Editorial

Diastolic Dysfunction
One Piece of the Heart Failure With Normal Ejection Fraction Puzzle

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It has recently become firmly established that patients can experience chronic and acute heart failure with a normal ejection fraction (HFNEF). We now know this disorder is the dominant form of HF in the community, and that compared with HF with reduced ejection fraction (HFREF), it is increasing in prevalence and incidence, causes at least as many hospitalizations and healthcare expenditures, causes at least as severe chronic symptoms and reduced objectively measured exercise tolerance, and, once patients are hospitalized, has death rates that are similarly grim. Until recently, however, we have invested nearly all our resources into understanding the pathophysiology and treatment of HFREF. As a result, a physician managing a patient with HFREF can rely on practice guidelines that are solidly supported by dozens of large trials demonstrating substantial improvements in each of the meaningful HF outcomes: mortality, hospitalizations, exercise intolerance, and reduced quality of life. When the patient instead has HFNEF, there is relatively little information about pathophysiology or treatment to guide the physician. This fact is reflected in outcomes, which a recent study indicates are improving in patients with HFREF but worsening in those with HFNEF. This disconcerting imbalance is magnified by sex and age, as the large burden of HFNEF falls primarily on older women.

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In the present issue of *Circulation*, Westermann and colleagues report a welcomed and important study aimed at addressing the dearth of information about the pathophysiology of HFNEF. They studied 70 very well-characterized patients with documented symptoms of HF, normal left ventricular (LV) EF, and no other detectable cause for their symptoms, including pulmonary and ischemic heart disease. The investigators used a conductance catheter to measure pressure–volume loops during supine rest, handgrip exercise, and atrial pacing to 120 bpm. They performed similar measurements in 20 subjects who had chest pain but no symptoms of HF and who were scheduled for coronary angiography. The authors are to be heartily congratulated for successfully performing detailed, state-of-the art, invasive measurements of LV function in a large number of well characterized subjects during supine rest, handgrip exercise, and pacing. This work provides an impressive amount of high-quality relevant data that further our understanding of this important disorder.

The study groups were well matched for age, sex, and body size, critical covariates in physiological studies. A potential limitation acknowledged by the authors is that the HFNEF patients were substantially younger (mean age 58 years) than in reported population-based studies (mean age 71 years). Information about the control group is sparse, however; patients referred for cardiac catheterization may differ from healthy patients in potentially important ways that could affect their responses, though it might be difficult to justify such an invasive protocol in the latter.

Compared with controls, the investigators found increased LV stiffness at rest in the HFNEF patients, and each intervention with responses shifted upward and to the left. End-diastolic volume (EDV), stroke volume (SV), and end-systolic volume were similar at supine rest; however, end-diastolic pressure (EDP) was substantially increased (16.1 versus 5.6 mm Hg), as were \(\tau\) and stiffness measures. During pacing to 120 bpm at rest, EDV and SV were significantly reduced, and \(\tau\) and stiffness were again abnormal compared with the control group. With handgrip, EDP increased modestly in control subjects but increased markedly to a mean of 23.7 mm Hg in patients with HFNEF. This increase was associated with a greater increase in systolic pressure, which can impair LV relaxation, and is indicative of abnormal vascular as well as ventricular stiffness. During handgrip exercise, EDV was not different between groups. Although stiffness was different between groups, this was primarily due to baseline differences, as stiffness did not change significantly within HFNEF patients during handgrip compared with supine rest.

The finding of increased EDP at supine rest strongly confirms the results of prior studies. The findings during handgrip and pacing are novel and significantly expand upon knowledge gained from other studies. The latter merits further discussion. In classic studies of the effect of pacing on LV volumes in healthy subjects during supine rest, increasing heart rate results in linear decreases in EDV and SV, such that there is blunting of the potential increase in cardiac output. This result is logical because at rest, the body has no use for increased cardiac output, and decreasing EDV and SV helps to minimize the increase in myocardial oxygen demand resulting from increased heart rate. The directional LV volume response to pacing in HFNEF in the present study follows the general pattern reported in healthy subjects. This is interpreted by the authors as abnor-
mally reduced LV filling resulting in abnormal EDV, SV, and cardiac output. Abnormal filling that produces reduced EDV and SV is usually associated with increased EDP, however, indicating abundant pulmonary venous return in the presence of limitations to LV inflow. Instead, in HFNEF, EDP decreased markedly, from 16.1 to 7.7 mm Hg. A drop in EDP is what has been reported in normal subjects, with a plateau at very high rates. In addition, although stiffness in HFNEF patients in the study by Westermann et al was statistically different from that in controls during pacing, it did not worsen compared with baseline supine rest values, nor did there appear to be worsening compared with baseline in other parameters of diastolic LV function. These responses, including lack of worsening in diastolic function with pacing, are similar to a previous report in Circulation that used a conductance catheter and pressure–volume loops in a small number of predominantly HFNEF patients.

Also confounding the interpretation of the pacing data is the fact that the control subjects demonstrated a response that was quite different from that described with pacing in healthy subjects at rest. Compared with their baseline values, pacing induced a small drop in EDP (from 5.6 to 4.5 mm Hg). This was paradoxically accompanied by a significant increase in EDV. As a result of increases in heart rate and SV, cardiac output nearly doubled. These EDV and SV responses are atypical of previously reported healthy subjects. These factors somewhat limit the strength of conclusions regarding the effect of pacing.

Exercise intolerance is the primary symptom of chronic HFNEF and the primary determinant of reduced quality of life; thus, understanding its pathophysiology and treatment is an important goal. Appreciating the contributions of the study by Westermann et al to this goal requires a brief review of exercise physiology principles. Exercise capacity can be quantified objectively as oxygen consumption ($V_o$) during exhaustive exercise. The relationships of the determinants of maximal exercise $V_o$ are shown by the Fick equation:

$$V_o = \text{stroke volume} \times \text{heart rate} \times \text{arteriovenous oxygen difference}.$$ Measuring at least 3 of these factors simultaneously during exercise and solving for the remaining one can provide insight into mechanisms of exercise intolerance.

The present study involved upright bicycle exercise in a separate setting and found markedly reduced peak workload and reduced 6-minute walk time in HFNEF patients compared with controls. Though this added to the already significant complexity of the protocol, it proved that the HFNEF patients had exercise intolerance, an essential characteristic of HF. Correlating the observed LV responses from supine rest, handgrip, and pacing with peak exercise capacity measures would support their relevance to exercise intolerance and strengthen inferences in this regard.

To fully understand the relative contribution of a specific variable to exercise intolerance, it must be measured during upright aerobic exercise and/or serial evaluations of exercise capacity before and after perturbations of a relevant component of the exercise response while controlling for others. During aerobic exercise, heart rate increases from parasympathetic withdrawal combined with sympathetic activation, and the latter combined with other mechanisms increase the velocity and magnitude of LV relaxation to allow adequate LV filling to increase EDV and SV during tachycardia with only modest increases in EDP. The upright position is important because LV pressure and volume responses differ greatly with posture because of the marked influence of gravity on venous return. Thus, the LV response during exercise is not easily studied except with the genuine article. It is therefore regrettable that the published literature for LV function during aerobic exercise in HFNEF appears to still consist of just 2 small studies involving a total of only 24 patients.

The study by Westermann et al is of particular interest because first Brubaker et al and recently Borlaug et al reported that a significant portion of HFNEF subjects have an abnormally blunted heart rate response to exercise. Furthermore, HFNEF patients with such chronotropic incompetence
have even more severe exercise intolerance than those without it.\textsuperscript{17} Although the mechanism of this finding is unknown, it is found in patients with HFREF as well (Figure).\textsuperscript{17} This fact has led to the hypothesis that selective, physiological pacing during exercise may improve exercise intolerance in HFNEF. To test this hypothesis, a group of investigators including this editorialist have planned a commercially funded clinical trial that is projected to launch soon. The success of the trial will depend on many factors, including avoidance of decreased LV filling and SV that could diminish pacing-induced increases in cardiac output during exercise. Thus, the observations by Westermann and colleagues\textsuperscript{8} have immediate relevance to the creation of a potential therapeutic intervention.

Investigations frequently focus narrowly on the LV component of the exercise response. However, the response to aerobic exercise in humans is a wonderful concert played by an orchestra comprising the cardiac, vascular, pulmonary, neural, endocrine, hematological, and skeletal muscle systems, all finely tuned and tightly coordinated to deliver the exact amount of oxygenated blood at the precise location and time required.\textsuperscript{14} In HFREF, major abnormalities have been found in each of the above systems, skeletal muscle in particular, and have been shown to significantly impact exercise intolerance independent of LV function. In fact, in HFREF, when all components of the exercise response are taken into account, LV abnormalities previously thought to have primacy, such as reduced EF and increased EDP, have more modest roles in determining exercise capacity than initially presumed. As with the history of HFREF research, the few small studies that have examined mechanisms of exercise intolerance in HFNEF to date have focused exclusively on LV and vascular function.\textsuperscript{3,16–19} An early study in HFNEF, however, found that invasively measured exercise arterial-venous oxygen difference was substantially reduced, indicating a potential role of peripheral factors, such as vascular and skeletal muscle.\textsuperscript{3} Thus, regardless of whether LV stiffness, chronotropic incompetence, or both are key contributors to exercise intolerance in HFNEF, as the authors\textsuperscript{8} to their credit imply, there is likely to be far more to the pathophysiology puzzle yet to be explored.

Another caveat is that our traditional view that understanding the pathophysiology of a disorder will inevitably provide the key to designing specific effective therapies has not fared well during the decades spent developing treatments for HFREF. In fact, the inotropes aimed at the most obvious pathophysiological abnormality in HFNEF, decreased LV contractility, paradoxically increased the rate of death. Thus, establishing LV stiffness as a pivotal pathophysiology of HFNEF may not necessarily translate directly to successful treatment whenever a direct lisutrop becomes available.

This elegant study by Westermann and colleagues\textsuperscript{8} provides further illumination of one potentially central piece of the HFNEF puzzle. However, our experience with the quest to understand HFREF, along with the mixed results from the few trials of HFNEF to date, suggests that we are likely a long way from a complete understanding of its pathophysiology and its optimal treatment. Although this may seem a grim view of the current status of HFNEF, it provides a mandate for a continued energetic and open-minded search for all the pieces of the HFNEF puzzle.

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