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An Update on Cardiac Troponins as Circulating Biomarkers in Heart Failure

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Abstract Circulating troponins and natriuretic peptides are the only biomarkers specifically released from cardiac myocytes that can be determined with robust and sensitive analytical methods, even in healthy subjects. These intracellular proteins are released from reversibly or irreversibly damaged cardiac myocytes into the bloodstream by mechanisms that are not entirely clear. The recent introduction of a new generation of highly sensitive assays of cardiac troponin I or T has not only improved the early diagnosis of acute myocardial infarction but also suggested that there are several causes for troponin release other than acute coronary syndromes. Circulating troponins are elevated in patients with acute or chronic heart failure and are strongly associated with outcome, independently of natriuretic peptides, the benchmark biomarkers in heart failure. In the absence of further experimental evidences, the pathophysiologic basis for the elevation of circulating cardiac troponins in patients with stable chronic heart failure remains speculative.

Keywords Troponin · Heart failure · Prognosis · Biomarkers

Introduction

Over the years, several markers of cardiac myocyte injury have been used in the diagnosis of myocardial infarction (MI) and in the assessment of infarct size. Measurement of the cytoplasmic creatine kinase-MB (CK-MB) was the gold standard for the assessment of myocardial injury for many years. However, the availability of specific and sensitive assays for the cardiac contractile proteins troponins (I or T) largely replaced the use of CK-MB. The most recent international guidelines now only recommend the use of troponins for making a diagnosis of MI [1]. Because more troponin is found in the heart per gram of myocardium, and a greater quantity is released during injury, troponin is more sensitive than CK-MB for the detection of cardiac damage [2]. Moreover, the recent introduction of new assays with better analytical sensitivity for cardiac troponins (typically in the low range of picograms per milliliter) has improved the early diagnosis of acute MI [3•, 4•]. However, it has also questioned the prevailing hypothesis that cardiac troponins are only released after irreversible injury of cardiac myocytes [5]. Indeed, circulating cardiac troponins may be detected in patients without typical symptoms of acute coronary syndromes, as those seen in patients with stable coronary artery disease. Even in such patients, circulating cardiac troponins are significantly associated with the adverse cardiovascular outcomes including heart failure (HF) [6]. Circulating troponins may be raised in many clinical conditions such as end-stage renal disease, acute respiratory diseases, infectious diseases, and envenomation by biological toxins, in the absence of acute coronary syndromes [7•]. The interpretation of troponin elevation in such situations can be very challenging for physicians and scientists.

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Traditional or Low-Sensitivity Troponin Assay

Most published clinical studies on cardiac troponins in chronic HF were performed before the introduction of the new high-sensitivity assays. The first evidence that myofibrillar cardiac troponins are released into the bloodstream

of patients with HF was reported by two groups almost simultaneously in 1997 [8, 9]. La Vecchia et al. [8] measured circulating cardiac troponin I (cTnI; limit of detection, 0.3 ng/mL) in a small group of patients with acute decompensated HF. Serial measurement of cTnI in these patients was related to clinical status or outcomes. Missov et al. [9] studied a slightly larger group of patients with severe congestive HF (n=35) and also reported and increased serum levels of cTnI (limit of detection, 3 pg/mL). Interestingly, they also found that the two other markers of myocyte injury, CK-MB isoenzyme mass and myoglobin concentration, remained within the normal range.

Since these pioneering studies, several other groups have confirmed these findings that cTnIs are increased in acute decompensated or severe HF and are related to unfavorable prognosis [10–13]. Repeated measurement over time of cardiac troponins was found to be useful in identifying and monitoring high-risk patients [14]. Some studies also found that measurement of troponin can be effectively combined with another well-established cardiac marker (natriuretic peptides) to improve risk stratification in patients with HF [15, 16]. The largest source of data on the prognostic value of cardiac troponins in acute HF comes from a recent report from the Acute Decompensated Heart Failure National Registry (ADHERE) [17]. These authors analyzed more than 67,000 patients hospitalized for acute decompensated HF and measured circulating troponins (either cardiac troponins I or T) within 24 hours of admission. Overall, 6.2% of the patients were positive for troponin (≥1 ng/mL for cTnI or ≥0.1 ng/mL for cardiac troponin T [cTnT]). On admission, patients with elevated troponins had lower systolic blood pressure and lower left ventricular ejection fraction (LVEF) and were less likely to suffer from atrial fibrillation compared with patients negative for troponins. Troponin-positive patients had a higher rate of in-hospital mortality (8.0%) than troponin-negative patients (2.7%; P<0.001), with an adjusted OR of 2.55 (95% CI, 2.24–2.89; P<0.001). Ischemic etiology of HF was not a determinant of troponin status and did not predict mortality. A negative troponin test may therefore aid in the identification of patients with acute HF for whom less intense monitoring and therapy could be appropriate.

As might be expected, the proportion of patients with elevated cardiac troponins is lower in patients with milder chronic and stable HF than in acute or severe HF. Hudson et al. [18] found abnormal cTnT (≥0.02 ng/mL) in only 24% of 136 ambulatory and stable patients with chronic HF (New York Heart Association functional classification [NYHA class], II-IV), a prevalence lower than observed in more instable patients (30%–83%) [10–13]. As noted above for acute HF, cardiac troponins concentration was similar in chronic HF patients with or without ischemic etiology, suggesting that troponin release was not related to ischemic events, but rather to ongoing myocardial damage or leakage of myofibrillar proteins, reflecting loss of viable cardiac myocytes characteristic of progressive HF [18]. Elevated cardiac troponins were an independent predictor of death or readmission for HF at 1 year after enrollment.

The prognostic value of cTnT, and other two traditional biomarkers in HF (C-reactive protein [CRP] and B-type natriuretic peptide [BNP]) was evaluated in 598 residents of the Olmsted County (southeastern Minnesota) presenting with HF [19]. In this community setting, troponin T was above the level of detection (>0.01 ng/mL) in 46% of patients. Elevated troponin level was more frequent in men, patients with diabetes, and patients with reduced renal creatinine clearance, and it was independently associated with the risk for 1-year mortality. Each biomarker tested (CRP, BNP, and cTnT) significantly improved predictive accuracy when individually added to a multivariable model based on clinical characteristics, as confirmed by three metrics such as c statistic, integrated discrimination improvement, and net reclassification improvement. The combination of CRP and BNP further improved the prediction of the model, whereas addition of cTnT to the other two markers conferred no added benefit [19].

In a recent community-based study from Sweden on 70-year-old men free from previous HF, valvular disease, or ECG LV hypertrophy, higher cTnI levels were associated with a higher risk of subsequent first hospitalization for HF (87 of the 1089 men during a median follow-up of 9 years; HR, 1.26 [95% CI, 1.15–1.38] for an increment of 0.01 ng/mL; P<0.0001) [20]. This relation was independent of established risk factors for HF (smoking, systolic blood pressure, antihypertensive medication use, diabetes, body mass index, serum cholesterol, and myocardial infarction). Adjusting additionally for serum N-terminal probrain natriuretic peptide (NT-proBNP) only slightly attenuated the risk (HR, 1.22 [95% CI, 1.11–1.34] per 0.01 mg/L of cTnI). Furthermore, cTnI predicted HF in individuals without previous MI and after censoring the ones with MI during follow-up, suggesting that cTnI also predicts subsequent nonischemic HF. The best cutoff level in this sample for discriminating those who subsequently suffered HF from those who did not was a cTnI of 0.04 mg/L [20].

The prognostic significance of serial measurements of cardiac troponins has been investigated in a small study of 62 patients with decompensated HF in whom cTnT was measured within 4 days of hospital admission and again 7 days later. Persistent elevation of cTnT levels was predictive of clinical events (death or hospital readmission for decompensated HF) [21]. The predictive value of serial measurements of cTnT concentrations has also been investigated in a cohort of 172 outpatients with chronic

HF (NYHA class, III-IV) [22]. cTnT (traditional assay, 99th percentile of normal reference population corresponding to 10 pg/mL) was measured at a 3-month interval for a total of 24 months, and the primary end point was death or cardiac transplantation. Patients were divided into three groups: those with no serial cardiac troponin elevation during the follow-up (n=53); those with at least one but not all serial elevations (n=57); and those with all serial measurements with elevated troponin (n=40). Patients with frequent or persistent elevation of cTnT levels were at increased risk of events (OR, 3.77; 95% CI, 1.28–11.07; P=0.02) compared with patients with no serial elevation, suggesting a role for serial measurements of this biomarker for risk assessment in ambulatory HF population [22].

High-Sensitivity Troponin Assay

The threshold for detecting myocyte injury has been continuously lowered and a new generation of highly sensitive troponin assays with improved analytical sensitivity and precision is ready for clinical evaluation [23, 24]. The new high-sensitivity assays for cardiac troponins can detect troponin in the range of few picograms per milliliter (Table 1). With these assays, measurable levels of circulating troponins are found in virtually all apparently healthy subjects in the general population. In one study, high-sensitivity troponin I (hsTnI) was detectable in three of four healthy Caucasian subjects for whom the presence of cardiac or systemic acute or chronic disease was excluded [25]. In another study, hsTnI was detected in 95% of healthy Swedish subjects [26].

Very few published studies have used the high-sensitivity troponin assays. In the Valsartan Heart Failure trial (Val-HeFT), plasma concentrations of the traditional and the high-sensitivity cTnT and several other biomarkers were measured at baseline and at a number of time points during follow-up, in 4053 patients with chronic and symptomatic HF with depressed systolic function [27••, 28]. Troponin T was measurable in 10.4% of the patients using the traditional assay with a limit of detection of 10 pg/mL. The median concentration (27 pg/mL) was lower than the diagnostic cutoff for acute MI. Patients with elevated cTnT were older, with worse HF, more depressed LV function, more comorbidities (eg, diabetes, atrial fibrillation), worse renal function, and more pronounced neurohormonal activation (higher levels of natriuretic peptides, norepinephrine, renin, and aldosterone) than those without cTnT elevation. Over a mean follow-up of 2 years, mortality was almost three times higher in patients with elevated cTnT (43%) compared with those with undetectable levels (16%). Elevated cTnT was the strongest predictor of death in a multivariable models adjusted for all traditional risk factors [27••].

In the Val-HeFT trial, a pre-commercial version of a high-sensitivity cTnT assay (hsTnT) was evaluated and compared with the traditional assay [27••]. The new reagents improved the sensitivity by five-to tenfold, lowering the limit of detection to 1 to 2 pg/mL, and with this, the fraction of patients with detectable plasma troponin T increased dramatically from 10% with the traditional assay to 90% with hsTnT reagents. A significant correlation was present between cTnT and hsTnT in the 420 patients with detectable cTnT (Spearman r=0.84; P< 0.0001). As observed with the traditional troponin assay, patients with elevated hsTnT (above the median concentration of 12 pg/mL) had all the features of worse HF. The circulating concentrations of hsTnT were directly related to LV internal diameter and inversely proportional to the EF. A similar association between cTnI (measured with a high-sensitive assay) and echocardiographic parameters of increased wall stress (relative LV wall thickness and early to late atrial mitral Doppler peak flow velocity ratio [E/A ratio]) has been reported in 71 patients with severe nonischemic HF [29]. In a retrospective analysis of 93 patients with HF and nonischemic heart

Table 1 Limit of detection, 99th upper reference limit and concentrations at a coefficient of variation of 10% for some highly sensitive immunoassays for circulating cardiac troponins

Study	Method	Troponin	Limit of detection (pg/mL)	99th upper reference limit (pg/mL)	Troponin concentration (pg/mL) at a CV of 10%
Prontera et al. [43]	Ultra ADVIA Centaur (Siemens Healthcare Diagnostics; Eschborn, Germany)	I	6	87	64
Kavsak et al. [44]	AccuTnI (Beckman Coulter; Brea, CA)	I	2	9.2	8.7
Hedberg et al. [45]	Innotrac Diagnostics (Duluth, GA)	I	7	≤ 30	20
Sabatine et al. [46]	Singulex Erenna (Alameda, CA)	I	0.2	9	0.9
Giannitsis et al. [24]	hsTnT (Roche Diagnostics; Rotkreuz, Switzerland)	T	5	13.5	8.7

CV coefficient of variation; *hsTnT* highly sensitive cardiac troponin T

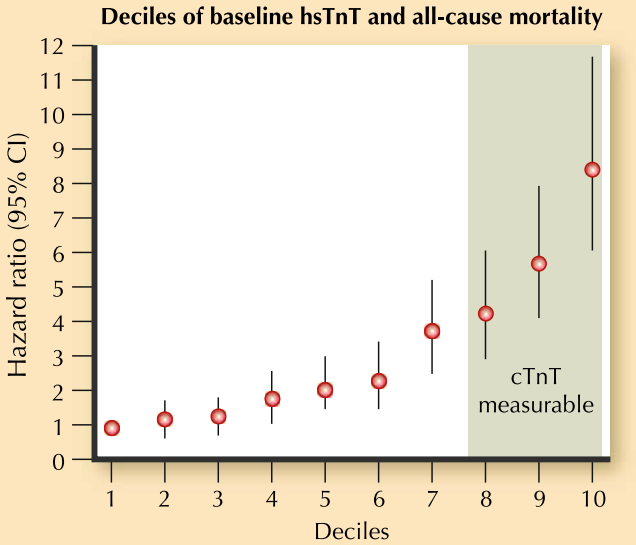

Fig. 1 All-cause mortality by decile concentration of high sensitive cardiac troponin T (hsTnT) in the Valsartan Heart Failure trial. Hazard ratios and 95% CI for the risk of mortality are shown for each decile of baseline hsTnT concentration. The concentration range where cardiac troponin T (cTnT) is above the detection limit of the traditional assay (0.01 ng/mL) is highlighted

disease recruited for elective diagnostic catheterization and followed for 40 months, elevated cTnT (≥10 pg/mL) was inversely related to an increase in echocardiographic LVEF of ≥5% and a decrease of LV end-diastolic diameter ≥5 mm from baseline [30].

Association With Adverse Outcomes

In the Val-HeFT trial, there was an almost linear increase in the risk of adverse clinical events with hsTnT concentration, even in a range of very low concentrations that could not be measured with the traditional assay (Fig. 1) [27••]. Thus, the prognostic accuracy of cardiac troponins was greatly increased with the hsTnT assay in patients with chronic and stable HF.

Natriuretic peptides are currently the most powerful biomarkers for risk stratification in HF [31••]. A comparison of BNP and hsTnT in the Val-HeFT trial showed that the two cardiac markers had substantially similar prognostic discrimination in these patients with chronic HF [27••]. Moreover, measurement of hsTnT added to prognostic information provided by natriuretic peptides alone. Patients with both cardiac markers elevated (a natriuretic peptide—either BNP or NT-proBNP—and hsTnT) had a worse prognosis than those with a single elevated marker. In addition, serial measurement of hsTnT over time improved its prognostic value. Patients were categorized according to the concentrations of hsTnT at study entry and at 4-month follow-up, 16 pg/mL (optimal cutoff levels for the prediction of mortality, identified by receiver-operating characteristics curve). Four groups were identified: patients with stable hsTnT concentrations below this cutoff at both time points (category low–low, n=2012); patients with stable hsTnT concentrations above this cutoff at both time points (high–high, n=1062); patients with hsTnT concentrations below the cutoff at study entry but above after 4 months (low–high, n=193); and patients with hsTnT concentration above the cutoff at study entry but below after 4 months (high–low, n=207). Interestingly, the rate of mortality was similar in patients with increasing hsTnT (21.8%) or those with decreasing hsTnT (19.3%), whereas, as expected, those with low stable hsTnT had the best outcome (8.5%) and those with persistently high hsTnT levels had the worst outcome (28.4%). In a multivariable model, however, the last hsTnT value of repeated measurement was the best predictor of future adverse events. After adjustment for major clinical and instrumental variables, including BNP, higher than the median levels of hsTnT

Table 2 Multivariable Cox models for the modes of death as endpoints in Val-HeFT

Risk variable[a]	CV death (n=645)		Sudden death (n=397)		Death for HF (n=189)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
hsTnT ≥ 12 pg/mL	2.02 (1.65–2.46)	< 0.0001	1.87 (1.47–2.37)	< 0.0001	2.69 (1.73–4.18)	< 0.0001
BNP ≥97 pg/mL	1.60 (1.33–1.91)	< 0.0001	1.49 (1.20–1.86)	0.0004	1.91 (1.33–2.75)	0.0005
Age ≥70 years	1.23 (1.03–1.45)	0.02	–	–	1.73 (1.28–2.35)	0.0004
NYHA class (3-4 vs 2)	1.34 (1.14–1.57)	0.0004	1.13 (0.93–1.39)	0.23	2.00 (1.46–2.72)	< 0.0001
Ischemic etiology	1.48 (1.25–1.75)	< 0.0001	1.40 (1.13–1.73)	0.0019	1.27 (0.93–1.73)	0.13
LVIDd >6.8 cm	1.54 (1.29–1.82)	< 0.0001	1.60 (1.28–1.99)	< 0.0001	1.70 (1.24–2.34)	0.001
Serum creatinine > 107 μM	1.20 (1.01–1.43)	0.04	0.89 (0.72–1.10)	0.27	2.58 (1.76–3.77)	< 0.0001

[a] Only variables found to be significantly associated to outcomes at univariate analysis were included in the multivariate Cox regression models

BNP brain natriuretic peptide; *CV* cardiovascular; *HF* heart failure; *HR* hazard ratio; *hsTnT* high-sensitivity cardiac troponin T; *LVIDd* left ventricular internal diameter in diastole; *NYHA* New York Heart Association; *Val-HeFT* Valsartan Heart Failure Trial

were independently associated to an increased risk of cardiovascular death overall, and death for HF or sudden death (Table 2).

Interpretation of Circulating Troponin T in Chronic HF

What is the physiologic significance of circulating cardiac troponins in chronic HF? Apparently healthy men appear to lose 1 g of myocardium per year, corresponding to 64 million cells. However, the exact mechanism (apoptotic or necrotic cell death) remains largely unknown [32]. Ongoing cardiomyocyte death has been observed in animal models of post-MI LV dysfunction [33] and in patients with chronic HF [34, 35]. If ongoing cardiac damage is assumed to be a determinant of circulating troponins, this phenomenon seems to be independent of an ischemic etiology of the disease. Stretching of cardiac myocytes might lead to leakage of the cytosolic pool of troponins by transient loss of cell membrane integrity. This reversible damage may contribute to the increase in circulating cardiac troponins caused by irreversible injury of cardiac myocytes. It is unknown whether and to what extent apoptosis contributes to troponin T elevation in chronic HF [36]. There are also alternative causes for elevated cardiac troponin levels including cardiopulmonary disease and chronic renal insufficiency [37]. For instance, decreased renal clearance of circulating troponin has been shown to contribute to elevated serum levels of this biomarker in patients with chronic HF and kidney disease [38]. To understand the relative contribution of the heart and impaired renal function of elevated troponin in patients with HF and chronic kidney disease (CKD), cTnT was measured in the aortic root and in the coronary sinus of 26 patients. The cTnT concentration in coronary sinus was almost twofold higher than in aortic root, similar to observations for BNP. No difference in this ratio was seen in patients with and without CKD (estimated glomerular filtration rate $\geq$ vs <60 mL/min/1.73 m^2). However, aortic concentration of cTnT was twofold higher in HF patients with CKD compared with those without CKD. These findings suggest that both decreased renal clearance and HF contribute to increased concentrations of circulating cTnT.

It has been repeatedly shown that cardiac troponins can be released from necrotic myocytes, mostly in animal models of acute cardiac injury induced by isoproterenol [39, 40]. In the absence of a quantitative correlation between the number of cardiac myocytes undergoing necrotic death and circulating concentrations of cardiac troponins, the relation between histologically assessed extent of cardiac injury and circulating cardiac troponins is convincing [41]. With the development of new pharmaceutical agents, the measurement of cardiac troponins in serum has become an important support to histologic studies of the myocardium for detection of myocardial injury [42•]. At present, cardiac troponins are the preferred translational cardiac safety biomarkers widely used in the preclinical evaluation of several classes of drugs, such as anthracyclines and other anticancer agents, phosphodiesterase inhibitors, and antiretroviral agents that may affect the myocardium [42•].

Conclusions

Several neuroendocrine systems (renin–angiotensin–aldosterone, sympathetic, endothelin) and inflammatory mechanisms are chronically activated in patients with HF and might contribute to myocyte injury and cell death progressing at a very slow rate over the years. Further studies are required to understand the role and rate of these mechanisms working not only in HF but, as more recently shown, also for stable coronary disease. Experimental investigations using well-characterized animal models of cardiac damage (myocardial infarction, cardiac overload, diabetes, renal dysfunction, neuroendocrine activation) and/or cultured isolated myocytes (hypoxia, hyperglycemia, hormonal stimulation) will probably help in deciphering the biological complexity finding cardiac contractile protein in the blood of patients with HF. It thus seems that the availability of high-sensitivity assays for cardiac troponins is expanding knowledge in cardiac diseases.

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