Association between troponin T and impaired left ventricular relaxation in patients with acute decompensated heart failure with preserved systolic function

Ravi V. Shah1, Annabel A. Chen-Tournoux2, Michael H. Picard2, and James L. Januzzi2*

1Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA; and 2Cardiology Division, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA

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Aims To examine relationships between cardiac troponin T (cTnT) and parameters of left ventricular (LV) structure and function in patients with acute destabilized heart failure (HF) with preserved LV ejection fraction.

Methods and results In 44 patients with acute heart failure (HF) with preserved left ventricular (LV) ejection fraction, parameters of LV structure and function were assessed via comprehensive two-dimensional Doppler echocardiography. There was no correlation between cTnT and LV wall thickness, left atrial volume index, or transmitral E wave velocity or deceleration time. There were associations between cTnT and LV end-diastolic dimension ($r = 0.34, P = 0.02$) and LV mass index ($r = 0.32; P = .04$). A lower tissue Doppler Ea wave peak velocity was associated with higher cTnT concentrations ($r = 0.90, P < .001$). In multivariate analyses, only LV end-diastolic dimension ($t = 2.2; P = 0.04$), LV mass index ($t = 2.3; P = .03$), and tissue Doppler Ea wave peak velocity ($t = - 4.7; P < .001$) emerged as significant predictors of cTnT.

Conclusion In patients with HF with preserved LV ejection fraction, cTnT is strongly associated with the extent of LV relaxation abnormalities and LV mass.

KEYWORDS Heart failure; Diastolic dysfunction; Biomarker; Echocardiography

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Introduction

Up to 50% of patients with clinical heart failure (HF) have preserved LV function ('non-systolic HF').1 In these patients, elevated filling pressures and symptoms of HF are likely due to abnormalities in LV relaxation, compliance, and filling.2 Apart from its diagnostic and prognostic importance in acute coronary syndrome, cardiac troponin (cTn) is elevated in up to 50% of patients with acute compensated HF without active myocardial ischaemia,3,4 and has been shown to indicate haemodynamic severity, need for escalated therapies, and greater risk for in-hospital and postdischarge mortality and LV dysfunction.3–8

Mechanistically, elevated cTn has been related to LV mass in patients without HF,9,10 and LV hypertrophy in patients with systolic HF.11 It remains unclear what, if any, association exists between cTn and diastolic function. Given diastolic filling abnormalities have been shown to have prognostic importance in HF,12–14 we hypothesized that magnitude of cardiac troponin T (cTnT) release in patients with acute decompensated HF and preserved LV function may be directly associated with the extent of abnormalities in LV relaxation. To this end, we examined associations between cTnT values among a group of patients with detailed echocardiographic analyses following onset of acute HF with preserved systolic function.

Methods

Patient population

The current study population consisted of a sub-group of 44 patients originally enrolled in a trial of acute dyspnoea; among those originally enrolled, the current study examined those with acute HF and an LV ejection fraction of ≥50% on transthoracic echocardiography performed during the index HF hospitalization.15 Exclusion
Cardiac troponin T measurements

All enrolled subjects had cTnT measured on blood drawn at the time of study enrolment (Roche Diagnostics, Indianapolis, IN, USA) on an Elecsys 2010 platform. The 99th percentile for a normal reference population using this assay is 0.01 ng/mL, while the lowest cut-point yielding 10% analytical imprecision with this assay is 0.03 ng/mL. Consistent with a prior analysis,5 we elected to define a 'measurable' cTnT using the 99th percentile cut-point.

Echocardiography

Transthoracic echocardiography was performed during the index HF hospitalization with standard techniques. LV ejection fraction, dimensions, wall thickness and mass, left atrial volume index, pulmonary arterial pressures, right ventricular (RV) fractional area change, transmitral Doppler imaging, and myocardial tissue Doppler imaging at the lateral mitral annulus were measured. All echocardiography was performed for standard of care reasons, and interpretation was done by a reader blinded to cTnT values (A.C-T.).

Statistical analysis

Non-normal data (identified using assessment of skewness, with a value greater than twice its standard error indicating non-normality) were log-transformed to achieve normality. Pearson correlation (at a significance level \( P = 0.05 \)) was used to assess the association between cTnT and echocardiographic variables. Multivariate linear regression with echocardiographic covariates was used to create a prediction model for cTnT. Variables included in the initial model included measures of cardiac structure (chamber size, wall thickness, and LV mass index), systolic function (LV and RV), as well as non-systolic parameters (standard parameters from transmitral Doppler, pulmonary vein Doppler, and tissue Doppler at the lateral annulus). In addition, measures of valvular disease were considered; this included visually assessed aortic, mitral, and tricuspid regurgitation (using standard scales of 0–4 severity), as well as transaortic gradients when appropriate. Only those variables with a significant \( P \)-value initially were included in the final model. In addition, clinical variables of age, diabetes prior HF, incident or prevalent coronary artery disease, and renal function were included in the final model. All statistics were performed with SPSS software (Chicago, IL, USA); \( P \)-values are two-sided, with 0.05 considered significant.

Results

Baseline patient characteristics

Baseline clinical and echocardiographic characteristics are shown in Table 1. Of the 44 patients studied, 43% had a detectable cTnT. As expected in a population of patients with HF and preserved LV function, the majority of patients studied were elderly females, with normal LV function, borderline LV hypertrophy, and a history of prior coronary artery disease and diabetes.

Correlation of cTnT and echocardiographic indices

Table 2 demonstrates correlation coefficients derived from linear regression analysis of cTnT and echocardiographic indices. There was no correlation between cTnT and LV wall thickness, left atrial volume index, transmitral E wave peak velocity, or E-wave deceleration time. There was an association between cTnT and LV end-diastolic dimension \( (r = -0.34, \ P = 0.02) \). Although transmitral E-wave to tissue Doppler Ea wave velocity ratio was not related to cTnT, a lower peak Ea wave velocity was strongly
associated with higher levels of cTnT among those with measurable troponin values \( (r = -0.90, \ P < 0.001; \text{Figure 1}) \).

In a multivariable linear regression analysis including clinical, laboratory, and echocardiographic data, among the 44 subjects with acute non-systolic HF, independent predictors of cTnT concentrations included the end-diastolic dimension of the LV \( (t = 2.2; \ P = 0.04), \) LV mass index \( (t = 2.3; \ P = 0.03) \) and especially tissue Doppler Ea wave peak velocity \( (t = -4.7; \ P < 0.001) \).

Discussion

Heart failure with preserved ejection fraction constitutes ~50% of all patients with HF and carries a four-fold increase in mortality over patients without the diagnosis.\(^1\) Whereas elevated cTnT during acute systolic HF is predictive of a worse haemodynamic profile and higher mortality,\(^2\) there is no evidence relating cTnT in patients with acute HF and preserved LV function to poor haemodynamics. In this study, we show that cTnT elevations are prevalent in patients with HF with preserved ejection fraction during the acute HF episode, and that the LV of patients with elevated cTnT in this context is more likely to be less compliant and more hypertrophied when compared with those with lower cTnT. Given that echocardiographic diastolic filling abnormalities in patients with undifferentiated HF are associated with mortality,\(^13\)–\(^15\) the relationship between cTnT and diastolic dysfunction in our study suggests that cTnT may serve as a point-of-care assessed surrogate for poor LV diastolic function in patients with HF and preserved ejection fraction in the acute HF setting.

We studied both transmitral Doppler flow and myocardial tissue Doppler velocities, finding a correlation with cTnT only with tissue Doppler Ea velocity. Transmitral Doppler flows are susceptible to loading conditions, whereas tissue Doppler velocities are thought to be less preload dependent.\(^17\) The lack of association between cTnT and these load-dependent indices of diastolic function may be explainable on this basis. Patients may have been significantly decongested prior to echocardiography, lowering filling pressures, and limiting any relationship between load-dependent transmitral E wave velocity and cTnT. Moreover, there was no correlation between cTnT and E-to-Ea wave ratio, a non-invasive surrogate of LV filling pressure.\(^17\) This observation further suggests that in patients with acute HF with preserved LV function, cTnT may depend more on intrinsic myocardial compliance (as measured by tissue Doppler) than on filling pressure-dependent echocardiographic indices.

In light of the associations between cTnT and tissue Doppler Ea velocity as well as LV diastolic dimensions, it is interesting that cTnT was not clearly associated with left atrial volume index. While an increased left atrial size is a hallmark of the chronicity and severity of LV diastolic dysfunction,\(^18\) we did not observe a relationship between cTnT and left atrial volume index in this cohort. It is possible that left atrial size was dynamic with volume status in these patients. Alternatively, given already substantially dilated left atria in our population (volume index 38 \( \pm \) 27 mL/m\(^2\)),\(^17\) it is possible that these patients had reached the limit of their left atrial size, again blunting a correlation with cTnT.

The aetiology of positive biomarkers of necrosis in patients with HF remains yet unclear.\(^19\) Our data suggest that one potential mechanism for a positive cTnT in patients with decompensated non-systolic HF is diastolic filling abnormalities, with increased LV wall stress, exacerbated by increased LV mass. In the setting of a non-compliant LV, increased filling pressures and increased myocardial work with transmural debt of oxygen, necrosis of myocardium—indicated by cTnT values—would supervene. In this light, a larger LV at end-diastole (reflecting greater LV volume) in a more hypertrophied LV may increase LV wall stress, and may lead to transient subendocardial ischaemia that further worsens LV compliance,\(^20\) causing an elevated troponin and worse HF in a circular fashion, with deleterious effects on prognosis.

Our study has several important limitations. We recognize that our sample size is small, and that ours need to be confirmed in a larger cohort. Though we are aware that echocardiography was not performed when the patient was most volume overloaded to reflect the most decompensated physiology (median time between hospital contact and echocardiography was 45 hours), our correlation analysis was most remarkable for a relatively preload-independent myocardial tissue Doppler index of diastolic function with a correlation coefficient that is extraordinarily strong. In addition, we only measured myocardial Ea wave velocity at one site as an index of global LV relaxation. Since this measure by itself may not fully capture global LV diastolic function, future investigation could focus on a technique (e.g. two-dimensional speckle tracking) to address global diastolic abnormalities.\(^17\) Further investigations on the relationship between cardiac biomarkers of necrosis in patients with HF and preserved ejection fraction and longer term mortality and cardiovascular morbidity in the acute HF setting would be important to extend the prognostic importance of cardiac troponin.

In conclusion, in patients with HF with preserved LV ejection fraction, the level of cTnT is strongly associated with the extent of LV relaxation abnormalities as assessed by tissue Doppler imaging. Patients with more severe diastolic dysfunction in the setting of normal LV systolic function
and a higher LV mass may be more likely to manifest a detectable cTnT during acute HF. Cardiac biomarkers of necrosis reflect the severity of diastolic dysfunction in HF with preserved LV ejection fraction.

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