JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 69, NO. 9, 2017

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2017.01.010

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

EDITORIAL COMMENT

Sedentary Lifestyle and the Risk for HFpEF

Are "Huff-Puff Health Clubs" the Answer?*

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Clinically overt heart failure with preserved ejection fraction (HFpEF) is an increasingly common and challenging syndrome that thus far lacks definitive treatment options (1,2). The level of debility experienced by patients with HFpEF rivals those with advanced chronic obstructive pulmonary disease and those undergoing dialysis (3); patients with HFpEF are literally "huffing and puffing" while frustrated clinicians stand by powerless to ameliorate the "huff-puff" syndrome. Given the difficulty in treating HFpEF, prevention of this syndrome is likely a better strategy, particularly at the population level. Based on the importance of HFpEF prevention, it is not surprising that understanding its risk factors, alone or in combination, is a major active area of investigation. Risk factors such as hypertension, obesity, diabetes, chronic kidney disease, and others are particularly important in HFpEF given the growing consensus that in most cases, the origins of HFpEF are systemic and lie in the periphery, with cardiac injury as a secondary phenomenon (2,4). This "peripheral" origin of HFpEF differs from heart failure with reduced ejection fraction (HFrEF) in which cardiac injury is most often primary and thus has a "central" origin (4).

Previously completed population-based studies, which have provided insight into the differential risk factors that lead to HFpEF compared with HFrEF, support the peripheral hypothesis of HFpEF (5), but just how, when, and why risk factors tip over into HFpEF remains unclear. Ongoing population-based studies such as MESA (Multi-Ethnic Study of Atherosclerosis) are attempting to study this question by examining how collections of risk factors transition into the earliest forms of HFpEF (i.e., dyspnea and exercise intolerance due to elevated left ventricular filling pressures but without overt, clinically recognized fluid retention).

Although our understanding of the transition from risk factors to HFpEF is incomplete at the present time, the aforementioned comorbidities for HFpEF are well known to clinicians and often diagnosed and treated in the clinical setting as a way to prevent or improve HFpEF given the lack of effective primary treatments for the disorder (6). Less well known, although increasingly apparent, is that in addition to these medical comorbidities, physical inactivity (i.e., a sedentary lifestyle) is associated with many of the underlying cardiac and skeletal muscle abnormalities often present in HFpEF (7-10). In addition, several studies have shown that physical inactivity is a risk factor for incident heart failure (HF) in general (and that high levels of physical activity are protective against development of HF) (11). However, no previous studies have examined whether lack of physical activity is particularly associated with HFpEF compared with HFrEF.

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In this issue of the *Journal*, Pandey et al. (12) conducted a high-quality analysis of pooled patient-level data on physical activity measures and HF outcomes from 3 population-based studies (WHI [Women's Health Initiative], CHS [Cardiovascular Health Study], and MESA). The analysis involved >50,000 participants and >3,000 incident HF events, the majority of which were HFpEF (among those with available

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ejection fraction data). Pandey et al. found that there was a dose-response relationship between physical activity level and incident HFpEF but not HFrEF after multivariable adjustment. These investigators also found a dose-response relationship between body mass index and increased risk for HFpEF (which was also more prominent in HFpEF compared with HFrEF). Interestingly, both physical inactivity and obesity seemed to be independent of each other in their relation to increased risk for HFpEF, which supports the notion that the mechanisms underlying the association between physical inactivity and HFpEF are likely to be multifactorial and complex and not simply mediated through increased adiposity. These findings also further support the hypothesis that the origins of HFpEF (as opposed to HFrEF) are peripheral rather than central.

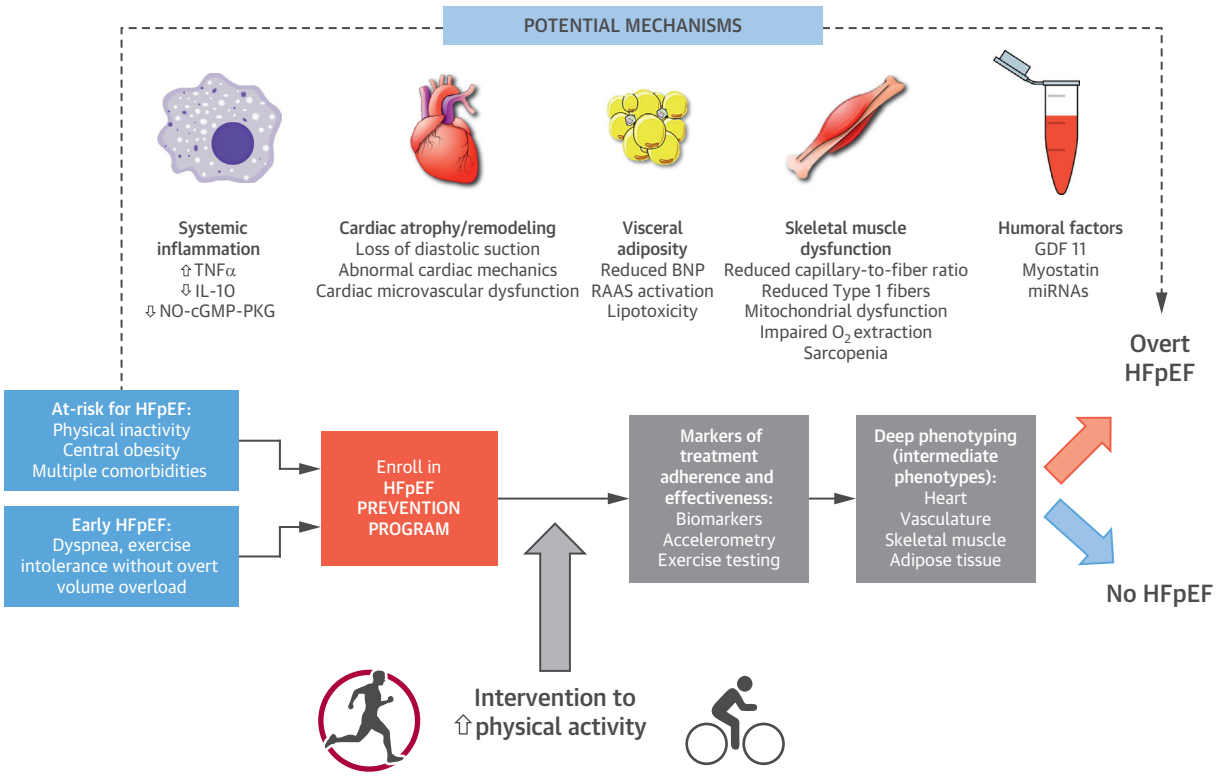
Strengths of the study by Pandey et al. (12) include its large sample size and number of HFpEF and HFrEF events; availability of patient-level data with corroboration of results by meta-analysis of study-level data across the 3 studies; the use of clinically relevant, guideline-recommended categories of leisure-time physical activity; the inverse dose-response relationship between physical activity and risk for HFpEF; and finally the exclusion of participants who developed HF within 2 years of enrollment (to exclude the possibility of reverse causation). Important limitations of the study are its inability to prove a cause-and-effect relationship; the self-reported nature of physical activity measures; and the possibility of unmeasured confounders that could explain the relationships between physical inactivity and incident HFpEF.

How does a sedentary lifestyle ultimately lead to the HFpEF syndrome? As mentioned earlier, the answer is more complex than simply increased adiposity. Based on several studies, it seems that a lack of physical activity results in abnormalities in multiple organ systems and molecular pathways that give rise to the "perfect storm" for the development and progression of HFpEF (13). Conversely, moderate or greater intensity of regular physical activity is protective against the development of these abnormalities. As displayed in **Figure 1** (top panel), a sedentary lifestyle triggers inflammation; results in cardiac atrophy, remodeling, and functional changes; increases metabolically active visceral adiposity; causes skeletal muscle abnormalities; and may be associated with circulating humoral factors that are deleterious to multiple organs, including the heart (7–9,13–17). The potential humoral factors involved in the pathogenesis of sedentary lifestyle-induced cardiac and extracardiac dysfunction (and its amelioration with exercise) is especially intriguing. Based on a parabiosis model of aging, growth differentiation factor 11 has been identified as a potential circulating factor involved in cardiac hypertrophy (14). Myostatin (also known as growth differentiation factor-8) is a myokine that is closely related to growth differentiation factor 11 and inhibits skeletal muscle myogenesis (18,19). It is possible that aging-induced sedentary changes result in increased myostatin, which results in skeletal muscle changes that are found in HFpEF (20). Other studies have shown the association between exercise training and cardiac microRNAs in the setting of HF (16). Taken together, these studies give rise to the exciting possibility that there may be circulating factors that could aid in diagnosis, serve as targets for treatment, and may be indicators of treatment response in sedentary individuals at risk for developing HFpEF.

Given the multiple ways in which a sedentary lifestyle can lead to HFpEF, how can we best use the results of the study by Pandey et al. (12) to improve the lives of our patients with HFpEF? The authors have previously published on (and are leading the charge for) increasing mid-life fitness levels as a long-term approach to preventing HFpEF (13). However, because of the potential difficulties in implementing sustained increases in physical activity in large portions of the population at mid-life, an alternate approach could be to target the individuals at highest risk for HFpEF and/or those with early-stage HFpEF.

A "huff-puff health club"—a patient-centered medical home with the ability to provide a structured intervention to increase physical activity in at-risk and/or patients with early HFpEF—may be the answer. A centralized diagnostic and intervention home for patients at risk for developing clinically overt HFpEF would solve several problems with the current care of patients with HFpEF. First, we need better ways to systematically diagnose patients who are at highest risk for the development of HFpEF and/or who have early HFpEF; in this regard, we can learn from the model of dedicated HFpEF clinical programs, which are steadily increasing in prevalence and seem to be effective in identifying and diagnosing patients with HFpEF and enrolling them in clinical trials (21). Second, we need a place where at-risk patients or patients with early HFpEF can receive holistic multidisciplinary care to optimally treat medical comorbidities common in patients with HFpEF ranging from diabetes to frailty to chronic kidney disease. Third, these at-risk patients need standardized, structured interventions to increase physical activity akin to evidence-based cardiac rehabilitation (22) for patients with HF. Finally, as is

FIGURE 1 Physical Inactivity and the Risk for HFpEF: Potential Mechanisms and Proposed Intervention Strategy



The **top part of the figure** displays potential mechanisms underlying the association between a sedentary lifestyle and overt heart failure with preserved ejection fraction (HFpEF). The **bottom part of the figure** describes a proposed intervention strategy for the prevention of overt HFpEF in at-risk patients or patients with early HFpEF. BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; GDF = growth-derived factor; IL = interleukin; miRNA = micro-ribonucleic acid; NO = nitric oxide; O_2 = oxygen; PKG = protein kinase G; RAAS = renin angiotensin aldosterone system; TNF = tumor necrosis factor.

the case with the wide variation in post-prandial glucose responses to different dietary interventions (23), there is likely a wide variation in type and magnitude of response to exercise training; the patient-centered medical home for HFpEF prevention would allow for the study and implementation of personalized diet/exercise programs by grouping at-risk patients in a single place.

Undoubtedly, we first need to thoroughly study the aforementioned HFpEF prevention program model in randomized controlled trials to prove its efficacy. However, there is reason to be optimistic. High-quality data exist showing that caloric restriction and aerobic exercise improve exercise tolerance in patients with overt HFpEF (24). Exercise training improves diastolic function, enhances skeletal muscle structure and function, reduces adiposity, and attenuates inflammation (18,25-29). As with other studies of primary prevention in cardiovascular disease, randomized controlled trials of increasing physical activity for the prevention of HFpEF will require large sample sizes and long-term follow-up. Therefore, in the near-term, we can take advantage of intermediate phenotypes to evaluate treatment adherence and efficacy, both in terms of increasing physical activity and exercise tolerance, and improving end-organ structure/function (**Figure 1**, bottom panel). Contemporary analysis of cardiac mechanics (e.g., speckle-tracking echocardiography), skeletal muscle function (e.g., magnetic resonance spectroscopy of skeletal muscle function during exercise), and physical activity (e.g., accelerometers, as were used in the NEAT-HFpEF [Nitrate's Effect on Activity Tolerance in HFpEF] trial [30]) are just a few of the ways that we can now conduct sophisticated studies to determine whether interventions aimed at increasing physical activity are effective for HFpEF prevention.

In conclusion, Pandey et al. (12) have provided strong evidence that lack of physical activity is associated with incident HFpEF. Given the critical need to focus on primary prevention to control HFpEF at the

population level, the mounting evidence of the harms of a sedentary lifestyle on the heart and extracardiac organs involved in HFpEF, and the fact that physical inactivity is a modifiable risk factor with a low-cost treatment, the time is ripe for considering patient-centered HFpEF prevention programs ("huff-puff health clubs") as a strategy to curb the HFpEF epidemic.

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KEY WORDS exercise intolerance, heart failure with preserved ejection fraction, physical activity