The association of Hs-Troponin I with cardiac dysfunction and structural changes in chronic heart failure with reduced ejection fraction patients

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ABSTRACT

Introduction: Cardiomyocyte death is the key pathological feature of heart failure with reduced ejection fraction (HFrEF). One of the circulating markers which represent myocardial cell death is cardiac troponin. High sensitivity-troponin I (hs-TnI) has been validated as an acute coronary syndrome diagnostic criteria. But its value and role in chronic heart failure, specifically HFrEF, has been variable in different studies. The aim of this study was to determine whether hs-TnI, an indicator of cardiomyocyte injury, is associated with functional and structural changes in HFrEF patients.

Methods: A hospital-based cross-sectional analytic study was conducted on 72 patients with stable chronic HFrEF between April and October 2022. All subjects underwent echocardiography (Philips EPIQ7 and Affinity 70) and hs-troponin I serum measurement (Abbott Architect assay). Spearman’s test was used to evaluate the correlation between hs-troponin I and left ventricular ejection fraction (LVEF), E/A ratio, left ventricular end-diastolic volume (LVEDV), tricuspid annular plane systolic excursion (TAPSE) and left atrial volume index (LAVI).

Results: hs-TnI concentrations were quantifiable in all samples ranging from 10 to 280.9 pg/mL. hs-TnI was associated significantly with LVEF (r=-0.39; p<0.01), E/A ratio (r=0.328, p=0.01), and LVEDV (r=0.278, p=0.04). hs-TnI was not correlated with TAPSE and LAVI (r=0.241; p=0.07 and r=-0.13; p=0.429, respectively). The correlation between hs-troponin I with LVEF, E/A ratio and LVEDV proved that the degree of myocardial injury is directly associated with left ventricle (LV) systolic and diastolic dysfunction and also with LV dilatation. While it is not correlated with right ventricle (RV) systolic function. Hs-TnI may represent the injury in LV better than RV.

Conclusion: These findings support the association of hs-TnI as a circulating marker of cardiomyocyte injury with LV dysfunction (systolic and diastolic) and dilatation in chronic HFrEF patients. This has expanded the role of hs-TnI in chronic heart disease.

Keywords: diastolic dysfunction, hs-troponin, heart failure, systolic dysfunction.


INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is a clinical syndrome characterized by heart failure (HF) clinical symptoms and signs with left ventricular ejection fraction (LVEF) <40%. The prevalence of HF is 64 million worldwide, with >500,000 cases in Indonesia.1-6 HFrEF constituted almost half of HF cases, with longer hospitalization, worse quality of life and higher mortality rate than HF with preserved and mildly reduced ejection fraction.3,4 One of the typical pathological changes in HFrEF that is not found in other phenotypes of HF is cardiomyocyte death. Cellular death is considered the terminal phase that cardiomyocytes go through in HF. This causes cardiac remodeling, which disrupts myocardial contractility. It leads to cardiac systolic and diastolic dysfunction and later progresses to HF.5,6,7

The contractility of the cardiac muscle depends on the cardiac troponin-tropomyosin complex. Cardiac troponin (cTn) release to the circulation is induced by myocardial injury of any cause. Available cTn assays measure the value of either cardiac troponin I (cTnI) and T (cTnT). Cardiac troponin I have more stable concentrations throughout the day and night. It is also only found in the myocardium (not in skeletal muscle), making it more specific as a cardiac injury marker.8 High-sensitivity cardiac troponin (hs-cTn) assays have enabled the quantification of low concentrations of cTn in circulation. These high-sensitive assays have been validated and become the diagnostic criteria for myocardial...
infarction (MI) in acute coronary syndrome (ACS) guidelines. The elevation of cTn in other situations has been recognized, including in acute and chronic heart failure (HF) patients. The increased cTn level correlates with the severity of HF.

In chronic HF, the elevated cTn level is relatively stable over time, unlike in ACS. Higher cTn concentration in circulation using the hs-cTn assays is associated with worse LV function, higher LV mass, and a high risk of adverse cardiovascular (CV) outcomes in the general population and coronary artery disease patients. But to date, there is not much information on the correlation of cTn level with cardiac function and structure in chronic heart failure with reduced ejection fraction (HFrEF) due to ischemic etiology. In this study, we hypothesized that hs-cTnI level is correlated with cardiac systolic and diastolic function and structure (defined by several echocardiography parameters) in patients with HFrEF.

**METHODS**

**Study Design**

This is a hospital-based cross-sectional analytic study involving patients with stable, chronic HFrEF patients (New York Heart Association functional class I-II) with ischemia etiology. Our inclusion criteria are patients with an established diagnosis of HFrEF (LVEF <40% by Simpson’s biplane method) and evidence of obstructive coronary artery disease (defined as >50% stenosis in at least one coronary artery) on clinically indicated coronary angiography. Patients with non-ischemic etiology of HFrEF, congenital and valvular heart disease, cancer therapy history, and severe renal impairment (eGFR < 30 ml/min/1.73 m²) were excluded from this study. We used a consecutive purposive sampling method to recruit patients who fulfilled the criteria in the outpatient clinic of the integrated cardiac center of Prof. I.G.N.G. Ngeorah General Hospital, Denpasar, Indonesia, from April to October 2022. Demographic data (age, sex, body weight and height) were recorded.

**Echocardiography examinations**

Echocardiography was done based on clinical indication and before blood collection using a Philips EPIQ 7 echocardiographic machine. The echocardiographic protocol was performed according to the recommendations of the American Society of Echocardiography. The left ventricular ejection fraction was obtained using the 2D biplane Simpson’s method. Echocardiograms were reviewed by a cardiologists-echocardiography consultant blinded to the research subjects.

**High-sensitivity cardiac troponin I assay**

Blood for the hs-cTnI assay was obtained at an outpatient clinic visit within a maximum of three months after the echocardiography examinations and at least one month after acute cardiac event or hospitalization of all causes. The hs-cTnI concentration was determined by the Alinity i STAT high-sensitivity troponin I assay (Abbott, IL, USA) with a measurement range of 3.5-5,000 pg/mL and 99th percentile value of 35 pg/mL for males and 17 pg/mL for female.

**Statistical Analysis**

Univariate and bivariate analyses were done using SPSS for Windows version 22.0 (IBM Corp., Armonk, NY). The univariate analysis describes the baseline characteristics, echocardiographic variables and hs-TnI level. Bivariate analysis was conducted to determine the correlation between hs-TnI and echocardiographic parameters, i.e., left ventricular ejection fraction (LVEF), E/A ratio, E/e’, left ventricular end-diastolic volume (LVEDV), left atrial volume index (LAVI), and tricuspid annular plane systolic excursion (TAPSE). The significance of the correlation was determined by using the appropriate test formula. A p-value <0.05 was considered significant. The protocol was approved by the IRBs at the Faculty of Medicine, Udayana University and Prof. I.G.N.G. Ngeorah General Hospital, Denpasar, Indonesia. All participants provided written informed consent.

**RESULTS**

A total of 72 patients with stable chronic HFrEF (New York Heart Association functional class I-II, LVEF <40% and no evidence of acute cardiac event in the past month) were enrolled in this study. There were 56 male and 22 female subjects with a mean age of 58.53±9.79 years. Most patients had a history of smoking (62.5%) and dyslipidemia (77.8%). Of all subjects, 44.4% had hypertension, and 52.6% had diabetes mellitus (DM). The mean body mass index (BMI) was 23.93±4.44 kg/m², as shown in Table 1. All patients had obstructive CAD based on coronary angiography. They were treated with guideline-directed medical therapy for HFrEF, including a combination of ACE inhibitor or angiotensin receptor blocker, beta blocker, spironolactone, and loop diuretic.

Hs-TnI was quantified in all subjects, ranging from 10 to 280.9 pg/mL, with a mean of 30.56 pg/mL and a median of 14.8 pg/mL. Twenty (28%) subjects had a hs-TnI value above the 99th percentile (the cutoff value for males is 35 pg/mL and for females is 17 pg/mL) despite their stable chronic condition. All subjects had LVEF <40%, with the mean EF being 30.75±6.13 %. The median of the E/A ratio and LVEDV was 0.97 (0.45-5.76) and 144.16 (64.74-314.22) ml, respectively. The average LAVI is increased with a mean value of 42.18±15.30 ml/m². While the mean TAPSE is 19.29±4.46 mm, as stated in Table 2.

Bivariate analysis of the correlation of hs-TnI and echocardiographic parameters was performed using Spearman’s test. It showed a weak significant correlation between hs-TnI and LVEF(r=−0.39; p<0.01), E/A ratio (r=0.328; p=0.01) and LVEDV (r=−0.278, p<0.04). There is no significant correlation between hs-TnI and TAPSE and LAVI (r=0.241; p=0.07 and r=−0.13; p=0.429, respectively), as seen in Table 3.

**DISCUSSION**

Troponin is a protein complex that modulates the contraction and relaxation of striated muscle. Both troponin-I and T are found in cardiac muscle. Although troponin-I is specifically found in cardiac muscle, troponin-T may also be found in skeletal muscle. Troponin is released from cardiomyocytes due to the damage that happens in the myocardium. The high-sensitive cTn assays have been widely used as a part of the diagnostic criteria of acute
**Table 1. Baseline and clinical characteristics.**

<table>
<thead>
<tr>
<th>Baseline and Clinical Characteristics</th>
<th>N = 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (mean±SD)</td>
<td>58.53±9.79</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (77.8)</td>
</tr>
<tr>
<td>Female</td>
<td>16 (22.2)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>45 (62.5)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>38 (52.6)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>56 (77.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m^2) (mean±SD)</td>
<td>23.9±4.44</td>
</tr>
</tbody>
</table>

**Table 2. Laboratory and echocardiographic parameters. IQR: interquartile range; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end-diastolic volume; LAVI: left atrial volume index; TAPSE: tricuspid annular plane systolic excursion.**

<table>
<thead>
<tr>
<th>Laboratory and Echocardiographic Parameters</th>
<th>N = 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-Troponin I (pg/mL), median (IQR)</td>
<td>14.8 (10-280.9)</td>
</tr>
<tr>
<td>LVEF (%), mean±SD</td>
<td>30.75±6.13</td>
</tr>
<tr>
<td>E/A ratio, median (IQR)</td>
<td>0.97 (0.45-5.76)</td>
</tr>
<tr>
<td>LVEDV (ml), median (IQR)</td>
<td>144.16 (64.74-314.22)</td>
</tr>
<tr>
<td>LAVI (ml/m^2), mean±SD</td>
<td>42.18±15.30</td>
</tr>
<tr>
<td>TAPSE (mm), mean±SD</td>
<td>19.29±4.46</td>
</tr>
</tbody>
</table>

**Table 3. Correlation between hs-troponin I and echocardiographic parameters.**

<table>
<thead>
<tr>
<th>Echocardiographic Parameters</th>
<th>hs-Troponin I</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>-0.39</td>
<td>&lt;0.01*</td>
<td></td>
</tr>
<tr>
<td>E/A Ratio</td>
<td>0.328</td>
<td>0.01*</td>
<td></td>
</tr>
<tr>
<td>LVEDV</td>
<td>0.278</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>LAVI</td>
<td>0.241</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.103</td>
<td>0.43</td>
<td></td>
</tr>
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</table>

r = correlation coefficient. *significant p-value.

MI, especially in ruling non-ST elevation MI. A value above the 99th percentile suggests a diagnosis of acute MI. But, chronic elevation of troponin can be seen in acute and chronic conditions, such as heart failure, chronic kidney disease, pulmonary embolism, and pulmonary hypertension. In chronic conditions, the troponin level is slightly increased and stable, unlike in ACS or other acute cardiac events that show the rise and fall of troponin.

In this study, one-third of our subjects had high hs-TnI values despite their chronic stable clinical symptoms of HF. Without evidence of an acute cardiac event, the elevation of hs-TnI reflects chronic myocardial damage. It also correlates with HF severity. The exact mechanism of elevated troponin in chronic heart failure is still unknown. In ischemic cardiomyopathy, significant coronary stenosis decreases the oxygen supply to the myocardium. The hypertrophied and dilated heart has a reduced number of capillaries that worsen the reduced oxygen delivery. The heart is not able to match the high myocardial demand. All of these lead to subendocardial ischemia and increased cardiomyocyte death, either by apoptosis and/or necrosis, eventually leading to elevation of troponin release to the circulation.

Troponin has also been studied as a prognostic marker of chronic HF. Heart failure patients with elevated troponin were more ill and had a worse cardiac function and adverse cardiac events than those with normal troponin levels. Our study showed a weak significant correlation between the hs-TnI level, LVEF, E/A ratio, and LVEDV. Hs-TnI is inversely correlated with LVEF, an echocardiographic parameter representing LV systolic function. This is similar to previous studies that showed troponin I level in the circulation correlates with infarction size and, therefore, inversely correlates with LVEF, as there is an inverse relation between infarct size and LVEF. Poor myocardial contractility happens as the impact of the myocardial injury due to ischemia etiology. As the damaged myocardium releases troponin into circulation, its systolic function is also reduced. Different studies showed similar results: the elevation of troponin in chronic HF, regardless of the LVEF, is associated with more severe LV remodeling, systolic dysfunction and worse cardiovascular outcome (higher hospitalization rate and death). The cTnT level in HFrEF patients is also significantly higher compared to HFP EF patients. Much evidence has confirmed that hs-TnI correlates negatively with LVEF.

Our study results showed that the hs-TnI level had a weak significant correlation with the E/A ratio. E/A ratio is one of the echocardiographic parameters representing LV’s diastolic function. A higher E/A ratio in HFrEF is categorized as more severe LV diastolic dysfunction. Diastolic dysfunction is well known as a sign of subclinical injury of the myocardium, mainly caused by elevated LV filling pressure. A recent study using invasive hemodynamic assessment of HFrEF patients suggests that elevated LV filling pressure and subendocardial ischemia due to the impaired myocardial oxygen supply-demand balance are two factors that induce troponin elevation in HFrEF patients. The association of troponin and LV diastolic function has also been studied in other populations. A study by Otsuka H et al. showed that hs-TnI reflects the presence of left ventricular hypertrophy and LV diastolic dysfunction in non-ACS patients.
the elderly population without HF, hs-TnT concentration correlates with worse LV diastolic function but not systolic, independent of LV mass. The higher hs-TnT level also predicts HF incidents in the elderly population without cardiovascular disease.20,21 This suggests the role of troponin as a marker of subclinical structural and functional changes in LV that may predispose one to develop HF in the future.

Our study also showed a weak significant correlation between hs-TnI with LVEDV. High LVEDV in HFrEF is caused by LV dilatation that holds more blood volume than normal LV size. Cardiomyocyte necrosis due to coronary artery disease leads to replacement fibrosis. This causes alteration of LV chamber and wall thickness (hypertrophy and dilatation) as an adaptive process to remodeling to attenuate more progressive LV dilatation and stabilize LV contractility.22,23 More severe necrosis, which releases a bigger amount of troponin, will eventually cause worse LV dilatation, hence a bigger LVEDV.

It has been known that troponin elevation correlates well with LV structure and function. But this may not happen in other chambers, such as the left atrium (LA) and right ventricle (RV). Left atrial volume index (LAVI), the value of LA volume divided by body surface area, is recommended by the American Society of Echocardiography to measure LA size.48 Left atrial dilatation occurs in both systolic and diastolic dysfunction. In our study, there is no significant correlation between hs-TnI and LAVI. This finding is supported by an earlier study showing the significant correlation between TnI value with LV volume index (LVVI) and RV volume index (RVVI), but not with LVAI and right atrial volume index (RAVI).24,25 Since the ventricles account for most of the myocardial mass, chronic ischemia presumably affects LV more and provokes more troponin release from ventricular cardiomyocytes than atrial cardiomyocytes. The left atrium is also more compliant than the LV and may endure ongoing stress better. Various studies have proven that troponin level is elevated significantly in acute RV events such as acute pulmonary embolism. High troponin level is associated with RV dysfunction in pulmonary embolism patients.24,26 A recent study by Ghidini S et al. in Covid-19 patients showed no significant difference in troponin values between different RV longitudinal strain tertiles. It is assumed that RV dysfunction occurs independently of myocardial injury. One of the most common echocardiographic parameters that indicate RV systolic function is TAPSE.27 The hs-TnI value in our study does not correlate significantly with TAPSE. We assume that without acute and severe pressure and/or volume overload in RV, such as our subjects in this study, the elevated level of troponin in circulation reflects myocardial injury occurring in LV. The limitation of this study is the small sample number; thus, studies with more subjects are needed to prove the independent association between hs-TnI and the echocardiographic parameters and the predictive value of hs-TnI in chronic HFrEF patients. Studies in a different clinical setting, such as acute RV dysfunction, may also tell us further about the correlation of hs-TnI with RV systolic function.

CONCLUSION
The result of this study shows the association of hs-TnI as a circulating marker of cardiomyocyte injury with LV dysfunction (systolic and diastolic) and dilatation in stable chronic HFrEF patients. Furthermore, it had shown that in these patients, the elevated hs-TnI in circulation represents the myocardial injury that occurred in LV rather than in LA and RV. This has expanded the role of hs-TnI in chronic heart disease, and further cohort studies are needed to confirm the prognostic value of hs-TnI in chronic HFrEF.

CONFLICT OF INTEREST
The authors declare there is no conflict of interest.

ETHICAL CLEARANCE
This study has been approved by the Ethics Commission of the Faculty of Medicine, Udayana University (No. 406/UN14.2.2.VII.14/LT/2022).

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AUTHOR CONTRIBUTION
Luh Oliva Saraswati Suastika conceptualized and designed studies, collected and reviewed data, analyzed and interpreted data, and prepared manuscripts; I Gde Raka Widianna conceptualized and designed studies; I Wayan Wita conceptualized and designed studies; Agung Pranoto conceptualized and designed studies; Ida Bagus Rangga Wibhuti analyzed and interpreted data; Ni Made Ayu Wulan Sari helped analyzed and interpreted data; Melissa Dharmawan led data collection; Rizky Darmawan led data collection; Bagus Made Indrata Saputra analyzed and interpreted data.

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