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Elevated troponin I level assessed by a new high-sensitive assay and the risk of poor outcomes in patients with acute heart failure

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ABSTRACT

Background: The interpretation and clinical usefulness of elevated levels of cardiac troponins in acute heart failure (AHF) remain controversial. We aimed to characterize the relationship between changes in cardiac troponin I (measured using a new high-sensitive immunoassay by single-molecule counting technology, Singulex, Alameda, USA; hs-TnI) during first 48 h of hospital stay and patients' characteristics and the outcomes.
Methods and results: We measured hs-TnI at baseline, after 24 and 48 h in 130 AHF patients (mean age: 65 ± 13 years, 77% men). The percentage of patients with elevated hs-TnI (i.e., above the upper reference limit [URL] > 10.19 pg/mL) were: on admission – 59%, after 24 h – 61%, and after 48 h – 58%. Elevated baseline level of hs-TnI was associated with more severe dyspnoea on admission but neither peak level nor changes in hs-TnI during first 48 h were related to the dyspnoea severity or magnitude of dyspnoea relief. During 1-year follow-up there were 32 (25%) cardiovascular deaths. Neither absolute baseline nor peak values of hs-TnI predicted cardiovascular mortality. Only changes in hs-TnI were independently associated with cardiovascular mortality with the strongest relationship seen in peak change in hs-TnI: patients with an increase vs. remaining patients - hazard ratio (95% confidence interval): 3.22 (1.52–6.82) $p = 0.002$.
Conclusions: Using the new assay (proved to be more sensitive that the other available troponin assays) we observed that approximately 60% of patients with AHF presented elevated hs-TnI above URL during first 48 h of hospital stay. Only significant increase in hs-TnI predicted cardiovascular mortality.

1. Introduction

The pathophysiology underlying acute heart failure (AHF) is complex, heterogeneous, and no longer linked entirely with impaired haemodynamics [1]. The dysfunction or damage of peripheral organs (heart, kidney, liver) may occur and complicate the natural history of hospital stay in patients with AHF, also identifying those at high risk of poor outcomes [2–5]. In AHF there is a certain milieu (related to ischaemia, neuroendocrine and proinflammatory activation, oxidative stress, haemodynamic stress, vasoconstriction) predisposing to injury of the myocardium which constitutes an important element of the pathophysiology of this clinical syndrome [6–8].

In clinical practice, the evaluation of the levels of cardiac troponins in blood is used for an early detection of cardiac injury, regardless of aetiology [9,10]. Recent advances in the troponin assays have led to the development of high-sensitive assays able to detect troponins at much lower concentrations, which potentially offers a tool to evaluate and monitor the magnitude of cardiac injury apart from traditional evidence-based use in acute coronary syndrome [11–13].

In the recent studies using more sensitive assays, detectable levels of troponins have been reported in majority of patients with AHF, also without concomitant, clinically evident myocardial ischaemia [14,15]. However, the interpretation and clinical usefulness of elevated levels of troponins in AHF still remain controversial [16]. In particular, it has not been established whether early dynamic changes in troponin level would identify patients at risk of poor outcomes, both inhospital and post discharge period [17–20]. It may well be related to an inadequate precision of the tests unable to detect minor myocardial damage.

In this study, we applied a new high-sensitive immunoassay which outperforms other currently available troponin assays regarding sensitivity [13,21] in order to characterize the relationship between dynamic changes in cardiac troponin I, occurring during the first 48 h

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of hospital stay, patients' clinical characteristics and outcomes defined as the severity of self-reported dyspnoea and cardiovascular mortality.

2. Methods

2.1. Study population

Patients enrolled in this study were hospitalized for AHF at the Centre of Heart Diseases, 4th Military Hospital, Wroclaw, Poland, between September 2010 and July 2012. The inclusion criteria were: (1) age ≥18 years; (2) a diagnosis of AHF as the primary cause of hospitalization (diagnosis was based on the European Society of Cardiology (ESC) guidelines criteria [22–24]; (3) Patients written agreement to participate. Exclusion criteria included: (1) clinical diagnosis of concurrent acute coronary syndrome; (2) cardiogenic shock; (3) end stage of renal disease requiring renal replacement therapy (or planned renal replacement therapy). All patients were treated in accordance with the recommendations of the ESC guidelines [22–24]. A treatment regimen was not controlled by the protocol and left for a physician discretion. However, it was requested by the study protocol to collect all this information. The study protocol was approved by the local ethics committee, and all subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Study design and procedures

After inclusion in the study, information on demographic characteristics, clinical history, comorbidities and previous therapies was collected together with a complete physical examination. In all the patients, venous blood samples were obtained within the first 4 h after admission, and subsequently after 24 and 48 h. After centrifugation, the plasma was immediately frozen at −70 °C until further assay.

The following laboratory parameters were assessed at baseline samples in all patients using standard methods in our laboratory: 1) blood count: haemoglobin (g/dL), leukocytes (*10^3/μL), platelets (*10^3/μL); 2) serum creatinine (mg/dL) and urea (mg/dL), the estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) was calculated from the Modification of Diet in Renal Disease equation [25]; 3) electrolytes: sodium (mEq/L), potassium (mEq/L); 4) liver function: bilirubin (mg/dL), aspartate transaminase (AST, IU/IL), alanine transaminase (ALT, IU/L); 5) plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP, pg/mL) using an immunoenzymatic method (Siemens, Germany);

High sensitivity TnI (hs-TnI) analysis was based on a new diagnostic platform from Singulex, Inc. (Alameda, CA, USA) with the Erenna immunoassay system using a microparticle immunoassay and single-molecule counting in a capillary flow system. This assay was proved to be more sensitive than other currently available troponin assays and has been validated using Clinical and Laboratory Standards Institute (CLSI) guidelines [26]. The assay limit of detection is 0.1 ng/L with lower and upper limits of quantification at 0.2 and 475 ng/L, respectively, and the 99th percentile upper reference limit (URL) is 10.19 ng/L [27]. The details of the assay procedure are provided elsewhere [28].

2.3. Definitions

Peak hs-TnI level was defined as the maximum value at baseline, 24 h and 48 h levels. Peak change in hs-TnI was the biggest change from log2-transferred baseline and log2-transferred peak hs-TnI values. On the basis of hs-TnI dynamics during first 48 h of hospital stay, the patients were grouped into three categories: increase, stable, decrease of hs-TnI. The significant increase of hs-TnI was defined as at least one hs-TnI value (at 24 or 48 h) 20% greater than baseline. The 20% threshold was based on the previous reports [15,29]. The significant decrease of hs-TnI was defined as at least one hs-TnI value (at 24 or 48 h) 20% less than baseline concentration with exclusion of those with hs-TnI increase. Stable hs-TnI was defined as all hs-TnI values within 20% of the baseline level.

2.4. Outcomes

In this study, we analysed the relationship between changes in hs-TnI and two specific clinical endpoints: severity of self-reported dyspnoea and cardiovascular mortality.

Self-reported dyspnoea was recorded daily on admission, after 24 and 48 h using absolute 10-point scale. Each time the patients were asked to judge their breathing with 10 point scale (10 points meaning dyspnoea of worst severity and 0 points – lack of dyspnoea).

Patients were seen after hospital discharge by the study investigators in the outpatient HF clinics with follow-up ≥12 months in all survivors. The information regarding survival was obtained directly from the patients or their relatives, from the HF clinic database or from the hospital system. In all cases of death this information was carefully evaluated to establish most likely cause of death. No patient was lost to follow-up. The primary end-point of the study was cardiovascular mortality. The length of follow-up of the survivors and patients in whom an event occurred after 12 months was censored at 365 days.

2.5. Statistical analyses

Normally distributed continuous variables were presented as means ± standard deviations. The intergroup differences were tested using Student's *t*-test, the Mann-Whitney *U* test, analysis of variance (ANOVA) or the χ^2 test, where appropriate. Variables with a skewed distribution were expressed as medians with lower and upper quartiles, and were log transformed in order to normalize their distributions. The categorical variables were expressed as numbers with percentages. The associations between hs-TnI and clinical and dyspnoea were tested using univariable and multivariable logistic regression models. To establish the effect of hs-TnI on survival, we performed univariable and multivariable Cox proportional hazard regression models for the biomarker and other clinical variables. A value of $P < 0.05$ was considered as statistically significant.

Statistical analyses were performed using the STATISTICA 12 data analysis software system (StatSoft, Inc).

3. Results

One hundred and thirty patients with AHF were included in the study with mean age of 65 ± 13 years, 100 (77%) were men and 30 (23%) had de novo AHF. Baseline characteristics and laboratory values of the study population are presented in Table 1. During hospitalization all patients received intravenous loop diuretic, 48 (36%) vasodilator (nitroglycerine) and 7 (5%) inotropic agents (dobutamine, dopamine), respectively.

3.1. Hs-TnI on admission and during early phase of hospital stay

The blood samples for hs-TnI assay were available in all 130 patients on admission, in 110 (85%) after 24 h, and in 99 (76%) after 48 h. At all these time-points hs-TnI levels were above the assay's limit of detection (0.1 ng/L) in all blood samples analysed.

The median [with IQR] of hs-TnI levels, together with the percentage of patients with hs-TnI above the URL (i.e. >10.19 ng/L) were: on admission: 13.13 [6.97–27.11] pg/mL (59%), after 24 h: 13.13 [6.76–25.88] pg/mL (61%), and after 48 h: 13.40 [6.03–21.16] pg/mL (58%), respectively (Fig. 1).

The comparison of the clinical and laboratory data of patients with baseline hs-TnI above vs. below the URL is presented in Table 1. Those with hs-TnI above URL had more often history of coronary artery disease, chronic kidney disease, and diabetes mellitus, higher creatinine and haemoglobin levels.

Table 2 summarizes baseline clinical and laboratory data of patients divided into those with significant increase ($n = 25$), stable levels ($n = 55$), and significant decrease ($n = 37$) in hs-cTnI during first 48 h of hospital stay (see Methods section for the definition of the groups). Overall, there were differences in: age (patients with hs-TnI decrease were younger), baseline heart rate (patients with hs-TnI decrease had fastest heart rate), history of HF (patients with hs-TnI decrease had more often de novo AHF), chronic kidney disease and diabetes mellitus (both more common in patients with hs-TnI increase).

3.2. Hs-TnI and the study outcomes

Table 3 summarizes the association between baseline and peak hs-TnI values, and the categories of changes in hs-TnI and the study outcomes.

An elevated baseline level of hs-TnI (i.e. above URL) was related to more severe dyspnoea on admission (categorized above median in the entire group) but neither peak levels nor category of changes in hs-TnI were related to the severity or relief in dyspnoea.

During 1-year follow-up there were 32 (25%) cardiovascular deaths Baseline levels of hs-TnI above URL were not associated with the worse survival (18 [23%] vs. 14 [26%], log-rank test $p = 0.704$). Neither absolute baseline nor absolute peak values of hs-TnI predicted cardiovascular mortality. Changes in hs-TnI were associated with the risk of cardiovascular mortality. In the univariable Cox models both peak change in hs-TnI and category of an increase in hs-TnI were associated with an increased risk of cardiovascular death with hazard ratios [95%CI]: 1.97 (1.27–3.06), $p = 0.003$, 3.84 (1.88–7.87), $p = 0.0002$, respectively. These relationships remained significant, when adjusted for other variables related to cardiovascular mortality (Table 3). Kaplan–Meier curves for 1-year cardiovascular mortality for hs-TnI peak change category are presented in Fig. 2.

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