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PRACTICE

RATIONAL TESTING

High sensitivity cardiac troponin in patients with chest pain

This article describes how high sensitivity troponin assays can be used to diagnose acute myocardial infarction in patients with chest pain

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com

A 55 year old woman presented to the emergency department with sharp retrosternal chest pain that resolved after 30 minutes en route to the hospital. She was a cigarette smoker with no relevant past medical history or other known cardiovascular risk factors. Clinical examination and a resting electrocardiogram were unremarkable.

What is the next investigation?

Electrocardiography remains the first line diagnostic test in patients with suspected acute coronary syndrome. However, despite excellent specificity (97%) it has low sensitivity (28%),[1] and diagnosis of acute myocardial infarction requires the complementary application of cardiac biomarkers.[2] Troponins are regulatory muscle proteins that are released into the circulation following acute myocardial injury. Assays that quantify cardiac isoforms of troponin have greater specificity and sensitivity for the diagnosis of myocardial infarction than do traditional cardiac enzymes. Measurement of creatine kinase MB and myoglobin in patients with chest pain is no longer recommended.[3]

Recent advances have led to greatly improved assay sensitivity permitting quantification of extremely low concentrations of troponin with excellent precision. High sensitivity cardiac troponin assays have limits of detection 10-fold to 100-fold lower than contemporary assays and are able to detect troponin in the circulation of most healthy people.[4] Myocardial injury is common in patients without acute coronary syndrome. High sensitivity troponin assays will inevitably increase the range of conditions associated with myocardial injury, so clear guidance on the use of high sensitivity assays is needed if we are to realise their potential to improve the early diagnosis of myocardial infarction.

What is the most appropriate diagnostic threshold for my patient?

The latest expert consensus document defines myocardial infarction as a rise and/or fall in cardiac troponin with at least one value above the 99th centile upper reference limit in the context of symptoms or clinical evidence of myocardial ischaemia.[2] The guidelines recommend the use of assays with optimal precision at the 99th centile, defined as a coefficient of variation of less than 10%. Although most contemporary sensitive assays do not meet these criteria, high sensitivity assays permit the 99th centile to be designated as the diagnostic threshold for myocardial infarction.

One of the major advantages of high sensitivity assays over contemporary sensitive assays is that troponin concentrations can be quantified above the limit of detection in more than 50% (and ideally more than 95%) of healthy people, so these assays are able to determine the 99th centile in the normal reference population with greater confidence.[4 5] It is now clear that the reference range may differ for men and women; some assays report a 99th centile that is more than twofold higher in men.[4] Using a single diagnostic threshold will potentially overestimate the incidence of myocardial infarction in men and underestimate it in women. The latest guidelines suggest that the use of sex specific diagnostic thresholds may be recommended when using high sensitivity troponin assays.[2]

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Learning points

- High sensitivity troponin assays can measure troponin in more than 50% of a normal reference population and can therefore identify people above or below the 99th centile with optimal precision (<10% coefficient of variation)
- With high sensitivity troponin assays, use the 99th centile of the normal reference population as the diagnostic threshold for myocardial infarction, and consider sex specific thresholds
- Measure troponin concentration on admission and three to six hours after admission, irrespective of the timing of onset of symptoms
- Many conditions other than myocardial infarction, such as septicaemia, renal failure, and heart failure, increase troponin concentration
- Demonstration of a rise and/or fall in troponin concentration is needed to identify patients with acute myocardial infarction

When should I measure troponin?

Current guidance on the timing of troponin sampling is based on contemporary troponin assays,[6 7] as few studies of high sensitivity assays have been published. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend measuring troponin on admission and 10-12 hours after the onset of symptoms, but they will need updating to reflect the more widespread use of high sensitivity troponin assays in the clinic.[8]

Lowering the diagnostic threshold with a more sensitive troponin assay increases the diagnosis of myocardial infarction by improving sensitivity (from 73% to 91%) with only modest reductions in specificity (from 94% to 90%).[6] Sensitivity is similar at three or six hours compared with 12 hours after the onset of symptoms when a high sensitivity troponin assay is used.[9] Perhaps more importantly, the negative predictive value of a normal troponin at three hours is over 99%, providing a safe early method of excluding myocardial infarction. Guidelines now recommend that troponin concentrations should be determined on admission and at three to six hours after admission, irrespective of the timing of onset of symptoms.[2 3]

What is the role of repeat testing?

For some time now, an elevated troponin concentration has been considered the sine qua non for the diagnosis of myocardial infarction. However, improvements in assay sensitivity have inevitably reduced specificity, as these assays do not define the cause of myocardial injury with troponin concentrations raised in other acute illnesses such as septicaemia, pulmonary embolism, and acute kidney injury.[10] The specificity of high sensitivity troponin assays will therefore be critically dependent on whether clinicians restrict the use of these assays to those patients with suspected acute coronary syndrome. Furthermore, troponin concentrations may be above the 99th centile in patients with chronic heart diseases, including stable coronary artery disease and congestive cardiac failure.[11 12] Demonstrating a rise and/or fall in troponin concentration is therefore essential to identify patients with acute myocardial infarction.[2 3]

The criteria used to define a significant rise and/or fall in troponin concentration are still being debated and will differ for individual assays,[3] but the change needs to be greater than that attributable to analytical or biological variation. The European Society of Cardiology (ESC) Working Group on Acute Cardiac Care defines a significant change in troponin concentration as 20% or greater.[3] However, this may not be appropriate for patients with very small troponin elevations, and in these patients a change of at least 50% is recommended.[3] On the basis of guidance from NICE and consensus opinion from the ESC Working Group, we include an algorithm to guide the use of high sensitivity troponin assays in the assessment of patients with chest pain (figure⇓).

Why should I consider introducing a high sensitivity troponin assay?

Implementation of a more sensitive troponin assay and lowering the diagnostic threshold have been shown to increase the diagnosis of myocardial infarction and improve clinical outcomes.[13 14] Recurrent myocardial infarction and death were halved in patients with small previously undisclosed increases in troponin concentration. These improvements were associated with better clinical care: more cardiology referrals, coronary angiography, and evidence based treatments. These observations highlight the importance clinicians place on troponin measurements in the assessment and management of patients with chest pain and suggest that high sensitivity troponin assays have the potential to improve patient care further. Although high sensitivity assays will permit earlier evaluation of patients with chest pain and improved precision will allow further reductions in the diagnostic threshold, particularly in women, the effect of these assays on clinical practice has not been formally evaluated and needs further investigation.

Outcome

Our patient's serum troponin concentration was 9 ng/L on admission, measured using a high sensitivity assay for which the upper reference limit was 26 ng/L for all, but 36 ng/L for men and 16 ng/L for women. An additional sample drawn three hours after admission measured 20 ng/L. Using the 99th centile for women as the diagnostic threshold, our patient had symptoms consistent with myocardial ischaemia and one troponin concentration above the upper reference limit with a more than 50% change on serial testing. She was diagnosed as having acute myocardial infarction.

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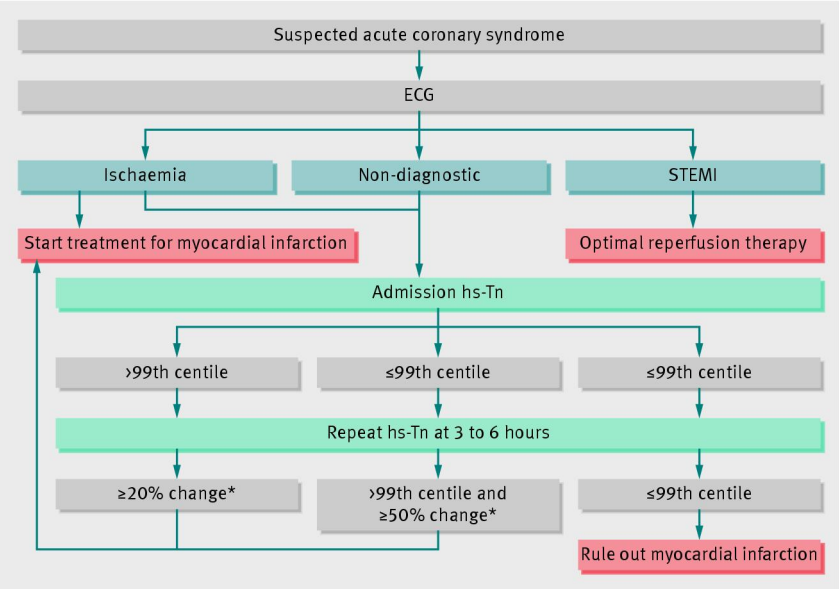
Figure



Algorithm for use of high sensitivity troponin (hs-Tn) assays in assessment of patients with suspected acute coronary syndrome. Based on NICE guidelines for assessment of recent onset chest pain and expert statement on use of high sensitivity troponins in clinical care from ESC Working Group on Acute Cardiac Care.[38] ECG=electrocardiogram; STEMI=ST segment elevation myocardial infarction. *If change in troponin concentration on repeat testing is not significant at 3 hours, consider retesting at 6 hours when clinical suspicion of myocardial infarction is high or consider alternative causes of presentation