Staying Young at Heart

A new look at the lifelong benefits of exercise

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Research Interests

My research interests include the contribution of traditional risk factors (i.e. hypertension, dyslipidemia, etc) to the lifetime risks of cardiovascular disease. More recently, my research program has established the unique contribution of exercise on the long-term risk for heart failure, particularly heart failure with preserved ejection fraction.

Purpose and Overview

Despite the marked successes cardiovascular medicine has achieved regarding coronary disease, the burden of heart failure in the community persists. Furthermore, the burden of heart failure with preserved ejection fraction (HFpEF) now represents the majority of the heart failure in the community. This represents an important problem because currently there are no established therapies for this disorder. HFpEF is a complex, heterogeneous disorder characterized by signs and/or symptoms of heart failure, normal ejection fraction, and abnormal diastolic filling patterns. Because of the failure of HFpEF treatment strategies, our approach at UT Southwestern has centered on its prevention which requires a more comprehensive understanding of its natural history. In particular, our work has established the contribution of normal variation of exercise capacity in middle-age on the long-term risk for heart failure—particularly HFpEF. Our work has also shown that the risks related to low fitness are modifiable, however, the dose of exercise required to prevent heart failure appears higher than current physical activity recommendations.

Objectives

1. To understand the rising prevalence of heart failure with preserved ejection fraction (HFpEF), its diagnostic criteria, and its lack of established therapies.
2. To understand the phenotypic and pathophysiologic heterogeneity in HFpEF that gives rise to its complex natural history.
3. To understand the contribution of exercise capacity in healthy, middle-aged adults on the long-term risk for heart failure. This will be highlighted by a comprehensive review of the phenotypic similarities between low exercise capacity and HFpEF.
4. To understand the unique role of exercise and its dose for the prevention of heart failure.

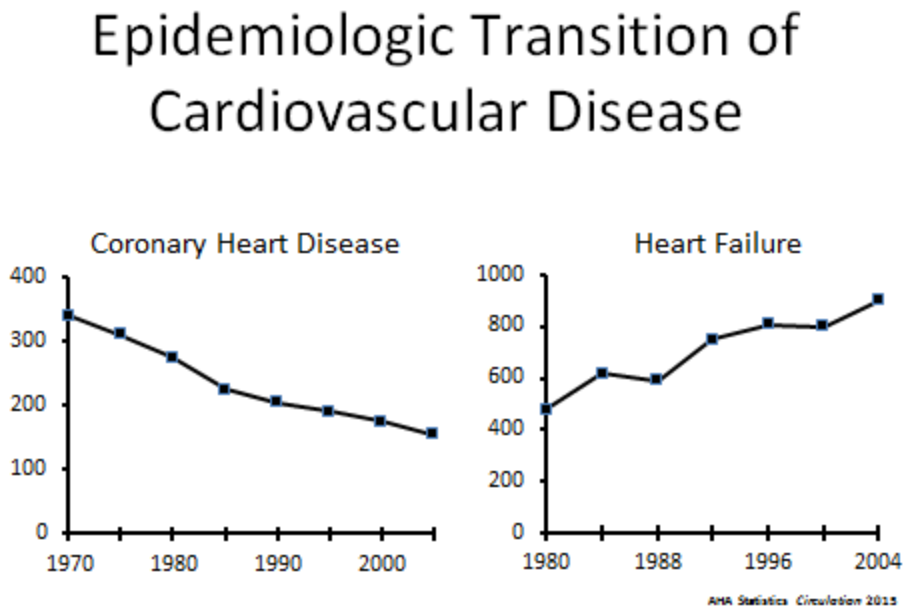
Introduction

The 20th century has witnessed marked epidemiologic changes in the leading causes of death, with marked declines in common infectious diseases (i.e. tuberculosis, diphtheria, etc). This so-called "epidemiologic transition" has led to a dramatic increase in the median survival in the population, increasing from 47 years in 1900 to nearly 80 years at the turn of the century. As a result of this transition and the aging of the population, we have observed a consequent decline in the public health burden of infectious disease and a parallel increase in the burden of non-communicable diseases such as cancer and cardiovascular disease. Thus, both now and into the future, aging and its associated diseases will dominate the needs of our health care system[1, 2].

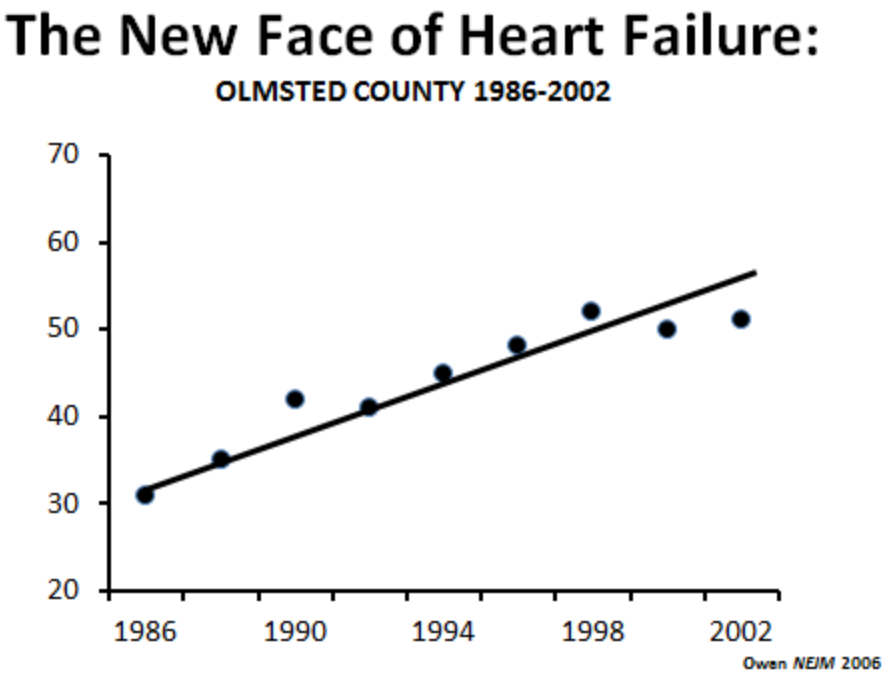
Cardiovascular disease has undergone its own epidemiologic transition in the latter part of the 20th century. From 1950 until now, coronary heart disease mortality has declined by approximately 50%[3]. The explanation for this decline is well-established and can largely be explained by marked change in population risk factor levels.[4] In particular, over the last 40-50 years, there has been favorable changes in health behaviors such as smoking cessation and dietary changes with consequent, and marked, decreases in serum cholesterol in the population.[4]

Heart Failure with Preserved Ejection Fraction: the new face of Heart Failure

While the incidence of atherosclerotic cardiovascular disease has decreased steadily over the past 40 years, heart failure incidence has remained largely unchanged, and the rate of heart failure hospitalization has increased (see Figure).[3, 5, 6] Heart failure currently affects approximately 5.8 million people and accounts for an estimated annual healthcare cost of $34.8 billion.[3]



A more detailed analysis of the current heart failure epidemic reveals important issues related to its prospect for treatment and prevention. In particular, the heart failure epidemic is not one but two separate epidemics: the epidemic of heart failure with reduced ejection fraction (HFrEF) and the epidemic of heart failure with preserved ejection fraction (HFpEF).[7] For decades it has been observed that there is a bimodal distribution of ejection fraction among heart failure patients. In addition, the burden of HFpEF has actually increased over the last 20 years. Data from Olmsted County suggest that the prevalence of HFpEF has increased from approximately 30% of all heart failure in the mid-1980s to well over 50% today[8].

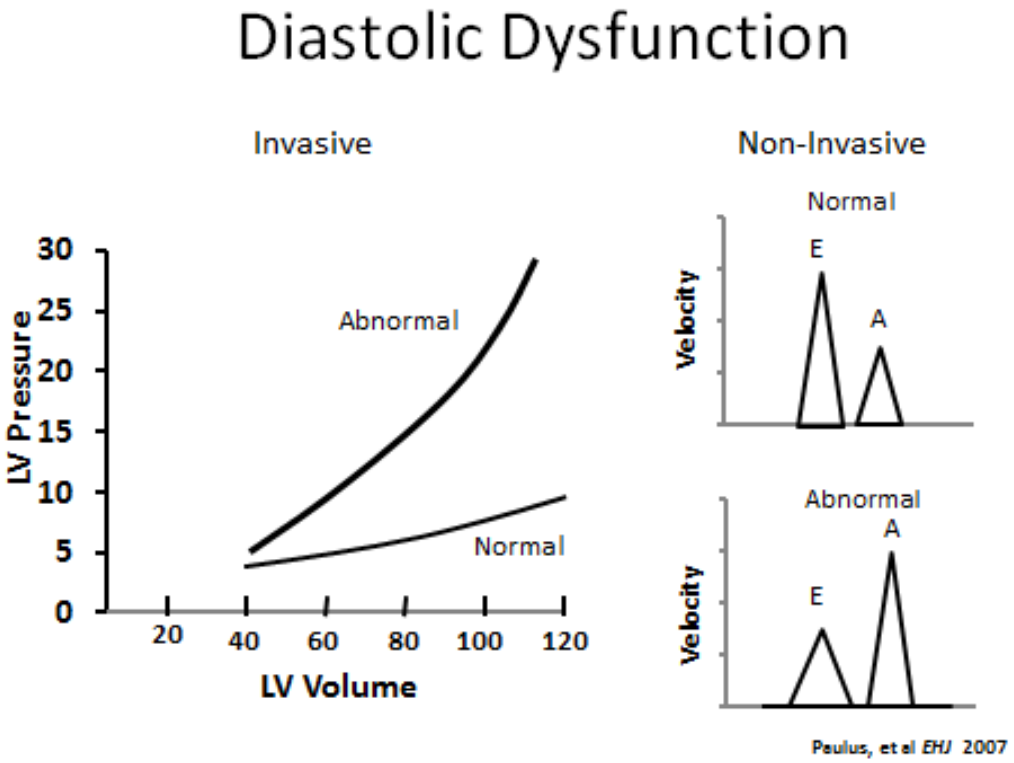


What is HFpEF?

HFPEF is a clinical syndrome of heart failure whereby the ejection fraction (EF) is grossly normal (i.e. > 50%)[9]. It is strongly associated with age (mean age > 74 years) and hypertension and is more common in women than in men (55% to 65% women).[5, 6, 10] Some investigators have suggested that HFpEF is merely an early form of HFrEF where hypertensive heart disease progresses from a pattern of concentric remodeling to eccentric remodeling[9]. While there are data from certain minority populations (i.e. African Americans) in which this appears to be a more common manifestation of the natural history of left ventricular hypertrophy, the more consistent finding in the literature confirms that HFpEF and HFrEF represent two distinct syndromes. This observation is suggested from a large literature that has confirmed the presence of a unique cardiovascular phenotype among patients diagnosed with HFpEF. For example, HFpEF is characterized by a distinct myocardial ultrastructure with prominent cardiomyocyte hypertrophy and associated increased resting tension[11]. In addition, a unique isoform of

titin, a prominent cytoskeletal protein, has been observed in biopsy specimens from HFpEF patients[12].

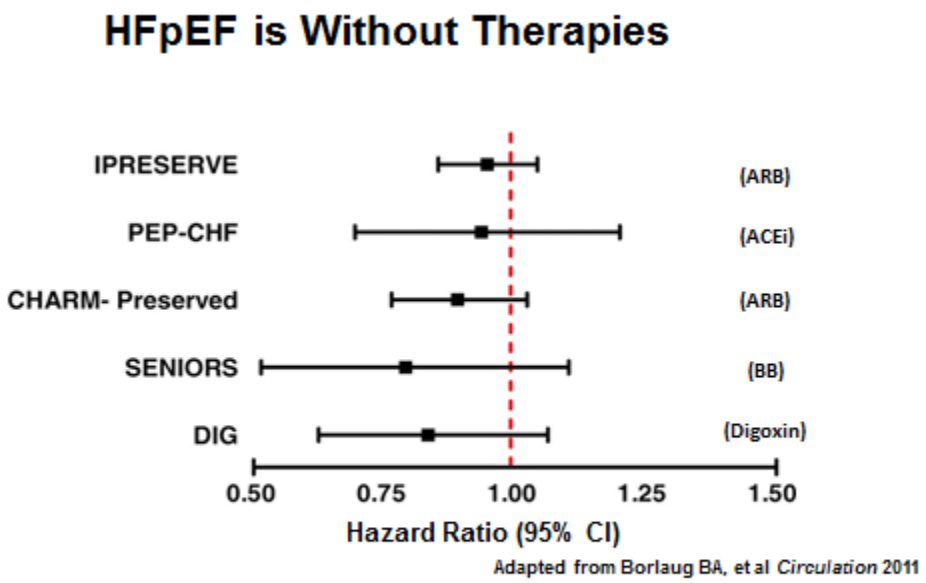
The diagnostic criteria are well-established and require the presence of the following: (1) signs and/or symptoms of heart failure, (2) normal or mildly reduced LV ejection fraction (> 50%) and a normal LV volume (LV end diastolic volume < 97 mL/m^2, and (3) evidence of abnormal LV relaxation, filling, diastolic distensibility, and/or diastolic stiffness[9]. The latter category can be fulfilled through the presence of either frankly abnormal markers of diastolic function or intermediate levels of diastolic dysfunction combined with LV remodeling, left atrial enlargement, or elevated cardiac biomarkers (i.e. BNP).



Prognosis of HFpEF and the Failure of Multiple Clinical Trials

The response to therapies represents the most robust evidence that HFpEF represents a unique syndrome. In contrast to the remarkable success story for the pharmacological management of HFrEF, multiple, large-scale clinical trials in HFpEF patients have failed. The PEP-CHF study[13] was first major randomized controlled trial on the use of ACEI in HFpEF. In this study, the use of perindopril to placebo in patients >70 years old with LVEF >40% was associated with no clinical benefit. Similar results were shown for angiotensin receptor blockers (ARBs) in the CHARM-preserved[14] and I-PRESERVE[15] trials. More recently, the role of aldosterone antagonism with spironolactone was assessed in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT)[16], ultimately showing no reduction in composite

primary outcome (death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF).



While there are differences across these trials regarding patient characteristics, inclusion criteria, and pharmacologic strategy, the consistent finding from these trials has been that antagonism of the renin-angiotensin-aldosterone pathway has not modified the natural history of HFpEF in the way that has been observed with HFrEF. The failure of these trials, particularly the failure of aldosterone antagonism in TOPCAT, suggests fundamental challenges to the current HFpEF paradigm.

Reevaluation of the Pathophysiology of HFpEF

The failure of clinical trials has provided a strong impetus to reconsider the HFpEF syndrome in its entirety. In addition to the clinical trial results, several additional observations have prompted the search for a more comprehensive understanding of this disorder. First, it has been observed that diastolic dysfunction is exceedingly common in otherwise healthy, asymptomatic, elderly adults. And second, as many as one-third of patients with a confirmed diagnosis of HFpEF have no evidence of diastolic dysfunction by non-invasive, echo imaging[17].

Thus, it is now well-recognized that the HFpEF phenotype is characterized by the combination of abnormal cardiac reserve across multiple domains, including not only diastolic dysfunction, but also subtle abnormalities in systolic function, increased vascular stiffness, abnormal peripheral oxygen extraction, and an increased burden of non-cardiovascular comorbidities[18]. For example, the Rochester Epidemiology Project demonstrated that although ventricular systolic stiffness was increased in both

hypertensive and HFPEF patients, myocardial contractility as measured by stress-corrected midwall shortening was decreased in patients with HFPEF but not in hypertensive patients [19]. More recently, myocardial deformation imaging using both echocardiographic and MRI techniques have been established to characterize a quantitative assessment of myocardial performance. This type of imaging, termed myocardial strain imaging, can provide more sensitive measures of systolic function in both the radial direction, circumferential direction, and longitudinal direction. It is now well-appreciated that HFpEF patients have evidence of abnormal strain despite the presence of a normal LV ejection fraction[20].

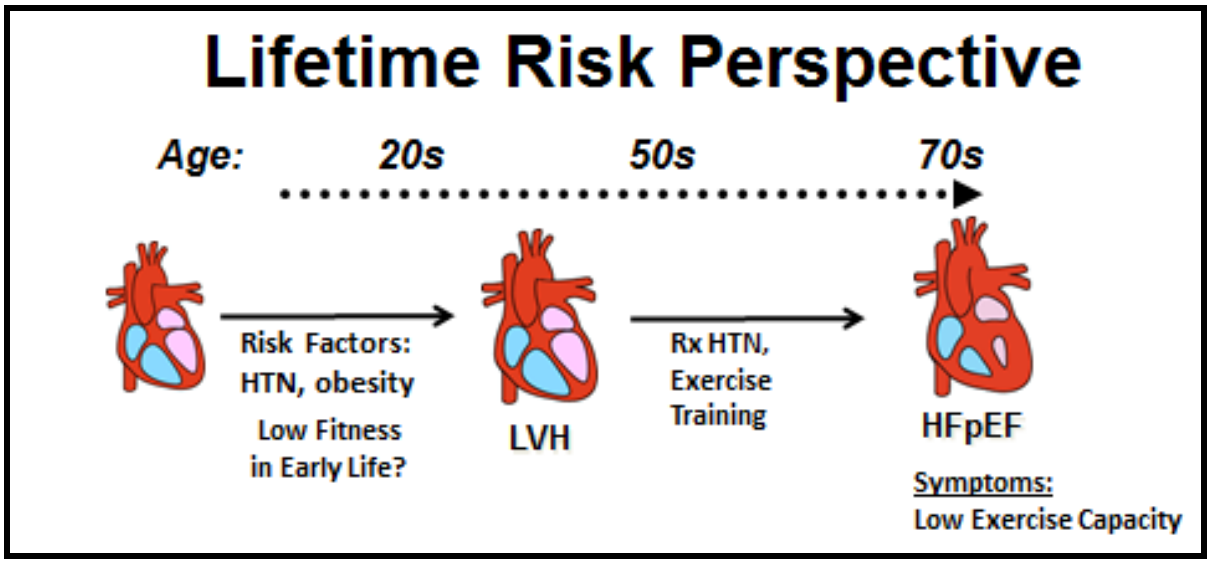
Abnormal vascular stiffness has also been observed commonly in patients with HFpEF. Given the near-universal presence of hypertension, the presence of abnormal vascular stiffness is not unexpected. Specifically, in a landmark observation from David Kass's group at Johns Hopkins, abnormal vascular stiffness itself was shown to promote abnormalities in diastole[21]. This observed interrelationship between abnormal vascular stiffness and diastolic dysfunction represents compelling evidence for the role of vascular stiffness in the pathophysiology of HFpEF.

The Future of HFpEF Treatment = Prevention

While the failure of HFpEF treatment is well-established, the explanation for this failure remains unresolved. In addition to the issues related to its complex pathophysiology, the natural history of HFpEF is particularly instructive. Multiple cohort studies and clinical trials have reported that the prognosis of HFpEF, once present, is similar to HFrEF. While this is true for overall mortality, a review of the causes of death among patients with HFpEF reveals a high burden of non-cardiovascular mortality. In observational data, the non-cardiovascular mortality rate approaches 50%[22]. In both clinical trials and observational data, the non-CVD mortality rate is approximately twice as high in HFpEF compared to HFrEF. More importantly, the more modifiable aspects of heart failure (i.e. sudden death and heart failure hospitalization) are much less common in HFpEF compared to HFrEF[23]. Thus, one very likely explanation for the failure of HFpEF treatment trials is that HFpEF itself represents a high-risk condition characterized by a high burden of non-modifiable substrate. Stated another way, the treatment of HFpEF may not represent the most viable strategy going forward. Rather, the most effective approach may represent a strategy based on the prevention of HFpEF.

The HFpEF Prevention Center here at UT Southwestern is based on the premise that a a HFpEF prevention strategy must be based on a more comprehensive understanding of its natural history. While this natural history is well-established in atherosclerotic cardiovascular disease, the natural history of HFpEF remains poorly understood. In particular, this approach has centered almost exclusively on traditional cardiovascular risk factors such as hypertension, diabetes, and obesity. However, until recently, relatively little attention has been given to the role of exercise capacity (or cardiorespiratory fitness) levels across the lifespan and its impact on HFpEF risk. Given the consistent finding of reduced exercise tolerance among patients with HFpEF, my research program here at UT Southwestern has sought to characterize the impact of

exercise capacity/fitness across the lifespan on the burden of heart failure risk in later life.



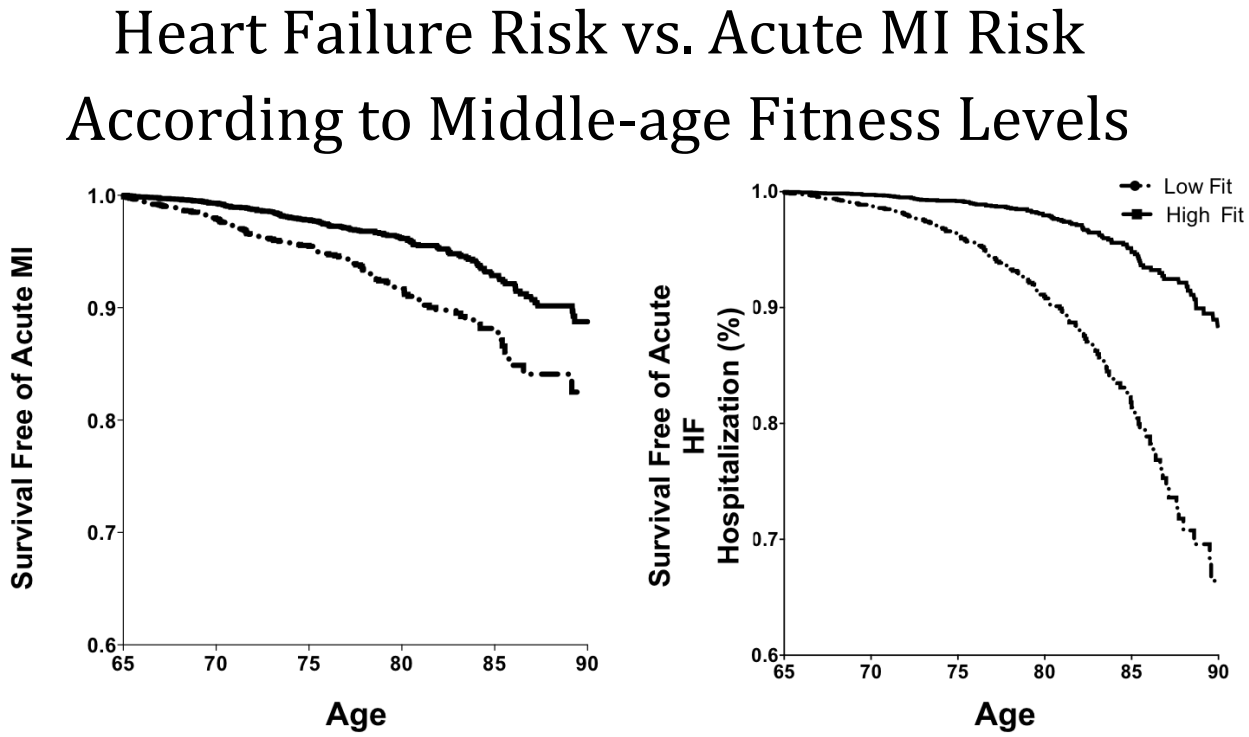
Low cardiorespiratory fitness in middle age

Cardiorespiratory fitness, an objective measure of peak aerobic capacity determined by maximal exercise test, has been known for decades to be strongly associated with both CVD and non-CVD mortality. In a series of studies, we have observed consistent associations between fitness and both short-term and lifetime risk for CVD mortality. In general, fitness is lower in women than in men and declines linearly with age. Data from the Baltimore Longitudinal Study of Aging suggests that this decline in fitness accelerates with advancing age, decreasing by 10% per decade through middle-age and decreasing by as much as 25% per decade in the elderly[24]. Because of these established age- and gender effects, fitness levels are commonly categorized according to age- and gender-specific thresholds, allowing comparison of fitness levels across individuals. In general, adults are much more likely to be physically inactive. For example, in the Cooper Center Longitudinal Study, 70% of low fit adults were sedentary[25].

It is well-established that low fitness is associated with a higher prevalence of obesity, with nearly 40% of low fit adults categorized as obese. However, despite this association, there remains a marked degree of heterogeneity in BMI levels across fitness levels**.** In addition, the impact of fitness on cardiovascular risk is distinct from the impact of obesity. The association between a risk factor and mortality diminishes across time for several different reasons, including changes in the risk factor over time, downstream treatment effects, and competing risks.[26] While most traditional risk factors appear to attenuate across longer periods of follow-up, other risk factors such as obesity confer the greatest risk in the long-term because of their contribution to the development of additional traditional risk factors in the future.[27] In a recent study, we observed that the association between low fitness and CVD mortality was relatively consistent in the short-term, intermediate-term, and long-term—similar to most other traditional risk factors[28].

Low fitness and long-term heart failure risk

Although the association between low levels of fitness and an increased risk for both cardiovascular and non-cardiovascular disease mortality is well established, the association between low fitness and non-fatal events is less well understood because few datasets with measured physical fitness have followed participants for non-fatal outcomes. Thus, in 2010, in collaboration with the Cooper Institute, I led the merging of the Cooper Center Longitudinal Study with Medicare claims files, providing a wealth of information regarding the natural history of low fitness[29]. We have observed a number of seminal findings from this work. Most notably, we observed, for the first time, that low fitness in middle-age was a robust determinant of long-term heart failure risk in a large cohort of 20,642 healthy men and women with objectively measured fitness and a large number of outcomes (832 acute MI hospitalizations and 1,052 heart failure hospitalizations). In particular, we observed that the association between low fitness and heart failure was several fold the observed association with atherosclerotic forms of cardiovascular disease. Therefore, this study represents a substantial contribution to the available literature on the association between fitness and non-fatal cardiovascular events, providing novel insights into the contribution of low fitness in midlife to cardiovascular risk at older ages. Since the publication of our paper, Khan et al.[30] have also reported a dose-dependent inverse association between cardiorespiratory fitness and heart failure risk in a Finnish cohort of middle-aged men.



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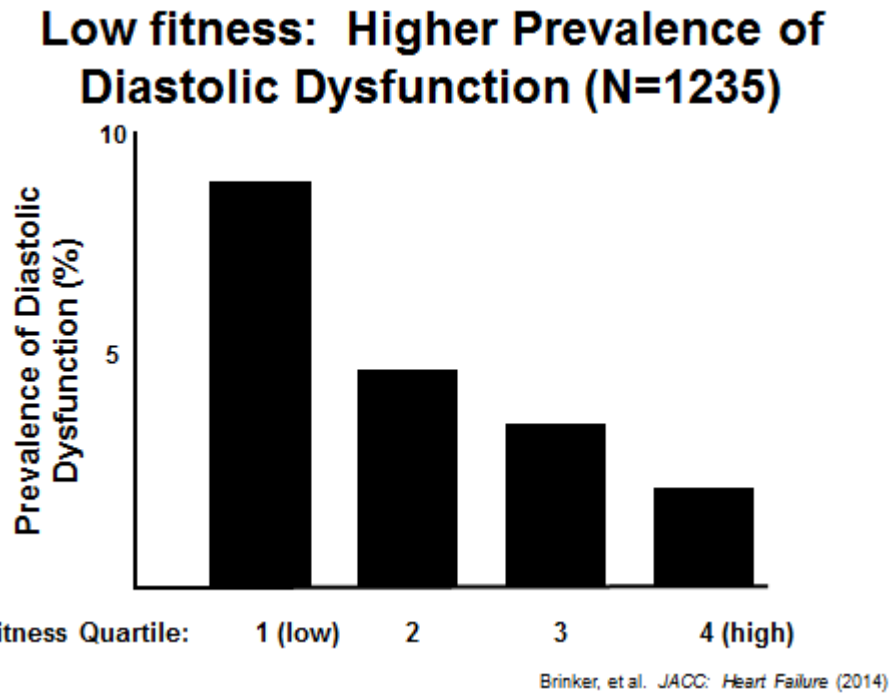
While obesity has also been associated with an increased risk of HF in several large cohort studies,[31-35] our data suggest that the association between fitness and HF risk is independent of BMI. We observed consistent associations between obesity and fitness with heart failure risk in the CCLS. However, there was no evidence of an interaction such that the association between fitness and HF risk was apparent across all levels of BMI. As shown below, we believe that the mechanism through which low fitness mediates its effects on HF risk are distinct and independent of obesity.

Association Between Fitness and Characteristic Abnormalities Observed in HFpEF

Non-invasive diastolic function and abnormal cardiac remodeling. Another potential mechanism through which fitness in middle age might lower HFpEF risk in later life is through more direct effects of exercise on cardiac structure and function. Diastolic dysfunction and abnormal LV remodeling represent important intermediate phenotypes in the natural history of symptomatic HFpEF. Athletes and individuals with higher levels of physical activity have larger heart size and improved early diastolic filling. Similarly, in a cross sectional analysis of healthy participants from CCLS, we observed a significant inverse association between cardiorespiratory fitness levels and prevalence of diastolic dysfunction and abnormal concentric remodeling[36].

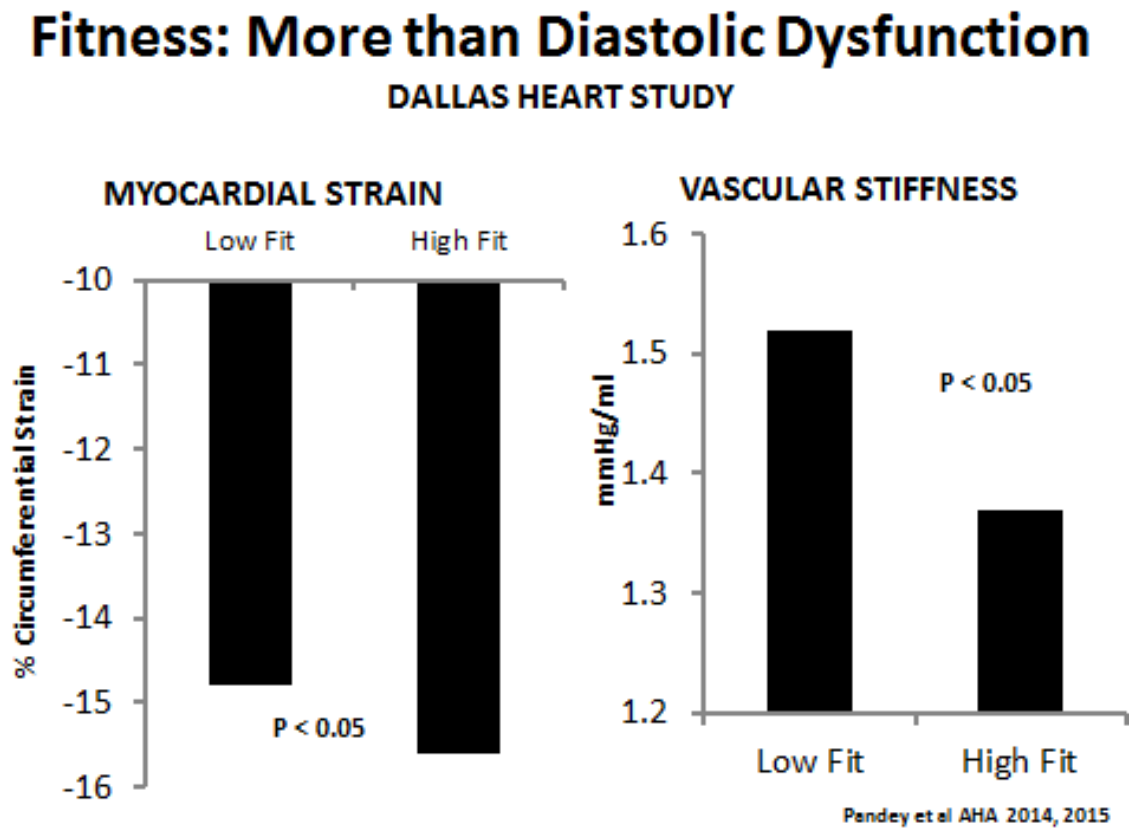


End diastolic stiffness These findings are also supported by the mechanistic studies from Levine et al. that have demonstrated an increased end-diastolic ventricular stiffness among participants with sedentary lifestyle and low cardiorespiratory fitness, similar to that observed among patients with HFpEF[37]. Adequate ventricular chamber compliance is important to allow cardiac filling at low pressures as well as to increase cardiac output via the Frank-Starling mechanism. Higher LV stiffness is associated with higher diastolic filling pressures after cardiac loading and may impair LV end-diastolic volume augmentation with exercise, leading to reduced exercise intolerance and dyspnea.

Taken together, these findings suggest that low fitness levels are associated with a greater prevalence of concentric remodeling and abnormalities in LV diastolic properties, which could lead to a greater risk for heart failure, specifically HFpEF at a later age.

Systolic function abnormalities Recently, there has been an interest in characterizing the contributions of subtle abnormalities in systolic function towards pathogenesis and progression of HFpEF with studies identifying significant impairment in peak systolic strain patterns among HFpEF patients[20]. Furthermore, unpublished preliminary work from our group has also identified an inverse association between cardiorespiratory fitness levels and degree of impairment in peak systolic circumferential strain among participants of the Dallas Heart Study[38]. These findings suggest that subtle abnormalities in systolic function may also contribute towards the progression from low cardiorespiratory fitness stage to HFPEF among sedentary adults.

Arterial Stiffness Low cardiorespiratory fitness is also associated with increased arterial stiffness similar to what is observed among HFpEF patients[39]. Increased arterial stiffness leads to increased LV afterload and limits the augmentation in cardiac output during exercise and may play a role in pathophysiology of heart failure with preserved ejection fraction among sedentary and low fit adults.



Cardiovascular and non-cardiovascular comorbidities One potential mechanism through which low cardiorespiratory fitness and physical inactivity might be associated with long-term risk for HFpEF is through its effects on cardiovascular and non-cardiovascular risk factors. Low cardiorespiratory fitness is associated with increased downstream prevalence of cardiovascular risk factors, such as diabetes mellitus, hypertension, and obesity that might promote the development of HFpEF in older age directly. Similarly, low mid-life cardiorespiratory fitness is also associated with a greater antecedent burden of chronic non-cardiac co-morbidities, which in turn predisposes to a greater risk for HFpEF in later life[25]. However, in a recent CCLS-medicare follow-up study we observed that lower midlife fitness was associated with a higher risk for heart failure hospitalization independent of and across all levels of chronic disease burden suggesting that the pathway through which higher fitness levels in middle age confer a lower risk for HF hospitalization decades later in older age is at least in part independent of the development of future established heart failure risk factors[40].

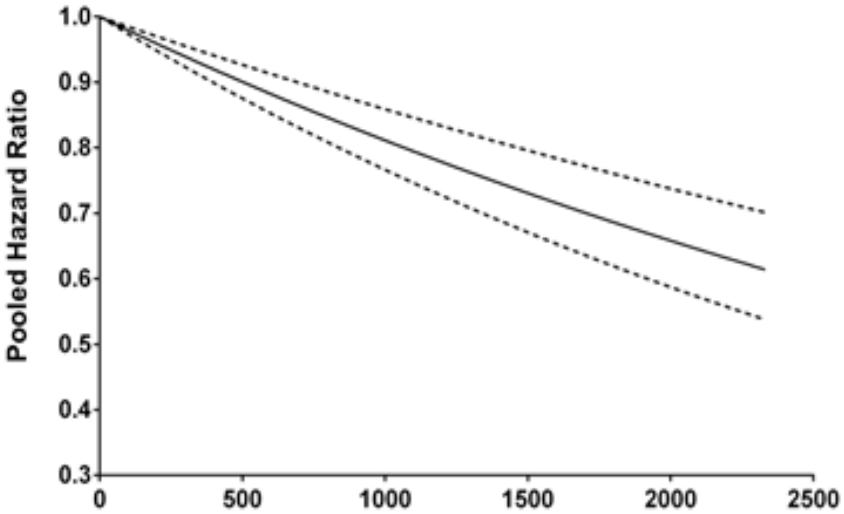
Low Cardiorespiratory fitness and risk for HFpEF: Is it modifiable?

Recent studies have reported a significant association between changes in physical activity and cardiorespiratory fitness levels and risk for heart failure.
In a Framingham heart study analysis, the investigators observed a significant increase in risk for heart failure among participants who had a decline in their physical activity levels between two consecutive examinations.[41]Similarly, in a recent study from the CCLS, we have demonstrated that 1 MET improvement in cardiorespiratory fitness over a period of 4.4 year follow-up was associated with a 17% reduction in HF risk at a later age.[40] Taken together, these observational study findings suggest that low fitness associated risk of HF may be modifiable and exercise training in sedentary middle age individuals could be an effective strategy to reduce the burden of heart failure in later life.

Exercise Training for HFpEF prevention: How much is enough?

While several epidemiological studies have reported that leisure time physical activity and recreational exercise is associated with significant reduction in heart failure risk, the dose of exercise training required to significantly reduce HF risk remains incompletely understood. In a recent dose response meta-analysis, we observed that participants engaging in guideline recommended minimum levels of physical activity (500 MET-min/week, 2008 US Federal Guidelines) had only modest reductions in heart failure risk (<10%) and doses of physical activity in excess of current guideline recommended levels are required to significantly reduce heart failure risk (19% at 1000 MET-min/week and 34% at 2000 MET-min/week).[42] These findings are further supported by the recently published mechanistic data by Bhella, et al.[43] which demonstrated that life-long moderate to high dose exercise training can significantly prevent most of the decrease in LV compliance and distensibility observed with sedentary aging.

Dose Response Association Between Physical Activity and HF Risk



Apart from dose, the intensity of exercise training associated with optimum cardiovascular benefit remains uncertain. There is a substantial body of evidence suggesting that higher intensity exercise—compared to moderate intensity—is associated with lower risk for cardiovascular morbidity and mortality. [44-46] In addition, exercise-training trials have reported nearly a two-fold greater improvement in peak VO2 with high intensity aerobic interval training compared to moderate intensity training.[47-50] Furthermore, a recent study observed that compared with moderate intensity training, high intensity aerobic interval training was associated with a significant improvement in diastolic function, systolic strain pattern and cardiorespiratory fitness in sedentary patients with type-2 diabetes mellitus who are at an increased risk for future HFpEF. [51] Taken together, these data suggest that high intensity aerobic interval training may represent a more effective exercise training strategy for HFpEF prevention.

A recent follow up study from the Framingham Heart Study demonstrated that the inverse association between higher levels of physical activity and heart failure is consistent for HFpEF but not HFrEF[41], suggesting that low physical activity and fitness levels may preferentially predispose to an increased risk for HFpEF over HFrEF at a later age. This notion is further supported by recent work from our group and others that have shown notable similarities in phenotypic characteristics associated with low fitness and HFpEF.

Exercise Training Prescription for HFpEF prevention: Does one size fit all?

Prior studies have observed a substantial amount of variability in the change in fitness in response to supervised exercise training.[52-54] In a recent sub-analysis from the DREW study, we reported that approximately 30% of obese, hypertensive, sedentary postmenopausal women, who are at increased risk for HFpEF, experienced no improvement in cardiorespiratory fitness after 6 months of moderate intensity exercise training.[55] We also observed that presence of LV hypertrophy and adverse LV remodeling were independent predictors of non-response to moderate intensity exercise training. [55]These findings have important implications for exercise training programs implemented among sedentary middle-aged adults to prevent HFpEF. First, it highlights the importance of early initiation of exercise training interventions in at risk participants before development of significant abnormalities in LV structure and function. Second, It highlights the need for more targeted, personalized interventions with higher intensity and/or dose of exercise training, or using specific modalities, such as a combination of resistance and endurance training, to improve fitness among at risk participants with underlying LV hypertrophy and adverse remodeling, which puts them at highest risk for HFpEF as well as non-response to conventional moderate intensity exercise training.

Exercise Training in Patients with clinical HFpEF: is it too late to exercise?

Apart from its potential role as a novel and effective tool for HFpEF prevention, exercise-training can also used a therapeutic strategy for management of patients with established HFpEF. In a recent meta-analysis, we demonstrated that exercise training is associated with significant improvements in cardiorespiratory fitness and quality of life among HFpEF patients. [56] Furthermore, we did not observe any significant improvement in left ventricular diastolic function with exercise training among these patients. Moreover, exercise training in HFpEF patients has not been associated with an improvement in cardiac output or measures of LV afterload (arterial stiffness). [57-59]Taken together, the available literature suggests that exercise training may improve exercise tolerance through peripheral mechanisms leading to an improved oxygen extraction in the active skeletal muscles. [57, 59] This is in contrast to the favorable effects of exercise training on LV structure, function and afterload that are reported among sedentary but otherwise healthy participants.[37, 51, 60-62]

Conclusion

Low cardiorespiratory fitness is an independent and modifiable risk factor for heart failure. Furthermore, findings from recent studies done by our group and others suggest that low fitness is more strongly associated with a greater increase in risk for HFpEF as compared with HFrEF. Exercise training is an effective tool for fitness improvement among sedentary low fit adults and is associated with favorable changes in cardiac structure and function that may delay progression from a low fit state to clinical HFpEF.

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