

EDITORIAL COMMENT

# Determinants and Correlates of Exercise Capacity in Heart Failure\*



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The heart, lungs, blood, vasculature, and skeletal muscle integrate in a complex way to allow humans to interact with their environment, through locomotion and other forms of physical exercise (1). This interaction becomes challenged in people with the clinical syndrome of heart failure (HF) (2). In addition to the very reasonable desire to live longer, people with HF also want to be able to do things, like ascending stairs, carrying groceries, or mowing the lawn. As health care providers, it is imperative for us to understand why they are limited, so that we can offer ideas for effective ways to improve exercise capacity and thus quality of life.

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In this issue of the *JACC: Heart Failure*, Shimiie et al. (3) present new data correlating indices of cardiovascular function with exercise capacity in people with and without HF. Cardiopulmonary exercise testing was performed with simultaneous echocardiography in 45 subjects—16 with HF and preserved ejection fraction (HFpEF), 15 with HF and reduced ejection fraction (HFrEF), and 14 with normal cardiac function. Data were acquired at rest, during unloaded cycling, at anaerobic threshold, and at peak exercise. Aerobic capacity was quantified by the peak rate of oxygen consumption ( $\dot{V}O_2$ ) achieved during exercise. Regression analysis was performed to identify correlates of peak  $\dot{V}O_2$  overall and within the 3 subject groups.

Patients with HF displayed impaired exercise capacity that was coupled with lower cardiac output (CO) (3) as shown in previous studies (4-7). The latter

was caused by impairments in both heart rate (HR) and stroke volume (SV) (3). Left ventricular (LV) function, assessed by mitral annular tissue velocities during systole and diastole, was impaired in both HF groups, and Doppler-estimated LV filling pressures ( $E/e'$  ratio) were higher in the HF subjects, as expected. Each of these indices was correlated with exercise capacity, both at rest and during exercise, reinforcing the importance of myocardial dysfunction in the pathophysiology of exercise intolerance in HF. In addition to central factors (CO, filling pressures), exercise capacity can also be constrained by factors peripheral to the heart—including the vasculature, endothelium, and skeletal muscle (2). Prior studies in both HFrEF and HFpEF have demonstrated clearly that these peripheral factors also play an important role (7-12). The peripheral contribution was quantified in the current study by the arterial-venous  $O_2$  content difference ( $AVO_2\text{diff}$ ) (3). This parameter was not directly measured, but rather calculated from the quotient of  $\dot{V}O_2$  and CO according to the Fick equation.

Peak  $\dot{V}O_2$  was correlated with HR, SV, and  $AVO_2\text{diff}$  in all 3 groups (HFpEF, HFrEF, and normal cardiac function), suggesting that these are key factors affecting exercise performance, regardless of HF status (3). Mitral regurgitation worsened during exercise in HFrEF subjects, as previously reported (13), and this correlated with peak  $\dot{V}O_2$  in this cohort (but not the other groups). This finding suggests that dynamic mitral regurgitation is an important factor specific to HFrEF. The authors estimated LV diastolic chamber compliance by the ratio of LV end-diastolic volume to  $E/e'$  (3). Estimated compliance was decreased in HFpEF compared with the other groups and was correlated with peak  $\dot{V}O_2$  in patients with HFpEF (but not the other groups) (3). These data support the idea that diastolic reserve limitations play an important role in people with HFpEF, confirming and extending prior invasive studies (14-16).

\*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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Multivariable analysis was then performed, combining all 3 groups into the same sample (3). The authors' goal was to identify "determinants" of exercise capacity, but these are only correlates because causality cannot be proven in a cross-sectional study. Multivariable analysis showed that HR and  $AVO_2$ diff were the strongest independent correlates of peak  $VO_2$ . The authors concluded from this observation that exercise intolerance in HF is predominantly owing to chronotropic incompetence and peripheral factors. The interpretation that is supported by the data is that exercise capacity is correlated independently with HR and  $AVO_2$ diff. A causal relationship is plausible but not proven by these data.

A stronger case can be made from the authors' data for HR as a "determinant" because this was both an independent predictor and markedly impaired in both HF groups (3). A caveat is that the absolute workload achieved was lower in HF patients, so it is hard to say whether lower HR was cause or consequence of exercise limitation. Did the HF patients stop exercising prematurely because of dyspnea before HR reserve was maximized? Or did the low HR truly limit them? The issue of HR response to exercise in HF remains an important unanswered question. The RAPID-HF trial (NCT02145351) is currently testing the hypothesis that improved HR responsiveness via rate-adaptive atrial pacing will improve exercise capacity in people with HFpEF.

A more controversial conclusion, at least based on the data provided by Shimiiaie et al. (3), centers on the role of the periphery. First, it should be noted that no direct measure of vascular, peripheral, or skeletal muscle function was performed.  $AVO_2$ diff was only weakly correlated with peak  $VO_2$  in univariate analysis ( $r = 0.30$ ;  $p = 0.05$ ). More important, there was no difference in  $AVO_2$ diff between the HFpEF and normal cardiac function groups at any stage of exercise, making it difficult to say that impaired  $AVO_2$ diff reserve was causing the limitation observed in HFpEF. Although some studies have shown impairments in  $AVO_2$ diff reserve in HFpEF (10-12), others have not (6,17), and it is likely that this is an important pathophysiologic distinction that contributes to the heterogeneity among people with HFpEF. This points to a potentially valuable role for exercise phenotyping in HFpEF, as recently suggested (6,11,17).

In the HFrEF group, Shimiiaie et al. (3) observed that  $AVO_2$ diff was higher during exercise, which could be interpreted to reflect enhanced peripheral function. However, a wealth of prior literature using more direct measures have clearly shown that this is not the case (8), and the higher  $AVO_2$ diff observed in the

current study in HFrEF is likely related to poor CO rather than enhanced peripheral/skeletal function (6,18). This difference harks back to the important distinction between "determinants" and "correlates" of lower peak  $VO_2$ , which are or can be 2 very different things.

The normal cardiac function group in the study of Shimiiaie et al. (3) was referred for evaluation of dyspnea; therefore, by definition, they are not truly "normal." They were significantly younger than the HF subjects and less likely to receive negative chronotropic medicines. This difference confounds the HR responses observed, although the authors did apply criteria that account for beta-blocker use in their definitions of chronotropic incompetence. The HFrEF patients enrolled seem fairly typical, but this was not the case in the HFpEF group in the current study (3). Patients with HFpEF in the community are typically older (75 to 85 years of age) women (2:1 ratio), hypertensive, obese, and likely to display multiple comorbidities (19). In the current sample, the HFpEF cohort was several decades younger (57 years), 93% male, nonobese (body mass index of 26.6 kg/m<sup>2</sup>), largely normotensive (only 47% with hypertension), with very few comorbidities (low Charlson index). Despite the absence of typical risk factors and comorbidities, there was marked concentric LV remodeling in the HFpEF group (3), with an average relative wall thickness of 0.54—much higher than previously reported (20)—and more suggestive of restrictive disease. These characteristics raise concerns about the generalizability of the current results to patients with HFpEF seen every day in the community.

The absence of an independent correlation between 2 variables does not exclude the possibility that improving 1 variable may benefit the other. For example, SV was not predictive of peak  $VO_2$  in multivariable analysis (3). This finding may relate to the fact that SV increases proportionately less with exercise (20% to 40%) than HR does (200% to 400%) (2). It is also clear that assessment of SV by echocardiography has limitations, especially compared with HR, which can be determined with very high accuracy and precision from an electrocardiogram. Therefore, it seems inappropriate for the authors to conclude that "therapies targeting cardiac function may never improve exercise capacity in HF." Indeed, even a modest 7-ml increase in SV would improve exercise CO by 1 l/min at a HR of 140 beats/min. The absence of a correlation should not be interpreted to prove absence for potential benefit from intervention, and therapies targeting both central and peripheral limitations continue to hold promise in HF.

The central implication raised by this study is that exercise phenotyping may be useful to individualize therapy, and this is a meritorious idea (3). However, before implementing this approach, one must first rigorously define what is normal and abnormal for HR, SV,  $AVO_2$ diff, LV tissue velocities, estimated LV compliance, and the host of other parameters that we can measure, both in men and women and across the age spectrum. Until those normative data are

available, exercise phenotyping in HF will remain a promising but unactionable concept, and we might continue to quibble over correlates and determinants when discussing people with HF and exercise intolerance.

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**KEY WORDS** exercise, heart failure, hemodynamics, periphery, ventricular function