High-Sensitive Troponin I and Re-Hospitalization in Patients With Decompensated Congestive Heart Failure

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Abstract- Patients with heart failure (HF) are frequently admitted for episodes of decompensation. Cardiac troponins are easily accessible biomarkers role of which for risk stratification of re-hospitalization among HF patients is less certain. We aimed to evaluate high-sensitive cardiac troponin I (hs-cTnI) levels among re-hospitalized patients with decompensated heart failure (D-HF). Consecutive subjects admitted with D-HF to 2 hospitals in Tehran, during the year 2014 were recruited. Excluded ones were patients with a suspected acute coronary syndrome or myocarditis/pericarditis, those with cardiopulmonary resuscitation/DC shock delivery, or major complications during or after hospitalization. Along with echocardiography parameters, level of hs-cTnI was checked at the first hour of hospitalization and 3 months after discharge. The patients were then categorized according to having or not having re-hospitalization during 3 months post discharge. A total of 97 patients were finally recruited. Among re-hospitalized patients, Left ventricular (LV) ejection fraction was significantly lower (38±14 % vs. 50 ± 12%; *P*=0.001), and LV end-systolic dimension was significantly higher (44±9 mm vs. 38±11 mm; *P*=0.012) compared to the other group. Moreover, levels of hs-cTnI were significantly higher among the re-hospitalized patients, both at initial visit (0.66±0.43 ng/ml vs 0.51±0.14 ng/ml, respectively; *P*=0.017) and at 3 months (0.59±0.48 ng/ml vs 0.48±0.23 ng/ml, respectively; *P*=0.030). This prospective study demonstrated that levels of hs-cTnI (both at the base and at follow up) are higher among patients who readmitted during 3 months of hospitalization for D-HF.

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Introduction

Heart failure (HF) is a highly common medical condition with a prevalence rate of about 2-3% in the general population and 10% (or even more) among people aged > 70 years (1,2). From a clinical viewpoint, patients with compensated or "stable" heart failure (S-HF) have no notable complaints. However, those with acutely decompensated HF (D-HF) are mostly presented to emergency departments with significant clinical symptoms such as severe dyspnea (3,4). Those episodes of decompensation are harbingers of poor prognosis in HF, characterized by 1-year and 5-year mortality rate of as high as 37.3% and 78.5%, respectively (5), which represents the importance of easily accessible measures for better risk stratification of the patients.

Cardiac troponin (cTn) is a complex of 3 proteins (cTnT, cTnI, and cTnC) that are essential for muscle contraction by regulating the interaction between actin and myosin (6). After myocardial necrosis, cTns are released into the circulation that makes them as useful biomarkers for diagnosing acute coronary syndrome (ACS). Furthermore, many studies have been reported the elevation of cTnI and cTnT levels both in S-HF (7-10) and D-HF (11-15) even in the absence of ACS. The prognostic influence of these biomarkers among patients

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with HF has also been an interesting field of research in recent years.

The cTnI, from a comparative perspective, is more often elevated than cTnT in patients with D-HF (16). Conversely, cTnT elevations are more frequently seen in the setting of renal failure that is highly prevalent among D-HF patients (17,18) making cTnT as less specific in this setting. Conventional assays of cTn have been used for many years, but high-sensitive cTn assays first were used by Missov *et al*., in 1997 (13) that provided a new non-invasive window for more exact assessment of cardiomyocyte damage. Today, the analytic capabilities of these assays offer several advantages over their conventional assay counterparts (19).

Taking those points into account, we designed the present study to confirm and further investigate the prognostic implication of cTnI level in patients with HF, using a high-sensitive cTnI (hs-cTnI) assay and with more focus on re-hospitalization as a primary prognostic endpoint.

Materials and Methods

Study patients

Study subjects were enrolled at two hospitals in Tehran, Iran: the Rasoul-e-Akram General Hospital and the Shahid Rajaei Heart Hospital. All consecutive patients presented with D-HF to the emergency departments during the year 2014 were initially recruited. Those patients with clinical diagnosis of ACS, both at initial evaluation and at follow up, were then excluded. Other exclusion criteria for the purposes of this study were: the suspected diagnosis of myocarditis or pericarditis, cardiopulmonary resuscitation or DC shock delivery at emergency department, major complications (such as pulmonary emboli, cardiogenic shock, sudden cardiac arrest, or death) during hospitalization, and being expired within 3 months of discharge from hospital. In order to prevent duplicate patient entry, if any repeated hospitalizations of each subject after the first time of inclusion were omitted.

Study protocol

The demographic information, as well as the result of trans-thoracic echocardiographic evaluation and baseline laboratory tests, were recorded for all recruited patients. In addition, a separate blood sample at the first hour of hospitalization was collected for each patient for measuring the level of hs-cTnI. That sample was sent to a single reference laboratory at Shahid Rajaei Heart Hospital that used the Acute Care™ cTnl assay on the Stratus® CS Acute Care™ Diagnostic System, with ≤10% CV at the 99th percentile of the normal population.

A next visit 3 months after discharge was planned for all enrolled participants who consented. Along with the clinical evaluation of the HF, a second sample for the hs-cTnI was sent to the same laboratory. The patients were then categorized according to re-hospitalization during 3 months after discharge, and measurements were compared between the two categories.

The study protocol was approved by the ethics committee of the Iran University of Medical Sciences, and the authors were committed to the Helsinki Convention Principles at all stages of research.

Statistical analysis

The collected information was entered into the SPSS 16.0 statistical software for analysis. Mean, median percentages and standard deviation (SD) were calculated. The Chi-square test, the Student’s *t*-test and the Pearson’s Correlation test with their non-parametric equivalents were used for data analysis as needed. Backward stepwise logistic regression was utilized to find the most important independent factors for re-hospitalization. Furthermore, the receiver operating characteristic (ROC) curve analysis was conducted for finding the best cut-off point to determine the patients with the most possibility of re-hospitalization. All tests were two-tailed, and P less than 0.05 was considered as significant.

Results

Baseline patient characteristics’

After applying the exclusion criteria for more than 200 patients, 97 were recruited for analysis among whom 47 (48%) were male; and 9 (9%) were expired after discharge. Of survived participants, 16 (%) were re-hospitalized during 3 months after discharge. Table 1 summarizes all baseline variables compared between the 2 groups of patients with and without re-hospitalization. As seen, most left ventricular (LV) echocardiographic indices differ significantly between the 2 groups. For example, LV ejection fraction (EF) was significantly lower (P=0.001) among the group of re-hospitalized patients (38±14 %) compared to the other group (50±12%); and LV-end systolic dimension (ESD) was significantly higher (P=0.012) in the former group (44±9 mm) when compared with the latter one (38±11 mm). Similar differences were found for LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) as seen in table 1. No statistically significant difference, however, was found in other comparisons such as patients' age, sex, medical background, and basic laboratory findings (Table 1).

Table 1. Baseline patient characteristics compared between the two groups with and without re-hospitalization*

Characteristic		Total (N=97)**	With Re-hospitalization (N=16)	Without Re-hospitalization (N=72)	*P*
Age (years)		48 ± 16	50 ± 14	44 ± 17	0.060
Male Sex: No (% of patients)		47(48)	3 (19)	35 (49)	0.097
Medical Conditions: No(% of patients)	**Diabetes**	15(16)	4 (25)	11 (15)	0.311
	Hypertension	21(37)	8 (50)	13 (18)	0.106
	Cigarette Smoking	23(24)	9 (56)	14 (19)	0.081
Laboratory Findings (mg/dl)	**Triglyceride**	141 ± 65	133 ± 71	148 ± 59	0.130
	Cholesterol	157 ± 38	161 ± 40	156 ± 36	0.831
	High Density Lipoprotein	45 ± 10	46 ± 10	45 ± 10	0.776
	Low Density Lipoprotein	91 ± 34	92 ± 33	91 ± 35	0.636
Creatinine					
Echocardiographic Indices	**LV Ejection Fraction (%)**	44 ± 14	38 ± 14	50 ± 12	0.001
	LV End-Systolic Volume (ml)	84 ± 36	96 ± 38	71 ± 31	0.016
	LV End-Systolic Dimension (mm)	41 ± 11	44 ± 9	38 ± 11	0.012
	LV End-Diastolic Volume (ml)	156 ± 45	158 ± 43	151 ± 48	0.045
	LV End-Diastolic Dimension (mm)	6.1 ± 9	62 ± 7	59 ± 11	0.065

*Plus-minus values are mean ±s standard deviation; NYHA: New York Heart Association, LV: Left ventricle
** Total of subjects include those who were expired after discharge

Measurement of hs-cTnI

Hs-cTnI levels had statistically significant difference among patients with and without diabetes (first-admission value: 0.69±0.37 vs. 0.61±0.46, respectively, *P*=0.015; follow-up value: 0.62±0.47 vs. 0.59±0.31, respectively, *P*=0.026). No such a meaningful difference was found for other baseline characteristics.

As shown in Table 2, levels of hs-cTnI were significantly higher among the re-hospitalized group compared to the other group, both at initial visit (0.66±0.43 ng/ml vs. 0.51±0.14 ng/ml, respectively; *P*=0.017) and at 3 months (0.59±0.48 ng/ml vs. 0.48±0.23 ng/ml, respectively; *P*=0.030).

Table 2. High-Sensitive Cardiac Troponin I (cTnI) levels compared between the two groups of patients

cTnI level (ng/ml)	With Re-hospitalization*	Without Re-hospitalization*	*P*
Initial value	0.66±0.43	0.51±0.14	0.017
Follow-up value (3-months after discharge)	0.59±0.48	0.48±0.23	0.030

*Values are a means±standard deviation

Discussion

According to the results of this prospective study, we found those patients with D-HF who re-hospitalized during 3 months post-discharge had worse echocardiographic parameters (LVEF, LVESV, LVESD, and LVEDD), and higher levels of hs-cTnI. In addition, diabetic patients had higher hs-cTnI level both at D-HF and S-HF phases.

HF as a ubiquitous public health problem has a wide spectrum of the clinical picture from completely asymptomatic patients with S-HF to those presented with near-death D-HF. The echocardiographic parameters, as well as biochemical markers (such as cTns), are helpful to have a better estimation of the HF status. Clearly, worse LV echocardiographic indices identify a subgroup of D-HF patients with the worse overall cardiac condition. Accordingly and predictably, our re-hospitalized patients demonstrated worse baseline D-HF state as shown on their LV echocardiographic parameters. Similar overall results have also been reported in other studies (20,21,22).

Prognostic significance of elevated cTn levels among D-HF patients has been demonstrated in many studies until now, most of which have been used cTnT rather than cTnI for risk stratification (9,10,12,23-25). Also for this setting, the novel high-sensitivity assays have less been studied than the conventional assays. Although Guisado Espartero *et al*., (26) found cTnT as not having a role in predicting re-hospitalization of D-HF patients, others proved cTnT as a useful predictor of re-hospitalization (4,27,28). Along with Tsutamoto *et al*., (29) and Parenti *et al*., (30) who showed higher cTnI levels have prognostic importance among HF patients, Yang Xue *et al*., (31) using a high-sensitivity assay for cTnI, similar to our study, demonstrated even very small hs-cTnI elevations are associated with increased 90-day D-HF readmission. The latter study (31) found patients with 90-day HF-related re-hospitalization had similar on-admission hs-cTnI level as patients who were event-free and thus emphasized the importance of serial measurements of hs-cTnI. In our study, however, a statistically significant difference for on-admission hs-cTnI levels were found among those with and without re-hospitalization. Collectively, the findings of these different studies are in favor of the theory of "ongoing myocyte injury." Considering elevated cTn levels as a marker of myocyte death or injury (32), higher levels of cTn (e.g. hs-cTnI in our study) among re-hospitalized patients could be translated as more ongoing myocyte damage which is a multifactorial event itself and several pathophysiologic mechanisms such as mechanical/oxidative stress, excessive adrenergic stimulation, etc. might have a role for it. Although several hypotheses have been proposed as an explanation, the exact mechanisms by which cTn levels are increased among HF patients (in the absence of ACS) remain uncertain. Those minimal differences in results of various surveys are best ascribed to the different population being studied and to different assays being used. For example, Christopher *et al*., (28) found the similar risk of major cardiac events between patients with positive on-admission cTn levels and those who converted to high cTn during hospitalization; a finding that best unifies our results with the results of Xue *et al*., (31) mentioned earlier.

Elevated levels of hs-cTnI among diabetics with the clinically stable cardiovascular state have been previously demonstrated by Yiu *et al*., (33) and higher hs-cTnI level was shown to be associated with increased risk of major cardiac event. We proved in this study, not only at S-HF state but also at D-HF phase the levels of hs-cTnI am higher in patients with type 2 diabetes. Arterial stiffening (34), as well as such factors as higher oxidative stress (35,36) and role of advanced glycosylated end-products (37), have been proposed for subtle myocardial injury and so elevated levels of cTns among diabetics.

As the main limitation, the present 2-center study recruited a relatively small population of HF patients. The higher sample size is needed to improve the power of future surveys. Moreover, we neither compared patients' medications among the 2 groups nor focused on the subjects' adherence to the standard HF treatment; issues that might be subjected as potential confounders for the results. Our strict exclusion criteria, however, made the results to be best limited to the HF population with no major confounding situation. Using high-sensitivity assay for cTn (rather than conventional assay), and using more sensitive cTnI rather than cTnT (33) might be considered as other advantages of the present investigation.

In conclusion, in a prospective evaluation, we demonstrated that levels of hs-cTnI (both at the base and at follow up) are higher among HF patients who readmitted during 3 months of hospitalization for D-HF.

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