Vasodilators Across the Heart Failure Spectrum
Not All Patients, and Not All Vasodilators, Are Created Equal*

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The term heart failure with preserved ejection fraction (HFpEF) has evolved to describe the broad clinical syndrome characterized by signs and symptoms of heart failure in patients in whom the ejection fraction (EF) falls within the low normal to normal range. This terminology is essentially descriptive, and implies neither etiology nor pathophysiology, although both continue to fuel vigorous debate. One of the most fundamental of these debates has been whether HFpEF is a truly distinct pathophysiologic entity from heart failure with reduced ejection fraction (HFrEF). While most would agree that the etiologic conditions that lead to heart failure differ between these 2 groups in the majority of cases, whether the pathophysiologic derangements that underlie the nearly identical signs and symptoms are also different at either end of the heart failure spectrum remains unclear.

Therapy for HFrEF has solidified over the past 2 decades, with multiple randomized clinical trials demonstrating benefit with a variety of pharmacologic agents and devices. Drugs with vasodilatory properties were the first to show benefit in randomized trials in HFrEF (1–4) and continue to play an important role in heart failure therapy (5). Indeed, physicians in training are taught that even if these drugs lower blood pressure, they can paradoxically improve cardiac output.

In contrast to the therapeutic advances in HFrEF, specific therapy for HFpEF has yet to emerge (6,7). The few large clinical trials to specifically target the HFpEF population have tested drugs with vasodilatory properties, including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (8–10), which have been shown to have effects on cardiac structure and function beyond afterload reduction. Although these trials have ranged from definitively negative (i.e., I-PRESERVE [Irbesartan in Patients With Heart Failure and Preserved Ejection fraction]), to suggestive yet falling short of statistical significance (CHARM [Candesartan in Patients With Chronic Heart Failure], PEP-CHF [Perindopril in Elderly People With Chronic Heart Failure]), the dramatic benefits associated with this pharmacologic approach observed in patients with HFrEF have simply not been realized in HFpEF. These disappointing findings force us to reconsider the possibility that the therapeutic approaches to these 2 groups of patients may need to be fundamentally different.

In this issue of the Journal, Schwartzenberg et al. (11) challenge the concept that vasodilation is equally beneficial in all forms of heart failure. They studied heart failure patients who were referred for right-side heart catheterization—174 with HFrEF and 83 patients with HFpEF. At baseline, they found that pulmonary capillary wedge pressures were similar between groups, although left ventricular end-diastolic pressure was higher in the low EF heart failure patients. As these investigators have previously shown, patients in both groups had elevated effective arterial elastance (Ea), a measure of afterload, although this was slightly higher in the HFpEF patients. In contrast, patients with HFrEF demonstrated considerably lower end-systolic elastance, a measure of end-systolic contractility, than did those with HFpEF, resulting in marked differences in the Ea/Ees “coupling ratio” between these 2 groups.

After initial hemodynamic assessment, all patients received infusions of sodium nitroprusside, which was titrated until they normalized pulmonary capillary wedge pressure, or hypotension or other intolerance developed. In response to this therapeutic challenge, they noted distinct hemodynamic differences between these 2 groups. Although both sets of patients demonstrated similar reduction in effective arterial elastance and left ventricular filling pressures with vasodilation, stroke volume increased substantially in HFrEF patients but minimally in HFpEF patients. The HFpEF patients experienced greater reduction in blood pressure, and the changes in blood pressure and stroke volume were greater per unit change of arterial elastance or filling pressure. In the right-sided circulation, they found that patients with HFpEF were more likely to demonstrate a drop in systolic arterial pressure despite similar reduction in pulmonary venous pressures.

This elegant experiment demonstrates clearly some fundamental mechanisms in heart failure and underscores inherent pathophysiologic differences between patients at either end of the heart failure spectrum. The marked differences in ventricular properties in the face of increased afterload, and the resultant disparity in ventricular-arterial stiffness ratios may in part explain the differential effects in...
response to the vasodilator. These data would suggest that in the setting of the marked afterload mismatch, as seen in HFrEF, where afterload is high but contractility is depressed, vasodilation would be an optimal form of treatment, and would be expected to lower Ea and thus restore the “coupling ratio” toward normal. In HFrEF, in contrast, the coupling ratio was not that dissimilar from that seen in normal patients (indeed, calculated this way the coupling ratio is essentially inversely related to EF), and lowering Ea would be expected to have less benefit. The finding that stroke volume decreased in 35% of patients with HFrEF compared with only 9% of patients with HFrEF would seem to support that notion.

Yet before concluding all vasodilator therapy would be futile for patients with HFrEF, we need to recognize several caveats to this analysis. First, as noted by Schwartzzenberg et al. (11), this was a highly selected group of patients referred for right-side heart catheterization. The majority of patients with HFrEF do not undergo invasive hemodynamic assessment, suggesting that these patients may have been more symptomatic than typical patients with this syndrome and may not be truly representative of the broader group of HFrEF patients. Moreover, these patients were quite hypertensive at baseline (mean systolic blood pressure 166 mm Hg), with blood pressures that were higher than those seen in community-based studies (12,13) and substantially higher than the well-controlled baseline blood pressures observed in clinical trials of HFrEF (7,8). Whether the hemodynamic findings in this cohort would have been different had the investigators studied a less hypertensive group of patients also remains unclear.

Not all drugs with vasodilatory properties would necessarily be expected to behave in a similar manner to nitroprusside, an extremely potent vasodilator (1). Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers would likely have less profound vasodilatory effects, and affect cardiac structure and function through additional mechanisms beyond afterload reduction. Indeed, in the CHARM-Preserved study, which enrolled patients with EF >40%, the incidence of hypotension in response to angiotensin-receptor blocker therapy was about half that in the patients enrolled in the CHARM-Added or the CHARM-Alternative trials (14,15), in which EFs were <40%. Moreover, compelling nonhemodynamic effects, such as reduction in myocardial fibrosis (16–18), have been different had the investigators studied a less hypertensive group of patients also remains unclear.

Although improvement in stroke volume that results from vasodilation may be a favorable outcome in patients with HFrEF, it is more difficult to argue that increases in stroke volume are necessarily beneficial (or conversely, that reductions are necessarily harmful) in HFrEF. Vasodilation lowered blood pressure substantially in the HFrEF patients in this study, but the authors do not report how many patients became symptomatically hypotensive in the respective populations. Congestion, rather than reduced forward output, represents the predominant pathophysiologic alteration in HFrEF at rest, although inability to increase stroke volume with exercise may be an important factor in this disease (21). Lowering blood pressure in patients with diastolic dysfunction is an effective approach to improving measures of diastolic function (22,23). Because stroke volume and cardiac output at rest were quite normal in the HFrEF patients in this study, lack of improvement or even slight reductions in stroke volume might be tolerable, especially if a therapy were also associated with long-term improvements in cardiac structure, such as reduction in ventricular hypertrophy or fibrosis.

Finally, the distinction between HFrEF and HFrEF has been relatively arbitrary, as evidenced by the multiple cutoffs used in this analysis and in the various definitions utilized in epidemiologic studies and clinical trials. When studied within the context of the same trial, patients with both reduced EF and preserved EF have virtually identical signs and symptoms (24). Regardless of the definition, there is significant overlap, and neither group of patients is homogeneous; just as etiologies can differ within these groups, so do the resultant pathophysiologic derangements. In highlighting the different hemodynamic responses to vasodilator challenge between HFrEF and HFrEF patients, Schwartzzenberg et al. (11) raise the possibility that the response to vasodilation could potentially be utilized to phenotype patients with heart failure regardless of EF, and even to direct patient-specific therapy, an approach that would need to be tested prospectively. Still, which drug or drugs we would use in those patients who respond less effectively to vasodilation remains the unanswered question.

References


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