Defining the System-Contributors to exercise Limitations in Heart Failure

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Abstract

One of the primary hallmarks of patients diagnosed with heart failure (HF), from all etiologies, is a reduced tolerance to exercise and compromised functional capacity. The physiological contributors of this limitation stems from poor pumping capacity but also major changes in functioning of the vasculature, skeletal muscle, and respiratory systems. There is a major body of literature that supports the relevance of each of these systems to our understanding of exercise intolerance during HF. While the literature has not yet identified the primary contributor to exercise intolerance in the context of HF, advances in our understanding of the central and peripheral mechanisms of exercise intolerance during HF (with preserved and reduced ejection fraction) are critical for the future design of therapeutic modalities that will improve this outcome. The interrelatedness between systems cannot be discounted. Therefore, the current review summarizes the current body of literature related to the pathophysiology of HF contributing to poor exercise tolerance and potential mechanisms involved.

Key Points

- Exercise intolerance is a hallmark symptom of heart failure that severely limits functional capacity the determinants of which include cardiovascular, skeletal muscle, and respiratory systems
- Chronotropic incompetence and poor heart rate reserve in the face of poor pump function further contributes to diminished exercise capacity during heart failure.
- Alterations in the ability of the peripheral and central vasculature to vasodilate at rest and during exercise in heart failure contributes to limit oxygen supply and demand matching
- The currently identified changes that occur in the skeletal muscles of patients with heart failure are not disease-specific, but are similar to those found in aging, deconditioning, and other chronic conditions associated with inflammation.
- The function and compensatory mechanisms of the heart and lungs are intimately related. The primary respiratory factors limiting exercise in patients with HF include ventilation, perfusion, and ventilation-perfusion abnormalities.

Introduction

Chronic heart failure (HF) is marked by severe exercise intolerance with fatigue and dyspnea on exertion. The underlying mechanism of reduced exercise capacity [measured as reduced peak oxygen consumption (VO_2)] is multi-factorial (**Box 1**). Reduced exercise tolerance is a strong prognostic indicator and contributes to poor quality of life[1]. The traditional concepts of exercise limitations have focused on central dysfunction related to poor cardiac pump function and pulmonary limitations related to congestion of the lungs and dyspnea. However, the mechanisms are not exclusive to the heart and lungs and the understanding of pathophysiology of this disease has evolved[2]. The constellation of numerous neuro-humoral effects activated by poor pump function can lead to severe changes in the peripheral systems (**Box 1**). Muscle fatigue and dyspnea are hallmark symptoms of HF that contribute to and exacerbate the symptoms of exercise intolerance (**Figure 1**). The interrelationships between the central hemodynamics and the peripheral systems (vascular, skeletal, and pulmonary) that impact exercise tolerance are poorly understood. However, this review will outline what is known about the contribution of these systems to exercise performance and the potential implications of these contributors to the symptoms of HF.

Cardiac Contributors to Exercise Limitations in Heart Failure

Heart failure is often defined as the inability to achieve and/or maintain an appropriate cardiac output (Q)[3] and one of the important sign of HF is exercise intolerance, as measured by low peak VO_2 values. Exercise intolerance in HF patients can be currently explained by numerous inadequacies ranging from peripheral to ventilatory, however, specific cardiac limitations will be discussed here, in particular in relation to the cardiac side of the Fick equation ($VO_2 = Q * a\text{-}vO_{2diff}$). With Q being

comprised of both stroke volume and heart rate (HR), HF patients often have diminished capacities on both of these fronts.

HF with Preserved Ejection Fraction Overview

HF with preserved ejection fraction (HFpEF e.g., diastolic HF) has recently been the focus of many investigations intent on understanding the pathophysiology behind low peak aerobic capacities in this population, which warrants discussion here. Despite a normal resting EF, patients with HFpEF exhibit an attenuated change in EF with exercise versus a comparison to hypertensive patients[4-7]. This demonstrates that EF may not be the "best" measure of contractility due to the dependence on load and remodeling effects. Yet, this smaller change in EF with exercise does not appear to have one firm culprit, but several contenders, which include either a smaller change in end-diastolic volume (EDV) (e.g., less EDV reserve)[6], and/or a smaller end-systolic volume (ESV) reserve [4,5,8]. Interestingly, most recent studies have not been able to support Kitzman's findings that demonstrated a lower EDV response with exercise, which would suggest the failure of the Frank-Starling mechanism[6]. Rather, several studies demonstrate similar EDV responses to exercise when comparing HFpEF patients to a control group[4,5,8,9], suggesting the left ventricle (LV) may fill to an appropriate EDV. However, this does not mean the Frank-Starling mechanism is fully operational, despite "normal" EDV reserve.

Evidence suggests indeed that both the static Starling[7] and the novel dynamic Starling mechanism[10] are compromised in HFpEF either at rest or with exercise[11], resulting in elevated LV filling pressures (LVFP). Increased LFVP are often coupled to increased LV elastance and prolonged relaxation[12,13], and collectively, contributing altered filling properties in HFpEF patients[14]. Skaluba et al.[15], found that high filling pressures were highly correlated with exercise intolerance in patients with HFpEF. Furthermore, global contractile indices are impaired among HFpEF patients, in that contractile and ventricular-vascular coupling reserve is diminished in HFpEF both at low level exercise and peak

exercise[8]. Contractile dysfunction among patients with HFpEF has also been supported by population-based work[16].

In addition to the pathophysiological LV changes and reduced reserves that occur with HFpEF, left atrial (LA) function is also impaired both at rest[17-20] and with exercise[21,22], which can help explain poor atrial compensation during late diastole and higher LVFP and thus poor systolic and diastolic performance in this population. Interestingly, a recent report on individuals without overt HF observed that LA volume index (LA volume/body surface area) was an important predictor for an abnormal exercise LVFP[23]. It is obvious that numerous impairments exist among patients with HFpEF that span across a wide array of both diastolic and systolic-related measurements, all contributing to reduced cardiac performance, with exercise possibly enhancing the lack of cardiac reserve available in patients with HFpEF thus contributing to exercise intolerance.

HF with Reduced Ejection Fraction Overview

Heart failure patients with reduced ejection fraction (HFrEF; e.g. systolic HF) also suffer from severe exercise intolerance, with maximal Q estimated to be approximately less than 50% of that compared to a healthy control group[24,25]. Earlier work by Sullivan et al.[26,27] demonstrate that HFrEF is associated with poor cardiac reserve during exercise, largely due to diminished SV and maximal HR responses. In many cases of HFrEF the LV is dilated, which corresponds with an inability to appropriately increase LVEDV, because the LV is at or near maximal volume, resulting in the failure of the Starling mechanism and reductions in preload and EF. The higher LVESV and LVEDV collectively contribute to augmented LVFP and pulmonary capillary wedge pressure, which are important contributors to pulmonary hypertension, dyspnea, and right ventricular dysfunction. In the many cases of HFrEF with diastolic dysfunction, resistance to filling exists due to higher ventricular elastance and lower distensibility.

Heart Rate and Chronotropic Incompetence

With Q reserve at less than 50% of healthy controls, HF patients must rely on cardio-acceleration in order to substitute for diminished SV during periods of increased physical activity. However, chronotropic incompetence, which is present in approximately 25-70% of the HF population[28], further contributes to diminished exercise capacity and demonstrates the integrated nature of multiple mechanisms contributing to poor exercise tolerance.

Despite several different ways to determine chronotropic incompetence (reviewed by Brubaker and Kitzman[28]) it serves as a strong determinant of exercise in tolerance in HF patients. In studies of patients with heart disease (not specifically HF), chronotropic incompetence is strongly related to observed myocardial perfusion abnormalities and increased risk of mortality[29,30]. Specifically in HF patients, HR reserve (difference between peak and resting HR) is attenuated and associated with peak VO_2. This diminished reserve, accounted for 16% of the differences in peak VO_2 among those defined as either having or not having chronotropic incompetence, which has clinical and functional manifestations when peak aerobic capacities average ~15 $mLO_2 \bullet kg^{-1} \bullet min^{-1}$ in the HF population[31]. In support of this, Witte et al.[32] observed that peak aerobic capacity was 14% lower in HF patients with chronotropic incompetence. Interestingly, this study found similar correlations between peak VO_2 and the change in HR among HF patients that were either taking or not taking β-blockers ($r = 0.56$ and 0.60), suggesting the importance of chronotropic incompetence[32]. Borlaug et al.[9] observed in patients with HFpEF that the HR response and afterload were primarily associated with Q, but that peak VO_2 was not associated with changes in either SV or EDV with exercise. This again suggests the importance of HR reserve as a determinant of exercise intolerance.

Chronotropic incompetence coupled with impaired HR recovery (HRR) following exercise suggests autonomic dysfunction, which is known to exist among HF patients as evidenced by heightened

sympathetic[33] and altered parasympathetic tone[34,35]. Corroborating this concept, Keller-Ross et al.[36] observed that locomotor metaboreflex stimulation using regional circulatory occlusion significantly altered both the arterial baroreflex and heart rate recovery (HRR) following exercise in patients with HFrEF. This again demonstrates the various levels of impairments throughout the "cardiovascular tree", with autonomic dysfunction quite possibly playing a central role with regards to cardiac issues at hand for exercise intolerance.

Molecular and Cellular Factors of Ventricular Dysfunction

Many structural and functional changes occur throughout the pathogenesis of HF at the molecular and cellular levels. Remodeling involves changes in cardiomyocyte physiology, factors involved in the intercellular/extracellular matrix, and vessel reorganization, which can lead to increased ventricular stiffness, impaired contractility or both[37]. It is important to remember, remodeling of one chamber will often result in negative consequences for another chamber (e.g. LV failure can lead to RV remodeling due to higher filling pressures).

With respect to cardiomyocytes, volume overloaded conditions (i.e., HFrEF) can cause increases in length, whereas pressure overload (i.e., HFpEF) can increase myocyte thickness[38]. Increased apoptosis and necrosis, combined with lower rates of autophagy can also contribute to adverse remodeling, especially in situations where infracts are present[37]. Furthermore, the renin-angiotensin system can be activated with wall stress that can lead to cardiac hypertrophy[39], with concomitant interstitial remodeling stemming from upregulation of aldosterone and angiotensin II, transforming growth factor, and alterations in matrix metalloproteinases (MMP) and tissue inhibitors of MMPs[37,40-42]. Adding further insult, calcium handling becomes impaired with HF thus limiting excitation-contraction coupling[43]. This is largely through diminished calcium uptake in the sarcoplasmic reticulum and/or

elevations in diastolic calcium-leak (specifically the ryanodine receptors) of the sarcoplasmic reticulum, or through changes in sodium handling[43].

Ventricular stiffness can also be attributed to changes in the extracellular matrix, since this matrix is important in preventing overstretch, myocyte slippage and tissue deformation during filling[42]. Furthermore, the extracellular matrix is also involved with factors of growth and tissue differentiation. For instance, collagen deposition is increased with pressure overload and has been associated with extracellular matrix-related stiffness[42,44]. While many of the above mechanisms have not been studied specifically in relation to exercise intolerance, it would follow these factors (and others) provide the molecular and cellular basis for the clinically measured LV dysfunction present in HF and contribute to poor exercise performance.

Vascular Contributors to Exercise Limitations in Heart Failure

Previous work has found that the often observed major exercise capacity limitations in HF is related to peripheral abnormalities in the exercising muscle and in the vasculature[27,45]. Cardiac output increases more than 7 fold during exercise and a major component of this increase is related to metabolic vasodilation of the exercising muscle[46,47]. In patients with HF, the impaired ability of the circulation to vasodilate and hence the restriction of enhanced perfusion in exercising muscle may have severe consequences to exercise tolerance (**Figure 1**). The causes of this apparent dysfunction at the level of the circulation during exercise appears to have multiple mechanistic contributors during HF including 1) increased sympathetic nervous system (SNS) activation; 2) activation of the renin angiotensin system that enhances vasonconstrictor tone; 3) impaired endothelial dependent vasodilation; 4) reduced blood vessel density; and 5) increased arterial stiffness, all of which limits tissue perfusion and distribution to the working muscle.[48]

Peripheral Vascular Impairments

Up to 85% of the total Q is used to perfuse the working muscle.[49] During acute exercise in healthy individuals there is rapid vasodilation of the resistance arteries with concomitant increases in muscle pumping action that serve to supply sufficient oxygen to the working muscles. At very high metabolic demand, the cardiovascular systems supply blood to working muscle is exceeded.[27] In patients with HF the mechanisms that serve to compensate and preserve cardiac output (i.e. activation of the renin angiotensin aldosterone system, increased SNS, and sodium and water retention) result in many physiological imbalances that damage the vasculature and contribute to an earlier mismatch between oxygen supply and demand.[50] The exercise response is hampered by the mechanisms outlined above resulting in reduced myocardial perfusion, reduced peripheral vasodilation, and increased afterload.

In terms of reduced blood flow to exercising muscle, there multiple contributing mechanisms. In patients with HF, there is a dramatic shift towards an increase in vasoconstrictor tone that hampers perfusion at rest and during exercise.[51] For example, chronic inhibition of the SNS with clonidine was shown to increase peak vascular conductance during exercise in a HF cohort.[52] Importantly, a high level of SNS activation that occurs during exercise is associated with reduced exercise capacity.[53,54] This exaggerated increase is likely to contribute to the impact of reduced vascular conductance during exercise and exercise capacity.[53]

Role of Endothelial Dysfunction

Physiologic impairment of the endothelium is known as vascular endothelial dysfunction. Reduced endothelial function is a hallmark of cardiovascular disease and in HF is severely reduced[55-57]. This condition, most commonly results from an imbalance between vasodilator and vasoconstrictor

substances produced by the endothelium. There is ample evidence demonstrating that the primary mechanism of endothelial dysfunction is a reduction in endothelium-derived nitric oxide (NO) bioavailability. Although the exact mechanism by which this reduction occurs is still under debate, several key mechanisms have been studied including: disturbances in the NO signaling pathway; reduced bioavailability of the endothelial nitric oxide synthase (eNOS) substrate L-arginine and/or tetrahydrobiopterin (BH_4); modified expression and functional activity of eNOS; extracellular scavenging of NO by reactive oxygen species (ROS); and increased production of endothelium-derived vasoconstrictors[58].

Mechanisms that contribute to reduce NO bioavailability include lower eNOS expression and/or increased quenching of NO by superoxide[59]. Treatment with antioxidants reduces superoxide levels and improves endothelium-dependent vasodilator function suggesting that ROS are integral to vascular dysfunction[60]. High levels of oxidative stress that overwhelms the vascular antioxidant systems are observed in HF[61] and superoxide has been linked to peripheral hypoperfusion, peripheral endothelial dysfunction, and exaggerated SNS activity in patients with HF, leading to further to exercise intolerance. Oxidative stress is closely related to peak VO_2 and severity of HF[61] suggesting that oxidative stress may be a contributor to exercise intolerance.

Endothelial cells are uniquely positioned between circulating blood and the fixed underlying vascular wall, exposing them to shear stress of up to 50 dyn/cm[62]. In the coronary circulation during HF, the endothelium that is exposed a reduced blood flow and shear stress, and adapts in manner that promotes endothelial dysfunction. During physiologic levels of shear stress, there is improved eNOS generation of NO by enzyme phosphorylation[62] and increases in eNOS expression and NO-dependent dilation[63]. Decreased coronary endothelium- dependent dilation can reduce myocardial perfusion resulting in reduced ventricular function[64,65]. The dysfunctional endothelium contributes to increased

vascular stiffness and impaired arterial distensibility facilitating further myocardial dysfunction. Furthermore, there is emerging evidence that NO itself may have a positive impact on myocardial function whereas reductions in NO are linked to myocardial necrosis[66]. Improved endothelial function and NOS expression is seen after aerobic exercise training[67] in patients with coronary disease and HF which is associated with improved exercise tolerance.

Role of Arterial Stiffness

In addition to reduced endothelial function, increased arterial stiffness is associated with cardiovascular mortality and contributes to premature elevations in blood pressure[7] and is increased in HF. The relationship between the structure of large vessels and arterial stiffness is strong. For example carotid artery intima-media thickness (another well know subclinical risk factor for cardiovascular disease) has been associated with pulse pressure and other markers of arterial stiffness[68]. However, in small blood vessels such as the arterioles where tissue blood flow is tightly regulated during exercise, smooth muscle tone can more directly influence arterial stiffness. These changes can occur in way that the loss of vasodilators such as NO and the enhancement of vascosconstrictor reactivity in HF enhances arteries stiffness. Increases in arterial stiffness contribute to increased velocity of the reflected pulse waves during the cardiac cycle as well as reducing aortic pressure during diastole[69]. These effects can lead to a decrease in myocardial perfusion leading to a potential mismatch between myocardial oxygen demand and supply, another vicious cycle in HF that leads to further muscle injury. As the artery stiffens during HF, left ventricular afterload (a milestone of HF) also increases. Increased arterial stiffness is associated with diastolic dysfunction[69] and is increased in patients with HFpEF[70]. While pulse pressure (PP) is a crude index of arterial stiffness, higher values predict cardiovascular events and mortality following a myocardial infarction in HF patients.[71] Arterial stiffness is related to walk time performance during a functional walk test[72] and aortic stiffness was strongly associated with peak VO_2 in patients with

dilated cardiomyopathy.[73] Finally, Kitzman et al. found that carotid arterial stiffness was significantly correlated with peak VO_2 and the 6 minute walk distance in patients with HFpEF[70].

Role of Inflammation on Peripheral Vasculature Contributors to Exercise Intolerance

Both acute and chronic inflammatory conditions have been associated with increased arterial stiffness [74-76] and reduced endothelial function in patients with HF[77]. Concentrations of inflammatory markers such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α have been shown to be greater in patients with HF[78]. There are multiple studies showing a strong relationship between elevated C-reactive protein (CRP) elevated during cardiovascular disease and HF and increased arterial stiffness[79-81]. High levels of CRP can decrease eNOS activity [82], and increase endothelin (ET)-1[83] resulting in reduced vasodilation, enhanced vasoconstriction, increased arterial stiffness. In addition, both IL-6 and TNF-α can induce vascular inflammation, which may be a critical component to the vicious cycle that occurs between inflammation of the vasculature and further cardiac insult during HF[84-86]. ET-1 is a potent vasoconstrictor peptide that is released from endothelium. The biologic effects of ET-1 include vasoconstriction, stimulation of vascular smooth muscle proliferation, and enhanced cardiac hypertrophy. ET-1 is increased in patients with HF and high plasma ET-1 levels are associated with poor prognosis in these patients[51]. The levels of TNF-α, IL-6, and ET-1 appear to be associated with severity of disease and peak exercise in these patients accentuates the inflammatory response suggesting that exercise itself may activate the pro-inflammatory systems that mitigates blood flow responses to exercise. In addition, this viscous cycle further compromises the ability of the working muscle arterioles to vasodilate. Thus, systemic and local inflammation has a dramatic negative effect on arterial function during exercise.

Vascular dysfunction in HFpEF and HFrEF

More than half of the patients with HF have preserved LVEF (HFpEF). This population has dramatic reductions in exercise intolerance that can be in part related to changes in peripheral vasculature. For example, peripheral vascular resistance in HFpEF patients is increased and appears to contribute to exercise intolerance (i.e., lower peak VO_2)[8,14]. Borlaug et al. demonstrated that endothelial function measured as the hyperemic response in finger blood flow following upper arm occlusion was reduced in HFpEF patients compared to patients with hypertension[8]. Interestingly, patients demonstrating endothelial dysfunction had more fatigue and dyspnea during submaximal exercise suggesting that vasodilator function may be critical for determining exercise capacity in HFpEF[14]. There are data corroborating this hypothesis in a study by Guazzi et al., where treatment of HFrEF patients with sildenafil improved endothelial function and this improvement was closely related to exercise tolerance[87]. In another study, Kitzman et al. found that improvements in peak VO_2 following 16 weeks of exercise training occurred without improvements in endothelial function or reduction in arterial stiffness suggesting that exercise training may impact other determinants of exercise capacity in patients with HFpEF[88]. Obviously, the timing and sequence of vascular dysfunction and arterial stiffness that occurs during HFpEF and HFrEF and the implications for exercise intolerance will require further investigation.

Skeletal Muscle Contributions to Exercise Intolerance

In patients with HF, the inability of the myocardium to meet the demands of skeletal muscle during exercise initiates compensatory mechanisms that include the neuroactivation of the SNS, renin-aldosterone angiotensin system, vasopressin, and natriuretic peptides. The over-activation of autonomic signals leads to hypoperfusion and tissue hypoxia of skeletal muscle resulting in progressive structural, metabolic and functional adaptations in the peripheral musculature, including atrophy. These critical changes contribute to fatigue during exercise, a cardinal symptom of HF (**Figure 1**).

The view that significant alterations in the structure (mass), metabolism and function of skeletal muscle (SM) play an important role in limiting exercise capacity in patients with HF is well accepted. It has been over 20 years since the SM hypothesis was first proposed.[89] Since then, accumulating evidence supports the view that the complex pathophysiology of HF may begin with reduced cardiac function but ultimately involves peripheral abnormalities in SM. The alterations in SM (locomotor and diaphragm) are an important determinant of exercise capacity, dyspnea, and fatigue, and increase in conjunction with deterioration of symptoms. From a clinical standpoint, improvements in SM alterations can significantly improve functional abilities similar to that of age-matched controls for patients with non-advanced HF.[90]

Alterations in Skeletal Muscle Structure

In patients with HF, reduced levels of physical activity lead to SM atrophy (disuse and loss of mass)[91] and a low-level systemic inflammatory state[92]. Skeletal muscle atrophy leads to a reduction in cross-sectional area of myofibers and an overall decrease in SM strength and endurance[93]. The underlying mechanisms that mediate SM atrophy are likely related to activation of signaling pathways that regulate protein degradation[48], decreased protein synthesis, or both[94,95] . Evidence from animals models and human studies indicate that an imbalance in anabolic factors such as growth hormone and insulin-like growth factor (IGF)-1[96,97] vs. catabolic factors such as myostatin,[98] TNF-α[99], interleukins[99] factors modulate apoptosis, inflammation, and protein synthesis and serve to reinforce the loss of SM mass.[95] Apoptosis has been detected in the SM of patients with HF and its presence has been shown to be negatively correlated with peak VO_2, length of illness and SM atrophy[100]. Atrophy is associated with increased SNS activation and increased levels of angiotensin II[101-103], which lead to vasoconstriction and reduced O_2 delivery. Increased angiotensin II and oxidative stress coupled with reduced IGF-1 concentration mediate SM inflammation. [92] This negative interaction between atrophy and inflammation is not exclusive to HF but is also associated with aging, deconditioning, diabetes, obesity,

chronic pulmonary disease, and chronic kidney disease [92]. Thus the progression of changes in the structure of SM may be driven by and related to the presence of one of several chronic conditions.

A consistent morphological SM change identified in muscle biopsies of patients with HF and later confirmed using 31^{P} magnetic resonance spectroscopy (MRS) is a shift in muscle fiber type from long endurance type I fibers (aerobic, oxidative) toward the easily fatigued, type IIb (anaerobic, glycolytic)[90,91,104] and a reduced capillary to fiber ratio[105]. Mancini et al.[90] and Lipkin et al.[104] were among the first to report a significant relationship between fiber type and peak VO_2 suggesting that a shift in fiber type might promote exercise intolerance. These fiber changes promote fatigue-related processes and incur an O_2 deficit in the working SM resulting in glyconeolysis and premature acidosis,[106] occurring independent of changes in blood flow. Furthermore, an augmented blood flow does not delay the onset of anaerobic metabolism or increase exercise capacity[107]. Taken together this suggests that SM myopathy in HF is metabolic in origin.

Alterations in Skeletal Muscle Metabolism

In addition to structural changes, intrinsic metabolic abnormalities such a decreased number of functional mitochondria[105], decreased capillary density[108], reduced production and release of endothelial derived vasodilator factors[109] and decreased oxidative enzymes affect the oxidative capacity of SM during HF. These changes result in early anaerobic metabolism and muscle fatigue. MRS studies have been used to examine phosphocreatine (PCr) and adenosine tri-phosphate (ATP) metabolism which showed that during exercise patients with HF deplete their energy stores at a lower O_2 capacity than age matched controls and have a lengthened recovery from exercise.[110] Recently, interest has focused on bioenergetics and the effects inflammatory cytokines and ROS as mediators of SM dysfunction and promoters of oxidative stress.[111]

Alterations in Skeletal Muscle Function

Reduced exercise capacity and some degree of muscle wasting is common even in mild HF.[112] Loss of leg SM mass seems to be an early event in the natural history of HF; while alterations in body composition of the arms occurs as disease progresses.[113] The pathological SM changes in HF are associated with progressive functional limitations such falls, bone fractures[114], disability and frailty.[95]

In patients with HF the working SM must compete with the demands of the respiratory muscles for a share of an already diminished Q and overcome amplified SNS, neurohormonal and reflex driven vasoconstriction. In addition, mechanosensitive and metabosensitive afferents within the contracting SM increase global sympathetic activation. In turn, lower VO_2, slower O_2 uptake and microvascular changes produce metabolites which accumulate and stimulate these afferents **(Figure 2).**[115] Skeletal muscles sense tension, displacement and fatigue via tendon organs, muscle spindles, joint receptors and small nerve endings. It is the sensory function of SM that likely contribute to the symptoms of dyspnea and fatigue via the exercise pressor reflex[116]. It is clear that SM myopathy may be triggered by alterations in central hemodynamics but becomes an independent phenomenon in HF[111].

Although the majority of evidence related to SM changes during HF has been established from studies in animal models and clinical studies of patients with HF and a reduced EF, many of the SM abnormalities discussed are not exclusive to HFrEF. Rather the same derangements occur in the co-morbid conditions associated with HFrEF (e.g., diabetes). Thus it is likely that patients with HFpEF are subject to the same SM abnormalities. Further investigation of these changes in HFpEF is warranted.

Physical deconditioning may contribute but intrinsic changes in SM induced by chronic hypoperfusion are important factors in exercise intolerance. These factors include SM atrophy, poor O_2 utilization, and delayed recovery of SM after submaximal exercise. It may be that the extent of atrophy and inflammation and the corresponding cross talk among these factors that mediate the mechanisms underlying exercise intolerance. However, unlike limb musculature which is underused, as the HF

syndrome progresses, the respiratory musculature are exposed to an ever increasing workload as lung compliance decreases.

Respiratory System Contributions to Exercise Intolerance

Respiratory contributions have been shown to limit exercise in patients with HF. The manner by which the respiratory system limits exercise is due to abnormalities in ventilation, perfusion, or both ventilation and perfusion.[117-121] However, the etiology of these abnormalities appears to be due to impairments in pulmonary function, respiratory muscle strength and endurance, as well as impairments in tissue perfusion both centrally and peripherally.[118,119,122-124] The effects of each of these impairments on exercise tolerance will be described within the context of ventilation, perfusion, and ventilation-perfusion abnormalities. Two key pathophysiologic consequences of ventilation-perfusion abnormalities in HF are a steep minute ventilation to carbon dioxide production (VE/VCO_2) slope and exercise oscillatory ventilation (EOV).[121,122,125,126] The VE/VCO_2 slope is captured during submaximal or maximal exercise with a slope greater than 30 associated with inefficient ventilation and EOV is usually identified during exercise, but can occur at rest and is identified as 3 or more oscillatory fluctuations in VE at a minimal average amplitude of 5 L/min persisting for a particular percentage of time during exercise.[121,125,126] The pathophysiological basis for a steep VE/VCO_2 slope and EOV will be discussed since both are key reasons why the respiratory system is a major factor limiting exercise and functional performance in patients with HF.[121,122,125,126] Furthermore, EOV will be used as a conceptual model highlighting the interrelatedness of cardiorespiratory and neurohormonal activity in the failing heart and providing the mechanisms by which the respiratory system limits exercise in HF.

Ventilation Abnormalities

Abnormalities in ventilation include those listed in **Box 1**. The key factors limiting ventilation in HF include pulmonary edema, loss of elastic recoil of the lungs, ascities, and inspiratory muscle

weakness.[117-119,127] Thus, in view of these key factors, the abnormalities in ventilation in HF appear to be mostly restrictive in origin. In fact, the ventilatory response during exercise in HF is more typical of a restrictive lung disorder in view of (1) decreased tidal volume, end-tidal carbon dioxide, peak VO_2, and tidal volume to ventilation ratio (VT/VE) and (2) increased respiratory rate, VE, peak dead space ventilation to tidal volume ratio (VD/VT), ventilation to VO_2 ratio (VE/VO_2), and the VE/VCO_2 slope.[123,125,128] In HF, a steep VE/VCO_2 slope above 30 is identified by substantially greater VE for a given level of VCO_2 and thus reflects inefficient ventilation.[125] Nonetheless, pulmonary function tests of patients with HF reveal restrictive, obstructive, and combined restrictive and obstructive patterns.[120,129] It is likely that these pulmonary function patterns reflect lifestyle, the pathophysiological consequences of HF, and the key factors limiting ventilation.[120,129] Of note is that non-invasive positive pressure ventilation (NIPPV) is a key modality in the management of patients with acute HF exacerbations highlighting the manner by which all of the above factors likely contribute to functional and exercise limitations in HF.[124] In fact, recent research has revealed that NIPPV provided to patients with stable HF during exercise can improve not only ventilation, but also cardiovascular performance.[130]

A seminal paper investigating the influence of pulmonary edema on exercise tolerance revealed that even sub-clinical fluid retention can significantly impair exercise ability, but that targeted therapy via diuresis alone can significantly increase exercise tolerance with improvement in symptoms and cardiorespiratory performance. Diuresis of 4.5 ±2.2 kg over 4 ±2 days to a resting right atrial pressure of 6 ±4 mm Hg and wedge pressure of 19 ±7 mm Hg increased exercise duration from 9.2 ±4.2 to 12.5 ±4.7 minutes which was associated with significant improvements in ventilation, lactate levels, and dyspnea.[117]

The above results support the likelihood of alveolar gas diffusion abnormalities limiting exercise tolerance in HF.[117] Furthermore, important correlations have been found to support the role of alveolar gas diffusion abnormalities in limiting exercise in HF despite a lack of significant arterial oxygen desaturation during exercise including significant correlations between (1) baseline diffusion capacity for carbon monoxide (DLCO) and peak VO_2, (2) alveolar-capillary membrane conductance and the VE/VCO_2, and (3) the improvement in DLCO and peak VO_2 after enalapril treatment.[118]

The most likely reason for the lack of arterial oxygen desaturation during exercise in patients with HF is due to the recruitment of alveolar-capillary membrane conductance areas to compensate for decreased pulmonary perfusion. Such recruitment suggests that the alveolar-capillary membrane is pliable, at least in less advanced HF, and accommodates to imposed demands which is important in regard to therapeutic efforts to improve exercise tolerance in patients with HF . Therapeutic efforts that promote such recruitment may improve arterial oxygenation despite poor pulmonary perfusion.[118]

Inspiratory muscle weakness is another key factor responsible for abnormal ventilation in HF.[119,127] A substantial body of literature has identified the relationship that inspiratory muscle weakness has to symptoms, exercise intolerance, inefficient ventilation, and abnormal cardiopulmonary exercise testing (CPX) results.[119,127] Poor inspiratory muscle endurance is also a key factor responsible for abnormal ventilation in HF, but has an even greater potential to limit exercise tolerance than inspiratory muscle weakness because respiratory muscle fatigue stimulates the respiratory metaboreflex.[127,128,131] The respiratory metaboreflex is stimulated by respiratory muscle fatigue and as outlined in **Figure 2** includes SNS activation and vasoconstriction in resting and exercising limbs to shunt oxygenated blood to fatiguing respiratory muscles providing exercising limb muscles with less available oxygenated blood

and limiting exercise tolerance.[128] It is important to note that expiratory muscle fatigue also has the capacity to contribute to the respiratory metaboreflex.[128]

A substantial literature has also identified the favorable role inspiratory muscle training (IMT) may have in patients with HF who have inspiratory muscle weakness and poor inspiratory muscle endurance.[128] In fact, patients with HF who have maximal inspiratory strength that is ≤ 75% of the predicted value appear to receive the greatest benefit from IMT with improvements in exercise and functional performance as well as many CPX results.[128] The role of expiratory muscle training in HF has received limited investigation despite the fact that expiratory muscle strength is poor in HF and is related to dyspnea in HF,[119] but preliminary findings on improving exercise and functional performance appear promising.[128]

Perfusion Abnormalities

Abnormalities in perfusion include those listed in **Box 1**. The key factors limiting perfusion in HF include poor right ventricular performance and elevated pulmonary artery pressure as well as pulmonary vascular resistance (PVR).[118,120,121] An elegant study examined the influence of right ventricular performance, the VE/VCO_2 slope, and PVR on right ventricular oxidative metabolism via positron emission tomography and found that the VE/VCO_2 slope was significantly correlated to right ventricular oxidative metabolism ($r=0.61$; $p=0.003$).[121] Additionally, right ventricular oxidative metabolism was significantly greater in patients with a VE/VCO_2 slope ≥ 34 compared to patients with a VE/VCO_2 slope < 34 (0.93 ± 0.16 versus 0.77 ± 0.16; $p=0.04$).[121] Thus, PVR appears to be a major determinant of ventilatory inefficiency in patients with HF.[118,121,123,125] Interventions aimed at improving PVR are likely to improve right ventricular performance and metabolism as well as the efficiency of ventilation all of which are likely to improve functional and exercise performance.[118,121,123]

Ventilation-Perfusion Abnormalities

Ventilation-Perfusion abnormalities in HF are due to the above factors as well as several other key potential factors including ventricular asynchrony, cardiac arrhythmias, and loss of viable and elastic lung tissue as in advanced HF. All of the above factors contribute to a ventilation-perfusion mismatch of varying degrees.

The influence of cardiac arrhythmias and ventricular asynchrony on ventilation-perfusion matching in patients with HF was keenly investigated via biventricular cardiac resynchronization therapy (CRT).[126] Ventilatory, cardiovascular, metabolic, and symptomatic parameters were studied in a randomized, double blind, crossover study by turning on and off the CRT modality. Ventilatory, cardiovascular, metabolic, and symptomatic parameters improved significantly with CRT "on" rather than "off" and was reflected by greater work, peak VO_2, oxygen pulse, and ventilatory threshold as well as a less steep VE/VCO_2 slope and decreased operating lung volumes expressed as a percentage of predicted total lung capacity as ventilation increased during incremental CPX.[126]

The restrictive constraints on tidal volume during incremental exercise in HF appear to be significantly reduced by CRT by favorably increasing lung volumes as shown in **Figure 3**. **Figure 3** shows that CRT increases lung volumes from both above (inspiratory reserve volume) and below (inspiratory capacity) and subsequently appears to improve all of the aforementioned CPX measures as well as symptoms throughout incremental exercise.[126] Thus, exercise tolerance can be markedly improved by modalities such as CRT which optimize the relationships between the cardiac and pulmonary systems, but also demonstrate the role of the respiratory system in limiting exercise in HF.[126]

Exercise Oscillatory Ventilation

The pathophysiologic mechanisms leading to EOV is not completely understood. In patients with HF, EOV has been hypothetically linked to: 1) instability in the feedback systems that control ventilation, stemming from an increased circulation time; 2) increased chemosensitivity to the partial pressure in CO_2 and O_2 in arterial blood; 3) impaired baroreflex activity; and 4) abnormally increased pulmonary pressures with right ventricle to pulmonary circulation uncoupling.[15] **Figure 4** presents a depiction of EOV and highlights the interrelatedness of the cardiorespiratory and neurohumoral systems as well as the method by which the respiratory system can be a major determinant of exercise and functional performance. This conceptual model provides a framework to understand and manage the factors responsible for EOV as well as respiratory limits to exercise.

Summary

The function and compensatory mechanisms of the heart and lungs are intimately related and linked since they both supply oxygen to the body and are coordinated by the autonomic nervous system. Because of the intimate and linked functional and compensatory relationships it is often difficult to identify the primary determinant limiting exercise in HF, but from the above review it is apparent that the vascular, SM, and respiratory systems contribute substantially to limitations in exercise and functional performance during HF. Future therapeutic strategies are needed to improve exercise tolerance by targeting the integrated functions of these systems.

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Figure Legends:

Figure 1. Conceptual Model of the Possible Contributors to Exercise Intolerance in Heart Failure

Figure 2. The Respiratory Metaboreflex. From Cahalin LP et al. *Expert Rev. Cardiovasc Ther* 2013; 11: 161-177, with permission).

Figure 3. The Effect of Cardiac Resynchronization Therapy (CRT) on Lung Volumes in Heart Failure. Lung volumes are expressed as %TLC as V_E increases during cycle exercise in patients with HF. CRT is represented by the closed circles. Off CRT is represented by the open circles. TLC: total lung capacity, $V_{T:}$ tidal volume, IC: Inspiratory capacity, From: Laveneziana P et al. *J Appl Physiol* 2009; 106: 1574-1583, with permission).

Figure 4. The Muscle Hypothesis of Chronic Heart Failure and Oscillatory Ventilation. LV: left ventricle. From: M Piepoli, P Ponikowski, M et al. *European Heart Journal* 1999; 20: 946-953, with permission.

Box-1: Summary of the System Contributors to Exercise Intolerance in HF

1. **Cardiac Contributors**

   ↓ Cardiac Reserve

   ↓ End-systolic volume

   ↓ or ↔ End-diastolic volume

   ↑ Left ventricular filling pressures

   Failure of the Starling mechanism

   ↓ Left atrial function

   Left and/or right ventricular remodeling

   ↑ Sympathetic outflow/autonomic dysfunction

   Chronotropic incompetence

   Altered cardiomyocyte physiology/calcium handling

2. **Vascular Contributors**

   ↓ Endothelial Function

   ↓ eNOS protein expression and activity

   ↓ Limb blood flow

   ↑ Arterial Stiffness

   ↑ Sympathetic Activity

   ↑ Oxidative stress

3. **Skeletal Muscle Contributors**

   Muscle atrophy with a shift in muscle fiber type

   ↓ Muscle bulk and fiber cross-sectional area

   ↓ mitochondria size and function

   ↓ capillary density

Increased intra-cellular acidosis

↓ phosphocreatine and glycogen content

Impaired calcium homeostasis

↓ Insulin-like growth factor-1 expression

4. **Respiratory Contributors**

Pulmonary edema

↓ Elastic recoil of the lungs

Ascities

Inspiratory muscle weakness

↓ Right ventricular performance

↑ Pulmonary artery pressure and vascular resistance

Ventilation-perfusion mismatch

Ventricular asynchrony

Cardiac arrhythmias

Loss of viable and elastic lung tissue