Understanding cardiac troponin part 1: avoiding troponinitis

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ABSTRACT

Cardiac troponin (cTn) is a highly specific biomarker of myocardial injury and is central to the diagnosis of acute myocardial infarction (AMI). By itself, however, cTn cannot identify the cause of myocardial injury. 'Troponinitis' is the condition that leads clinicians to falsely assign a diagnosis of AMI based only on the fact that a patient has an elevated cTn concentration. There are many causes of myocardial injury other than AMI. Clinicians are required to differentiate myocardial injury caused by AMI from other causes.

In part 1 of this series on cTn, we provide a structured overview to help practising clinicians to interpret 'positive' cTn results appropriately. There are three core principles. First, when reviewing a cTn result, clinicians must carefully consider the clinical context. Only this can distinguish primary (termed type 1) AMI caused by coronary artery disease from secondary (termed type 2) AMI caused by another condition with an imbalance in the supply and demand of oxygen to the myocardium. Second, clinicians must consider the patient's baseline condition in order to determine the presence or absence of factors that may predict a chronic cTn elevation. Third, clinicians should routinely use serial sampling to detect a change of cTn that is expected in patients with acute (rather than chronic) myocardial injury. Using these simple principles, clinicians can avoid underdiagnosis and overdiagnosis of AMI.

CASES

Case 1

A 70-year-old man presented to the Emergency Department (ED) having experienced 30 min of central, non-radiating, indigestion-like chest pain while at rest. Physical examination is normal but for some mild epigastric tenderness. He has a previous history of hypertension and hyperlipidaemia. He also had an anterior ST elevation myocardial infarction 3 years ago and underwent primary percutaneous coronary intervention (PCI). The ECG recorded on arrival shows anterior Q waves but no other abnormalities.

Cardiac troponin concentration, measured 3 hours after symptom onset with the Roche high sensitivity cardiac troponin T (hs-cTnT) assay (which has a 99th percentile upper reference limit of 14 ng/L), is 25 ng/L.

Case 2

An 80-year-old woman presented to the ED with a 6-hour history of palpitations and dyspnoea. Paramedics recorded an ECG, which showed rapid atrial fibrillation at a rate of 180/min with widespread ST depression. On arrival in the ED, her observations are normal and the ECG now demonstrates normal sinus rhythm. The cardiac troponin concentrations, measured with a contemporary assay (Siemens troponin I Ultra), are 65 ng/L on arrival and 90 ng/L 3 hours later (99th percentile 40 ng/L).

Question

Do either of these patients have acute myocardial infarction (AMI)?

To answer that question, we will provide an overview of cardiac troponin (cTn) and a practical guide to the interpretation of 'positive' cTn results for clinicians.

WHAT IS CARDIAC TROPONIN?

There are three troponins: troponin T, troponin I and troponin C, each of which is a structural protein that enables myocytes to contract. When myocytes are damaged, troponin leaks into the circulation, which can be detected using simple blood tests.

Those tests can identify isoforms of troponin that are highly specific for cardiac muscle ('cardiac troponin'), which we measure in practice to diagnose AMI. Assays are available to measure cardiac troponins T and I, but there are no assays for troponin C. When we talk about cTn, therefore, we are referring to either cTnI or cTnT. To understand how each should be used to diagnose AMI, we should not just consider whether we are measuring cTnI or cTnT but the overall performance of the individual assay (which is further discussed below). It is vital to recognise, however, that cardiac troponin (both cTnI and cTnT) will be released into the circulation following any myocardial injury. AMI is only one possible cause of myocardial injury.

THE THIRD UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION

The criteria for diagnosis of AMI are explicitly stated in the universal definition of myocardial infarction, which was published in 2012 by an international task force (see box 1). By this definition, cTn is central to the diagnosis of AMI. Detection of a rise and/or fall of cTn with at least one concentration above the 99th percentile upper reference limit (URL) is the one essential criterion for establishing a diagnosis of AMI.[1] Crucially, however, cTn concentrations alone are not sufficient to make the diagnosis. Patients must also meet any one of the four additional criteria.

Another important point to note is that 'universal definition' also clearly states the cTn cut-off should be used to diagnose AMI. The URL is set at the 99th

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Box 1 Summary of the third universal definition of myocardial infarction[1]

Essential: Detection of a rise and/or fall of cTn with at least one concentration above the 99th percentile upper reference limit. Plus at least one of the following.

- Symptoms compatible with myocardial ischaemia (importantly, these symptoms may be atypical).
- Appropriate ECG changes (including ST segment or T wave changes, new or presumed new left bundle branch block or the development of pathological Q waves).
- Imaging evidence of new loss of viable myocardium.
- Intracoronary thrombus identified at coronary angiography or postmortem.

percentile of concentrations measured in apparently healthy individuals (who are not further defined) and is assay-specific, for example, 14 ng/L for Roche high-sensitivity cTnT or 40 ng/L for Siemens Ultra cTnI. This is routinely reported by cTn manufacturers in their product information. The International Federation of Clinical Chemistry also publishes an online table reporting the 99th percentile for each commercially available cTn assay.[2] All emergency physicians should be aware which assay they use in practice and know its 99th percentile URL.

Some people may wonder whether a higher threshold, above the 99th percentile URL, would help to avoid problems with the so-called 'false-positive' cTn elevations. However, diagnosing small AMIs does benefit patients. For example, it is clear that cTn elevations just above the 99th percentile URL are clearly associated with adverse short-term cardiovascular prognosis.[3]

Importantly, this prognosis improves with treatment. Mills *et al* conducted a service evaluation in Edinburgh, where local clinical protocols had set the diagnostic threshold for AMI at 200 ng/L (well above the 99th percentile of the contemporary cTnI assay that was in use at the time, which was stated to be 12 ng/L in the manuscript[2]). The incidence of death or AMI at 12 months was found to be disproportionately high in patients with cTnI concentrations between 50 ng/L and 200 ng/L (figure 1). This group then changed its clinical protocol such that the cTnI threshold for making a diagnosis of AMI was set to 50 ng/L. On repeating the service evaluation, Mills *et al* noted that the prognosis of patients with cTnI concentrations between 50 and 200 ng/L had dramatically improved. The same group went on to show that patients with cTnI >12 ng/L had an adverse prognosis compared to those with cTnI <12 ng/L.[4] In the absence of direct

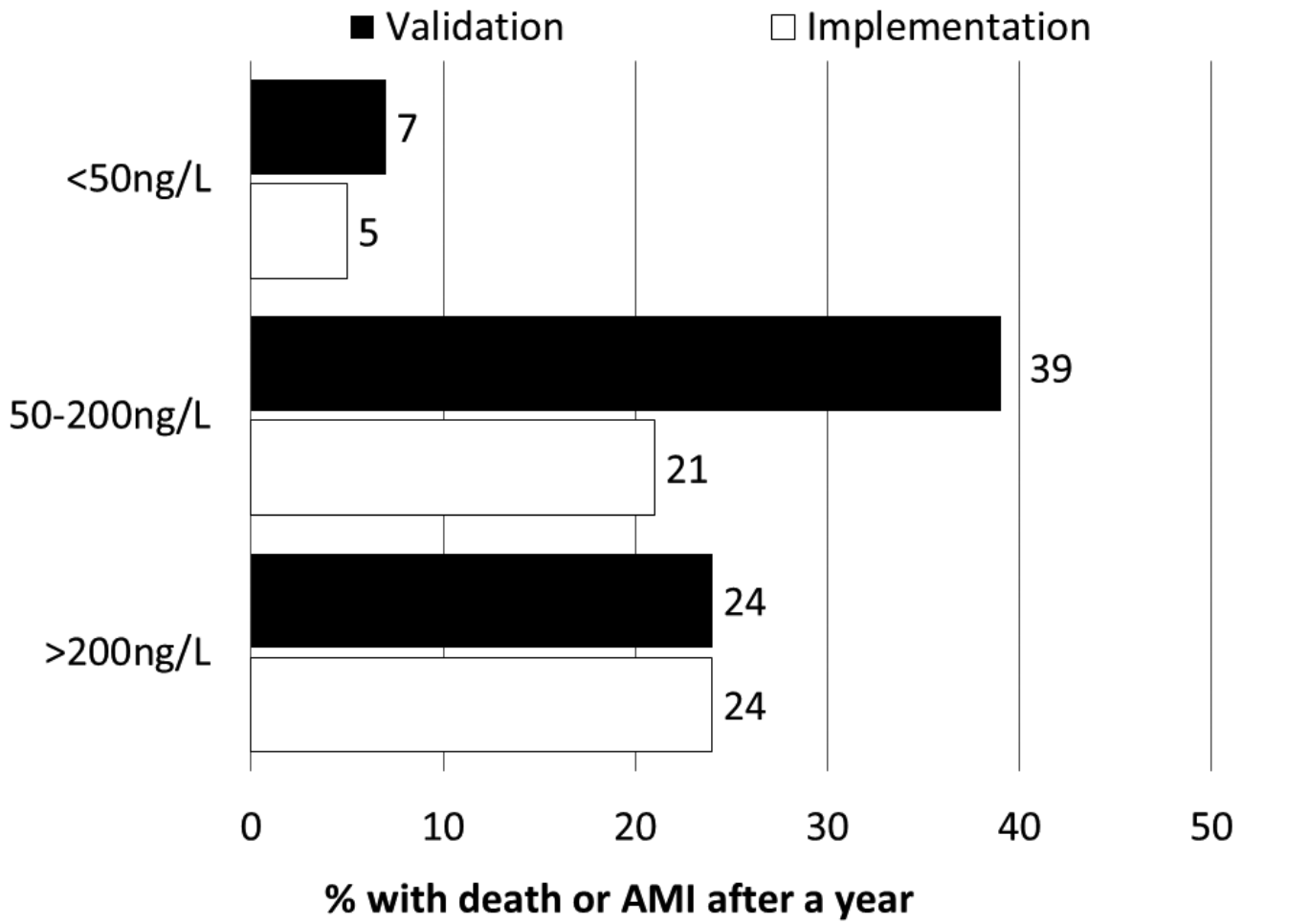

Figure 1 Incidence of death or acute myocardial infarction (AMI) within 12 months stratified by cardiac troponin I (cTnI) concentrations in the 'validation phase' (diagnostic threshold for AMI 200 ng/L) and 'implementation phase' (revised diagnostic threshold for AMI 50 ng/L), from the study by Mills *et al*.[25]

evidence from randomised controlled trials, such evidence presents a strong argument for retaining the current 99th percentile URL.

WHAT IS HIGH SENSITIVITY CARDIAC TROPONIN (HS-CTN)?

Hs-cTn assays have greatly improved our ability to rapidly and accurately 'rule in' and 'rule out' AMI. However, many people remain concerned that these assays may increase the prevalence of 'false-positive' results, that is, detecting elevated hs-cTn concentrations in patients who do not have AMI. To address this concern, it is important to understand exactly what is meant by a 'hs-cTn' assay.

The criteria for labelling an assay as 'high sensitivity' have been clearly defined.[5] Hs-cTn assays must meet two standards, both of which are based on analytical (ie, laboratory) characteristics rather than diagnostic accuracy.

First, hs-cTn assays must have adequate precision. 'Precision' describes the reliability of the test results and relates to the 'spread' of results that may be obtained if the same sample is tested repeatedly. It is measured using the coefficient of variation (CV). The CV is defined as the SD divided by the mean concentration obtained when the same sample is repeatedly analysed and is expressed as a percentage. A lower CV indicates a more precise assay. The CV varies according to the actual concentration of cTn and tends to be higher (indicating lower precision) at low cTn concentrations. In order for a cTn assay to be labelled as 'high sensitivity', the CV must be <10% when measuring a sample with a cTn concentration equal to the 99th percentile URL of the assay.

Second, hs-cTn assays must be able to detect cTn concentrations in at least 50% of apparently healthy individuals. This relates to the 'analytical sensitivity' of the assay and depends on the ability of the assay to detect small concentrations of cTn below the 99th percentile URL. The fact that hs-cTn assays can detect concentrations in apparently healthy individuals demonstrates that a low level of turnover of cTn is a normal phenomenon. However, neither of these criteria imply that a hs-cTn assay should necessarily yield more 'false-positive' results. The definition of the URL, for example, remains unchanged.

WHAT HS-CTN ASSAYS ARE CURRENTLY USED IN PRACTICE?

According to a recent appraisal by the National Institute for Health and Care Excellence (NICE) in England and Wales, there are currently only two commercially available hs-cTn assays ready for clinical use.[6] The key characteristics of each assay are shown in table 1.

Other assays either (a) do not meet both criteria for being 'high sensitivity' (eg, the Siemens cTnI Ultra assay, which cannot detect cTn concentrations in >50% of apparently healthy individuals), (b) did not provide sufficient data to NICE to demonstrate that the assay met criteria (the Beckman Coulter Access AccuTnI +3 assay, which has a 99th percentile URL of 40 ng/L) or (c) do not yet have a commercially available platform to deliver results with sufficiently low turnaround time for use in acute settings (eg, the Singulex cTnI assay). There are currently no point of care troponin assays that meet 'high-sensitivity' criteria. Assays that do not meet 'high-sensitivity' criteria are generally labelled as 'contemporary' troponin assays.

There are some important differences between the two available hs-cTn assays. For example, when testing patients with suspected acute coronary syndrome (ACS) at the time of arrival in the ED, the hs-cTnT assay (Roche) is more sensitive for AMI than the Abbott hs-cTnI assay (90% vs 77%).[7] This means that the first blood test in the ED is less likely to give a 'false-negative' result when the hs-cTnT assay (Roche) is used. However, with that first blood test the hs-cTnT assay is also more likely to give a so-called 'false-positive' result than the Abbott hs-cTnI assay. (The specificity for AMI is 78% for hs-cTnT vs 93% for hs-cTnI.) This does not suggest that one assay is better than the other. It is simply important to be aware that, when compared with hs-cTnI, hs-cTnT is more sensitive and less specific for AMI using the first blood test in the ED.

DO HS-CTN ASSAYS GIVE MORE 'FALSE-POSITIVE' RESULTS THAN CONTEMPORARY ASSAYS?

'Troponinitis' is commonly thought to be a problem relating to the use of hs-cTn assays. On the contrary, however, 'troponinitis' may occur with any cTn assay. In fact, the Abbott hs-cTnI assay is no more likely to give a 'false-positive' result for AMI than the previous generation of cTn assay, also manufactured by Abbott.[8]

However, the hs-cTnT assay (Roche) is more likely to give a 'false-positive' result than the older cTnT assay from the same manufacturer.[9 10] There is a clear explanation for this. When the same sample of blood is analysed with both the (current) hs-cTnT and (older) cTnT assays, the result will appear higher with the hs-cTnT assay, especially at low cTn concentrations.[8] A reading of 10 ng/L with the cTnT assay equates to approximately 30 ng/L when measured with the hs-cTnT assay. Patients with hs-cTnT concentrations between 14 ng/L (the URL of the hs-cTnT assay) and 30 ng/L will therefore now test 'positive' for troponin, whereas they would have had 'negative' tests with the contemporary cTnT assay.

This means that the hs-cTnT assay can detect smaller AMIs. Therefore, more patients are diagnosed with AMI and fewer with unstable angina (a troponin negative state).[9] It also means that the assay can detect smaller amounts of myocardial injury caused by conditions other than AMI.

This explains why there are more 'positive' results in patients who do not have AMI when hs-cTnT is used. However, such results should not really be considered as 'false positives' as for the test is identifying genuine myocardial injury. The single most important factor in avoiding 'troponinitis' is therefore to recognise that cTn is a marker of myocardial injury, not AMI. AMI is only one of many possible causes of myocardial injury. Cardiac troponin cannot, by itself, tell us the cause of the myocardial

Table 1 Analytical characteristics of available high sensitivity cardiac troponin (hs-cTn) assays

Assay	99th percentile (ng/L)	Lowest concentration with a coefficient of variation <10%	Limit of blank (ng/L)*	Limit of detection (ng/L)†
Hs-cTnT (Roche Elecsys fifth generation)	14	13	3	5
Hs-cTnI (Abbott Architect STAT)	26 (often reported as 34 in men and 16 in women)	5	0.7–1.3	1.2

*Limit of blank: two SD above the mean average of repeated measurements made on a sample containing no cardiac troponin.
†Limit of detection: the lowest concentration that can be reliably distinguished from the limit of blank.

injury. To establish the cause, we must pay attention to the following three key points

Interpret the current clinical context

In the information-light environment of the ED where rapid access to investigation results is crucial, we must accept that cTn concentrations will sometimes be measured in patients for whom the clinical context does not suggest a suspected ACS. Thus, when interpreting a troponin concentration, clinicians must always consider the clinical context.

The universal definition of myocardial infarction describes five distinct subgroups of AMI, only two of which (labelled as 'type 1' and 'type 2' AMI) are directly relevant to everyday practice in *Emergency Medicine*.[10] Type 1 AMI is a 'primary AMI' caused by a plaque rupture or similar event related to coronary artery disease. Patients with type 1 AMI will benefit from early treatment with antiplatelets, anticoagulants and coronary revascularisation. Type 2 is a 'secondary AMI' caused by an imbalance in the supply and demand of oxygen to the myocardium and is secondary to a condition other than coronary artery disease (eg, sepsis, cardiac arrhythmias and major haemorrhage). While type 2 AMI has a worse prognosis than type 1 AMI,[11] initial management should focus on treatment of the underlying condition.

Consider the patient's baseline condition

While considering the patient's *current* clinical condition will help to identify the cause of an *acute* myocardial injury, considering the patient's *baseline* condition (prior to attendance at the ED) will help to identify factors that are expected to cause a *chronic* cTn elevation.

A study that determined the reference ranges (ie, the 99th percentile URL) for three different cTn assays (one of which was a high-sensitivity assay) in apparently healthy people helps us to understand how high patient's baseline cTn concentrations can be. The study demonstrated that the URLs we use in practice are entirely appropriate for patients without any significant comorbidities (eg, vascular disease, hypertension, alcoholism, hyperglycaemia, renal impairment and heart failure). However, if we were to derive the 99th percentile URL in 'all comers', regardless of their comorbidities, the 99th percentile would more than double for hs-cTnT (from 14 ng/L to 30 ng/L), increase by more than 50% for the Beckmann AccuTnI assay (from 40 ng/L to 67 ng/L) but remain the same for the Siemens cTnI Ultra assay (40 ng/L).[12] This shows that cTn concentrations of up to twice the usual 'normal range' may be expected at baseline in patients with comorbidities such as pre-existing cardiovascular disease or even risk factors for coronary artery disease, although not all cTn assays are affected.

Advancing age is also strongly associated with higher cTn concentrations at baseline,[13] although again this phenomenon appears to be more pronounced with the hs-cTnT assay.[14] In ED patients aged >65 years without an apparent cause for cTn elevation, hs-cTnT levels as high as 82 ng/L (which was the 95th percentile of the results obtained) may be seen.[15] Clearly, many patients with hs-cTnT levels of that magnitude will have other important acute pathology (and are not, therefore, representative of the general population), but this research demonstrates how high cTn concentrations can be in elderly patients without AMI in the ED.

It is also well known that chronic kidney disease (CKD) often leads to chronic cTn elevations. In these patients, the detection of elevated cTn concentrations in apparent health indicates an adverse prognosis[16] but the extent to which this is modifiable remains uncertain. Understanding the potential magnitude of chronic cTn elevations in patients with CKD may help to avoid initial overtreatment, which is important given the increased risk of haemorrhagic complications in CKD. In a study of 89 apparently otherwise healthy patients with CKD, the 95th percentile of hs-cTnT ranged from 52 ng/L in CKD stage 3 to 297 ng/L in CKD stage 5.[17] While this should alert clinicians to the potential magnitude of chronic cTn elevations in patients with CKD (and thus help to prevent initial over-reaction to apparently high cTn concentrations on arrival in the ED), it is important to recognise that a bespoke URL for patients with CKD has not been established. As not all patients with CKD will have a chronically elevated cTn concentration, it remains essential to appraise each case individually.

Box 2 Criteria for calculation of the relative and absolute delta troponin. Abbreviations: cTn1, first cardiac troponin concentration recorded; cTn2, second cardiac troponin concentration recorded.

- Relative delta= (cTn2−cTn1) / [(cTn1+cTn2)/2]
- Absolute delta = cTn2−cTn1

Detection of a rise and/or fall of cardiac troponin

The universal definition of AMI stipulates that a rise and/or fall of cTn is required in order to make the diagnosis. Serial sampling is therefore routinely required to determine the 'delta' (or change) in cTn over time. Only after serial sampling can clinicians be certain about whether an observed cTn elevation is due to an acute myocardial injury or a chronic state. In the former, we would usually expect to see a change in the cTn concentration over time, with the possible exception of very late presenters. In the latter, we would not expect to see a substantial change in cTn concentration over time.

Serial sampling for cTn is conventionally undertaken over 3–6 hours. A 20% relative change (delta) in cTn concentration between samples is generally considered significant based on the precision of contemporary cTn assays. Recent evidence suggests that the absolute (rather than relative) change in cTn concentration has greater diagnostic accuracy (box 2).

The amount of change required depends on the particular cTn assay being used but, as a rule of thumb, a change of at least half the 99th percentile URL is significant.[18] For example, if the 99th percentile URL is 14 ng/L, then an absolute change >7 ng/L is significant and compatible with AMI. It is worth bearing in mind that if the time between samples is shorter, the amount of change required to make a diagnosis of AMI is likely to be smaller. For example, the optimal delta for hs-cTnT has been shown to be an absolute change of 7 ng/L using samples drawn 2 hours apart[19] but 9.2 ng/L when samples are drawn 6 hours apart.[20]

Are there any factors that might obscure the change in troponin on serial sampling?

There are several situations where serial sampling will not detect a significant change in cTn concentrations, even if the patient does have AMI. Clinicians need to be aware of this as patients in this situation may require a third cTn sample in order for us to be certain that the cTn concentrations really are static.

First, a patient who has ongoing intermittent symptoms caused by myocardial ischaemia may have intermittent cTn release into their circulation. This would give a 'double peak' in cTn

concentrations and may mean that a change is not detected on serial sampling. The observed change may be minimal in patients who present late. The rate of troponin egress from the coronary circulation may also affect the change observed on serial sampling. For example, in patients who have acute coronary occlusion (eg, in the context of ST elevation AMI), it may take several hours for any rise in cTn concentrations to be observed. Finally, haemolysis will lead to a falsely high reading with cTnI and a falsely low reading with cTnT. Samples affected by haemolysis should not be used to calculate the change on serial sampling. In circumstances such as these when there is uncertainty about the significance of the observed delta, it may be necessary to take a third sample of blood for cTn analysis. It is important to note that published data on delta criteria consistently report imperfect sensitivity and specificity, even with optimal criteria.[18] Human interpretation is therefore always required to interpret the clinical context and to determine the need for a third sample.

Are there any circumstances when AMI can be diagnosed without serial sampling?

According to the third universal definition of AMI, detection of the rising or falling pattern of cTn is always required to make the diagnosis, except in the case of late presenters who have a high pretest probability of AMI.[1] However, there is recent evidence to suggest that a single, very high cTn concentration means that the probability of AMI is very high. For example, a single hs-cTnT concentration >60 ng/L at baseline has a positive predictive value of 87% for AMI.[21] By combining cTn concentrations with other clinical information in a computerised clinical prediction model, it has been possible to achieve positive predictive value >90% for the diagnosis of ACS.[22]

Special situations

Post-AMI

Cardiac troponin concentrations can remain elevated for up to 2 weeks after AMI,[23] although this is likely to depend on the magnitude of cTn elevation following the initial event. Elevated cTn concentrations should never be disregarded as an expected phenomenon: serial sampling is highly important. A rising pattern suggests recurrent AMI, whereas a gradual fall is consistent with an uncomplicated post-AMI course.

Periprocedural AMI

Following invasive coronary angiography without intervention (and after direct current cardioversion), we would not normally expect to see a cTn rise. However, cTn concentrations do often rise after PCI or coronary artery bypass grafting (CABG).[24] If the cTn concentration exceeds five times the 99th percentile URL of the assay following PCI or 10 times the URL following CABG, then a periprocedural AMI may be diagnosed.[10] These cut-offs are, however, arbitrary, and patients meeting the criteria do not appear to have a worse prognosis than those without periprocedural AMI.[24] Despite this, the detection of a new cTn rise after initial hospital discharge should alert the emergency physician to the possibility of complications such as stent thrombosis.

CASES: OUTCOME

Returning to Case 1, the clinical context is compatible with a type 1 AMI, and there is currently no other apparent condition that may confound interpretation of cTn concentrations. At baseline, the hs-cTnT concentration is elevated to around twice the 99th percentile URL. However, the patient does have some factors associated with chronic cTn elevation: he is 70 years old, has a history of coronary artery disease and has hypertension and hyperlipidaemia. It would therefore be inappropriate to 'diagnose' this patient with AMI based on a single troponin result. Serial sampling is an absolute requirement. If the repeat sample were to show an absolute change of >7 ng/L at 2–3 hours or >9.2 ng/L at 6 hours, this would fulfil the criteria in the universal definition and is highly suggestive of AMI.

In Case 2, the cTn concentration is above the 99th percentile URL, and there has been a significant change on serial sampling (a relative change of >50% and an absolute change of 35 ng/L, which is more than half of the value of the 99th percentile). The patient therefore meets the cTn criteria for a diagnosis of AMI and also has ECG changes compatible with ischaemia (ST depression in the ambulance). This means that the patient does have AMI. However, the clinical context suggests that this is a type 2 AMI, secondary to a dysrhythmia. Initial treatment should therefore focus on management of the dysrhythmia, although further investigation for underlying coronary artery disease should also be considered.

SUMMARY

Cardiac troponin enables detection of myocardial injury with high specificity. With the advent of hs-cTn assays that can detect smaller amounts of myocardial injury, clinicians must be careful to interpret cTn concentrations alongside (a) the clinical context, (b) the patient's baseline condition (including factors that are associated with a chronically elevated baseline cTn concentration) and (c) the 'delta troponin' or change on serial sampling.

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Notes