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REVIEW

Troponins in Heart Failure – a Perpetual Challenge

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ABSTRACT

Increased troponin levels in HF are a frequent and significant finding, as it strongly correlates with the underlying pathogenic mechanisms, diagnosis and prognosis. The advent of hs-cTn testing, as opposed to conventional troponin testing, led to additional difficulties in result interpretation.

Most frequently, though not exclusively, increased cTn levels in acute or chronic failure is correlated, with myocardial necrosis (AMI); the diagnosis of AMI is confirmed if other criteria are fulfilled, as described in the fourth Universal Definition of Myocardial Infarction. Increased cTn levels below the cut-off for AMI suggest acute or chronic injury, depending on the ascending and/or descending trend curve or stable levels of cTn on serial testing.

In acute or chronic HF with reduced or preserved EF, increased cTn levels carry prognostic value for adverse outcomes.

Acute and chronic HF, as well as other ischemic or non-ischemic conditions, may lead to a transient increase in cTn levels: hypertensive crises, tachyarrhythmias, valvular regurgitation, myocarditis, stroke, mandating differential diagnosis with ACS.

There are multiple mechanisms that explain increased levels of cTn: myocardial necrosis or coronary thrombosis (type I MI), supply-demand mismatch with subendocardial ischemia/injury, cardiomyocyte apoptosis, inflammatory cytokines, neurohomonal changes.

Screening for cTn levels in the population at high cardiovascular risk yields prognostic information on development of de novo *HF or other cardiovascular adverse events.*

Keywords: heart failure, troponins.

INTRODUCTION

Acute and chronic heart failure (HF) represent a significant clinical entity within the cardiovascular and general pathology. There has been great progress in the diagnosis, evolution, prognosis and therapy of HF, concurrent with the study of cardiac biomarkers. Among these, cardiac troponins (cTnT and cTnI) are a central focus when discussing heart failure.

The troponin complex (Tn) consists of three structural proteins (TnC, TnT and TnI), localized on the fine filaments of the myocardial contractile apparatus. Within the myocardium, cTnI (inhibitor) and cTnT (tropomyosin binding) are the most important, as they mediate the interaction between actin and myosin and have an essential role in cardiac contraction (1).

When disruption of the myocyte membrane ensues due to ischemic (in the majority of cases) or non-ischemic causes, the troponins in the cy-

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tosol, followed by the structural troponins – including troponin fragments – pass into the extracellular space and bloodstream. Increased troponin levels correlate with the extent of cellular injury, reaching itspeak when ischemic myocardial necrosis occurs. As a consequence, an increase in serum troponin levels are a key diagnostic element in acute myocardial infarction (STEMI and NSTEMI) (2, 3).

Data from studies conducted in the past 10-15 years revealed that serum troponins levels can be increased in several conditions such as acute coronary syndromes (ACS), non-ischemic myocardial injury (*e.g.*, myocarditis, cardiotoxicity) or in other conditions with multifactorial injury (*e.g.*, heart failure, pulmonary embolism, stress cardiomyopathy). High levels of hs-cTn above the detection limit can also be found in healthy subjects (4).

As such, increased cTn levels are demonstrated in various clinical scenarios; however, when associated chronic and acute heart failure, they pose a difficult challenge in terms of diagnosis (infarction or other type of myocardial injury), evaluation methods (hs-cTn or conventional troponin), clinical and pathogenic significance. Increased cTn levels in patients with HF and in the absence of defining criteria for ACS makes the interpretation difficult for a marker otherwise indicative for MI (5).

In this review some of the issues regarding acute and chronic HF with increased levels of cTn above the detection limit or reference limit will be discussed, the most important being prevalence, the dynamics of cTn levels in various clinical scenarios; distinguishing myocardial infarction from acute or chronic injury in HF; prognostic value in HF with increased cTn; troponin and other biomarkers in HF; pathogenic mechanisms leading to cTn increase in HF; increased troponins as predictive factors in *de novo* HF.

Furthermore, for an easier understanding, a few definitions should be presented, in their current form (6):

- ***Reference value*** for cTn is the maximum value found in 99% of the general population; the 95th percentile in the general population; for conventional evaluation cTnT = 0.01 ng/L;
- ***Myocardial injury*** is defined as increased cTnabove the 99th percentile of the upper reference limit (URL); myocardial injury can be acute or chronic;
- ***Acute myocardial infarction*** is defined as acute myocardial injury, associated with increase and/or decrease in cTn levels, with at least one value above the 99th percentile of the URL.

Currently, there is no standardized method to define the reference value for hs-cTnT; depending on the assay type, hs-cTnT levels suggestive for AMI should be at least > 90 ng/L or >14 ng/L in the first three hours. For AMI, hs-cTnt levels can reach >1000 ng/L at 3-6 h from onset (7). ❑

CARDIAC TROPONINS IN ACUTE HF

Acute heart failure (acute HF) is one of the most frequent causes of hospitalization, requiring timely diagnosis and urgent treatment. It can present as a primary cardiovascular event (*de novo*) or, more frequently, as an acute decompensation of chronic heart failure. Acute coronary syndromes (ACS) are a relatively frequent primary cause of acute HF (*e.g.*, STEMI) or represent a trigger leading to rapid deterioration of cardiac function. Current guidelines recommend ruling out AMI (type I) on index evaluation of patients with suspected or demonstrated acute HF.

In clinical practice, cTn (currently hs-CTn) is the biomarker of choice to test in emergency settings, corroborated with clinical, electrocardiographic and imaging data, in order to diagnose ischemia or myocardial necrosis, as well as the cause(s) of acute HF.

In acute HF, cTn levels can be either increased above the 99th percentile of URL on index testing or moderately increased above the detection limit, or they remain negative. If hs-cTnI levels are high or very high, with an ascending and/or descending curve trend, STEMI or NSTEMI is an evident diagnosis, if other criteria such as clinical presentation, EKG and/or imaging suggestive of AMI are also fulfilled (6).

If cTn levels remain negative (beyond 3-6 h from clinical onset of acute heart failure), then AMI can be ruled out and pursue other causes of acute HF (8).

In scenarios where cTn levels are increased, but below the cut-off for MI, then the differential diagnosis becomes challenging.

Firstly, the most frequent scenario is represented by acute cardiac decompensation in preexistent chronic heart failure (approximately

2/3 of HF are of ischemic cause). Under these conditions, the moderate increase in cTn levels represent acute ischemic myocardial injury – depending on increasing and/or decreasing trends of cTn (acute injury) or chronic injury (chronic HF with stable cTn levels). Subendocardial ischemia, strain (parietal tension) increase, sympathetic overdrive and the effects of inflammatory cytokines can explain increases in cTn levels above the reference limit. In this case, acute ischemic myocardial injury would be the cause of progressive reduction in cardiac function and development of advanced heart failure (9).

Secondly, other pathological conditions that determine acute HF can be associated with increases in cTn levels – besides AMI – through ischemic or non-ischemic myocardial injury, *e.g.*, hypertensive crises, atrial/ventricular tachyarrhythmias or severe conduction disturbances, acute valvular regurgitation, acute myocarditis, pulmonary embolism, stroke (10). In these situations, cTn levels can rapidly increase, and, on serial testing, can decrease rapidly, remain stable or become undetectable. In several cases, ischemic or non-ischemic acute myocardial injury can develop in HF associated with other pathological conditions (persistent atrial fibrillation, left ventricular hypertrophy, renal dysfunction, diabetes mellitus) and can therefore influence cTn levels, in addition to MI (2).

Moreover, several studies have focused on the prevalence of increased levels of cTn in acute heart failure and its prognostic significance in heart failure in the short- and medium-term.

The ADHERE trial remains a benchmark study (11). It enrolled 61397 patients who had conventional cTn levels taken on admission; 6.2% of these had positive troponin tests. A positive cTn test was defined as cTnT equal to,, or above 0.1 ng/L. Patients who had increased levels of cTnT had higher rates of adverse events and mortality during hospitalization compared to the negative troponin group (8% *vs* 2.7%, respectively, $p = 0.0001$).

For risk stratification in acute HF, index low blood pressure, renal function and troponin levels were important elements.

The advent of a more sensitive method to detect lower levels of cTn (hs-cTnT and hs-cTnI) offered additional information concerning the diagnostic and prognostic value of cTn in patients with acute HF.

In the ASCEND-HF study, with sensitive troponin level testing (s-cTnT) (VITROS-TOP) on 808 patients with acute HF, positive troponin levels (cTn 0.034 ng/mL) were demonstrated in 50% of patients. Patients with cTnT levels exceeding the 99th percentile of URL had HF worsening during hospitalization ($p = 0.01$). In addition, they were older, had higher NT-proBNP and worse renal function. The study did underline that increased levels of s-cTnT exceeding the 99th percentile URL did not represent an independent predictor of worse outcomes at 90 days and one year, respectively (12).

Moreover, with regards to its prognostic significance, similar results were seen in a study conducted by Arenja N *et al* (13). Out of 667 patients with acute dyspnea examined in the Emergency Department, 357 (57%) had acute HF, the majority of whom were presenting for acute decompensation of chronic HF (46.5%); 41% of patients with acute HF had increased levels of s-cTn and 58% normal values or undetectable troponin. The threshold for increased cTnI levels was established at 0.028 ng/L, and the reference range was between 0.1 and 0.27 ng/L, respectively. The highest levels of s-cTnI were registered in patients with acute HF and ACS or shock, compared to acutely decompensated chronic HF. Patients enrolled in this study were followed for 371 days. In patients with acute HF, mortality at 30 days and one year increased, correlating with s-cTnI levels (2%, 5% and 14%, respectively; $p < 0.0001$ for mortality at 30 days and 21%, 33% and 47%, respectively, $p < 0.002$ at one year).

Consequently, this study demonstrates that s-cTnI levels are a short- and long-term strong prognostic predictor in acute HF and, therefore, cTn levels help in stratifying patients according to their mortality risk.

In conclusion, various studies have explored the significance of increased cTn levels on both index and serial testing in acute HF, with results demonstrating the association with adverse outcomes in the short-term and, most likely, in the long-term as well. ❑

CARDIAC TROPONINS IN CHRONIC HF

cTn levels above the detection limit have been observed in chronic HF with reduced (HFrEF) and preserved EF (HFpEF). The majority

of studies have been conducted in patients with chronic HF of ischemic and non-ischemic cause.

The Val-HeFT study (Valsartan in Heart Failure Trial) studied patients with chronic heart failure. The detection limit for cTnI was 0.01 ng/mL, with 10.4% of patients having increased cTn levels (14). Increased troponin levels correlated with NYHA heart failure functional class and mortality rate at two years. For hs-TnT, the detection limit was established at 0.001 ng/mL, thus measuring troponin levels 10 times lower than the conventional inferior limit of TnT. The prevalence of detectable troponin was found in 92% of patients. In a systematic review of troponins in HF, the incidence of increased levels of hs-TnT was 63% and 31%, respectively, when troponin testing was done by conventional methods.

In patients with chronic HF, increased levels of troponin generally correlate with HF severity and particularly with acutely decompensated chronic HF.

For a pertinent interpretation of increased troponin levels in HF, serial testing should be performed over a longer timespan, as opposed to single testing on admission. In chronic HF, increased troponin levels on serial testing follow a relatively flat line, with little variations, and are more stable over time, compared with the rapidly ascending and descending curve over a few days in myocardial necrosis – ACS.

The correct interpretation of increased cTn in HF depends on the diagnosis – myocardial necrosis or (acute or chronic) myocardial injury, as well as on the prognostic significance of increased troponin levels on serial testing.

Acute MI (STEMI, NSTEMI) is diagnosed if criteria according to the fourt Universal Definition of Myocardial Infarction are fulfilled; the criterion for cTn is increasing and/or decreasing levels of cTn or hs-cTNT with at least one value above the 99th percentile URL (6). The absence of clinical or other criteria suggestive of MI make the diagnosis unlikely (8). In patients with history of coronary heart disease, diagnostic work-up should involve other methods (coronary angiography, CT angiography, cardiac MRI) to establish recent MI in patients with chronic HF.

When cTn or hs-cTnT levels are below the cut-off for AMI, increased troponin levels are suggestive of acute myocardial injury (if a pattern of increasing and/or decreasing levels is present) or chronic (if there are stable levels on serial testing). However, moderate transient troponin increases can be found in acutely decompensated chronic HF, though they are not suggestive of MI, in the absence of additional criteria.

The clinical significance of increased troponin levels in chronic HF should also be regarded in correlation with the outcome and prognosis of the study groups.

Various studies (with a small-to-moderate number of patients) have analyzed the prognostic significance of increased cTnI and hs-cTnT levels in patients with chronic HF. The results of the two studies are concordant: increased levels of troponin was associated with a two-fold increase in mortality at five years and re-admission, all cause and cardiovascular mortality (15, 16).

These results have been confirmed in two meta-analyses regarding outcomes and prognosis in patients with chronic HF and increased troponin levels. One of the meta-analyses compared prognosis in correlation with increased levels of cTn and hs-cTn or hs-cTnI, respectively, concluding that there was no difference between the two methods of troponin measurement on outcomes in patients with chronic HF (7).

Furthermore, another recent meta-analysis focused on the prognostic value of hs-TnT as a predictive factor of all cause mortality, cardiovascular mortality and admission due to cardiovascular causes (9289 patients with chronic HF, 60% of ischemic cause). The analysis correlated other main prognostic factors in HF, including NT-proBNP. In a 2.4 year-follow-up, hs-cTnT has been independently associated with all cause mortality (HR 1.48, CI 95%), cardiovascular mortality (HR 1.42, CI 95%). In conclusion, troponin is an important additional prognostic factor in chronic HF (18).

Moreover, increased cTn levels also correlate with adverse clinical outcomes in both HFrEF and HFpEF. Between 26% and 50% of patients with decompensated HF have increased troponin levels. In the GWTG (Get with the Guidelines) Registry analysis, which included 34 233 patients with HFpEF, 21.4% of these had increased levels of hs-cTnI and hs-cTnT, respectively.

Increased levels of cTn (in the absence of MI or chest pain) is associated with increased in-hospital mortality (OR > 1.9), as well as mortality at 30 days (HR 1.59) and at one year (HR 1.31) (19).

Serial troponin testing helps in identifying potential adverse outcomes in patients with HFpEF. The correlation with the dynamics of other cardiac biomarkers (NT-proBNP, GAL-3 and sT2) increases negative prediction of (moderately) increased cTn levels in HFpEF and HFrEF.

In conclusion, in chronic HF troponin levels can be moderately or severely increased, above the detection limit in almost all patients, if using hs-cTnT. Increased troponin levels, however below the cut-off for AMI, suggests ongoing myocardial injury with an underlying ischemic or non-ischemic mechanism.

Troponin levels above the 99th percentile associates with adverse outcomes in HF – progressive reduction in cardiac function, increased mortality. ❑

TROPONINS AND MULTIMARKER TESTING IN HF

Troponin testing in HF is one of several options of biomarker testing. Additional cardiac biomarkers may aid in a more comprehensive definition of current or ongoing pathological processes, following myocardial necrosis or injury in the context of HF. Natriuretic peptides, soluble ST1, ST2, galactin-3 and C reactive protein are among the more frequently used.

Serial testing of NT-proBNP is a fundamental step in the workup for acute or chronic HF. Increased NT-proBNP levels associate with longitudinal and circumferential strain, with left ventricular end-diastolic pressures and ejection fraction. NT-proBNPyields data regarding diagnosis and severity of cardiac dysfunction, as well as prognosis. NT-proBNP is considered an independent marker of prognosis in acute and chronic HF (20).

Increased troponin levels and increased NT-proBNP levels can reveal the underlying cause (myocardial injury, myocardial necrosis). In addition, testing for both biomarkers offers prognostic information regarding short- and long-term outcomes (21).

Soluble ST2 (sST2) is a cardiac biomarker associated with left ventricular hypertrophy (LVH), fibrosis and cardiac remodeling. It is used in the multimarker evaluation of acute and chronic HF, and increased sST2 levels are found in HF; however, results are age-dependent, influenced by the presence of DM, LVH, but not renal dysfunction (22). The lower reference limit is standardized incompletely. In a recent study, where NT-proBNP, hs-TnT and sST2 have been tested in 6268 HF patients (EF $\leq$ 40%), sST2 levels $\geq$ 28 ng/L were independently predictive of all cause and cardiovascular mortality as well as hospitalization for chronic HF. Patients were studied over a 2.4-year period. Other data suggest that serum sST2 levels above 35 ng/L are in particular associated with rather acute HF than chronic HF (24).

Concomitant testing for sST2, NT-proBNP and hs-cTn offers valuable additional prognostic information. Patients with all three biomarkers above the optimal cut-off have a two-fold higher risk of death in acute HF (24). ❑

UNDERLYING MECHANISMS OF INCREASED TROPONIN LEVELS IN HF

The underlying mechanisms that determine increases in cTn in acute and chronic HF are either partly demonstrated or presumed. There are multiple pathophysiological mechanisms, similar in both acute and chronic HF, with minimal differences.

Acute MI takes the forefront as the main cause of increased troponin levels in acute and chronic HF. Prolonged ischemia leads to myocardial necrosis, cell membrane disruption with consequent release of structural and cytosol troponins. Hs-cTnT levels increase rapidly, within hours, reaching high and very high levels and, on serial testing, form an ascending and/or descending curve within hours or days.

The diagnosis of AMI in preexistent HF entails not only an increase/decrease in cTn levels, but also mandatory fulfillment of other criteria (clinical, EKG, imaging criteria) defined in the fourth Universal Definition of MI (6). In practice, there are other pathological conditions leading to increased troponin levels, *e.g.*, pulmonary embolism, acute myocarditis or sepsis (2, 10). Acute MI in the context of plaque erosion or intimal rupture or thrombosis is relatively frequently associated with acute decompensation of stable chronic HF or development of acute HF.

More frequently than AMI, an increase in troponin levels in the context of HF is found through a demand ischemia mechanism, also known as supply-demand mismatch, particularly in the case of chronic HF (25).

Myocardial ischemia and injury can occur due to either an increase in oxygen demand or a decreased supply, in the absence of an acute primary coronary thromboembolic event. The main mechanism consists of subendocardial ischemia, determined by excessive parietal strain and followed by myofibrillar alteration. Increase in parietal stress leads to subendocardial ischemia, regardless of preexistent coronary heart disease. Decreased myocardial oxygen supply can be mediated by increased filling pressures, tachyarrhythmias or bradyarrhythmias, arterial hypotension, anemia, endothelial dysfunction.

In myocardial injury, the myocyte cell membrane becomes permeable, allowing for cytosol troponin and troponin fragments with low molecular weight to pass into the interstitium and bloodstream (26, 27).

Other possible mechanisms leading to an increase in troponin levels have also been described – increased parietal stress induces cardiomyocyte apoptosis, autophagia and alteration of the contractile apparatus, with consequent cTn release (28). Inflammatory cytokines, neurohormonal changes in HF and cardiomyocyte turnover have a direct effect on cardiomyocytes. In addition, advanced age and renal dysfunction or other comorbidities (DM) may contribute to increased levels of cTn in patients with chronic HF (28).

Januzzi T *et al* created an illustration to summarize causes of troponin release in HF syndromes (7):

- coronary ischemia due to epicardial coronary disease or endothelial dysfunction;
- subendocardial ischemia in conditions of supply-demand mismatch due to decreased oxygen supply or/and increased myocardial oxygen demand;
- myocardial apoptosis or autophagia;
- proteolysis or myocardial contractile protein turnover;
- direct toxicity of inflammatory neurohormones, infiltrative processes.

In conclusion, subendocardial ischemia due to increased parietal stress (volume-pressure ratio), increased cell membrane permeability and exocytosis of cytosol troponin, sympathetic and renin-angiotensin-aldosteron system overdrive are the main pathogenic processes that lead to variable increases in troponin levels in heart failure as well as worsening cardiac function and HF progression (2). Of note, in acute and chronic HF, increase and/or decrease or relatively stable troponin levels, the underlying mechanisms are both ischemic and non-ischemic. ❑

TROPONIN AS A PREDICTOR OF CARDIOVASCULAR EVENTS AND *DE NOVO* HF

Cardiac biomarkers are useful for diagnosis and risk stratification in various cardiovascular conditions, particularly in coronary heart disease and HF. Earlier studies have shown that natriuretic peptides, along with clinical risk factors, may predict future cardiovascular events (4). Extensive use of cTn in the population, including subjects with no apparent heart disease, has demonstrated the importance of troponin as a predictor for future cardiovascular adverse events, particularly for HF.

A longitudinal cohort study has shown that hs-cTnT was a predictor of *de novo* HF and cardiovascular death (29). Approximately 60% out of 4221 people over 65 and with no history of HF had detectable hs-cTnT levels. At the two-year follow-up visit, index levels and consequent increase >50% correlated with an increased risk of HF development (HR 1.61) and cardiovascular death (HR 1.61). In a similar analysis, an ARIC (Atherosclerotic Risk in Community) substudy, an association between cTnT levels and hospitalization for HF has been observed (30).

Another two-population study have confirmed the role of hs-cTnT in predicting cardiovascular events. Consequently, 1089 men aged approximately 70 were followed-up for nine years and it was shown that cTn levels above baseline on repeat testing were an independent predictor of hospitalization for HF, after ruling out for MI (cTn > 0.01 ng/L) (31).

Furthermore, a meta-analysis studying the data from 16 studies conducted in the general population and six studies in high-risk population (stable coronary disease, DM, CKD) revealed a strong correlation between hs-cTn and the risk of primary HF event (32).

In conclusion, serial hs-cTn testing in apparently healthy subjects or with cardiovascular risk, with results above the detection limit, may predict *de novo* HF or other cardiovascular adverse events. ❑

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