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Invited critical review

Cardiac troponin assays in the management of heart failure

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ABSTRACT

Cardiac troponins I and T are established biomarkers of cardiac injury. Testing for either of these two cardiac troponins has long been an essential component of the diagnosis of acute myocardial infarction. In addition, cardiac troponin concentrations after acute myocardial infarction predict future adverse events including development of ischemic heart failure and chronic elevations of cardiac troponin correlate with heart failure severity. These predictions and correlations are particularly obvious when cardiac troponin concentrations are measured using the new high sensitivity cardiac troponin assays. Thus, a growing body of literature suggests that cardiac troponin testing may have important clinical implications for heart failure patients with reduced or preserved ejection fraction. In this review, we explore the prognostic utility of measuring cardiac troponin concentrations in patients with acute or chronic heart failure and in populations at risk of developing heart failure and the relationship between cardiac troponin levels and disease severity. We also summarize the ongoing debates and research on whether serial monitoring of cardiac troponin levels may become a useful tool for guiding therapeutic interventions in patients with heart failure.

Contents

1. Introduction

The myocyte contractile apparatus is composed of actin, myosin, and numerous regulatory proteins. Three such proteins, troponin C (TnC — calcium binding, 18 kDa), troponin I (TnI — inhibitory, 24 kDa), and troponin T (TnT — tropomyosin binding, 37 kDa), form the troponin heterotrimeric complex, which plays an integral role in calcium-mediated excitation–contraction coupling in the skeletal and cardiac muscles.

Low concentrations of the two cardiac specific isoforms – cardiac TnI (cTnI) and cardiac TnT (cTnT) – are present in the plasma of healthy individuals, and the concentration of these cardiac troponin (cTn) molecules increases, often dramatically, following cardiac myocyte injury. Assays quantitating serum cTn can be classified based on the percentage of samples taken from healthy subjects that exceed the assay's limit of detection [1]. Medium sensitivity (ms) assays can quantitate cTn concentrations exceeding the 99th percentile in a healthy reference population. However, they can only detect cTn in a small subset of healthy individuals. High sensitivity (hs) assays, according to the International Federation of Clinical Chemistry and Laboratory Medicine recommendations, should be able to quantitate cTn in more than 50% — and ideally more than 95% — of healthy subjects [2].

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cTnT and cTnI have become the preferred cardiac biomarkers to aid in the diagnosis of myocardial infarction (MI) [3] and have been shown to be of significant prognostic value in predicting both short and long-term morbidity and mortality in patients with acute coronary syndrome [4–6]. However, elevated cTn can be observed in numerous other conditions [7], and cTn is beginning to have important clinical implications for other conditions such as heart transplant rejection, cardiorenal syndrome, and heart failure (HF). Although not part of standard practice, quantifying cTn could be a promising additional measure for the diagnosis of HF and for stratification of future HF-related morbidity and mortality. This is important for several reasons. HF is a common disease, affecting an estimated 5.8 million people in the United States [8], with significant decrements to quality of life and economic burdens. The prevalence and associated direct costs of HF are estimated to increase by 25% and 200%, respectively, over the next twenty years [9,10].

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT proBNP) – indicators of cardiac wall stress – have been the traditional gold standard biomarkers for HF. However, there is a growing understanding that there are numerous pathophysiologies underlying HS such as myocardial injury, oxidative stress, neurohormonal activation, inflammation, fibrosis, apoptosis, etc. and that a single biomarker that describes only one facet of this complex process might not adequately capture the full extent of the disease [11].

In this review, we will discuss the clinical utility of quantifying cTn in post-MI patients at risk for developing HF, members of the general population, and patients with acute decompensated HF (ADHF) or chronic HF (CHF). In addition, we will review information on the potential use of cTn as an additional biomarker that may guide HF therapy, similar to the role that is being established for natriuretic peptides [12]. We also briefly discuss the potential role of cTn in the management and prognosis of HF patients with preserved ejection fraction.

1.1. Cardiac troponin as a potential biomarker for predicting heart failure in the general population

Multiple studies have examined the prognostic utility of measuring cTn in the general population to predict cardiovascular morbidity and mortality [13–18]. In the Dallas Heart Study [16], investigators obtained baseline cTnT in 3546 patients aged 30–65 using both ms and hs assays and followed the patients for a median of 6.4 years. Using hs cTnT values, several important observations were made. Firstly, increasing age, male gender, and African ancestry were associated with higher cTnT. Secondly, higher cTnT was associated with a higher rate of overall/cardiac mortality and cardiac structural changes typical for HF. Thirdly, there were significant performance differences between the hs and ms cTnT assays. The hs assay detected cTnT in 25% of the study cohort, while the ms assay detected cTnT in only 0.7% of patients. The ms assay failed to detect cTn in two-thirds of patients in the highest hs cTnT category. Overall, these findings demonstrated that chronic, low-level myocyte injury was occurring in the study population that, over time, resulted in cardiac dysfunction and HF.

deFilippi et al. [17] measured cTnT with an hs assay in specimens obtained 15 to 21 years earlier from individuals (≥65 years old) enrolled in the Cardiovascular Health Study. Participants' baseline cTn and two to three year follow-up cTn were used for subsequent analysis. 66% of patients had detectable cTnT at baseline. After the first blood sampling, patients were stratified into quintiles according to cTnT levels and followed for mortality and development of HF for a median of 11.8 years. Higher levels of cTnT were associated with increased incidence of HF, with individuals in the highest cTnT category (>12.94 ng/L) having an adjusted hazard ratio of 2.48 (2.04–3.00, 95% CI) compared to individuals with undetectable cTnT. Importantly, changes in concentration of cTnT from baseline had additional prognostic value. For patients with detectable cTnT at baseline, a ≥50% increase at follow-up was associated with a greater risk for developing heart failure (adjusted HR 1.61; 1.32–1.97, 95% CI) and a ≥50% decrease at follow-up was associated with a lower risk for developing HF (adjusted HR 0.73; 0.54–0.97, 95% CI) compared to those whose follow-up cTnT remained within 50% of baseline. In accordance with the Dallas Heart Study, the Cardiovascular Health Study demonstrated that even minor elevations of cTnT have important prognostic value for the development of HF. In addition, the rise or fall of cTnT concentration over time is important for risk stratification.

Data from the Atherosclerosis Risk in Communities (ARIC) Study [18], obtained in a cohort of 9698 individuals ranging in age from 54 to 74, showed that elevated baseline hs cTnT was a predictor of HF as well as mortality over the mean follow-up time of 9.4 years, consistent with the previously described studies. In a subsequent analysis, Nambi et al. [19] examined whether or not the addition of biomarkers to the ARIC HF Model, an established clinical risk prediction tool for HF [20] that uses patient age, ethnicity, gender, coronary heart disease, systolic blood pressure, use of blood pressure-lowering medication, diabetes, smoking status, heart rate and body mass index, improves its predictive value for the ten-year risk of developing HF. They found that inclusion of hs cTnT and NT-proBNP into the ARIC HF Model increased the area under the curve (AUC) from 0.779 (0.763–0.800, 95% CI) to 0.836 (0.821–0.857, 95% CI) for men and from 0.776 (0.760–0.797, 95% CI) to 0.817 (0.803–0.837, 95% CI) for women.

Predictive value of cTn concentration measure using hs assays has also been studied in patients with chronic conditions. Elevated cTn was associated with increased risk of HF in ambulatory patients with type II diabetes [21] and in patients with stable coronary artery disease [22,23].

Summary: In the general population, measurement of cTn might have important prognostic value for the future development of HF. hs cTn assays identify more individuals who might be at risk than ms assays. Combined biomarker risk models and serial cTn testing appear to have added prognostic utility.

1.2. Cardiac troponin as a predictor of post-MI heart failure

Direct myocardial damage, including injury from MI, can lead to ventricular remodeling [24] with consequent decrease in cardiac function, predisposing patients to HF. It is estimated that around 65% of patients will be diagnosed with HF within six years from MI [25].

In the post-MI setting, infarct size is positively correlated with the concentration of circulating cTn and the extent of future adverse cardiac remodeling [26,27]. This pathophysiologic relationship illustrates how cTn can potentially allow clinicians to stratify patients by risk of developing post-MI HF. The prognostic value of cTn in predicting future HF has been validated in rodent models of MI. In one study [28], rodents who underwent surgical MI or sham surgery had their cTnT measured 24 h after the procedure. Left ventricular wall motion abnormalities, which are both indicators of systolic dysfunction and imaging phenotypes relevant to HF, were monitored at two and five weeks post-surgery. Higher early cTnT concentrations were positively associated with the severity of wall motion abnormalities. There was a positive correlation between cTnT and the histologic size of infarct. In another study [29], rodents who underwent surgical MI and were then administered a cardioprotective agent had reduced infarct size and a subsequent reduction in incidence of post-MI HF compared to rodents who received placebo, further strengthening the association between infarct size and risk of HF.

Importantly, quantification of circulating cTn can help distinguish myocyte injury in HF from myocyte injury in MI. Ischemic myocyte necrosis in MI results in the release of higher concentrations of cTn compared to that seen in HF and is characterized by an acute rise and fall pattern of cTn [30]. In HF, ongoing myocyte injury is mediated by several proposed mechanisms, such as supply–demand subendocardial ischemia, neurohormonal modulation, intracellular calcium accumulation, inflammatory cytokines, and oxidative stress, all of which ultimately result in the release of low levels of cTn [31–34].