High-Sensitivity Cardiac Troponin: From Patient Phenotypes to Clinical Events in Patients With Heart Failure With Preserved Ejection Fraction

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Previous studies have established the prognostic value of elevated troponin levels in patients with heart failure (HF), even in the absence of chest pain or myocardial infarction.1–4 Furthermore, contemporary high-sensitivity cardiac troponin I (hs-TnI) assays are able to detect low levels in otherwise healthy individuals without known cardiovascular disease, but with future risk for development of HF, cardiovascular disease, or death.5 This introduced the role for detection of ongoing maladaptive myocardial changes before full features of the phenotype become manifest, and the diagnosis of subclinical disease. This is supported by findings that there is a strong association between elevated high-sensitivity cardiac troponin (hs-cTn) levels and left ventricular hypertrophy,6 and future development of HF almost a decade later.7,8

Thus, the diagnostic and prognostic role of hs-cTn in HF straddles a wide spectrum,1–4 and can be incorporated for better characterization of stages of HF that ranges from an asymptomatic individual without macroscopic cardiac structural changes, but with future risk of HF (Stage A); an asymptomatic individual with cardiac hypertrophy or other myocardial structural changes, and with future risk of HF (Stage B); to symptomatic (Stage C) and advanced heart failure (Stage D) (Figure 1). In all these stages, elevated hs-cTn levels have been associated with increased risk of mortality.1–4

Though most studies of hs-cTn in HF have been performed in patients with reduced ejection fraction, a few have addressed its prognostic role in patients with HF with preserved ejection fraction (HFpEF).2,9–12 These demonstrated a similar association of higher troponin levels and risk of future HF rehospitalization or death among symptomatic patients with HFpEF.2,9–11

In this issue of the Journal of the American Heart Association (JAHA), using the pooled data from DOSE (Diuretic Strategies in Patients with Acute Decompensated Heart Failure),13 CARRESS-HF, (Cardiorenal Rescue Study in Acute Decompensated Heart Failure)14 and RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction)15 trials, Fudim and colleagues16 demonstrate that hs-TnI levels were elevated among 86% of the hospitalized, and among 53% of the ambulatory patients with HFpEF. The pooled data provide us an opportunity to recognize a potential longitudinal pattern of hs-TnI elaboration in these specific populations of HFpEF (Figure 2A), and a better understanding of its role in different disease stages (Figure 1) or phenotypes, ranging from stable ambulatory to hospitalized HF (Figure 2B). In ambulatory, stable NYHA (New York Heart Association) II/III HFpEF patients, hs-TnI levels appeared to be chronically elevated, slightly above the 99% upper reference limit, but not

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Figure 1. Potential new algorithm for stages of HF with incorporation of elevated high-sensitivity biomarkers such as cardiac troponin (hs-cTn) levels to symptoms and cardiac structural changes. Incremental role of hs-cTn as being diagnostic or prognostic is noted in parentheses. HF indicates heart failure; hs-cTn, high-sensitivity cardiac troponin I; LV, left ventricular.
as high as the hospitalized patients, and did not change significantly over 6 months. In hospitalized patients with HFP EF, levels were significantly elevated, approximately twice of the 99% upper reference limit, and remained elevated without a significant change during hospitalization, and decreased only modestly by approximately 17% at 60 days, suggesting a sicker population with a higher biomarker expression profile even after hospitalization (Figure 2A and 2B). In addition to potential scenarios depicted in Figure 2, it is also possible that with longer follow-up, these levels might have come down further.

The trial populations in this study were quite different from each other, and possibly from other HFP EF cohorts. Ambulatory HFP EF patients (RELAX study) required objective evidence of HF by history of hospitalization, need for diuretics with left atrial enlargement, invasively documented elevation in left ventricular filling pressures, reduced exercise capacity, and elevated natriuretic peptide levels.15 The majority of patients were overweight or obese and had hypertension, NYHA II/III HF symptoms, reduced peak VO2 at baseline, and were on Angiotensin-converting-enzyme inhibitor/Angiotensin II receptor blocker (ARB), beta blockers, and diuretics.15 Only 48% were women, 37% had history HF hospitalization, 43% diabetes mellitus, 39% ischemic heart disease, 45% jugular venous pressure >8 cm, and 60% edema.15 This phenotype may be different than other HFP EF subtypes with a higher representation of women, diabetes mellitus, chronic kidney disease, and edema; and therefore, the levels and changes over time may differ in other populations with HFP EF. Lack of changes in the hs-TnI levels over time observed in this group implies stability of the patients, but lack of a decline <99% upper reference limit suggest an ongoing myocardial pathology that does not seem to normalize. (Figure 2B).

Within this group, patients with elevated hs-TnI levels above the median (median levels were close to the 99% upper reference limit) appeared to be older, more likely to be male, with higher prevalence of congestion markers (elevated jugular venous pressure, diuretics, higher NT-proBNP levels), and with echocardiographic parameters demonstrating worse diastolic dysfunction, higher filling pressures, and left ventricular hypertrophy compared with lower hs-TnI levels. Interestingly peak VO2 levels were not different, but they had lower walk distances. Lack of differences in peak VO2 may be because of differences in sex distribution (more males in higher hs-TnI group, who have higher peak VO2), small sample size, and homogeneity of the trial population on exercise performance. And also in HFP EF, exercise capacity is strongly associated with factors such as obesity, anemia, and chronotropic incompetence, but not with resting measures of ventricular and vascular structure and function.17

As expected, hospitalized HFP EF patients in DOSE,13 CARRESS-HF14 trials were sicker than the ambulatory patients. Though they did not require objective echocardiographic, invasive hemodynamic, or exercise performance criteria or elevated natriuretic peptide levels on entry, patients had to have symptoms or signs of HF by physical exam or

![Figure 2](https://example.com/figure2.png)

**Figure 2.** A, Characterization of the trajectory of a hypothetical patient with HFP EF, changing from ambulatory state to hospitalization, and subsequently post/discharge. For characterization, hs-TnI median levels reported by Fudim et al were used.16 **B,** Characterization of hypothetical HFP EF phenotypes, according to trajectories of hs-TnI levels reported by Fudim et al16. Normal hs-TnI phenotype: HFP EF patient with hs-TnI levels under the 99th percentile upper reference limit. These patients are likely to be asymptomatic (Stages A or B) or if symptomatic, stable (Stage C, NYHA Class II); Ambulatory phenotype: HFP EF patients with hs-TnI levels just above normal and their levels do not change significantly. They can be symptomatic, but stable (Stage C, NYHA II); Hospitalized phenotype: sicker HFP EF patients with chronically elevated hs-TnI levels, much higher than normal or ambulatory patients with HFP EF, and levels decline slightly after discharge, but do not reach normal or levels of the ambulatory patients.

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As expected, elevated hs-TnI levels were associated with worse clinical outcomes, reported as the combined end point of emergency room visits, readmissions, and death at 60 days in this study.14 These findings were similar to other studies which reported elevated hs-cTn levels were associated with increased mortality and readmission rates in patients with acute decompensated HF regardless of LVEF.3 In some studies, this association was even stronger in patients with HFpEF than HFrEF,20 suggesting that elevated hs-cTn levels may be a reflection of a sicker phenotype with long-term implications of higher risk in patients with HFpEF.

High-sensitivity biomarkers such as hs-cTn have allowed us to recognize subclinical disease and future risk and will likely shift the paradigm for individualization of therapies in different phenotypes. Whether elevated hs-cTn levels are a reflection of episodic worsening, such as decompensation requiring hospitalizations (Figure 2A), versus fingerprints of characterization of chronic elevations in different phenotypes of patients (Figure 2B), or both, remain unanswered in HFpEF.

It is intriguing to imagine the possibility of targeted therapies to prevent HF in patients with elevated hs-cTn levels, but without symptoms of HF or structural changes; or to prevent worsening and adverse clinical outcomes among those who are higher risk with symptomatic HF and elevated hs-cTn levels. It is critical to recognize that a significant proportion of the general adult population has detectable hs-cTn levels associated with future HF risk,6,8 which expands the definition of Stage A HF and the possibility of preventive strategies to large populations. Furthermore, approximately half of the ambulatory and the majority of the hospitalized HFpEF patients have elevated hs-cTn levels associated with higher risk.16 This may provide us an opportunity to define a common pathway for targeted therapies in these high-risk patients, for whom currently no definitive therapy exists.

Disclosures

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