JACC: HEART FAILURE
VOL. ■, NO. ■, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.01.009

EDITORIAL COMMENT

Unraveling the Relationship Between Aging and Heart Failure With Preserved Ejection Fraction

The Importance of Exercise and Normative Reference Standards*

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Heart failure with preserved ejection fraction (HFpEF), the most common form of heart failure (HF) in the general adult population, is inextricably related to aging. It is rare in persons younger than 55 years and increases linearly with age thereafter. Among women ≥65 years old, 85% of new HF cases are HFpEF. Despite this marked age (and gender) disparity in HFpEF, relatively little is known regarding the mechanisms of how aging impacts HFpEF and one of its primary manifestations, exercise intolerance.

In this issue of *JACC: Heart Failure,* 2 separate, innovative studies provide important new insights into this relationship (1,2). In the first study, Wolsk et al. (1) address the fundamentally important question: How does aging affect the cardiovascular hemodynamic response to exercise stress, particularly key parameters often used to diagnosis HFpEF? Cardiac output and left ventricular (LV) diastolic pressure are common, critically important measurements in a variety of cardiovascular disorders. Yet, as Wolsk et al. highlight, available data regarding normative standards for these measures in older persons, especially LV diastolic pressure, are surprisingly sparse, particularly during exercise stress. Prior studies either had small samples or were contaminated by using convenience samples of patients referred for clinically indicated cardiac catheterization. Such patients are fundamentally neither healthy nor normal, basic requirements for determining normative reference standards. Yet, determining whether a subject is healthy becomes increasingly challenging with advancing age, given the high prevalence of atherosclerotic cardiovascular disease in older persons, often occult, which can markedly affect cardiovascular hemodynamic responses, particularly during exercise.

In order to overcome this impediment, Wolsk et al. (1) recruited volunteer subjects from the community who had no symptoms, had no known cardiac or pulmonary disease, and were nonsmokers. They then undertook extensive screening, including echocardiography, spirometry, blood tests, and exercise electrocardiography. Such extensive methods, although infrequently undertaken, are required to verify that an older study population is healthy and therefore qualified to provide valid reference standards. The resultant healthy population (n = 62) was ages 20 to 80 years, was divided into 3 separate, 20-year age categories, evenly divided by sex. Subjects underwent a maximal, upright cardiopulmonary exercise test in order to determine maximal work load. This allowed the subsequent supine cardiovascular hemodynamic measurements to be performed at

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

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3 work loads (25%, 50%, 75%) relative to each person's individual maximal work load, in addition to rest and during leg raise.

At rest, systolic blood pressure and the ratio of Doppler early LV filling to annular velocity (E/e′) were increased with aging. With leg raise, pulmonary capillary wedge pressure (PCWP) was significantly increased (16 mm Hg) in the oldest group compared to the younger group (12 mm Hg). During progressive supine exercise, although PCWP was essentially unchanged in the younger group, reflecting normal LV chamber compliance and relaxation during exercise challenge, PCWP rose progressively in the older group to a mean of 23 mm Hg, and in some patients exceeded 25 mm Hg, the traditional upper threshold for normal. Remarkably, this occurred even though these subjects were well screened and healthy, and they also had substantially lower (130 W) absolute 75% maximal work loads than their younger comparison group (174 W). Cardiac output was significantly lower and LV stroke volume was numerically lower; this resulted in an upward, left-shifted relationship between change in PCWP with change in cardiac output, indicating increased LV diastolic stiffness. Mean pulmonary artery pressure, another hemodynamic measure highly relevant to HFpEF pathophysiology, was also increased in the older age group, as were systolic blood pressure and systemic and pulmonary vascular resistances. Most of these results are in general accordance with observations from other investigators (3-5). There are minimal data on PCWP in healthy aging subjects during exercise with which to compare. Higginbotham et al. (3) found no significant increase in PCWP with aging in healthy subjects but did not study subjects older than 50 years.

These results have several important implications. They again highlight the importance of performing exercise or some other challenge in assessing cardiovascular performance for evaluation of patients with HF (4). They also highlight the very strong impact of aging on cardiovascular exercise function, particularly aspects that are thought to play key roles in the pathophysiology of HFpEF. These findings may help explain why HFpEF is particularly common in older persons, because even when healthy and normal, older persons have substantial limitations in cardiovascular reserve, including cardiac output, heart rate, stroke volume, heart rate, and systolic and diastolic function, compared to younger persons. These alterations are present in this population even before the additional adverse effects of chronic hypertension, diabetes, obesity, and pulmonary and renal disease that are all highly prevalent in the HFpEF population.

The authors suggest that 1 implication is that thresholds for PCWP used to support the diagnosis of HFpEF should be individualized by age, and this seems reasonable. However, rigidly applying a substantially higher than currently accepted threshold (25 mm Hg with exercise) could potentially exclude patients with valid HFpEF, so this merits further discussion and replication. The supine exercise work load used in the present study, although 75% of upright max, was likely nearly 100% of supine maximal effort. This is a substantially higher exercise work load endpoint than used in clinical measurement of exercise PCWP, which rarely aims for a maximal endpoint. This might have contributed to the relatively high PCWP measurements observed in the older subjects. In addition, v waves can have a marked influence on PCWP measurements, particularly during exercise, and the present report does not mention whether these were present and how they were addressed. In addition to the expected measurement variability of PCWP, the conditions under which clinical cardiac catheterization is conducted (diuresed, stable, well-compensated, optimal volume status) differ markedly from those when a patient presents with an exacerbation, biasing toward underestimation of true LV filling pressure.

Beyond these considerations, diagnosis of HFpEF should not rely solely on any single piece of data, even one as pivotal to the HFpEF syndrome as LV diastolic pressure. Indeed, the current (2013) American College of Cardiology/American Heart Association guideline (Online Appendix) does not require any measurement of LV diastolic function (or B-type natriuretic peptide either), or meeting any specific threshold, for diagnosis of HFpEF. Instead, it defines HFpEF phenomenologically as signs and symptoms of HF, preserved EF, and no alternative explanation for the patient's symptoms. All observations supportive of the diagnosis should be considered and given relative weight in accordance with the goals of the evaluation, which can vary considerably depending on whether the goal is clinical diagnosis or inclusion in a clinical trial. Even when LV diastolic pressure is available, the constellation of symptoms and signs consistent with HF is of critical importance, and when no other explanation for these symptoms is apparent, deviations from expected measurement thresholds should not necessarily dissuade clinicians from diagnosing HFpEF. Failure to consider the totality of evidence for HFpEF could lead to missed diagnosis.

In the second study in this issue of *JACC: Heart Failure,* Pandey et al. (2) report another important finding regarding exercise and HFpEF. Using the large, population-based CARDIA (Coronary Artery

Risk Development in Young Adults) study, they examined cardiorespiratory fitness (CRF) via maximal treadmill exercise test in young (ages 18–30 years) adults and in middle-aged persons, and then 25 years later they performed a comprehensive Doppler echocardiographic examination. They also performed repeat exercise testing in a subset. They found that lower CRF in young age was associated with subsequently smaller LV size and higher Doppler-estimated LV filling pressure as well as lower systolic function (measured by LV strain) during middle age. Interestingly, although the changes in systolic function were related to traditional cardiovascular risk factors, the changes in Doppler diastolic function were independent of other cardiovascular risk factors. Deterioration in CRF during follow-up was associated with greater abnormalities in systolic function, LV diastolic and systolic function, and concentric LV remodeling (relative wall thickness), although interestingly, not left atrial size.

These interesting findings further emphasize the relationships among diastolic function, aging, and exercise function. Although relationships with subsequent HF events were not reported and association does not confirm causality, these data suggest the possibility that lifelong maintenance of CRF could favorably impact subsequent development of HFpEF in late life. This hypothesis is compatible with evidence from multiple studies showing that exercise training improves symptoms, exercise capacity, and quality of life in older patients with established HFpEF (6). Because CRF is adversely impacted by obesity, this hypothesis is also compatible with recent evidence that dietary weight loss in obese HFpEF patients improves exercise intolerance and quality of life to a similar degree as exercise training, and the 2 interventions are additive in their effect (6).

It's intriguing that these 2 interventions, exercise training and caloric restriction, both of which favorably impact CRF, have been successful in improving HFpEF whereas most other strategies tested to date have not been as successful. The mechanisms of the relationship between changes in CRF and HFpEF are not well understood. However, habitual exercise improves a range of cardiovascular risk factors and improves function in a broad array of organs in addition to the heart, and it can favorably impact many of the comorbidities that are common in HFpEF and independently contribute to poor outcomes, all important considerations given increasing recognition that HFpEF may be a systemic disorder (7).

Unfortunately, maintaining or improving CRF requires a lot more effort than taking a pill. The magnitude of the inexorable, age-related decline in CRF can be significantly reduced with regular exercise. However, individual efforts at improving CRF are usually short-lived. However, if we hope to harness the wide-ranging and robust benefits of exercise and diet for our patients with a variety of age-related cardiovascular conditions, including HFpEF, we will have to learn a lot more regarding the behavioral aspects of successfully using these potent interventions and maintaining them during long-term follow-up.

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KEY WORDS aging, diastolic function, exercise, fitness, heart failure with preserved ejection fraction

APPENDIX For supplemental references, please see the online version of this article.