Sensitive cardiac troponin assays: sense and sensibility

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This editorial refers to 'Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays'†, by M. Reiter et al., on page 988

Is analytical improvement mirrored in clinical advantages?
To meet the criteria defined in the universal definition of acute myocardial infarction (AMI), sensitive assays for cardiac troponins I and T have recently been introduced into clinical medicine. Such assays are commonly understood to have a detection limit <99th percentile of a reference population and a total imprecision at the 99th percentile ≤10%.¹ The analytical performance of these assays, i.e. the detection limit and imprecision profile, is clearly improved compared with previous generation assays.¹ Among clinicians, however, there has been scepticism as to whether use of more sensitive assays represents a clinically significant improvement.² Initial clinical studies of patients with acute chest pain and suspected acute coronary syndromes (ACS) demonstrated that sensitive assays provide enhanced diagnostic accuracy, particularly in patients with a short duration from symptom onset to hospital admission.³,⁴ Thus, the principal advantage of the sensitive assays is, not surprisingly given their name, the enhanced sensitivity to identify troponin elevation in early presenters. The enhanced sensitivity comes at a cost, however, i.e. decreased specificity. This decreased specificity has raised concerns among both emergency room physicians and cardiologists who fear that an increased rate of patients with troponin elevation of causes other than ACS will complicate triage in the emergency room and lead to overdiagnosis of AMI. Moreover, there are concerns that use of sensitive troponin assays with reduced specificity will lead to an increasing number of requests for cardiological assessment of patients with an elevated troponin test result from other departments. It has also been argued that the problem of decreased specificity has been underestimated because published studies, in particular those from specialized chest pain units or invasive centres, may not accurately reflect the patients seen in the emergency rooms of general hospitals, where older patients with complex comorbidities and higher troponin levels are frequently seen.

Troponin levels in patients with stable coronary artery disease
Studies using sensitive assays have demonstrated that cardiac troponins are frequently found circulating and elevated in a substantial number of patients with a wide range of conditions other than ACS. These conditions are commonly observed in the emergency room, and include heart failure,⁵ chronic obstructive pulmonary disease,⁶ and sepsis.⁷ Moreover, the great majority of patients with stable coronary artery disease (CAD) have detectable levels of cardiac troponin T, and >10% of such patients have levels above the 99th percentile of a reference population.⁸ As a history of CAD is common in patients presenting with acute chest pain, and the pre-test probability of AMI in these patients is high, it is important to establish the performance of sensitive cardiac troponin assays for diagnosing AMI and ACS in this patient group. Thus, the recent study of Reiter and co-workers⁹ addresses a number of pertinent questions that are highly relevant for both emergency room physicians and cardiologists alike.

Diagnosing myocardial infarction in patients with prior coronary artery disease
The results reported by Reiter and colleagues are based on the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) study, an ongoing, multicentre prospective observational study of patients presenting in the emergency room with chest...
pain suggestive of AMI. The primary results of the trial on the diagnostic performance of sensitive troponin assays were published in 2009. In the current report, the diagnostic and prognostic accuracy of a conventional fourth-generation cardiac troponin T assay was compared with those of a sensitive assay for cardiac troponin T and two sensitive assays for cardiac troponin I. Complete data for all four assays were available from 1098 patients.

As expected, the incidence of AMI was significantly higher in patients with a history of CAD than in those without such a history. Confirming results in stable CAD, the authors found that in patients without a final diagnosis of AMI, a diagnosis of prior CAD was associated with higher median levels of cardiac troponins. The optimal diagnostic decision limits, according to receiver operating characteristics analysis, were correspondingly higher in patients with prior CAD (e.g. cardiac troponin T 30 ng/L vs. 20 ng/L in those with and without prior CAD). Importantly, in patients with CAD, sensitive assays performed significantly better than the fourth-generation cardiac troponin T assay, and there were no significant differences in the overall diagnostic performance between the different sensitive assays.

**Does the diagnostic accuracy of troponin T and I differ?**

A surprising observation in the study of Reiter and colleagues was the finding that there were marked differences between the rates of elevated cardiac troponin levels between the different assays. Thus, 40% of patients without a final diagnosis of AMI but with a history of CAD had elevated levels with the sensitive cardiac troponin T assay, whereas the rates for cardiac troponin I elevation were substantially lower; i.e. 15% and 13% for the two assays evaluated. The rate of troponin elevation at baseline with the sensitive assays was substantially lower in those patients without a history of CAD, but the pattern was similar, with a higher prevalence of cardiac troponin T than cardiac troponin I elevation (18% vs. 9% and 7%). Not unexpectedly, given the higher levels of cardiac troponins in patients with stable CAD, the assay specificity was lower for patients with prior CAD than those without. The lower specificity was particularly pronounced for the sensitive cardiac troponin T assay. Whether this pattern is based on real pathobiological differences between troponin T and I or whether it reflects differences between the reference groups of the various assays, remains unclear. One strategy to address this question would be the use of an identical reference population for the different assays evaluated. Given the relatively strong effects of age and gender on circulating troponin levels in the population, and the fact that current decision limits are based on younger populations than those patients typically presenting in the emergency room with acute chest pain, the use of age-dependent decision limits is likely to enhance diagnostic specificity, and probably overall diagnostic accuracy.

**Making sense of sensitive troponin assays**

The question many clinicians currently are asking is how best to incorporate sensitive troponin assays in clinical practice. Existing data clearly suggest that these assays provide a superior means for early identification of patients with AMI, making other early markers of myocardial injury redundant. By obtaining the second troponin sample earlier than previously recommended, e.g. after 2 h rather than after 6 h, the diagnostic process can be speeded up. Using the absolute rather than a relative increase in troponin levels also appears to enhance diagnostic performance. Increased awareness of alternative causes of chronic, low-grade troponin elevation, as well as thorough assessment of the pre-test probability of AMI, history, and clinical symptoms and signs, will be increasingly important for the correct interpretation of cardiac troponin test results. From this perspective, the article by Reiter and colleagues on the impact of prior CAD on diagnostic accuracy represents an important, new piece in the...
puzzle of making sense of sensitive troponin assay test results in patients with acute chest pain.

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**References**