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EDITORIAL COMMENT

Heart Rate Modulation in Heart Failure

Time to Slow Down?*

Neal A. Chatterjee, MD,[a] Gregory D. Lewis, MD[a,b]

Exercise intolerance is a cardinal manifestation of heart failure (HF) that potently predicts adverse outcomes. The gold standard indicator of exercise tolerance is oxygen consumption at peak exercise (pVo_2) (1). In HF, there is impairment in the reserve capacity of each component of the coordinated metabolic machinery that permits increased oxygen utilization during exercise (**Figure 1**) (2,3). Our understanding of how exercise capacity is influenced by selectively altering single components of this integrated metabolic machinery remains incomplete. Insights into the relative contribution and interaction of variables that affect exercise capacity in HF may ultimately guide individualized therapeutic interventions.

Of the myriad components of the metabolic machinery, abnormal heart rate (HR) augmentation during exercise (i.e., chronotropic incompetence [CI]) has been a focal point, given its prevalence (estimated to be 60% to 80% in HF with reduced ejection fraction [EF]), the potential for its modulation (e.g., via adjustment of nodal agents, cardiac pacing), and its association with adverse clinical outcomes (4). There remains, however, considerable debate regarding the benefits of HR augmentation in HF with reports of marked improvement in exercise capacity (5) counterbalanced by null associations (6).

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In this issue of the *Journal*, Jamil et al. (7) examine the relationship between exercise heart rate rise (HRR) and exercise capacity in patients with HF and reduced EF (HFrEF). They report a retrospective analysis of 195 patients referred for cardiopulmonary exercise testing (CPX) as well as 2 randomized, crossover interventional studies in patients with HFrEF, clinical stability, and previous pacemaker implantation. Prospectively evaluated interventions included: 1) exercise HR augmentation in 79 patients via rate-adaptive pacing (vs. fixed-rate pacing); and 2) exercise HR decrement in 40 patients using either pharmacotherapy (ivabradine) or lowering of the programmed pacemaker rate. Exercise testing was performed using a modified Bruce protocol with an initial low-level phase. The efficacy of HR interventions were assessed based on their impact on pVo_2, exercise time, and other CPX measures known to influence prognosis in HF such as exercise ventilatory efficiency (i.e., V_E/V_{CO2}).

In their retrospective analysis, the correlation between HRR and pVo_2 was highest for participants without HF ($r^2 = 0.42$) and progressively weaker for those with HF and modest left ventricular (LV) dysfunction (LVEF 35% to 50%; $r^2 = 0.37$) or severe (LVEF <35%; $r^2 = 0.18$). In this referral population, the prevalence of CI (defined as a ratio of observed HR increment to age-adjusted expected HR increment <0.80) in those with HF was 73%. Those with CI had lower exercise time and pVo_2 compared to those without CI. In prospective analyses, the impact of HR modulation was examined separately for those in sinus rhythm (SR) and atrial fibrillation (AF). HR augmentation was associated with an increased pVo_2 in AF but not SR. In contrast, HR decrement during exercise was associated with a prolonged exercise time

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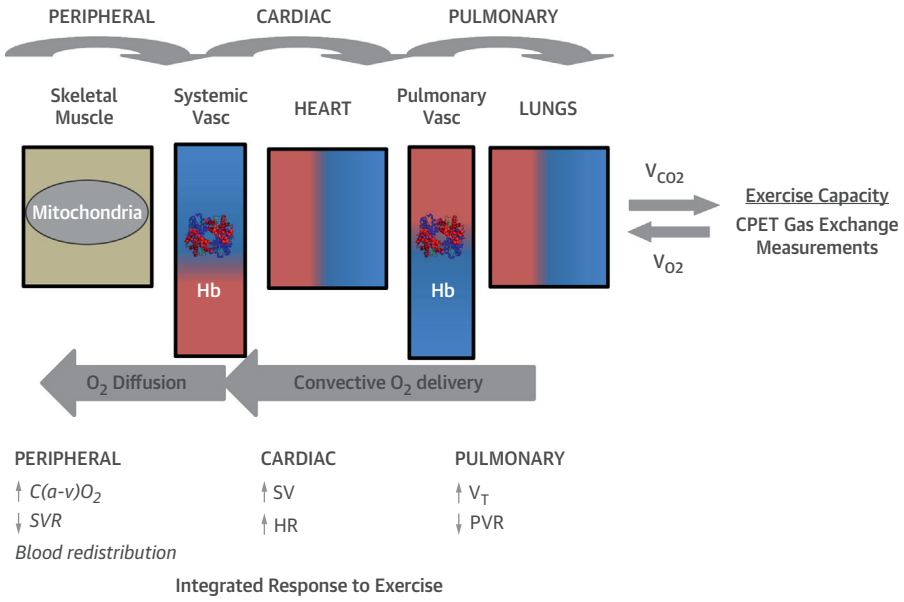
From the [a]Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; and the [b]Pulmonary and Critical Care Unit of the Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. This work was supported by NHLBI T-32 HL-007575 and does not represent a relevant disclosure but does support time for writing (Dr. Chatterjee). Dr. Lewis was supported by NIH R01 HL119154 (Bethesda, Maryland), American Heart Association 15GPSGC24800006 (Dallas, Texas), and the Hassenfeld Clinical Scholar Award (Boston, Massachusetts).

FIGURE 1 The Integrated Metabolic Machinery of Exercise



Shown are the multiple, coordinated components of the exercise metabolic machinery and the role of cardiopulmonary exercise testing in their assessment. Highlighted are changes associated with exercise within each component including central augmentation of stroke volume and heart rate as well as peripheral augmentation of oxygen extraction. $C(a\text{-}v)O_2$ = arterio-venous oxygen content difference; CPET = cardiopulmonary exercise testing; Hb = hemoglobin; HR = heart rate; PVR = pulmonary vascular resistance; SV = stroke volume; SVR = systemic vascular resistance; Vasc = vasculature; V_{CO2} = carbon dioxide output; V_{O2} = oxygen consumption; V_T = tidal volume.

but no change in pVo_2 in AF; there was no impact on exercise indices with HR decrement for those in SR.

Jamil et al. (7) should be congratulated on this important contribution to our understanding of the relationship between HR and exercise capacity in HF. In particular, the use of prospective randomized crossover design interventions focused on HR modulation and the inclusion of gas exchange measures related to prognosis in HF are features that distinguish these data from the previous literature. The study is particularly important and timely in light of the growing body of evidence linking lowering resting HRs to improved outcomes in HF and recent approval of ivabradine for the treatment of HFrEF (8). The findings of Jamil et al. (7) cast significant doubt on the causative role of CI in exercise intolerance in HF and on a uniform strategy aiming for higher exercise HRs among unselected HF patients. However, patient selection, study design, and analytic measures utilized are important to consider for contextualizing these findings and help frame opportunities for future investigation.

First, the mode of CPX has important implications in the analysis of exercise intolerance and HR interventions in HF. Although treadmill exercise is preferable to cycle ergometry to trigger rate-responsive pacing, this study utilized a Bruce protocol that employs significant stepwise increments that pose a challenge to HF patients. Indeed, the exercise times in the HR intervention arms of this study appear to cluster just beyond the steep transition from stage 1 to 2 of the Bruce protocol. Moreover, the lower respiratory exchange ratio values in HF patients compared to controls suggests that HF patients may have stopped exercising prematurely due to challenges with the ramp protocol, potentially confounding the reported HRR-Vo_2 relationships. To the extent that exercise was limited by mechanisms related to the protocol itself, there may have been decreased power to detect differences in the effects of HR interventions in this study. In contrast, more gradual treadmill ramp protocols such as the modified Naughton protocol used in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) (9) or the National Heart, Lung, and Blood Institute Heart Failure Network Protocol (10) may better reflect "real-world" exertion in HF patients and better capture the impact of HR interventions during different phases of exercise (e.g., submaximal vs. maximal).