Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction
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Approximately half of patients with heart failure (HF) have a preserved ejection fraction (HFpEF), and with the changing age and comorbidity characteristics in the adult population, this number is growing rapidly. The defining symptom of HFpEF is exercise intolerance, but the specific mechanisms causing this common symptom remain debated and inadequately understood. Although diastolic dysfunction was previously considered to be the sole contributor to exercise limitation, recent studies have identified the importance of ventricular systolic, chronotropic, vascular, endothelial and peripheral factors that all contribute in a complex and highly integrated fashion to produce the signs and symptoms of HF. This review will explore the mechanisms underlying objective and subjective exercise intolerance in patients with HFpEF.  (Circ J 2014; 78: 20–32)

Key Words: Aging; Diastolic dysfunction; Exercise; Heart failure; Hemodynamics

Review of Basic Hemodynamics
Cardiovascular hemodynamics, reviewed in detail elsewhere, are fundamentally dictated by cardiac-specific properties, autonomic tone, and external forces that modulate cardiovascular performance (afterload and preload). Afterload can be broadly defined as the forces that oppose cardiac ejection. Afterload is often incorrectly conceptualized as arterial blood pressure, but is more accurately reflected as systolic wall stress or aortic input impedance. The use of wall stress is problematic because it is potently affected by ventricular properties, as wall stress is directly related to chamber dimension and inversely to wall thickness. The ideal measure of afterload would be completely independent of the ventricle. Aortic input impedance provides a measure of the total vascular opposition to ejection that is independent of the heart, but is cumbersome to use because it is expressed in the frequency domain and is therefore difficult to use with time-domain measures of ventricular function. Effective arterial elastance (Ea) is an alternative time-domain measure that incorporates both mean resistive and oscillatory components of arterial load and is defined by the ratio of end-systolic arterial pressure to stroke volume (SV). Ea is directly related to mean systemic vascular resistance (SVR) and heart rate (HR) and inversely related to total arterial compliance.

Preload can be defined by the magnitude of distention or “stretching” of ventricular myocytes prior to contraction, which dictates the extent of myofiber shortening in the subsequent contraction. Preload is often erroneously conceptualized in practice as being equivalent to LV filling pressures (LVP), when in fact, the most accurate measure of LV preload is chamber volume prior to the onset of isovolumetric contraction.

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(LV end-diastolic volume, LVEDV). Filling pressures are related to preload by the compliance properties of the heart and the kinetics of relaxation, especially at higher HRs. Preload is affected by venous return, diastolic function, the right heart, and the pericardium.

The ventricle can be characterized by its capacity to eject blood (systolic function) and to fill with blood (diastolic function). Systolic function reflects the heart’s pumping ability and is most often measured clinically by the EF. However, EF varies directly with preload and inversely with afterload (as is true of all measures of systolic shortening or thickening). Alternative measures that account for both preload and afterload, such as LV end-systolic elastance (Ees), stress-corrected fractional shortening, or preload-recruitable stroke work are more specific measures of LV chamber contractility that are independent of load.

Diastolic function is often dichotomized into “active” and “passive” functions, though these distinctions are arbitrary and there is considerable overlap between them. “Active” function generally refers to early diastolic processes involved in crossbridge detachment, calcium reuptake and rapid pressure decay during isovolumic relaxation and early filling. Active diastolic function is usually measured by the time constant of early diastolic pressure decay (τ) or the velocity/extent of tissue motion during early filling. Passive diastolic function generally refers to the mechanical properties of heart muscle that dictate the degree of pressure elevation to achieve a given preload volume (end-diastolic chamber elastance or Eed, an approximation for the slope of the end-diastolic pressure-volume relationship). Eed is determined by stiffness within the cardiac myocytes as well as the extracellular matrix, chamber, and pericardium.

If systolic and diastolic ventricular properties are held constant, an isolated increase in afterload will increase blood pressure and decrease SV, whereas an isolated increase in preload will increase blood pressure and increase SV. The converse effects will occur with reductions in afterload and preload. Autonomic tone potently influences cardiovascular status: increases in sympathetic stimulation peripherally enhance venous return, contractility, chronotropy andlusitropy, whereas increases in parasympathetic tone reduce HR and vascular resistance. Ventricular reserve function reflects the heart’s capacity to deal with the increases in preload and afterload that accompany physiologic stresses such as exercise. As shall be discussed, reserve capacity is often dissonant with resting, steady state cardiovascular function, particularly in patients with HFpEF.

### Normal Exercise Physiology

To cope with the increased metabolic demands of physical exercise, the human body relies upon complex interactions among the heart, lungs, vasculature, endothelium, skeletal muscle and autonomic nervous system. Exercise capacity is most often quantified as the peak oxygen consumption (peak VO₂) achieved during maximal effort exercise. According to the Fick principle, VO₂ is defined by the product of cardiac output (Qₑ) and arterial-venous oxygen content difference (AVVo2diff). In normal men, VO₂ increases 7.7-fold during maximal exercise, achieved by a 3.1-fold increase in Qₑ and 2.5-fold increase in AVO2diff. Cardiac output is equal to the product of SV and HR, whereas AVO2diff is determined by the abilities to oxygenate blood in the lungs, transport O₂ to tissues bound to hemoglobin, and then distribute, extract and utilize O₂ in exercising muscle. The variable that “drives” increases in Qₑ with exertion is, not surprisingly, metabolic demand for O₂, and studies dating back over 50 years have shown that in general, for each 1 ml increase in VO₂, there is an approximately 6 ml increase in Qₑ in healthy humans.⁵⁰,⁵¹

SV increases by approximately 40% during upright exercise, owing to both augmentation in LVEDV and reduction in LV end-diastolic volume (ESV). Increases in RV EDV occur in response to enhanced venous return mediated by muscle and ventilatory pumps, and possibly dynamic reductions in blood volume in the large-capacity splanchic veins. This increase in venous return to the thorax during early exercise is optimally coupled to 2 compliant ventricles that can accommodate increases in EDV without excessive rises in ventricular filling pressure (end-diastolic pressures, EDP). Net ventricular chamber compliance (change in volume per change in pressure) is related to chamber volumes as well to factors within the cardiac myocyte (eg, cytosolic calcium levels, titin phosphorylation and isomyotype expression), the extracellular matrix (collagen content and cross-linking), the right heart and the pericardium. Increases in EDV lead to increased stretch of cardiac myocytes that serves to enhance the force of contraction via the Frank-Starling mechanism. To allow the ventricle to fill to a larger EDV in a shorter interval of time, without pathologic increases in EDP, there is exercise-induced enhancement in early diastolic relaxation, suction and untwist that is mediated predominantly by adrenergic stimulation. Recent research indicates that LV chamber stiffness can be dynamically reduced by cyclic adenosine monophosphate- (cAMP) and cyclic guanosine monophosphate- (cGMP) dependent phosphorylation of macromolecules in the cardiac myocyte, such as titin, though it is unknown if this protein phosphorylation affects elastance (stiffness) acutely during exercise. Protein kinase C also phosphorylates titin, but in contrast to the cAMP- and cGMP-dependent pathways, PKC phosphorylation increases stiffness. Titin affects chamber stiffness via additional phosphorylation-independent mechanisms such as variable expression ratios between the more compliant (N2B2A) and Stiff (N2B) titin isoforms as well oxidation of N2B spring elements.

To achieve adequate filling of the LV, there must be sufficient augmentation of RV ejection during exercise. This is achieved via RV contractile reserve as well as by pulmonary artery (PA) vasodilation. Owing to the high compliance and low resistance in the pulmonary vasculature, normal individuals accommodate large increases in pulmonary cardiac output (Qₑ) without significant increase in PA pressure. However, recent studies have suggested that at least mild to moderate increases in PA pressure during exercise may be part of normal aging, particularly above the age of 50.⁵⁹

Although EDV may increase by 20–40%, this reserve becomes exhausted quite early on during the course of exercise, and further increases in SV must be mediated by more vigorous emptying of the heart (reduction in ESV). This is achieved by increases in contractility and enhanced arterial vasodilation. Depending on the parameter used to assess it, LV contractility increases 1–3-fold during exercise.⁵¹ There is also vasorelaxation, mediated by muscular arteriolar dilation, endothelium-dependent dilation and reduction in mean SVR. However, total arterial afterload, expressed by effective Ea, increases at maximal exercise. This is because increases in HR and decreases in compliance exceed the reduction in SVR at peak exertion. The coupling of the heart to the vasculature can be expressed by the ratio of Ea to Ees, a load-independent measure of contractility.⁴⁰ This coupling ratio (Ea/Ees) varies inversely with EF and drops significantly during exercise to...
allow for greater ejection capacity.

SV recruitment typically plateaus during exertion at approximately 50% peak VO₂, and further increases in Qₑ are achieved purely by HR. The rapid increase in HR from rest to approximately 100 beats/min is mediated by acute withdrawal of parasympathetic tone; further increases are mediated by increased sympathetic outflow. The dominant contributor to the age-related drop in maximal Qₑ during exercise is loss of chronotropic reserve.

Enhanced peripheral O₂ distribution, utilization and extraction (ie, AVODiff reserve) during exercise plays an equally important role as Qₑ reserve. Although the heart increases its output, this enhanced flow needs to be matched to tissues where perfusion is most needed, which is achieved by regional vasodilation in skeletal and cardiac muscle and vasoconstriction in non-exercising regions such as the skin, splanchnic beds, and kidneys. The importance of the latter is appreciated by considering that when fully dilated, the body’s blood vessels can hold over 20L of blood (4-fold greater than the usual blood volume), meaning that without regional vasoconstriction during exercise, systemic hypotension would routinely develop. The capacity of the vasculature to rapidly dilate or constrict allows for redistribution of blood volume and flow to meet metabolic requirements while optimizing blood pressure to maintain perfusion. Many of these changes in local perfusion are regulated by central neural command, but distribution of flow is also importantly regulated at the tissue level by factors generated by contracting skeletal muscle. Local decreases in pH as well as increases in potassium, adenosine diphosphate, carbon dioxide, and temperature serve to dilate arterioles and precapillary sphincters to optimally couple delivery of blood flow to meeting local demands. Among the local factors generated, elaboration of nitric oxide (NO) plays a critically important role in enhancing regional blood flow during stress.

Chemoreceptors and metaboreceptors located within muscle and vasculature provide further neural feedback that modulates central efferent autonomic output and may contribute to symptoms of dyspnea and fatigue.
Pathophysiology of Exercise Intolerance in HFpEF

Diastolic Limitations

Diastolic dysfunction remains fundamental to HFpEF and is the most richly studied component of the pathophysiology. In the first study to examine the hemodynamic changes during exercise in HFpEF, Kitzman et al used nuclear scintigraphy to assess LV volumes during right heart catheterization of 7 HFpEF patients and 10 age-matched controls performing maximal effort upright exercise. They observed markedly depressed peak VO2 in the HFpEF patients, which was related predominantly to an inability to enhance SV and EDV. Despite the flat EDV response, patients developed marked increases in EDP (estimated as the pulmonary capillary wedge pressure, PCWP), leading the authors to conclude that exercise intolerance in HFpEF is related predominantly to failure of the Frank-Starling mechanism. However, more recent studies have questioned whether the increase in EDP with exercise is truly impaired in HFpEF. Borlaug et al performed maximal effort exercise testing with simultaneous nuclear scintigraphy in HFpEF patients compared with closely matched aged hypertensive controls, and observed no difference in the ability to recruit EDV during exercise. There was no correlation between the change in EDP with exercise and peak VO2 in that study, further questioning the contributory role of reduced aerobic capacity. A more recent study using echocardiography to assess LV volumes noted a slightly greater increase in EDV with exercise in HFpEF patients as compared to controls. Thus, despite the common presence of diastolic dysfunction, it does not appear that exercise limitation in HFpEF is related to an inability to adequately fill the LV to a large enough EDV.

However, despite apparent preservation of EDV reserve, there is compelling evidence for failure of the Frank-Starling mechanism (the ability to translate an increase in filling pressure to an increase in cardiac ejection) in HFpEF. Shibata et al observed that the increase in SV relative to beat-to-beat changes in LV end-diastolic pressure (LVEDP: estimated by PA diastolic pressure) was impaired in HFpEF patients compared to age-matched controls. In a separate study, Abudiab et al noted that for any increase in LVEDP, the increase in cardiac output was markedly attenuated in patients with HFpEF compared to controls. 

Clinically, this failure of the Frank-Starling reserve is most clearly manifest as an elevation in LVFP, and recent studies have provided insight into the pathogenesis of this process. Westermann et al performed conductance catheter analysis in 70 HFpEF patients and 20 controls, and observed both prolonged relaxation and increased diastolic elastance. Although elastance did not change during isometric handgrip, filling pressures increased as would be predicted by the upward shift in the resting LV diastolic pressure-volume relationship. In another invasive exercise study, Borlaug et al measured LV pressures using high-fidelity micromanometer catheters with simultaneous echocardiography to determine LV volumes at rest and during dynamic supine exercise in patients with HFpEF. LV diastolic pressures increased by approximately 50% with exercise (P<0.0001), despite a trend towards a re-

Figure 2. Filling pressures and pulmonary artery (PA) pressures during exercise in early heart failure with preserved ejection fraction (HFpEF). (A) Despite normal resting pulmonary capillary wedge pressures (PCWP), patients with early-stage HFpEF develop a dramatic elevation in PCWP with even 1 min of low level (20 Watts) exercise, that rapidly returns to baseline values with cessation of exercise. (B) This increase in PCWP is secondary to exercise-induced elevation in LV end-diastolic pressure (LVEDP) in HFpEF and is coupled with secondary, passive elevation in PA pressures (C), causing exercise-induced PA hypertension. (Adapted with permission from Borlaug et al.)
who are clinically euvoletic, with normal resting hemodynamics and normal B-type natriuretic peptide (BNP) levels. The increase in LVEDP during exercise in HFpEF is extraordinarily rapid, occurring in the first minute at low workload, and mercurial, with pressures rapidly returning to normal almost immediately upon cessation of activity (Figure 2). This intermittent nature of the filling pressure elevation confounds treatment and also likely explains why BNP levels are frequently normal in HFpEF.

Abnormal patterns of gas exchange correlate with the kinetics of elevated filling pressures in patients with HFpEF undergoing exercise during cardiac catheterization, providing further insight into the nature of expired gas abnormalities observed during metabolic stress testing. In a noninvasive echocardiographic exercise study, Tan et al found that patients with HFpEF displayed lower tissue Doppler early diastolic (E') velocities at rest coupled with inadequate enhancement in E' during exercise. Similar impairments in E' reserve have been reported in response to dobutamine infusion in HFpEF. In addition to relaxation, E' velocity is determined by left atrial pressure at the mitral valve.

Figure 3. Contractile reserve limitations during exercise in heart failure with preserved ejection fraction (HFpEF). Bar graphs show the changes from baseline to 20 Watts of workload in preload-recruitable stroke work (PRSW, A), end systolic elastance (Ees, B), and peak power index (PWR/EDV) in healthy controls (blue), asymptomatic hypertensive patients (HTN, green) and HFpEF patients (red). Even at low level submaximal workload, there is substantial systolic reserve limitation in the HFpEF patients when using these load-independent measures. (D) The ability to enhance contractility tightly correlates with exercise capacity (peak VO₂), supporting a mechanistic contribution. (Adapted with permission from Borlaug et al.)
Exercise Intolerance in HFpEF

Studies have shown that despite overall preservation of EF, patients with HFpEF display subtle but significant abnormalities in chamber and myocardial contractility, as well as impairments in regional deformation as detected by tissue Doppler and strain-based imaging techniques. In addition, although the resting EF is normal, the exercise-induced enhancement in EF is impaired in patients with HFpEF when compared to matched controls. Impaired EF reserve could be caused by afterload mismatch or impaired contractile reserve, and although there is clearly evidence of vascular stiffening and abnormal vasorelaxation in HFpEF, Borlaug et al used load-independent measures to show that contractile reserve is markedly impaired in HFpEF patients compared to age-matched healthy and hypertensive controls, even at low submaximal matched workloads (Figure 3). In their study, the magnitude of contractile response directly correlated with peak VO2 (Figure 3D), further supporting a role for systolic reserve dysfunction in the exercise intolerance in HFpEF.

**Systolic Limitations**

Although EF is the measure that is used most often clinically to assess systolic function, it is a rather poor measure of LV contractility, because of its high load-dependence. Numerous studies have shown that despite overall preservation of EF, patients with HFpEF display subtle but significant abnormalities in chamber and myocardial contractility, as well as impairments in regional deformation as detected by tissue Doppler and strain-based imaging techniques. In addition, although the resting EF is normal, the exercise-induced enhancement in EF is impaired in patients with HFpEF when compared to matched controls. Impaired EF reserve could be caused by afterload mismatch or impaired contractile reserve, and although there is clearly evidence of vascular stiffening and abnormal vasorelaxation in HFpEF, Borlaug et al used load-independent measures to show that contractile reserve is markedly impaired in HFpEF patients compared to age-matched healthy and hypertensive controls, even at low submaximal matched workloads (Figure 3). In their study, the magnitude of contractile response directly correlated with peak VO2 (Figure 3D), further supporting a role for systolic reserve dysfunction in the exercise intolerance in HFpEF.
Similar impairments in systolic reserve in HFrEF have been described with dobutamine infusion \cite{17,19} and rapid pacing \cite{57} in HFrEF patients, though not all studies have observed systolic limitations. \cite{20,48} Even subtle impairment of contractility at rest may indicate marked limitations in reserve, which may explain why impaired resting myocardial contractility (despite normal EF) predicts increased mortality in HFrEF. \cite{12} Systolic reserve limitation in HFrEF affects diastole as well, because the ability to contract to smaller LV volumes at end-systole enhances the recoil and suction forces during early diastole, \cite{52} which are also known to be impaired in HFrEF. \cite{14,58}

**Vascular Stiffening and Dysfunction**

In addition to impaired contractile reserve, inadequate vasodilation appears to contribute to the inability to reduce ESV in HFrEF. Borlaug et al first reported attenuated reductions in mean SVR during matched and peak exercise in HFrEF, \cite{10} and most, \cite{15,49,50,55,59} though not all \cite{18} subsequent studies have corroborated this finding. In another HFrEF population, Borlaug et al performed direct assessment of peripheral blood flow during exercise using a finger-tip plethysmographic device and observed impaired increases in digital flow in HFrEF patients compared to hypertensive and non-hypertensive controls, providing further evidence of inadequate vasodilation. \cite{15} The inability to adequately dilate, coupled with the inability to enhance contractility, leads to dynamic abnormalities in ventricular-arterial coupling with exercise in HFrEF. \cite{13,15,59}

Central and conduit vessel stiffening is common in HFrEF and contributes to exercise limitation and blood pressure lability. \cite{59,62} Beyond vascular stiffening, the mechanisms for abnormal exercise vasodilation remain unclear. Borlaug et al reported that HFrEF patients commonly display endothelial dysfunction, and the extent of dysfunction directly correlated with greater symptoms of dyspnea and fatigue during submaximal exercise and inversely correlated with peak VO\textsubscript{2} in HFrEF (Figure 4). \cite{15} Recently, Akiyama et al reported that the presence of endothelial function predicts increased risk of HF hospitalization in patients with HFrEF. \cite{63} In an elegant study, Guazzi et al administered the phosphodiesterase inhibitor sildenafil to patients with HFrEF, and noted improvements in endothelial function that closely paralleled decreases in ventricular contractility, supporting the notion that there is cross-talk between microvascular function in skeletal muscle and symptoms of effort intolerance. \cite{44} However, not all studies have observed endothelial dysfunction in HFrEF. Haykowsky et al observed no difference in endothelial function in HFrEF.

**Figure 5.** Chronotropic incompetence in heart failure with preserved ejection fraction (HFrEF). (A) Compared with controls (red), patients with HFrEF (black) display markedly lower increases in heart rate (\(\Delta HR\)) during maximal effort exercise. (B) The increase in HR with exercise correlates with exercise capacity (peak VO\textsubscript{2}) in both groups (bivariate \(P<0.0001\)), but for any increase in VO\textsubscript{2}, there was less enhancement of HR in HFrEF patients compared to controls. This difference persisted after adjusting for age and \(\beta\)-blocker use. Heart rate acceleration during the onset of exercise (C) and deceleration during early recovery (D) were abnormal in HFrEF compared to controls. (Data taken from Borlaug et al.\cite{15} and Abudiab et al.\cite{23})
Exercise Intolerance in HFP EF

compared with healthy age-matched controls, or any correlation between endothelial function and peak VO2 in multivariate analysis.46 In another study, this group observed no improvements in vascular stiffness or endothelial function after 16 weeks of exercise training in HFP EF.45 This is in contrast to older studies in non-HF populations where habitual exercise has been associated with improvements in age-associated losses in endothelial function.66 Part of the discrepancy in results between various studies may be related to the methods used to assess endothelial function, which may be performed in larger conduit vessels such as the brachial or femoral arteries (as in the Haykowsky study) compared with the microvasculature (as in the Borlaug and Akiyama studies). Indeed, recent work from the Framingham group has shown significant differences in the risk factor associations and overall prevalence of endothelial dysfunction when assessed using these different methods, suggesting that they may provide distinct information regarding vascular function.57

Just as systolic dysfunction begets diastolic dysfunction by impairing elastic recoil during early diastole, vascular stiffening may also impair diastolic function.25 Increases in arterial afterload prolong relaxation, particularly in the failing heart.68 Loading sequence appears to also be important, with later-systolic afterload increases having more deleterious effects upon LV ejection and relaxation.69-71 This provides another mechanism whereby vascular stiffening and elevated afterload contribute to elevation in filling pressures observed with stress in HFP EF.60

Heart Rate and Rhythm

As discussed earlier, enhancement in HR plays a critical role in allowing for adequate Qc reserve, and several studies have identified impairments in chronotropic reserve in HFP EF (Figure 5).3,9,10,15,18,23,49,72,73 Borlaug et al observed significantly depressed peak HR in HFP EF patients compared to controls, which was coupled with abnormalities in cardioacceleration and HR recovery after cessation of exercise.10 The latter is a marker of autonomic health, which is associated with longevity, even after controlling for the presence or absence of cardiovascular diseases. Other groups have also observed impaired HR recovery in HFP EF, even when accounting for ß-blocker usage,73 and abnormal arterial baroreflex sensitivity has also been documented,10 further supporting a role for autonomic dysfunction in HFP EF. Although not all studies have observed abnormal HR reserve in HFP EF,50 it has been found to be extremely common in several large recent studies, ranging from as high as 56% to 78%.15,72 This observation, coupled with the tight correlation between HR reserve and peak VO2,9,10,15 suggests that restoration of chronotropic competence may enhance exercise capacity in HFP EF. However, increases in HR may compromise LV filling in patients with prolonged relaxation, and a recent small study reported dramatic improvements in peak VO2 after just 7 days of treatment with the negative chronotropic drug, ivabradine.74 Clearly, further research is needed regarding the management of HR responses to exercise in HFP EF patients, and a prospective trial testing the effects of rate-adaptive pacing in patients with chronotropic incompetence is currently being planned.

In addition to HR reserve, heart rhythm appears to be important in HFP EF. A recent study has shown the presence of atrial fibrillation (AF) portends greater risk of death in HFP EF patients.75 In an ancillary study from the RELAX trial, Zakeri et al demonstrated that similar HR responses to exercise, HFP EF patients with AF displayed much more severe exercise intolerance, even after adjusting for other key determinants of exercise capacity.76 Intriguingly, the presence of AF in HFP EF was found to be an independent predictor of RV dysfunction, which may additionally explain the adverse outcome and greater impairment in exercise capacity in subjects with AF.24 However, at this time it remains unclear whether AF causes the RV dysfunction or vice versa.

Right Heart, Pulmonary Vasculature and the Pericardium

Pulmonary hypertension (PH) is common in HFP EF,77 particularly during exercise,49 because downstream elevations in left heart pressures add in series with components of pressure-related resistance and Qc.22 The presence of PH increases the risk of death in HFP EF,78 and recent studies have shown that progression in pulmonary vascular disease in HFP EF is associated with a deterioration in RV function that is potently associated with adverse outcome, independent of other established predictors of mortality.24 Tedford et al have shown that increases in PCWP are associated with lower PA compliance at any given resistance, increasing the oscillatory load on the RV, and this effect occurs even acutely during exercise in patients with HFP EF.79 Because they are connected in series, inadequate RV output could contribute to exercise limitation by promoting “underfilling” of the left heart during stress. Although this phenomenon has been demonstrated in HFr EF,79 it has not been documented in patients with HFP EF.

Complicating this assessment is the fact that right-sided chamber and left atrial enlargement in HFP EF with RV failure creates the substrate for increased pericardial restraint and diastolic ventricular interaction,59 where the right heart influences the left in parallel.22 In this circumstance, left heart filling pressures may be elevated even if LVEDV is normal or reduced.81 Janicki observed that a significant number of patients with advanced HFrEF display this phenomenon of enhanced diastolic ventricular interaction during exercise, whereby PCWP and right atrial pressure increase in tandem with no further enhancement in SV, because of the restraining effects of the pericardium that prevent additional preload recruitment.82 Further study is required to determine whether this phenomenon contributes to exercise intolerance in HFP EF, or perhaps whether surgical mitigation of pericardial restraint might improve exercise capacity.

Peripheral Factors

There are numerous lines of evidence to support the notion that true maximal VO2 is limited by central (Qc) rather than peripheral (AVO2diff) determinants. These include the observations that (1) VO2max is achieved by activation of only 50% of total body muscle mass, and activation of additional muscle does not increase Qc or VO2 beyond this level, (2) when additional muscles are activated at VO2max, arterial blood pressure is maintained by vasoconstriction to exercising muscles, and (3) the capacity of skeletal muscle to consume O2 greatly exceeds what the heart can deliver.27 However, true VO2max is rarely achieved in patients with HF, and VO2max is not equivalent to what is routinely measured in practice (peak VO2).

Recently, Haykowsky et al examined the determinants of peak VO2 in patients with HFP EF and age-matched controls free of HF. Although they observed that peak VO2 was tightly correlated with both Qc and AVO2diff, in both their HFP EF and control groups, the change in AVO2diff with exercise was the strongest independent predictor of peak VO2.18 In a separate study, this group examined body composition in the same cohort and observed a decrease in the percent of lean total body and leg mass.80 Although peak VO2 increased with increasing lean mass in healthy controls, this was not observed in HFP EF...
patients, suggesting that impaired skeletal muscle perfusion or oxidative capacity might be present. An alternative possibility might be that increased Qc during exercise is inappropriately directed to non-exercising tissues, such as adipose. In a different cohort, Bhella et al. found that while Qc reserve was depressed in HFP EF (as previously demonstrated by other groups), when normalized to VO2, HFP EF patients displayed an overly exuberant increase in Qc, with markedly impaired AVO2diff reserve. Those authors proposed the provocative conclusion that exercise capacity in HFP EF is limited by premature skeletal muscle fatigue and/or by metabolic/neural signals originating in muscle that stimulate excessive Qc responses to exercise.

However, in a subsequently published, invasive study in which arterial and mixed venous O2 contents were directly measured, no differences in maximal exercise AVO2diff were observed between HFP EF patients and controls (Figure 6). Furthermore, when AVO2diff was normalized to peak VO2 achieved, it was higher rather than lower in patients with HFP EF. The authors speculated that this represents a chronic adaptation to inadequate Qc, citing the fact that with a lower Qc, there is greater time available for gas exchange in the capillaries, which may serve to counterbalance any potential abnormalities in convective and diffusive O2 transfer. In that study, for any increase in VO2, there was on average a 20% lower increase in Qc in the HFP EF patients (Figure 6), indicating that limited cardiac output reserve, rather than peripheral dysfunction, was the dominant contributor to the reduction in peak VO2. When contemplating the reasons for the divergent findings between this study and those of Haykowsky and Bhella, it is important to consider that HFP EF is a heterogeneous disease, and it is highly likely that there are subgroups of patients in whom exercise capacity is more or less constrained by central vs. peripheral mechanisms. Further efforts to subtype these categories may be helpful in the classification and individualization of treatment of HFP EF.

Regardless of the primacy of peripheral and skeletal muscle abnormalities in limiting peak VO2 in HFP EF, they could be highly viable therapeutic targets. Haykowsky et al noted that improved peak VO2 in HFP EF patients after 4 months of exercise training was predominantly related to higher AVO2diff at peak exercise, with no significant change in Qc. It may be that there is greater plasticity and potential for rejuvenation in peripheral factors such as blood flow distribution, microvascular function, capillary density, skeletal muscle function, energetic stores and mitochondrial oxidative capacity as compared with cardiac properties. Although some groups have noted improvements in the LV diastolic function of HFP EF.

Figure 6. Central vs. peripheral mechanisms of exercise impairment in heart failure with preserved ejection fraction (HFP EF). (A) Compared to controls (red), patients with HFP EF (black) display less increase in cardiac output (ΔCO) during exercise. (B) This cardiac limitation is maintained when normalizing ΔCO to metabolic demands (ΔVO2). (C) Total increases in arterial-venous O2 content differences (ΔAVO2diff) with maximal exercise were similar in HFP EF patients and controls, but when normalized to ΔVO2, there was greater reliance in the HFP EF subjects on enhanced peripheral O2 extraction and utilization (D), likely to compensate for inadequate skeletal muscle perfusion because of CO limitation. (Adapted with permission from Abudiab et al.)

Circulation Journal Vol.78, January 2014
Exercise Intolerance in HFpEF

Figure 7. Summary of mechanisms of exercise intolerance in heart failure with preserved ejection fraction (HFpEF). “Central” impairments are shown in the ovals and “peripheral” impairments in the rectangles. Arrows indicate where an abnormality directly contributes to another. Question marks indicate theoretical but unproven mechanistic relationships. See text for additional details. AVO2, arterial-venous oxygen content; β-AR, beta-adrenergoreceptor; LVFP, left ventricular filling pressures; PA, pulmonary artery; RV, right ventricle; VA, ventricular-arterial.

patients doing exercise training, a more recent study observed no changes in cardiovascular mechanics. Although the latter study (n=11) reported no change in peak VO2 with exercise training, 2 much larger randomized trials (n=64 and 46, respectively) have demonstrated fairly substantial improvements in aerobic capacity with training (2.6–3.3 ml · min⁻¹ · kg⁻¹). Other Factors

The lungs function as the first step in the transport of O2 from the external environment to the tissues for utilization, and abnormalities in ventilation or gas exchange (alveolar membrane O2 conductance, capillary blood volume, ventilation-perfusion matching) might be expected to contribute to exercise impairment in HF. Pulmonary limitations have not been considered as a significant contributor to reduced peak VO2, given the dramatic reserve capacity of the lungs, but pulmonary mechanics and gas exchange have not been adequately studied in HFpEF, and it is certainly conceivable that with acute increases in LVFP, interstitial edema develops, changing the compliance properties of the lungs, possibly leading to greater respiratory muscle fatigue that may discourage further exercise. Adequate delivery of O2 from the lungs to muscle and tissues requires hemoglobin, and anemia is common in HFpEF patients. However, a recent trial of erythropoietin-stimulating therapies failed to detect an improvement in submaximal exercise capacity (6-min walk distance) of HFpEF patients, despite a significant increase in hemoglobin while on treatment. Figure 7 summarizes the roles of multiple mechanisms in the pathogenesis of HFpEF as has been described.

Exercise Reserve, HFpEF and Normal Aging

LV diastolic stiffness increases with normal aging, and the age-related increase is greater in women than in men and correlates with increases in body mass, all consistent with the typical demographic characteristics of HFpEF: older, hypertensive, obese females. In addition, the ability to tolerate volume loading without excessive increase in LVFP decreases in older women. Given these observations, together with the foregoing findings, therapies targeting age-related LV diastolic stiffening would appear to hold promise to help improve exercise capacity and outcomes in HFpEF. Indeed, better understanding of the reasons for age-related reductions in cardiac reserve and exercise capacity may allow for the development of novel therapies to improve outcome in both HFpEF patients and the broader population of older adults without HF but with deterioration in functional capacity related to normal aging.
Conclusions and Future Directions

In summary, numerous recent studies have changed the way we conceptualize the pathophysiology of HFrEF: away from being simply a disorder of diastolic dysfunction to more of a global impairment in the multiple components of cardiovascular function39,23 and peripheral18,26 reserves, which limits the ability to cope with physiologic stresses such as exercise. Further research is required to refine our understanding, enabling more optimal treatment for patients with HFrEF. A potential area of particular interest might be rigorous phenotyping of the nature of exercise limitation in a given patient (eg, predominant diastolic vs. systolic limitation, or peripheral vs. central limitation), which may allow for more precise individualization of therapies.21,22 Clearly, better understanding the mechanisms of the age-related reductions in cardiovascular reserve from the cellular to the organ system level needs further probing, and innovative new studies have just begun to make strides in this regard.98 Given the plurality of reserve limitations noted in HFrEF, it begs the question as to whether there are overarching or unifying processes that affect the ventricle, vasculature and periphery that can be treated to improve global reserve, with possibilities including increased nitroso-oxidative stress, abnormal NO/cGMP-dependent signaling pathways,99 or tissue deposition of misfolded proteins acquired with senescence.100 Finally, although clinical trials in HF have traditionally targeted mortality and HF hospitalizations, it is time to think more globally and remember that quality of life is often just as important as quantity in patients with HFrEF. It is an inescapable fact that the number of people with HFrEF is going to increase dramatically during the next 30 years, and further studies examining the determinants and opportunities for improvement of exercise intolerance are critically important to ensure that these people can enjoy independent, productive and active lifestyles in the years to come.

Disclosures

Conflicts: None.

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Exercise Intolerance in HFpEF


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