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REVIEW | *Mechanisms of Respiratory Modulation of Cardiovascular Control*

The interactions between respiratory and cardiovascular systems in systolic heart failure

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Cross TJ, Kim CH, Johnson BD, Lalande S. The interactions between respiratory and cardiovascular systems in systolic heart failure. *J Appl Physiol* 128: 214–224, 2020. First published November 27, 2019; doi:10.1152/japplphysiol.00113.2019.—Heart failure (HF) is a complex and multifaceted disease. The disease affects multiple organ systems, including the respiratory system. This review provides three unique examples illustrating how the cardiovascular and respiratory systems interrelate because of the pathology of HF. Specifically, these examples outline the impact of HF pathophysiology on *1*) respiratory mechanics and the mechanical "cost" of breathing; *2*) mechanical interactions of the heart and lungs; and on *3*) abnormalities of pulmonary gas exchange during exercise, and how this may be applied to treatment. The goal of this review is to, therefore, raise the awareness that HF, though primarily a disease of the heart, is accompanied by marked pathology of the respiratory system.

INTRODUCTION

It is straightforward that heart failure (HF) should refer primarily to the fact that, in this condition, the "heart" is "failing" to perform its chief function: to adequately distribute blood throughout the pulmonary and systemic vasculature. One may consider HF solely as a disease of the heart. However, while HF—by definition—begins with a "failing heart," its pathology extends far beyond this site to affect multiple organ systems. Perhaps the most underappreciated victim of HF pathology is the respiratory system—the principal focus of this review. The heart and lungs are intimately linked. These two organs interact with each other via hemodynamic, mechanical, and neurohumoral pathways. Thus, by virtue of these interrelationships, the presence of chronic disease or maladaptive changes in one organ system can markedly influence the health and function of the other. For example, in the case of left HF, as the heart fails, and the myocardium enlarges, sympathetic excitation occurs, and hydrostatic pressures begin to "build up" within the vasculature of the lungs. Remodeling may occur along the alveolar-capillary membrane in response to the altered fluid-balance within the lungs and elevations in vascular pressure (congestion). As the lungs become increasingly "wetter", or remodeling occurs to prevent fluid accumulation, the parenchyma become stiffer and alveolar gas exchange is impaired. Stretch reflexes from the heart and rising left atrial pressures may also result in the engorgement of the bronchial circulation, partially impinging on the airways. Sustained pulmonary congestion may even promote airway hyperresponsiveness and enhanced bronchomotor tone. These maladaptations contribute to an increased ventilatory demand (hyperventilation), and/or a heightened mechanical cost of breathing during exercise in HF. Importantly, the hyperventilatory response to exercise is characterized by an increased rate (frequency) rather than an increased depth (tidal volume) of breathing. Emerging evidence suggests that HF patients adopt such a "rapid shallow" breathing pattern to avoid the adverse effects of large intrathoracic pressures swings on cardiac preload and afterload.

In light of the above, it is clear that HF encompasses complex interactions between the cardiovascular and respiratory systems—interactions that become more relevant during physical exertion (Fig. 1). Accordingly, this review will discuss three areas of HF pathology in which the respiratory and cardiovascular systems interact. First, we review current concepts of how the mechanics of breathing are altered by HF. Second, we discuss the mechanical influence of the respiratory muscles during breathing on cardiac hemodynamics in HF patients during exercise. Lastly, we explore novel ideas surrounding the use of respiratory "signals" (i.e., gas exchange, breathing patterns, and ventilatory control) to potentially guide the optimization of therapies in HF patients, particularly those therapies using cardiac devices. It must first be acknowledged, however, that the syndrome of HF describes a heterogenous clinical population. Although HF patients with reduced ejection fraction (i.e., HFrEF) may be most familiar to the reader, there is an increasing prevalence of HF patients with preserved ejection fraction (i.e., HFpEF; 66). Notwithstanding the growing relevance of this subpopulation, a thorough discussion of respiratory and cardiovascular interactions in HFpEF is beyond

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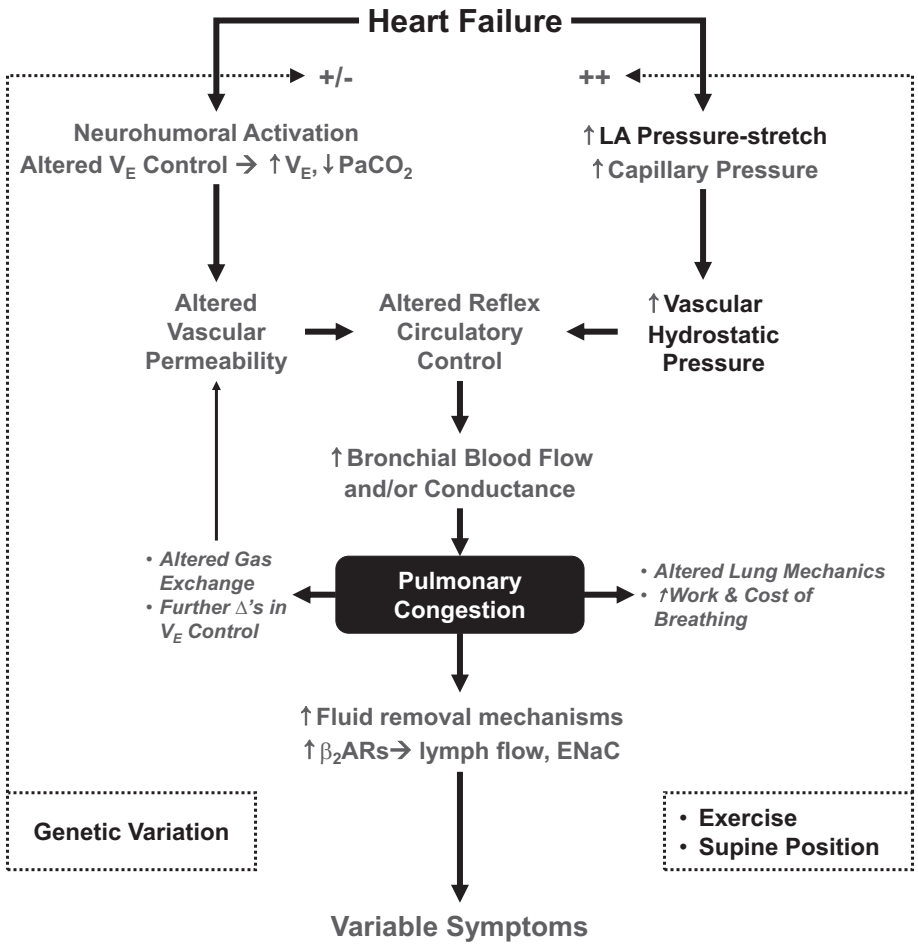

Fig. 1. A schematic overview of the interrelationships between the heart and lungs in the pathophysiological processes of heart failure. The lungs lie in series with the right and left sides of the heart and receive nearly all of the cardiac output; they compete for intrathoracic space, share a common surface area and are exposed to similar intrathoracic pressures. As the left heart fails, pressures rise in the heart and are transmitted back into the pulmonary circulation. Numerous compensatory mechanisms develop to compensate for the reduction in cardiac output, including a large and sustained sympathetic nervous system overactivation. A peripheral vasoconstriction and an enlarging heart result in a centralization of blood volume, expanded pulmonary and bronchial circulations, edematous lung parenchyma and a reduction in lung compliance. This results in altered ventilatory control, accentuated mechanical interdependence between the heart and lungs, changes in breathing pattern, increased work and cost of breathing and deranged pulmonary gas-exchange. These interrelationships are enhanced dynamically with exercise and contribute to reduced functional capacity. $\dot{V}_E$, expired minute ventilation; Pa_{CO_2}, arterial partial pressure of carbon dioxide; LA, left atria; β_2ARs, β_2 adrenergic receptors; ENaC, epithelial Na^+ channel.

the scope of this review. For this reason, the following sections deal with observations made on stable, ambulatory patients with HFrEF.

IMPACT OF HEART FAILURE ON RESPIRATORY MECHANICS

The mechanical work contributed by the respiratory muscles is inordinately higher in HF patients during physical activity (22, 27, 36, 59, 70). There are two primary factors which contribute to this greater overall mechanical cost of breathing in HF: *1*) exercise hyperventilation; and *2*) mechanical derangement.

A Failing Heart Breathes Too Much

Exercise hyperventilation is a hallmark of the failing heart. Several mechanisms have been proposed as mediators of this "excessive" ventilatory response, including *1*) alveolar ventilation-perfusion mismatching (93), *2*) increased humoral stimuli (e.g., lactate and H^+) due to skeletal muscle hypoperfusion and deconditioning (54, 55, 90), *3*) juxta-capillary receptor stimulation consequent to pulmonary vascular congestion and/or hypertension (32), *4*) augmented central and peripheral chemosensitivity (23, 74, 75), and *5*) an inordinately high degree of afferent neural traffic originating from within the locomotor muscles (i.e., the ergoreflex or "skeletal muscle" hypothesis; 72). It is difficult to comment on the relative contributions of these factors to exercise hyperventilation in HF. It is likely that their contributions depend on the clinical status of the patient (e.g., stable vs. decompensated), and vary with disease severity (e.g., NYHA class I vs. IV). Nevertheless, the following is clear: the HF patient breathes too much during exercise. And the problem with breathing too much is straightforward: a higher ventilatory demand begets an increase in the mechanical work expended by respiratory muscles at a given external work rate. However, not only is respiratory muscle work greater in HF patients due to exercise hyperventilation, but the work contributed by the respiratory muscles at a given level of $\dot{V}_E$ (and presumably $\dot{V}_A$) is also inherently higher in this population (i.e., mechanical derangement).

A Failing Heart Imposes a Load on Breathing

Christie and Meakins (21) were the first to document that patients with congestive HF require larger swings in intrathoracic pressures to achieve a similar tidal volume compared with their healthier counterparts; that is, the distensibility or compliance of the lung is markedly reduced in this population. Since then, many investigators have corroborated their findings, reporting that dynamic lung compliance in HF patients is systematically lower compared with healthy individuals, and appears to worsen during physical exertion (4). This reduced compliance (increased "stiffness") of the lungs has been attributed to the mechanical constraints imposed on lung inflation due to an enlarged heart (i.e., competition for intrathoracic

space); the erectile nature of an engorged pulmonary and/or bronchial vasculature; the development of pulmonary interstitial edema, particularly during exercise; and remodeling of the lung parenchyma due to elevated circulating cytokines and/or chronic hydrostatic insult (3, 5, 19, 62, 69). The primary consequence of such decreased lung compliance in HF patients is an increased elastic load imposed on the respiratory muscles during inspiration.

The mechanisms contributing to the increased lung stiffness in HF patients are also likely to augment the resistive load to breathing. For example, pulmonary interstitial edema is believed to increase airway resistance via encroachment of the airway wall on the luminal space ("concentric" thickening). Moreover, the accumulation of fluid within the interstitial compartment and/or on the airway surface affects the distribution of radial and interfacial forces acting on the airway wall itself (17, 73). This maldistribution of extra-luminal forces impacts the geometry and stability of the airways, such that smaller dependent conduits become more susceptible to dynamic closure at lower transmural pressures during forceful expiration. Indeed, HF patients typically display obstructive defects in resting pulmonary function, and severe ventilatory constraint during physical exertion (e.g., expiratory flow-limitation and dynamic hyperinflation; 41, 94).

Sustained pulmonary congestion may also cause an increase in airway hyperresponsiveness in these patients (17, 95). Although an enhanced bronchomotor tone may serve to stabilize the airways, it significantly reduces airway diameter and increases lung resistance. Here, lung "hysteresivity" is the sum of airway resistance and the viscosity of parenchymal tissues. Accordingly, it is important to note that pulmonary congestion and an enhanced bronchomotor tone are both known to increase lung tissue resistance (44). It can, therefore, be reasoned that pulmonary congestion, through primary and/or secondary influences, may lead to an increase in airways and lung tissue resistance, increasing the resistive load to breathing during exercise in patients with HF.

Mechanical Cost of Breathing with Heart Failure

It is clear from the above that HF patients must breathe against abnormally high elastic and resistive loads during exercise (i.e., mechanical derangement). These higher loads must be overcome by a commensurate increase in the mechanical work performed by respiratory muscles. Certainly, many investigators, including our laboratory, have suggested that total respiratory muscle work is substantially higher in HF patients compared with healthy controls during exercise (22, 27, 36, 59, 70). It is worth noting at this conjecture that the work of breathing (Wb) is often reported in units of joules per minute in the wider literature. It is important to clarify that such units provide a measure of muscular power, and not the amount of work expended by respiratory muscles per breath. This distinction between the work and power of breathing (Wb and Pb, respectively) is especially important when differences in respiratory frequency exist between groups. Indeed, HF patients often display a pronounced tachypnoea during exercise and, as such, may perform larger amounts of respiratory muscle work simply because more breaths are taken per minute, not because a greater amount of work has been expended per breath. In a recent study (27), we reported that the overall Wb is systematically higher in HF patients at a given $\dot{V}_E$ during exercise compared with healthy controls. Furthermore, we stated that the greater total Wb in HF patients was contributed by larger amounts of inspiratory elastic, and inspiratory, and expiratory resistive Wb. Because our Wb data were reported in joules per minute, we are obliged—as argued above—to reinterpret these findings as differences in the power of breathing (Pb). Hence, for the purposes of this review, we have reexpressed these data such that the distinction between Wb and Pb is made clearer (Fig. 2).

In Fig. 2, we see that total respiratory muscle work performed per minute (i.e., Pb) and per breath (i.e., Wb) are, indeed, systematically higher in HF patients at any given $\dot{V}_E$ during exercise compared with healthy controls. Furthermore, the inspiratory and expiratory resistive Wb remain higher for HF patients despite accounting for differences in respiratory frequency between groups during exercise. Conversely, while the inspiratory elastic Pb may be larger in HF patients over modest elevations in $\dot{V}_E$ (i.e., $40-60\ L\cdot min^{-1}$), the inspiratory elastic Wb is similar between groups. By viewing our data in this way, we arrive at the following conclusions: *1*) HF patients suffer with inordinately higher amounts of total Wb and Pb at any given $\dot{V}_E$ during exercise; and *2*) when differences in respiratory frequency are accounted for between groups, the inspiratory and expiratory resistive components of Wb are the primary contributors to the overall higher mechanical cost of breathing in HF. Of course, these conclusions must be prefaced by the statement that HF is a continuum of disease severity, and that data illustrated in Fig. 2 are taken from HF patients with mild symptoms (NYHA class $\leq$II). It is not known whether these same conclusions apply to patients with more severe HF symptoms (i.e., NYHA class $\geq$III). Further, the components of Wb displayed in Fig. 2 were obtained using the modified Campbell diagram—a method that does not account for work expended in distorting the rib cage and abdomen at high $\dot{V}_E$. Hence, future studies are needed to quantify the impact of this residual component of respiratory muscle work on the overall mechanical cost of breathing in HF.

Physiological Implications of a High Mechanical Cost of Breathing in Heart Failure

The larger the work and power of breathing, so too becomes the O_2 and blood flow requirements of the active respiratory muscles (1, 58). Seeing that HF is typified by an impaired cardiac output response to exercise, it follows that little reserve exists for the heart to meet the O_2 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. Fatiguing contractions of the respiratory muscles may evoke a sympathetically mediated reflex vasoconstriction of the limb vasculature (84, 85), favoring a redistribution of cardiac output away from the exercising limbs and toward the muscles of breathing (i.e., a "respiratory steal"). In turn, it stands to reason that reducing the overall Wb may attenuate this "respiratory steal" of cardiac output in HF patients and improve limb perfusion during physical activity. Certainly, we and others have shown that unloading the Wb (via assisted ventilation or reduced-density gases) improves O_2 delivery to

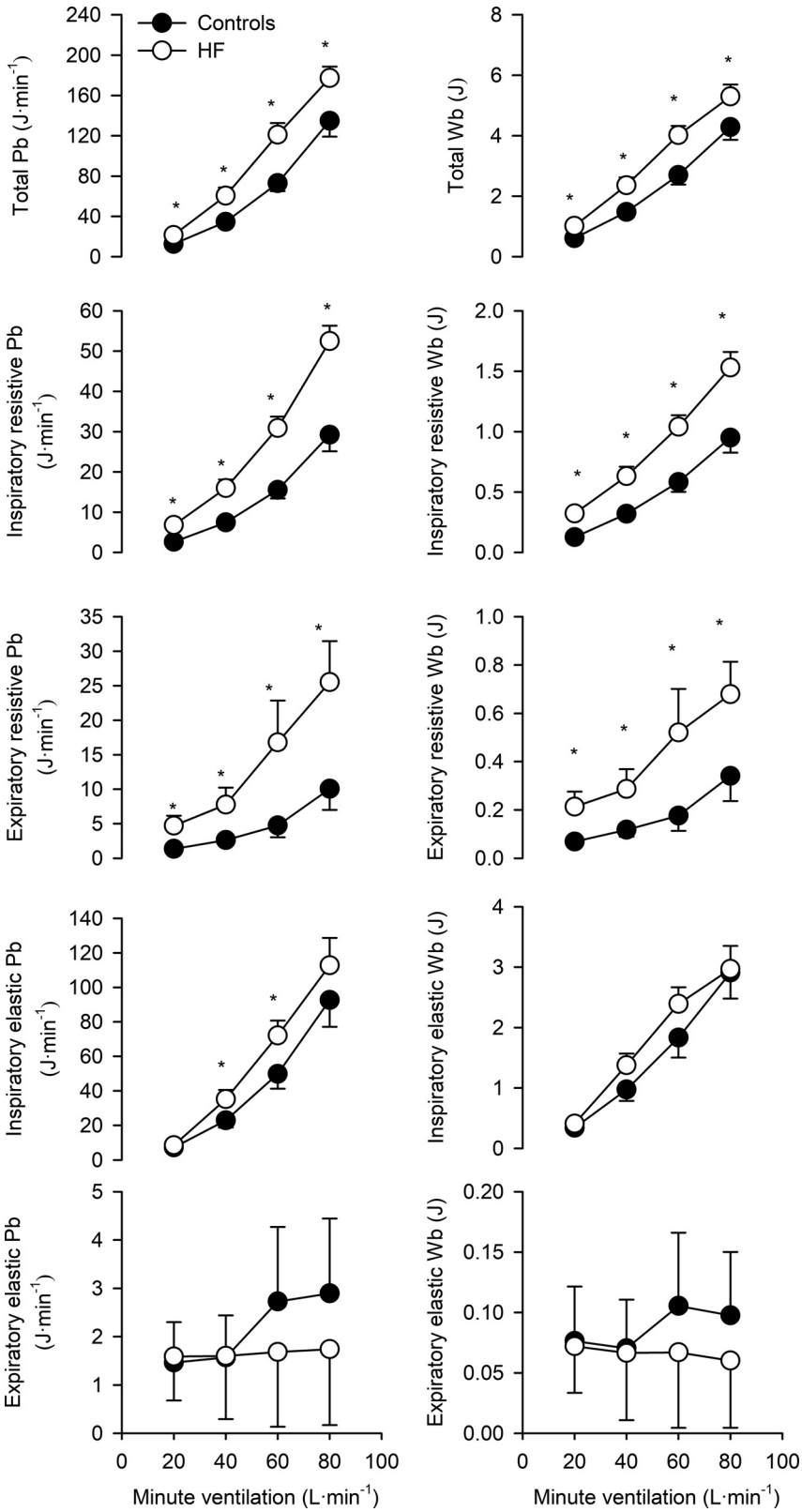

Fig. 2. The work and power of breathing (Wb and Pb) during graded exercise in patients with heart failure (HF) and healthy age-matched control subjects. Data are presented as means ± SE *$P < 0.05$, compared with control group.

the locomotor muscles, and increases exercise tolerance in patients with HF (11, 57, 65, 70). Similarly, inspiratory muscle training improves limb O_2 delivery in HF patients, most probably by decreasing the energetic demands of respiratory muscle work at a given $\dot{V}_E$. Decreasing the O_2 cost of breathing may, thus, attenuate the respiratory metaboreflex, and reduce competition between vascular beds when the overall Wb is high in patients with HF (20, 63, 64, 86, 87).

Key Points

- HF patients hyperventilate during exercise.
- The Wb and Pb are inordinately higher during exercise in HF.
- The higher mechanical cost of breathing is primarily due to an increased resistive load to breathing.
- Respiratory and limb muscles may compete for an adequate share of cardiac output during exercise in patients with HF.
- Decreasing the Wb and Pb improves tolerance to exercise in HF.

IMPACT OF INTRATHORACIC PRESSURE SWINGS ON LEFT VENTRICULAR FUNCTION IN HEART FAILURE

Respiratory Modulation of Left Ventricular Function in the Healthy Heart

The changes in intrathoracic pressure accompanying each breath greatly contribute to heart and lung interactions at rest, and to a greater extent, during exercise. Although the increasingly negative intrathoracic pressures during inspiration increases right ventricular filling and right ventricular output, and augment left ventricular afterload, the simultaneous reduction in left ventricular preload causes the transient decrease in left stroke volume (7, 47, 79). During expiration, however, the increasingly positive intrathoracic pressures acutely enhance left stroke volume (34). Thus, manipulating intrathoracic pressure over several breathing cycles causes sustained changes in stroke volume. Indeed, the healthy left ventricle is remarkably insensitive to a wide range of acute changes in afterload (13), while preload is exquisitely sensitive to small changes in pressure (40). Therefore, a continuous less negative inspiratory intrathoracic pressure reduces stroke volume in healthy men (25, 35, 39), while a sustained more negative inspiratory intrathoracic pressure increases systemic venous return, which leads to an increased stroke volume despite the accompanying increase in left ventricular afterload (40). Exercise induces an increase in ventilation through increases in respiratory rate and tidal volume (40). Exercise also accentuates the fluctuations in intrathoracic pressure with peak inspiratory intrathoracic pressure becoming more negative (from −8 to −30 cmH_2O) and peak expiratory intrathoracic pressure becoming more positive (from –5 to +5–30 cmH_2O) with increasing intensities (67). The greater swings in intrathoracic pressure during exercise contribute to an augmented venous return and stroke volume (40, 83). In fact, reducing the intrathoracic pressure swings during maximal exercise causes significant decreases in stroke volume attributable to reductions in metabolic demand by the respiratory muscles and/or to the effects of a less negative inspiratory intrathoracic pressure on venous return (35).

Respiratory Modulation of Left Ventricular Function in the Failing Heart

Patients with HF often exhibit excessive ventilation for a given workload, which is characterized primarily by an increase in respiratory rate rather than tidal volume (14, 41). With increased exercise intensities and despite significant room to increase tidal volume by encroaching further on the inspiratory reserve volume, the rise in exercising tidal volume of patients with heart failure seems blunted (41). Moreover, patients with HF also breathe at lower operational lung volumes, so that the majority of expiratory flows produced during tidal breathing meet or exceed the maximal available expiratory flows, resulting in wasted expiratory effort (41). HF patients tend to be less sensitive to changes in left ventricular preload as a result of decreased left ventricular compliance, suggesting a failure of the Frank-Starling mechanism (i.e., inability to augment stroke volume consequent to increased left ventricular filling; 49).

Moreover, the failing left ventricle is sensitive to changes in left ventricular afterload (40). Therefore, depending on the function of the heart, changes in intrathoracic pressure induce opposite effects on stroke volume, such that a more positive intrathoracic pressure decreases stroke volume in the healthy heart yet increases stroke volume in the failing heart, as demonstrated during submaximal exercise in healthy dogs and dogs with HF (63). Indeed, a more positive expiratory intrathoracic pressure increases resting cardiac output in patients with elevated left ventricular filling pressures (33), and continuous positive airway pressure dampens the negative intrathoracic pressure swings, and improves left ventricular ejection fraction in patients with systolic HF and obstructive sleep apnea (45). Thus, lessening the negative inspiratory pressure, and augmenting the positive expiratory pressure through "rapid shallow" breathing pattern and lower operational lung volumes, may preserve, or even enhance, cardiac output during exercise in patients with HF. Accordingly, it was hypothesized that a less negative inspiratory intrathoracic pressure and a more positive expiratory intrathoracic pressure would increase stroke volume during exercise in HF patients, yet they would reduce stroke volume in healthy individuals (50).

In an initial experiment, the effect of two levels of inspiratory unloading (a less negative inspiratory intrathoracic pressure) on stroke volume was determined during moderate-intensity exercise in patients with a history of ischemic or stable idiopathic HF with reduced ejection fraction (HFrEF) (NYHA class I and II, ejection fraction ≤40%) and healthy individuals (51). In healthy individuals, inspiratory unloading elicited reductions in stroke volume during exercise (Fig. 3*B*), confirming that the normally produced inspiratory intrathoracic pressure helps to maintain left ventricular filling during exercise in these individuals. In contrast, both levels of inspiratory unloading elicited increases in stroke volume during exercise in patients with HFrEF (Fig. 3*B*), possibly due to a decreased left ventricular afterload. In a second experiment, expiratory loading of +5 cmH_2O and +10 cmH_2O (a more positive expiratory intrathoracic pressure) elicited reductions in stroke volume during exercise in healthy individuals (Fig. 3*D*), further supporting the contention that reductions in preload outweigh reductions in afterload in a healthy population (6, 76, 82). Conversely, both levels of expiratory loading induced increases in stroke volume during moderate-intensity exercise in patients with HFrEF (Fig. 3*D*), possibly caused by a decreased left ventricular afterload combined with a beneficial reduction in left ventricular preload (52). These findings suggest that exercise tolerance may be improved by manipulating intrathoracic pressure during exercise in patients with HFrEF. Accordingly, a less negative intrathoracic pressure resulted in marked improvement in heart rate, blood pressure, and performance during resistance exercise in patients with ischemic heart failure (28). In addition to its effect on preload and

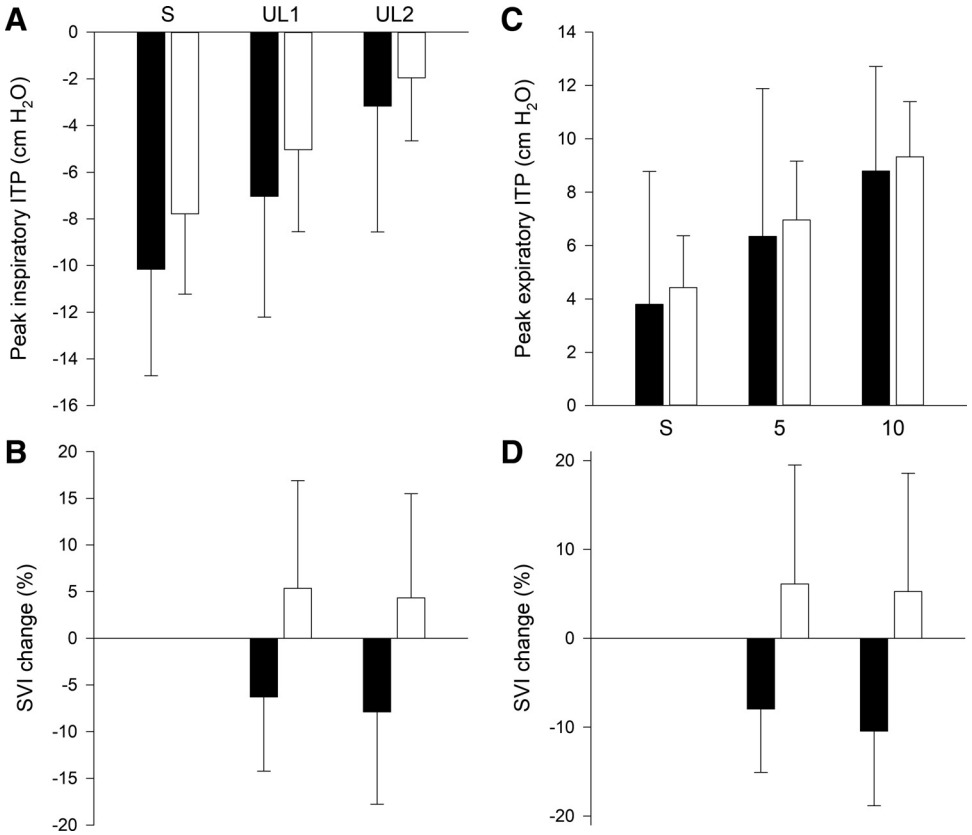

Fig. 3. Peak inspiratory intrathoracic pressure (ITP) during spontaneous breathing (S) and two unloading conditions (UL1 and UL2) during moderate-intensity exercise (main effect for condition $P < 0.05$) (*A*) and accompanying changes in stroke volume index (SVI) (group and condition interaction $P < 0.05$) (*B*). Peak expiratory intrathoracic pressure during spontaneous breathing (S) and expiratory loading at 5 cmH_2O and 10 cmH_2O during moderate-intensity exercise (main effect for condition $P < 0.05$) (*C*) and accompanying changes in SVI (*D*) in healthy individuals (solid bars) and patients with heart failure (open bars). This figure is based on data previously published by the authors (51, 52).

afterload, it must be considered that inspiratory unloading, via reducing the Wb and Pb, may improve exercise intolerance by attenuating the competition for cardiac output between respiratory and locomotor muscles. Indeed, as mentioned earlier, inspiratory unloading via proportional assisted ventilation increases limb muscle perfusion and improves exercise tolerance in HF patients (11, 65, 70).

It is emphasized that many factors associated with disease severity, such as pulmonary vascular pressures, right ventricular enlargement, heart size, and fluid volume status, may alter cardiorespiratory interactions in HF. For example, severe right ventricular dilation commonly observed in systolic HF shifts the interventricular septum toward the left ventricle and stretches the pericardium. These mechanical changes lead to an increase in left ventricular diastolic pressure, and a fall in left ventricular diastolic volume, and/or or a decreased left ventricular compliance (40). These mechanical effects of right ventricular dilation on the left heart are also likely contributors to the observed insensitivity of the left ventricle to increases in preload induced by negative intrathoracic pressures. Moreover, in HF patients with acute volume overload and/or elevated pulmonary vascular pressures, it is conceivable that expiratory loading (i.e., more positive intrathoracic pressure), and inspiratory unloading (less negative intrathoracic pressure) would decrease venous return and left ventricular preload, which may optimize left ventricular filling by moving the operating point to a more optimal range on the Frank-Starling curve. In turn, stroke volume and cardiac output would increase, thereby improving the overall functional capacity of the overdistended heart in this population. In conclusion, unloading the inspiratory intrathoracic pressure swing during exercise, through inspiratory pressure-assisted ventilation, could allow patients with HF to train at higher workloads.

Key Points

- The blunted tidal volume response, low operational lung volumes, and expiratory flow limitation may preserve the cardiac response to exercise in HF patients.
- A less negative inspiratory and a more positive expiratory intrathoracic pressure improves stroke volume during moderate-intensity exercise in patients with HFrEF.

IMPACT OF HEART FAILURE ON PULMONARY GAS EXCHANGE

Patients with HF frequently demonstrate an abnormal breathing pattern and pulmonary gas-exchange response to exercise. These abnormalities include but are not limited to *1*) a steepened slope of the relationship between $\dot{V}_E$ and pulmonary CO_2 output ($\dot{V}_{CO_2}$) (92, 96, 98); *2*) an impaired diffusing capacity for carbon monoxide (D_{LCO}), and a blunted rise in D_{LCO} with increasing exercise intensity (68, 77); *3*) an increased dead space ventilation (46); *4*) a rapid shallow breathing pattern (i.e., small tidal volume, high respiratory frequency); *5*) a reduced quotient of $\dot{V}_{O_2}$ over heart rate (i.e., O_2 pulse; 26, 53); *6*) reductions in the gas exchange-based estimate of pulmonary vascular capacitance, GX_{cap} (92); and *7*) a lower O_2 uptake efficiency slope (i.e., OUES; 8). Importantly, the presence and severity of these gas-exchange abnormalities reveal the extent of the underlying pathophysiology of the HF condition. For example, the heightened $\dot{V}_E/\dot{V}_{CO_2}$ slope is most likely due to a compensatory rise in $\dot{V}_E$ to overcome a larger

physiological dead space, consequent to an increased mean alveolar ventilation-to-perfusion ratio across the entire lung (78, 91), and/or the mechanical constraint imposed on increasing tidal volume during exercise in HF patients (41, 43). It has also been suggested that a higher $\dot{V}_E/\dot{V}_{CO_2}$ slope is contributed, at least in part, by increased ventilatory drive emanating from central and peripheral chemoreceptors (23, 74, 75), and/or ergoreceptors within the active skeletal muscles (71, 89). On the other hand, the systematically lower D_{LCO} observed in HF patients may reflect ultrastructural changes at the alveolar-capillary interface that, in turn, may protect against the lung-fluid accumulation from sustained elevations in pulmonary vascular pressures (78) at the expense of reducing alveolar membrane conductance (i.e., D_m). Furthermore, a reduced O_2 pulse may reflect the severity of impairment in stroke volume during exercise in HF (26, 53). Recently, we have shown that GX_{cap} [i.e., $GX_{cap} = O_2$ pulse $\times$ end-tidal CO_2 ($P_{ET_{CO_2}}$)] is negatively correlated with mean pulmonary arterial pressure and pulmonary vascular resistance during exercise in HF patients (92), suggesting that GX_{cap} may be used to track changes in the pulmonary vascular response to exercise in these patients. Lastly, it has been reported that the further that $P_{ET_{CO_2}}$ declines, the greater is the impairment in pulmonary and, by consequence, systemic cardiac output during submaximal exercise in HF patients—a finding reflective of an increasing difference between arterial and $P_{ET_{CO_2}}$ rather than of frank hyperventilation (60, 96, 97).

It is clear from the above that simple, noninvasive measurements of pulmonary gas exchange offer insight into the underlying pathophysiology in patients with HF. If one agrees that such abnormalities reflect the duration and severity of the HF condition, the following question arises: can pulmonary gas exchange be used to optimize therapies in HF?

Pulmonary Gas Exchange as a Target for Optimization of Therapy in Heart Failure

The clinical management of mild-to-moderate HF often entails a combination of physical rehabilitation, pharmacotherapies, and dietetic interventions. As the condition progresses, and prognosis worsens, therapies such as heart transplant or cardiac devices are considered. To this end, ~30% of patients with advanced HF demonstrate abnormal electrical activation of the left ventricle (37, 61, 80). In this group of patients, cardiac resynchronization therapy (CRT) devices are indicated. CRT device therapy seeks to improve left ventricular pump function by electrically pacing the atria and ventricles with customized atrioventricular (AV) and interventricular (VV) timing intervals. Certainly, the use of CRT has been associated with reduced mortality and morbidity, augmented hemodynamics, increased functional capacity, and improved quality of life in this clinical population (12, 16, 24, 31, 38). Notwithstanding these reported benefits, roughly one-third of patients do not respond to the therapy after successful implantation (i.e., "nonresponders"; 29, 99). It has been argued, however, that the response rate to CRT may be improved by taking an individualized approach to finding optimal AV and VV timing intervals (2, 9, 10, 15, 18). Moreover, preliminary evidence suggests that more frequent optimization of CRT device settings during the postimplantation follow-up period may also improve clinical outcomes in advanced HF patients (30).

The current "standard" method of optimizing CRT timing intervals is via echocardiography, whereby AV and VV delays are systematically changed until left ventricular filling and ejection patterns are considered "optimized" (56). Yet, not only is this method time-consuming, it requires highly trained technical staff and, as such, suffers from limited reproducibility within and between sonographers. These drawbacks are particularly relevant if frequent CRT optimizations are planned. Other methods of CRT optimization exist that utilize information recorded from the intracardiac electrocardiogram (88) or via micromechanical sensors implanted with the device (i.e., SonR signal; 81). However, these "device-driven" methods of CRT optimization are not standard across all implants, and it may not be feasible to upgrade a patient's existing CRT device for the sole purpose of obtaining such features.

How else then may CRT be optimized? Given that abnormalities in pulmonary gas exchange are strong predictors of prognosis in HF, we have hypothesized that using a pulmonary gas-exchange-based approach to CRT optimization will improve clinical outcomes in patients with advanced HF, partic-

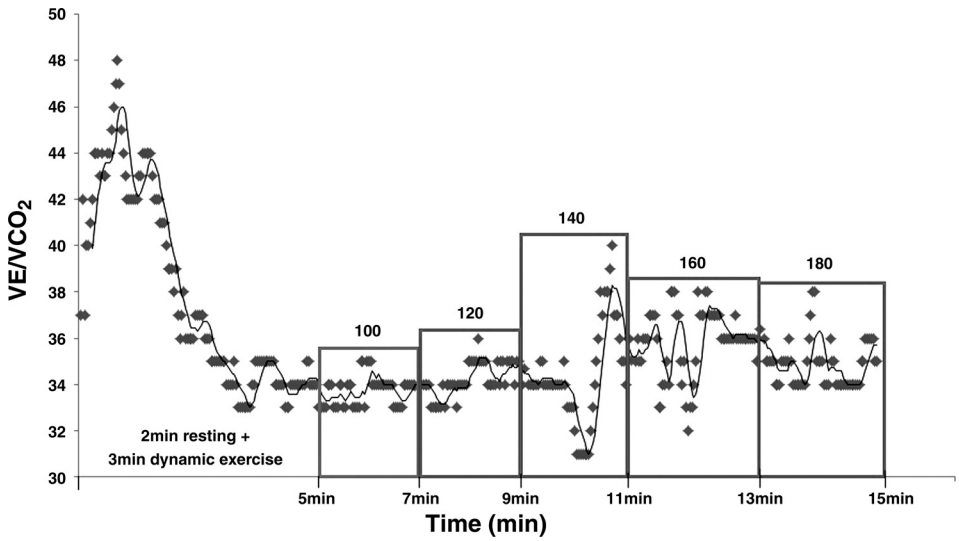

Fig. 4. Changes in breath-by-breath $\dot{V}_E/\dot{V}_{CO_2}$ across atrioventricular (AV) timing intervals in a representative heart failure patient with a cardiac resynchronization therapy device (sex: female; age: 69 yr; body mass index: 31 kg·m^{-2}; NYHA class: III). Black boxes indicate the 2-min window for each AV timing interval setting. The numbers shown above the boxes are AV timing intervals (ms). [Reprinted from Kim et al. (48) with permission from Elsevier.]

ularly during mild exercise when there is a light load imposed on the heart and heart-lung interactions are enhanced. As a proof of concept, we recently investigated (48) the effects of changing AV and VV delays on several parameters of pulmonary gas exchange during low-intensity exercise in a small cohort of HF patients with moderate-to-severe symptoms (n = 20; NYHA Class II–IV). We demonstrated that AV and VV delays can be adjusted, such that pulmonary gas exchange improves during low-intensity treadmill exercise (i.e., reduced $\dot{V}_E/\dot{V}_{CO_2}$, increased $P_{ET_{CO_2}}$, and O_2 pulse; Fig. 4). Importantly, however, the precise AV and VV settings, which elicited such improvements, varied widely between patients, emphasizing the need for taking an individualized approach to optimizing CRT device setting when using pulmonary gas exchange as the target. A pulmonary gas exchange-based approach to CRT (GX-CRT) optimization has several benefits over current methods, insofar as it *1*) requires minimal technical skills, *2*) is not affected by operator error/bias (cf., echocardiography), *3*) can be performed on all patients regardless of the specific CRT implant (cf., "device-based" methods), and *3*) is a relatively expedient process (<15 min). Perhaps most importantly, the GX-CRT approach incorporates submaximal exercise and, as such, AV and VV delays are optimized under conditions that more closely reflect activities of daily life in HF patients. What remains to be determined is whether GX-CRT optimization confers a sustained improvement in pulmonary gas exchange over the long term and whether these improvements translate into better clinical outcomes for the HF patient.

Key Points

- HF pathophysiology includes several abnormalities in pulmonary gas exchange, the most prominent of which are a systematically lower $\dot{V}_{O_{2peak}}$ and D_{LCO}, and an augmented $\dot{V}_E/\dot{V}_{CO_2}$ slope.
- CRT optimization using pulmonary gas exchange (GX-CRT) is a promising alternative to current methods of CRT optimization; however, further studies are necessary to demonstrate a clinical benefit of GX-CRT optimization over the long term in patients with advanced HF.

SUMMARY

It is emphasized in this review that one should not discount the impact of heart failure on the respiratory system. Elevated pulmonary venous pressures may promote engorgement of the pulmonary and bronchial vasculature with associated changes in lung fluid, particularly during exercise. These alterations in pulmonary and bronchial hemodynamics not only increase ventilatory requirements during exercise (i.e., increased dead space), but also serve to "stiffen" the lungs, and decrease airway caliber by impacting on airway geometry and/or enhancing bronchomotor tone. These derangements in respiratory mechanics augment the amount of work that respiratory muscles must expend to adequately ventilate the lungs during exercise; as such, the mechanical work and power of breathing is higher in patients with HF (27). The higher mechanical cost of breathing may place the respiratory muscles in direct competition with exercising limbs for an adequate portion of cardiac output.

We also discussed the influence of respiratory modulation of intrathoracic pressure and its mechanical influence on left ventricular function. Interestingly, the specific effects of intrathoracic pressure swings on left heart function differ between healthy and HF patients. Whereas the "healthy" heart is positioned on the steep portion of the Frank-Starling operating curve, the "failing" heart is shifted rightward and upward onto the flatter, stiffer portion of this curve. Accordingly, while left ventricular output of the "healthy" heart changes in proportion with variations in left ventricular preload, the "failing" heart does not and instead varies in proportion to changes in afterload. These observations support the hypothesis that HF patients breathe at low lung volumes, and precipitate relatively more expiratory flow limitation than their healthier counterparts, to create more positive swings in intrathoracic pressure, thereby preserving stroke volume and cardiac output during exercise (50).

The pathophysiological processes that contribute to the increased mechanical cost of breathing and altered heart-lung interdependence are also responsible for the abnormalities observed in the pulmonary gas-exchange response to exercise in HF (i.e., reduced D_{LCO} and augmented $\dot{V}_E/\dot{V}_{CO_2}$ slope). Given that these abnormalities are strong predictors of disease prognosis, it follows that therapies designed to normalize the "abnormal" pulmonary gas exchange may improve clinical outcomes. For example, our laboratory has recently demonstrated that it is possible to acutely improve pulmonary gas exchange in HF patients with implanted CRT devices by optimizing AV and VV timing intervals (48); whether these improvements in pulmonary gas exchange confer a benefit to patient outcomes over the long term remains the focus of future investigations.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.J.C., C.-H.K., B.D.J., and S.L. conceived and designed research; T.J.C., C.-H.K., B.D.J., and S.L. performed experiments; T.J.C., C.-H.K., B.D.J., and S.L. analyzed data; T.J.C., C.-H.K., B.D.J., and S.L. interpreted results of experiments; T.J.C., C.-H.K., B.D.J., and S.L. prepared figures; T.J.C., C.-H.K., B.D.J., and S.L. drafted manuscript; T.J.C., C.-H.K., B.D.J., and S.L. edited and revised manuscript; T.J.C., C.-H.K., B.D.J., and S.L. approved final version of manuscript.

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