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HEART FAILURE WITH PRESERVED EJECTION FRACTION AND SKELETAL MUSCLE PHYSIOLOGY

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Introduction

Heart failure (HF) is an enormous health problem, effecting over 5 million Americans and millions more worldwide.[1] Close to half of the patients hospitalized with HF can be categorized as having HF with preserved ejection fraction (HFpEF) previously named diastolic heart failure.[2,3] Regardless of the etiology, patients with heart failure suffer from a similar constellation of signs and symptoms including exercise intolerance, fluid accumulation and increased mortality. While there has been success at improving the morbidity and mortality of HF with reduced ejection fraction (HFrEF) through both pharmacologic and device based therapies, there have been little progress in treating HFpEF. However, recent studies have greatly increased our understanding of the pathophysiology of HFpEF. No longer a simple disease of inadequate cardiac relaxation, new data support that the primary risk factors for HFpEF also contribute to impairments in skeletal muscle physiology. In this review we will explore the varied physiologic derangements present in HFpEF, the relationship between HFpEF and aging and their effects on skeletal muscle physiology.

Epidemiology of HFpEF

The American College of Cardiology/American Heart Association defines HFpEF as a syndrome of signs and symptoms of heart failure in the setting of a resting ejection fraction >50% with no major valve disease.[4] While morbidity and mortality from most cardiovascular diseases has improved over the past 20 years, HF represents the most common Medicare hospital admission diagnosis, reflecting its high incidence in the population > 65 years of age.[5] Due in part to the advancing age of the U.S. population and improved therapies for acute cardiac disease, the prevalence of HF is projected to increase by nearly 50% over the next 20 years.[6] Currently, HFpEF is estimated to encompass roughly 50% of all heart failure patients.[1] However, this statistic may increase in the future as the prevalence of several key HFpEF risk factors–advancing age, diabetes and chronic kidney disease–are increasing as the “baby boom” generation ages. [2,3,7,8] Finally, although established therapies for systolic heart failure have reduced morbidity and mortality, the lack of understanding of basic mechanisms and heterogeneity of HFpEF in both demographics

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and comorbid conditions are likely to continue to contribute to the morbidity and mortality of HFpEF.[9]

Pathophysiology of HFpEF

Though our knowledge of HFpEF has greatly improved, it is incompletely understood how risk factors induce structural and physiologic changes present in HFpEF. Below we will review our understanding of the mechanisms that contribute to the syndrome of HFpEF.

Structural Changes: Left Ventricular Remodeling

While not universal, concentric left ventricular hypertrophy is common in HFpEF. Ventricular hypertrophy results from both pathologic cardiomyocyte hypertrophy and myocardial fibrosis, both thought to be in response to increased afterload (from hypertension) and stimulation by neurohormones (norepinephrine, angiotensin II and/or aldosterone). [10] The extent that cardiomyocytes undergo further pathologic changes including apoptosis *in-vivo* in response to elevated neurohormonal levels is unclear. [11] Myocardial infarctions, often small in size, also contribute to adverse remodeling with increased replacement fibrosis and resulting in the HFpEF phenotype. Expansion of interstitial or perivascular fibroblasts with subsequent pathologic extracellular matrix deposition contributes to all facets of cardiac dysfunction in HFpEF including chronotropic incompetence, microvascular ischemia, systolic and diastolic dysfunction. [12–14]

Defects in Diastolic Function

Normal Diastolic Physiology—To meet the metabolic demands of exertion, the heart must efficiently augment cardiac output. This goal is achieved by increases in both stroke volume and heart rate. Stroke volume is modulated by many factors including intrinsic myocardial contractility, the Frank Starling mechanism and ventricular-arterial coupling (the increase in stroke volume in response to decreased afterload).[15] Diastole influences these parameters both at rest and during exercise. In early diastole, after completion of left ventricular systole, there is elastic recoil followed by myocardial relaxation. This negative pressure first draws blood from the left atrium and then contributes to passive filling via the left atrial to left ventricular gradient. These two functions define early diastole and constitute roughly 80% of ventricular filling.[16–19] After a pause (diastasis), atrial contraction contributes the remainder of ventricular filling. At the point of maximal ventricular dilation, or preload, ventricular contraction occurs with circumferential and torsional forces, wringing out the ventricle for the next cycle to begin.

With exercise, parasympathetic withdrawal and enhanced beta-adrenergic activity increases cardiac output by promoting: 1) peripheral arterial vasodilation, 2) inotropy, 3) lusitropy (myocardial relaxation) and 4) chronotropy. The latter two are often seen as in opposition as increased heart rate decreases cardiac filling time potentially negatively influencing lusitropy. However, increased beta-adrenergic stimulation directly affects diastole by promoting upregulation of ATP-dependent calcium uptake and dynamic filament uncoupling, causing an increase in rate of relaxation and enhanced suction effect.[20] These processes ensure adequate chamber filling at increased heart rates without effecting filling

pressures. Unfortunately in HFpEF, many if not all of these important physiologic requirements are dysfunctional and partly contribute to exercise intolerance.

Diastolic Dysfunction in HFpEF—Echocardiographic evidence for impaired diastolic dysfunction has been the *sine qua non* of diagnosis in HFpEF. However, when absent, it cannot exclude a cardiac cause of a patient's exertional symptoms.[21] Furthermore, normal aging, day-to-day changes in blood pressure and volume status can significantly alter echocardiographic findings. [17,22,23] These confounding variables may influence the definition of disease and the perceived response to medical therapies in clinical studies.[24]

More sensitive and specific invasive studies have demonstrated two components to diastolic dysfunction in HFpEF: impairments in active relaxation and increased passive stiffness. The combination of these changes results in increased ventricular filling pressures during exertion. [9,20,25,26,27,28] Elevated filling pressures are then transmitted to the left atrium and pulmonary venous system, ultimately leading to symptoms of dyspnea.

Impairments in *active relaxation* are multiple and include decreased ATP-dependent cytosolic calcium uptake and myofilament uncoupling. Decreased myocyte ATP production is thought to be due to mitochondrial dysfunction induced in part by decreased NO production, increased reactive oxygen species, endothelial dysfunction, and microvascular ischemia. In addition, impaired elastic recoil from impaired systolic function and abnormal arterial pulsation contribute to worsened active relaxation.[21]

Both sarcomere dysfunction and increased extracellular matrix (ECM) contribute to increased *myocardial stiffness* in HFpEF. Pathologic sarcomeric stiffness has been attributed to abnormal titin phosphorylation and isotype switching however there is emerging evidence for abnormal contractile protein phosphorylation also influencing myocardial stiffening.[29,30] Interactions between sarcomeric and matrix components of stiffness were elegantly displayed by Zile et al using myocardial strips acquired from subjects undergoing coronary bypass grafting.[31] They stratified the groups based on the presence of hypertension (HTN), HTN + HFpEF and neither as control. Whereas myofibers from subjects with HTN were slightly stiffer than controls, the samples from patients with HTN and HFpEF were markedly stiffer. Furthermore, they determined that myofibers from HTN + HFpEF subjects had contributions of pathologic stiffness from both ECM and titin in an additive manner. They also showed a marked increase in crosslinked collagen and abnormal phosphorylation patterns of titin in the HTN + HFpEF cohort. Interestingly, the effect of collagen correlated better with elevated PCWP than changes in titin-mediated stiffness.[31]

Excess matrix (fibrosis), is both a significant contributor to increased stiffness and an independent predictor of morbidity and mortality in HFpEF.[32,33] The degree to which ECM is produced, degraded and possibly contributes to patient outcomes can also be assessed by measuring biomarkers such as procollagen type I amino-terminal peptide, procollagen type III amino-terminal peptide, and others. Elevated levels of biomarkers of ECM synthesis correlated with disease severity in I-PRESERVE, the large multicenter study determining the effect of Irbesartan for HFpEF, however after multivariable analysis biomarker levels were not significant.[34] Another, smaller study with 48 women with HFpEF (24 placebo, 24

treated with 25 mg of spironolactone) assessed the role of spironolactone and showed that levels of procollagen type III amino-terminal peptide correlated with disease severity and improvement after 6 months of treatment. [35] The mechanism that ECM deposition promotes tissue stiffness is thought to be due to production and cross-linking of high tensile strength type I and III triple helical collagen.[36] The contribution of other ECM proteins including fibronectin, laminin, proteoglycans and others to myocardial stiffness are unclear but are relevant as they promote pro-fibrotic signaling, transmit tissue strain and contribute to tissue stiffness by binding to collagen, cardiomyocytes and fibroblasts.[37,38]

Cardiac Aging

It is accepted that aging is a risk factor for HFpEF[39] and some of the changes seen in HFpEF are seen in cardiac aging. The aging heart is characterized by progressive ventricular hypertrophy in response to increased vascular stiffness. This hypertrophy occurs despite decrease in total cardiomyocyte numbers and is due to cardiomyocyte hypertrophy as well as interstitial and perivascular fibrosis.[39,40] Human and animal studies demonstrated increased cardiac collagen content with aging.[41–43] This enhanced cardiac fibrosis in the aging heart is mainly due to decreased collagen degradation in contrast to other pathologic conditions that are due to increased collagen production.[40,44] Not only there is increased collagen in the aging heart, the collagen is more cross-linked contributing to the increased stiffness.

Despite having minimal change in systolic function in the healthy older individuals, there is a clear decline in exercise tolerance with aging. In fact there is a about 50% decline in V_{O2max} from age 20 to 80 that isdue to both decline in cardiac output and oxygen extraction.[45] The decline in cardiac output is due to impaired maximal heart rate, while impaired oxygen extraction is due to decreased peripheral muscle mass, muscle mitochondrial efficiency and impaired ability for the blood flow to redistribute to the working muscle.[46]

Cardiac aging is associated with significant alterations in the diastolic phase of cardiac cycle. Aging is associated with a lower proportion of the diastolic filling occurring in the early passive phase due to prolonged isovolumic relaxation time. This means that the atrial filling is making a greater contribution to the total end-diastolic volume and can be measured echocardiographically with a decrease in the E/A ratio.[19]

On a cellular level, the aging cardiomyocyte exhibits changes in calcium handing that are similar to those in HFpEF. The rate of action potential transient and rate of contraction are both increase and measured clinically by lower maximal heart rate with exercise. These findings can be partially explained by a reduced rate of calcium uptake, which is due to dowregulation of SERCA2, increase in levels of Na+/Ca2+ exchanger and decreased phospholamban phosphorylation. In addition, there is an increase in L-type Ca2+ current and reduction of outward directed K+ current with aging. All these changes contribute to the prolonged action potential.[46,47] Defects in Systolic Function Although defects in diastolic function are felt to be the major contributor to symptoms in HFpEF, impairments in systolic function also play an important role. Many studies have shown that stroke volumes in HFpEF are decreased during exercise as compared to normal subjects. Initially researchers hypothesized that impaired ventricular dilation (and thus decreased stroke volume) during

exercise was the sole contributor to decreased cardiac output with exertion in patients with HFpEF. However, despite ventricular hypertrophy and remodeling in HFpEF, left ventricular end diastolic volumes during exercise are often normal in response to exercise. [15] These data support a model that impaired contractility contributes to poor stroke volume augmentation. This hypothesis is supported by evidence of decreased systolic reserve in patients with HFpEF using invasive hemodynamics. [20,27] Although a recent study demonstrated that stroke volume did not correlate with symptom-limited exertion, the non-invasive measurements of stroke volume used were suboptimal. [48] To date, cardiac MRI, the gold standard to assess ventricular volumes, has not been used during invasive hemodynamic studies of systolic function in HFpEF. [49] Factors contributing to systolic impairment include abnormal beta adrenergic signaling, interstitial fibrosis and increased vascular resistance. [15, 50, 21] In particular, the role of fibrosis in physically impeding the ability of cardiomyocytes to contract has been previously underestimated.

Impaired Chronotropy

In exercise, the heart rate can increase more than three-fold and is the major factor in cardiac output augmentation upon exertion. With normal aging, maximally predicted heart rate decreases and is thought to contribute to decreased exercise tolerance in healthy aged adults. [51–53] Chronotropic incompetence–impairment of the normal age adjusted increase in heart rate with exertion–is widely described in HFpEF although many studies are confounded with the concomitant use of beta-blockers and calcium channel blockers. [27, 28, 48, 54, 55,56] In addition to impaired augmentation of heart rate, delayed heart rate recovery is often present in HFpEF, is suggestive of poor vagal autonomic tone and is associated with increased mortality as well as HFrEF. [56, 57,58] Finally, poor heart rate increase correlates with disease severity and is independent of sex. [9]

Defects in Peripheral Vascular Function

Patients with HFpEF often have associated comorbidities such as hypertension and metabolic syndrome contributing to impaired endothelial function.[15] This in turn adversely remodels aortic and downstream arterial hemodynamics, worsening the pathophysiology in HFpEF. Central aortic pulse pressures and the velocity of antegrade pulse waves are increased in HFpEF consistent with less distensible aortae. In addition, there is enhanced rebound retrograde pulse waves which impart excessive ventricular afterload in late systole and early diastole, thus increasing myocardial demand. [50] Exaggerated central pulse pressures and carotid bulb signaling are also thought to contribute to exertional presyncope and labile blood pressure responses in patients with HFpEF. [15]

Similarly, aging is also associated with a decreased ability of peripheral arteries to dilate in response to exercise.[59,60] As HFpEF increases with age, changes in vascular function could be compounded in subjects with both conditions. However, a study comparing arterial endothelial function as assessed by flow-mediated dilation of the brachial artery, did not find any abnormalities in HFpEF subjects as compared to healthy age-matched adults. There was reduced flow mediated dilation in both groups compared to young individuals. [61] Another study used phase contrast magnetic resonance imaging and did not find any difference in superficial femoral artery cross section and velocity at baseline or after exercise between

HFpEF patients and healthy older individuals.[62] These studies provide evidence that large arterial vascular function is not a limiting factor in HFpEF.

Impact of HFpEF on Exercise Tolerance

Numerous studies have shown that HFpEF patients have reduced VO2 max. [63,64] Thus, HFpEF provides a unique opportunity to understand the effects of the cardiovascular consequences of aging (decreased relaxation) without other associated changes in the peripheral muscle and vasculature that occur with normal aging. Here we will review the hemodynamic and local skeletal factors that contribute to exercise intolerance in HFpEF and compare to similar issues with aging alone.

Hemodynamic Factors

As most patients are asymptomatic at rest with HFpEF, much of what is known about the physiology of this disorder comes from exercise testing. Patients with HFpEF have considerably higher filling pressures at rest but as this disorder develops chronically, there are physiologic adaptations. For example, M.M. Abudiab et al. studied 109 subjects with HFpEF and 73 controls. As compared to normal controls, diseased subjects' resting right atrial (RA) and pulmonary capillary wedge pressure (PCWP) were nearly double at rest. In response to exercise, the PCWP went from 9 to 14 mmHg in normal subjects (normal < 15 mmHg) but doubled from16 to 33 mmHg in HFpEF subjects. Although, HFpEF subjects had normal cardiac outputs at rest, with exercise cardiac stroke volume, work and output were markedly reduced by >30% from normal subjects. [28] These findings are similar in other invasive hemodynamic studies, however there are conflicting data from studies that were smaller or in which measurements were made non-invasively. [9,15,48, 54] These are difficult measurements; however, the preponderance of the evidence generally suggests there is impaired cardiac output with exercise. In addition to the impaired cardiac output, there is inefficient distribution of the blood delivered to the skeletal muscle in HFpEF due to both central and peripheral aterial changes discussed above.[60]

Skeletal Muscle Factors

It is now recognized that the exercise intolerance observed in patients with HFpEF is not only due to acute hemodynamic changes with exertion. A growing literature demonstrates that primary changes in skeletal muscle occur in this syndrome. This concept was demonstrated by a recent study showing that HFpEF patients have significantly lower peripheral O2 extraction,[65,66] indicating a differential functioning of skeletal muscle between normal subjects and those with HFpEF . Structural, metabolic, and biomechanical changes to skeletal muscle in HFpEF will be discussed below.

Structural Changes—Skeletal muscle of patients with HFpEF exhibits significant changes on both the macroscopic and microscopic levels. In a study comparing patients with HFpEF to healthy age-matched individuals, it was found that these patients have a decreased total and leg mean mass. Intriguingly, VO2 max remained severely reduced when indexed to the leg lean mass, indicative of deeper issues than loss of muscle mass alone.[67] Indeed, MRI assessment of the lower extremities of HFpEF patients shows increased intermuscular fat

(IMF) and IMF to skeletal muscle (SM) ratio by 60% and 36% respectively. In multivariable analyses, both IMF area and IMF/SM ratio were independent predictors of peak VO2.[68] Muscle function may be altered by increased adipose tissue via multiple pathways including induction of a pro-inflammatory response, insulin resistance and alterations oxygen delivery.[69] Further studies to address these mechanisms are clearly needed.

On a microscopic level, there are alterations in muscle fiber morphology in response to HFpEF. In the Dahl salt-sensitive rat model of HFpEF, there is a decrease in cross sectional area of the Type I (slow twitch, fatigue resistant) fibers in the soleus muscle. Biopsy of vastus lateralis muscle of HFpEF human subjects showed a reduced percentage of the type I fibers (39% vs. 54%) and a concordant increase in the type II, fast twitch, easily fatigable fibers. These findings were accompanied by a decrease in the capillary-to-fiber ratio. The same study showed that in multivariate analyses, both the percentage of type I fibers and the capillary-to-fiber ratio were predictors of peak VO2 independent of age, sex and body surface area.[70] The authors hypothesized that a reduction in the percentage of type I skeletal muscle fibers could contribute to decreased oxidative capacity in the muscle, early fatigue, and thus lowered peak VO2.

Biomechanical Changes—There is limited data on skeletal muscle mechanical changes in HFpEF. In the Dahl salt-sensitive rat, *in-vitro* isometric muscle function experiments showed a preserved force-frequency relationship and normal twitch characteristics. Howevere, there was impaired fatigue and a higher twitch to tetanus ratio. These changes are suggestive of a primary calcium deficit rather than a myofilament dysfunction contributing to the skeletal muscle phenotype in HFpEF. [71]

Metabolic Changes—Active skeletal muscle is responsible for the majority of the oxygen consumed at peak exercise.[67] Therefore, deficiencies in skeletal muscle metabolism will profoundly influence exercise tolerance. As discussed above, the change from type I to type II fibers will alter metabolism; however, there is also evidence of primary defects in skeletal muscle metabolism in HFpEF. Using ^{31} phosphate magnetic resonance spectroscopy, it was shown that skeletal muscle of HFpEF patients demonstrated lower oxidative phosphorylation ATP production rates, higher anaerobic glycolysis ATP production rates and decreased recovery times to regenerate phosphor-creatine. [54] Mechanistic studies to explore this finding in the Dahl salt-sensitive rat model, revealed reduced soleus citrate synthase activity, indicating lower mitochondrial content. Furthermore, superoxide dismutase activity was significantly decreased activity in the soleus muscle of HFpEF rats compared to controls. This may suggest a role of oxidative stress in this process. However, these investigators did not reactive oxygen species, but did not report any differences in the enzymes xanthine oxidase and NAPDH oxidase, which can both contribute to reactive oxygen species generation.[71] Together, the combination of fewer mitochondria with poor anti-oxidant activity could explain the decreases in oxygen consumption seen in the skeletal muscle of patients with HFpEF.

While the skeletal muscle changes in HFpEF are well documented, the exact mechanism is unclear. Some potential causes neurohormonal activation, oxidative stress, abnormal Ca2+ cycling and excitation-contraction coupling.[69] Skeletal muscle dysfunction can be seen with

normal aging, a condition termed sarcopenia. However, sarcopenia has both similarities and differences with skeletal muscle changes in HFpEF. Both these conditions are associated with structural changes in muscle, alteration in capillary to muscle ratio and ultimately decreased peak VO2.[60,72] The increased muscle fat in the aging skeletal muscle creates a pro-inflammatory state as well as insulin resistance, resulting in increased muscle catabolism, mitochondrial dysfuntion and alterations in protein synthesis. All these changes can make the aging skeletal muscle, susceptible to further dysfunction if HFpEF is present.[69] The differences between sarcopenia and HFpEF is highlighted in one study where elderly HFpEF patients were compared to age-matched healthy subjects and found to have increased thigh intermuscular fat and this was an independent predictor of the reduced peak VO2.[68] On the microscopic level, aging results in a decrease in type II fiber area and the type II/type I fiber ratio.[73] As previously discussed, HFpEF is associated with reduced type I fibers.[70]

Exercise Training as Treatment for HFpEF

Although there are no proven pharmacologic therapies for HFpEF, there is evidence that exercise training can improve both cardiac and skeletal muscle abnormalities.[74,75] In a study where patients with HFpEF were randomized to endurance/resistant training or usual care, after 3 months there was an increase in peak VO2 from 16.1± 4.9 to 18.7± 5.4 ml/min/kg. Interestingly, the left atrial volume index and the E/e' also decreased significantly, which are indicative of improved left ventricular remodeling in response to exercise.[74] In a follow up study, the mechanism for the improved peak VO2 after exercise in patients with HFpEF was evaluated. After four months of exercise training, HFpEF patient demonstrated higher peak VO2, peak heart rate, but no change in peak end-diastolic volume or cardiac output. However, the peak arterial-venous oxygen difference was increased in exercise training patients compared to control (19.8±4.0 vs. 17.3± 3.7 ml/dL).[76] This means that the improved exercise capacity in patients with HFpEF after endurance training is largely due to peripheral factors such as improved microvascular endothelia or skeletal muscle function.

Summary

HFpEF is a complex condition characterized by exercise intolerance due to a combination of dyspnea and skeletal muscle fatigue. The incidence of HFpEF increases with aging and affects a significant proportion of Americans over the age of 65. Although decreased cardiac output is at the "heart" of these symptoms, multiple alterations in cardiovascular hemodynamics contribute including decreased stroke volume due to both poor filling and emptying of the ventricle, chronotropic abnormalities, and increased peripheral vascular resistance. Furthermore, direct impairments in skeletal muscle function via alterations in sarcomeric phenotype and energetics potentiate the effect of lower cardiac output on muscle fatigue.

Several major unanswered questions in the field have impeded the development of therapeutics for HFpEF. At the cardiac level, both increased stiffness due to excess matrix accumulation and decreased relaxation due to changes in sarcomeric energetics and function contribute. However, it remains uncertain if these two processes occur independently, sequentially or advance in a feed-forward system. Likewise, it is unknown if changes in

skeletal muscle energetics occur due to or independent of alterations in cardiovascular hemodynamics. Finally, data suggest that exercise training may have significant benefits on both the cardiovascular and skeletal muscle pathology of HFpEF. Understanding the mechanisms by which exercise training can alter both cardiac hemodynamics and skeletal muscle function could point toward candidate pathways do develop therapeutics. In all cases, development of more robust animal models of HFpEF will be crucial to addressing these mechanistic questions.

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