Cardiac troponin testing is commonly performed in patients with heart failure (HF). Despite being strongly linked to spontaneous (Type I) acute myocardial infarction (MI)—a common cause of acute HF syndromes—it is well recognized that concentrations of circulating troponins above the 99th percentile of a normal population in the context of both acute and chronic HF are highly prevalent, and frequently unrelated to Type I MI. Other mechanism(s) leading to troponin elevation in HF syndromes remain elusive in many cases but prominently includes supply–demand inequity (Type II MI), which may be associated with coronary artery obstruction and endothelial dysfunction, or may occur in the absence of coronary obstruction due to increased oxygen demand related to increased wall tension, anaemia, or other factors provoking subendocardial injury. Non-coronary triggers, such as cellular necrosis, apoptosis, or autophagy in the context of wall stress may explain the troponin release in HF, as can toxic effects of circulating neurohormones, toxins, inflammation, and infiltrative processes, among others. Nonetheless, across a wide spectrum of HF syndromes, when troponin elevation occurs, independent of mechanism, it is strongly predictive of an adverse outcome. Clinicians should be aware of the high frequency of troponin elevation when measuring the marker in patients with HF, should keep in mind the possible causes of this phenomenon, and, independent of a diagnosis of ‘acute MI’, should recognize the considerable ramifications of troponin elevation in this setting.

Keywords
Troponin • Heart failure • Prognosis

Introduction

Although troponin testing is the biomarker gold standard for the diagnosis of acute myocardial infarction (MI), elevation of troponin may occur in situations other than acute coronary ischaemia. Heart failure (HF) is one such situation; indeed, troponin elevation in the context of acute and chronic HF has been long recognized, and is accepted to be a potent predictor of an adverse outcome across the spectrum of HF syndromes. However, the frequent elevation of troponins in patients with HF in the absence of obvious acute coronary ischaemia complicates the interpretation of these markers for the diagnosis of classical acute MI. Nonetheless, the importance of troponin testing in patients with HF is considerable. Compounding the situation is the growing use of highly sensitive assays for troponin, which are even more frequently abnormal in patients with HF and lack inclusion in contemporary summaries of this topic.

Accordingly, in recognition of these facts, the Universal Task Force for the Definition of MI determined the importance of a contemporary summary of troponin elevation in HF syndromes, updating the available data to include results for highly sensitive troponin testing, reviewing the proposed causes of troponin...
elevations in HF, and discussing the clinical implications of troponin elevation across the spectrum of HF syndromes.

Acute heart failure syndromes

It is important to emphasize that a significant percentage of patients with acute HF syndrome have a Type I acute MI as the cause of incident HF. Accordingly, contemporary consensus guidelines recommend the exclusion of Type I MI during the initial evaluation of patients with suspected or proven acute HF syndromes. Interpretation of troponin values in patients with HF should be consistent with guidelines for the diagnosis of MI, which require supportive evidence such as a typical rise and/or fall of the marker above the 99th percentile of a normal reference population, electrocardiographic changes, or imaging evidence for new loss of functional myocardium in a setting typical of coronary ischaemia.

A large amount of data exists regarding the use of troponin testing in patients with acute HF syndromes (Supplementary material online, Table S1). Depending on the report, troponin elevation in acute HF syndromes may range from relatively uncommon to ubiquitous. For an example, in an analysis of >105,000 patients, the ADHERE investigators reported that while 75% of patients had a detectable troponin result, only 6.2% had a value above the upper reference limit. This finding was based on a mixture of troponin assays of varying quality, all utilizing an upper reference limit corresponding to the cut-point providing 10% imprecision for each. Nonetheless, in this analysis, a troponin above the upper reference limit was associated with more severe HF, including worse left ventricular function (although a large percentage of patients with HF and preserved left ventricular function had elevated troponin); also, troponins were associated with more severe symptoms, more need for aggressive supportive measures, including inotropic therapy, and worse outcomes. Interestingly, troponin levels were not clearly associated with HF due to ischaemic heart disease or prevalent acute MI.

Most other studies have reported a somewhat higher incidence of elevated serum troponin in the context of acute HF syndromes than the ADHERE report (Supplementary material online, Table S1). The percentage of patients with 'elevated' troponin in HF syndromes depends heavily on the severity of HF, the cut-point chosen, as well as the sensitivity of the assay employed. For example, if lowering the cut-point to the limit of detection, considerably more patients are found to have measurable troponin values. For example, among a cohort of acute HF patients without obvious acute coronary syndrome, Sakhuja et al. found that 46% had measurable troponin T (≥0.01 ng/mL) while 33% had a troponin T in excess of the 10% imprecision cut-point (≥0.03 ng/mL). Findings such as this imply that with the use of high-sensitivity troponin methods optimized for use at the troponin 99th percentile (corresponding to the upper reference limit of a healthy, normal population), a higher percentage of elevated results in the context of acute HF failure will be detected. Indeed, in two recent reports, Xue et al. and Pascual-Figal et al. reported that nearly all patients with acutely decompensated HF had a highly sensitive troponin I or T value above the 99th percentile.

The frequent phenomenon of measurable or frankly elevated troponin values in acute HF—which may occur independently of a Type I MI—has repeatedly been associated with an increased risk for mortality, independently of other markers of risk such as ventricular function, age, and other biomarkers such as natriuretic peptides (Figure 1). It is reasonable to expect that highly sensitive troponin assays will improve the ability to risk stratify above conventional troponin tests when concentrations of the latter are below their ability to deliver precise results. The value of highly sensitive troponin for prognosis appears particularly strengthened when it is measured serially, allowing for the identification of highest risk patients, who typically have a rising pattern (Figure 2).

Chronic heart failure

Much as in acute destabilization of the diagnosis, measurable or frankly elevated troponin concentrations are common in patients with chronic—ostensibly stable—ambulatory HF, most often observed in the absence of clear coronary ischaemia, and often seen in patients with well-documented non-ischaemic HF. Using conventional (i.e. non-high sensitivity) assays, the frequency of troponin concentrations above the limit of detection in chronic HF may be anywhere from as low as 10% to as high as 60% (Supplementary material online, Table S2); when examining patients using highly sensitive troponin assays, detectable troponin is found in nearly 100%, with a significant majority above the 99th
percentile.\textsuperscript{3,26} (Supplementary material online, Table S2). Moreover, serial sampling in patients with chronic HF shows that a considerable number with unmeasurable troponin develop a value above the limit of detection or the 99th percentile for the assay used.\textsuperscript{25,27,28,31} Such troponin changes are not usually associated with symptomatic decompensation, but do associate with a more deleterious phenotype, with a greater tendency towards ventricular remodelling, and risk for death or hospitalization (Figure 3).

Similar to acute HF syndromes, measurable, and/or rising levels of troponin at baseline or follow-up correlate with more severe disease and worse prognosis in chronic ambulatory HF, with higher rates of hospitalization and death compared with those with stably low troponin values, and may be additively prognostic to other biomarkers such as natriuretic peptides.\textsuperscript{26} In a large pooled analysis using a highly sensitive assay, concentrations of troponin T predicted death and the risk for hospitalization, while a follow-up measure 4 months later added a prognostic value for predicting the risk for death.\textsuperscript{3} Whether therapies for HF affect the risk for an adverse outcome associated with an elevated troponin remains unclear.

**Causes of troponin release in heart failure**

A wide variety of causes may lead to troponin elevation in patients with HF (Figure 4).

**Type I and Type II myocardial infarction**

Clinically, a most important cause of troponin elevation in HF is coronary ischaemia; thus, as noted, a Type I MI (i.e. an event related to atherosclerotic plaque rupture, ulceration, or fissuring) must always be considered when a patient with an acute HF syndrome demonstrates an elevated troponin, particularly if clinical
evidence for an acute coronary syndrome is present. Unfortunately, typical symptoms are not universally present, even in patients with Type I MI, and non-invasive diagnostic testing such as electrocardiography or echocardiography may be less specific in patients with chronic abnormalities such as prior MI or left ventricular dysfunction.

Besides Type I MI, another coronary mechanism for troponin release in HF is Type II (supply–demand inequity) MI from increased transmural pressure. Small-vessel coronary obstruction may also lead to a Type II MI in patients with HF, and should be considered especially possible in patients with other signs of general atherosclerosis or diabetes mellitus. Endothelial dysfunction is common in HF, and could, in theory, produce significant ischaemia and myocardial necrosis in this setting. It is widely held that in the absence of coronary artery disease, Type II MI in HF may follow subendocardial ischaemia alone; this may be worsened by reduced oxygen delivery secondary to anaemia (prevalent in HF) or hypotension (Figure 4). Indeed, cardiovascular stress such as that which occurs during stress testing or rapid transvenous pacing may lead to measurable troponin elevation using highly sensitive assays. Lending support to this paradigm, patients with HF and an elevated troponin typically present with a more decompensated profile, including prevalent atrial fibrillation, higher filling pressures, elevated endocardial and mid-wall stress and lower tissue perfusion, lower ejection fraction, worse cardiac performance, and stiffer myocardium. Such patients are more likely to develop negative myocardial remodelling and worsening ventricular function.

**Mechanisms other than Type I or II myocardial infarction**

While Type I or Type II MI explains a great percentage of circumstances when measurable or frankly elevated troponin is observed in both acute and chronic HF syndromes, other mechanisms should be kept in mind; these causes of troponin release in HF syndromes are clinically relevant in many cases. Indeed, while troponin release from cardiomyocytes is best understood in the context of MI, it is by no means restricted to this situation. Using highly sensitive troponin methods a wide range of values may now be measured in normal subjects, implying a certain degree of ‘normal’ cardiomyocyte turnover. Furthermore, as noted wall stress may directly lead to a Type II MI, but intriguingly, cardiomyocyte apoptosis and autophagy directly consequent to wall stretch has been experimentally demonstrated, as has proteolysis of the cardiac contractile apparatus; it is reasonable to expect troponin
Troponins in heart failure

Figure 5 Additive value of highly sensitive troponin T to NT-proBNP and the interleukin receptor family member ST2 for risk stratification in acutely decompensated heart failure. In a multi-marker risk model, the risk for death rose in parallel to the number of each biomarker elevated (from none to all). Reproduced with permission from Pascual-Figal et al.6

Conclusions to note

Troponins in heart failure

Troponin tests have been reported in the context of heterophile anti-inflammatory/autoimmune reactions.47 Whether an inflammatory response related to reduced clearance of troponin complexes due to inflammation may mimic acute MI.44,45 Infiltrative processes associated with HF such as amyloidosis are well documented to result in troponin release and progressive loss of cardiac function,41 while troponin elevation following toxic exposures (e.g., alcohol or chemotherapy agents) may identify the risk for ventricular dysfunction.62 Other important causes of acute HF syndromes to keep in mind that may cause troponin elevation are myocarditis43 as well as stress cardiomyopathy (also called Tako-Tsubo cardiomyopathy);44 both of these latter syndromes may represent challenging diagnostic situations as they may mimic acute MI.44,45

Extra-cardiac causes

Besides cardiac-specific causes of troponin release in HF, other mechanisms that influence troponin values should be kept in mind when interpreting values in patients with HF. A comprehensive summary exists in this regard,46 but certain circumstances warrant discussion. On occasion, troponin concentrations persistently elevated above the 99th percentile in patients with HF may be related to reduced clearance of troponin complexes due to inflammatory/autoimmune reactions.47 Whether an inflammatory response to troponin leads to a heightened risk for cardiomyopathy onset or exacerbation of chronic HF remains unclear. Diseased skeletal muscle may lead to a significant rise in troponin T concentrations, related to up-regulation of foetal gene programmes.48 Abnormal troponin tests have been reported in the context of heterophile antibodies without obvious cardiovascular dysfunction.49–51

An important extra-cardiac factor associated with measurable or elevated troponin in patients with HF is renal failure. Mechanistically, the cause of troponin release in patients with kidney disease is poorly understood, but the source of the troponin is clearly of cardiac origin. The exact degree of dependence of troponin I or T on renal function for their clearance remains unknown; however, it is increasingly held that a large percentage of circulating troponins in patients with chronic kidney disease may be explained by underlying structural heart disease and/or direct toxic effects of renal failure on the myocardium, rather than any effect on troponin clearance.52 Based on the molecular weight of troponin, its clearance should be less dependent on glomerular filtration. Indeed, when elevated in a patient with renal failure, troponins are markedly prognostic.52,53 Thus, a troponin above the 99th percentile in an HF patient with renal failure should not be simply discarded as a ‘false positive’ due to reduced clearance. While troponin T appears to be more likely to be measurable or frankly elevated in patients with renal failure compared with troponin I, with the growing use of highly sensitive methods for troponin testing, it remains to be seen if this difference between troponin T and I in renal patients will persist.

Special topics

Troponins and development of heart failure

It has been suggested that concentrations of troponin (as detected by highly sensitive assays) may predict future HF across a wide spectrum of the baseline risk, including ‘apparently well’ subjects,54 those at risk due to advanced age55 as well as those with stable coronary artery disease.56 In addition changes in highly sensitive troponin T concentrations over time were potently predictive of events.2 Whether the release of troponin in ‘apparently well’ patients is due to coronary ischaemia or a non-coronary mechanism is not known, although the medical profile of such at-risk patients with elevated troponin is more complex with more prevalent risk factors for coronary disease and/or heart muscle disease.56–59 There is not yet any therapeutic implication associated with the detection of troponin in these situations; the development of therapeutic strategies to reduce the risk associated with a troponin above the 99th percentile in ambulatory primary care patients would be of enormous significance.

Multi-marker testing with troponins in heart failure

Clinicians should be aware that studies suggest that the use of multiple biomarkers providing ‘orthogonal’ biological information may improve risk stratification in patients both with acute and chronic HF. As noted, detection of myocardial necrosis using troponin testing is useful for risk stratification across the spectrum of HF syndromes. Other markers reflecting various pathophysiologicals in HF, such as natriuretic peptides (wall stress), mid-regional pro-hormones, soluble ST2, or growth differentiation factor-15 (remodelling), C-reactive protein (inflammation), anaemia markers, or biomarkers of renal dysfunction, have all been shown to be additive to troponin testing for prognosis in chronic HF6,12,22,60–63 (Figure 5). However, while these results are intriguing, insufficient data exist to recommend routine testing with multiple biomarkers to risk stratify patients with HF syndromes.
at this time, particularly as specific therapies to address the risk associated with each biomarker are not yet known. Nonetheless, those patients found to have abnormalities of multiple biomarkers such as those mentioned above are at a considerable risk for an adverse outcome.

Conclusions and recommendations

A summary of recommendations regarding troponin measurement in patients with HF is made in Table 1. It is important to emphasize that HF is not a single disease, per se, but a manifestation of different cardiac and non-cardiac co-morbidities; the reason and the significance of troponin concentrations in a patient with HF will depend on a number of issues: the underlying cause of HF (e.g. coronary artery disease), the initiating mechanism (e.g. arrhythmia), and potential amplifying mechanism(s) (e.g. renal dysfunction). Biomarkers such as troponin should be considered within the context of the specific pathophysiology of the presentation in which they are measured; indeed, troponins may ultimately be viewed as one further piece of information to inform a phenotype within the syndrome of HF. With the growing use of highly sensitive troponin methods, an even larger percentage of HF patients will be recognized as having measurable or elevated troponin concentrations. Despite this complex issue, certain recommendations may be made regarding the use of troponin testing in HF syndromes.

**Acute heart failure**

In the context of an acute HF presentation, troponin I or T should always be promptly measured, with the goal to identify or exclude Type I MI as the precipitant. Whether a rising and/or falling troponin value above the 99th percentile in a patient with acute HF syndrome clarifies or confuses diagnostic evaluation depends entirely on the clinician interpretation of the result; however, given the frequency of acute plaque rupture or fissuring with consequent acute coronary ischaemia as a trigger for acute HF, an elevated troponin result should always be interpreted with a high level of suspicion for Type I MI, particularly in the context of a very significant rise or fall of the marker, or when accompanied by typical symptoms, and/or signs of ischaemia or loss of myocardial function on non-invasive testing.

In the context of an acute HF syndrome, the coronary artery anatomy may often be well known; such knowledge may be leveraged to interpret abnormal troponin results; if normal coronaries are present, either a Type II event or a non-coronary mechanism for troponin release may be invoked. On the other hand, when the coronary anatomy is not established, the recognition of myocardial necrosis reflected in a troponin value above the 99th percentile alone is not sufficient to make a diagnosis of acute MI due to coronary artery disease, nor is it able to identify the mechanism for the abnormal troponin value (i.e. Type I vs. Type II vs. non-coronary); in this context, clinicians are thus advised to consider troponin values above the 99th percentile in a patient with an acute HF syndrome indicative of myocardial necrosis, but a troponin value above the 99th percentile is not necessarily diagnostic of MI, without supportive evidence as above. In this setting, further information (such as myocardial perfusion studies or coronary angiography as well as haemodynamic assessment) is often required to better understand whether a Type I MI, Type II MI, or non-coronary cause for abnormal troponin values is present. In many cases, it may be difficult to establish the reason for troponin abnormalities, even after such investigations.

Although troponin values may rise in the acute setting and fall during recompensation of HF in hospitalized patients, patterns of release cannot be used to infer a coronary vs. non-coronary mechanism, particularly in the absence of corroborative information.

**Chronic heart failure**

In chronic HF, concentrations of troponins above the 99th percentile are commonly noted in chronic HF, and when this scenario

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**Table 1  Recommendations on the use of troponin in heart failure**

<table>
<thead>
<tr>
<th>General concepts</th>
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<tr>
<td>• Troponins should be interpreted within the context of the specific clinical presentation in which they are measured</td>
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<tr>
<td>• In patients with HF, there are numerous causes for circulating troponin concentrations above the 99th percentile, including coronary and non-coronary mechanisms. The recognition of a troponin that is above the 99th percentile and its rising and/or falling does not absolutely indicate the presence of a Type I MI</td>
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<tr>
<td>• With the growing use of highly sensitive troponin methods, an even larger percentage of HF patients will have measurable or elevated troponin concentrations (compared with conventional troponin assays)</td>
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In acute heart failure

- The troponin value should be promptly measured, with the goal to confirm or exclude Type I MI as the precipitant
- An elevated troponin should always be interpreted with a high level of suspicion for Type I MI, particularly in the context of a rise or fall of the marker, typical symptoms, or signs of ischaemia on non-invasive testing or evidence for new loss of myocardial function
- Troponin values may rise in the acute setting and fall during treatment of HF in hospitalized patients. Patterns of troponin release cannot be used to infer a coronary vs. non-coronary mechanism and no assumptions regarding the presence or absence of an acute coronary syndrome should be made
- Troponin values above the 99th percentile have consistently been associated with a high likelihood for an adverse outcome in acute HF independent of incident MI. Higher concentrations are associated with a worse outcome
- Besides appropriate treatment for Type I MI, data are lacking about specific therapeutic intervention for troponin values above the 99th percentile in acute HF

In chronic heart failure

- Troponin values above the 99th percentile have consistently been associated with a high likelihood for an adverse outcome in chronic HF. Higher concentrations are associated with a worse outcome
- Troponin measurement may be considered for the purpose of prognostication
- Data are lacking about specific therapeutic intervention for a patient with chronic HF and a troponin value above the 99th percentile
occurs, it is of considerable prognostic meaning. Thus, it is reasonable to consider troponin measurement for this purpose. Therapies for HF should be reviewed to ensure that the goals of care are met in an effort to address this risk as optimally as possible. Indeed, for both acute or chronic HF, it warrants repeating that irrespective of the mechanism, elevated troponin concentrations (above the 99th percentile) in patients with HF syndromes have consistently been associated with a high likelihood for an adverse outcome independent of incident MI; accordingly, such elevated troponin in a patient with HF should be taken very seriously as a clear predictor of risk. Unfortunately, at present, data are lacking about specific therapeutic intervention in this context, but assiduous review and optimization of care are recommended.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**References**


