The quest for diagnostic certainty: an unreal expectation in a real world

'When I say a word it means what I want it to mean, nothing more and nothing less.'
Humpty Dumpty (Alice through the Looking Glass)

When is an infarct not an infarct? When it is an infarctlet, a necroset or a troponinosis.[1] The advent of the cardiac-specific troponins as diagnostic tests has created confusion in the minds of some cardiologists. The fact that cardiac troponins may be used to diagnose previously unsuspected myocardial damage in patients presenting with acute coronary syndromes, when acute myocardial infarction (AMI) has been ruled out by conventional World Health Organization criteria, has been amply demonstrated since the original report by Hamm *et al*.[2] The value of the cardiac troponin in predicting outcome in patients presenting with both ST elevation myocardial infarction (STEMI)[3] and non-ST elevation acute myocardial infarction (NSTEMI)[4,5] has been shown and confirmed by meta-analysis.[6] Indeed, in no report has troponin failed to predict an increased risk of an adverse outcome in patients presenting acutely with chest pain. This is a remarkable achievement for a biochemical test.

At the same time, the cardiospecificity of troponin measurements has been demonstrated in a number of situations, such as physical training, where it is particularly useful for the differential diagnosis of cardiac damage in the presence of elevated values of the more traditional markers such as creatine kinase (CK) and its MB isoenzymes (CK-MB).[7,8]

Possible pitfalls in troponin estimation

The power of troponin measurements has led to two types of diagnostic confusion. The first pertains to the clinical significance of an undetectable troponin value in a patient with chest pain. The article by Rao and Evans in this issue of *The British Journal of Cardiology* (see pages 221–2) illustrates this point. Three patients are presented, all of whom have negative troponin but all of whom have cardiovascular disease. Clearly, the presence of a negative troponin alone does not preclude the presence of extensive vascular disease. This fact needs to be appreciated by all those practising in general medicine, cardiology and the emergency department.

Why should a patient with cardiac disease have undetectable troponin values? There are a number of possibilities. The first and most important thing to realise is that detectable troponin is the marker of an active unstable plaque which is generating platelet aggregates and downstream platelet embolisation.[9,10] It is these platelet microemboli which cause micronecrosis and cardiac troponin release. Paradoxically, such lesions do not tend to occur on coronary artery stenoses, which are already flow-limiting, but on previously clinically silent lesions. In contrast, severely stenotic lesions with downstream ischaemia can occur in the absence of troponin elevation, as is demonstrated in these three cases. The recent European and British guidelines[11] recognise this possibility stating that further testing is required in patients who are troponin-negative. This reflects the fact that a negative troponin does not exclude prognostically significant coronary artery disease. The combination of a negative troponin and a negative provocative test is, however, a very good indicator of a favourable outcome.[12]

The other factor that must be taken into consideration is timing. Biochemical markers are limited in that their release follows a distinct kinetic profile. A popular misconception has arisen that troponin elevation 12 hours from onset of symptoms is 100% sensitive. Unfortunately, this is not the case, as has been illustrated in the results of a recent consensus conference on the use of biochemical markers.[13] Rather, 100% sensitivity is achieved 12 hours from admission to hospital. The timing of symptoms by patients is unreliable in 50% of cases. In our own studies of patients with non-ST-segment-elevation acute coronary syndromes (ACS), we have found that 100% sensitivity requires at least 12 hours of observation.

Troponins in clinical context

The second realisation is that elevation of cardiac troponins occurs in a range of conditions other than acute coronary syndromes. Cardiac troponins are completely specific for cardiac damage, but cardiac damage can occur in a range of other situations. These range from the clearly obvious, such as myocardial laceration, bypass surgery and the severe coronary vasospasm caused by cocaine, to the more paradoxical incidental elevations noted in patients following a cerebrovascular accident or pulmonary embolus. It is important to realise

that in all cases the troponin elevation carries prognostic significance, even though its release is a secondary rather than a primary event.

There is no such thing as a biochemical test for acute myocardial infarction, but merely a biochemical test which is specific for myocardial damage. The diagnosis of acute myocardial infarction is clinical and will remain so. The great advantage of cardiac troponin is that it provides a specific test which, in combination with other clinical and electrocardiographic features, as appropriate, allows a highly accurate diagnosis of AMI in patients with suspected acute coronary syndromes. This is recognised in the recent consensus document on the diagnosis of AMI.[14]

Elevations of troponin can, therefore, be considered under three categories:

- primary ischaemic cardiac injury (PICI) occurs with troponin release corresponding to rupture of an atheromatous plaque
- secondary ischaemic cardiac injury (SICI) occurs due to ischaemic cardiac damage which is not primarily due to a ruptured coronary plaque, such as clot or atheroma embolising distally during PCI
- the third group, non-ischaemic cardiac injury (NICI), occurs where primary cardiac damage is a result of a non-ischaemic mechanism.

Examples would include myocarditis, cytotoxic chemotherapy, cardiac trauma or involvement in some other multi-organ disease, such as polymyositis. The three categories of cardiac injury are summarised in table 1. Hence troponin, like all tests, must be interpreted in the appropriate clinical context.

Table 1. Classification of troponin elevation by pathophysiology

Primary ischaemic cardiac injury		
Thrombotic coronary artery occlusion due to platelets/fibrin	ST elevation MI Non-ST elevation MI (non-Q-wave AMI plus troponin-positive unstable angina)	
Secondary ischaemic cardiac injury		
Coronary intervention	Primary PTCA	Distal embolisation from clot or atheroma Side branch occlusion
	Elective PTCA	Distal embolisation from atheroma or debris Side branch occlusion
	CABG	Global ischaemia from inadequate perfusion, myocardial cell protection or anoxia
Sympathomimetics	Cocaine Catecholamine storm	Head injury, stroke, intracerebral bleed
Pulmonary embolus	Presumed right heart strain or hypoxia	
Coronary artery spasm	Japan - up to 10% of admissions	
Coronary artery embolisation	Clot Air	
Coronary artery inflammation with microvascular occlusion	Vasculitides Connective tissue disease SLE	
End stage renal failure	More severe CAD but 50% have normal coronaries	
Rhythm disturbances	Prolonged tachyarrhythmia or bradyarrhythmia with IHD	
Acute heart failure	Only if due to IHD	
Direct coronary artery trauma		
Extreme endurance exercise	Extreme marathons Extreme training	Wall motion abnormalities cTn +ve deaths presumed due to extreme oxygen debt producing ischaemia
Non-ischaemic cardiac injury		
Known causes of myocarditis	Infection	Bacterial Viral
	Inflammation	
	Autoimmune	Polymyositis Scleroderma Sarcoid
	Drugs	Alcohol Chemotherapy
Cardiac trauma	Direct	RTA Stabbing
	Cardiac surgery	
Metabolic/toxic	Renal failure Multiple organ failure	

Key: MI = myocardial infarction; AMI = acute myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft; SLE = systemic lupus erythematosus; CAD = coronary artery disease; IHD = ischaemic heart disease; RTA = road traffic accident

Logical assessment of patients

There is clearly a range of pitfalls in using troponin to assess patients in the emergency department. Can these be reconciled? The answer is yes: the clues are apparent both from these case reports and from the published literature. A number of publications have shown that three to six hour observation periods can be used safely.[15,16] The essence of these studies is case selection.

Patients can be divided into three categories. The first are those that present with definite ECG changes of an acute coronary syndrome, such as ST segment elevation. Management of these patients is a 'no brainer'. The patients are at high risk and the objective of management is to open the occluded artery. The second group of patients are those who are at medium to high risk. These are patients with multiple risk factors, a suspicious ECG or suspicious clinical features. The three cases of Rao and Evans fall into this category. The final group are those patients with an atypical history and a normal ECG who would be considered clinically at low

risk and sent home. An audit of such cases shows that 5% with prognostically significant myocardial damage are missed,[17] but it is this group which was considered in the two studies cited above. In both studies, patients had a prior probability of AMI of 5%. A completely normal ECG has in itself a good prognostic outcome and, when combined with a negative troponin at 4–6 hours from admission, it denotes a low-risk population. This population is not event-free, as both studies showed, and further assessment is required.

Conclusions

Troponin measurement provides an excellent tool for the clinician for risk stratification but must be considered as a part of (and not the whole of) the diagnostic process. Positive troponins will occur in a range of conditions and clinicians need to be aware of this. Similarly, a negative troponin does not exclude significant coronary artery disease. A negative troponin should be followed up by subsequent appropriate investigations according to the risk group; within 24 hours of hospital admission for the high-risk group or via a chest pain evaluation clinic for the low-risk group. This is the standard at which we should aim.

The clinical benefits are obvious and it also provides a way of decongesting blocked hospital beds and trolleys. For a typical district general hospital, we have estimated the financial savings of a rapid discharge policy to be of the order of £1.2 million per annum.

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Paul Collinson
Consultant Chemical Pathologist
Second Floor, Jenner Wing, St George's Hospital,
Blackshaw Road, London, SW17 0QT.

Peter Stubbs
Consultant Cardiologist
Mayday Hospital, London Road, Thornton Heath,
Croydon, Surrey, CR7 7YE.

Correspondence to: Dr P Collinson
(email: poctrop@poctrop.demon.co.uk or
paul.collinson@stgeorges.nhs.uk)