Published in final edited form as:

Med Sci Sports Exerc. 2016 March ; 48(3): 368–376. doi:10.1249/MSS.0000000000000782.

The Mechanoreflex and Hemodynamic Response to Passive Leg Movement in Heart Failure

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Abstract

Background—Sensitization of mechanosensitive afferents, which contribute to the exercise pressor reflex (EPR) has been recognized as a characteristic of patients with heart failure (HF), however, the hemodynamic implications of this hypersensitivity are unclear.

Objectives—The present study utilized passive leg movement (PLM) and intrathecal injection of fentanyl to blunt the afferent portion of this reflex arc to better understand the role of the mechanoreflex on central and peripheral hemodynamics in HF.

Methods—Femoral blood flow (FBF), mean arterial pressure (MAP), femoral vascular conductance (FVC), heart rate (HR), stroke volume (SV), cardiac output (CO), ventilation (V_E), and muscle oxygenation of the vastus lateralis, were assessed in 10 NYHA class II HF patients at baseline and during 3-min of PLM both with fentanyl and without (control).

Results—Fentanyl had no effect on baseline measures, but increased ($p < 0.05$, control vs. fentanyl) the peak PLM-induced change in FBF (493 ± 155 vs. 804 ± 198 mL/min), and FVC (4.7 ± 2 vs. 8.5 ± 3 mL/min/mmHg), while norepinephrine spillover (103 ± 19 vs. 58 ± 17 %), and retrograde FBF (371 ± 115 vs. 260 ± 68 mL/min) tended to be reduced ($p < 0.10$). Additionally, fentanyl administration resulted in greater PLM-induced increases in muscle oxygenation, suggestive of increased microvascular perfusion. Fentanyl had no effect on the V_E , MAP, HR, SV, or CO response to PLM.

Conclusions—Although movement-induced central hemodynamics were unchanged by afferent blockade, peripheral hemodynamic responses were significantly enhanced. Thus, in patients with HF a heightened mechanoreflex appears to augment peripheral sympathetic vasoconstriction in response to movement, a phenomenon that may contribute to exercise intolerance in this population.

Keywords

Blood flow; mechanoreceptors; passive leg movement; muscle afferents

INTRODUCTION

Heart Failure (HF) is typically the result of a myocardial insult or exaggerated afterload, both of which compromise myocardial performance and subsequently systemic hemodynamics (27). While compromised central hemodynamics are the hallmark of HF, the notion that peripheral dysfunction exacerbates these central hemodynamic abnormalities, the “muscle hypothesis” (7), has been increasingly recognized (10,19,27,38). Specifically, the exercise pressor reflex (EPR) has been reported to be upregulated in both animal models of HF (31) and in patients with HF (25,26), leading to excessive increases in heart rate (HR), ventilation (V_E), sympathetic nerve activity, and mean arterial pressure (MAP). The sensitization of this reflex has the potential to result in greater exertional dyspnea and increased cardiac afterload, exaggerating myocardial work, reducing exercise tolerance, and subsequently enhancing disease progression due to inactivity.

The hypersensitivity of the EPR in patients with HF is now recognized to be mediated by exaggerated afferent signaling via the thinly myelinated “mechanosensitive” group III afferents and/or the unmyelinated “metabosensitive” group IV afferents (3). Indeed, our group (3) recently demonstrated that partial afferent blockade with the μ -opioid agonist, fentanyl, reduced central hemodynamic responses, MAP, and norepinephrine spillover, resulting in an improvement in leg blood flow and oxygen delivery during knee extensor exercise in patients with HF. Unfortunately, with this integrative physiological model, it was not possible to determine the contribution of mechanosensitive and metabosensitive afferent signals to the overall cardiovascular response. However, given the experimental design we were able to exclude the role of feed-forward signaling (3). Prior studies that have selectively activated the metaboreflex suggest this reflex is normal (6), or even reduced (19,34), in those with HF. Moreover, Middlekauff and colleagues (20) used low intensity handgrip and passive wrist flexion, as a means to selectively activate and study the mechanoreflex, and revealed an exaggerated renal vasoconstriction (20) paralleled by an excessive rise in muscle sympathetic nerve activity in those with HF (18). Although, in combination, these findings and other work in animal models (27) imply that an enhanced mechanoreflex is the likely factor mediating the sensitization of the EPR in this population, a comprehensive assessment of the role of the mechanoreflex and the central and peripheral hemodynamic consequences in humans with HF, has yet to be performed.

Previously our group (35,40) and others (11,22) have used dynamic passive leg movement (PLM) as a model to study exercise-induced hyperemia and the contribution of the

mechanoreflex in mediating this response. Importantly, Trinity et al. (35), revealed that the partial blockade of afferent signals with fentanyl significantly reduced both the central and peripheral hemodynamic responses to PLM in young healthy individuals, highlighting an important role of mechanosensitive afferents in facilitating the hemodynamic response to movement. Witman et al. (40) subsequently demonstrated a significant attenuation of the PLM-induced hyperemia in patients with HF compared to healthy controls. However, to date, the pharmacological blockade of afferent signals during PLM has not yet been used to determine the role of the mechanosensitive afferents in the EPR of patients with HF.

Accordingly, this study sought to determine the contribution of mechanosensitive afferents in patients with HF, using a reductionist approach employing PLM and the intrathecal injection of fentanyl to blunt neural feedback in patients with HF. We hypothesized that the attenuated afferent feedback would suppress the central hemodynamic, but peripheral hemodynamics would be significantly improved, suggestive of a negative role of the mechanoreflex in HF. This, if proven to be correct, would provide considerable insight into the mechanisms responsible for the exercise intolerance, such as excess sympathetic vasoconstriction, in this patient population.

METHODS

Subjects and General Procedures

Ten patients diagnosed with NYHA class II heart failure (reduced ejection fraction; HFREF) participated in this study. The protocol was approved by the Institutional Review Boards of the University of Utah and the Salt Lake City VA Medical Center. Written informed consent was obtained from all subjects prior to their participation in the study. All studies were performed in a thermoneutral environment (22°C) at an elevation of ~1,419m. Subjects reported to the laboratory in a fasted state and without caffeine or alcohol use for 12 and 24 h, respectively. They also had not performed any exercise within the past 24 h. For safety and ethical reasons, all subjects maintained their medication regimen on the day of the study.

Passive Leg Movement (PLM) Protocol

All subjects underwent a non-invasive familiarization trial on a day prior to the catheter-based experiment, to become acquainted with the instrumentation and PLM protocol. On the study day, prior to the experimental protocols, arterial and venous catheters were placed, under local anesthesia (1% Lidocaine), in the right common femoral artery and vein using sterile technique. After catheter placement, the patients rested for 30 mins. Once recovered, subjects were moved to a comfortable chair for the hypercapnic ventilatory response test (HCVR), to establish a baseline hyperventilatory response to 3 and 6% CO₂, a process which was repeated in the fentanyl condition to ensure the drug had not migrated cephalically (1). Subjects were then escorted to the knee extensor ergometer and rested in an upright seated position for 20 min prior to the start of data collection.

The lower leg of the subject was fitted into a boot attached to a custom built single leg knee extension ergometer, as described elsewhere (4,10). The protocol consisted of a 60 s resting

baseline followed by a 3 min bout of single leg PLM performed in an upright seated position, as described previously (35). After completion of the control trial subjects rested for 1 hour. After the rest period, subjects were positioned in the upright seated position, and under sterile conditions, subjects were administered local anesthesia (1% lidocaine) at the level of the L₃-L₄ intervertebral space. As described previously (2), 1 mL of fentanyl (0.05 mg/ml) was injected into the intrathecal space to pharmacologically blunt afferent feedback, which was confirmed in each subject with the assessment of cutaneous hypoesthesia to a pinprick and cold perception as well as paresthesia to hand strokes on the torso and lower limb dermatomes. Subjects remained in the upright seated position for the remainder of the protocol to minimize potential cephalic migration of the fentanyl. The HCVR test was repeated, followed by the baseline measurements and passive movement protocol, as described above.

Measurements

Central Hemodynamic Variables—Heart rate (HR), Stroke Volume (SV), and Cardiac Output (CO) were determined with a Finometer (Finapres Medical Systems BV, Amsterdam, The Netherlands). Stroke volume was calculated using the modelflow method (37) which includes age, sex, height, and weight in its algorithm (Beatscope v. 1.1; Finapres Medical Systems, Amsterdam, The Netherlands), and has previously been documented to accurately track SV at rest and during exercise (8,14,21,28) including those with cardiovascular disease (5). Cardiac output was then calculated as the product of HR and SV. Arterial and venous pressure transducers placed at the level of the catheter and measurement site (common femoral artery and vein), were used for real time determination of mean arterial and venous pressure and then used to calculate perfusion pressure across the leg.

Femoral Blood Flow—Measurements of femoral arterial blood velocity and vessel diameter were performed in the passively moved leg distal to the inguinal ligament and proximal to the bifurcation of the superficial and deep femoral arteries with a Logic 7 Doppler ultrasound system (General Electric (GE) Medical Systems, Milwaukee, WI, USA) operated by a trained technician. The Logic 7 system was equipped with a linear array transducer operating at an imaging frequency of 12 MHz. Vessel diameter was determined at a perpendicular angle along the central axis of the scanned area. Blood velocity was 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 degrees 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 angle-corrected, and intensity weighted mean velocity (V_{mean}) values were then calculated using commercially available software (GE Medical Systems, Milwaukee, WI, USA). Using arterial diameter and V_{mean} , FBF was calculated as: $V_{\text{mean}} \cdot \pi \cdot (\text{vessel diameter}/2)^2 \cdot 60$, where FBF is in milliliters per minute (mL/min). To account for potential differences in MAP, FVC was calculated as: FBF/MAP.

Tissue Oxygenation—Frequency-domain, multi-distance, near infrared spectroscopy (NIRS) of the vastus lateralis muscle (Oxiplex TS, ISS, Champaign, IL) in the passively moved leg allowed the absolute quantitation of the absorption and scattering coefficients of

the chromophores, hemoglobin (Hb) and myoglobin (Mb) (12). While subsequent calculations allowed the determination of tissue oxygen saturation ($StO_2\%$), oxy-Hb and oxy-Mb ($Hb+MbO_2$), deoxy-Hb and deoxy-Mb ($HHb+Mb$), and total Hb+Mb concentrations (all expressed in μM). Prior to use, in the control and fentanyl conditions the probe was calibrated using a phantom block with known absorption and scattering coefficients. Prior to placement the site of assessment over the vastus lateralis was extensively cleaned, the diode was attached with double sided adhesive tape and the area covered and further secured with coban wrap (3M, St. Paul, Minn). The data were acquired at 0.5 Hz averaged over 30 sec at baseline and during the passive movement. Although frequency-domain, multi-distance, NIRS in combination with skinfold measurements can allow a correction for overlying fat, due to the nature of this investigation, PLM in a thermoneutral environment, this approach was not employed in the current study.

Ventilation—The ventilatory responses (V_E , tidal volume (V_T), and breathing frequency (B_f)) to the HCVR test and passive movement were assessed using a non-rebreathing mouthpiece connected to a mixing chamber and gas analysis system (Parvo medics, Salt Lake City, UT). Data were collected breath-by-breath and averaged over 10 sec prior to analysis.

Blood Sampling—Arterial and venous blood samples, obtained at rest and during passive movement, were drawn into heparinized syringes and used for blood gas analyses or saved for biochemical analyses. Blood gas samples were analyzed using standard clinical technique (GEM 4000, Instrumentation Laboratory, Bedford, MA). Remaining blood samples were analyzed for epinephrine and norepinephrine using a quantitative enzyme immunoassay (2-CAT ELISA, Labor Diagnostika Nord GmbH & Co. KG). Samples were measured in triplicate. From these measurements, norepinephrine spillover was determined using the following formula:

$$NE_{\text{spillover}} = ((NE_{\text{Venous}} - NE_{\text{Arterial}}) + (NE_{\text{Arterial}} \cdot \text{Fractional Epi extraction})) \cdot \text{Plasma Flow}$$

Where, NE=norepinephrine and Epi=epinephrine.

Data Acquisition—Throughout the protocol signals reflecting HR, SV, CO, MAP, and knee joint angle underwent A/D conversion and were simultaneously acquired (200 Hz) using commercially available data acquisition software (AcqKnowledge, Biopac Systems Inc., Goleta, CA, USA). In addition, the audio antegrade and retrograde signals from the Doppler ultrasound system were acquired (10,000 Hz) to serve as qualitative indicators of blood velocity changes and to ensure accurate temporal alignment of blood velocity measurements obtained from this system and the other variables collected (i.e. HR, SV, CO, and MAP).

Data Analysis

From the velocity and femoral artery diameter, net FBF was calculated on a second by second basis for the passively moved leg. Prior to analysis, all hemodynamic data were smoothed using a 3 s rolling average. To identify condition-specific responses across time,

two way (condition $\times$ time) repeated measures ANOVA were used. The steady state FBF responses (2nd-3rd minute of movement) were also assessed in all subjects (n=10), to pair with the blood samples that were drawn during the last 30 s. As the responses to passive movement are transient and vary between individuals, a peak response was determined for all variables on an individual basis for a subset of patients (n=6). This was then compared between the control and fentanyl conditions by paired t-tests as was the determination of individual baseline, maximal, absolute and relative changes, and time to maximal response in all measured variables. Alpha was set at 0.05 for all comparisons. All data are presented as mean $\pm$ standard error (SE).

RESULTS

Subject and clinical characteristics are listed in Table 1. All subjects produced a similar hyperventilatory response to the hypercapnic gas in the control and fentanyl conditions, indicating that the fentanyl had not migrated cephalically to the brainstem, leaving central chemoreceptor function intact. The efficacy of the blockade was verified in all subjects who uniformly exhibited sensory reductions at the level of T₅-T₆ and below, including the lower limbs, while no such changes were observed above this level and in the upper limbs.

Central Hemodynamic Responses

Fentanyl had no significant effect on resting central hemodynamics, such that CO (6.5 ± 0.6 , vs. 5.9 ± 0.6 L/min), SV (108 ± 10 , vs. 94 ± 7 mL/beat), and HR (61 ± 2 , vs. 62 ± 3 beats/min) were similar between control and fentanyl conditions, respectively (Figure 1). The peak PLM-induced changes in CO (1.3 ± 0.2 , vs. 1.3 ± 0.2 L/min), SV (19 ± 3 , vs. 20 ± 2 mL/beat), and HR (6 ± 1 , vs. 9 ± 3 beats/min) were not different following fentanyl injection (Figure 1). The area under the curve for CO tended to be reduced (0.59 ± 0.09 , vs. 0.39 ± 0.10 L, control vs. fentanyl), but this did not reach statistical significance ($p = 0.10$). There was no effect of fentanyl on the time to peak response for any of the central hemodynamic variables.

Peripheral Hemodynamic Responses

Fentanyl had no effect on resting FBF (278 ± 97 , vs. 246 ± 49 mL/min), MAP (108 ± 2 , vs. 108 ± 6 mmHg), FVC (2.6 ± 0.9 , vs. 2.6 ± 0.7 mL/min/mmHg), nor the oscillatory nature of FBF; antegrade (416 ± 81 , vs. 369 ± 57 mL/min) and retrograde (138 ± 52 , vs. 101 ± 29 mL/min). The peak PLM-induced hyperemia was significantly greater following fentanyl (493 ± 155 vs. 804 ± 198 mL/min; Figure 2). As the MAP response was not different between control and fentanyl trials (7 ± 1 , vs. 10 ± 3 mmHg), FVC was also augmented with fentanyl blockade (4.7 ± 2 vs. 8.5 ± 3 mL/min/mmHg) (Figure 3). Area under the curve (AUC) analysis of the first minute of passive movement also revealed that net FBF AUC was significantly increased following fentanyl (153 ± 30 , vs. 314 ± 70 mL), although neither antegrade FBF AUC (254 ± 25 , vs. 401 ± 62 mL), nor retrograde FBF AUC (143 ± 43 , vs. 110 ± 49 mL), were statistically different (Figure 2). Assessment of the peak microvascular responses using NIRS revealed a significant effect of PLM resulting in increased tissue oxygen saturation (StO₂%), Hb+MbO₂, and THb+Mb, while HHb+Mb was decreased (Table 2). Intrathecal fentanyl enhanced the PLM-induced increase in StO₂%, but

had no effect on Hb+Mb O₂, HHb+Mb, or THb+Mb. There was no effect of fentanyl on the time to peak response for any of the peripheral variables.

Analysis of the steady state peripheral hemodynamic responses, obtained during minutes 2-3 of PLM, revealed a significantly elevated net blood flow (481 ± 85 , vs. 583 ± 86 mL/min, $p < 0.05$), no difference in antegrade FBF (779 ± 68 , vs. 810 ± 57 mL/min, $p > 0.05$), and a tendency for a reduction in retrograde FBF (303 ± 67 , vs. 232 ± 46 mL/min, $p = 0.07$), in the presence of fentanyl. In parallel, the NIRS data revealed a significant PLM-induced increase in tissue oxygen saturation, which was enhanced in the fentanyl condition (Table 2). There was a significant main effect of passive movement on HHb+Mb, however there was no effect of fentanyl (Table 2).

Ventilation

Analysis of the individual peak responses in the control trial, revealed that PLM significantly increased V_E , breathing frequency (B_f), and tidal volume (V_T), (Table 3). Fentanyl had no effect on resting V_E , B_f , or V_T (Table 3). Fentanyl had no effect on the peak V_E response to PLM, as V_E , B_f , and V_T responses were similar between conditions (control vs. fentanyl, respectively).

Analysis of the steady state responses during minutes 2-3 of PLM in the control condition, revealed a small but significant effect of PLM on V_E , but did not significantly alter respiratory rate, or tidal volume. Fentanyl also had no effect on the PLM-induced change in V_E , B_f , or V_T (all, $p > 0.05$, control vs. fentanyl, respectively).

Blood Analyses

The analyses of blood variables are presented in Table 3. PLM reduced venous oxygen content, oxyhemoglobin, increased oxygen delivery, fractional oxygen extraction, and leg VO₂ (Table 3). Fentanyl resulted in a greater PLM-induced increase in oxygen delivery, and reduction in venous saturation, oxygen content, and oxyhemoglobin (Table 3). Biochemical analysis of the blood samples revealed, a clear increase in norepinephrine spillover as a result of PLM ($p < 0.05$), an effect which tended to be attenuated following intrathecal fentanyl injection (103 ± 19 vs. 58 ± 17 % , $p = 0.06$).

DISCUSSION

This study sought to elucidate the role of mechanosensitive muscle afferents on cardiovascular responses to passive leg movement (PLM) in patients with HF. During PLM, pharmacological blunting of afferent feedback with fentanyl had no effect on central hemodynamics or pulmonary ventilation, but significantly improved the peripheral hemodynamic response. Indeed, the partial blockade of afferent signaling tended to reduce both the PLM-induced increase in norepinephrine spillover and retrograde FBF, which significantly improved FBF, oxygen delivery, and tissue oxygen saturation. These findings suggest that, under normal conditions, in patients with HF a heightened mechanoreflex augments peripheral sympathetic vasoconstriction, a phenomenon that may confound existing central hemodynamic abnormalities, further contributing to exercise intolerance in this patient population.

The Mechanoreflex and Central Hemodynamics in HF

In terms of the contribution of cardiac output to the EPR in HF and the role of the mechanoreflex in mediating this response, previous work in animal models of HF using passive muscle stretch has revealed either a significant augmentation of the HR response (31,32), or no change at all (15). Subsequent animal studies have revealed that passive static stretch increased group III, but not group IV afferent nerve discharge, an effect which was exaggerated by HF (36). Previous studies in humans with HF documented either no change in HR as a result of passive wrist flexion (18), or the authors did not report HR, SV, and CO during passive knee extension (29), the latter making any comparison between the current work and these investigations impossible. Of note, the authors who reported no change in HR during passive wrist flexion (18) did not indicate the frequency of the passive movement, and previous studies suggests that mechanoreceptors are likely frequency dependent (16). Therefore, unlike the current study (Figure 1), it is possible that the movement in this previous study (18) was not performed at a high enough frequency to elicit a significant increase in HR. In support of this interpretation, our group has demonstrated, in young healthy individuals, that slow passive movement (1°/sec) produced no cardioacceleration (17), unlike the 1 Hz used in the current study. Additionally, mechanoreflex activation of CO may be muscle mass dependent, with the small muscle mass perturbed during passive wrist flexion not providing enough afferent feedback to stimulate an increase in HR.

In the current study, using passive knee extension, in agreement with our prior work (40), we observed a significant increase in HR and CO in response to PLM. Although there was not a statistically significant effect of the fentanyl on these responses, CO tended to be lower ($p = 0.10$) following partial afferent blockade (Figure 1). Our findings contrast with those of Smith et al (32), who found that afferent neural blockade with gadolinium significantly reduced, but did not abolish, the tachycardia as a result of tendon stretch in rodents with dilated cardiomyopathy. However, dynamic PLM likely elicits lower levels of tendon stretch compared to the static approach used by Smith et al. (32) and others (33), and, furthermore, fentanyl (a targeted μ -opioid agonist that reduces afferent feedback) and gadolinium (a paramagnetic rare earth metal that alters stretch activated channels) are very different pharmacological approaches. In summary, utilizing the current PLM method, humans with HF appear to exhibit only a modest afferent-sensitive cardiac output response.

The Mechanoreflex and Peripheral Hemodynamics in HF

During exercise, patients with HF often exhibit reduced muscle blood flow and convective O₂ transport (3,10,27,38), as well as exaggerated renal vasoconstriction (19), implicating exaggerated total peripheral resistance (TPR) as a contributor to the EPR in HF (39). Recent work performed by our group, revealed that during knee extensor exercise patients with HF exhibit reduced femoral blood flow (3), which following partial blockade of lower limb muscle afferents was somewhat restored to the level of controls. This fentanyl-induced increase in femoral blood flow in the patients with HF was paralleled by a blunted MAP response, augmenting femoral vascular conductance during knee extensor exercise over a wide range of exercise intensities (3). These observations suggest a role of afferent neurons in altered peripheral hemodynamics in these patients. However, the cardiovascular response

to exercise is a composite of central command as well as metabo- and mechano-sensitive reflexes, confounding the ability to ascertain which factor may be responsible for the greater TPR and reduced muscle blood flow during exercise. Interestingly, there has been little work investigating the peripheral hemodynamic consequences of selective mechanoreflex activation in animals or humans with HF.

Middlekauf and colleagues (20), used a human model of low intensity involuntary muscle contractions to selectively activate the mechanoreflex in the absence of central command, and found that patients with HF displayed a disproportionate rise in renal vascular resistance compared to age matched controls, suggestive of an enhanced mechanoreflex. Subsequently, the same group (18) demonstrated that the contribution of the metaboreflex to muscle sympathetic nerve activity during handgrip exercise in patients with HF was minimal and that neither pH nor lactate appeared to sensitize the mechanoreflex. Additionally, using passive wrist flexion-extension, the authors documented an increase in muscle sympathetic nerve activity in patients with HF, but not controls, confirming an enhanced mechanoreflex in this population (18). However, in this study (18), the peripheral vascular response was not measured, thus they were unable to determine if the rise in muscle sympathetic nerve activity did, in fact, impact muscle blood flow. Subsequently, our group (40) utilized PLM to assess the peripheral hemodynamic response in patients with HF and age matched healthy controls, revealing a significantly blunted femoral blood flow response to PLM in those with HF. Although a blunted hyperemia was observed, the exact mechanism responsible could not be identified in this prior study, but was suggested to be peripheral in nature.

In the current study, activation of the mechanoreflex with PLM resulted in an increase in MAP (Figure 3), FBF (Figure 2), and FVC (Figure 3). However, this vasodilatory response appears to be restrained by muscle sympathetic nerve activity, as norepinephrine spillover tended to increase concomitantly. Furthermore, pharmacological blunting of afferent feedback with fentanyl, revealed a tendency for less of an increase in norepinephrine spillover and lower retrograde FBF resulting in significantly greater peak and steady state net FBF (Figure 2) and FVC (Figure 3). Padilla and colleagues (24), using multiple sympathoexcitatory maneuvers (e.g. Cold Pressor Test), have documented that increases in muscle sympathetic nerve activity result in increased retrograde FBF, highlighting retrograde FBF as an index of vascular resistance downstream from the conduit artery (13). In this context, we propose that PLM stimulates mechanosensitive afferent nerves, leading to a reflex increase in muscle sympathetic nerve activity-mediated norepinephrine release, which increases resistance downstream, restraining FBF, and FVC (Figure 3). This sympathetic restraint of FBF ultimately results in less tissue oxygenation ($\text{StO}_2\%$), as detected by NIRS, such that fentanyl improved the PLM-induced peak and steady state $\text{StO}_2\%$ (Table 2). Based upon the previously observed mechanoreceptor-induced increase in muscle sympathetic nerve activity in patients with HF, but not controls (18), and the current tendency for an increase in norepinephrine as a result of PLM, it is likely that such enhanced afferent feedback, specific to the mechanoreflex is, at least in part, responsible for the reduced leg blood flow and muscle perfusion, often associated with this population, during exercise (27). Additionally, although small in magnitude due to the passive experimental model, the documented improvement in oxygen delivery in the leg being moved, the reduced venous oxygen content, and the resultant greater arterial-venous oxygen difference

and leg oxygen uptake (Table 3), following fentanyl-induced blockade support this contention.

The Mechanoreflex and Ventilation in HF

Prior work (26,29) suggests that patients with HF exhibit an enhanced ergoreflex, as measured by the hyperventilatory response to exercise, and that this disproportionately elevated hyperpnea contributes to their exercise intolerance, as suggested in the “muscle hypothesis” (7). These authors, through the use of post exercise circulatory occlusion to isolate the metaboreflex, suggest that ergoreflex activation is likely mediated by metabosensitive afferents (29), which can be ameliorated by reducing H^+ concentration with infusion of sodium bicarbonate (30). To further determine if mechanosensitive afferents were contributing to the exercise-induced hyperpnea, Scott et al. (29), used passive knee extension, as in the current study, and found an increase in V_E , VO_2 , and the ratio of VO_2 to V_E which was similar in both patients with HF and age matched healthy controls. Our data are in agreement with those of Scott et al. (29), revealing a small but significant increase in peak ventilation, in parallel with increased leg VO_2 (Table 3). Interestingly, the increased VO_2 observed with fentanyl may be interpreted, as others have (27), that HF shifts metabolic control, at least in part, from the mitochondria to the vasculature. Somewhat surprisingly, blunting of afferent feedback, via intrathecal fentanyl, had no effect on V_E in the current patients with HF, a finding that contrasts with those of Olson et al. (23) that revealed a fentanyl-induced reduction in ventilation during cycling exercise. The results from the current study suggest little or no role of mechanosensitive afferents alone in mediating the exaggerated hyperpnea often observed in patients with HF during exercise.

Experimental Considerations

The current study and findings are not without experimental considerations. First, the patients enrolled in this study were all designated as NYHA Class II heart failure and therefore it is unclear how variations in HF severity would affect the results of this study, thus the current findings cannot be confidently extrapolated to all classes or type of HF. Second, although a clinically relevant dose of fentanyl was administered, used in routine clinical practice and in previous research studies in health (1,2) and HF (3,23), which resulted in significant physiological changes in this and prior studies, likely through partial blockade of afferent feedback, the actual degree of blockade remains unknown. Additionally in terms of the impact of fentanyl blockade, while the HCVR test, to rule out the cephalic migration of fentanyl, was performed before the PLM, this assessment was not repeated following PLM to again assess potential fentanyl migration. However, previous work (23), also in HF, measured the HCVR after exercise and found no evidence of cephalic migration in patients with HF who were maintained upright post fentanyl delivery, as in the current study. Third, although we contend that with this passive movement model the mechanosensitive afferents are being activated, there is a possible contribution from other afferent nerves, and thus, the exact mechanism (e.g. extramuscular/joint or metabosensitive afferents) responsible for the fentanyl-induced changes observed in this study cannot be definitively identified and remains an area to be further explored. Finally, to minimize subject burden, the current study did not include age-matched controls. Such an assessment, employing exactly the same protocol, would be a useful future endeavor.

Conclusion

Utilizing a comprehensive and integrative approach to understand the role of the mechanosensitive component of the EPR in patients with HF, the current study provides evidence that feedback from mechanosensitive muscle afferents may play a negative role in patients with HF. Specifically, likely as a consequence of peripheral sympathetic vasoconstriction, mechanosensitive afferent feedback attenuates the hyperemic response to PLM and tissue oxygenation. This phenomenon may contribute to exercise intolerance in patients with HF and may help to guide future pharmacological therapy or exercise interventions to minimize the impact of mechanosensitive muscle afferents in this population.

ACKNOWLEDGEMENTS

The authors would like to thank the gracious participation of the patients, as well as the staff at the Cardiology clinic at the SLC VA Hospital, Dr. Josef Stehlik, and nurse practitioners Mary Beth Hagan and Robin Waxman. Additionally, we would like to acknowledge financial support from NIH P01 HL-091830 (R.S.R), NIH R01 HL118313 (D.W.W), VA RR&D 1121RX001418-01 (D.W.W), and VA Merit grant E6910R (R.S.R). Advanced Fellowships in Geriatrics from the Department of Veterans Affairs supported S.J.I and M.A.H.W. We would like to thank Van Reese for performing the blood assays. The results of the present study do not constitute endorsement by the ACSM.

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Figure 1.

Central hemodynamic responses to passive leg movement. A) Cardiac Output, B) Stroke Volume, and C) Heart Rate, with and without (control) intrathecal fentanyl. Area under the curve, AUC, (n = 10).

Figure 2.

Femoral blood flow (FBF) responses to passive leg movement. A) Net FBF, B) Antegrade FBF, and C) Retrograde FBF, with and without (control) intrathecal fentanyl. * $p < 0.05$ vs. control, (n = 6).

Figure 3. Peripheral hemodynamic response to passive leg movement, A) Femoral Mean Arterial Pressure (n=10) and, B) Femoral Vascular Conductance, with and without (control) intrathecal fentanyl (n = 6). * $p < 0.05$ vs. control.

Table 1

Subject characteristics

	Mean $\pm$ SE
Age (yrs)	62 $\pm$ 3
Height (cm)	180 $\pm$ 2
Weight (kg)	96 $\pm$ 5
Body Mass Index (kg/m ²)	29.5 $\pm$ 1
Systolic Blood Pressure (mmHg)	113 $\pm$ 3
Diastolic Blood Pressure (mmHg)	73 $\pm$ 2
Glucose (mg/dL)	106 $\pm$ 9
Total Cholesterol (mg/dL)	160 $\pm$ 15
HDL Cholesterol (mg/dL)	40 $\pm$ 2
LDL Cholesterol (mg/dL)	96 $\pm$ 11
Triglycerides (mg/dL)	164 $\pm$ 19
Leukocytes (K/uL)	8.0 $\pm$ 0.5
Erythrocytes (M/uL)	4.9 $\pm$ 0.2
Hemoglobin (g/dL)	14.9 $\pm$ 0.4
Hematocrit (%)	44.2 $\pm$ 1.4
Ejection Fraction (%)	27 $\pm$ 3
Ischemic/non-ischemic etiology (no. of cases)	7/3
NYHA Class II (no. of cases)	10
Diabetic (no. of cases)	4

High density lipoproteins, HDL; Low density lipoproteins, LDL; New York Heart Association, NYHA

Table 2

Near infrared spectroscopy derived variables assessed in the vastus lateralis at rest and during passive leg movement (PLM - peak and steady state (SS) responses) with and without (control) intrathecal fentanyl.

	Control			Fentanyl		
	Baseline	PLM - Peak	PLM - SS	Baseline	PLM - Peak	PLM - SS
StO ₂ (%)	61.7±1.7	65.2 ± 1.6 *	62.5 ± 1.9 *	61.5 ± 1.4	66.5 ± 1.5 *†	63.8 ± 1.5 *†
Hb+MbO ₂ (uM)	36.1±2.7	38.9 ± 3.3 *	35.5 ± 3.3	37.2 ± 2.5	41.5 ± 3.0 *	37.0 ± 2.5
HHb+Mb (uM)	22.7±2.2	19.3 ± 2.3 *	21.3 ± 2.3 *	22.5 ± 2.1	18.8 ± 1.9 *	20.3 ± 2.0 *
THb+Mb (uM)	58.7±4.4	61.0 ± 5.0 *	56.8 ± 5.1	56.8 ± 5.2	59.6 ± 5.5 *	54.7 ± 5.6

Tissue oxygen saturation, StO₂; oxygenated hemoglobin and myoglobin, Hb+MbO₂; deoxygenated hemoglobin and myoglobin, HHb+Mb; total hemoglobin and myoglobin, THb+Mb.

* $p < 0.05$ vs. baseline,

† $p < 0.05$ vs. control

Table 3

Ventilation and blood gas variables at rest and in response to passive leg movement (PLM) with and without intrathecal fentanyl.

	Control		Fentanyl	
	Baseline	PLM	Baseline	PLM
V_E (L/min)	12 ± 3	$18 \pm 6^*$	14 ± 6	$19 \pm 6^*$
B_f (breaths/min)	18 ± 4	$30 \pm 14^*$	17 ± 4	$34 \pm 15^*$
V_T (L/breath)	0.7 ± 0.2	$1.3 \pm 0.5^*$	0.8 ± 0.3	$1.3 \pm 0.7^*$
PaO_2 (mmHg)	76 ± 3	80 ± 3	78 ± 3	79 ± 2
PvO_2 (mmHg)	31 ± 1	29 ± 1	32 ± 1	$29 \pm 1^*$
$PaCO_2$ (mmHg)	32 ± 1	32 ± 1	31 ± 1	32 ± 1
$PvCO_2$ (mmHg)	42 ± 2	40 ± 3	43 ± 2	43 ± 2
$PvCO_2$ (g/dL)	13.6 ± 0.5	13.1 ± 0.6	13.5 ± 0.5	13.3 ± 0.4
SaO_2 (%)	96 ± 1	96 ± 1	96 ± 0.5	96 ± 1
SvO_2 (%)	50 ± 2	48 ± 2	47 ± 3	$41 \pm 2^{\dagger}$
CaO_2 (mL/dL)	18.2 ± 0.7	18.1 ± 0.5	18.3 ± 0.6	18.1 ± 0.4
CvO_2 (mL/dL)	9.6 ± 0.8	$8.4 \pm 0.6^*$	8.8 ± 0.8	$7.6 \pm 0.5^{*\dagger}$
$a-vO_2$ (mL/dL)	8.5 ± 0.4	$9.6 \pm 0.4^*$	9.5 ± 0.5	$10.5 \pm 0.4^{*\dagger}$
$aHbO_2$ (%)	18.1 ± 0.6	18.0 ± 0.5	18.2 ± 0.5	18.0 ± 0.4
$vHbO_2$ (%)	9.6 ± 0.8	$8.4 \pm 0.6^*$	8.8 ± 0.7	$7.6 \pm 0.5^{*\dagger}$
O_2 Delivery	0.04 ± 0.01	$0.07 \pm 0.02^*$	0.04 ± 0.01	$0.08 \pm 0.02^{*\dagger}$
VO_2 (L/min)	0.02 ± 0.0	$0.04 \pm 0.01^*$	0.02 ± 0.0	$0.05 \pm 0.01^*$
O_2 Extraction (%)	48 ± 3	$54 \pm 3^*$	52 ± 3	$58 \pm 2^*$
apH	7.42 ± 0.01	7.41 ± 0.01	7.43 ± 0.02	7.43 ± 0.02
vpH	7.36 ± 0.01	7.35 ± 0.01	7.34 ± 0.01	7.35 ± 0.01
aLactate (mmol/L)	0.92 ± 0.2	0.88 ± 0.1	1.01 ± 0.1	0.99 ± 0.1
vLactate (mmol/L)	1.11 ± 0.2	1.05 ± 0.2	1.26 ± 0.2	1.19 ± 0.2

Ventilation, V_E ; Breathing frequency, B_f ; Tidal volume, V_T ; Arterial partial pressure of oxygen PaO_2 ; venous partial pressure of oxygen PvO_2 ; arterial partial pressure of carbon dioxide $PaCO_2$; venous partial pressure of carbon dioxide, $PvCO_2$; arterial oxygen saturation, SaO_2 ; venous oxygen saturation, SvO_2 ; arterial oxygen content, CaO_2 ; venous oxygen content, CvO_2 ; arterial-venous oxygen difference, $a-vO_2$; arterial hemoglobin oxygen saturation, $aHbO_2$; venous hemoglobin oxygen saturation, $vHbO_2$; oxygen delivery, O_2 Delivery; arterial pH, apH; venous pH, vpH; arterial lactate, aLactate; venous lactate, vLactate.

* $p < 0.05$ vs. baseline,

† $p < 0.05$ vs. control