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Review

Cardiac troponin and heart failure in the era of high-sensitivity assays

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ABSTRACT

The Joint European Society of Cardiology-American College of Cardiology Foundation-American Heart Association-World Heart Federation Task Force for the Redefinition of Myocardial Infarction recommends cardiac troponin (cTn)-T as a first-line biomarker, and suggests the use of the 99th percentile of a reference population with acceptable precision (i.e. a coefficient of variance ≤10%) as a cut-off for the diagnosis of acute myocardial infarction. Recently developed troponin assays fulfill this analytical precision. While conventional cTnT assays have often been used as a positive or negative categorical variable, stepwise rises in high sensitivity (Hs)-cTnT in patients presenting with chronic heart failure (HF) have been associated with a progressive increase in the incidence of cardiovascular events. Similar observations have been made in the general population. Hs-cTnT at baseline and during follow-up is a powerful predictor of cardiac events in patients with HF and in the general population. Whether it is the ideal biomarker remains to be confirmed, however. We review the potential contributions of TnT assays in the assessment of risk of HF, in HF, and in myocardial diseases that cause HF.

Contents

Introduction

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. As it relates to heart failure (HF), the ideal biomarker should (1) be accurate in low serum concentrations, (2) be practical when added to conventional diagnostic methods, (3) have a prognostic value, and (4) predict cardiac events when its concentration varies [1,2]. In the guidelines published by the National Academy of Clinical Biochemistry Laboratory Medicine Practice, measurements of B-type natriuretic peptide (BNP) and amino N-terminal proB-type natriuretic peptide (NT-proBNP) in the blood are both described as diagnostic markers and predictors of risk in patients presenting with HF outside of the acute phase of myocardial infarction (MI) [3]. On the other hand, the

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cardiac troponin (cTn) assay was as a marker of MI. The current Joint European Society of Cardiology-American College of Cardiology Foundation-American Heart Association-World Heart Federation Task Force for the Redefinition of Myocardial Infarction recommends measurements of cTn as a first-line biomarker [4]. However, elevated cTn concentrations in the absence of myocardial disease, for instance after cardiac trauma, cardioversion, sepsis, and pulmonary embolisms, have also been reported and reviewed elsewhere [5–9]. We review here the current clinical role of troponin assays in HF.

Troponin assays

The three-unit troponin I, T, and C complex, located along with tropomyosin on the actin filament, is essential for the calcium-mediated regulation of skeletal and cardiac muscle contraction. While troponin T (37 kDa) and I (23 kDa) are both structural proteins, 6–8% of cTnT and approximately 3.5% of cTnI are found in the cytosole [7,8]. It has been hypothesized that, (a) during reversible ischemia, loss of membrane integrity causes the transient leakage of cTn from the cytosolic component, and (b) when the ischemic injury becomes irreversible, the release of troponin T or I becomes continuous [7,8]. However, this hypothesis has not been verified and it remains controversial whether cTn can be released from myocytes in the absence of cell death [10]. cTn is released from the myocytes as ternary (cTnT–cTnI–TnC) or binary (cTnI–TnC) complexes, or as free cTnT in patients with MI [7,11].

While troponin C is not cardiac specific, and thus is not used for the diagnosis of cardiac injury, cTnT and I are specific markers of myocardial injury in acute coronary syndromes (ACS) [4]. Acute MI is diagnosed by a rise and/or fall of cardiac biomarkers, with at least one measurement >99th percentile of the upper reference limit, together with (a) symptoms, (b) electrocardiographic changes, or (c) imaging findings, consistent with myocardial ischemia. Importantly, the professional guidelines recommend the use of the 99th percentile of a reference population with acceptable precision (i.e. a coefficient of variance $\leq$10%) as a cut-off value for the diagnosis of acute MI. However, until recently, the cTnT and cTnI assays were insufficiently precise to define reliably the 99th percentile of a normal reference population. The delayed rise in circulating concentrations of cTn after initial patient presentation was another major limitation of conventional assays. These analytical weaknesses have been successfully overcome by the development of newer assays. For example, the 99th percentile value of a healthy reference population, using Roche Diagnostics' (Basel, Switzerland) High-Sensitivity Troponin T assay, was 0.014 ng/ml, and the 10% coefficient of variability (CV) was 0.013 ng/ml [12]. With the Centaur® cTnI Ultra assay (Siemens, Munich, Germany), the 99th percentile of a healthy reference population was 0.04 ng/ml and 10% CV was 0.03 ng/ml [13].

Furthermore, the diagnostic performance of these new assays of cTnT and I is high as early as upon presentation of the patients in the emergency department, and allows the prediction of adverse clinical events [13–15]. The diagnostic performance of the troponin assay by areas under the receiver-operating-characteristic curves in patients presenting within 3 h after the onset of chest pain was 0.92 for the Roche high-sensitivity (Hs) and 0.76 for the standard cTnT assay ($p = 0.005$) [14].

Not only a diagnostic and short-term prognostic marker in patients with acute MI, cTn is also a predictor of long-term prognosis in patients with stable coronary artery disease. Using a cut-off value of 0.01 μg/l with the Beckman Access Accu TnI assay (Fullerton, CA, USA) (the 99th percentile of a healthy reference population was 0.04 ng/ml and 10% CV was 0.06 ng/ml), the FRagmin and Fast Revascularization during InStability in Coronary artery disease II trial found that cTnI was a reliable, independent predictor of mortality in patients stabilized after an episode of non-ST segment elevation ACS [16]. Furthermore, in the Prevention of Events with Angiotensin Converting Enzyme Inhibition trial, concentrations of Roche Hs-cTnT <99th percentile in a healthy population were strongly associated with the incidence of cardiovascular death and HF but not with MI in patients presenting with stable coronary artery disease [17]. This is in contrast with observation that elevated cTn concentrations predict recurrent MI more reliably than HF events in patients with ACS [18]. The source of cTn release in patients with chronic stable coronary artery disease needs to be clarified.

Finally, a new definition of Hs assay has recently been released. Besides the CV analytical issue mentioned earlier, it includes the requirement that measurable concentrations <99th percentile value and above the assay's limit of detection are ideally attainable in >95% of healthy individuals [19].

Factors that influence the concentrations of troponin

In most studies, elevated cTnT concentrations have been associated with increasing age, male gender, renal failure and left ventricular (LV) hypertrophy in the general population [20–23]. However, Clerico et al. found age and male gender to be associated with elevated Siemens TnI Ultra concentrations in 692 healthy subjects [24]. On the other hand, Eggers et al. reported no influence by gender on the Beckman Access TnI [25]. Therefore, the clinical characteristics that influence the concentrations of cTnT and cTnI must be studied with each assay.

The mechanisms of cTnT or I elevation in patients with renal insufficiency are also unresolved. They are often both elevated in patients presenting with end-stage renal disease, even in the absence of manifestations of myocardial ischemia. Apple et al. reported an increase in mortality rate with changes in cTnT from <0.01 ng/ml, to between >0.01 and 0.04 ng/ml, >0.04 and 0.1 ng/ml, and >0.1 ng/ml in end-stage renal failure [26]. In a pooled analysis of 28 studies, Khan et al. found that cTnT concentrations >0.1 ng/ml were associated with a significant increase in all-cause mortality and a high risk of cardiac death in end-stage renal disease [27]. It has been reported that current assays do not cross-react with isoforms expressed in skeletal muscle obtained from patients suffering from end-stage renal disease [28] and hypothesized that the elevated cTnT concentrations observed in end-stage renal disease are unlikely to be false positive results. On the other hand, forms have recently been found in diseased skeletal muscle that might increase the concentrations of cTnT [29]. Furthermore, while it was thought, because of its relatively large molecular size, that cTnT is cleared by the reticulo-endothelial system, it is fragmented into small enough molecules to be cleared and excreted by the kidney [30,31]. Therefore, the serum concentration of cTnT may be partially determined by renal clearance. However, it has also been suggested that the clearance of cTnI is not changed by renal failure [32]. The results of the measurements of cTn renal clearance might depend on which of the epitopes that are detected by individual assays and by the degradation of troponin.

Finally, there are hour-to-hour and week-to-week biological variations in both cTnT [33] and cTnI [34] assays. While these biological variations do not influence the interpretation of high cTn concentrations measured in acute MI, they are important to interpret the small serial changes in Hs-cTnT or I concentrations observed in the absence of acute MI.

Mechanisms of troponin elevation in heart failure

Although the mechanisms of troponin release in patients with HF remain unclear, several studies in vitro have yielded some clues.

In isolated rat hearts, an increased ventricular preload causes a degradation of cTn independently of myocardial ischemia [35]. An increased myocardial wall stress and LV end-diastolic pressure might decrease the subendocardial perfusion, and increase the concentration of cTn. In concentrations measured in the failing heart, norepinephrine caused necrosis of the myocytes [36]. Renin might also cause myocyte injury via the renin–angiotensin system, since angiotensin II causes the necrosis [37] and apoptosis of neonatal and adult ventricular myocytes [38]. Likewise, tumor necrosis factor-α, an inflammatory cytokine, causes myocyte apoptosis [39]. Finally, stretch due to myocardial overload can induce myocyte necrosis and apoptosis [40]. Recent studies have shown that the cardiomyocytes can release cTn by a stretch-related mechanism mediated by integrin [41]. In congestive HF, these pathophysiological changes are all putative causes of myocyte injury [42], which, in turn, further activates these mediators.

Despite these experimental observations, few human studies have directly compared the concentrations of cTnT or I with pathogenic molecules. Horwich et al. [43] and Eggers et al. [25] observed correlations between elevated serum concentrations of cTnT and I, and an elevated pulmonary capillary wedge pressure. Our group [44] and Latini et al. [45] found correlations between elevated serum concentrations of cTnT and elevated serum concentrations of BNP, renin, norepinephrine, and C-reactive protein. These observations suggest that myocardial load, activation of the renin–angiotensin–aldosterone and of the sympathetic nervous system, and inflammation, are causes of myocyte injury in patients with chronic HF. However, relationships between (a) apoptosis or necrosis and (b) cTn serum concentrations, remain to be shown.

In our study, patients presenting with acutely decompensated (AD) HF and increased cTnI concentrations despite treatment had a significantly lower blood pressure on admission and received more inotropes [46]. An analysis of the Acute Decompensated Heart Failure National (ADHERE) Registry also showed that patients whose cTn concentrations were elevated had a lower mean systolic blood pressure on admission, and patients with elevated cTnT treated with inotropes had the highest in-hospital mortality [47]. Therefore, a low myocardial perfusion resulting from low blood pressure may cause subendocardial ischemia due to a mismatch between myocardial oxygen supply and demand, and exogenous inotropes administered to maintain blood pressure and organ perfusion, might also promote the loss of myocytes in patients with ADHF [48,49]. Despite the organ protective effects of natriuretic peptides observed in vitro [50] neither carperitide (a recombinant α-human atrial natriuretic peptide) [51] nor nesiritide (BNP) [52] lowered the serial concentrations of cTn in patients presenting with ADHF.

Finally, the interpretation of elevated cTnT and I in patients presenting with ischemic heart disease is somewhat problematic. Patients with HF may have asymptomatic stenoses of one or more large or small coronary arteries. Therefore, the elevation of biochemical markers of myocyte injury observed in patients presenting with chronic HF and coronary stenoses may be a consequence of ischemia of the myocardium supplied by the stenosed artery. However, in the Val-HeFT trial, an ischemic etiology was present in 60% and 57% of patients with versus without elevation of cTnT, respectively, by conventional assay, versus 59% and 55% of patients, respectively, using the Hs-cTnT assay [45]. Moreover, in patients with acutely decompensated HF, the ADHERE Registry showed that "ischemic heart failure" was the cause of acute cardiac decompensation in 53% and 52% of patients with versus without elevated cTn, respectively, and concluded that the presence of underlying ischemic heart disease was not a major discriminator of cTn elevation [47]. Thus, an ischemic substrate does not seem to be a major cause of cTn increase in patients with both chronic and acute HF.

Troponin and risk stratification in heart failure

In 1997, Missov et al. reported a significant elevation of cTnI in advanced HF [53], and we reported that elevated cTnT and procollagens are prognostic markers in patients with chronic HF [54]. We later reported that patients presenting with dilated cardiomyopathy and serum concentrations of cTnT persistently ≥0.02 ng/ml during follow-up had higher rates of long-term adverse outcomes and developed cardiac remodeling [55]. On the basis of these observations, we hypothesized that cTnT is a marker of subclinical myocyte injury. Since then, several reports have been published pertaining to the use of cTnT or I in the risk stratification of patients with congestive HF of ischemic or non-ischemic origin [43,45,56–59] although the concentrations of cTn in HF are generally lower than in patients presenting with acute MI. Latini et al. reported that in 4053 patients with chronic HF enrolled in the Valsartan Heart Failure Trial (Val-HeFT), a cTnT concentration ≥0.01 ng/ml (median = 0.027 ng/ml) was detectable in 10.4% of patients, compared with a ≥0.001 ng/ml concentration (median of 0.012 ng/ml) in 92.0% of patients, using the Roche Hs-cTnT assay [45]. In contrast to the conventional cTnT assay, often described as a positive or negative categorical variable, these authors first reported the prognostic significance of the Roche Hs-cTnT assay as a continuous variable in patients with chronic HF. It is noteworthy that when hazard ratios for mortality were plotted by increasing deciles of the Roche Hs-cTnT concentrations at baseline, the risk of death increased progressively.

Since HF is a complex clinical syndrome, a single biomarker might not reflect all of its characteristics. BNP is a peptide chiefly secreted by the ventricular myocardium in response to strain, and the serum concentrations of BNP and NT-proBNP are being used increasingly in the diagnosis and prognosis of HF [3]. BNP and NT-proBNP may be viewed as markers of myocardial load and cTnT and cTnI as markers of myocyte injury [60]. Combining these biochemical markers may provide new insight in the management of HF and reports support the additional prognostic value of cTnT or cTnI with BNP or NT-proBNP [43,56,57,59]. In a study of 238 patients with advanced HF referred for cardiac transplantation, BNP and cTnI provided independent prognostic information and the combination of increased BNP and increased cTnI identified patients with a 12-fold increase in risk of death [43].

cTn is also a prognostic factor in patients with ADHF without ACS [47,61–65]. The largest set of data has been collected by the ADHERE Registry [47,65]. Although that registry included several different cTnI assays with different cut-off points, Fonarow et al. showed that BNP and cTnT or I on admission to the hospital are significant independent predictors of in-hospital mortality and, in over 42,500 admissions for management of HF, elevations of both BNP and cTnT or cTnI were associated with the highest risk of death [65]. Peacock et al. measured the in-hospital mortality in >61,000 patients included in ADHERE, divided in quartiles of cTnT concentrations between ≤0.01 and >0.06 ng/ml, and quartiles of cTnI between ≤0.04 and >0.20 ng/ml, and found a correlation (adjusted odds ratio for death in the group of patients with a positive troponin test: 2.55; 95% confidence interval, 2.24–2.89; $p < 0.001$) between cTn concentrations and prognosis [47].

Serial measurements of troponins in heart failure

The cTn concentrations measured during long-term follow-up are equally powerful prognostic markers. The Val-HeFT study showed that baseline and 4-month Hs-cTnT were both independently correlated with mortality [45], and the same authors reported recently that very small changes in Hs-cTnT over time are predictors of cardiovascular events in patients with HF enrolled in

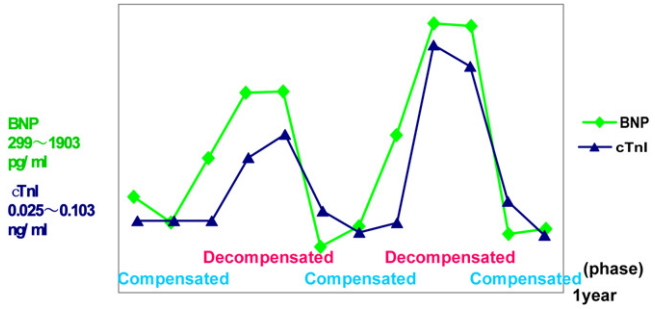

Fig. 1. Concentrations of B-type natriuretic peptide (BNP) and cardiac Mitsubishi PATHFAST cardiac troponin (cTn) I measured in a 69-year-old man with dilated cardiomyopathy. BNP and cTnI both increased rapidly from the compensated to the decompensated phase of heart failure [48].

Val-HeFT and GISSI-HF [66]. These observations suggest that serial measurements of cTnT may be of clinical relevance for the management of chronic HF. With a conventional assay, Miller et al. reported that a decrease in cTnT concentrations to normal values was associated with a decrease in risks of death or cardiac transplantation, whereas a normalization of BNP concentrations did not change these risks [67,68]. Even small elevations of cTnT concentrations might be an indication for more aggressive treatment.

In 2002, we reported that a persistent elevation of cTnT despite a decrease in BNP was a marker of poor prognosis in patients with ADHF [61]. However, serial measurements of cTn in these patients are challenging because (1) the onset of acute cardiac decompensation might be difficult to detect, and (2) increases or decreases in cTn concentrations are modest when compared with acute MI, requiring a highly accurate assay at low concentrations. Using the Mitsubishi (Tokyo, Japan) PATHFAST cTnI assay, we observed not only elevated BNP, but also cTnI in decompensated HF (Fig. 1) [48] and we observed poor outcomes in patients presenting with acute cardiac decompensation, in whom the concentration of cTnI increased on day 1 after hospital admission, despite treatment for decompensated HF and a decrease in the serum concentrations of BNP [46]. Increases in cTn concentrations despite treatment of ADHF have been reported by others [62,69,70]. Biolo et al. recently reported an elevation of the Siemens Centaur Ultra cTnI concentrations despite a decrease in NT-proBNP in patients with ADHF being discharged from the hospital. When compared with stable HF, concentrations of cTnI in patients with ADHF were twice as high [69]. Xue et al. reported that an elevation of Nanosphere cTnI after the initiation of therapy is a marker of poor prognosis [70].

Serial measurements are also important to predict cardiac remodeling [71–73]. We reported that cTnT at follow-up, but not upon admission to the hospital, is a predictor of cardiac remodeling [71]. In the REVE-2 study, Fertin et al. recently observed that cTnI at baseline was not an independent predictor of LV remodeling, whereas persistently elevated Siemens Advia Centaur cTnI concentrations during follow-up predicted LV remodeling after acute MI [73].

Troponin in the assessment of the risk stage of heart failure

The prevalence of cTn elevation, and the prognostic value of cTn in the general population has been recently reported [20–23]. In a population-based sample of 3557 subjects enrolled in the Dallas Heart Study, the prevalence of cTnT elevation was 0.7% among participants without congestive HF, LV hypertrophy, chronic kidney disease, or diabetes mellitus [20]. The authors suggested that the merits of cTnT measurements as a cardiovascular screening test deserve further study. de Lemos et al. reported that a concentration >0.003 ng/ml was detectable by Hs-cTnT assay in 25% of the nearly 3500 subjects enrolled in the Dallas Heart Study, versus 0.7% by the conventional cTnT assay [23]. Hs-cTnT >0.003 ng/ml was associated with male sex, older age, black race, history of HF, lower renal function, and a greater LV mass. We measured concentrations of Hs-cTnT ≥0.003 ng/ml (mean = 0.008 ng/ml) in 80% of patients suffering from essential hypertension [74]. Age, renal function, and LV hypertrophy on electrocardiogram were independently associated with elevated Hs-cTnT.

Minimally elevated serum cTn concentrations in the general population have also been found to predict coronary events, HF, and cardiac death. In 2006, Zethelius et al. reported that elevated Beckman Accu cTnI concentrations in 70-year-old men free from clinical manifestations of cardiovascular disease were associated with an increased risk of death and first coronary event in the next 10 years [75]. These authors hypothesized that subclinical myocyte injury precedes the development of HF, and reported that elevated Beckman Accu cTnI concentrations are an independent predictor of HF in 70-year-old men without HF [76]. The Atherosclerosis Risk in Communities reported that a Hs-cTnT concentration ≥0.003 ng/ml in a general population was associated with an increased risk of coronary heart disease, mortality and hospitalization for HF [77]. It is noteworthy that the hazard ratio of a Hs-cTnT ≥0.003 ng/ml was 2.29 for coronary heart disease and 5.95 for HF, and that, in the general population, mildly elevated concentrations of Hs-cTnT seem to be a predictor of HF rather than a predictor of coronary events. The Cardiovascular Health Study enrolled adults ≥65 years of age, without history of HF, who underwent measurements of Hs-cTnT, at baseline and 2–3 years later [78]. The baseline cTnT concentrations and subsequent changes were correlated with incident HF and cardiovascular death. The patients with the highest baseline concentrations of Hs-cTnT were at highest risk of experiencing subsequent cardiovascular events [23,77,78]. Although several survival analyses have revealed a stepwise increase in cardiac events at Hs-cTnT concentrations ≥0.003 ng/ml [23,77,78], further studies are needed to identify the optimal threshold of cTn concentrations in the population at risk of HF.

Other myocardial diseases

Hypertrophic cardiomyopathy

Few reports have examined the significance of cTn in patients presenting with hypertrophic cardiomyopathy (HCM). In 2003, we reported increased cTnT concentrations in 50% of patients suffering from HCM in its non-dilated phase [79]. Most of these patients had increased cTnT concentrations, which persisted over several years, and fractional shortening and intraventricular septum thickness decreased significantly during follow-up, indicating that cTnT is a marker of myocyte injury in these patients. Moreno et al. measured serum concentrations of Hs-cTnT >0.014 ng/ml in 42% of 95 patients with HCM. The elevated Hs-cTnT concentrations correlated positively with maximum LV wall thickness, left atrial diameter, and LV outflow tract gradient [80]. Kubo et al. reported that elevated cTnI was associated with (a) LV wall thickness, (b) peak early transmitral filling velocity/peak early diastolic mitral annulus velocity on tissue Doppler imaging, and (c) male gender in 162 patients suffering from HCM [81]. The same authors observed, in 167 patients, that cTnI was a prognostic marker of HCM-related death, hospitalization for management of HF and stroke, and that the combined measurements of cTnI and BNP further increased the prognostic accuracy [82]. Cambronero et al. suggested that cTn is one of the biomarkers in HCM from a pathophysiological perspective [83].

Myocarditis

Myocarditis is most often caused by a virus, and less often by an autoimmune reaction, hypereosinophilic syndrome or sarcoidosis [84]. Besides acute MI, severe myocarditis is often diagnosed in patients presenting to the emergency room with acute chest pain and elevated cTn, who usually undergo coronary angiography to rule out MI [85,86]. In the absence of coronary artery disease, the endomyocardium is biopsied with a view to make a diagnosis. Although the pathophysiology of cTn release in patients presenting with myocarditis has not been clarified, myocyte death and ischemia due to vasospasm seem likely causes of elevated cTn [84]. However, at the present time, the diagnostic importance of cTn in myocarditis has not been elucidated.

From a therapeutic perspective, some studies, including our own, have observed a decrease in the serum concentrations of cTn after successful immunosuppressive therapy in patients with viral myocarditis [87] or eosinophilic myocarditis [88], and after interferon therapy in patients with viral myocarditis [89]. While the significance of Hs-cTn assay has not been clarified, it might be useful as a therapeutic monitoring tool in the management of myocarditis.

Cardiac amyloidosis

Light chain amyloidosis is a plasma cell dyscrasia characterized by the extracellular deposition of pathologic, insoluble, β-fibrillar immunoglobulin light chain in several organs. Cardiac involvement is the most important determinant of the clinical outcome. In 2003, Dispenzieri et al. reported that cTnT, cTnI, septal thickness, LV ejection fraction, urine M-spike, age, and clinical symptoms of congestive HF were correlated with overall survival, and that detectable cTnT was the strongest predictor of overall survival by multiple variable analysis [90]. With a dedicated assay, it has been reported that even slightly increased serum concentrations of Hs-cTnT might indicate cardiac involvement that remains undetected by echocardiography or electrocardiography, and the outcome of patients with Hs-cTnT >0.05 ng/ml has been associated with adverse outcomes [91]. Besides a single report of serial measurements of cTn in 5 patients suffering from light chain amyloidosis [92], Palladini et al., who studied 171 consecutive patients with the disease, found that Hs-cTnT at baseline was a predictor of survival, and that a >75% increase in Hs-cTnT after treatment predicted poor outcomes [93].

Chemotherapy

Chemotherapy is administered for several types of cancers. However, its clinical efficacy is often limited by cardiotoxicity, which causes LV dysfunction and HF. Cardinale et al. reported that cTnI early after high-dose chemotherapy predicts a decrease in LVEF [94], and that persistently elevated concentrations of cTnI predict adverse cardiac events [95]. However, since most deaths in patients suffering from cancer are not cardiac, most studies examined the relationship between serum cTn concentrations and changes in echocardiographic LVEF [96,97]. Sawaya et al. reported that Hs-cTnI measurements (Siemens Healthcare Diagnostics) made after 3 months of chemotherapy independently predicted the changes in LVEF observed at 6 months [98]. It is noteworthy that most patients in whom cTn remained persistently undetectable did not develop echocardiographic deterioration of LV function.

Perspectives

HF develops from risk factors ranging from LV hypertrophy and MI, to cardiac remodeling and HF. Troponin measurements of all these stages have been discussed in recent articles (Fig. 2) and stepwise elevation is seen from hypertension to acute HF (Fig. 3). Therefore, cTn is a promising, clinically applicable biomarker. While the definition and practice guidelines for MI suggest that the cut-off cTn serum concentration is the 99th percentile of a normal reference population [4], individuals, whether in the general population or suffering from essential hypertension, whose serum Hs-cTnT concentration is <99th percentile may have structural abnormalities, such as myocardial hypertrophy [22,23,74], and may have a poor prognosis [22,23,77,78]. The 99th percentile in healthy subjects may also be influenced by gender and age [24,25]. Therefore, the definition of the 99th percentile might be derived from a younger healthy population, while the cut-off value for HF and the general population remains to be determined.

Serial measurements have shown that cTn at baseline and cTn at follow-up are powerful predictors of cardiac remodeling and adverse cardiac events [55,71,73]. Whether cTn can be used as a surrogate marker of HF [2] needs to be studied further. Whether aggressive treatments that attenuate the rises in cTn improve the clinical outcomes should also be studied. Finally, although Tn assays have been developed for humans, some cross-reactivity has been reported, which allow their application in animal models [99,100]. These animal studies may elucidate the pathophysiology of heart failure based on Tn assay.

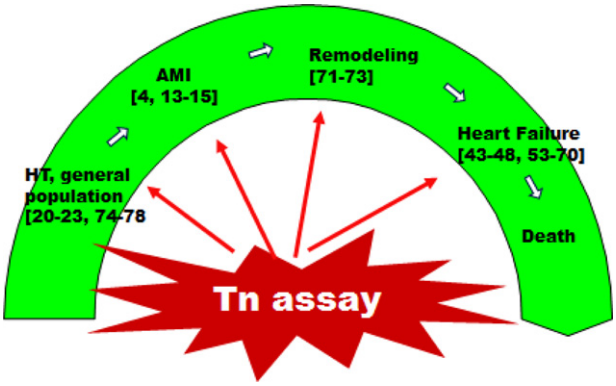

Fig. 2. Elevation of cardiac troponin (cTn) in various stages of heart diseases. HT, hypertension; AMI, acute myocardial infarction.

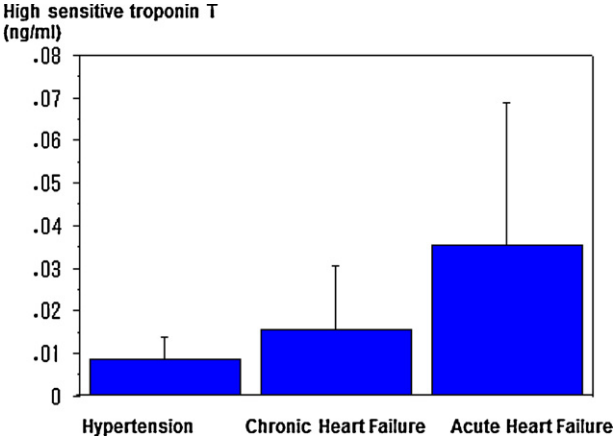

Fig. 3. High sensitive troponin (Hs-Tn)T (Roche Diagnostics) concentrations in patients with hypertension (0.009 ± 0.005 ng/ml, $n = 98$), chronic heart failure (0.015 ± 0.015 ng/ml, $n = 93$), and acute heart failure (0.035 ± 0.033 ng/ml, $n = 91$) (unpublished data). Stepwise elevation of Hs-TnT is seen.

Conflict of interest

The authors have no potential conflict of interest to disclose.

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