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Intrathecal fentanyl blockade of afferent neural feedback from skeletal muscle during exercise in heart failure patients: Influence on circulatory power and pulmonary vascular capacitance

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Abstract

Background—Secondary pulmonary hypertension is common in heart failure (HF) patients. We hypothesized that inhibition of feedback from locomotor muscle group III/IV neurons contributes to reduced pulmonary vascular pressures independent of changes in cardiac function during exercise in HF.

Methods—9 HF patients (ages, 60±2; EF, 26.7±1.9%; New York Heart Association class, I-III) and 9 age/gender matched controls (ages, 63±2) completed five-minutes of constant-load cycling (65% $Workload_{peak}$) with intrathecal fentanyl or placebo on randomized separate days. Mean arterial pressure (MAP), heart rate (HR), end-tidal partial pressure of CO₂ (P_{ETCO_2}), and oxygen consumption (VO_2) were measured at rest and exercise. Non-invasive surrogates for cardiac power (circulatory power, $CircP=VO_2 \times MAP$), stroke volume (oxygen pulse, $O_2pulse=VO_2/HR$), and pulmonary arterial pressure ($GX_{CAP}=O_2pulse \times P_{ETCO_2}$) were calculated.

Results—At rest and end-exercise, differences between fentanyl versus placebo were not significant for $CircP$ in HF or controls. Differences between fentanyl versus placebo for GX_{CAP} were not significant at rest in HF or controls. At end-exercise, GX_{CAP} was significantly higher with fentanyl versus placebo in HF (691±59 versus 549±38 mL/beat×mm Hg), but not controls (536±59 versus 474±43 mL/beat×mm Hg). Slopes (rest to end-exercise) for GX_{CAP} were significantly higher with fentanyl versus placebo in HF (95.1±9.8 versus 71.6±6.0 mL/beat×mm

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Hg), but not controls (74.3 ± 9.5 versus 60.8 ± 6.5 mL/beat $\times$ mm Hg). CircP slopes did not differ between fentanyl versus placebo in HF or controls ($p > 0.05$).

Conclusion—We conclude that feedback from locomotor muscle group III/IV neurons may evoke increases in pulmonary vascular pressures independent of changes in cardiac function during exercise in HF.

Keywords

ergoreceptors; metaboreceptor; mechanoreceptor; pulmonary hypertension; fentanyl

Introduction

Secondary pulmonary hypertension (PH) is a frequent consequence of chronic heart failure (HF) and is closely linked to increased morbidity and mortality [1–5]. The initial elevation in pulmonary vascular pressures are associated with decreases in left ventricular relaxation and contractility which contribute to increases in cavity filling pressures and augmented backward pressure toward the pulmonary venous circulation (passive PH) [6, 7]. In some cases, however, despite efforts which reduce the hemodynamic volume of the pulmonary circulation, the transpulmonary gradient between mean pulmonary arterial pressure (mPAP) and pulmonary capillary wedge pressure remain elevated (i.e. >15 mm Hg) and high pulmonary vascular resistance persists [6, 7]. This exacerbated form of secondary PH has been termed “reactive” or “mixed,” although the pathogenic mechanisms are not fully understood [2, 6–8].

Another debilitating consequence of HF syndrome is dysregulation of the autonomic nervous system (ANS) which contributes to chronically elevated sympathetic nervous system activity. Although it is recognized that sympathoexcitation contributes to increases in vascular resistance of the periphery [9–11], it remains unclear if the pulmonary vasculature responds similarly to this heightened neurohumoral state in HF. Therefore, because of the close link between secondary PH in HF and increased morbidity and mortality, it is critical to improve the understanding of mechanisms linking elevated adrenergic drive, impaired cardiac function, and pulmonary vascular health in these patients [2–4, 7, 8].

Recent observations suggest that a primary contributor to sympathoexcitation during exercise in HF originates from mechanically (group III mechanoreceptors) and/or metabolically (group IV metaboreceptors) sensitive skeletal muscle neurons [12–16]. Group III/IV unencapsulated nerve fibers are embedded near venules, capillaries, and within collagenous tissue of skeletal muscle and have been shown to aid in mediating changes in peripheral vascular pressures and ventilatory control in humans [12–14, 16–18].

In healthy individuals, an ample body of evidence now suggests that feedback from group III/IV nerve fibers particularly during exercise contributes to normal regulation of ventilation, cardiac, and circulatory function which work in parallel to maintain cardiovascular homeostasis [16, 19, 20]. In contrast, observations in HF suggest that feedback from skeletal muscle group III/IV nerve fibers contribute to altered ventilatory control as well as peripheral hypertension which are recognized as cardiovascular responses

that contribute to reductions in functional capacity and exertional symptoms in this population [10, 12, 14, 15].

Assessment of the influence of feedback from group III/IV nerve fibers during exercise in humans remains challenging. However, μ -opioid receptors which can be found superficially located on the lumbar dorsal horn of the spinal cord where group III/IV nerve fibers synapse represent a feasible target for pharmacological manipulation of afferent neural signaling [21–24]. The selective μ -opioid receptor agonist has been shown to inhibit the cortical projection of group III/IV neural feedback in human and animal models [16, 21, 25]. Indeed, it has been observed that intrathecal administration of fentanyl at the lower-lumbar level prior to exercise in healthy individuals may contribute to exercise hypoventilation, a decrease in the ventilatory equivalent for carbon dioxide (V_E/V_{CO_2}), and lower mean arterial pressure (MAP) without affecting efferent neuromuscular control or the force-generating capacity of skeletal muscle related to central command [16, 25].

Intrathecal injection of fentanyl at the lower-lumbar level prior to submaximal exercise decreases minute ventilation (V_E), breathing frequency (f_B), V_E/V_{CO_2} , and MAP in HF [9, 12]. Although, the influence of this experimental technique on cardiac hemodynamics in human HF remains open to question despite previous observations which suggest that inhibition of group III/IV afferents contributes to significant attenuations in cardiac output (Q), heart rate (HR), and stroke volume (SV) during exercise in HF [9]. Further, although studied in healthy individuals, the influence of group III/IV afferents on changes in mPAP during exercise in HF patients has not been investigated [26, 27].

A number of studies in HF have suggested that non-invasive gas-exchange based indices including oxygen pulse (O_2 pulse) [1], circulatory power (CircP) [28, 29], and pulmonary vascular capacitance (GX_{CAP}) [1] are robust surrogates of direct measures of SV, cardiac power, and pulmonary vascular pressures during exercise in this population, respectively. The close relationships between surrogates and direct measures are important because cardiac power is a robust indicator of cardiac function during exercise in HF [30]; and, invasive assessment of pulmonary vascular capacitance during exercise may be used to discriminate HF with secondary PH compared to HF patients without [1].

The present study aimed to test the hypothesis that selective μ -opioid inhibition of feedback from group III/IV nerve fibers using intrathecal fentanyl at the lower-lumbar level during submaximal constant-load exercise would be associated with increases in CircP and GX_{CAP} in HF patients.

Methods

Participants

Nine Caucasian systolic HF patients along with nine Caucasian healthy control participants matched for gender and age were recruited and participated in this study (participant demographics, Table 1). Inclusion criteria for HF patients included diagnosis of ischemic or dilated cardiomyopathy with duration of HF symptoms >one year; stable HF symptoms (>three months); left ventricular ejection fraction percentage $\geq 35.0\%$ (from clinical records

within three months); body mass index (BMI) <35.0 kilograms/meter² (at enrolment); and current non-smokers with a past smoking history <15 pack-years (at enrolment). All patients were on standard optimum pharmacological therapy for HF at the time of the study. Heart failure patients were recruited through the Mayo Clinic Heart Failure Service and the Cardiovascular Health Clinic. Control participants were recruited through advertisement in the surrounding community. Control participants had normal cardiac function without evidence of exercise-induced ischemia and were without history of hypertension, lung disease, or coronary artery disease. The experimental procedures were approved by the Mayo Clinic Institutional Review Board, all participants provided written informed consent prior to study, and all aspects of the study were performed in accordance with the ethical standards of the Declaration of Helsinki. Parts of these data have been reported previously in a separate study aim specifically describing the ventilatory responses to inhibition of group III/IV afferents during exercise in HF [12]. However, the data presented in the current manuscript represent a new analysis based on an a priori novel hypothesis.

Overview

Each individual participated in three testing sessions separated by 48-hours each in an environmentally controlled physiology laboratory. For all study visits, participants were asked to avoid strenuous physical activity for 24-hours prior to the visit and refrain from eating or consuming caffeine for three hours prior to arrival at the physiological laboratory for testing.

Upon arrival, participant characteristics were assessed, which included height, weight, and medication history. Participants were then fitted with a 12-lead electrocardiogram (Marquette Electronics, Milwaukee, WI) to continuously monitor HR and rhythm. Participants were seated on a recumbent cycle ergometer and fitted with a nose clip and mouthpiece attached to a PreVent Pneumotach (Medical Graphics, St Paul, MN) connected to a breath-by-breath ventilation system (MedGraphics CPX/D; Medical Graphics), which was calibrated for volumes (3.0 liter syringe) and gases immediately prior to each protocol. In this seated position, resting measures of oxygen uptake (VO_2), VCO_2 , respiratory exchange ratio (RER), f_B , tidal volume (V_T), V_E , and $P_{ET}\text{CO}_2$ were performed. Blood pressure was measured using manual sphygmomanometry at rest and near the end of each stage during the peak exercise test (session 1). During the second and third study sessions, blood pressures were monitored continuously via indwelling radial artery catheter during constant-load submaximal exercise sessions. For all three study sessions, measures of ventilation and flow analysis as well as HR and oxygen saturation were continuously monitored and averaged every three seconds at rest and throughout exercise.

We calculated the SV estimate O_2pulse as, VO_2/HR [1]; the non-invasive surrogate for pulmonary vascular capacitance as, $\text{GX}_{\text{CAP}} = \text{O}_2\text{pulse} \times P_{ET}\text{CO}_2$ [1]; and the cardiac power estimate CircP as, $\text{VO}_2 \times \text{MAP}$ [28, 31]. The slopes for O_2pulse , GX_{CAP} , and CircP were calculated as, $(\text{end-exercise} - \text{baseline})/5$. We calculated BMI as, $\text{weight}/\text{height}^2$; and, body surface area as, $\sqrt{(\text{height} \times \text{weight})/3600}$.

Exercise protocols

The first study day included a peak exercise test beginning at 20 watts (W) and increased by 20 W (HF) and 40 W (controls) every three minutes while maintaining a cadence of 65 revolutions per minute until volitional fatigue (i.e. rating of perceived exertion 17 [Borg Scale = 6–20] or RER of 1.10). Study days two- and- three were randomized to either intrathecal injection of fentanyl at the lumbar level (fentanyl) to produce blockade of feedback from locomotor muscle group III/IV afferents or sham injection (placebo) in a single-blind fashion (described in detail below). Each exercise session on days two and three consisted of five minutes of constant-load exercise at 65% of previously determined peak work (session 1), and were followed by static recovery for five minutes. Relative constant-load workloads were selected for HF and control participants because we suggest that matched absolute workloads would have likely resulted in controls not eliciting the same level of exertion and exercise intensity compared to HF patients, and therefore we would not be able to adequately assess direct comparisons between HF and controls for cardiovascular responses to the experimental conditions.

Radial intra- arterial blood pressure and gases assessment

During study days two- and- three, blood pressures and blood gases were measured using radial intra-arterial catheterization. Briefly, a 20-gauge Teflon catheter (FA-04020; Arrow International Inc., Reading, PA) was placed into a radial artery after induction of local anesthesia (1.0% lidocaine). Real-time blood sampling and measurement of arterial pressure was recorded from a pressure transducer (PXMK099; Edwards Lifesciences, Irvine, CA) and exported to a digital oscilloscope for offline analysis of SBP, diastolic blood pressure (DBP), and MAP. Partial pressure of arterial oxygen and CO₂ were also measured from anaerobically drawn arterial blood samples from the same catheter over a period of 10–15 seconds at rest and immediately before cessation of exercise (ABL825 Flex Blood Gas/CO-ox analyzer; Radiometer America Inc., Westlake, OH).

Intrathecal injection to influence neural feedback from locomotor muscles, fentanyl versus placebo

The following approach used in the present study was similar to the approach used in a variety of clinical anesthesiology settings and research laboratories, as described previously [12, 16]. Study days two- and- three, irrespective of randomization order, were identical except for intrathecal injection of fentanyl or placebo. Briefly, on study days two- and- three participants were seated in an upright position. Immediately following arterial catheter placement, using aseptic technique, the skin and subcutaneous tissue were anaesthetized at the L3—L4 vertebral interspace with 2.0–4.0 mL of 1.0% lidocaine. A 22-gauge Whitaker needle was advanced to the subarachnoid space between L3—L4 with placement confirmed by visualization of free-flowing cerebrospinal fluid, then 1.0 mL of fentanyl (0.05 milligram/mL) was injected into the subarachnoid space following aspiration of a small amount of cerebrospinal fluid. The participants remained seated in the upright position to minimize cephalad migration of fentanyl.

During the placebo visit, the physician provided the same technical guidance and description of the technique compared to the fentanyl visit. The area was prepped, cleaned, and draped

identical to the fentanyl visit. Briefly, subcutaneous lidocaine was used to numb the area and direct pressure was then applied to the area using an empty syringe to simulate the process of conducting the intrathecal injection.

Central chemosensitivity assessment

To assess for potential cephalad migration of fentanyl within the cerebrospinal fluid we measured central chemosensitivity using a CO₂ rebreathing method immediately following the five minute static recovery period [12]. This timing was selected based on previous observations of bupivacaine injections at the L3–L4 level which suggests that cephalad migration of anesthetic drugs similar to fentanyl may take upwards of 75 minutes [32]. Therefore, it was determined that performing central chemosensitivity assessment prior to exercise would be inadequate in detecting whether cephalad migration of fentanyl indeed occurred during exercise sessions. We suggest that if cephalad migration of fentanyl within cerebrospinal fluid were to occur it would be most readily detectable at post-exercise when sufficient time for migration had elapsed.

For the CO₂ rebreath test participants breathed into a non-rebreathing three-way pneumatic switching valve (Hans Rudolph, Kansas City, MO) that was connected to a pneumotachometer (Hans Rudolph, Kansas City, MO) and ventilation system (MedGraphics CPX/D; Medical Graphics). The inspiratory port of the switching valve allowed for rapid switching from breathing room air to the 6.0 L anesthesia rebreath bag (Hans Rudolph, Kansas City, MO) containing a gas-mixture volume of 5.0% CO₂ and 95.0% O₂ depending on initial V_T of the subject. Participants breathed room air for two minutes that was followed by a slow maximal expiration to residual volume where the participants were then switched into the rebreath bag. Participants began with a maximal full inspiration of rebreath bag air that was followed with relaxed breathing for four minutes. Continuous measures of P_{ET}CO₂, end-tidal partial pressure of oxygen, and V_E occurred. The test was stopped prior to the conclusion of the four minute maneuver period if one of the following occurred: P_{ET}CO₂ of 65.0 mm Hg; end-tidal partial pressure of oxygen of 160.0 mm Hg; V_E of 100 L/min; or participant wished to stop. The sensitivity to CO₂ was assessed using the slope of the relationship between measures of V_E and P_{ET}CO₂. On study days two- and-three, the CO₂ rebreath test was performed three separate times with three- to- five minutes of exposure to room air to allow V_E and P_{ET}CO₂ to return to baseline between attempts. The coefficient of variation for CO₂ rebreath testing was: HF placebo = 0.29; HF fentanyl = 0.27; CTL placebo = 0.28; and CTL fentanyl = 0.36. The V_E/P_{ET}CO₂ slopes were averaged for the three trials and the results have been reported previously which suggest no cephalad migration of fentanyl occurred in participants [12].

Statistical Analyses

All data are presented at means ± standard deviation. The data were distributed normally. Homogeneity of variance of the data was confirmed using Levene's test. Specific comparison between groups (i.e. controls vs. HF) were assessed using unpaired two-tailed Student's t-tests. Multiple comparisons for group, time, experimental condition, and interaction (group × experimental condition) effects were tested using a two-way repeated measures analysis of variance test. Post-hoc Bonferroni testing was used to correct for

multiple comparisons in the event of a significant F-test statistic. The alpha level was set at 0.05 to determine significance. Computations were made using SAS statistical software, v. 9.4 (SAS Institute, Cary, NC).

Results

Participant characteristics

We demonstrate in Table 1 that the total sample was predominantly male but with equal numbers of males and females in HF and control groups. The overall age range was 52-to-73 years. Height did not differ between groups, whereas controls weighed on average ~18.0% less than HF which contributed to the differences in BMI and body surface area between groups. Ejection fraction percentage was characteristic of systolic HF (range = 20.0–35.0%). Exercise capacity was significantly lower in HF compared to controls ($\text{VO}_{2\text{peak}}$, range = 14.0–23.1 vs. 22.0–36.7 mL/kg/min, respectively; $P < 0.05$). Heart failure patients were of New York Heart Association (NYHA) classification range I–III, ischemic or idiopathic etiology, and optimally medicated for HF using standard pharmacological therapy.

Baseline ventilation and hemodynamics

Baseline measures of ventilation and hemodynamics for both groups and experimental conditions are presented in Table 2. No significant drug $\times$ group interactions were observed. No differences in VO_2 , VCO_2 , V_E , V_T , f_B , or P_{ETCO_2} were observed between HF and controls ($P > 0.05$, for all). Heart rate did not differ significantly between or within groups. Systolic blood pressure and MAP were lower in HF compared to controls ($P < 0.05$, for all). Accordingly, because of the predominately lower blood pressure in HF, CircP was significantly lower in HF compared to controls.

Exercise ventilation and hemodynamics

Exercise intensity, ventilation, and hemodynamic measures averaged over the final 30 seconds of exercise for both groups and experimental conditions are presented in Table 3. No significant drug $\times$ group interactions were observed.

Although there was a significant difference in exercise workload between groups, percentage of $\text{VO}_{2\text{peak}}$ between groups was not different ($P > 0.05$). Null differences between groups and experimental conditions for VO_2 and VCO_2 were also reflected in RER. The similar RER values suggests that the groups were similarly matched for metabolic intensity. Whereas, although no significant differences appeared for VCO_2 and V_T , V_E was significantly lower in HF with fentanyl compared to controls with fentanyl; and, both V_E and f_B were less in HF with fentanyl compared to HF with placebo. The average difference for P_{ETCO_2} between experimental conditions for HF was 7.2 ± 0.1 mm Hg ($P < 0.05$), whereas the average difference for controls was 2.1 ± 0.8 mm Hg ($P > 0.05$). There were no other significant between experimental condition differences for ventilation in HF and controls.

Heart failure patients in both experimental conditions demonstrated significantly lower HR and CircP compared to controls. However, differences between HF and controls for O_2pulse

were not significant; although, these null differences at end-exercise were consistent with baseline O_2 pulse differences between HF and controls ($P>0.05$). For HR, CircP, and O_2 pulse there were no significant differences between experimental conditions in HF or controls. However, exercise with fentanyl in HF and in controls resulted in consistently lower blood pressures compared to exercise with placebo in both groups ($P<0.05$).

Exercise with fentanyl in HF resulted in differences in GX_{CAP} which were significantly higher compared to exercise with placebo (142 ± 62 mL/beat $\cdot$ mm Hg); whereas, exercise with fentanyl in controls showed non-significant differences compared to exercise with placebo (62 ± 47 mL/beat $\cdot$ mm Hg). Accordingly, the significantly higher P_{ETCO_2} during exercise with fentanyl in HF compared to exercise with placebo appeared to facilitate the higher GX_{CAP} values observed during the fentanyl experimental condition in these individuals. The effect of P_{ETCO_2} on GX_{CAP} observed in HF was not demonstrated in controls.

Figure 1A shows that the differences in absolute change () from baseline to end-exercise for CircP was similar for placebo and fentanyl conditions between HF and controls. In contrast, presented in Figure 1B, fentanyl was associated with significantly higher for GX_{CAP} compared to placebo in HF. This suggested that inhibition of group III/IV afferents was related to an increased absolute GX_{CAP} reserve in HF.

The percentage (%) increases from baseline to end-exercise for CircP in Figure 2A were similar to Figure 1A for group and experimental condition. Figure 2B contrasts the s shown in Figure 1B, demonstrating that in controls fentanyl was associated with significantly higher % GX_{CAP} compared to placebo. Although not significantly different, % GX_{CAP} was higher with fentanyl in HF, suggesting an increase in relative GX_{CAP} reserve was associated with inhibition of group III/IV afferents.

Presented in Figure 3(A and B) are the averages for CircP and GX_{CAP} during the exercise period in 30 second intervals, respectively. Note in Figure 3A there were no significant between experimental condition differences presented throughout exercise for either HF or controls. In contrast, Figure 3B shows GX_{CAP} was consistently higher throughout exercise with fentanyl compared to exercise with placebo in HF, eventually reaching significance near the end of exercise; but, this pattern was not present between experimental conditions in controls. The higher GX_{CAP} during exercise with fentanyl in HF suggested that sympathetically mediated vasoconstriction of the pulmonary vasculature decreased as a result of inhibition of group III/IV afferents.

Presented in Figure 4(A and B) are indices which comprise CircP, VO_2 and MAP, during the exercise period in 30 second intervals, respectively. Consistent with Figure 3A, in Figure 4A for VO_2 there were no significant between experimental condition differences present for HF or controls. In contrast, responses reported in Figure 4B show throughout exercise with fentanyl, MAP was lower compared to placebo in both HF and controls. These observations in Figure 4B suggested that inhibition of group III/IV afferents may have resulted in attenuations in sympathetically mediated peripheral vasoconstriction in older individuals.

Lastly, presented in Figure 5(A and B) are indices which comprise $G\dot{X}_{CAP}$, $P_{ET}CO_2$ and O_2 pulse, during the exercise period in 30 second intervals, respectively. Similar to Figure 3B, the changes reported in Figure 5A for $P_{ET}CO_2$ mirror the differences between fentanyl and placebo for $G\dot{X}_{CAP}$ in HF patients. In contrast, similar to Figures 3A and 4A, O_2 pulse in Figure 5B was not significantly different between experimental conditions in HF or controls at any point throughout exercise. These observations suggested that pulmonary vascular pressures decreased in the absence of changes in myocardial contractility in the presence of group III/IV afferent inhibition in HF.

Discussion

In this randomized, single-blind, placebo-controlled crossover study, we observed that inhibition of centrally projecting feedback from locomotor muscle group III/IV nerve fibers using intrathecal fentanyl during constant-load submaximal exercise was associated with increases in $G\dot{X}_{CAP}$ in HF (i.e. decreases in pulmonary vascular pressures [1]). In contrast, despite an apparent influence on lowering both pulmonary and peripheral vascular pressures (i.e. decreases in afterload), inhibition of feedback from locomotor muscle group III/IV nerve fibers during exercise did not appear to evoke increases in O_2 pulse or CircP in HF.

An ample body of evidence suggests that during periods of increased metabolic demand such as exercise in healthy individuals, the ANS appropriately functions to increase sympathetic drive to organs of the cardiovascular system such as the heart and peripheral vasculature [16, 19, 20, 25]. The elevation in adrenergic drive to these organs and others work in concert to maintain blood flow and perfusion pressure to highly metabolically active tissue (e.g. skeletal and respiratory muscles) for oxygen and nutrient delivery in order to meet the continued and augmented metabolic demands of exercise. The acute reflex response of the sympathetic nervous system during times of hemodynamic stress is contributed to by feedback from group III/IV nerve fibers found dispersed within skeletal muscle, and assists in the sustained maintenance of cardiovascular function during exercise in healthy individuals [16, 19, 20, 25]. In HF, however, the interactions between components of the cardiovascular system, which include skeletal muscle (where group III/IV afferents are located) and neural systems are deranged and contribute to persistently elevated adrenergic drive at rest which is exacerbated during exercise [9, 10, 12, 14, 15]. Our group and others have demonstrated that the impaired group III/IV neural feedback pathway contributes to detrimental changes in ventilatory and peripheral vascular control resulting in tachypnea and hypertension, respectively, during exercise in HF patients [9, 10, 12, 14, 15].

To date, despite evidence to suggest group III/IV afferents contribute to increases in inotropy and cardiac hemodynamics in healthy humans and animals [20, 33, 34], limited in number and less clear are the data examining these relationships during exercise in human HF [9]. Amann et al. recently observed that inhibition of group III/IV afferents via intrathecal fentanyl resulted in significant attenuations in Q, SV, and HR during exercise compared to exercise with placebo in human HF [9]. This group further observed reductions in Q, SV, HR, and blood pressure; although, perhaps somewhat unexpected, they also demonstrated that femoral blood flow was significantly higher compared to exercise with placebo in HF patients and, hence, it remains unclear what mechanism was facilitating

perfusion pressure and oxygen and nutrient delivery to skeletal muscle given these individuals performed exercise to completion for all exercise protocols [9].

As such, a major finding of the present study suggests that increases in $G\dot{X}_{CAP}$ (i.e. decrease in pulmonary vascular pressures [1]) occurred independent of increases in cardiac function (i.e. O_2 pulse) during exercise with group III/IV afferent inhibition in HF. This was a noteworthy finding because it emphasizes the critical nature of the pathophysiology of secondary PH in HF. Heart failure patients with secondary PH demonstrate remodeling of the pulmonary vasculature associated with stiffening and loss of elastance of both pulmonary arterial and venous vasculature that contributes to tonic elevations in pulmonary arterial pressures and resistance, even when attempts are made to alleviate the hemodynamic backup in the pulmonary vasculature [2, 6–8]. Accordingly, we suggest that the present observations of increases in $P_{ET}CO_2$ during exercise in HF with fentanyl may reflect the direct associations which have been shown between $P_{ET}CO_2$ and pulmonary blood flow, mixed venous CO_2 content, mPAP, and pulmonary vascular resistance [1, 35–37]. The present observations extend findings from two previous studies which demonstrate neural feedback from skeletal muscle contribute to increases in mPAP during and immediately following submaximal exercise in healthy individuals [26, 27].

Although older healthy individuals in the present study did not demonstrate changes in $G\dot{X}_{CAP}$ during exercise with intrathecal fentanyl which were commensurate with the observations of Lykidis et al. [26] and White et al. [27] in healthy younger individuals, it is important to point out that the techniques utilized in these previous studies differed considerably from the current study. Lykidis et al. [26] and White et al. [27] stimulated feedback responses from group IV (and perhaps group III) neural fibers during exercise using regional circulatory occlusion of exercising limbs. Additionally, it was noted in the more recent study of White et al. [27] that based on those observations, in addition to previous findings in Lykidis et al. [26], that regional circulatory occlusion in the absence of exercise does not generate significant pressor responses compared to exercise with concurrent regional circulatory occlusion. Therefore, and in contrast to Lykidis et al. [26] and White et al. [27], the present cross-over study implemented neural feedback inhibition during exercise which was compared to matched exercise under placebo conditions. Hence, Lykidis et al. [26] and White et al. [27] comparisons of the influence of neural feedback from locomotor muscle on pulmonary vascular responses between regional circulatory occlusion with exercise and regional circulatory occlusion independent of exercise may overestimate the influence of this pathway on increasing pulmonary vascular pressures in healthy individuals relative to the observations of the present study.

Although not measured directly, it is likely that increased vascular conductance and decreased systemic vascular resistance during exercise with intrathecal fentanyl lead to a reduction in afterload and mPAP in HF [38, 39]. Because HF patients are afterload dependent, these reductions in vascular resistance would be expected to facilitate increased Q and SV which contribute to the maintenance of arterial pressure. However, in the present study, inhibition of locomotor muscle group III/IV feedback did not significantly alter O_2 pulse [1, 31], CircP [28, 29], or HR during exercise in HF. This further suggests that myocardial contractile reserve may not be increased by pathways related to feedback from

locomotor muscle group III/IV neural fibers in HF patients similar to what has been observed in healthy models [20, 33, 34]. The comparable O₂pulse responses between HF and control participants at baseline was likely caused by the presence of larger ventricular cavities related to dilated cardiomyopathy, and not because of preserved cardiac function since patients also demonstrated significantly attenuated CircP at rest and at end-exercise, as well as reduced HR at end-exercise in comparison to control participants. Whereas, similar O₂pulse responses between HF and controls at end-exercise may have been attributable to the influence of myocardial β -blockade therapy which could have contributed to significant attenuations in HR in HF patients compared to controls that may have resulted in potentially exaggerated O₂pulse values in patients.

Cardiac pumping capacity is impaired in HF at rest and during exercise despite heightened cardiac adrenergic drive [30, 40, 41]. This may be related to impaired mechanisms intrinsic to HF such as a failing Frank—Starling mechanism (related to ischemic wall segments and/or dysfunctional cardiac β -adrenergic receptors) [41–45]. Therefore, because HF patients demonstrate limited myocardial contractile reserve, this suggests that augmented afterload associated with exercise and feedback from group III/IV neural fibers should attenuate increases in cardiac hemodynamics and the ability to contribute to the maintenance of peripheral arterial pressure. However, this relationship between afterload, group III/IV afferents, and cardiac function were not observed in the present study. The lack of overall significant increases in CircP and O₂pulse despite decreases in afterload during exercise with intrathecal fentanyl was likely related to mechanisms (e.g. failing Frank-Starling mechanism) which contribute to impaired myocardial contractile reserve that is native to HF syndrome. As such, this could explain why elevated cardiac adrenergic drive during exercise with placebo also did not result in significant increases in O₂pulse, CircP, or HR in HF patients.

Clinical Implications

The present findings suggest that feedback from locomotor muscle group III/IV nerve fibers contributes to increases in pulmonary vascular pressures independent of changes in cardiac hemodynamics during submaximal exercise in HF; and, perhaps more importantly, provides further insight into the mechanisms contributing to exertion-related symptoms at work intensities equivalent to those of daily living. These observations are also important because it is well-accepted that HF patients commonly develop secondary PH which is closely linked to increased morbidity and mortality [2–5]. The current findings extend those of others by highlighting a novel contributory mechanism of secondary PH in HF.

Limitations

Because this study focused on patients with systolic HF, the sample of HF patients included disproportionately represented males compared to females as males have a higher incidence of systolic HF compared to women [46]. We included patients characterized as NYHA class I–III, whereas NYHA class IV patients exhibit more severe cardiac and/or pulmonary impairment in parallel with diminished vascular health which are commonly associated with signs and symptoms at rest and during low-level activity. Therefore, while it might be

expected that the findings of the present study would be exacerbated in patients exhibiting increased exertional symptoms, overall these data are generalizable to the patients studied. Further research is necessary to confirm our findings in a larger patient population. Also, although we did not directly assess sympathetic nervous system activity during exercise, the intrathecal fentanyl technique has been used previously to inhibit group III/IV neural feedback during exercise in healthy individuals and HF patients [9, 12, 16]. Finally, although O₂pulse is a validated surrogate of SV [1], and CircP for cardiac power in HF [28, 29], we did not directly measure SV or Q in the current study. Nevertheless, cardiac power and its estimate CircP are robust surrogates of cardiac hemodynamic function [28–31], and therefore it is important to point out that our use of indirect indices were adequate to address our study objectives since we aimed to study relative changes in central hemodynamics between experimental conditions as opposed to absolute capacities.

Conclusion

The observations of the present study suggest that inhibition of feedback from group III/IV nerve fibers originating within locomotor muscles using intrathecal fentanyl during submaximal exercise decreases pulmonary vascular pressures independent of changes in cardiac function in HF patients.

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Figure 1.

Data are presented as means $\pm$ standard deviation (A) Absolute change () circulatory power (CircP) from rest to end-exercise. *Significant between groups, heart failure vs. control, $p<0.05$. (B) in $GXCAP$ from rest to end-exercise. *Significant between fentanyl and placebo for heart failure, $p<0.05$.

Figure 2.

Data are presented as means $\pm$ standard deviation. **(A)** Circulatory power (CircP) at end-exercise as a percentage (%) of CircP at baseline. *Significant between groups, heart failure vs. control, $p<0.05$. **(B)** Pulmonary vascular capacitance (GX_{CAP}) at end-exercise as a % of GX_{CAP} at baseline. *Significant between fentanyl and placebo for control, $p<0.05$.

Figure 3.

Data are presented as means $\pm$ standard deviation. (A) HF, heart failure; CTL, control. Pattern of change for circulatory power (CircP) as increments of 30 second averages from rest to end-exercise. * $p < 0.05$, HF-Fentanyl vs. CTL-Fentanyl and HF-Placebo vs. CTL-Placebo. (B) Pattern of change for pulmonary vascular capacitance (GX_{CAP}) as increments of 30 second averages from rest to end-exercise * $p < 0.05$, HF-Fentanyl vs. CTL-Fentanyl. † $p < 0.05$, HF-Fentanyl vs. HF-Placebo.

Figure 4.

Data are presented as means $\pm$ standard deviation. (A) HF, heart failure; CTL, control.

Pattern of change for oxygen uptake (VO₂) as increments of 30 second averages from rest to end-exercise. * $p < 0.05$, HF-Fentanyl vs. CTL-Fentanyl and HF-Placebo vs. CTL-Placebo.

(B) Pattern of change for mean arterial pressure (MAP) as increments of 30 second averages from rest to end-exercise * $p < 0.05$, HF-Fentanyl vs. CTL-Fentanyl and HF-Placebo vs. CTL-Placebo. † $p < 0.05$, HF-Fentanyl vs. HF-Placebo and CTL-Fentanyl vs. CTL-Placebo.

Figure 5.

Data are presented as means $\pm$ standard deviation. **(A)** HF, heart failure; CTL, control. Pattern of change for end-tidal partial pressure carbon dioxide ($P_{ET}CO_2$) as increments of 30 second averages from rest to end-exercise. * $p < 0.05$, HF-Fentanyl vs. CTL-Fentanyl. † $p < 0.05$, HF-Fentanyl vs. HF-Placebo. **(B)** Pattern of change for oxygen pulse (O_2 pulse) as increments of 30 second averages from rest to end-exercise.

Table 1

Participant characteristics

	Healthy Control	Heart Failure	<i>P</i>
Demographics			
Age, years	63±8	60±6	0.37
Gender, male/female	7/2	7/2	0.99
Height, cm	175.7±9.8	175.9±9.5	0.97
Weight, kg	80.1±12.4	97.8±9.2	0.003
BMI, kg/m ²	25.9±3.4	31.9±4.4	0.005
BSA, m ²	2.0±0.2	2.2±0.1	0.02
VO _{2peak} , L/min	2.2±0.6	1.8±0.3	0.13
VO _{2peak} , mL/kg/min	26.8±5.2	18.4±2.8	0.001
LVEF, %		26.7±5.7	
Etiology (ischemic/idiopathic)		5/4	
NYHA class		1.9±0.8	
I		3	
II		3	
III		3	
Medications			
ACE inhibitor		6 (67)	
Angiotensin II receptor blockers		3 (33)	
β-blocker		9 (100)	
Aspirin		5 (56)	
Diuretics		6 (67)	

Data are mean±SD, n, or percentage (%). ACE, angiotensin converting enzyme; BMI, body mass index; BSA, body surface area; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VO_{2peak}, peak oxygen consumption.

Table 2

Resting measures

	Healthy Control		Heart Failure	
	Placebo	Fentanyl	Placebo	Fentanyl
Ventilation				
VO ₂ , L/min	0.34±0.03	0.33±0.07	0.36±0.03	0.38±0.05
VCO ₂ , L/min	0.31±0.03	0.30±0.05	0.34±0.04	0.36±0.05
RER	0.87±0.08	0.85±0.04	0.94±0.09	0.94±0.09
V _E , L/min	12±2	12±2	14±2	13±2
V _T , L	0.76±0.11	0.72±0.14	0.74±0.12	0.75±0.07
f _B , breaths/min	17±3	18±4	19±2	18±2
P _{ET} CO ₂ , mm Hg	34.9±2.2	35.2±3.0	36.5±8.2	38.8±4.5 [†]
Hemodynamics				
HR, beats/min	73±13	72±9	70±10	70±17
SBP, mm Hg	148±17	145±18 [†]	122±9 [*]	115±8 ^{*†}
DBP, mm Hg	68±10	64±8	59±8	57±9
MAP, mm Hg	95±11	91±10 [†]	80±6 [*]	76±8 ^{*†}
O ₂ pulse, mL/beat	4.9±1.1	4.7±1.2	5.3±0.8	5.6±1.1
CircP, mL/kg/min · mm Hg	411±70	381±80	299±38 [*]	300±53 [*]
GX _{CAP} , mL/beat · mm Hg	170±41	165±45	191±47	216±35 [*]

Data are presented as means±SD. CircP, circulatory power; DBP, diastolic blood pressure; f_B, breathing frequency; GX_{CAP}, pulmonary vascular capacitance; HR, heart rate; MAP, mean arterial pressure; O₂pulse, oxygen pulse; P_{ET}CO₂, end-tidal partial pressure CO₂; RER, respiratory exchange ratio; SBP, systolic blood pressure; VO₂, oxygen consumption; VCO₂, carbon dioxide production; V_E, minute ventilation; V_T, tidal volume.

* p<0.05 compared with control after Bonferroni correction.

[†] p<0.05 compared with placebo after Bonferroni correction.

Table 3

End-exercise measures

	Healthy Control		Heart Failure	
	Placebo	Fentanyl	Placebo	Fentanyl
Exercise intensity				
Workload (watts)	120±37	-	78±23 [*]	-
Percent of VO _{2peak}	77±13	77±13	82±14	84±15
Ventilation				
VO ₂ , L/min	1.7±0.4	1.7±0.5	1.5±0.3	1.5±0.3
VCO ₂ , L/min	2.0±0.5	2.0±0.5	1.5±0.3	1.6±0.3
RER	1.09±0.06	1.08±0.05	1.05±0.02	1.04±0.04
V _E , L/min	63±16	63±19	51±9	44±10 ^{*†}
V _T , L	2.1±0.6	2.1±0.6	1.7±0.4	1.7±0.3
f _B , breaths/min	30±4	30±5	33±12	26±5 [†]
P _{ET} CO ₂ , mm Hg	37.1±2.7	39.2±3.5	36.3±3.6	43.5±3.7 ^{*†}
Hemodynamics				
HR, beats/min	131±15	125±21	99±19 [*]	97±21 [*]
SBP, mm Hg	239±20	225±26 [†]	161±24 [*]	152±29 ^{*†}
DBP, mm Hg	75±9	66±6 [†]	62±9 [*]	56±11 ^{*†}
MAP, mm Hg	130±6	119±8 [†]	95±11 [*]	88±15 ^{*†}
O ₂ pulse, mL/beat	12.8±3.5	13.9±4.9	15.1±2.5	16.0±4.3
CircP, mL/kg/min · mm Hg	2721±618	2475±673	1413±257 [*]	1365±333 [*]
GX _{CAP} , mL/beat · mm Hg	474±130	536±177	549±115	691±176 [†]
<i>Slope</i>				
O ₂ pulse, mL/beat	1.59±0.53	1.83±0.80	1.96±0.39	2.08±0.66
CircP, mL/kg/min · mm Hg	462±125	419±127	223±50 [*]	212±66
GX _{CAP} , mL/beat · mm Hg	61±19	74±29	72±18	95±30 [†]

Data are presented as means±SD. CircP, circulatory power; DBP, diastolic blood pressure; f_B, breathing frequency; GX_{CAP}, pulmonary vascular capacitance; HR, heart rate; MAP, mean arterial pressure; O₂pulse, oxygen pulse; P_{ET}CO₂, end-tidal partial pressure CO₂; RER, respiratory exchange ratio; SBP, systolic blood pressure; VO₂, oxygen consumption; VCO₂, carbon dioxide production; V_E, minute ventilation; V_T, tidal volume; slope = rate of change baseline to end-exercise;

^{*} p<0.05 compared with control after Bonferroni correction;

[†] p<0.05 compared with placebo after Bonferroni correction.