

EDITORIAL COMMENT

Heart Failure With a Preserved Ejection Fraction

What Is in a Name?*

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The terminology for what has become the most common form of heart failure (1) has evolved in the medical literature. Two decades ago, Kitzman et al. (2) studied a small group of patients with heart failure and normal left ventricular ejection fraction and demonstrated that exercise-induced increases in pulmonary capillary wedge pressure were not accompanied by increases in end-diastolic volume. As a result of this and other observations of ventricular diastolic dysfunction (3,4), the term *diastolic heart failure* became popular and remains in common use today. As the epidemic of this condition grew (1), efforts to measure diastolic function, to understand the mechanisms of diastolic dysfunction, and to develop strategies to enhance diastolic performance intensified. Unfortunately, although important advances have been made, this approach has not yet led to significantly better outcomes. Much controversy now exists over the role of diastolic dysfunction in heart failure with normal left ventricular ejection fraction.

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Accordingly, in this issue of the *Journal*, Haykowsky et al. (5) sought to replicate their previous observation that effort intolerance in patients with heart failure and normal ejection fraction relates to failure of the Frank-Starling mechanism (i.e., a blunted end-diastolic volume response to exercise that limits exercise stroke volume and cardiac output). They studied 48 well-characterized patients with heart failure with preserved ejection fraction (HFPEF), and 28 sedentary but otherwise healthy age-matched controls.

Participants exercised to exhaustion on an upright cycle ergometer with concomitant oxygen consumption testing and transthoracic echocardiography. Cardiac output at the various workloads was estimated using myocardial volumes from the 4-chamber apical view, enabling algebraic estimation of the arteriovenous oxygen difference ($A-V_{O_2}$).

The provocative findings in this study in many ways did not support commonly accepted assumptions about HFPEF. Measured end-systolic and -diastolic ventricular volumes were lower in HFPEF patients than in controls, both at rest and at peak exercise. However, patients and controls had similar percentage increases in end-diastolic volume, stroke volume, and cardiac output at matched workloads, suggesting that HFPEF patients did not have difficulty filling the left ventricle during exercise. In fact, the percentage of increase in end-diastolic volume at peak exercise was actually greater in the HFPEF patients than in the controls. Interestingly, the 2 factors limiting cardiac output at peak exercise in HFPEF patients were impaired ventricular systolic and heart rate reserve. Moreover, although peak VO_2 was partially determined by peak cardiac output, the change in $A-V_{O_2}$ from rest to peak exercise was a stronger predictor of peak VO_2 in HFPEF patients. The authors concluded that exercise limitations in HFPEF patients are not primarily due to diastolic dysfunction and hypothesized that noncardiac factors are important drivers for symptoms in HFPEF.

We commend Haykowsky et al. (5) not only for their willingness to reevaluate widely held assumptions, but also for conducting a technically demanding study in a patient population that is notoriously difficult to recruit. Their HFPEF study patients were similar to large epidemiological cohorts, which helps reduce uncertainty about the generalizability of their results. Despite a population likely to have poor echocardiographic windows, they obtained adequate images during upright cycle ergometry to evaluate ventricular volumes in 48 of 59 patients. Notably, the authors present important findings that are not consistent with their initial hypothesis.

Some additional aspects of the study population deserve mention. Overall, the patients reported relatively mild symptoms and had modest evidence of neurohormonal activation. In addition, subjects had relatively “pure” HFPEF, with no known coronary, pulmonary, or renal disease. Although these exclusions facilitated recruitment of a cohort that could perform adequate exercise and enabled analysis of the specific physiological factors that limit exertional capacity, in community and hospitalized HFPEF patients, multiple medical comorbidities are the rule, not the exception. Conditions such as diabetes and renal insufficiency impair endothelial function and could affect $A-V_{O_2}$; skeletal muscle wasting (sarcopenia), often present in older heart failure patients, could reduce peripheral oxygen extraction. Many HFPEF patients are anemic, which would exacerbate problems related to impaired peripheral oxygen

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extraction in the setting of reduced oxygen delivery. It is not known whether HFPEF patients with a more severe phenotype or those with commonly found comorbidities would have similar physiological findings with exercise.

Exercise oxygen consumption testing is commonly used to evaluate patients with heart failure. However, particularly in frail older adult heart failure patients, measured peak VO_2 does not always predict heart failure symptom burden (6). As seen in Figure 1 from the Haykowsky et al. study (5), at low matched workloads (rest to 25 W), curves for measured cardiac output, A- VO_2 diff, and VO_2 are nearly identical in HFPEF patients and controls; between-group differences in these parameters become apparent only at peak exercise. Older adult patients with systolic heart failure have impaired oxygen kinetics with submaximal exercise (i.e., take longer to increase oxygen consumption at the start of exercise and have an oxygen “debt” to repay after activity (7). Submaximal oxygen kinetics have not previously been reported in HFPEF, but could further clarify the relationships between cardiac output, A- VO_2 , and the intolerance of low-workload activities reported by many HFPEF patients.

As noted by Haykowsky et al. (5), the results of their present study should now not be surprising. Their original paper (2) included a small cohort ($n = 7$) in whom several had etiologies of heart failure (amyloid cardiomyopathy and obstructive hypertrophic cardiomyopathy), which are now well recognized to have limited use of the Frank-Starling mechanism due to impaired diastolic filling during exercise (8). These disorders are also not associated with long-standing systemic hypertension, the most common contributing factor to HFPEF. Pulmonary capillary wedge pressures were used in their original cohort as a surrogate of the left ventricular end-diastolic pressure. At high exercise heart rates, these pressures can dissociate, making the true contribution of ventricular diastolic function difficult to determine (9). As summarized in their Table 5 (5), several other contemporary studies also show that impaired ventricular diastolic filling does not limit exercise tolerance in the majority of HFPEF patients.

The 1995 ACC/AHA guidelines referred to heart failure with normal left ventricular ejection fraction as “heart failure due to diastolic dysfunction” (10). The realization that not all patients had diastolic dysfunction (11) and the heterogeneity of the population with this syndrome (12,13) contributed to a change in nomenclature. In 2001, guidelines used the term “heart failure with preserved systolic function” (14), until subsequent studies (including the present investigation [5]) documented impaired ventricular systolic reserve in these individuals. The data presented by Haykowsky et al. (5) and others raise the intriguing possibility that vascular, skeletal muscular, and/or other peripheral factors contribute to HFPEF, and such areas are ripe for further investigation.

Regardless of the physiological mechanisms that are most significant in an individual patient, HFPEF probably takes decades to develop. Particularly in older patients with

multiple comorbidities, HFPEF may be difficult to reverse. Strategies aimed at HFPEF prevention and improving quality of life in patients with prevalent disease are sorely needed (1,15). In recent years, the scope of HFPEF research has broadened in an attempt to define the common underlying mechanisms that mediate the diverse cardiac and vascular abnormalities of this syndrome. One emerging risk factor consistently associated with cardiovascular remodeling and dysfunction in HFPEF animal models (16,17) and recently confirmed in human HFPEF (18) is chronic inflammation, which independently predicts incident HFPEF in community-dwelling older adults (19).

Viewed in this context, studying the response to acute and chronic exercise in HFPEF can provide much more than hemodynamic information. Kitzman et al. (20) previously showed that exercise training improves peak VO_2 , submaximal exercise tolerance, and quality of life in HFPEF. Exercise training reduces chronic inflammation in some populations, including obese, insulin-resistant hypertensives (21) and frail, obese older adults (22) who may be at risk of developing HFPEF. The effects of dietary patterns, the key instigator of inflammation and adverse cardiovascular remodeling in HFPEF animal models (16,17), have not been extensively investigated in prevalent HFPEF (23) but appear similar in potential HFPEF precursors (24,25). Given the largely disappointing results of clinical drug trials to date in HFPEF, further lifestyle modification studies could produce valuable adjuncts to therapy, provide a window into pathophysiology, and eventually lead to preventive strategies for this major public health threat.

The most recent heart failure guideline updates (26,27) use the descriptive term HFPEF. This evolution in nomenclature is appropriate for several reasons. First, the term diastolic heart failure suggests a single operative mechanism, which is not present in every patient with HFPEF and, to date, has not been targetable by any specific intervention. Second, the change in nomenclature keeps pace with the recent scientific discovery. Because the HFPEF terminology is observational of the phenotype without suggesting a predominant mechanism, it paves the way for new studies that will perhaps lead to innovative ways to understand and treat the condition. As our scientific knowledge evolves, we will develop newer methods to classify subjects with HFPEF and likely different names, ideally based on treatable pathophysiological mechanisms. The past 20 years suggest that keeping an open mind about the nomenclature of HFPEF contributes to a broader, more inclusive, and, we hope and expect, a more productive view of this complex and heterogeneous syndrome.

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