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EDITORIAL COMMENT

Adding Troponin to the Puzzle of Heart Failure With Preserved Ejection Fraction

Marker or Mediator?*

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To date, heart failure (HF) with preserved ejection fraction (HFpEF) has been one of the most frustrating and sobering conditions in cardiovascular medicine. Clinical outcomes and long-term survival are poor and comparable to patients with HF with reduced ejection fraction (HFrEF) and many forms of cancer (1). Functional capacity is substantially impaired, and quality of life is akin to patients with end-stage renal disease (2). Although patients with HFrEF have seen a number of advances in both pharmacological and device-based treatment, HFpEF patients remain without a conclusive disease modifying therapy. Unfortunately, this debilitating and mortal condition is also extremely common. HFpEF accounts for approximately one-half of HF patients worldwide with a prevalence projected to surmount HFrEF in the coming years (3).

A key challenge to successful HFpEF drug development remains a rigorous definition of etiological and pathophysiological pathways, in an inherently heterogeneous clinical syndrome. In this respect, recent data on troponin elevation in HFpEF deserve attention (4,5). Although troponin is best recognized for its fundamental role in defining myocardial injury in patients with acute coronary syndrome, troponin levels are known to be elevated in a substantial number of HFrEF and HFpEF patients in the absence of overt clinical ischemia (4-6). While the exact mechanism of troponin release in these patients has been unclear, troponin elevation has been near uniformly associated with adverse outcomes. However, although these data do suggest a state of ongoing end-organ injury in many HF patients, it remains unknown whether troponin elevation is simply a marker of risk or directly linked to a central causal pathway mediating worsening HF. Distinguishing between these 2 potential roles remains important across the spectrum of HF, but is arguably most urgent in HFpEF given the less well-understood pathophysiology, the need to develop validated phenotypes, and the unmet therapeutic need (7).

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In this issue of the *Journal*, Obokata et al. (8) present a prospective mechanistic study investigating the relationship between troponin elevation and HFpEF physiology. The study included 38 patients with clinical and invasive hemodynamic evidence of HFpEF and 20 control patients undergoing evaluation of dyspnea on exertion without HFpEF. Patients with clinically significant epicardial coronary artery disease (CAD) requiring revascularization were excluded, but a prior history of nonobstructive CAD, myocardial infarction, or revascularization was permissible. All patients underwent simultaneous right heart catheterization and echocardiographic assessments at rest followed by a stepwise exercise protocol. Measurements of intracardiac filling pressures, cardiac index, myocardial oxygen supply

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and demand, systolic and diastolic function, and high-sensitivity troponin T were acquired serially at each stage in the protocol. HFpEF patients were found to have significantly higher troponin levels than control subjects at rest (after adjustment for renal function and other factors), with the degree of elevation directly correlated to higher pulmonary capillary wedge pressure and worse systolic and diastolic tissue Doppler velocities. Troponin levels were unrelated to measures of myocardial oxygen demand, but correlated with reductions in oxygen supply and a corresponding greater degree of supply-demand mismatch. With exercise, differences between HFpEF and control patients were exaggerated, with HFpEF patients having greater increases in filling pressures, less augmentation of cardiac output, and greater decline in myocardial oxygen supply. Likewise, HFpEF patients had greater exercise-induced increases in troponin level (despite a lower peak exercise workload), with the degree of elevation correlating with severity of impairment in hemodynamics, aerobic capacity, systolic and diastolic reserve, and oxygen supply-demand imbalance.

Obokata et al. (8) are to be congratulated for executing an elegant and timely mechanistic study linking myocardial injury to multiple cardiac derangements central to the HFpEF syndrome. Nonetheless, several limitations of this work should be acknowledged. First, although patients with unrevascularized obstructive CAD were ineligible, the rigor of the baseline CAD assessment was modest. Only 75% of control subjects and 68% of HFpEF patients were evaluated with coronary angiography; 15% of control subjects and 16% of HFpEF patients had CAD evaluated by clinical history alone without any invasive or noninvasive testing. In addition, the recentness of ischemic testing relative to study enrollment is unclear. A granular description of the nature and severity of underlying CAD would provide further reassurance that epicardial CAD did not contribute to study findings. Such details may be particularly relevant given: 1) histories of CAD and diabetes mellitus were nearly 2-fold more common among HFpEF patients (although not statistically significant); and 2) subgroup analyses showed HFpEF patients without CAD had troponin levels more comparable to control subjects and markedly lower than HFpEF patients with CAD. Second, although meticulous characterization of this HFpEF cohort is appreciated, results would have been strengthened by comparison to a group of nonischemic HFrEF patients. Both HFpEF and HFrEF are similarly characterized by elevated intracardiac pressures, and it is unclear whether the reported links between higher filling pressures, decreased myocardial oxygen supply, and troponin release are unique to HFpEF biology or specific to the hemodynamics. Third, although statistically significant differences in high-sensitivity troponin T were seen between HFpEF and control subjects at rest and each stage of exercise, interquartile ranges surrounding HFpEF data are wide. Thus, the degree to which purported differences in troponin levels between study groups were driven by a particular HFpEF subset versus generalizable to a broader HFpEF cohort is less certain. Similarly, although the incremental increase in troponin from rest to exercise was greater among HFpEF patients in absolute terms, the overall change was modest and comparable to control subjects in terms of proportional change from baseline. Lastly, and as well acknowledged by the authors, this cross-sectional experience cannot prove causality or the directionality of the relationship (i.e., the "chicken or egg" dilemma) between troponin levels and any of the cardiac parameters tested.

When combining the current mechanistic data with previously described correlations with longitudinal cardiac remodeling and clinical outcomes, it is tempting to declare troponin a surrogate for clinically meaningful HFpEF endpoints (4,5). However, although certainly worthy of investigation, caution must be applied and confirmation of troponin as a reasonable surrogate or therapeutic target can only be shown with clinical trials adequately powered for clinical events and/or improvement in patient-centered endpoints (e.g., functional status, quality of life). Indeed, the history of HF and cardiovascular drug development includes several examples of premature false confidence in surrogate endpoints (9). Moreover, in the specific case of HFpEF, additional hurdles to successful therapeutic targeting of troponin may apply. Although Obokata et al. (8) clearly associate troponin elevation with filling pressures, systolic and diastolic reserve, and aerobic capacity, it is notable that HFpEF patients can have impaired exercise reserve for a variety of reasons. Of note, a recent analysis found the most consistent and severe hemodynamic reserve abnormality in HFpEF to be chronotropic incompetence, and it is less clear how this could be improved with a therapy targeting troponin (10). It is also notable that long-acting nitrates, a therapy that (aside from other potential properties) could possibly attenuate troponin elevation via reductions in cardiac preload and subendocardial ischemia and/or treatment of microvascular dysfunction, showed a suggestion of harm in a modest-sized randomized trial (11). Furthermore, the limited understanding of HFpEF