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Chest pain and high-sensitivity troponin: What is the evidence?

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Abstract

The number of attendances and admissions of patients with chest pain to hospitals in England and Wales is increasing. Initial assessment may be unrewarding. Consequently, cardiac troponin has become the mainstay of investigation for non-ST-segment-elevation myocardial infarction and unstable angina, although only a small proportion of patients are eventually diagnosed as such. Current National Institute for Healthcare and Clinical Excellence guidance recommends measuring cardiac troponin levels on presentation and 10–12 h after onset of symptoms. A more effective diagnostic tool is needed. The aims are twofold: to increase accuracy of acute coronary syndrome diagnosis thus implementing the most appropriate management at an earlier stage while reducing costs and to provide a more rapid diagnosis to ease the anxieties of patients. Three key issues have been highlighted. The first is that many current studies do not have a 'normal/reference' population, making comparison between two studies difficult to interpret. Second, whether newer 'high-sensitivity' cardiac troponin tests can be used to rule out a myocardial infarction in a patient with chest pain is discussed. Third, whether a 'high-sensitivity' cardiac troponin has great enough specificity to differentiate between the number of other causes of raised troponin in a single test or whether serial testing is needed is assessed. A strategy for such serial testing is discussed. Finally, use of 'high-sensitivity' cardiac troponin in risk stratification of other disease processes is highlighted, which is likely to become common practice, changing the way we manage patients with, and without, chest pain.

Keywords

Acute coronary syndrome, cardiac care diagnosis

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Introduction and aims

Acute coronary syndrome (ACS) is a group of conditions including ST-segment-elevation myocardial infarction (STEMI), non-ST-segment-elevation myocardial infarction (NSTEMI) and unstable angina. The current definition of acute myocardial infarction (MI) can be seen in Box 1;[1] there must be evidence of myocardial necrosis with a clinical setting of myocardial ischaemia. There are more than 700,000 attendances to accident and emergency (A&E) with chest pain (CP) in England and Wales,[2] and admissions have more than doubled in the last 12 years to over 250,000.

Box 1. Third universal definition of myocardial infarction (MI).[1]

> The detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischaemia, new or presumed new significant ST-segment-T wave changes or new left branch bundle block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or identification of an intracoronary thrombus by angiography or autopsy.

Classic presentation is with sudden onset, severe, 'crushing' central CP that radiates to the left jaw or arm, associated with breathlessness, nausea and vomiting; many CP presentations are not like this and add to the diagnostic challenge. Initial assessment may be unrewarding and electrocardiogram

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(ECG) changes are not often present. As such, much reliance on cardiac biomarkers, namely, cardiac troponins (cTn), has become the mainstay of investigation for NSTEMI and unstable angina. Current National Institute for Healthcare and Clinical Excellence (NICE)[3] guidance recommends measuring cTn levels on presentation and 10–12 h after onset of symptoms. This is to assess whether any change in cTn level occurs, and because standard cTn assays are at optimal sensitivity at that time point.

This report begins with a brief discussion of the role of cTn in muscle contraction. Then, the need for high-sensitivity cardiac troponin (hs-cTn) assays is discussed, along with a detailed analysis of three key issues surrounding the implementation of hs-cTn. Finally, use of cTn assays in primary prevention for risk stratification is highlighted.

Methods

The following databases were used: Embase 1947–October 2013, MEDLINE 1946–October 2013 and Ovid MEDLINE® In-Process & Other Non-Indexed Citations. Search terms were in the title of the journals. A similar search method was performed in PubMed, and the reference lists of selected journals were examined as well. Search terms were as follows: acute coronary syndrome, ACS, myocardial infarction, angina, ST-elevation, non-ST elevation and chest pain; results of which were combined with results from the following search terms: troponin, troponin assay, high-sensitivity troponin, high-sensitivity cardiac troponin, hs-troponin, and hs-cTn. The studies were limited to English articles. Original articles were also gathered from the reference lists of selected articles.

Key aspects

High-sensitivity troponin: a necessary move forward?

The cTn complex consists of three separate proteins – cardiac troponin I (cTnI, binds to actin and inhibits actin–myosin coupling), –T (cTnT, binds to tropomyosin and stabilises the complex) and –C (cTnC, binds to Ca^{2+} ions and initiates contraction). This complex attaches tropomyosin to actin. In the presence of Ca^{2+}, the troponin–tropomyosin complex undergoes conformational changes that allow actin to bind myosin and muscle contraction takes place.[4] Two pools of troponin exist – a small cytosolic pool that is released upon initial myocardial injury and a second pool bound to myofilaments that offers sustained release. As cTnT and cTnI are only found in cardiac muscle, these biomarkers are measured in patients suspected of an MI. High-sensitivity cardiac troponin T (hs-cTnT) has been most extensively researched and will form the basis of discussion in this review unless specifically stated otherwise.

The aim of a more accurate cardiac biomarker would be twofold. First, from a clinical perspective, if the hs-cTnT was negative (hence not ACS), it may reduce admission to hospital for serial (12 h) cTn testing, thus reduces costs to the National Health Service (NHS), allowing more effective bed management. Second, from a patient perspective, during a period of much anxiety, patients can be given an accurate diagnosis and the most appropriate management. Both the hospital and patient experiences are further compounded if the patient suffers complications of a delayed diagnosis of an MI.

With each generation of cTn tests, diagnostic cut-offs have continued to be reduced. Hs-cTnT assays will further reduce this threshold by 10- to 100-fold to 0.003 µg/L (i.e. 3 ng/L).[5] For an assay to be classified 'hs-cTnT', it must have a coefficient of variance (CV), a measure of precision, of less than or equal to 10% at the 99th percentile of a normal population (also called the upper reference limit (URL)).[1] These URLs are assay-specific and differ depending on assay manufacturer. Also, the assay must be able to measure cTn concentration in at least 50% of the normal population above an assay's limit of detection.[3,6]

Problem – what constitutes a 'normal/reference' population? NICE[3] guidelines refer to the reference population as a healthy population within which elevated cTn levels would not be expected. But the cTn levels can be detected in healthy populations, or even patients with stable angina, using hs-cTn assays.[7] Whereas standard assays detect elevated cTn in 0.7% of a healthy population, unfortunately the detection rate using hs-cTnT assays can be greater, ranging between 25% and 66.5% according to two studies.[7–9] High-sensitivity cardiac troponin I (hs-cTnI) assays may do so in up to 80% of healthy individuals.[7,9]

Subgroups of patients with CP emerge which may affect the sensitivity and specificity of hs-cTnT assays. The 99th percentile value of each assay is based upon the population it was tested on. As studies comprise different populations, comparison between different assays is difficult. A study of 525 apparently healthy individuals attempted to address this, clearly highlighting that almost every 99th percentile of 19 currently available hs-cTnT, standard cTn and point-of-care (POC) cTn tests is different; so, a different correction factor is not possible.[9] In terms of implementing any new assay, laboratory and POC assays must be the same; otherwise, interpretation of cTn values by clinicians will be difficult given the different 99th percentiles.

Consequently, different assays have different cut-offs which apply for patients with a different background history. More research is needed into the performance of CP in all subgroups before safe and effective clinical implementation.

hs-cTn – can we rule out an MI? As previously stated, only a small proportion of patients admitted to hospital with ACS are eventually diagnosed as such. Having an hs-cTnT could give the capacity to rule out an MI with a patient presenting with CP. An international, multicenter study of 718 patients suspected of acute MI, of which 17% and 16% were

eventually diagnosed with an MI and unstable angina, respectively, assessed four hs-cTnT assays (only one of which would be considered 'high-sensitivity' by recent hs-cTnT assay standards). Within 3 h of presentation, sensitivity was 95%–96%, with much tighter confidence intervals, compared to only 76% with the standard cTn assay which also had wider confidence intervals; all were statistically significant.[10] At 2, 3 and 10 h after the onset of CP, the hs-cTnT assays outclassed the standard cTn assay, all significantly more sensitive at each time point.[10] Diagnostic performance of the hs-cTnT did not change significantly with serial measurements, and the negative predictive value was 97%–99%. The levels of hs-cTnT did not vary for sexes or patients >70 years old. Although it would appear that hs-cTnT could be used diagnostically to rule out an MI, it is worth noting that hs-cTnT levels were similar for other cardiac causes of CP, and 26% (32) of patients who had an MI had previously had an MI. Consequently, a thorough history and examination to isolate the most likely cardiac cause is necessary. An even larger multicenter prospective study of over 2000 patients corroborates these results, but suggested hs-cTnT is more sensitive than hs-cTnI. Undetectable hs-cTnT at presentation ruled out an MI in over a quarter of patients.[11]

Specifically considering the Roche Diagnostics Elecsys hs-cTnT assay which was investigated as part of this study and had a 100% sensitivity using the 3-ng/L lowest limit of detection as a cut off, it is worthy to note this perfect sensitivity remained for patients presenting beyond 3 h.[12] In fact, even at 6 months, only two patients with a cTnT <3 ng/L had died, one from a non-cardiac cause and the other as a result of percutaneous coronary intervention complications. Consequently, if this cut off was implemented in the emergency department, more than a quarter of patients would have had an MI ruled out immediately.[12] On implementing this strategy clinically, the second part of this study also found that of another cohort of 915 patients, only 1 patient had a cTnT <3 ng/L subsequently had a rise. Using this cut off to rule out an MI, however, 17.5% of patients would not have had serial testing.[12] Whether the risk of a single patient having an MI following discharge due to being ruled out after a negative hs-cTnT is acceptable is of debate and medico-legally this is unclear.[12] It must be borne in mind that the clinical picture needs to be considered in every case, treating the patient and not a single result.

As with the definition of MI, it is not only the level of cTn but the change in cTn level over time (delta value) that is of importance. Consequently, one study developed an algorithm that incorporated the delta value from a mini-study of 436 patients and then applied this prospectively to another 436 patients to validate the results.[13] cTnT levels were measured on presentation and after 1, 2, 3 and 6 h. Within the validated sample, 17% had a final diagnosis of an MI. Optimal 'rule out' criteria (cTnT level <12 ng/L and a delta change <3 ng/L at 1 h) were used that resulted in a 100% sensitivity and 100% negative predictive value.[13] This allowed for 60% (259 patients) to be ruled out with absolute confidence. 'Rule in' criteria included a cTnT level of >52 ng/L or a delta change of >5 ng/L at 1 h. Almost 90% of patients with an MI were ruled in (64 of 72 patients) at 1 h.[13] Overall, over three-quarters of patients with CP were given a definitive diagnosis at 1 h of presentation. Patients not fulfilling either criteria were in the 'observational zone', of which 8% were diagnosed with an MI.

Ultimately, hs-cTnT tests allow patients to be accurately diagnosed as to whether they are having an MI and may negate the need for serial testing. Current European Society of Cardiology (ESC) guidelines recommend sampling of hs-cTnT at 3 h after admission and after 6 h if still at high risk.[14]

Delta change/value – is it needed to rule in an MI? In order to make a diagnosis of an MI, the third universal definition of an MI emphasises the need for a 'rise and/or fall of cardiac biomarkers' in cTn levels (delta value).[1] Furthermore, as sensitivity increases, specificity, the ability to rule in a disease, is likely to decrease. In fact, cTn levels can also be detected in healthy subjects.[15] As such, a raised hs-cTnT does not mean an MI, despite being pathognomonic for cardiac injury of some degree. Triaging patients based on an elevated hs-cTnT may not be sufficient in the future, and terminologies such as 'positive' or 'negative' hs-cTnT are less helpful. A large study of over 3300 patients with CP found more than two-thirds of elevated hs-cTnT were due to other causes than MI; these patients also had a greater mortality after 1 year.[16] Without repeat testing, which invariably improves specificity, an elevated hs-cTnT may lead to more invasive procedures for those suspected of having an MI. Repeat cTn testing is necessary.

The National Academy of Clinical Biochemistry define a significant change as a delta value >20% baseline; and if the baseline cTn was small initially, the delta value should be increased to 50%.[17] Varying degrees of relative increases of cTn have been proposed, some up to >234% delta value.[16] A multicentre study of 836 patients found changes in relative hs-cTnT levels were significantly higher than baseline levels in an MI compared to any other final diagnosis.[18] However, absolute changes were superior to relative changes.[18] And at each time point cTn levels were measured, absolute values were diagnostically more accurate than relative changes when compared to hs-cTnT at presentation; only absolute delta values were statistically predictive of survival at 10 years.[18,19] This superiority was observed in subgroups where MI may be missed or the diagnosis delayed due to other complications, such as renal impairment or cardiac failure in females and elderly. As highlighted earlier, each assay is likely to employ a different absolute delta value.[20] An algorithm summarising the relative and absolute values and when hs-cTnT ought to be tested is thoroughly explained by Shah et al.[21]

Future perspectives

Besides a measure for ACS, cTn also provides information on prognosis; even small elevation of cTn worsens prognosis.[7,22] In fact, all-cause mortality has been shown to be independently associated with hs-cTnT.[7] Consequently, much research has been into the risk stratification of elevated cTn in ACS, heart failure, pulmonary embolism, sepsis and chronic kidney disease among others.[22] Extending the use of POC hs-cTnT tests into primary care as a tool for risk stratification in apparently healthy individuals is being investigated. Increasing hs-cTnT levels is significantly correlated with the presence of other risk factors of cardiovascular disease, including hypertension, diabetes, metabolic syndrome and kidney failure. Increasing hs-cTnT levels are associated with increasing risk of structural cardiac abnormalities mortality in individuals defined as low risk based on the Framingham Risk Score, and given this group accounts for the majority of cardiovascular events raise the possibility that a more accurate stratification method is needed.[7] However, there is some debate as to whether hs-cTnT can be used as a 'snapshot' of a healthy individual's risk or whether serial measurements are needed. Ultimately, hs-cTnT appears to dominate the future of how we manage CP and identifying those at risk.

Conclusion

With increasing presentations of CP to the community and hospital setting, and an increase in admissions to hospital for serial cTn testing, a more effective diagnostic tool is needed. The aims are twofold: to increase accuracy of ACS diagnosis thus implementing the most appropriate management at an earlier stage while reducing costs and to provide a more rapid diagnosis to ease the anxieties of patients.

Three key issues have been discussed – the necessity for a standard 'reference' population, whether hs-cTnT can be used to rule out an MI at various time points, and whether there is a need for serial testing. These issues are complicated by the range of assays available and heterogeneous inter-assay analytical capability. This substantially acts as a major hurdle to research and clinical implementation of hs-cTn assays. Finally, use of hs-cTnT in risk stratification of other disease process such as pulmonary embolisms and sepsis as well as in 'low risk' healthy individuals in the community is a new concept that may become common practice. What is clear is that the advent of hs-cTnT is set to dominate how we manage patients with CP, and possibly, without CP.

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Declaration of conflicting interests

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