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Heart Failure with Preserved Ejection Fraction: Failure to Preserve, Failure of Reserve, and Failure on the Compliance Curve

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Keywords

contractility; heart failure; hypertension; pathophysiology

Epidemiological studies have established that approximately half of all patients with congestive heart failure have a preserved ejection fraction (HFpEF). This syndrome predominantly afflicts older hypertensive individuals. The prevalence of HFpEF is increasing (1), paralleling the demographic shift in the population towards older ages. Although HFpEF was previously thought to have a more favorable course than heart failure with reduced ejection fraction (HFrEF), recent studies have shown that the mortality rate (1), the hospital re-admission rate (2) and the economic cost (3) of HFpEF rival those of HFrEF. The morbidity and mortality of patients with HFrEF have gradually improved over the past two decades, reflecting the impact of several evidence-based interventions that have been incorporated into the care of patients with chronic HFrEF. In contrast, the prognosis of patients with HFpEF has remained steadfastly unchanged over the same time period (1), reflecting both the dearth of therapeutic interventions that have been evaluated in HFpEF, and the failure of these therapies to show any benefit on survival in patients with this syndrome. Thus, there is an urgent need to develop novel and efficacious strategies for the treatment of HFpEF, particularly ones that specifically target the pathophysiologic mechanisms that underlie HFpEF.

Several features of the pathophysiology of HFpEF have been well characterized. These include structural and functional alterations in the heart, such as hypertrophy of the myocytes, changes in the composition of the extracellular matrix and abnormalities in intracellular calcium handling (4). These cellular and biochemical alterations likely underlie the impaired LV diastolic relaxation and the decreased LV compliance that are observed in HFpEF (5,6). However, these diastolic abnormalities are not specific to HFpEF, as they can be found in patients with HFrEF and in hypertensive individuals without heart failure (7). Thus, some investigators have proposed that the pathophysiology of HFpEF may involve additional cardiovascular alterations beyond diastolic dysfunction (reviewed 8), such as impairment in systolic function. Consideration of systolic function in patients with HFpEF may appear surprising at first since EF, by definition, should fall within the “normal” range (“preserved” EF). However, it is important to note that EF is only a crude measure of LV systolic function, and that it is influenced by several factors beyond contractility *per se*, including loading conditions and chamber geometry. Thus, recent studies of systolic function in patients with

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HFpEF have focused on indices other than EF. However, these studies have yielded conflicting results, with some reporting abnormalities (9,10), and others observing no abnormality (11), in systolic function. These inconsistent findings could be due, in part, to differences in the populations being studied, or to differences among the various measures of systolic function that were examined across studies.

In this issue of the *Journal*, Borlaug et al. (12) provide important insights into the systolic function of patients with HFpEF. Using the landmark Rochester Epidemiology Project, the authors examined 3 groups of subjects: healthy controls without cardiovascular disease (N=617), hypertensive controls without heart failure (N=719), and patients with HFpEF (N=244). They non-invasively assessed load-independent indices of chamber-level contractility (preload recruitable stroke work, and wall stress-corrected endocardial fractional shortening) and of myocardial contractility (stress-corrected midwall fractional shortening). These indices were higher in the hypertensive than in the normotensive control groups. In contrast, these indices were lower in patients with HFpEF than in both the hypertensive and the normotensive control groups. These findings indicate that in spite of the apparently "preserved" EF, patients with HFpEF exhibit evidence of impaired contractile function. The strengths of this study include the large sample size, which makes this by far the largest study that has evaluated contractility in HFpEF; the non-selected nature of the study cohort, which avoids the selection and referral biases that have plagued many of the small studies of HFpEF; and the inclusion of a hypertensive control group, which allows the proper distinction between alterations that are specific to HFpEF vs. those that are simply due to hypertension. Importantly, because the impairment in contractility in HFpEF is mild, it is unlikely to be the culprit mechanism that underlies the pathogenesis of HFpEF. Instead, the authors speculate that the impaired contractility in HFpEF is due to other alterations in myocardial structure and function, and that these alterations are the ones that are responsible for the transition of a hypertensive heart to a failing heart.

In the study by Borlaug et al. (12) all the cardiovascular measures were assessed in the resting state. From a clinical perspective, one of the hallmarks of HFpEF is that symptoms are not usually reported at rest, but may become clinically manifest during low levels of exertion and may impose marked limitations in exercise tolerance. Only a handful of studies have investigated the alterations in the cardiovascular response to exercise that characterize patients with HFpEF (13–16). In this issue of the *Journal*, Phan et al. report their findings from a study of 20 healthy controls and 37 patients with HFpEF who were examined at rest and during submaximal aerobic exercise (17). Consistent with findings from previous studies (15,16,18), patients with HFpEF had evidence of chronotropic incompetence during exercise, manifest as a deficit in their heart rate reserve. Cardiac PCr/ATP ratio, an index of cardiac energetics, was assessed in the resting state with ^{31}P magnetic resonance spectroscopy, and was noted to be 27% lower in patients with HFpEF than in controls. Although cardiac energetics were not measured during exercise, the authors speculate that the lower resting values likely denote impaired myocardial energy reserves. In this study, several indices of systolic and diastolic function were evaluated with radionuclide ventriculography. In the resting state, these indices did not significantly differ between the two groups, whereas during exercise, some interesting differences were noted. For example, the LV active relaxation period, which is the energetically demanding stage of early diastole, became prolonged during exercise in patients with HFpEF, in contrast to the control group in whom it was shortened. Whether this exercise-induced impairment in LV relaxation is specific to HFpEF, or whether it can be found in other hypertensive individuals can not be ascertained from this study, because a hypertensive control group was not examined. During exercise, patients with HFpEF also exhibited significant deficits in their ability to augment several indices of systolic function. However, it should be noted that these patients exercised at absolute workloads that were lower than those of the

control group, because the submaximal stage of exercise was defined as the workload corresponding to 50% of heart rate reserve.

The studies by Borlaug et al. (12) and Phan et al. (17) provide valuable incremental insights to our understanding of the pathophysiology of HFpEF. However, additional studies are sorely needed. Some should be directed at further elucidating the pathophysiologic mechanisms that underlie HFpEF, whilst others should focus on developing interventions that target the specific mechanisms which have already been identified in patients with this condition. These patients suffer from abnormalities in diastolic function, deficits in their exercise reserve, and some compromise in their systolic function, as well as from the failure of the medical community, so far, to develop efficacious interventions that improve their morbidity and mortality. Given the rising prevalence of HFpEF, the economic burden it is imposing on society, the suffering it inflicts on afflicted individuals, and the compromise in their quality of life, it is imperative that clinicians, researchers, funding agencies and policy makers urgently recognize that HFpEF is a clinical frontier in the cardiovascular field that is in dire need of attention.

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