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Exercise intolerance in heart failure: central role for the pulmonary system

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Short title: Exercise intolerance in heart failure

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Abstract

We propose that abnormalities of the pulmonary system contribute significantly to the exertional dyspnea and exercise intolerance observed in patients with chronic heart failure. Interventions designed to address the deleterious pulmonary manifestations of heart failure may therefore yield promising improvements in exercise tolerance in this population.

Summary

Pulmonary abnormalities are central to exercise limitation in patients with heart failure.

Key words

Heart failure; Exercise tolerance; Work of breathing; Bronchial vasculature; Ventilatory inefficiency; Pulmonary hypertension; Intrathoracic pressure.

Key points

- Engorgement of the bronchial vasculature due to increased pulmonary vascular pressure and pulmonary congestion results in greater bronchial conductance and airflow obstruction in heart failure.
- Patients with heart failure show an abnormally high work of breathing during exercise, largely due to an excessive ventilation and a greater resistive load of breathing.
- Skeletal muscle mass and an overactivation of group III/IV afferents contribute to ventilatory inefficiency during exercise in patients with heart failure.
- Pulmonary hypertension limits exercise tolerance in patients with heart failure by negatively impacting ventilation-perfusion matching, pulmonary gas exchange and oxygen delivery to exercising muscles.

- A less negative inspiratory intrathoracic pressure and a more positive expiratory intrathoracic pressure automatically improves the cardiac response to exercise in patients with heart failure.

INTRODUCTION

Chronic heart failure (HF) is a complex multi-organ syndrome characterized by pathophysiological changes in cardiac, vascular, musculoskeletal, endocrine and pulmonary function. Exercise limitation is a hallmark of HF (1), and an increasing degree of intolerance to exercise is associated with poor prognosis. However, despite the typical pathophysiological sequelae of HF, no relationship exists between cardiac function (e.g., left ventricular ejection fraction, left ventricular volumes, and cardiac output) and exercise tolerance in HF patients (2). Indeed, it is now clear that the physiological underpinning of exercise intolerance in HF is multifactorial, and that several non-cardiac mechanisms play a significant role. Of each of the major organ systems negatively affected by HF, the pulmonary system is the most centrally integrated into the syndrome. As HF progresses, several pulmonary abnormalities may become apparent, such as increased physiological dead space, mild ventilation-to-perfusion mismatch, increased bronchial conductance and congestion, impaired lung diffusing capacity, and pulmonary hypertension (Figure 1). It is our contention that the "dysfunctional" pulmonary system is a key determinant of exertional dyspnea and exercise intolerance in HF. In this review, we will present up-to-date evidence and mechanistically discuss our current understanding of the central role that the pulmonary system plays in exercise limitation in patients with HF.

AIRWAY BLOOD FLOW AND PULMONARY FUNCTION

Changes in the caliber of the airway mucosal vasculature, or bronchial circulation, may contribute to changes in pulmonary function in HF (3). The bronchial circulation runs concurrent with the airways to the terminal bronchiole level and supplies blood flow to the

highly vascularized bronchial mucosa (3, 4). The bronchial mucosal capillaries are located within 100 µm of the airway lumen. With this close proximity, it has been hypothesized that engorgement of the bronchial vasculature, reflected by an increased bronchovascular conductance, could result in a displacement of the tissue towards the adjacent lumen airspace, thereby narrowing the internal diameter of the compliant distal airways and contributing to the increased airway resistance seen in HF (3-5). Bronchial blood flow is regulated through α-adrenoreceptor and cholinergic autonomic vasoconstrictor mechanisms as well as by nitric oxide-dependent vasodilatory pathways (3, 4). There is evidence that airway vascular conductance is sensitive to changes in pulmonary vascular pressures, inflammatory mediators and increased firing from cardiac stretch receptors (3). Given that many of these changes are pathophysiological alterations associated with HF, the vascular tone and conductance of the bronchial circulation may well be altered in this patient group. Indeed, as cardiac filling pressures rise and pulmonary congestion progressively develops in HF, blood flow may back up into the bronchial circulation and influence airway caliber resulting in airflow limitation.

The development of a modified soluble gas technique has allowed the non-invasive measurement of bronchial blood flow in HF (4, 6). Briefly, measuring the disappearance or uptake of inert and highly soluble dimethyl ether gas over time during a series of breath-hold maneuvers allows estimation of bronchial blood flow; this technique has been validated against direct bronchial blood flow measurements in animals using radiolabeled microspheres (4). To test the hypothesis that bronchovascular engorgement may affect pulmonary function in HF, Ceridon et al. (7) examined the relationship between bronchial blood flow, bronchovascular conductance and pulmonary function in individuals with HF by measuring bronchial blood flow and bronchovascular conductance at rest using the modified soluble gas technique in 30 individuals with HF (NYHA Class I-IV, ejection fraction: 26 ± 7 %) and 12

age-matched controls (ejection fraction: 61 ± 6 %). Resting bronchovascular conductance was >40% higher in HF when compared to control. Moreover, there was a positive relationship between airflow obstruction and bronchovascular conductance in HF only. That is, greater airflow obstruction was associated with higher bronchovascular conductance in HF.

Indirect evidence appears to support the hypothesis of bronchovascular engorgement being related to altered airway function at rest and during exercise in HF. Cabanes et al. (5) reported that in individuals with HF, inhalation of methacholine resulted in airway hyper-responsiveness, similar to the response observed in bronchial asthma. Methacholine causes both constriction of the airways and dilation of the bronchial blood vessels, and the authors suggested that the constriction of the airways was partly mediated by the dilation of the bronchial blood vessels, or bronchial engorgement. Indeed, administration of methoxamine, an α1-agonist known to constrict bronchial blood vessels, fully prevented the methacholine-induced hyper-responsiveness. . Furthermore, the protective effect of methoxamine was in turn blocked by the administration of an α-adrenergic antagonist. In a separate study (8), individuals with a history of HF treated with methoxamine had an improved exercise tolerance and reduced exertional breathlessness. These findings support the contributing role of bronchovascular engorgement to the exertional dyspnea and exercise intolerance observed in patients with HF.

LUNG DIFFUSING CAPACITY

Diffusing capacity of the lungs for carbon monoxide (DL_{CO}) represents the rate at which the lung can take up the inhaled test gas carbon monoxide. Whilst there was no relationship

between DL_{CO} and bronchial blood flow in HF (9), DL_{CO} is clearly reduced in HF (10). DL_{CO} represents the sum of two subcomponents, the conductance of the alveolar-capillary membrane and pulmonary capillary blood volume and as such, alterations in either the conductance of the alveolar-capillary membrane or pulmonary capillary blood volume will affect DL_{CO}. Using a novel single breath technique (11), several studies examined DL_{CO} and subcomponents at rest and during exercise in HF individuals with both preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) (12, 13). When compared to an age-matched healthy group, Olson et al. (12) found that both resting DL_{CO} and the change in DL_{CO} during exercise were significantly less in HFrEF (ejection fraction: 24 ± 2%). Moreover, the rise in DL_{CO} relative to the increase in cardiac output during exercise was lower for the HFrEF group, suggesting a reduced alveolar-capillary recruitment. In a separate study, Olson et al. (13) also found DL_{CO} to be significantly lower for HFpEF patients at rest and during exercise. Interestingly, whilst pulmonary capillary blood volume was lower compared to healthy individuals at rest and peak exercise in HFpEF, the initial relative rise in pulmonary capillary blood volume from rest to low-intensity exercise (20 W) was significantly greater in HFpEF than in healthy individuals (Figure 2). Presumably, this rapid increase in pulmonary capillary blood volume was related to a greater increase in pulmonary venous pressures coupled to a higher ventilation, due to a higher breathing frequency, and an increased ventilatory drive relative to exercise workload in patients with HFpEF in comparison to healthy individuals. From 20 W to peak exercise, there was no further increase in pulmonary capillary blood volume in HFpEF patients despite an increase in cardiac output, indicating that the ability to recruit greater pulmonary capillary blood volume becomes rapidly saturated in HFpEF. The authors speculated that increases in venous return at the onset of exercise cannot be accommodated by the left ventricle such that right ventricular output transiently exceeds left ventricular output, and blood pools in the pulmonary

circulation. Healthy individuals, on the other hand, had a significant increase in both pulmonary capillary blood volume and cardiac output throughout exercise. Thus, patients with HF display altered lung diffusing capacity at rest and during exercise, indicating that a lower pulmonary capillary blood volume and an impaired ability to transfer gases through the alveolar-capillary membrane contributes to exercise intolerance in this population.

WORK OF BREATHING

The work of breathing (Wb) is inordinately higher in HF patients during physical exertion (14). Exercise hyperventilation and mechanical derangement primarily contribute to this greater overall mechanical cost of breathing in HF. Exercise hyperventilation is a hallmark of HF, and several mechanisms have been proposed as mediators of this excessive ventilatory response, including but not limited to: (i) alveolar ventilation-perfusion mismatching; (ii) skeletal muscle hypoperfusion and deconditioning; (iii) juxta-capillary receptor stimulation consequent to pulmonary congestion and/or hypertension; (iv) heightened central/peripheral chemosensitivity; and (v) increased firing of group III/IV skeletal muscle afferents (i.e. the "skeletal muscle" hypothesis) (15-18). Notwithstanding these many different mechanisms, the following is clear: the HF patient breathes more than a healthy individual during exercise, and this hyperventilation begets an increase in the overall Wb at a given exercise intensity. However, not only is total Wb higher at a given work rate, respiratory muscle work is also greater at a given level of ventilation in this population (i.e. mechanical derangement). There are two principal loads imposed on the respiratory muscles during spontaneous breathing: the resistive and elastic loads (inertive loads are often neglected due to their small magnitude). Patients with HF suffer from an increased elastic load to breathing. Certainly, dynamic lung compliance is systematically lower compared with healthy individuals, and

appears to worsen during physical exertion (19). Such increased lung "stiffness" has been attributed to: competition between lung and cardiac tissue for intrathoracic space (e.g., cardiomegaly); the engorged pulmonary and/or bronchial vasculature; pulmonary interstitial edema (particularly during exercise); and remodeling of the lung parenchyma (7, 20). Patients with HF may also present with a relatively stiffer chest wall (14). Taken together, the stiffer lungs and chest walls of HF patients contribute to a greater elastic Wb at moderate expired minute ventilations during graded exercise (14).

Inspiratory and expiratory resistive Wb is higher in HF patients compared with healthy controls at standardized minute ventilations during graded exercise (14). The larger resistive load to breathing may be due to the incipient pulmonary congestion impacting on airway geometry and distribution of radial and interfacial forces (5), an enhanced bronchomotor tone and/or hyperresponsiveness (5), and/or increased collapsibility of the smaller airways during expiration (i.e. expiratory flow limitation) (21, 22). In addition, pulmonary congestion and an enhanced bronchomotor tone may also serve to increase lung tissue resistance (23). When the elastic and resistive components of respiratory work are expressed relative to the total Wb incurred during exercise, inspiratory and expiratory resistive Wb appear to make larger contributions to the overall mechanical cost of breathing compared with healthy individuals (Figure 3). By extension, the contribution of inspiratory and expiratory elastic Wb to the total mechanical cost of breathing is lower in patients with HF at a given minute ventilation during exercise.

The larger mechanical cost of breathing results in larger oxygen and blood flow requirements of the active respiratory muscles (24). Seeing that HF is often accompanied by an impaired cardiac output response to exercise, little reserve exists for the heart to meet the oxygen and blood flow demands of both the respiratory and locomotor muscles, simultaneously. As such,

the respiratory and locomotor muscles may compete for an adequate share of the prevailing cardiac reserve, hastening the onset of exertional fatigue in HF patients during exercise. Indeed, reducing the overall Wb seemingly improves oxygen delivery to the locomotor muscles, and increases exercise duration in this population (25). It is therefore important to consider the mechanical cost of breathing as a contributing factor to exercise intolerance in HF. Not only is the mechanical cost of breathing inordinately greater in HF patients compared with healthy individuals, this higher overall Wb appears largely due to differences in the resistive rather than elastic loads of breathing.

VENTILATORY CONTROL: THE ROLE OF SKELETAL MUSCLE

Skeletal muscle group III/IV afferents are a major contributor to excessive exercise ventilation in HF patients. Mechano- and metaboreceptors sense changes in muscle length, volume and by-products of muscle contraction and feedback through group III/IV afferents via the dorsal horn of the spinal cord to the medullary respiratory centers (i.e. rostral ventral medulla, caudal ventrolateral medulla and nucleus tractus solitarius) to increase ventilation (26, 27). It is well-known that patients with HF experience significant changes to the skeletal muscle and these alterations likely results in excessive group III/IV afferent feedback and therefore, greater ventilation during exercise.

The "skeletal muscle hypothesis" suggests that cardiac patients experience skeletal muscle myopathies, in part, due to alterations in blood perfusion to the muscle, which contribute to skeletal muscle fatigability (28), exercise intolerance and subsequently symptoms of dyspnea and fatigue (Figure 1) (18). These muscle myopathies include muscle wasting and a shift in fiber type distribution leading to a greater metabolic build-up during exercise in HF (18, 29-

31). As such, there is an early dependence on anaerobic metabolism, excessive early depletion of high energy phosphate bonds and excessive early intra-muscular acidification during exercise, which leads to an exaggerated metaboreflex in patients with HF (32). Mechanoreflex sensitivity is shown to be enhanced in animal models of HF (33) but this is less clear in patients with HF as it is more difficult to isolate the mechanoreflex in humans (33). Collectively, both the animal and human literature suggests that mechano- and metaboreflex and subsequently group III/IV skeletal muscle afferent activity is exaggerated during exercise in these patients (29, 32). The over-activation of group III/IV afferent activity causes aberrant increases in ventilation in patients with HF (Figure 1). Our work (34, 35) and work of others (29) confirms the importance of the contribution of the skeletal muscle to an enhanced ventilatory response and impaired exercise tolerance in patients with HF.

Work by Scott et al. (29) demonstrated that when activating the metaboreflex by post-exercise circulatory occlusion in the lower extremity, ventilation was elevated in patients with HF compared with age-matched controls. These investigators then demonstrated that the excessive elevation in ventilation in HF was associated with elevated hydrogen ion levels and increased lactate concentration (36). Further, an infusion of sodium bicarbonate to reduce serum hydrogen ion concentration completely abolished the ventilatory response. The aforementioned findings clearly demonstrate the importance of the metabolic contribution to the ventilation response in patients with HF. During passive movement of the lower extremity to activate the mechanoreflex, a small increase in ventilation was observed in HF and controls, but the increase was similar between groups (29, 37). Both animal and human studies suggest that metabolites, such as adenosine triphosphate and/or lactic acid can sensitize muscle mechanoreceptors (33), but the direct response of this metabolically-induced mechanical sensitization on ventilation is unclear. Collectively, these studies suggest that

during exercise, the over-activation of group III/IV afferents cause an exaggerated ventilatory response in patients with HF.

Ventilatory efficiency, characterized by the relationship between minute ventilation and the production of carbon dioxide ($\dot{V}_E/\dot{V}_{CO2slope}$), is a powerful predictor of mortality, even more so than VO_{2peak}, in patients with HF (38). Olson et al. (39) demonstrated that $\dot{V}_E/\dot{V}_{CO2slope}$ was elevated in mild HF compared with controls during exercise and activation of metaboreflex with lower extremity post-exercise circulatory occlusion. Indeed, when group III/IV afferent activity was inhibited with fentanyl (a μ-opioid receptor agonist), $\dot{V}_E/\dot{V}_{CO2slope}$ was reduced significantly, indicating that partial blockade of group III/IV afferent activity improved ventilatory efficiency during exercise in HF patients. As further evidence for the important role of skeletal muscle to the exercise ventilatory response, it was recently demonstrated that low muscle mass was strongly associated with a high $\dot{V}_E/\dot{V}_{CO2slope}$ in patients with HF (Figure 4A). Concurrent with muscle wasting, HF patients also demonstrate histological changes indicating a shift in fiber type proportion and myosin heavy chain isoform expression. The loss of myosin heavy chain type I and gain of myosin heavy chain type IIx results in greater metabolic activity, reduced oxidative capacity and therefore greater activation of group III/IV afferents. Subsequently, when afferent feedback is inhibited, the signals from group III/IV afferents to the nucleus tractus solitarius of the brainstem are attenuated, which will lower the ventilatory response during exercise (34, 39). Further, the greatest reductions in $\dot{V}_E/\dot{V}_{CO2slope}$ with afferent blockade occurred in patients with the least leg muscle mass (Figure 4B) and lowest VO_{2peak} (34). Thus, in this study, patients with HF who experience exercise intolerance (low VO_{2peak}), have the greatest improvement in breathing efficiency during exercise when afferent feedback is blunted (34). It should be noted, however, that it is likely not the low muscle mass per se that is causing the greater activation of group III/IV afferent

activity, it is likely the histological changes that are concurrent with muscle wasting that influence group III/IV afferent activity in individuals with HF. In conclusion, the skeletal muscle is a major contributing factor to the control of ventilation and intolerance to exercise in HF patients. Clinically, this is relevant and is consistent with the evidence that exercise training of the skeletal muscle causes significant improvements in tolerance to exercise in HF.

PULMONARY VASCULAR DYSFUNCTION

Pulmonary hypertension is a common complication of HF, often occurring as a "symptom" of the underlying condition. It is estimated that pulmonary hypertension develops in ~60% and ~70% of HF patients with severe left ventricular systolic dysfunction or isolated left ventricular diastolic dysfunction, respectively (40). The presence of pulmonary hypertension is associated with more severe symptoms, worse exercise tolerance, and poor prognosis in these patient populations (41). Exercise introduces an impressive stress to the lungs, where elevations in venous return increase pulmonary blood volume and blood flow by 50% and 300%, respectively. While the healthy, highly compliant and low resistance pulmonary vasculature can readily accommodate these marked increases in blood volume and flow, this reserve is compromised in HF patients, particularly those with pulmonary hypertension (42). In agreement with others (43, 44), our unpublished data suggest that in HFrEF patients: (i) the ratio of mean pulmonary arterial pressure-to-cardiac output is greater at peak exercise in HF with vs. without pulmonary hypertension; (ii) pulmonary arterial compliance at peak exercise is significantly lower in HF with compared to without pulmonary hypertension; and (iii) a greater mean pulmonary arterial pressure-to-cardiac output ratio and lower absolute pulmonary arterial compliance at peak exercise are related to impaired exercise capacity

across all HF patients (Figure 5). These findings unequivocally demonstrate that the response to exercise in HF with pulmonary hypertension is characterized by an exaggerated rise in pulmonary vascular pressures and limited or no pulmonary vascular reserve, both of which are key determinants of exercise limitation in these patients. Mechanistically, pulmonary hypertension likely contributes to exercise intolerance in HF through a substantial increase in right ventricular afterload that restricts right ventricular contractile reserve and forward-flow of blood from the right ventricle to the pulmonary vasculature and systemic circulation. This, in combination with impaired recruitment and distension of the lung vasculature secondary to pulmonary hypertension-related remodeling of the pulmonary resistance vessels, negatively impacts ventilation-perfusion matching, pulmonary gas exchange, and systemic oxygen transport to the exercising muscles, limiting a patient's ability to exercise (Figure 6).

The pathogenesis of pulmonary hypertension in HF is complex. Two distinct subsets of pulmonary hypertension due to HF have been identified: isolated post-capillary pulmonary hypertension (IpcPH) caused by backwards transmission of increased left ventricular filling pressure into the pulmonary circulation, and combined pre- and post-capillary pulmonary hypertension (CpcPH) caused by abnormalities in pulmonary arterial structure and function that are characterized by an excessive rise in pulmonary arterial pressure and pulmonary vascular resistance. The reader is directed towards Vachiéry et al. (40) for a detailed hemodynamic definition and differentiation of IpcPH and CpcPH. The presence of CpcPH more greatly impairs aerobic capacity in HF (45). While the precise mechanisms that underpin the development of CpcPH remain debated, it may be related to increasing severity and chronicity of the underlying HF (46). Moreover, the presence of CpcPH is thought to reflect "superimposed" pulmonary vasoconstriction secondary to decreased nitric oxide availability, increased endothelial expression of endothelin-1, and desensitization to

natriuretic peptide-induced vasodilation (47). Rather provocatively, we have previously suggested that the aforementioned increase in endothelin-1 concentration in CpcPH is hypoxemia-mediated, and as such, there may be a role for systemic hypoxemia in the CpcPH component of pulmonary hypertension in HF (48). In 39 patients with stable systolic HF, it was found that, despite relative uniformity in HF disease severity, patients with CpcPH were hypoxemic relative to patients with no pulmonary hypertension or IpcPH (48).
The transpulmonary pressure gradient (i.e. the severity of pulmonary hypertension) was inversely related to partial pressure of arterial oxygen and oxygen saturation in the CpcPH patients only. Additionally, plasma endothelin-1 concentration correlated with partial pressure of arterial oxygen and transpulmonary pressure gradient in CpcPH patients only. These data provide compelling evidence that systemic hypoxemia plays a role in the CpcPH of HF, potentially via a hypoxia-induced increase in endothelial release of the vasoconstrictor endothelin-1.

It has also been reported that derangements in ventilatory and pulmonary gas exchange indices at rest and during submaximal and maximal exercise in HF are likely related to the development and severity of pulmonary hypertension (49, 50). For example, at an equivalent oxygen consumption, end-tidal CO_2 ($P_{ET}CO_2$) and arterial oxygen saturation were greater in no pulmonary hypertension and IpcPH vs. CpcPH patients (49). Conversely, dead-space ventilation and the $\dot{V}_E/\dot{V}_{CO2slope}$ were lower in no pulmonary hypertension and IpcPH vs. CpcPH patients (49). Interestingly, the exercise-induced change in dead-space ventilation, $\dot{V}_E/\dot{V}_{CO2slope}$ and $P_{ET}CO_2$ correlated significantly with the change in mean pulmonary arterial pressure, diastolic pressure difference and transpulmonary pressure gradient in CpcPH patients only (49). The mechanisms by which the elevated pulmonary vascular pressures associated with CpcPH worsen exercise pulmonary gas exchange in these patients are

multifactorial, but likely include an inability to adequately increase pulmonary vascular perfusion during exercise resulting in impaired ventilation-perfusion matching and a reduction in oxygen delivery to the working tissues with subsequent stimulation of ergoreceptors and/or chemoreceptors and a consequent relative hyperventilatory response to exercise (Figure 6).

INTRATHORACIC PRESSURE AND EXERCISE TOLERANCE

In patients with HF, altered interactions between the heart and lungs exist due to decreased lung and left ventricular compliance, increased cardiac size, high cardiac filling pressure and altered receptor sensitivity to neural activation. Exercise further affects these cardiopulmonary interactions by stimulating an increase in the depth and frequency of breathing, which accentuates the fluctuations in intrathoracic pressure with peak inspiratory intrathoracic pressure becoming more negative and peak expiratory intrathoracic pressure becoming more positive with increasing exercise intensities. Patients with HF often exhibit excessive ventilation for a given exercise intensity, primarily characterized by an increased respiratory rate rather than tidal volume despite significant room to increase tidal volume by further encroaching on inspiratory reserve volume (21), possibly due to weakened inspiratory muscles (51). The avoidance of high lung volumes during exercise, often at the expense of seemingly unnecessary large positive expiratory intrathoracic pressures, results in significant wasted effort in patients with HF (21, 52).

Inspiration and the accompanying decrease in intrathoracic pressure results in increased intraluminal pressure, left ventricular preload and afterload. Patients with HF tend to be less sensitive to changes in left ventricular preload due to a decreased left ventricular compliance

(1), therefore, a reduction in left ventricular preload through a less negative intrathoracic pressure in patients with elevated filling pressures may decrease effective filling to a level more acceptable for left ventricular performance (53). In accordance with the strong inverse linear relationship between stroke volume and left ventricular afterload (54), an overriding influence of left ventricular afterload in patients with HF suggest that the negative intrathoracic pressure accompanying inspiration may reduce stroke volume in these individuals (53). Thus, a less negative inspiratory intrathoracic pressure and a larger positive expiratory intrathoracic pressure could preserve cardiac function during exercise in patients with HF.

The effect of manipulating inspiratory intrathoracic pressure and expiratory intrathoracic pressure on stroke volume during moderate-intensity exercise was investigated in patients with HRrEF (NYHA class I-II). During moderate-intensity exercise, inspiratory unloading using a ventilator (less negative intrathoracic pressure) increased stroke volume, possibly due to a reduction in left ventricular afterload, while inspiratory loading using resistors (more negative intrathoracic pressure) did not affect stroke volume in patients with HFrEF (55). Accordingly, expiratory loading (more positive expiratory intrathoracic pressure) elicited increases in stroke volume during moderate-intensity exercise in patients with HFrEF (56), which may be caused by a beneficial reduction in left ventricular preload. Thus, manipulation of intrathoracic pressure, through a less negative inspiratory intrathoracic pressure and a more positive expiratory intrathoracic pressure, automatically improves stroke volume in patients with HFrEF. Furthermore, inspiratory unloading increased exercise endurance in patients with HF (57). Thus, strategies designed to limit the negative cardiorespiratory interactions during exercise, such as volitionally altering breathing pattern or the use of positive pressure breathing during expiration could be beneficial to patients with HF.

CONCLUSION

In summary, we propose that derangements in the pulmonary system, including engorgement of the bronchial vasculature, ventilatory inefficiency, elevated muscular work of breathing, inspiratory muscle weakness, impaired pulmonary gas exchange and pulmonary hypertension are central determinants of exercise intolerance in HF. Our work and that by others identifies the importance of the pulmonary system in limiting exercise tolerance in HF, and highlights that treating the pulmonary manifestations of HF such as pulmonary pressure and congestion as well as adopting exercise training intervention to improve inspiratory muscles resistance/endurance and increase skeletal muscle mass may yield promising results in improving exercise tolerance in this population.

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FIGURE LEGENDS

Figure 1. Schematic representation of key pulmonary manifestations of HF and their contribution to exercise limitation. RV: right ventricular; V_D/V_T: dead-space ventilation; $\dot{V}_E/\dot{V}_{CO2}$: minute ventilation to carbon dioxide ratio; V/Q: ventilation-to-perfusion ratio.

Figure 2. A: Pulmonary capillary blood volume (V_C) as a function of cardiac output ($\dot{Q}$) during exercise. Circles: healthy individuals, squares: patients with HFpEF. *$p<0.05$ versus healthy individuals. B: Percent change from rest to matched submaximal absolute workload (20 W). Black bar: healthy individuals, white bar: patients with HFpEF. Modified from Olson et al. (13).

Figure 3. The relative contributions of resistive and elastic respiratory work to the total work of breathing (Wb) during graded exercise. Both panels illustrate the general relationship between each component of the Wb and minute ventilation during graded exercise for patients with HF and healthy controls, respectively. Fine stippling (▩) represents inspiratory resistive Wb. Coarse stippling (⬚) denotes expiratory resistive Wb. The horizontal hatching (▤) represents inspiratory elastic Wb, whereas vertical hatching (▥) denotes expiratory elastic Wb. N.B.: the relative contribution of inspiratory and expiratory resistive Wb to the total mechanical cost of breathing appears larger for HF patients than controls during graded exercise.

Figure 4. Relationship between leg muscle mass (%) and $V_E/V_{CO2slope}$ during the placebo condition (A) and change in V_E/V_{CO2} with afferent blockade (injections of fentanyl) (B). $V_E/V_{CO2slope}$ during the placebo condition was associated with leg muscle mass in HF

(r^2=0.58, p=0.02), but not in controls (CTLs) (r^2=0.30, p=0.16). With blocking afferent feedback, the relationship between $V_E/V_{CO2slope}$ and leg muscle mass was abolished in HF (r<1.0, p=0.96) and remained non-significant in CTLs (r^2=0.16, p=0.32).

Figure 5. Unpublished data collected in 36 patients with HFrEF shows that: 1) mean pulmonary arterial pressure-to-cardiac output ratio (mPAP-$\dot{Q}$) is greater (A) and pulmonary arterial compliance (PAC) is lower (C) at peak exercise in pulmonary hypertension (PH)-HF (n=22) compared to HF without PH (HF) (n=14); and 2) a greater mPAP-$\dot{Q}$ ratio (B) and lower absolute PAC (D) at peak exercise are significantly related to lower peak oxygen consumption ($\dot{V}O_{2peak}$) across all HF patients. **P<0.01 HF vs. PH-HF.

Figure 6. The right ventricular (RV) and pulmonary gas exchange response to exercise in health (A) and in heart failure patients with pulmonary hypertension (PH-HF) (B). In PH-HF: "exercise" PH, defined as mean pulmonary arterial pressure (mPAP) > 30 mmHg and total pulmonary vascular resistance (TPVR) > 3 Wood units (WU), presents a substantial increase in RV afterload, limiting RV fractional area change (FAC) and forward flow of blood, and impairing pulmonary capillary perfusion. Hypoperfused alveoli leads to alveolar ventilation-to-perfusion ($V_A/\dot{Q}$) mismatch, increased dead-space ventilatory (V_D/V_T), elevated ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}_{CO2}$), and decreased partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) (i.e. impaired pulmonary gas exchange). LV, left ventricle; PA, pulmonary artery.

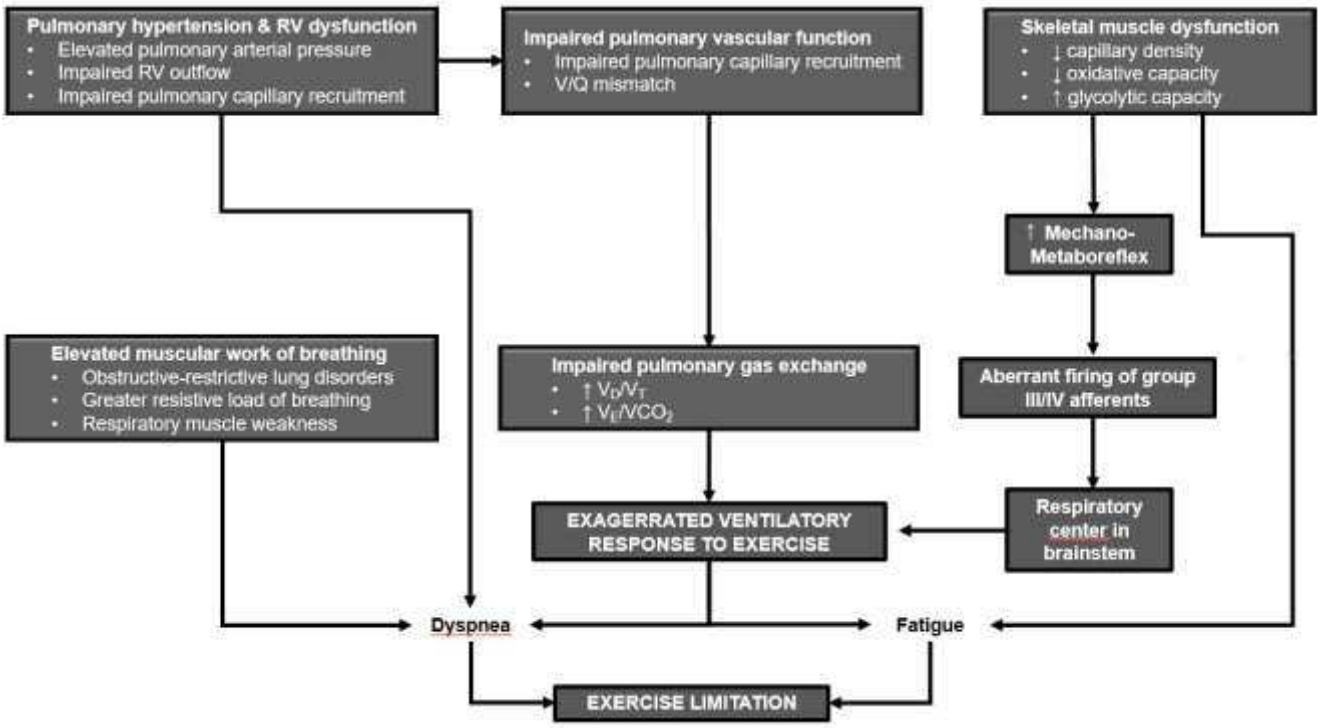
Pulmonary hypertension & RV dysfunction
• Elevated pulmonary arterial pressure
• Impaired RV outflow
• Impaired pulmonary capillary recruitment
Impaired pulmonary vascular function
• Impaired pulmonary capillary recruitment
• V/Q mismatch
Skeletal muscle dysfunction
• ↓ capillary density
• ↓ oxidative capacity
• ↑ glycolytic capacity
↑ Mechano-Metaboreflex
Elevated muscular work of breathing
• Obstructive-restrictive lung disorders
• Greater resistive load of breathing
• Respiratory muscle weakness
Impaired pulmonary gas exchange
• ↑ V_D/V_T
• ↑ V_E/VCO_2
Aberrant firing of group III/IV afferents
EXAGERRATED VENTILATORY RESPONSE TO EXERCISE
Respiratory center in brainstem
Dyspnea
Fatigue
EXERCISE LIMITATION

Figure 1

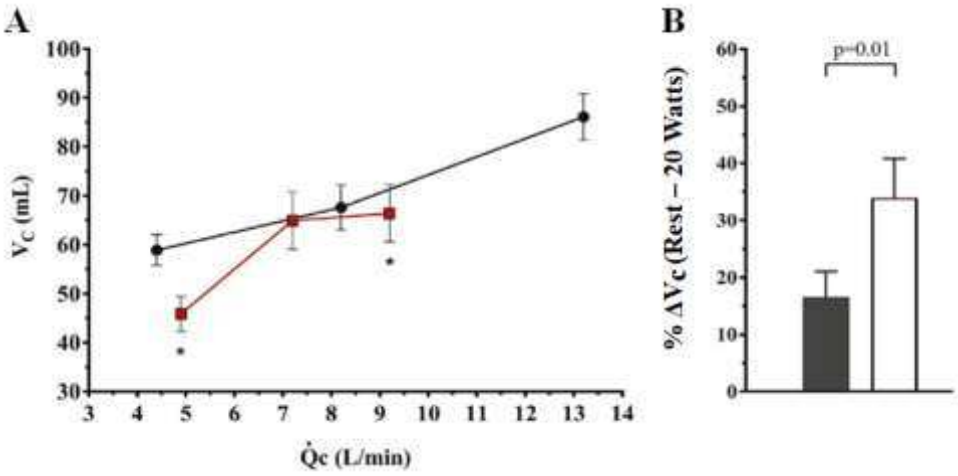
A
B
100
90
80
70
60
50
40
30
V_C (mL)
3
4
5
6
7
8
9
10
11
12
13
14
$\dot{Q}c$ (L/min)
*
*
60
50
40
30
20
10
0
% ΔVc (Rest – 20 Watts)
p=0.01

Figure 2

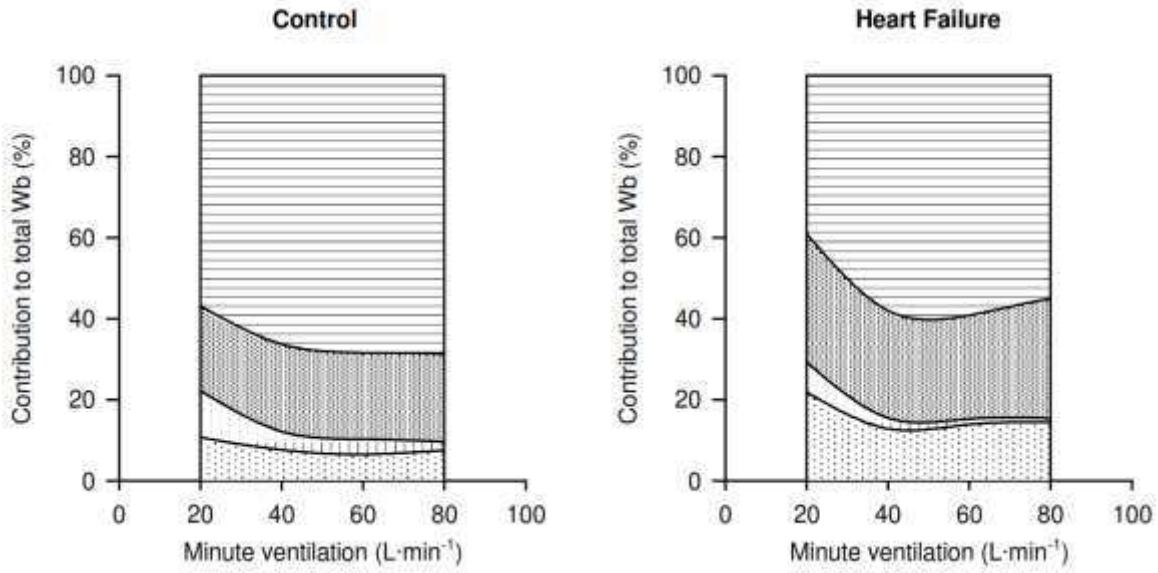
Control
Heart Failure
Contribution to total Wb (%)
Minute ventilation (L·min⁻¹)
0
20
40
60
80
100

Figure 3

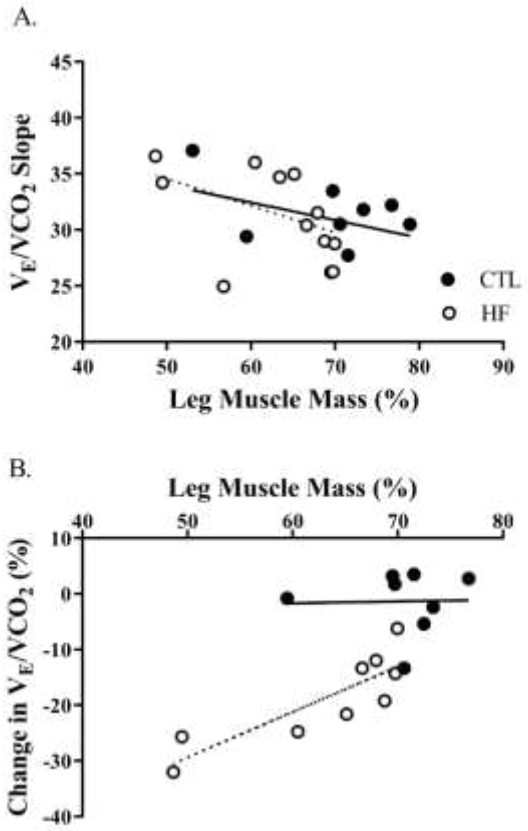
A.
45
40
35
30
25
20
V_E/VCO_2 Slope
40
50
60
70
80
90
Leg Muscle Mass (%)
CTL
HF
B.
Leg Muscle Mass (%)
40
50
60
70
80
10
0
-10
-20
-30
-40
Change in V_E/VCO_2 (%)

Figure 4

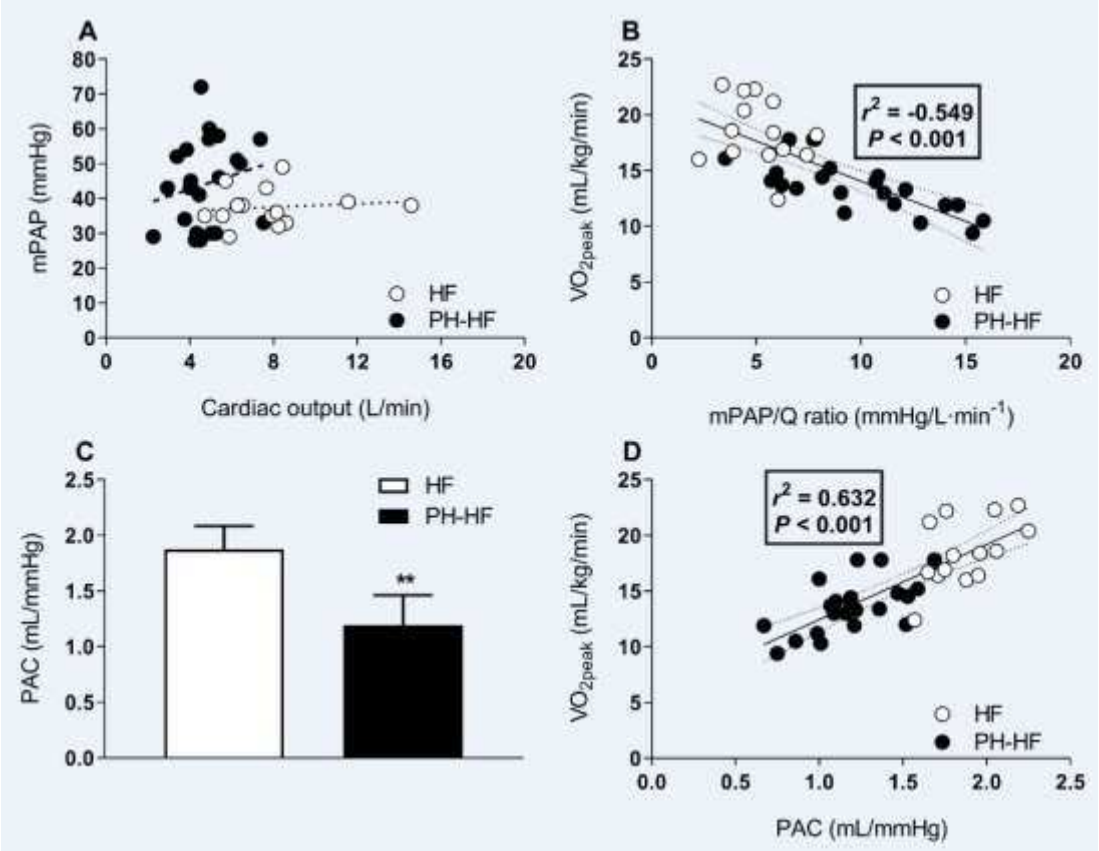
A
mPAP (mmHg)
Cardiac output (L/min)
HF
PH-HF
B
VO2peak (mL/kg/min)
mPAP/Q ratio (mmHg/L·min-1)
r2 = -0.549
P < 0.001
HF
PH-HF
C
PAC (mL/mmHg)
HF
PH-HF
**
D
VO2peak (mL/kg/min)
PAC (mL/mmHg)
r2 = 0.632
P < 0.001
HF
PH-HF

Figure 5

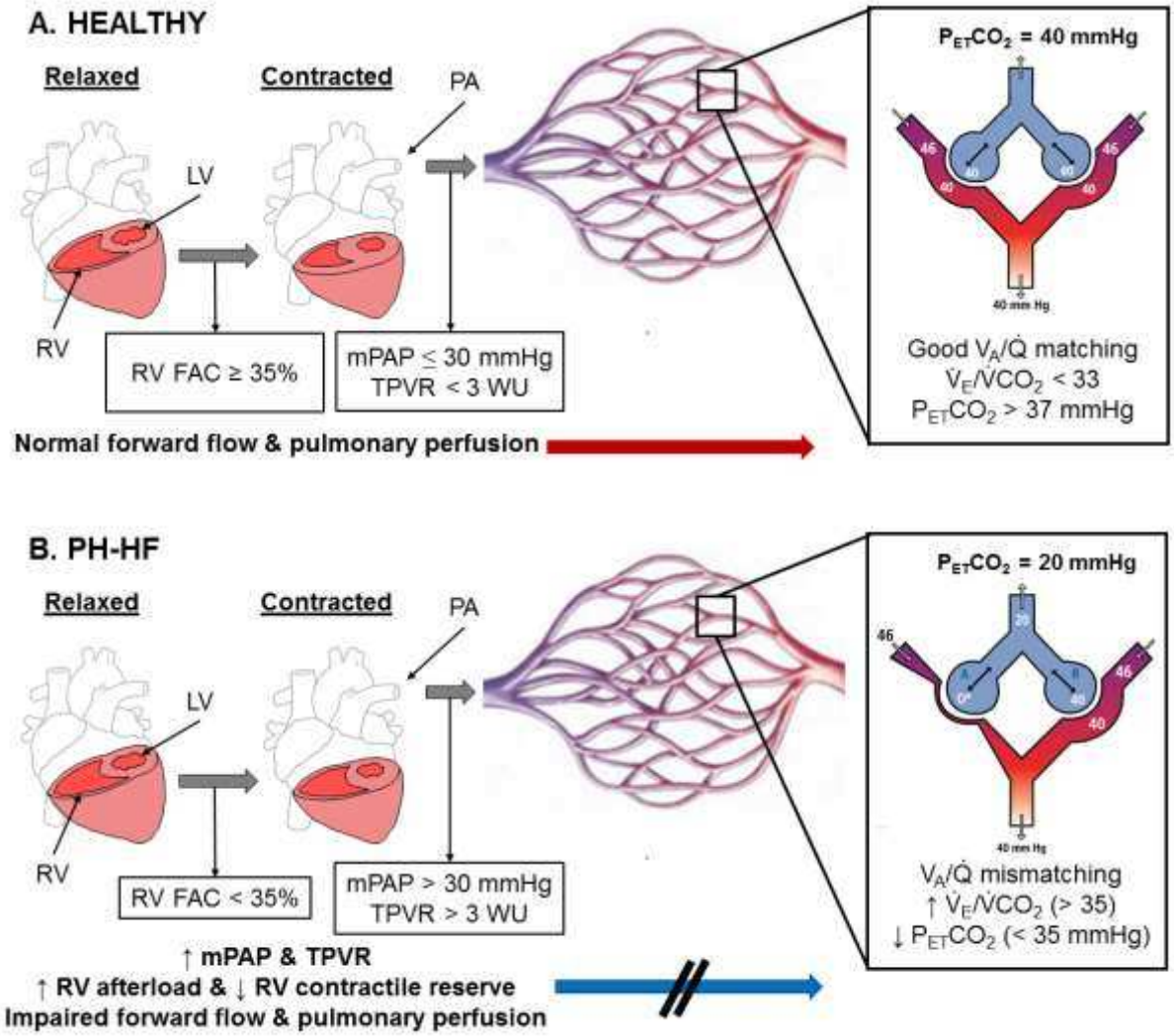
A. HEALTHY
Relaxed
Contracted
PA
LV
RV
RV FAC ≥ 35%
mPAP ≤ 30 mmHg
TPVR < 3 WU
Normal forward flow & pulmonary perfusion
PETCO2 = 40 mmHg
40 mm Hg
Good VA/Q̇ matching
V̇E/V̇CO2 < 33
PETCO2 > 37 mmHg
B. PH-HF
Relaxed
Contracted
PA
LV
RV
RV FAC < 35%
mPAP > 30 mmHg
TPVR > 3 WU
↑ mPAP & TPVR
↑ RV afterload & ↓ RV contractile reserve
Impaired forward flow & pulmonary perfusion
PETCO2 = 20 mmHg
40 mm Hg
VA/Q̇ mismatching
↑ V̇E/V̇CO2 (> 35)
↓ PETCO2 (< 35 mmHg)

Figure 6