Troponin measurement in patients with suspected acute coronary syndromes - walking beyond the wall.

1232 words

13 references

The measurement of cardiac troponin for diagnosis of acute myocardial infarction (AMI) marked a paradigm shift in the role of laboratory testing in patients with suspected acute coronary syndrome. Previously, diagnosis of myocardial infarction had been focussed on clinical features and the electrocardiogram (ECG) with measurement of “cardiac enzymes” either creatine kinase (CK) or its MB isoenzyme (CK-MB) seen as useful but supplementary. It was shown that elevations of cardiac troponin T (cTnT) or cardiac troponin I (cTnI) occurred in approximately one third of patients said to have unstable angina on by measurement of CK or CK-MB(1). These troponin elevations were predictive of major adverse cardiac events (MACE) during the follow-up period. Measurement of cTnT and cTnI became the key diagnostic test for the diagnosis of AMI(2) and subsequently went on to define management pathways for patients with acute coronary syndromes (ACS)(3).

There has been progressive improvement in the analytical performance of troponin assays. This improvement has been driven in part by the desire of assay manufacturers to improve analytical quality and in part by the redefinition of AMI(4). The redefinition stipulates that an assay is able to measure a diagnostic discriminant of the 99th percentile of a reference population. In addition, the redefinition requires minimum level of assay imprecision at this 99th percentile, a coefficient of variation (CV) of 10%. The first generation of troponin assays did not approach this level of analytical sensitivity. The analytical performance of troponin assays is based on the ability to measure at the 99th percentile with an imprecision of 10% or better and the proportion of a reference population in which troponin can be reliably detected(5, 6). Currently, troponin assays (contemporary sensitive assays) are able to measure troponin in in normal healthy individuals at the 99th percentile with a CV of 10% or less. Such assays will measure troponin reliably in a portion of the upper end of the normal distribution (typically up to 25%). High sensitivity assays are able to measure cTnT and cTnI in 50% or more of a healthy reference population.

Improvement in assay sensitivity has produced an existential crisis in cardiologists and emergency medicine physicians. The progressive improvement in assay sensitivity has resulted in increasing numbers of patients without ACS, without chest pain and even without any acute illness with troponin elevation. The detection of troponin in patients with other pathophysiology has resulted in claims of non-specificity for cTnT and cTnI and invention of the terms “troponitis” and “troponin leak”. It has also produced the term “Type 2 AMI” to confuse clinicians further(7). A reality check is required.

It is a truth universally acknowledged, that a single man (or woman) in possession of an elevated troponin, must be in want of a good doctor. But, unlike a fortune, some troponin is worse than no troponin and, more troponin is worse than less troponin. It has been demonstrated, universally, that troponin elevation, whatever the clinical situation (acute or chronic), predicts an adverse outcome. Troponin is an absolute predictor of myocardial injury but the presence of myocardial injury does not automatically equate to a myocardial infarction. Six inches of sharpened steel inserted in the fifth left intercostal space is likely to cause acute chest pain, myocardial injury, death (if untreated), and troponin release. But this is not a myocardial infarction.

The majority of patients who are investigated for suspected ACS do not have elevated troponin and can be rapidly and safely ruled out for any form of acute cardiac injury and equally can be shown to be in a very low risk group for subsequent cardiac and non-cardiac death. This can be done rapidly with high sensitivity troponin assays by serial measurement on admission and at three hours, possibly even on admission and one hour later(3). A single measurement on admission can be used to identify a very low risk cohort on the basis of very low troponin values(8, 9). Troponin elevation is due to myocardial injury and is absolutely cardiac specific. This myocardial injury may be acute or chronic. Acute myocardial injury is characterised by a change in troponin, a delta troponin. AMI is one of the causes of acute injury but is not the sole cause of acute troponin elevation. It must be remembered that AMI is a clinical diagnosis. Other acute causes of troponin elevation are secondary to the primary pathology, which may be obviously cardiac such as myocarditis, but may represent another cardiac pathophysiology, as in pulmonary embolus. In conditions where there is chronic troponin elevation, there is minimal change over a short time period. In chronic disease such as chronic renal failure, troponin elevation predicts an adverse outcome(10). It has been shown that cardiac troponin is one of the strongest predictors of an adverse outcome in patients with cardiac failure(11). Even in the healthy population, the magnitude of troponin elevation within or above the 99th percentile as a powerful predictor of subsequent cardiac events (12).

The recent paper by Stelzle provides an interesting contribution to the information on interpreting troponin results in the suspected ACS population. The authors have examined 4748 consecutive patients presenting with suspected ACS to 3 secondary and tertiary care hospitals. All had troponin measured as part of their routine management and they examined the predictive power of the highest value obtained (when more than one troponin measurement was performed). All patients had a final diagnosis according to current diagnostic criteria of type 1 or type 2 myocardial infarction(2). Patients with troponin elevation without evidence of ischaemia characterised as myocardial injury. Outcome data was obtained on all the patients enrolled. The authors examined the ability of the troponin measurement to predict readmission with heart failure.

Patients where troponin exceeded the 99th percentile had a significantly higher risk of hospitalisation with heart failure than patients with a value below the 99th percentile. This is something which might be expected as those above the 99th percentile will by definition have myocardial injury including myocardial infarction. More intriguingly, there was a non-linear association between the magnitude of troponin elevation and subsequent risk of heart failure hospitalisation. Risk rose progressively for increasing values (stratified by quartile) below the 99th percentile but plateaued at a value close to the 99th percentile. This graded risk increase indicates that even in the acute population, troponin values within the reference interval are predictive of subsequent events. It also follows the same dictum that more troponin is worse than less troponin. The plateau effect, indicating that once above the 99th percentile magnitude of elevation is not predictive, is somewhat more puzzling. It is usually considered that the degree of biomarker elevation is predictive of the magnitude of myocardial injury and subsequent impairment of ventricular function(13, 14) and risk of heart failure. It may be that the sampling times used did not reflect peak troponin release or that the relationship between the magnitude of troponin elevation and subsequent myocardial injury is more complex.

The strength of this study is that it reflects routine clinical practice and has examined a large cohort of patients. It provides further information on the value of troponin measurement at levels below the 99th percentile and an intriguing overlap with the data derived from population studies. It also provides further information that suggests that troponin measurement is moving beyond the realms of a marker of acute myocardial injury and that it will have a significant role to play in chronic disease assessment and management.

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