JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 3, 2020

EDITORIAL COMMENT

Decoding the Pathophysiology of HFpEF With High-Resolution Phenotyping*

Nicholas E. Houstis, MD, PhD

The barriers to creating new treatments for heart failure with preserved ejection (HFpEF) have so far proven impenetrable. To prevail, the field may require a more rigorous understanding of HFpEF pathophysiology. This knowledge would serve interlocking objectives, from refining disease nosology to guiding discovery efforts. Knowledge of the cause(s) of symptoms and outcomes, coupled with the ability to measure them at scale, would enable the subtyping of patients by matching pathophysiology. Knowledge of these causal mechanisms would also enable rational therapy design, and, in a well selected population, improve the odds of a successful clinical trial.

A chief complaint among patients with HFpEF is exercise intolerance, a phenotype whose pathophysiology has been the subject of intense scrutiny. To this end, many investigators have applied a reductionist framework premised on defining exercise capacity as the rate of oxygen (O_2) consumption at peak exercise (Vo_2). Mechanisms of exercise intolerance are then taken to be defects in the individual steps of O_2 transport and consumption that move O_2 from the mouth to skeletal muscle mitochondria (the O_2 pathway). This breakdown of Vo_2 into its constituent O_2 pathway steps has the attractive feature that it can be performed quantitatively. Another attractive feature is it can be performed hierarchically, although this requires care. For example, the most common approach is to decompose Vo_2 in to 2 terms: $\dot{V}_{O_2} = Q \cdot \Delta AV_{O_2}$. The first term, cardiac output, reflects convective O_2 transport mediated by the heart. The second term, peripheral O_2 extraction, lumps all noncardiac O_2 pathway steps together, including alveolar ventilation, diffusive O_2 transport in the lungs, O_2 carried by hemoglobin, vascular redistribution of blood flow, diffusive O_2 transport to skeletal muscle, and mitochondrial respiration. The measurements needed for this 2-term analysis can be performed with familiar tools of clinical cardiology, including cardiopulmonary exercise testing, echocardiography, and arterial and venous catheters. Unfortunately, the appeal of this approach to decoupling the cardiac and noncardiac components of VO_2 is deceptive because the value of ΔAV_{O_2} depends on cardiac output as well, a consequence of the competition between convective and diffusive transport of O_2. To truly decouple the O_2 pathway into independent steps requires finer measurements and a more exacting analysis. Such an approach was adopted by Zamani et al. (1), to analyze Vo_2 in HFpEF in this issue of *JACC: Basic to Translational Science*.

SEE PAGE 211

Zamani et al. (1) sought to improve our understanding of the noncardiac causes of exercise intolerance in patients with HFpEF. Study participants performed 2 types of exercise: supine cycle ergometry with echocardiographic monitoring; and forearm exercise (isometric handgrip) with invasive monitoring. Cycle ergometry confirmed the widely recognized phenotype of reduced peak Vo_2 in HFpEF. Moreover, using echocardiographic estimates of peak cardiac output, the investigators calculated peak ΔAV_{O_2} and found that it too was reduced in HFpEF, as others have also demonstrated. The second exercise

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts. Dr. Houstis has reported that he has no relationships relevant to the contents of this paper to disclose. The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2020.02.003

modality, isometric handgrip, was monitored with a catheter in the antecubital vein and a brachial artery flow probe. These tools permitted the measurement and estimation of O_2 transport properties in the local muscle bed, including blood flow, arterial and venous blood gases, and Vo_2. The investigators then used this high-resolution phenotyping to calculate the forearm muscle diffusion conductance for O_2 (D_M). Unlike prior efforts to characterize D_M in HFpEF, the investigators' estimate did not rely on assumptions regarding local blood flow and local venous O_2 tension, because they measured these quantities directly. This forearm technique had the added advantage that it could be scalable to a broader population than is currently reachable with alternative techniques (e.g., the use of pulmonary artery catheters).

A key finding from Zamani et al. (1) was that forearm ΔAV_{O_2} was reduced in patients with HFpEF relative to control subjects, but forearm D_M was not. This finding prompts at least 2 important questions: 1) if forearm D_M is similar between patients and control subjects, can it be extrapolated that locomotor muscle D_M might also be similar between groups, contrary to previous estimates? (2); and 2) what explains the drop in forearm ΔAV_{O_2} in lieu of a defect in D_M?

Several observations likely preclude the extrapolation of the forearm findings to other muscle beds. First, at least 2 other studies used similar methodology to Zamani et al. (1) to estimate D_M in distinct muscle beds (3,4). Among control participants from all 3 studies, the values of D_M (normalized to muscle mass) in the forearm (1), whole arm (3), and single-knee extensors (4) differed widely. Similarly, muscle mass-normalized Vo_2 in these 3 muscle beds was also distinct. Though it could be argued that the control groups from each of these studies were not identical, data from within the Zamani et al. (1) study itself casts doubt on the likelihood that D_M is an invariant property across muscle beds. In particular, it was notable that in addition to D_M forearm Vo_2 (normalized to muscle mass) was also quite comparable between patients with HFpEF and control subjects. In other words, the drop in peak Vo_2 observed in patients during cycle ergometry was not recapitulated by the forearm muscles. This strongly suggests that the O_2 pathway determinants of Vo_2 in locomotor muscle differ from those of forearm muscle in patients with HFpEF. Finally, previous work has shown that modulation of arm Vo_2 and its determinants can be dissociated from whole-body Vo_2 (cycle ergometry). Boushel et al. (3) performed an exercise training study in which they found peak Vo_2 and D_M in the arm (arm exercise) increased after training, whereas peak whole-body Vo_2 remained unchanged.

If D_M differs between patients with HFpEF and control subjects in some muscle beds but not others, this fact may have important implications. It would argue against the existence of a circulating factor that uniformly compromises microcirculatory structure or function—and thus D_M—across all muscle beds. Rather, it is not difficult to imagine that differences in locomotor activity between patients and control subjects could explain differences in locomotor O_2 transport and consumption. Forearm activity might simply be more similar between groups, thereby explaining the similarities in Vo_2 and D_M. Another possibility is that patients with HFpEF are not less mobile per se, but their locomotor muscles adapt less to a given amount of mobility—they are less trainable.

To explain the drop in forearm ΔAV_{O_2} in patients with HFpEF in the absence of a defect in forearm D_M, the investigators considered alternative O_2 pathway steps. First, they noted that forearm blood flow trended higher in patients with HFpEF. An isolated rise in blood flow, *ceteris paribus*, would be expected to cause a fall in ΔAV_{O_2}, together with a sublinear rise in Vo_2. That Vo_2 was unchanged suggested the existence of additional O_2 pathway defects. The investigators entertained the possibility that anemia and or impaired mitochondrial function in HFpEF could contribute to the drop in forearm ΔAV_{O_2}. To this end, they noted that patients with HFpEF were more obese than control subjects and the degree of adiposity was correlated with the drop in forearm ΔAV_{O_2}. Furthermore, a strong epidemiological association between HFpEF and obesity has been previously recognized (5). Although it can be difficult to tease apart correlation from causation, the latter is made plausible by biological links between adiposity and anemia, muscle metabolism, and mitochondrial function.

The repeated failure of clinical trials in HFpEF strongly suggests that its pathophysiology remains insufficiently understood. The prototypical chronic symptom of this syndrome, exercise intolerance, is governed by mechanisms that are distributed over multiple organs, cell types, and subcellular systems. The resulting system properties of Vo_2 in turn give rise to tremendous mechanistic heterogeneity among patients with HFpEF (2). In the face of this

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 5, NO. 3, 2020
MARCH 2020:226–8

complexity, progress will likely require comprehensive high-resolution phenotyping combined with quantitative causal analysis. Careful studies such as the work by Zamani et al. (1) will ultimately pave the way to improving disease nosology and discovering new therapies.

ADDRESS FOR CORRESPONDENCE: Dr. Nicholas Houstis, Cardiology Division, Department of Medicine, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: nhoustis@partners.org.

REFERENCES

1. Zamani P, Proto EA, Mazurek JA, et al. Peripheral determinants of oxygen utilization in heart failure with preserved ejection fraction: central role of adiposity. J Am Coll Cardiol Basic Trans Science 2020;5:211–25.

2. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. Circulation 2018;137:148–61.

3. Boushel R, Ara I, Gnaiger E, et al. Low-intensity training increases peak arm VO2 by enhancing both convective and diffusive O2 delivery. Acta Physiol (Oxf) 2014;211:122–34.

4. Esposito F, Mathieu-Costello O, Shabetai R, Wagner PD, Richardson RS. Limited maximal exercise capacity in patients with chronic heart failure: partitioning the contributors. J Am Coll Cardiol 2010;55:1945–54.

5. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. Circ Heart Fail 2013;6:279–86.

KEY WORDS diffusion, exercise intolerance, HFpEF, peripheral oxygen extraction