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EDITORIAL COMMENT

Understanding Results of Trials in Heart Failure With Preserved Ejection Fraction

Remembering Forgotten Lessons and Enduring Principles*

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In this issue of the *Journal*, Holland et al. (1) provide a valuable contribution to the literature by reporting the first meta-analysis of medication trials for heart failure (HF) with preserved ejection fraction (HFpEF). This work is important, since HFpEF is the most common and fastest growing form of HF in the United States (2). The prognosis for HFpEF is worsening, while it is improving for HF with reduced ejection fraction (HFREF) (2). The burden on patients and society from HFpEF is similar to that from HFREF, measured by healthcare costs (3), rehospitalizations, mortality after hospitalization, exercise intolerance, and quality of life (4–6). Despite its importance, there are large gaps in our understanding of the pathophysiology and treatment of HFpEF. This is demonstrated by a review of the current American College of Cardiology/American Heart Association statement on management of HF. There are 21 pages discussing HFREF treatments supported by definitive trials, but just 3 paragraphs regarding HFpEF (7).

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By pooling data from reported treatment trials, Holland et al. (1) help fill this chasm. Their meta-analysis focuses on the key outcomes in HF: exercise intolerance, hospitalizations, and death. The authors conclude that medical treatments may improve exercise intolerance, but not mortality. They rightly highlight that this is still an important benefit, since exercise capacity is a strong determinant of health-related quality of life, and since these patients are usually advanced in age (5). In older persons, it can be a more important and achievable goal to "add life to the remaining years than to add years to the remaining life" (8). Another conclusion to add is that there were no negative trends in any outcomes, giving reassurance when these medications are needed for other indications in HFpEF patients (9).

Holland et al. (1) point out that our work is far from finished, noting that their conclusions regarding exercise capacity are based on data from only 183 total treated patients drawn from 6 trials. Further, if one excludes the largest trial, which enrolled elderly men after myocardial infarction with EF as low as 40%, then more than one-third of the remaining patients were drawn from a single, adequately powered study that was decidedly neutral (10). This is potentially consequential because, as Holland et al. (1) highlight, there can be substantial bias against publication of trials, particularly smaller ones, that have neutral or negative results. This creates an important unknown in meta-analyses. In addition, the few available studies did not allow Holland et al. (1) to examine whether there are differences between medication classes. Thus, while this timely meta-analysis supports a positive trend, additional trials focused on the important outcome of exercise capacity in HFpEF are needed.

Holland et al. (1) report 2 findings that seem to contradict conventional wisdom. The first is that improvements in exercise capacity among HFpEF patients have not been accompanied by improvements in mortality. Numerous observational studies indicate that exercise capacity and survival are closely related in HF patients. However, a lesson learned during the 5-decades-old quest to determine optimal therapy for HFREF is that treatment effects on exercise capacity and survival can diverge (11). For example, inotropes produced the most potent improvements in exercise capacity but uniformly worsened survival (12). Renin-angiotensin-aldosterone inhibitors produced only small improvements in exercise capacity, but large improvements in survival (13). Beta-adrenergic blockers can acutely worsen exercise capacity, but produced the largest improvements in survival (14). This divergence in treatment effects in HFREF has not been fully explained, and is frequently forgotten, only to be remembered when a promising new drug shows the same pattern (11). Therefore, for HF, theoretical models regarding mortality based on exercise pathophysiology eventually need testing in large clinical trials. However, that does not diminish the value of exercise capacity as an independently important clinical endpoint in HFpEF (15–17).

The second paradox reported by Holland et al. (1) is the lack of improvement in resting diastolic function despite significant improvements in exercise capacity. Because exercise intolerance is the central nonfatal outcome of chronic HF, this might give us pause to consider whether diastolic dysfunction is the main abnormality to which HFpEF

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treatment should be targeted. Indeed, a second often-forgotten lesson from the legacy of HFREF trials is that the pathophysiology of exercise intolerance is complex and rarely explained by a single abnormality, no matter how obvious or compelling. For instance, reduced EF, the most obvious abnormality in HFREF, was found to correlate poorly with exercise capacity (18). Increased pulmonary artery wedge pressure, the other compelling cardiac abnormality, correlated relatively modestly with exercise capacity (18). Instead, the less-apparent peripheral abnormalities, including abnormal vascular function and abnormal skeletal muscle function, emerged as strong determinants of reduced exercise capacity in HFREF (18). That was confirmed by studies showing that increasing cardiac output by organ replacement or other means had relatively modest acute effect on exercise capacity (18).

An important limitation of most HF exercise outcomes trials, including those that reported diastolic function in the present meta-analysis, is that mechanistic measurements were made only at rest. An enduring principle of exercise physiology is that definitive conclusions regarding mechanisms of exercise intolerance require assessment of candidate variables during exercise to test reserve capacity (17). By the Fick equation, peak exercise oxygen consumption, an objective measure of exercise capacity, is the product of cardiac output and arteriovenous oxygen difference. In healthy subjects the 4-fold increase in oxygen consumption during exercise is achieved by a 2.5-fold increase in cardiac output and a 1.5-fold increase in arteriovenous oxygen difference (19). The increase in cardiac output is achieved primarily by increased heart rate, whereas stroke volume increases only about 0.3-fold (19). Thus, absent significant chronotropic incompetence, peripheral vascular and skeletal muscle abnormalities would be expected to be candidates for a role in severely reduced exercise capacity. Yet, work to date on HFpEF has focused predominantly on factors that influence stroke volume, with little focus on peripheral abnormalities. Remembering these 2 important lessons from HFREF research and understanding exercise physiology principles may facilitate a more direct and expeditious route in the discovery process for HFpEF treatments.

This discussion leads us to examine 2 suggestions made by Holland et al. (1), which are that future trials might be more fruitful if they select patients with "endorsed" or "objective" criteria of HFpEF, and select more "homogenous" samples. The first of the endorsed criteria, a normal range EF, is logical to avoid overlap with HFREF. The 2 other main endorsed criteria are abnormal diastolic function and brain natriuretic peptide (BNP). However, as discussed in the preceding text, current studies indicate that improvements in outcomes can occur with no change in measures of resting diastolic function. Furthermore in HFREF, inotropes that specifically targeted low EF, the most obvious cardiac abnormality, paradoxically increased mortality. Thus, it is not assured that a pure "lusitrope" would be the "magic bullet" for HFpEF. Increased BNP has good performance characteristics in acutely decompensated patients. However, traditional trials, such as those in this meta-analysis, focus on stable, ambulatory outpatients in whom BNP levels should be lower (5,10,20,21) Furthermore, BNP levels tend to be lower in obese persons, and are less specific among women and the elderly, all of which are key characteristics of typical HFpEF in population studies (21). Finally, in I-PRESERVE (Irbesartan in Patients With Heart Failure and Preserved Ejection Fraction), the largest clinical trial of HFpEF to date, treatment effect was unrelated to BNP level (9). Admittedly, the criteria favored by Holland et al. (1) have been recommended in a prominent consensus statement and are supported by other authorities as well (22). However, they have not been systematically tested in prospective population-based studies of stable, community-dwelling elderly outpatients, but were developed largely on the basis of theoretical models of the pathophysiology of acute HFpEF. The experience in HFREF research illustrates the potential pitfalls of such an approach (23).

The other suggestion, to select more homogenous samples, should also be examined. This approach has already contributed to the present state where trial-based treatment guidelines for HF do not apply to the majority of patients who actually have the disease (24,25). The typical HFpEF patient is an elderly woman with multiple comorbidities that commonly constitute exclusions in clinical trials (25,26). By nature, HFpEF is heterogeneous (as is HFREF). Furthermore, several studies indicate that approximately 50% of adverse outcomes during long-term follow-up of elderly HFpEF patients are noncardiac events, likely driven by their multiple comorbidities and physical debilitation (9,25–27). This instructive finding confirms there are important aspects we do not fully understand regarding the complex pathophysiology of HFpEF and suggests avenues for novel intervention strategies. It also suggests there is merit to the selection criteria traditionally used for HFpEF: signs and symptoms of HF, normal range EF, and no obvious alternate or clearly treatable explanation (20,21,28,29). This approach embraces the complexity and heterogeneity that characterize HFpEF in the population, and ensures that resultant treatment advances will be immediately and broadly generalizable (25). If any additional objective confirmation is desired, perhaps it should be with cardiopulmonary exercise testing, which reliably quantifies the central feature of chronic HFpEF, excludes others such as primary pulmonary disease, forces no assumptions regarding mechanisms, and can assess reserve capacity of both cardiac and peripheral components of the exercise response (15–17,20,21,30).

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