Diagnosing a heart attack – are biomarkers the be-all and end-all?

Stewart Mann, MA, DM, FRCP, FRACP, Associate Professor of Cardiovascular Medicine, University of Otago, Wellington

Forty years ago, at the peak of the coronary epidemic in western societies, diagnosis of myocardial infarction (MI) was often a qualitative and imprecise exercise. Then, as now, evidence was largely assembled from clinical symptoms, ECG changes and serum biomarkers. However, there were no biomarkers specific to myocardium and interpretation of changes to lactic dehydrogenase and serum glutamic oxaloacetic transaminase (later rechristened aspartate transaminase) was necessary despite known alternative sources of excess from liver. There was a high incidence of major and unequivocal myocardial infarctions with ST elevation on the ECG – “STEMIs” but also occasional more borderline syndromes. Treatment often involved prolonged bedrest (followed by similarly prolonged rehabilitation) and a focus on the management of arrhythmia with some controversy around the benefit of anticoagulation. Sudden death, cardiogenic shock and pulmonary oedema were common so both the clinical and social implications of a diagnosed heart attack were profound.

Symptoms continue to be the key in diagnosis and ECG technology has not changed. While imaging technology has improved radically, it is rarely easily available in the acute phase of an evolving coronary syndrome so the focus of improving diagnosis has been the development of rapid assays of much more sensitive and specific biomarkers. Creatine kinase was of course specific to muscle and its MB fraction more so to myocardium but even this has now been swept away by the troponin revolution. Cardiac troponins T and I (cTnT and cTnI) are highly specific to the myocardium and ever more sensitive assays pick up lower and lower levels, including now levels found in healthy subjects.

The presentation, management and outcomes of acute coronary syndromes have changed over these 40 years. Age-standardised death rates from coronary disease are now some 40% of their levels in 1968, due both to changing risk factors and to medical interventions; case incidence and case fatality have both fallen. The falls in smoking rates, blood pressure levels and lipids which have been responsible for the largest part of the reduction are however in danger of being offset by increasing obesity and consequent diabetes (1). We have also seen a decline specifically in sudden death and larger infarcts (eg STEMIs) and admissions now consist much more frequently of smaller, more borderline syndromes (non-STEMIs and unstable angina). Coronary disease has become less focused on single major events and more typically follows a chronic disease pattern with occasional recurrent crises.

The availability of new treatments has dictated a need to have internationally standard classifications of acute coronary syndromes to facilitate scientific evaluation of treatments. Committees convened under the auspices of the American College of Cardiology, American Heart Association, European Society of Cardiology and World Heart Federation deliberated in 2000 and again in 2007 (2) to produce definitions of myocardial infarction. These have focused on biomarkers (and in the latest version specifically on troponins) as being a fundamental component of the diagnosis and exhorted diagnostic companies to come out with assays that would meet a requirement of measuring the 99th percentile of a healthy population with a coefficient of variation of 10% or less. In 2010 this has now been achieved although the increased sensitivity has come at a cost of decreased clinical specificity. To guard against over-diagnosis of MI, the definition requires a rise or fall in biomarker level to be documented although did not specify the degree of change needed to satisfy the diagnosis.

Despite a changing level being a requirement for diagnosis even in the 2000 definition, in recent years many clinicians had come to regard a single raised level in combination with a suggestive clinical history as a positive diagnosis. Over this period conventional management of a non-STEMI has included admission and a trip to the cardiac catheter laboratory for angiography, stenting of a “culprit” stenotic coronary lesion if identifiable and treatable, or other indicated intervention such as coronary bypass surgery. For this commonly diagnosed condition, this has necessitated transfer of many patients to an interventional centre during their index admission. A positive diagnosis has therefore had major clinical (not to mention financial) implications.

Those in New Zealand who utilise Troponin T assays are currently in the process of changing to a new 5th generation assay. Whereas the 4th generation one was reliable down to levels of 0.03ng/mL, the new one is accurate to 0.014 ng/mL (3) which is the 99th percentile (as specified by the international definition). An overseeing clinical reference group has decided to take advantage of the change in assay to use more sensible units so that 0.14 ng/mL becomes 14 ng/L. Detectable levels (below this threshold) can be found in some 50% of normal healthy individuals and levels above the 99% threshold can be found associated with a growing list of alternative conditions. A number of different approaches have been made to assess the impact of the new test but it is clear that a single level in the new high sensitivity range is not nearly specific enough to use as a triage tool in an acute coronary syndrome. Early work in Wellington does suggest that around 30% of those with possible acute coronary syndromes and negative 4th generation troponin T tests will have a level above the 99th percentile but only around 3% will show changes in sequential samples that would qualify for a diagnosis of myocardial infarction (4). From a combination of method comparison studies and stability studies in healthy individuals and those with consistently raised levels (e.g. cardiomyopathy), a minimum change of 20% in level if above 50 ng/L and 50% change if below that threshold seems to accord best with clinical diagnosis. This accords closely with a published proposed triage algorithm (5).

Another advantage of a more sensitive test is that patients with a myocardial infarction will show diagnostic changes earlier. It is still a little unclear how soon an infarct can be ruled out but a negative test (<14 ng/L) 6 hours after the onset of chest pain appears to confer about 90% rule-out confidence. The algorithm we have advised in the Wellington region is shown in Figure 1.

One consequence of moving to the new test is the need for medical staff to think more carefully about the significance of a positive test in the context of the clinical presentation of the patient. In recent years, a ‘positive’ troponin test has been used as the key decision breaker for admission and for triage to angiography. In truth, the patients who benefit most from acute intervention are those at highest risk as calculated from a range of factors, of which a raised biomarker is just one. To get the maximum benefit from our resources in this area, we need to introduce routine risk scoring

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systems such as proposed by the TIMI group (6), GRACE researchers (7) or a simple one derived from a recent meta-analysis (8) that interestingly, does not include biomarker results at all!

In some ways the new tests have made life more complicated for clinicians, both in assessing patients with possible acute coronary syndromes and when troponin tests are requested in a myriad of other circumstances where relevance is questionable. Commentaries on the new high sensitivity tests have rued the transition from “a lousy assay but a great test” to a “great assay but a lousy test” (9) and challenged the results to fit into a neat Bayesian model (10). However, the reintroduction of a need for additional thought and clinical reasoning into the assessment and triage of patients must surely be welcome along with the increased precision and speedier processing of patients that the sensitive assays can provide.

References

Address for correspondence: Stewart Mann, Department of Medicine, School of medicine and health Sciences, University of Otago, PO Box 7343, Wellington South 6242, New Zealand. Email: stewart.mann@otago.ac.nz

Table 1. Elevations of cTn above the 99th percentile in the absence of an acute coronary syndrome.

<table>
<thead>
<tr>
<th>“Healthy population”</th>
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<tbody>
<tr>
<td>• 1/100 (by definition)</td>
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<tr>
<td>• Endurance exercise</td>
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<tr>
<td>Cardiac Causes</td>
</tr>
<tr>
<td>• Chronic stable angina</td>
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<tr>
<td>• Congestive heart failure</td>
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<tr>
<td>• Arrhythmias, heart block</td>
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<tr>
<td>• Cardiac contusion, ablation, pacing, cardioversion, biopsy</td>
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<tr>
<td>• Cardiomyopathy: HCM, Takotsubo</td>
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<tr>
<td>• Inflammation - e.g. myocarditis, endocarditis, rejection</td>
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<tr>
<td>• Rhabdomyolysis with cardiac injury</td>
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<tr>
<td>• Infiltrative diseases, e.g., amyloidosis, haemochromatosis, sarcoidosis, scleroderma</td>
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<tr>
<td>• Drug toxicity, e.g., adriamycin, herceptin, clozapine</td>
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<td>• Aortic dissection, aortic valve disease</td>
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Non-cardiac clinical causes

• Acute and chronic renal failure
• Acute neurological disease, including stroke, or subarachnoid haemorrhage

Figure 1. Algorithm introduced in the Wellington region for triage of acute coronary syndrome diagnosis using high-sensitivity troponin T.