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EDITORIAL COMMENT

What Limits Functional Capacity in Heart Failure With Preserved Ejection Fraction?

Unravelling the Knots of an Enigma*

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Conventional wisdom is that breathlessness in patients with heart failure is caused by high left heart filling pressures and stiff lungs ("backwards failure"), but the evidence that this is always the predominant mechanism is not overwhelming. Exercise can also be limited by failure to increase cardiac output ("forwards failure") and by inadequate oxygen delivery to exercising skeletal muscles, causing lactic acidosis and breathlessness mediated by the rapid activation of central chemoreceptor reflexes. Using ejection fraction to define heart failure makes limited sense because it tells us nothing about filling pressures and because it is a ratio that indicates neither stroke volume nor cardiac output. Instead, we need to discern from detailed pathophysiologic studies what limits functional reserve in individual patients. We would not diagnose inducible myocardial ischemia without stress testing, and some form of functional testing should similarly become the norm to define chronic heart failure.

SEE PAGE 117

Consensus would be invaluable, but there seem to be almost as many theories about the mechanisms of heart failure with preserved ejection fraction (HFpEF) as there are investigators. The report by Pandey et al. (1) in this issue of *JACC: Heart Failure* is therefore timely. They performed a systematic review of 17 cohorts of patients with HFpEF in whom hemodynamic data were obtained invasively at rest and during exercise, together with oxygen consumption. The authors present results from a pooled analysis of 910 patients and 476 control subjects. Because they had no access to individual patient data and because there were variations in methods used among studies, they report results as standardized mean differences (SMDs) (also known as Cohen's d).

Impaired exercise capacity in HFpEF patients was related in order of effect size to chronotropic incompetence (SMD: −1.9), elevated pulmonary capillary wedge pressure (SMD: +1.8), blunted augmentation of arteriovenous oxygen content difference (SMD: −1.6), and reduced stroke volume reserve (SMD: −1.3). These relationships were all moderately strong. The weighted mean differences (Supplementary Table S4 in Pandey et al. [1]) indicate that, on average, patients with HFpEF had a peak heart rate of >20 beats/min lower than that of controls, a higher pulmonary capillary wedge pressure (by 9 mm Hg), and a lower stroke volume index (by 6 ml/m^2), as well as lower peak oxygen consumption. In addition, the investigators confirmed (with data from 8 cohorts) an inverse relationship between functional capacity and pulmonary hypertension.

These data are interesting, but they also demonstrate the difficulties of performing clinical research in HFpEF. In particular, the subjects included in this analysis are not typical of most patients. Their mean age was only 61.3 years, and only 14% were in atrial fibrillation. Notably, and inexplicably, 51% of control subjects had hypertension, and 13% had diabetes; because both conditions are strong risk factors for HFpEF, their inclusion is likely to have reduced differences between the groups. These risk factors in

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controls may explain why the investigators found no significant associations between age, body mass index, or hypertension with exercise reserve. Hemodynamic studies have shown that it is late systolic rather than peak blood pressure that impairs left ventricular LV diastolic untwisting and reduces rapid early diastolic filling (2). That was not investigated, however, so a direct effect of central arterial pressure on diastolic function and exercise capacity cannot be discounted.

There was significant heterogeneity among studies for all the measured variables. Patients were upright or semisupine during exercise in 12 studies and supine during 6. It is likely that hemodynamic responses vary according to posture, with increased venous return during supine exercise increasing the probability that elevated end-diastolic pressures are a limiting factor. There is increasing evidence from many studies (although not this meta-analysis) that limited stroke volume reserve due to adverse ventricular-arterial coupling may be an equally important factor. That may be more important in early stages of HFpEF, whereas impaired compliance with an upward shift of the end-diastolic pressure-volume relationship and an increase in end-diastolic pressure may become more important in later stages when there is established interstitial myocardial fibrosis.

Left ventricular end-diastolic volume (LVEDV) appeared to increase less in patients than in controls, when they were upright rather than supine during exercise, but the difference was insignificant perhaps because of imprecision in its measurement; Figure 3C in the article by Pandey et al. (1) shows much wider confidence intervals for LVEDV than for other variables. In 1 study included in the analysis, patients were investigated during both upright and supine exercise, and there were significant differences, with a greater increment in cardiac output when upright; unfortunately data for filling pressures were obtained only during the supine protocol (3).

No data are reported for peripheral blood flow, but patients with HFpEF were less able than controls to increase peripheral oxygen extraction (as indicated by the differences in arteriovenous oxygen content). Abnormal microvascular perfusion of exercising muscles due to endothelial dysfunction and/or to increased vascular resistance, and metabolic changes, may also contribute to poor exercise capacity (4).

A concern for interpreting this pooled analysis is that at least 7 cohorts were recruited by using an elevated LV filling pressure as an entry criterion, whereas 8 cohorts did not require any objective evidence of resting diastolic dysfunction. It remains debatable whether an elevated LV filling pressure is essential for diagnosing HFpEF, but certainly some older patients with severe dyspnea on exertion from a cardiac cause may have normal diastolic pressures (and normal brain natriuretic peptide concentrations) at rest. There is insufficient evidence to support the use of a noninvasive index such as the E/e′ ratio as a surrogate for invasive measurements during exercise (5), so it is prudent not to use E/e′ as a single diagnostic criterion for diastolic dysfunction, especially when recruiting to clinical trials. In their pooled analysis, the investigators analyzed changes in pulmonary capillary wedge pressure only in the 9 studies in which it was measured directly, but most of those studies applied the same measurement to define HFpEF. This might have introduced some bias and overemphasized the impact of high LV filling pressures on exercise capacity in older people with dyspnea. Beta-blockers were withheld only in 6 studies, so the contribution of chronotropic incompetence could also have been exaggerated.

For all the relationships reported, we cannot be sure if they are incidental associations, causal links, or consequences of disease. Chronotropic incompetence, for example, could be caused by sympathetic insensitivity, limiting the increase in cardiac output, or it could be a manifestation of the fact that patients stop exercising at lower heart rates because they have already developed lactic acidosis or high filling pressures. More detailed studies in larger numbers of patients will be needed to assess if there is concordance between the inability to recruit stroke volume and the increase in filling pressures, or if these are independent mechanisms. Almost certainly, different factors or combinations of factors will be variably important in individual patients, perhaps related to their stage in the natural history of HFpEF. Different mechanisms may influence function during low and high workloads during different exercise protocols in different postures.

Already, we should be jettisoning recruitment to trials based mainly on the crude and uninformative criterion of ejection fraction. In my opinion that should include the illogical division of patients into 3 categories (now with “mid-range” ejection fraction added) because the limited precision of many methods of measuring ejection fraction means that a variation of ±10% lies within the range of variability of repeated measurements. Alternative approaches should be explored, such as using machine learning to study global and regional LV function throughout the cardiac cycle (6) in order to determine what is most efficient for categorizing patients and for predicting outcomes. We need longitudinal studies to

determine which resting or stress indices correlate best with responses to treatment and to show whether simpler exercise protocols could give us similar information.

In summary, the meta-analysis by Pandey et al. (1) is helpful, but its interpretation is laden with caveats; we are left with almost as many questions as answers. That is not a criticism of their report but an acknowledgment that it illustrates the limitations of our current knowledge. Too many studies of exercise in HFpEF patients have been small, with so much variation in methods that it is difficult to get a proper overview (7). HFpEF, of course, is not a discrete disease but a clinical syndrome that has many underlying basic mechanisms and probably many overlapping and interacting clinical pathophysiological consequences. Hypertensive heart disease in a 60-year-old, cardiac amyloidosis in a 70-year-old, and unsuccessful cardiovascular aging in an 85-year-old may all cause dyspnea, but lumping them together as one diagnosis because they all have a normal LV ejection fraction has been counterproductive. Unless we can split patients according to shared characteristics identified by precise clinical phenotyping during exercise, we will continue to struggle to establish effective treatments.

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