What will Change with Highly Sensitive Troponin Assays?

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ABSTRACT

In the not too distant future, high-sensitivity cardiac troponin assays will be introduced for use in the United States. They bring with them many exciting new opportunities within cardiovascular practice including the ability to confirm or refute a diagnosis of acute myocardial infarction more rapidly as well as the ability to risk stratify and guide treatment decisions in patients with a variety of acute and chronic noncoronary diseases. However, clinicians and researchers must be aware of the new facets introduced with troponin testing and, in particular, the new issues that will arise with high sensitivity assays. Emphasis must also be placed on reiterating the same principles of the effective use of troponin testing that applied to conventional assays, as these are likely to become even more important. This review outlines a number of important issues related to high sensitivity assays with a focus on their use in acute hospital settings.

Keywords: Troponin, Highly sensitive troponin assay, Acute coronary syndrome, Non-ST segment elevation myocardial infarction, Acute myocardial infarction.

Abbreviations: ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; COPD: Chronic obstructive pulmonary disease; cTn: Cardiac troponin; CV: Coefficient of variation; ED: Emergency department; hs-cTn: High-sensitivity cardiac troponin; JVD: Jugular venous distension; LVH: Left ventricular hypertrophy; MRI: Magnetic resonance imaging; ng/ml: Nanogram per millilitre; PE: Pulmonary embolism; URL: Upper reference limit.

How to cite this article: Sara JD, Jaffe AS. What will Change with Highly Sensitive Troponin Assays? MGM J Med Sci 2014; 1(4):174-186.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

High-sensitivity cardiac troponin (hs-cTn) assays have already been introduced throughout much of the world and in the next few years will become common place in the United States as well. Their use will change cardiovascular practice in many ways. For this change to be effective, there will need to be even more emphasis on the principles surrounding the effective use of cardiac troponin (cTn) testing.1 In addition, there are a number of issues that will require particular consideration. These include the management of the increased number of patients who will have elevated levels of cTn detected; the use of hs-cTn in nonischemic heart disease settings for risk stratification and the optimal strategy for ruling out and ruling in acute myocardial infarction (AMI).

Table 1 summarizes important advantages brought with hs-cTn assays in addition to some disadvantages and their potential solutions. This review will address these issues in addition to laboratory considerations and nomenclature by contrasting aspects of contemporary assays with those of hs-cTn and is directed toward clinicians and researchers alike. Its emphasis is not comprehensive but will consider to the greatest extent, the hospital use of hs-cTn testing.

DEFINITION

As it is the case with contemporary cTn assays, there is great variability among putatively hs-cTn assays. The importance and utility of elevated levels with one assay may not correlate with that of another assay. This depends on the way in which different assays are calibrated and developed. However, what is consistent is the accepted definition of what constitutes a ‘high-sensitivity’ troponin assay. This has been established as an assay that measures cardiac troponin values in at least 50% of a reference population.2,3 As hs-cTn assays have evolved, their ability to measure cTn in increasing proportions of a reference population has increased and 3rd generation high sensitivity assays are now able to measure cTn in more than 95% of a reference population, in contrast to those deemed 1st generation which detected cTn in 50 to 75%.4 These assays should have a coefficient of variation (CV), which is a measure of an assay’s variability at the 99th percentile upper reference limit (URL), of <10% to reduce the amount of change necessary to detect a rising and/or falling pattern of values.5

This issue of definition could become controversial. The 5th generation cTnT assay has been billed as hs-cTn assay, but in most studies it measures values above the limit of detection of the assay (5 ng/l) in far less than 50% of a reference population.6,7 However, in comparison
This enhanced sensitivity, however, brings with it an increased vulnerability to analytical problems. As with conventional assays, hs-cTn is most commonly measured using enzyme linked immunosorbent assays relying on the detection of analytes (in this case, cTn) with tagged reagent antibodies. Where there is interference in this binding process there are likely to be analytical confounds.9 Up to 20% of all individuals have auto antibodies to cTn.10,11 With more conventional assays, these lowered the levels of cTnl detected but rarely resulted in false negative findings. However, with hs-cTn, it is possible that their impact may be much greater. Conversely, fetal cTnT isoforms re-expressed by diseased skeletal muscle may be detected by more sensitive cTnT assays12 and can result in false positives.

As with conventional assays, blocking reagents and novel assay designs in addition to other strategies have been used to negate these issues13,14 but fail to eradicate them entirely. Furthermore, with some assays, inaccurately increased or decreased hs-cTn levels may be detected in hemolyzed blood samples.15 This is most often the case among patients in whom there is difficulty obtaining peripheral venous samples or when blood samples are obtained from indwelling lines, as is often the case in the most unwell patients in hospital who tend to undergo testing most frequently. Analytical problems including cross reacting or heterothallic antibodies may also cause marked elevations in cTn levels both with conventional and high sensitivity assays. Importantly, these levels do not change over time and will not fit with the clinical picture. This issue can be addressed by re-running these samples using additional blocking agents, such as HBT tubes16 that are readily available.

Until recently, clinicians hesitated to use the 99th percentile URL with contemporary cTn assays. Instead, higher threshold values were used, equivalent either to the lowest value at which the cTn assay achieved a 10% CV or to diagnostic thresholds associated with previously used less sensitive biomarkers such as the creatinine kinase-MB isoenzyme. This was done to reduce the number of elevations that would be difficult to explain in clinical practice but at the same time led to missing many definitive diagnoses in patients. The 99th percentile URL has repeatedly proven to enhance the sensitivity and specificity for diagnosing AMI and structural heart disease17 and has thus been advocated in clinical guidelines. Its use should continue with hs-cTn assays.

The value of the 99th percentile URL must be derived from suitable reference population, the characteristics of which should be clearly defined. To date, with regards to contemporary cTn assays, this has been done inconsistently.3 Groups of participants recruited for this purpose have often comprised of heterogeneous samples of the population as they are often enrolled using simple clinical studies with other hs-cTn assays that meet these criteria, the putatively hs-cTnT assay detects more elevations.8 Thus, either the analytical criteria proposed fail to reflect clinical sensitivity or this assay may have some false positives that will need to be unmasked. If the latter is the case, which in the authors’ opinion is more likely, this assay should not be designated as an hs-cTn assay.

LABORATORY CONSIDERATIONS

Hs-cTn assays have been able to emerge as a result of improvements in laboratory measures including superior performance of buffering agents, enhanced antigen binding by detection antibodies and increased concentrations of detection probes on tag antibodies.3 This enhanced sensitivity, however, brings with it an
screening procedures that typically do not include physical examinations, ECGs and laboratory or imaging tests. It is known that comorbidities, such as renal disease, heart failure and structural heart disease, particularly left ventricular hypertrophy (LVH), are associated with elevated cTn levels at baseline. Consequently, the 99th percentile URL will vary depending on the characteristics of the individuals in the reference group and the extent of evaluations done to exclude abnormal subjects. In addition, it is also now clear that men and women and perhaps members of different ethnic groups will have different cut-off values with hs-cTn assays. Figure 1 demonstrates the proportion of patients with detectable cTnT levels using a high sensitivity assay among approximately 3,500 participants from the Dallas Heart Study, a representative population-based cohort both for all patients and patients stratified by comorbidity, age, gender and ethnicity. cTnT was detectable in 25% of all participants. The frequency of elevations will be substantially greater with still more sensitive assays. The differences between genders will vary from assay to assay. This has been demonstrated in a number of studies, which have assessed both chronic and acute elevations and have ultimately shown that different values will be necessary to optimize the detection of disease. Similarly, elderly patients, who have a higher prevalence of comorbidities, will also have higher values. Knowledge of this fact will enhance the specificity of an elevated cTn level for an acute event in this group. With hs-cTn, where elevated levels will be detected more frequently, this awareness will be critical. However, problems may arise among those elderly patients who are healthier than their peers and therefore have lower baseline cTn levels. They could/would be disadvantaged if higher cut off values are used. A better approach is for clinicians to be aware that many older patients will have elevations but to rely on a changing pattern of values (a ‘delta’) to make a diagnosis of an acute pathology.

Generating population specific reference values are an arduous endeavor, particularly if one has to evaluate each gender, age group and ethnic group separately. It requires 320 subjects per group to generate statistically robust values and finding such patients, especially among older individuals, can be a challenge, especially if screening is done carefully. There are good data that the more rigorous the screening, the lower the 99th percentile URL. Indeed, it is clear that imaging can contribute to this evaluation but whether the cost of doing this for all patient groups required is worthwhile remains unclear. Some of us have advocated that this would be best done using a unified national recruitment effort that diagnostic companies support. This would reduce the cost to individual groups by allowing the various reference samples to be used by all companies. In addition, it would allow for valid comparisons to be made between different cTn assays. The alternative is to use one reference population with only younger individuals predicated on the concept that all changes detected with age are due to comorbidities. One could screen prospective participants with a questionnaire and blood biomarkers without using imaging to reduce cost. This would result in some confidence limits around the 99th percentile URL, which clinicians would need to remain cognizant of. This should not be a major issue for the diagnosis of acute events since elevated hs-cTn levels in isolation should not be considered synonymous with an acute event. Instead, a rising/falling pattern in serially obtained troponin levels is what is required. This is as relevant to hs-cTn as it has been with conventional assays. Furthermore, it appears (see below) that in most instances, the cut off values for chronic disease categorization will require values below the 99th percentile URL. Thus, it is unlikely that the difficulty with assigning an absolute 99th percentile URL will be a clinically confounding issue.

Finally, values with hs-cTn assays would have a large number of zeros, which runs the risk that diagnoses are missed and inappropriate patient care is delivered. Accordingly, there is agreement that for hs-cTn assays, only whole numbers will be used and documented in ng/l. This means that at times values in the many thousands of ng/l may be observed.
Are Elevated Levels due to an Acute Event?

Hs-cTn assays will detect minimal concentrations of cTn. Using a relatively insensitive contemporary fourth generation cTnT assay, only 0.7% of subjects in the general population had levels above the 99th percentile URL, while using a putative hs-cTnT assay among the same population, this number was 2%. Such elevations were invariably associated with cardiovascular comorbidities such as diabetes, heart failure, renal failure and LVH and were associated with an adverse prognosis. Since, patients who present to the hospital with cardiovascular problems are usually those with such comorbidities, the frequency of elevations is likely to be substantially higher. Recent data suggest that the increment in elevated hs-cTn levels associated with AMI will be modest and that most elevations will be due to heart failure or primary noncardiac disease presentations. This increased sensitivity brings with it the advantage of significantly higher negative predictive values for truly normal cTn levels, allowing clinicians to rule-out acute events with greater certainty. However, increased sensitivity will come at the expense of specificity for a diagnosis of AMI, which means that elevations related to acute events must be distinguished from chronic elevations related to other noncoronary causes. Confounding this issue further is the fact that some of these patients are likely to have cardiac abnormalities that are too subtle to be detected with even magnetic resonance imaging (MRI).

To help deal with this problem, the concept of the ‘delta’ hs-cTn (Δ hs-cTn) has been developed. The use of a delta is not necessary when cTn values are very high since in reality, with the exception of an occasional analytical issue or a renal failure patient, marked elevations of cTn are usually due to either AMI or myocarditis. For less elevated values, detecting a changing pattern of values is essential. This equates to a measurement of change in the hs-cTn value over time and requires serial levels to be drawn. This approach has been shown to increase the specificity of hs-cTn for the diagnosis of an acute cardiac event. The problem lies in identifying an appropriate delta value, which is likely to change in different situations. At present, there are significant issues in the literature. Studies have often relied on patient samples being evaluated for different reasons such as to rule out AMI. Thus, late samples are often not present. In addition, the gold standard diagnosis has at times been made using less sensitive assays, which exaggerates the magnitude of the delta change required and excludes smaller infarctions. These problems have recently been reviewed and a template for better studies has been provided. Thus, it is not surprising that there are heterogeneous recommendations in the literature at present.

Most studies suggest that an absolute delta may be better than a relative or percentage change in values. They further indicate that the utility of delta changes depends on the initial cTn level and that the benefit of an absolute delta is greatest among patients with higher baseline values. Other studies have also found absolute deltas to be superior compared to relative deltas with or without elevated baseline levels. Meanwhile the Australia-New Zealand group continue to advocate using relative delta changes, suggesting a 50% change for baseline hs-cTnT values below 53 ng/l and 20% changes for values above. Regardless of the approach utilized, the use of fixed intervals for obtaining samples will be important and comparisons between values obtained over substantial periods of time are likely to be problematic. Many would argue that sample collection at zero, 3 and 6 hours might be optimal. The reality is that if the patient presents late after the onset of symptoms, fewer samples will be needed than if the patient presents early. It now appears that most patients will manifest a changing pattern within 3 hours and that most rule-ins can occur in that time frame. However, there will be patients who rule in late. It is likely those will be ones with poor coronary perfusion in the ischemic area with poor wash out of cTn. One size is unlikely to fit all.

It should be noted that the 20% change criteria in addition to most absolute delta criteria will be within the change that might be expected from joint biological and analytical variation. With contemporary assays, only analytical variation can be taken into account since biological variation cannot be measured accurately in diseased individuals. At elevated levels, the variability in precision amongst assays (as defined by the CV) is 5 to 7%. Imprecision is greater at values closer to the 99th percentile URL. For values to be truly different, they should differ by roughly 3 standard deviations around the measurement from each other; thus, 20% at elevated values and greater near the 99th percentile URL where imprecision is higher. Consequently, investigators can conclude that a delta change in cTn greater than these values cannot be attributed to analytical variation alone and would therefore represent an acute event. With hs-cTn assays, biological variation (or within patient variation) can be added to the equation. As each assay has its own CV, delta changes must be determined based on the assay in use. Data in this area indicated that delta change values (or so-called reference change values—RCV) range from roughly 50% to as much as 85%. These values greatly exceed many delta change values used in clinical practice, resulting in a proportion of patients being admitted under the premise of having had an acute event when in fact the changes detected
are secondary to this variation alone.\textsuperscript{38,39} However, were one to rely solely on this metric (the RCV) many patients with acute disease would be inappropriately discharged. Thus, the proper approach is to decide on a cut-off value for routine use as a group and then allow the subset in which there is ambiguity to be triaged based on clinical judgment. However, there will still be instances in which the value is not rising but a diagnosis of AMI may still be made. In one study, this occurred in as many as 14\% of patients\textsuperscript{38} and was thought to be due to a late presentation where the timing of the patient’s presentation precluded finding a changing pattern. Furthermore, a changing pattern indicates only that an acute event has occurred, which may not necessarily be an acute infarction. Patients with heart failure, sepsis, atrial fibrillation or other forms of paroxysmal supraventricular tachycardia and pulmonary emboli can also have a rising pattern of values. The interpretation of any testing depends on the clinical scenario. Bayesian thought advocates evaluating the pretest likelihood of disease and then adjusting this according to features identified in the history and physical examination. Further adjustment is then made using likelihood ratios associated with the results of clinical tests, ultimately leading to a post-test probability of disease. Figure 2 provides a schematic approach to the use of Bayesian principles in identifying patients with AMI using cTn, but this thinking can/should be applied to all diagnoses. Thus, the appropriate integration of clinical information is essential for the proper use of cTn testing, particularly with high sensitivity assays.

Appropriate delta changes are often determined using receiver operating curves, a statistical method that determines a suitable threshold value by evaluating the sensitivity and specificity of a series of potential values. The highest c-statistic, or area under the receiver operator curve, relates to the value which should be chosen as it represents the highest combined sensitivity and specificity. This method however gives equal importance to both sensitivity and specificity which is not consistent with clinical requirements in different settings. For example, emergency department (ED) physicians are faced with a plethora of patients presenting with chest pain and given the mortality associated with acute coronary syndromes (ACS) left unmanaged, are only willing to discharge patients in whom the likelihood of an acute event is extremely low, with a target ‘miss rate’ of <1\%.\textsuperscript{40} Thus, while they prefer a test with high sensitivity, internists and certainly cardiologists would prefer a test with greater specificity, in order to establish a diagnosis with greater certainty before proceeding to

![Fig. 2: Schematic outlining the use of Bayesian principles for the optimal management of patients presenting with chest pain [Adapted from: Sara JD, Holmes DR Jr, Jaffe AS. Fundamental concepts of effective troponin use—important principles for internists. Am J Med 2014. Used with permission. Steps 1-4 should be performed simultaneously] (AMI: Acute myocardial infarction; ECG: Electrocardiogram)](image)
invasive treatment which itself is associated with risk.\textsuperscript{41,42} This tension will be exacerbated by the subset of patients in whom there is suspicion of AMI but in whom delta criteria are not met. This situation will require interaction between the ED and cardiology and it may be that the presence of a facile out-patient follow-up system will help in many instances.

In the absence of a changing pattern, assuming the timing of presentation allows for such a pattern to be observed, there should be consideration of structural cardiac abnormalities, such as LVH and left ventricular dilation, which also cause elevated hs-cTn levels. Elevations can also be due to toxic and/or metabolic insults, such as hypothyroidism, carbon monoxide poisoning or toxicity due to chemotherapy agents to name but a few. Furthermore, women have less marked elevations in cTn in the presence of coronary artery disease compared with men;\textsuperscript{43} have a lower frequency of any degree of elevation in cTn levels\textsuperscript{44} and in the setting of an AMI, and have a higher frequency of pathology unrelated to coronary artery atherosclerosis, including endothelial dysfunction, microvascular dysfunction and coronary artery dissection. There may therefore be a need to develop delta values specific not only for each assay and gender but also for each pathology being investigated, an aspect of testing which is likely to evolve rapidly with hs-cTn.

**Distinguishing Type 1 from Type 2**

**Acute Myocardial Infarction**

Coronary artery atherosclerosis forms the substrate for the majority of ACS. When there is plaque disruption and the formation of a platelet thrombus that occludes a coronary vessel, infarction ensues and these are labeled type 1 events.\textsuperscript{45} It is known that when these patients present acutely, those with an elevated conventional cTn value benefit from aggressive anticoagulation and an early invasive approach. Patients with pre-existing coronary artery disease may also present with ischemia that leads to myocardial damage when there is a mismatch between the supply and demand of oxygenated blood, as in states of tachycardia, hypo or hypertension and anemia. These, along with other nonthrombotic causes of ACS such as endothelial dysfunction and coronary artery vasoconstriction or dissection, are designated as type 2 events.\textsuperscript{46,47} The incidence of type 2 events is likely to increase with the increased sensitivity of the new assays because these infarctions, as a group, generally elaborate less cTn than type 1 events.\textsuperscript{48} Distinguishing the two is crucial as the management for each is very different. Type 1 events are typically managed with aggressive anticoagulation and revascularization, whether percutaneous or surgical\textsuperscript{26} and type 2 events require management of the underlying cause. It is unclear and we would argue unlikely that these individuals will benefit from the same care that those with type 1 AMI should receive.\textsuperscript{46} While delta changes in hs-cTn levels can help discriminate acute infarctions from nonacute events, at present they are not helpful in distinguishing type 1 events from type 2 events.\textsuperscript{49} Validated clinical criteria are not available at present, but persistent ST-segment changes and hemodynamic instability should lead clinicians to consider a more aggressive evaluation. In addition, for patients presenting spontaneously, the use of a so-called anchor value may be helpful. This is a value derived from the 99\textsuperscript{th} percentile URL from a prior assay that is extrapolated to the new hs-cTn assay. For example, for hs-cTnT, a value of 0.01 ng/ml comports to a value of 30 ng/l. For the hs-cTnl Abbott assay, the prior 99\textsuperscript{th} percentile value was 0.024 ng/ml and this fortuitously comports to 24 ng/l with the hs-cTnl assay. Doing this will allow one to apply the data generated from previous clinical trials to patients with values above these levels. These studies have shown that among patients with levels above the anchor value, aggressive anticoagulation and an invasive strategy improves outcomes. For values below the anchor values, additional individualization will be necessary because there are no clinical trial data for this population.

The distinction between type 1 and 2 AMI becomes even more crucial when considering a significant proportion of type 2 events occur in critically ill and postoperative patients.\textsuperscript{50} These events are associated with a substantial increase in short and long-term mortality. Indeed, some studies suggest a higher mortality associated with type 2 events compared with type 1 event, perhaps due to the severity of associated illnesses.\textsuperscript{46} Although most believe that the majority of events after noncardiac surgery are type 2 AMIs, autopsy studies have demonstrated that coronary plaque rupture\textsuperscript{51} occurs in almost 50\% of cases, implying a type 1 etiology. Thus, type 2 events might be more common postoperatively, but type 1 events may be associated with a higher mortality. Importantly, these events require a rising and/or falling pattern of hs-cTn for a diagnosis. The concept that isolated elevations of cTn in this setting should be considered secondary to acute ischemia is not warranted. Patients with gastrointestinal bleeding may also suffer from type 2 events and form another group in which an accurate diagnosis is crucial to ensure management decisions do not adversely influence outcomes.

Some patients and particularly women may have AMI clinically but with angiograms that fail to show a culprit lesion. Some of these events can be documented
with MRI through the demonstration of delayed subendocardial hyperenhancement. Studies with intravascular ultrasound suggest that some of these events are plaque rupture events undetected by angiography. Recently, spontaneous coronary artery dissection has been diagnosed with more aggressive intracoronary imaging. This too could be the cause of AMI that can be missed angiographically.

**High Sensitivity Troponin Assays and Ruling Out Acute Myocardial Infarction**

The greater sensitivity of the hs-cTn assays means that ever smaller concentrations of cTn are detected with these assays. Patients who therefore present with normal or undetectable cTn levels may be considered to almost certainly not have had an acute event. Unfortunately, although this speculation makes sense, studies that have been done to evaluate this have often been structured in less than ideal fashions. In one study, the investigators found that patients who had undetectable levels of cTn in the initial sample tested with an hs-cTn assay, defined as levels less than the ‘level of blank’ characterized as the value, at which noise can be separated from baseline, were unlikely to suffer from adverse events during follow-up. Unfortunately, late samples were not consistently available. In another study, Bandstein et al found that among greater than 14,000 patients presenting with chest pain to the ED, those with undetectable cTn levels (defined as levels < 5 ng/l with the hs-cTnT assay), in addition to ECGs showing no new ischemic changes could have AMI excluded on almost every occasion (negative predictive value, 99.8). However, only about 20% had serial samples drawn and the criteria used to diagnose AMI were not included in the report. Importantly, undetectable cTn levels correlated with 100% survival at 30-day follow-up. These retrospective studies need to be validated with prospective randomized trials. In addition, undetectable cTn levels correlate not only with the absence of an AMI but also with an absence of other structural cardiac abnormalities including LVH, valvular disease and even coronary artery disease itself. Thus, the survival observed among these patients may be a reflection of their inherently lower baseline risk and not the superior discrimination of the highly sensitive assay. Furthermore, studies that assess the utility of hs-cTn assays in ruling out acute events typically use less sensitive conventional cTn assays as the gold standard test to establish the diagnosis. Consequently, they underestimate the prevalence of AMI in their patients and in doing so may overestimate the negative predictive value of the hs-cTn. Many investigations also claim that all acute events may be ruled out sooner, often within 3 to 4 hours. This is out of keeping with the findings of one study that included all new AMIs that were detected using the hs-cTn assays. Here, the time to diagnose all myocardial infarctions was 8.5 hours from the onset of symptoms and that is perhaps the more accurate figure. Nevertheless, patients who are deemed to be at low risk and have good follow-up outside of the ED are likely to be safely discharged as early as 2 hours after presentation. Claims that a 1 hour rule out based on change criteria validated over 6 hours and then divided by 6 are unlikely to be valid in our opinion. It is unlikely that coronary perfusion and the release of cTn is continuous, especially early after the onset of AMI and the small changes required for detection appear to be below the precision of the hs-cTnT assay used in the analysis cited.

Although an approach using detectability may be applicable to the hs-cTnT assay where only 25% of normal subjects have detectable values, it may be problematic for the very high sensitivity assays, which detect values in everyone. For those assays, a very low value that comports to the undetectable level with hs-cTnT will need to be found. The Australia-New Zealand group has shown that with an hs-cTnI assay that has sufficient precision to see changes within the normal range, unchanging values over 2 hours can effectively rule out AMI in patients with a TIMI risk score of zero or one. With regards to confirming a diagnosis of an acute event, a significant majority of patients will rule in within 3 hours. However, there will continue to be a subset of patients in which 6 hours of evaluation will be required. Figure 3 outlines a suggested algorithm for the effective use of high sensitivity troponin assays to facilitate rapid ruling-in of AMI.

**Causes of Elevated Troponin Levels Unrelated to Acute Myocardial Infarction**

With contemporary cTn assays, any degree of elevation should be considered abnormal. This is not to say that all elevations are synonymous with acute coronary events. When levels are rising and/or falling, then providing the clinical scenario fits, these elevations can be classified as due to acute cardiac injury and patients are at risk in the short-term and should be admitted. However, if elevations are elevated but are not rising and/or falling, providing the timing of presentation allowed for a changing pattern to be detected were it to be present, acute cardiac injury is unlikely. These patients are still at increased risk because elevated cTn levels are associated with a two-fold increased risk for long-term all-cause mortality and cardiovascular death compared to normal cTn values, in a dose-dependent relationship. However, when levels are chronically elevated, the increased risk,
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though significant, often plays out in the long-term and so these patients can usually be discharged and followed-up in the outpatient setting providing they are clinically stable and appropriate systems are in place. It is noteworthy that these patients will still have some sort of cardiac abnormality and so any follow-up must be early and comprehensive. With hs-cTn, the proportion of these patients will increase and so the need for a well-developed outpatient follow-up system will be even more crucial.

There are four situations in which clinicians may encounter marked increases in cTn levels and these are particularly noteworthy when switching to hs-cTn assays. They include AMI, myocarditis, and on rare occasions, patients with renal failure and rarer still, analytical problems. Table 2 summarizes important clinical and troponin characteristics that may be useful in distinguishing these entities. Myocarditis can present in a myriad of fashions and with a variety of cTn patterns. It is an important mimic of myocardial infarction as it can present with chest pain elevated cTn levels, sometimes even higher than those seen with ST-segment elevation myocardial infarctions (STEMI).

Elevated levels of cTn are common in patients with end-stage renal failure. Elevations increase with time as the duration of dialysis increases and are associated with lower survival. However, in these patients cTn levels are rarely markedly elevated. The increased levels are not the consequence of reduced glomerular filtration as cTn is not renally excreted but instead are related to concurrent cardiac abnormalities, such as LVH and coronary artery disease as well as metabolic changes. The frequency of elevations due to skeletal muscle abnormalities in this group is small. Obtaining baseline cTn levels in patients with end stage renal failure at routine outpatient clinic visits would facilitate this process. With hs-cTn, elevations are seen in stages of renal failure earlier than end-stage disease and increase in a gradual manner as the severity of disease increases. The relative prognostic importance of elevations in cTn at each incremental stage of renal failure are yet to be determined, but this situation reiterates the importance of obtaining regular baseline levels to facilitate accurate evaluation in the setting of a potential acute event.

PROGNOSTIC USE OF HIGH SENSITIVITY TROPOVIN ASSAYS

Patients with elevated or rising cTn levels are known to be at increased risk of adverse events, in the long and short-term respectively. With high sensitivity assays, the frequency of these elevations will increase and provide the opportunity to be better utilized and even calibrated to place patients with elevations into clinically useful risk brackets which can inform management decisions.

In acute situations with rising and/or falling patterns, multiple entities should be considered. Pulmonary embolism often causes cTn elevations as a result of right ventricular strain and associated cardiac injury even with conventional assays. More sensitive assays will increase the number of patients with elevated levels, which may

Fig. 3: Algorithm outlining the use of a high sensitivity cardiac troponin assay to allow the rapid ruling-in of an acute myocardial infarction [Adapted from: Thygesen K, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. EHJ 2012 Sep;33(18):2252-2257. Used with permission. Value of the upper reference limit (URL) will vary depending on the assay used at each institution] (hs-cTn: High sensitivity cardiac troponin assay; URL: Upper reference limit; 3 h: 3 hours; 6 h: 6 hours)
Table 2: Distinguishing clinical features between the four causes of significant elevations in troponin levels

<table>
<thead>
<tr>
<th></th>
<th>Acute myocardial infarction</th>
<th>Myocarditis</th>
<th>Renal failure</th>
<th>Analytical error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Classic ischemic chest pain</td>
<td>Chest pain</td>
<td>Fatigue and weakness</td>
<td>No specific clinical features</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath</td>
<td>Shortness of breath</td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autonomic symptoms</td>
<td>Symptoms associated with viral infection (fever, headache, sore throat, diarrhea, body aches)</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(diaphoresis, nausea, vomiting)</td>
<td></td>
<td>Shortness of breath</td>
<td></td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>Usually sudden onset</td>
<td>Usually gradual onset</td>
<td>Gradual onset (over months and years) and progressive deterioration</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>(over minutes to hours)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical exam</strong></td>
<td>In pain and anxious</td>
<td>In pain but usually not anxious</td>
<td>Fatigued</td>
<td>No specific clinical features</td>
</tr>
<tr>
<td></td>
<td>Sometimes in respiratory distress</td>
<td></td>
<td>Pallor/uremic yellow hue</td>
<td></td>
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<tr>
<td></td>
<td>Pallor and diaphoresis</td>
<td></td>
<td>Peripheral bruising</td>
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<tr>
<td><strong>Cardiovascular</strong></td>
<td>Tachy/bradycardia</td>
<td>Tachy/bradycardia</td>
<td>Parasternal heave</td>
<td>No specific clinical features</td>
</tr>
<tr>
<td></td>
<td>Hyper/hypotension</td>
<td>Hyper/hypotension</td>
<td>Possible murmur</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible added S3 and/or S4</td>
<td>Possible added S3 and/or S4</td>
<td>Possible pericardial friction rub</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible new regurgitation murmur</td>
<td>Possible pericardial friction rub</td>
<td>Possible chest rales</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible rales on chest auscultation</td>
<td>Possible rales on chest auscultation</td>
<td>Possible elevated JVD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible elevated JVD</td>
<td>Possible elevated JVD</td>
<td>Possible elevated JVD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Possible pedal edema</td>
<td>Possible pedal edema</td>
<td>Possible pedal edema</td>
<td></td>
</tr>
<tr>
<td><strong>Troponin testing</strong></td>
<td>Detectable cTn</td>
<td>Detectable cTn</td>
<td>Detectable cTn</td>
<td>Detectable cTn</td>
</tr>
<tr>
<td></td>
<td>Markedly elevated hs-cTn</td>
<td>Markedly elevated hs-cTn</td>
<td>Markedly elevated hs-cTn</td>
<td>Markedly elevated hs-cTn</td>
</tr>
<tr>
<td></td>
<td>Almost always</td>
<td>Can be markedly elevated</td>
<td>Rare</td>
<td>Invariably</td>
</tr>
<tr>
<td><strong>cTn pattern</strong></td>
<td>Rising and falling pattern in values (except late presentations)</td>
<td>Variable</td>
<td>Chronically elevated baseline levels that increase with severity of renal disease and duration of dialysis and predict poor outcomes</td>
<td>Unchanging pattern over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can have rising and falling pattern in values</td>
<td>Changing pattern with acute events</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can have elevated values that persist</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac imaging</strong></td>
<td>Regional wall motion abnormalities</td>
<td>Highly variable but often the epicardial lateral wall is involved</td>
<td>Ventricular hypertrophy and/or dilatation</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>Acute ventricular dilatation</td>
<td></td>
<td>Pericardial effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acquired mechanical defects</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

be useful in predicting outcomes. In one study, 526 normotensive patients with acute pulmonary embolism were evaluated with an hs-cTnT assay. Levels above the pre-defined cut-off value of 14 pg/ml predicted early death and complications (OR 4.97, 95% CI 1.71 to 14.43; p = 0.003) and were associated with a decreased probability of survival at 6 months (p = 0.001). When used in conjunction with the simplified pulmonary embolism severity index (sPESI), patients with a sPESI of 0 and hs-cTnT<14 pg/ml at baseline had a 42% reduction in the risk of death (HR 0.58, 95% CI 0.01-0.42; p = 0.005). The authors concluded that hs-cTnT assay used in conjunction with the sPESI could improve risk stratification of patients with pulmonary embolism. One wonders if the importance of these findings might be even more significant if sex specific cut-off values had been used and if a more sensitive and precise assay had been utilized. Prospective trials to determine the appropriate means of managing patients categorized as low and high risk using hs-cTn assays in isolation and in combination with the sPESI are needed.
In acute heart failure, cTn levels are likely to be elevated in the vast majority of patients as a result of global ventricular wall stretch and subendocardial coronary hypoperfusion. In chronic heart failure, these causes may be compounded by the degradation of contractile protein and cellular injury secondary to mechanical, oxidative and neurohumoral factors. The best correlate of elevated hs-cTn values is elevated left ventricular end-diastolic pressure. Patients with elevated hs-cTn values are at increased risk both in the short and long-term. In one study, investigators found cTn to be as good a predictor of mortality and readmission with heart failure as brain natriuretic peptide (BNP). In the acute setting, they also found that patients with rising levels of cTn during hospitalization for acute decompensated heart failure were at increased risk of 90-day mortality. All such patients should not be labeled as having sustained an acute coronary event, though a subset may have and these need to be identified clinically and managed with anticoagulation and revascularization as appropriate. The above study evaluated only 144 patients and so may be underpowered to determine the precise role of hs-cTn in heart failure. The authors also evaluated the hs-cTnI assay and used the 99th percentile URL (in this case 4.5 ng/l) to demarcate elevated levels. Patients with lesser degrees of elevation may still be at risk and therefore, larger studies looking at the role of less marked cTn elevations are required in addition to studies that evaluate serial cTn measurements and the combined role of cTn and BNP to identify ways in which patients with heart failure can be better risk stratified. The authors also did not control for renal failure which is commonly associated with heart failure and may confound the identified association between cTn and heart failure. Studies of chronic heart failure have indicated something similar, demonstrating that measuring changes in cTn levels with conventional assays is an effective way of following patients. With hs-cTn assays, greater discrimination and predictive accuracy can be achieved.

Patients with sepsis often have elevated cTn levels secondary to cytokine and endotoxin mediated myocardial toxicity and in the case of septic shock, from an oxygen supply/demand mismatch. Elevations are associated with both short and long-term mortality. With high sensitivity assays, these findings are more common and again may predict outcomes. In one study, the investigators found that in patients with severe sepsis and septic shock, hs-cTn levels were higher among hospital nonsurvivors compared to survivors (median 0.054, Q1-3, 0.022-0.227 vs median 0.035, Q1-Q3 0.015-0.111 μg/l; p = 0.047) but that hs-cTn was not an independent predictor of in-hospital mortality. In other studies, hs-cTn levels have been independent predictors. Importantly, recent data suggest that in this setting, cTn elevations are associated with diastolic and right ventricular abnormalities, which has the potential to lead to therapeutic interventions.

With conventional assays, elevated cTn levels predict very high mortality in patients with acute respiratory failure. Studies with hs-cTn in this group of patients have not yet been reported. In addition, a number of respiratory disorders result in cardiac abnormalities that may lead to elevated cTn levels. For example, in chronic obstructive pulmonary disease (COPD) patients, chronic hypoxia leads to elevated pulmonary arterial pressures which in turn results in increased ventricular strain and remodeling and the subsequent release of cTn. Acute exacerbations may result in further changes influencing cTn levels. In one study, 99 patients hospitalized for acute exacerbations of COPD had hs-cTn levels measured on admission and were followed up for a median duration of 1.9 years until death or study termination. Even after adjusting for covariates, elevated hs-cTn levels independently predicted death in a dose response fashion. This effect was significantly increased in patients who had tachycardia at baseline, suggesting that perhaps a type 2 event may be responsible for both the elevated cTn levels and the increased mortality. Once again, further studies are required to determine the best course of management for patients deemed to be at higher risk.

The principles articulated above are good examples of how hs-cTn elevations will define high risk subsets among acutely unwell patients. Eventually, studies such as those by Landesberg will lead to new therapies directed at those at greater risk.

**CONCLUSION**

Hs-cTn assays offer many opportunities to clinicians, including greater negative predictive values, more rapid ruling in and out of AMI and the opportunity to risk stratify and individualize the management of patients with both acute and chronic illnesses. However, these advantages come at the expense of an increased vulnerability to analytical problems, a vastly compromised specificity of an isolated elevation in cTn for a diagnosis of AMI and a lack of utility in discriminating type 1 events from type 2 events. While the advantages are compelling and the disadvantages require further studies to be addressed, effective use of these newer assays requires adherence to the same important concepts that held true with conventional assays. These include using the 99th percentile URL, looking for a rising and/
or falling pattern in values when appropriate to diagnose AMI and to employ clinical judgment when clear answers are not provided by cTn values alone.

REFERENCES

31. Jaffe AS. Chasing troponin: how low can you go if you can see the rise? J Am Coll Cardiol 2006;48(9):1763-1764.


