Troponin measurement and the new assays: how low can we go?

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*More sensitive assays may provide more information,
but we are not yet sure of the clinical relevance of this information*

The introduction of troponin measurement into clinical practice in Australia 10 years ago led rapidly to its widespread use as the marker of choice for diagnosis and risk stratification of patients with acute coronary syndrome (ACS). However, opportunities remain for improving risk assessment in "troponin-negative" patients, many of whom will have adverse events. This has led to the development of new, improved assays that are able to measure down to much lower concentrations than before (10–100-fold lower than current assays), and that increase the detection of acute myocardial infarction, as shown in two recent cohort studies.[1,2] The improved analytical performance of these assays may be particularly useful in the early period following the onset of chest pain. These two studies indicated improved diagnostic accuracy of samples taken from patients with chest pain, both at the time of presentation to the emergency department (ED), and within 3 hours of symptom onset.[1,2] This improved early sensitivity may lead to significant benefits in ruling out ACS, and in risk assessment, diagnosis and management of patients with

ACS, although neither of these studies provided corroboration with clinical outcome.

The development of these new "highly sensitive" assays for cardiac troponin raises many questions about their clinical application, including the degree of analytical precision, the medicolegal definition of myocardial infarction, earlier detection and improved management of patients with ACS, as well as the interpretation of elevated cardiac troponin levels in other clinical situations.

The current accepted international definition of myocardial infarction — the "universal definition of myocardial infarction"[3] — requires a rise or fall in the level of cardiac biomarkers (preferably troponin) with at least one value above 99th percentile of the upper reference limit, along with at least one clinical indicator (symptoms of ischaemia, new ischaemic changes or new Q waves on electrocardiogram, new imaging evidence of loss of viable myocardium or a new regional wall motion abnormality). The use of assays that do not have optimal precision (coeffficient of variation [CV] < 10% at the decision level) is not recommended,

although, a variety of the older, less precise assays are still in clinical use. New, highly sensitive (hs) assays have the recommended degree of analytical precision, and the first (Roche hsTnT, Roche Diagnostics) has been launched while others are in preparation. Their use would lead to an increase in the diagnosis of myocardial infarction. Measuring low levels of troponin introduces an additional confounder — that of significant biological variability[4] — which would require an increase in the traditionally accepted 20% serial change of troponin level over baseline values that is required to meet the definition of myocardial infarction.[5]

The application of cardiac troponin measurement in risk stratification of patients presenting with ACS has been strongly supported by clinical data. Measurable cardiac troponin levels in these patients, even concentrations below that corresponding to the recommended assay precision (CV < 10%), are associated with adverse clinical outcomes. In addition, aggressive management has been shown to improve clinical outcome in these high-risk patients. It is possible that the hs assays will improve the identification of high-risk patients who benefit from aggressive management, but this will require clinical validation. From an ED perspective, the new assays present the possibility of identifying patients at very low risk of 7-day or 30-day adverse events at a much earlier stage. Two hs troponin assays at least 3 hours apart, or one assay taken at least 6 hours after symptom onset may be accurate in ruling out myocardial infarction in the ED, but the evidence for this approach is so far limited.[2] This should allow for more immediate decision making in relation to proceeding to further testing (such as an exercise stress test or stress echocardiography) and discharge from the ED, and could significantly decrease overnight admissions of patients with possible cardiac chest pain. The use of any biomarker assay in managing chest pain or possible ACS should always be done in conjunction with a full clinical assessment to ensure appropriate risk stratification.

The other common clinical question is how to interpret cardiac troponin levels in patients without clinical features of ACS. There have been several reports suggesting that normal healthy people without cardiac disease may have very low, but detectable levels of troponin present at all times.[6,7] This raises the intriguing possibility of cardiomyocyte turnover and renewal.[8] Low levels of cardiac troponin have also been identified, and have been shown to be correlated with structural heart disease, diabetes mellitus and chronic kidney disease in a small percentage of the general population.[9] Screening of asymptomatic elderly men for serum troponin predicted the risk of future cardiac events.[10] Although troponin release has traditionally been thought to be caused by cardiomyocyte necrosis, recent information suggests that troponin may be released after ischaemia without necrosis in patients undergoing stress testing.[11] A 10-fold increase in low-level troponin concentration has also been identified in athletes after marathon running.[7]

Elevated troponin levels are not uncommon in patients in intensive care units, and possible causes include supply/demand ischaemia and alterations in myocyte membrane permeability or leakage. The likelihood of ACS in these patients is low in the absence of usual symptoms or evidence of acute ischaemia or infarction. Cardiac troponin levels may also be elevated by non-coronary causes including myocarditis, aortic dissection, Tako-tsubo syndrome, pulmonary embolism, cardiac trauma, sepsis, tachycardia, severe heart failure, and "false positives" that include heterophile antibodies and analytical imprecision. All elevations in cardiac troponin concentrations, and particularly in low-level measurements, should be inter-preted in the context of the pretest probability of ACS, as well as possible non-coronary causes of troponin release.

In conclusion, our understanding and interpretation of troponin concentration and use of the new highly sensitive assays continue to evolve. This may offer us greatly enhanced opportunities for early diagnosis, risk assessment and improved management, but their widespread use will require clinical validation. More than ever before, however, there is a clinical imperative not to immediately equate detectable troponin concentration with ACS, but to interpret each result in its clinical context.

Competing interests

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References

1 Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009; 361: 858-867.
2 Keller T, Zeller T, Peetz D, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009; 361: 868-877.
3 Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007; 28: 2525-2538.
4 Wu AH, Lu QA, Todd J, et al. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. *Clin Chem* 2009; 55: 52-58.
5 Wu AHB, Fukushima N, Puskas R, et al. Development and preliminary clinical validation of a high sensitivity assay for cardiac troponin using a capillary flow (single molecule) fluorescence detector. *Clin Chem* 2006; 52: 2157–2159.
6 Kavsak PA, MacRae AR, Yerna M-J, Jaffe AS. Analytical and clinical utility of a next-generation, highly sensitive cardiac troponin I assay for early detection of myocardial injury. *Clin Chem* 2009; 55: 573-577.
7 Mingels A, Jacobs L, Michielsen E, et al. Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. *Clin Chem* 2009; 55: 101-108.
8 Bergmann O, Bhardwaj RD, Bernard S, et al. Evidence for cardiomyocyte renewal in humans. *Science* 2009; 324: 98-102.
9 Wallace TW, Shuaib MA, Abdullah MD, et al. Prevalence and determinants of troponin T elevation in the general population. *Circulation* 2006; 113: 1958-1965.
10 Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70 year old men. *Circulation* 2006; 113: 1071-1078.
11 Sabatine MS, Morrow DA, de Lemos JA, et al. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. *Eur Heart J* 2009; 30: 162-169. ❑