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Heart Failure With Preserved Ejection Fraction: An Opportunity for Reflection

Deepak K. Gupta, MD, MSCI

Clinical research is not easy to conduct, and heart failure with preserved ejection fraction (HFpEF) is a difficult syndrome to study. Fortunately for patients, many physicians, scientists, and research teams are committed to investigating this complex and challenging syndrome and are driven by the facts that HFpEF is increasing in prevalence, portends an adverse prognosis with high morbidity and mortality, and lacks efficacious therapies proven in large-scale randomized trials to improve clinical outcomes. A major contributor to the difficulty in reducing the burden of HFpEF has been that the underlying pathophysiologic mechanisms are poorly understood. Thus, when favorable targets for therapeutic intervention are identified, it is with cautious optimism that researchers proceed with pilot and early-phase trials to test the safety and possible efficacy of new therapies.

Reflected Wave Magnitude

A potentially important mechanism for HFpEF is increased late systolic left ventricular afterload imparted by higher magnitude arterial wave reflections due to vascular stiffness.[1] Reflected wave magnitude is the ratio of backward to forward pressure wave amplitudes, which are typically measured by echocardiography and arterial tonometry. Animal models of hypertension induced by aortic constriction implicate increased reflected waves in the pathogenesis of left ventricular hypertrophy, a major risk factor for heart failure.[2] Longitudinal data from the Multi-Ethnic Study of Atherosclerosis (MESA) support a strong association between the magnitude of reflected waves and the risk of incident heart failure, independent of traditional cardiovascular risk factors including blood pressure.[3] Cross-sectional studies demonstrate greater arterial stiffness and wave reflections in patients with HFpEF compared with hypertensive and healthy controls.[4] Moreover, blood pressure lowering in hypertensive patients reduces reflective wave magnitude, which is associated with regression of left ventricular hypertrophy.[5] Together, these data suggest that reduction in reflected wave magnitude may be a promising therapeutic target among patients with HFpEF.

Targeting Reflected Wave Magnitude With Isosorbide Dinitrate and Hydralazine in HFpEF

In this issue of *JAHA*, Zamani et al report the results of a pilot randomized placebo-controlled double-blind clinical trial designed to test the hypothesis that isosorbide dinitrate with or without hydralazine reduces reflected wave magnitude compared with placebo among patients with HFpEF.[6] The research team randomized 44 patients (13 to isosorbide dinitrate, 15 to isosorbide dinitrate plus hydralazine, and 16 to placebo). The active treatments were poorly tolerated with ~60% of subjects experiencing side effects such as headache or orthostatic hypotension, such that only 21 subjects (7, 5, and 9 in each of the 3 arms) completed the study to provide data for the primary endpoint of 6-month change in reflected wave magnitude. A number of secondary endpoints were also assessed, including 6-month changes in cardiac MRI-assessed left ventricular mass and extracellular volume, 6-minute walk test distance, diastolic function, N-terminal pro-b type natriuretic peptide (NT-proBNP), and quality-of-life score. With the small sample size and substantial rate of subjects not completing the study, the authors performed within-group analyses. Reflected wave magnitude did not meaningfully change from baseline to 6 months in any of the 3 groups. Left ventricular mass, extracellular volume, diastolic function, NT-proBNP, and quality-of-life scores did not substantially change in any of the groups. The 6-minute walk test distance declined in the isosorbide plus hydralazine group, but was unchanged

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From the Division of Cardiovascular Medicine, Vanderbilt Translational and Clinical Cardiovascular Research Center, Vanderbilt University School of Medicine, Nashville, TN.

Correspondence to: Deepak K. Gupta, MD, MSCI, Division of Cardiovascular Medicine, Vanderbilt Translational and Clinical Cardiovascular Research Center, Vanderbilt University School of Medicine, 2525 West End Ave, Suite 300, Nashville, TN 37203. E-mail: d.gupta@vanderbilt.edu

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in the other 2. The interpretation of these results is challenging given the sample size and rate of attrition. However, this study does provide an opportunity for reflection regarding clinical research in HFpEF, including the utility of pilot studies, choice of endpoints, being patient centered, and aligning patients with appropriate therapies.

Utility of Pilot Data

Rather than provide formal evidence of benefit, the goals of pilot studies are often to provide estimates of the range of possible responses and to garner sufficient evidence that a larger definitive trial be undertaken.[7] In this regard, in the isosorbide dinitrate group Zamani et al observed an average reduction in reflective wave magnitude of 0.02 with a standard deviation of 0.09.[6] The corresponding 95% confidence interval indicates that isosorbide dinitrate use could be associated with anywhere between a 0.09 reduction to a 0.05 increase in reflective wave magnitude in HFpEF patients over a 6-month follow-up. Similarly, the results for the isosorbide dinitrate plus hydralazine group also spanned a range indicating potential improvement or worsening in reflective wave magnitude. These data do not support moving forward with a larger clinical trial of these medications for the purpose of reducing reflective wave magnitude among HFpEF patients. Nevertheless, valuable information is provided by the placebo group, which provides an estimate of the natural variation in reflected wave magnitude among HFpEF patients over a 6-month period. These placebo group data could be used for power and sample size calculations for future studies in HFpEF that seek to utilize reflected wave magnitude as a primary endpoint.

Endpoints in HFpEF

The study by Zamani et al does raise the question of whether reflective wave magnitude is an appropriate primary endpoint for future clinical trials in HFpEF. Surrogate endpoints should reliably predict clinically relevant patient-centered outcomes. Prior literature suggests that reflected wave magnitude may be inversely associated with exercise tolerance among patients with HFpEF.[8] However, exercise capacity is readily and directly obtained by 6-minute walk test distance, exercise treadmill test, or cardiopulmonary exercise testing compared with measuring and calculating reflective wave magnitude. In addition, patients would much rather feel improvements in exercise capacity or quality of life than know that their reflected wave magnitude declined, particularly in the absence of robust data that reflected wave magnitude is associated with hard outcomes among HFpEF patients, such as heart failure hospitalizations or death. Therefore, reflective wave magnitude may be better suited as a secondary mechanistic endpoint rather than as a primary endpoint, at least for now. In this light the secondary endpoint finding that 6-minute walk test distance substantially declined among patients randomized to isosorbide dinitrate plus hydralazine is informative and of potential clinical relevance.[6]

Patient Centered: First Do No Harm

HFpEF patients are quite symptomatic such that interventions that cause non-life-threatening, but limiting, side effects are often not acceptable to many patients. Indeed, in this study by Zamani et al, half of the patients who dropped out after randomization did so due to side effects, and ~60% overall reported some side effect or adverse event while on active therapy.[6] In addition, HFpEF patients often have impaired cardiac reserve, such that a decline in exercise capacity is quite pronounced.[9] For example, the average 6-minute walk test distance in this study was around 350 m, which is well below even the lowest 10th percentile (~450-475 m) for healthy men and women aged 60 to 69 years old.[10] A decline in 6-minute walk test distance of 66 m (~20%) in the isosorbide dinitrate plus hydralazine group is substantial, such that the average distance walked after 6 months of therapy in this group was around 250 m, consistent with New York Heart Association class III to IV limitation.[10] It is not clear whether this decline was unique to hydralazine because findings from the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) Trial in which HFpEF patients received isosorbide mononitrate for 6 weeks also showed a decline in physical activity measured by accelerometer but not by 6-minute walk test.[11] In any case, the poor tolerance of isosorbide dinitrate with or without hydralazine and the potential worsening of exercise capacity in the hydralazine-added group provide a signal, even from this small pilot study, and an important reminder to clinicians to first do no harm.

Aligning HFpEF Patients With Appropriate Therapies

Aligning individual patients with appropriate therapies that maximize benefit and minimize harm is a fundamental goal of all clinicians. Zamani et al enrolled mostly black patients who had previously been shown to have a relative deficiency in the nitric oxide pathway and more vascular dysfunction.[12] Thus, it was reasonable to expect that this group may benefit the most from isosorbide dinitrate with or without hydralazine. This approach was successful in the African-American Heart Failure Trial (A-HeFT) in which 1050 black patients with heart failure and reduced ejection fraction were randomized to combination isosorbide dinitrate plus hydralazine or

placebo.[13] In that trial, combination therapy significantly improved quality of life while reducing the risk of heart failure hospitalization or death.[13] Although we cannot draw definitive conclusions regarding the efficacy of isosorbide dinitrate with or without hydralazine for HFpEF patients from Zamani's study, it is intriguing that yet another therapy with demonstrated benefit in heart failure with reduced ejection fraction may not work as well in HFpEF, as has been seen with angiotensin receptor blockers, ACE inhibitors, β-blockers, and to some extent aldosterone antagonists.[14-18] This highlights the pressing need for more research in HFpEF, to understand the heterogeneous phenotypes, elucidate mechanisms, identify targets for intervention, and develop novel therapies that improve clinically important outcomes without making patients feel worse.

The study by Zamani et al provides an opportunity for reflection regarding clinical research in HFpEF, including the utility of pilot studies, choice of endpoints, being patient centered, and aligning patients with appropriate therapies. Their work also reflects a deep commitment to HFpEF patients to understand this complex syndrome and attempt to find therapies that will reduce morbidity and mortality. For those of us who care for and study HFpEF patients, we must continue to confront this challenge together if we hope to reduce the magnitude of the HFpEF problem.

Disclosures

None.

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