout, 2005), and has been documented to accurately track CO during a variety of experimental protocols including exercise (Sugawara *et al.*, 2003; van Lieshout *et al.*, 2003; de Vaal *et al.*, 2005; de Wilde *et al.*, 2009). Pulse pressure (PP), a measure of pulsatile arterial afterload, the non-resistive oscillatory component of arterial afterload (Kelly *et al.*, 1992; Chemla *et al.*, 1998) was calculated as: PP (mmHg) = systolic arterial pressure (SAP) – diastolic arterial pressure (DAP). Total arterial compliance (TAC), an index of pulsatile arterial afterload which takes into account the effect of SV (Chemla *et al.*, 1998; Reil *et al.*, 2013) was calculated as: Total arterial compliance (ml/mmHg) = SV/PP. MAP was calculated as: MAP (mmHg) = DAP + (PP*0.33). End systolic arterial pressure (P_{es}) was calculated as (Kelly *et al.*, 1992): P_{es} = 0.9*SAP. CO was calculated as: CO (L/min) = SV*HR. SVC, a measure of systemic vascular tone and the non-pulsatile (mean resistive) component of arterial afterload (Kass & Kelly, 1992) was calculated as: SVC (ml/min/mmHg) = CO/MAP. Systemic vascular resistance (SVR) was calculated as: SVR (mmHg/L/min) = MAP/CO. Ea, an index of total arterial afterload (both pulsatile and non-pulsatile arterial afterload) (Kelly *et al.*, 1992; Reil *et al.*, 2013) was calculated as: Ea (mmHg/ml) = P_{es}/SV. Stroke work (SW), a measure of functional left ventricular systolic work (Sunagawa *et al.*, 1985; Kass & Kelly, 1992) was calculated as: SW (mmHg*ml) =

P_{es}*SV. Rate pressure product (RPP), an index of myocardial oxygen consumption (Kitamura *et al.*, 1972) was calculated as: RPP (AU) = SAP*HR.

Near Infrared Spectroscopy—To determine muscle microvascular deoxyhemoglobin (DeLorey *et al.*, 2003) during exercise and metaboreceptor activation, in a subset of subjects (HFrEF = 13; control = 9), near infrared spectroscopy (NIRS) measurements were made in the brachioradialis and the flexor carpi radialis muscles. A frequency-domain multi-distance NIRS system was utilized (Oxiplex TS, ISS, Champaign, IL) that allows the absolute quantification of deoxyhemoglobin concentrations, expressed in μM (Hueber *et al.*, 2001). Prior to use, the probe was calibrated using a block with known absorption characteristics to calculate the absorption and scattering coefficients. Prior to placement, the skin covering the brachioradialis and the flexor carpi radialis was cleaned and double-sided adhesive tape was used to seat the diode, which was covered and further secured with coban (3M, St. Paul, MN). The data were acquired at 0.5 Hz, and 1 minute averages were calculated during the last minute of each exercise bout and during the final minute of PECO.

Data Analysis

Statistics were performed using commercially available software (SigmaStat 3.10; Systat Software, Point Richmond, CA). For both the exercise and metaboreceptor activation portion of the protocol, a 2×4 repeated measures ANOVA ($\alpha < 0.05$) (group: 2 levels; controls vs. HFrEF) (workload or metaboreflex activation: 4 levels; rest, 15, 30, and 45% of MVC) was utilized to determine the exercise and metaboreflex-induced alterations in hemodynamic measurements. The Holm-Sidak method was used for alpha adjustment and post hoc analysis.

Results

Subject characteristics

Baseline characteristics of the control subjects and HFrEF patients are displayed in Table 1. Disease-specific characteristics and medications of patients with HFrEF are presented in Table 2. Handgrip MVC force was similar between controls (27 ± 6 kg) and patients with HFrEF (25 ± 7 kg).

Rest and exercise hemodynamics

Cardiac and peripheral vascular hemodynamics for both groups are presented in Table 3. At rest, there were no significant differences in deoxyhemoglobin, MAP, CO, or SVC in HFrEF patients compared to controls. Exercise elicited similar intensity-dependent increases in deoxyhemoglobin and MAP between groups. The changes in MAP were dictated by increases in CO across workloads in control subjects, and reductions in SVC in HFrEF patients. This was complemented by substantially attenuated increases in SAP and exaggerated increases in DAP in HFrEF compared to control subjects. These blood pressure differences resulted in a lower PP across exercise intensities in HFrEF compared to controls. However, when factoring in the differences in SV on PP, as expressed by TAC, there were no significant differences in TAC between groups at any workload. Ea was significantly increased across all workloads in both groups, however, the increases were significantly

greater in HFrEF patients compared to controls at the two highest workloads. SW increased significantly across all workloads in the control subjects, with no significant difference from rest demonstrated by the HFrEF patients. In contrast, RPP was similar across all workloads in both groups.

Metaboreflex-induced changes in hemodynamics

Cardiac and peripheral vascular hemodynamics during metaboreceptor activation via PECO are presented in Table 4. Metaboreceptor activation provoked similar increases in tissue deoxyhemoglobin and MAP (Figure 1, top panel) across increasing levels of activation between groups. However, the metaboreflex-induced increases in MAP were due exclusively to increases in CO in controls (Figure 1, middle panel), and reductions in SVC in the patients with HFrEF (Figure 1, bottom panel). Similar to exercise, HFrEF patients exhibited a blunted increase in SAP across increasing levels of metaboreceptor activation and exaggerated increases in DAP compared to controls (Table 4). This led to a significantly attenuated increase PP in the patients with HFrEF, who only established an increase in PP at the highest level of metaboreceptor activation. However, when factoring in the significantly greater increases in SV induced by the metaboreflex exhibited by the control subjects compared to HFrEF patients (expressed as TAC), no difference was evident between groups at any level of metaboreceptor activation (Table 4). Metaboreceptor activation provoked minimal increases in Ea in controls, who only exhibited a significant increase at the highest level (Figure 2). In contrast, HFrEF patients had significant increases in Ea across all levels of metaboreceptor activation and were significantly different from controls at the highest two levels (Figure 2). SW was significantly increased by metaboreceptor activation at every level in the control group, and only at the highest activation level in HFrEF patients, but was significantly lower across all levels of metaboreceptor activation in HFrEF compared to controls (Figure 3, top panel). These differences in SW between groups were due to significantly blunted changes in P_{es} (Figure 3, middle panel) and SV (Figure 3, bottom panel) induced by metaboreceptor activation in HFrEF patients compared to the control group. Across all levels of metaboreceptor activation, RPP was similar between groups.

Discussion

This study sought to comprehensively examine the muscle metaboreflex in HFrEF patients and healthy control subjects of a similar age, with an emphasis on investigating the cardiac and peripheral vascular hemodynamic contributions to the metaboreflex-induced pressor response. Across multiple levels of metaboreceptor activation, the increase in MAP was similar between groups, providing new evidence refuting a disease-related exaggeration of the muscle metaboreflex-induced pressor response in HFrEF. However, a disease-specific, discrete pattern of cardiac and peripheral vascular hemodynamic changes was observed between groups. In control subjects, the pressor response induced by metaboreceptor activation was driven by an increase in CO, with no significant change in SVC. In contrast, progressively greater reductions in SVC contributed to the pressor response in patients with HFrEF, while CO remained unchanged. The functional consequence of relying upon changes in SVC to govern the pressor response during metaboreflex activation in the patients with HFrEF was evident through marked increases in total arterial afterload, which

appears to have provoked a reduction in myocardial efficiency during metaboreceptor activation. Together, these findings indicate a preserved role of the muscle metaboreflex-induced pressor response in HFrEF. However, the shift to an increase in peripheral vasoconstriction to drive this response in patients with HFrEF appears to represent a maladaptive process which places a substantial hemodynamic load on the left ventricle, potentially exacerbating the underlying impairment in left ventricular systolic function and thereby contributing to the exercise intolerance present in this patient population.

Metaboreflex contribution to the exercise-induced changes in mean arterial pressure

It is well established that patients with HFrEF suffer from a nearly insurmountable intolerance to physical exertion (Wilson *et al.*, 1983; Sullivan & Hawthorne, 1995), which may be due, at least in part, to maladaptations in skeletal muscle. Indeed, Drs. Coats and Piepoli (Coats *et al.*, 1994; Piepoli *et al.*, 1999) have hypothesized that abnormalities in sensory reflex activity in skeletal muscle may contribute to the exercise limitations in HFrEF, the so-called “muscle hypothesis” of heart failure. Located within the skeletal muscle are two distinct sensory afferent fiber types; group III afferent fibers, which are predominately mechanically sensitive (mechanoreceptors) and group IV afferent fibers (metaboreceptors) which are principally sensitive to metabolites produced during exercise (Kaufman & Hayes, 2002). Collectively, these reflex pathways serve to increase sympathetic nervous system activity, which ultimately increase perfusion pressure (O'Leary & Augustyniak, 1998; Crisafulli *et al.*, 2007; Amann *et al.*, 2011). In HFrEF patients, some aspect of this reflex response appears to be dysfunctional.

While it is difficult to completely isolate these respective reflex pathways, PECO has become a widely adopted experimental approach whereby metabolic byproducts produced during exercise are trapped distal to the point of occlusion, activating group IV afferent fibers with minimal input from the group III fibers (Alam & Smirk, 1937). Interestingly, despite extensive use of this technique over the past 80 years in both healthy humans and patient populations, the exact role of metaboreceptor activation in the cardiovascular response to exercise in HFrEF remains a topic of ongoing debate. Indeed, using microneurography for direct assessment of muscle sympathetic nerve activity (MSNA), evidence can be found for blunted (Sterns *et al.*, 1991), similar (Middlekauff *et al.*, 2004), and increased (Notarius *et al.*, 2001) activity during PECO in HFrEF patients compared to healthy individuals. Likewise, evidence exists for both similar (Sterns *et al.*, 1991; Carrington *et al.*, 2001; Notarius *et al.*, 2001; Kon *et al.*, 2004) and exaggerated (Piepoli *et al.*, 1996; Shoemaker *et al.*, 1998; Silber *et al.*, 1998; Piepoli *et al.*, 1999; Piepoli & Coats, 2007) reflex increases in MAP during metaboreflex activation in HFrEF patients, indicating that significant uncertainty remains as to whether the metaboreflex-induced pressor response is altered in this patient group.

In the present study, we employed the PECO technique following three different handgrip exercise intensities in an effort to comprehensively evaluate the muscle metaboreflex in HFrEF patients compared to healthy control subjects of a similar age. As illustrated in Figure 1 (top panel), we observed a metaboreflex-induced pressor response that was almost identical between groups across all levels of metaboreceptor activation. These results are in

disagreement with some of the earliest work on this topic (Shoemaker *et al.*, 1998; Piepoli *et al.*, 1999), and may be explained by differences in experimental protocols, including differing handgrip exercise paradigms and methods of activating the muscle metaboreflex (PECO vs. limb positive pressure). To our knowledge, this is the first study to perform PECO following multiple intensities of static-intermittent handgrip exercise, providing a comprehensive and systematic assessment of the pressor response across multiple levels of metaboreceptor activation. The present findings thus confirm and extend observations from previous work (Sterns *et al.*, 1991; Carrington *et al.*, 2001; Notarius *et al.*, 2001; Kon *et al.*, 2004), providing new evidence refuting a disease-related exaggeration of the pressor response induced by the muscle metaboreflex in patients with HFrEF.

Cardiac and peripheral vascular hemodynamic contributions to metaboreflex-induced changes in MAP

While a large number of studies have focused on elucidating the strength of the metaboreflex-induced pressor response in HFrEF, limited work has been undertaken to examine the variables contributing to this rise in MAP. In a healthy animal model, Augustyniak *et al.* (Augustyniak *et al.*, 2001) documented that the rise in MAP triggered by metaboreceptor activation was achieved via two distinct, but complimentary, mechanisms. Specifically, during mild and moderate exercise intensities, the increase in MAP was due solely to increases in CO, with a shift towards a reliance on SVC to increase MAP only during high intensity exercise, when the ability to increase CO was compromised. In contrast to this somewhat dichotomous response, work from the same group reported that the metaboreflex-induced increases in MAP in an animal model of systolic HF were primarily due to reductions in SVC (Hammond *et al.*, 2000), indicating that the pressor response was achieved almost exclusively via sympathetic vasoconstriction of the peripheral vasculature. Based on these findings, the authors concluded that the inability of the metaboreflex to increase CO in this animal model of HF is likely detrimental, as only a single mechanism appears to be available for this reflex pathway to increase perfusion pressure, and ultimately, blood flow to exercising skeletal muscle.

The present study builds upon the previous findings to human HF, documenting metaboreflex-induced increases in MAP in patients with HFrEF (Figure 1, top panel) that were primarily accomplished through reductions in SVC (Figure 1, bottom panel), with virtually no changes in CO (Figure 1, middle panel). This was in marked contrast to the response observed in healthy control subjects, where increases in CO played a dominant role in increasing MAP during metaboreceptor activation (Figure 1, middle panel). To our knowledge, only one other study in humans has examined the roles of CO and SVC in increasing MAP during metaboreceptor activation in patients with HFrEF. Crisafulli *et al.* (2007) reported a metaboreflex-induced increase in MAP which was predominantly driven by an increase in CO in healthy individuals and by a reduction in SVC in patients with HFrEF, suggesting a greater role of the peripheral vasculature in governing the metaboreflex-induced pressor response in the patient group. However, this previous study only investigated the hemodynamic alterations induced by one level of metaboreceptor activation (30% MVC), compared to the three levels of exercise in the present study. The importance of examining multiple levels of metaboreceptor activation should not be

underestimated. Indeed, as outlined above, the relative contribution of CO and SVC to the pressor response evoked by metaboreceptor activation has been shown to differ according to exercise intensity in an animal model (Augustyniak *et al.*, 2001), and it was thus anticipated that a similar, intensity-dependent response would be observed in the present study. This was indeed the case, and thus the current study may be viewed as providing a comprehensive investigation into the role of CO and SVC in the metaboreflex-induced pressor response in systolic HF in humans by identifying an intensity-dependent reduction in SVC during metaboreflex activation in HFrEF, thus indicating a proportionally greater role of SVC in increasing MAP in this patient group.

Arterial afterload and left ventricular systolic function

The manner by which metaboreceptor activation elicits an increase in MAP may be particularly significant when considering the relationship between the left ventricle and the peripheral vasculature in HFrEF patients. Indeed, SVC represents the non-pulsatile component of arterial afterload (Yin & Avolio, 1987; Kass & Kelly, 1992) and it is well-established that patients with HFrEF are afterload-sensitive (Asanoi *et al.*, 1989; Kameyama *et al.*, 1991; Schwartzenberg *et al.*, 2012a). Thus, these patients face certain impairment in left ventricular systolic function if arterial afterload is increased (Kameyama *et al.*, 1991). In the present study, at all levels of metaboreceptor activation, HFrEF patients exhibited an exaggerated increase in Ea, an index of total arterial afterload, compared to control subjects who only exhibited a significant augmentation in Ea at the highest level of metaboreceptor activation (Figure 2). As there were no differences between groups in the reduction in TAC (Table 4), a measure of the pulsatile component of arterial afterload, SVC is likely the primary contributor to the exaggerated increase in total arterial afterload induced by metaboreceptor activation exhibited in HFrEF. These findings thus confirm and extend former work (2007), providing additional evidence for an augmented arterial afterload induced by the metaboreflex-driven changes in SVC in HFrEF.

This metaboreflex-induced increase in arterial afterload in HFrEF appears to have deleterious cardiac effects. Indeed, metaboreceptor activation provoked much smaller increases in SW (a measure of functional left ventricular systolic work) in patients with HFrEF compared to healthy control subjects (Figure 3, top panel), an impairment that is likely related to the exaggerated increase in arterial afterload in this cohort. This reduction in SW is particularly relevant when viewed in the context of the metabolic cost, as determined by RPP, which was similar between groups across all levels of metaboreceptor activation (Table 4). Taken together, the SW and RPP responses point to a reduction in myocardial efficiency in HFrEF, as less left ventricular systolic work was performed for a similar metabolic cost in the patient group. These cardiac indices therefore suggest that the metaboreflex-induced reductions in SVC and the associated increases in arterial afterload come at a steep cost to HFrEF patients, and may actually limit functional left ventricular systolic work and reserve capacity by placing a substantial hemodynamic load on the failing heart. Further studies with direct measurements of left ventricular hemodynamics are warranted to explore this interesting possibility.

Experimental Considerations

The present study is not without limitations. We acknowledge that the arterial afterload calculations used in the current study are typically based on aortic pressure measurements (Kelly *et al.*, 1992), and this variable was calculated from measurements obtained non-invasively via finger photoplethysmography in the present study. Though peripheral ABP measurements may not always reflect central pressures due to wave amplification descending the arterial tree (Williams *et al.*, 2006; Safar *et al.*, 2009), central ABP measurements may also be augmented due to reflected pressure waveforms (Safar *et al.*, 2009), limiting the discrepancy between central and peripheral pressure measurements (Kroeker & Wood, 1955; Kelly *et al.*, 1992; Nussbacher *et al.*, 1999). While effective arterial elastance has been used as an index of total arterial afterload in many studies with diverse clinical populations (Kussmaul *et al.*, 1993; Borlaug & Kass, 2008; Borlaug *et al.*, 2009; Schwartzenberg *et al.*, 2012b; Eleid *et al.*, 2013), we recognize that this index has not directly been validated in HFrEF patients. Recent evidence suggests that the cardiovascular response to metaboreflex activation is also abnormal in heart failure patients with a preserved ejection fraction (HFpEF) (Roberto *et al.*, 2017), findings that are relevant to the current study given that many patients with systolic dysfunction also suffer from some level of diastolic dysfunction, ranging from abnormal relaxation to restrictive filling (Naqvi, 2003; Lang *et al.*, 2015). However, patients in the present study did not demonstrate any echocardiographic evidence of diastolic dysfunction as defined by current guidelines (Nagueh *et al.*, 2016), suggesting the reported findings are specific to the HFrEF phenotype. We enrolled HFrEF patients on optimized pharmacotherapy, and no medications were withheld on experimental days. We therefore cannot exclude the possibility that existing drug therapy may have affected our measurements, particularly cardiac responses, though it is noteworthy that this represents the “real world” in which optimally medicated patients live. Finally, we acknowledge that use of the Modelflow method for estimation of stroke volume may not provide the same level of precision as that provided by more invasive techniques, though it is noteworthy that good agreement in tracking CO changes has recently been documented with these two methodologies in heart disease patients (de Wilde *et al.*, 2007).

Conclusions

This study has identified a preserved role of the metaboreflex-induced pressor response in HFrEF patients, and provides evidence that the rise in MAP is governed almost entirely by the peripheral circulation in this patient population. The net effect of this response appears to be maladaptive, as it places a substantial hemodynamic load on the heart, exacerbates the underlying impairment of systolic function, and likely contributes to exercise intolerance in this patient group.

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New Findings: The central question of this study is whether HFrEF patients exhibit a greater dependence on cardiac or peripheral vascular hemodynamics across multiple levels of muscle metaboreflex activation provoked by post-exercise circulatory occlusion. The main findings of this study is that the metaboreflex-induced pressor

response in HFrEF patients is governed almost entirely by the peripheral circulation, which places a substantial hemodynamic load on the failing heart. This maladaptive response exacerbates the disease-related impairment of systolic function that is a hallmark feature of HFrEF, and may therefore contribute to exercise intolerance in this patient group.

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Abbreviations

ABP	Arterial Blood Pressure
CO	Cardiac Output

DAP	Diastolic Arterial Pressure
Ea	Effective Arterial Elastance
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
MAP	Mean Arterial Pressure
MVC	Maximal Voluntary Contraction
NIRS	Near-Infrared Spectroscopy
PECO	Post-Exercise Circulatory Occlusion
P_{es}	End-Systolic Arterial Pressure
PP	Pulse Pressure
RPP	Rate Pressure Product
SAP	Systolic Arterial Pressure
SVC	Systemic Vascular Conductance
SVR	Systemic Vascular Resistance
SW	Stroke Work

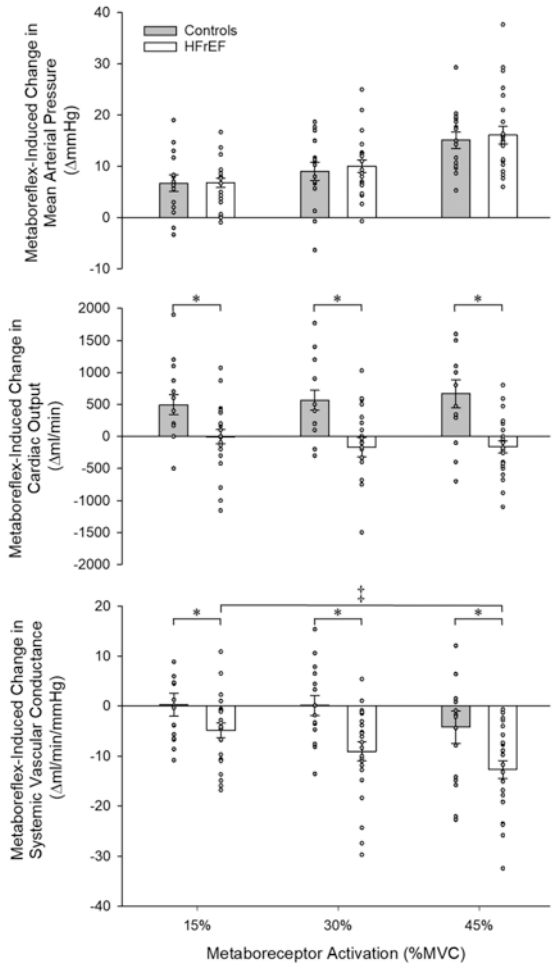

Figure 1.

Metaboreflex-induced changes in mean arterial pressure (*top*), cardiac output (*middle*), and systemic vascular conductance (*bottom*), in control subjects and heart failure patients with reduced ejection fraction (HFrEF). * Significant difference from control, P<0.05; ‡ Significant difference from 15% MVC, P<0.05.

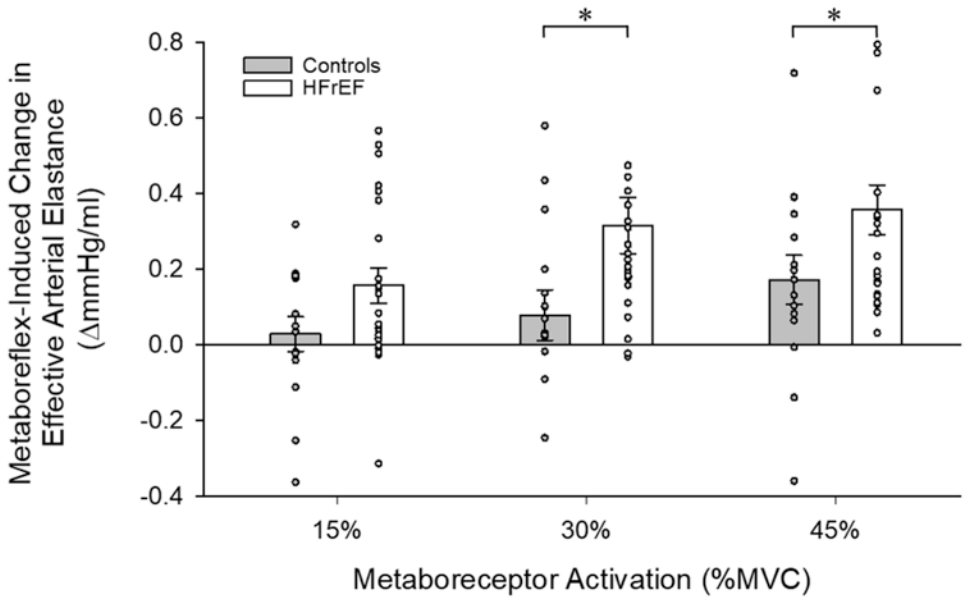

Figure 2.

Metaboreflex-induced changes in effective arterial elastance in control subjects and heart failure patients with reduced ejection fraction (HFrEF). * Significant difference from control, $P<0.05$.

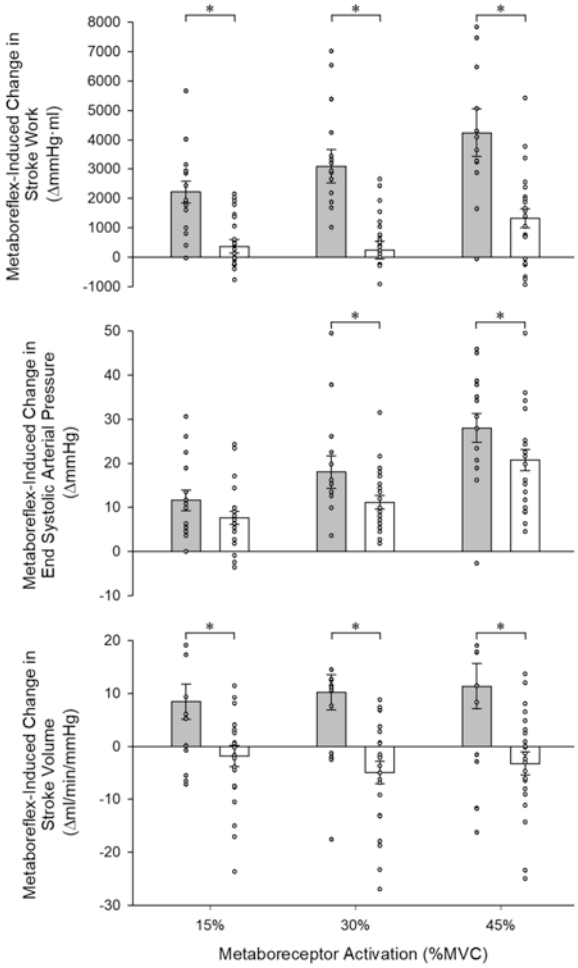

Figure 3.

Metaboreflex-induced changes in stroke work (*top*), end systolic pressure (*middle*), and stroke volume (*bottom*) in control subjects and heart failure patients with reduced ejection fraction (HFrEF). * Significant difference from control, P<0.05.

Table 1

Subject characteristics

	Controls (n = 15)	HFrEF (n = 23)
Age, yrs	64 ± 11	63 ± 10
Height, cm	176 ± 7	175 ± 5
Weight, kg	80 ± 15	85 ± 16
Body mass index, kg/m^2	26 ± 5	28 ± 4
Maximum voluntary contraction, kg	27 ± 5	25 ± 5
Glucose, mg/dl	85 ± 17	99 ± 18
Total cholesterol, mg/dl	192 ± 35	155 ± 40
Triglycerides, mg/dl	143 ± 66	131 ± 56
HDL, mg/dl	49 ± 11	39 ± 10 *
LDL, mg/dl	124 ± 29	96 ± 27

HFrEF, heart failure with reduced ejection fraction; HDL, high density lipoprotein; LDL, low density lipoprotein. Data are expressed as mean ± SD.

* Significant difference from control, P <0.05.

Table 2
Disease - specific characteristics and medications

	HFrEF (n =23)
Disease-specific characteristics	
Left ventricular ejection fraction, % (mean ±SEM)	22 ± 12
Diagnosis (ischemic)	14 / 23
Diagnosis (non-ischemic)	9 / 23
NYHA class II	16 / 23
NYHA class III	7 / 23
Diabetic	4 / 23
Medications	
β-Blocker	23 / 23
ACE inhibitor	17 / 23
Angiotensin receptor inhibitor	4 / 23
Statin	18 / 23
Diuretic	18 / 23
Aldosterone inhibitor	4 / 23
Calcium channel inhibitor	1 / 23
Digoxin	4 / 23
Anticoagulant	13 / 23
Antiarrhythmic	1 / 23
Erythropoiesis - stimulating agent	1 / 23

HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme.

Table 3
Cardiac and peripheral vascular hemodynamics at rest and during acute exercise

Workload (%MVC)	Rest	15%	30%	45%
Controls				
Mean arterial pressure, mmHg	83 ± 7	92 ± 9†	96 ± 9†	103 ± 7†
Systolic arterial pressure, mmHg	119 ± 11	140 ± 15†	143 ± 19†	154 ± 12
Diastolic arterial pressure, mmHg	66 ± 6	68 ± 8	73 ± 6†	77 ± 6†
Pulse pressure, mmHg	53 ± 7	71 ± 14†	70 ± 16†	77 ± 10†
Heart rate, beats/min	57 ± 6	64 ± 7†	65 ± 9†	68 ± 9†
Stroke volume, ml/beat	109 ± 19	110 ± 18	111 ± 17	110 ± 16
Cardiac output, L/min	6.3 ± 1.2	7.0 ± 1.4†	7.2 ± 1.4†	7.4 ± 1.4†
Systemic vascular conductance, ml/min/mmHg	75 ± 14	77 ± 18	75 ± 14	72 ± 14
Systemic vascular resistance, mmHg/L/min	14 ± 2	14 ± 3	14 ± 2	14 ± 2
Total arterial compliance, ml/mmHg	2.2 ± 0.6	1.6 ± 0.5†	1.7 ± 0.8†	1.5 ± 0.3†
Effective arterial elastance, mmHg/ml	1.0 ± 0.2	1.2 ± 0.2†	1.2 ± 0.2†	1.3 ± 0.2†
Stroke work, mmHg*ml	11,700 ± 2,293	13,920 ± 3,149†	14,357 ± 3,243†	15,308 ± 2,645†
Rate pressure product, AU	6,821 ± 983	8,924 ± 1,311†	9,354 ± 1,987†	10,417 ± 1,706†
Deoxyhemoglobin, μM (n=9)	27 ± 7	34 ± 8†	37 ± 8†	39 ± 8†
HFrEF				
Mean arterial pressure, mmHg	84 ± 15	93 ± 16†	95 ± 17†	102 ± 16†
Systolic arterial pressure, mmHg	117 ± 20	128 ± 23†	131 ± 24†	141 ± 25*†
Diastolic arterial pressure, mmHg	67 ± 14	75 ± 14†	77 ± 16†	83 ± 13†
Pulse pressure, mmHg	50 ± 6	53 ± 15*	53 ± 17*	58 ± 18*†
Heart rate, beats/min	67 ± 9*	69 ± 12†	71 ± 11†	73 ± 14†
Stroke volume, ml/beat	83 ± 17*	81 ± 17*	79 ± 20*	76 ± 20*
Cardiac output, L/min	5.4 ± 1.3	5.5 ± 1.2*	5.6 ± 1.6*	5.4 ± 1.3*
Systemic vascular conductance, ml/min/mmHg	68 ± 19	62 ± 16*†	61 ± 21*†	55 ± 15*†
Systemic vascular resistance, mmHg/L/min	17 ± 1	18 ± 1†	20 ± 3*†	21 ± 1*†
Total arterial compliance, ml/mmHg	1.8 ± 0.6	1.6 ± 0.3	1.6 ± 0.7	1.4 ± 0.6†
Effective arterial elastance, mmHg/ml	1.4 ± 0.6	1.6 ± 0.7†	1.6 ± 1.0*†	1.8 ± 0.9*†
Stroke work, mmHg*ml	8,654 ± 2,223	9,253 ± 2,250*	9,192 ± 529*	9,562 ± 3,097*
Rate pressure product, AU	7,677 ± 1,488	8,902 ± 2,158†	9,215 ± 2,184†	10,322 ± 2,774†
Deoxyhemoglobin, μM (n=13)	28 ± 4	32 ± 4†	35 ± 5†	36 ± 4†

MVC, maximum voluntary contraction; HFrEF, heart failure with reduced ejection fraction. Data are expressed as mean ± SD.

*Significant difference from control, P<0.05;

†Significant difference from rest, P<0.05.

Table 4

Cardiac and peripheral vascular hemodynamics at rest and during metaboreceptor activation

Metaboreceptor activation	Rest	15%	30%	45%
Controls				
Mean arterial pressure, mmHg	83 ± 7	90 ± 11†	93 ± 3†	100 ± 2†
Systolic arterial pressure, mmHg	119 ± 11	132 ± 18†	139 ± 5†	150 ± 5†
Systolic arterial pressure, ΔmmHg	-	13 ± 10†	19 ± 3†	34 ± 4†
Diastolic arterial pressure, mmHg	66 ± 6	69 ± 8†	70 ± 2†	74 ± 1†
Diastolic arterial pressure, ΔmmHg	-	4 ± 5†	4 ± 1†	8 ± 1†
Pulse pressure, mmHg	53 ± 10	62 ± 13†	68 ± 14†	75 ± 19†
Pulse Pressure, ΔmmHg	-	9 ± 5†	16 ± 3†	23 ± 4†
Heart rate, beats/min	57 ± 6	58 ± 8	59 ± 2	58 ± 2
Stroke volume, ml/beat	109 ± 19	118 ± 19†	118 ± 5†	118 ± 5†
Cardiac output, L/min	6.3 ± 1.2	6.8 ± 1.2†	6.9 ± 0.3†	6.8 ± 0.3†
Systemic vascular conductance, ml/min/mmHg	75 ± 14	76 ± 13	75 ± 3	68 ± 3†
Systemic vascular resistance, mmHg/L/min	14 ± 3	14 ± 2	14 ± 1	15 ± 1
Total arterial compliance, ml/mmHg	2.2 ± 0.6	2.0 ± 0.5	1.8 ± 0.7†	1.7 ± 0.6†
Total arterial compliance, Δml/mmHg	-	-0.2 ± 0.5	-0.3 ± 0.8†	-0.3 ± 0.9†
Effective arterial elastance, mmHg/ml	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	1.2 ± 0.2†
Stroke work, mmHg*ml	11,700 ± 2,293	13,921 ± 2691†	14,799 ± 3,469†	15,941 ± 3,904†
Rate pressure product, AU	6,821 ± 983	7,659 ± 1,653†	8,217 ± 1,843†	8,680 ± 1,260†
Deoxyhemoglobin, μM (n=9)	27 ± 5	48 ± 9†	50 ± 9†	51 ± 10†
HFrEF				
Mean arterial pressure, mmHg	84 ± 15	90 ± 16†	94 ± 3†	100 ± 4†
Systolic arterial pressure, mmHg	117 ± 21	125 ± 24†	129 ± 5†	140 ± 6†
Systolic arterial pressure, ΔmmHg	-	8 ± 8†	12 ± 2*†	23 ± 3*†
Diastolic arterial pressure, mmHg	67 ± 14	73 ± 15†	77 ± 3†	81 ± 3†
Diastolic arterial pressure, ΔmmHg	-	7 ± 4†	9 ± 1*†	13 ± 1*†
Pulse pressure, mmHg	50 ± 14	52 ± 17	53 ± 16*	59 ± 19*†
Pulse pressure, ΔmmHg	-	3 ± 4*	3 ± 6*	10 ± 8*†
Heart rate, beats/min	67 ± 9*	68 ± 11*	70 ± 11*	68 ± 2*
Stroke volume, ml/beat	83 ± 17*	81 ± 18*	77 ± 4*	80 ± 4*
Cardiac output, L/min	5.4 ± 1.3	5.5 ± 1.2*	5.3 ± 0.3*	5.4 ± 0.3*
Systemic vascular conductance, ml/min/mmHg	68 ± 19	63 ± 18*†	58 ± 4*†	55 ± 4*†
Systemic vascular resistance, mmHg/L/min	17 ± 10	18 ± 9†	20 ± 2*†	21 ± 3*†
Total arterial compliance, ml/mmHg	1.8 ± 0.6	1.7 ± 0.6	1.6 ± 0.6	1.5 ± 0.6†

Metaboreceptor activation	Rest	15%	30%	45%
Total arterial compliance, Δml/mmHg	-	-0.1 ± 0.3	-0.2 ± 0.4	-0.5 ± 0.8 †
Effective arterial elastance, mmHg/ml	1.4 ± 0.6	1.6 ± 0.7 *†	1.7 ± 0.8 *†	1.7 ± 0.8 *†
Stroke work, mmHg*ml	8,654 ± 2,223	9,021 ± 2,266 *	8,896 ± 2,541 *	9,982 ± 3,043 *†
Rate pressure product, AU	7,677 ± 1,489	8,572 ± 1,131 †	8,990 ± 2,044 †	9,445 ± 2,286 †
Deoxyhemoglobin, μM (n=13)	28 ± 5	47 ± 8 †	50 ± 8 †	53 ± 7 †

MVC, maximum voluntary contraction; HFrEF, heart failure with reduced ejection fraction. Data are expressed as mean ± SD.

*Significant difference from control, P<0.05;

†Significant difference from rest, P<0.05.