International Journal of Cardiology 201 (2015) 384–393

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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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ARTICLE INFO

Article history:
Received 4 March 2015
Received in revised form 2 June 2015
Accepted 9 August 2015
Available online 14 August 2015

Keywords:
Ergoreceptors
Metaboreceptor
Mechanoreceptor
Pulmonary hypertension
Fentanyl

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 classes, 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 CO_2 ($P_{ET}CO_2$), and oxygen consumption (VO_2) were measured at rest and exercise. Non-invasive surrogates for cardiac power (circulatory power, CircP = VO_2 × MAP), stroke volume (oxygen pulse, O_2pulse = VO_2/HR), and pulmonary arterial pressure (GX_{CAP} = O_2pulse × $P_{ET}CO_2$) 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 Hg), but not controls (74.3 ± 9.5 versus 60.8 ± 6.5 mL/beat × 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.

1. 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

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
☆☆ This work was supported by American Heart Association (AHA) grant 12GRNT1160027 (T.P.O.), National Center for Advancing Translational Sciences (NCATS) grant KL2TR000136 (T.P.O.), National Institutes of Health grants HL71478 (B.D.J.) and HL46493 (M.J.J.) and the Frank R. and Shari Caywood Professorship (M.J.J.).
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http://dx.doi.org/10.1016/j.ijcard.2015.08.101
0167-5273/

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/VCO_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/VCO_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_2pulse) [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.

2. Methods

2.1. 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 ≤35.0% (from clinical records within three months); body mass index (BMI) <35.0 kg/m^2 (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.

Table 1
Participant characteristics.

	Healthy control	Heart failure	p
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.

2.2. Overview

Each individual participated in three testing sessions separated by ≥48 h each in an environmentally controlled physiology laboratory. For all study visits, participants were asked to avoid strenuous physical activity for 24 h 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 $P_{ET}CO_2$ 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, $GX_{CAP} = O_2\text{pulse} \times P_{ET}CO_2$ [1]; and the cardiac power estimate CircP as, $VO_2 \times$ MAP [28,31]. The slopes for O_2pulse, GX_{CAP}, and CircP were calculated as, (end-exercise − baseline) / 5. We calculated BMI as, weight/height^2; and, body surface area as, $\sqrt{(\text{height} \times \text{weight})/3600}$.

2.3. 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