PAPER: HYPER-TROPONINAEMIA – A LABORATORY RESULT, NOT A CLINICAL DIAGNOSIS

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INTRODUCTION

Measurement of cardiac troponin in patients presenting with typical symptoms of angina and myocardial ischaemia has become an established component of risk assessment, guiding the clinical management of acute coronary syndromes. Troponin assays are extremely sensitive for cardiomyocyte damage; the incorporation of a troponin elevation into diagnostic criteria for myocardial infarction (MI) has led to a redefining of this term to encompass a wider population of patients who until recently would have been diagnosed with unstable angina.[1] This article briefly reviews the detection and new diagnostic criteria for MI, and explores the benefits as well as some problematic issues that have arisen from the adoption of troponin testing in clinical practice.

DETECTION OF NECROSIS OF MYOCARDIAL CELLS

The presence, extent and degree of myocardial damage resulting from prolonged ischaemia can be assessed by different means including pathologic examination, measurement of myocardial proteins in the blood, ECG recordings (ST-T segment changes, Q waves) and imaging modalities, such as myocardial perfusion imaging and echocardiography. Myocardial necrosis can be recognised by the appearance of different proteins released into the blood from damaged myocytes including myoglobin, cardiac troponins T and I, creatine kinase and lactate dehydrogenase. The cardiac troponins (I or T) are the most recently described and preferred biomarkers of cardiomyocyte damage owing to their near absolute myocardial tissue specificity and high sensitivity with even microscopic foci of myocardial necrosis giving rise to detectable troponin elevations.[2] Troponin I is the regulatory subunit of the troponin complex associated with actin filaments of muscle. Troponins C, I and T control muscle contraction in response to intracellular calcium. Three isoforms of troponin I are encoded by separate genes, two are found in skeletal muscle with molecular weight around 19,800 and the third larger cardiac isoform (molecular weight 24,000 Daltons) has a 40% difference in amino acid sequence from the skeletal isoforms. Unlike the creatine kinase MB isoform and troponin T, the cardiac form of troponin I is not found in other tissues nor is it produced in response to regeneration of damaged muscle cells.[3] Myocardial ischaemia results in damage to the cell membrane and loss of the soluble cytoplasmic proteins including creatine kinase. The poor circulation in the affected area results in a gradual clearance of these proteins via the lymphatic system and a gradual increase in their circulating levels: they become elevated beyond the reference range after four to six hours. Structural components, such as troponin I, are released later than soluble enzymes such as creatine kinase. Peripheral blood levels of all markers subsequently fall due to the clearance of the proteins from the blood and a loss of enzymatic activity. Peak levels of creatine kinase typically occur from 12–24 hours after the onset of pain, and decline to normal by about three days. Troponin I rises to a peak by 13–60 hours.[3] Its decline is much slower, remaining elevated for three to ten days post-infarction. An increased value for cardiac troponin should be defined as a measurement exceeding the 99th centile of a reference control group.[4] Significant variations exist between different assays and each laboratory should define a reference range for its own assay protocol.[1,4]

REDEFINING MI

The recent incorporation of elevation of cardiac troponins into the definition of MI by the European Society of Cardiology and the American College of Cardiology (Table I) has led to patients with presumably microscopic amounts of necrosis caused by ischaemia being defined as having had myocardial infarcts. This change was spurred on by the fact that any amount of myocardial damage as evidenced by troponin elevation is associated with impaired clinical outcome. A rise in the incidence of new MI and a fall in case fatality rates are immediate epidemiological results of adopting the new

TABLE 1

European Society of Cardiology/American College of Cardiology definition of myocardial infarction.

Any of the following criteria satisfy diagnosis of an acute, evolving or recent MI.

1 Typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase-MB) of biochemical markers of myocardial necrosis with at least one of the following:
- **a)** ischaemic symptoms;
- **b)** development of pathological Q-waves on the electrocardiogram;
- **c)** electrocardiogram changes indicative of MI (ST-segment elevation or depression);
- **d)** coronary artery intervention (e.g. coronary angioplasty).

2 Pathological findings of acute MI.

definition, as more cases with smaller amounts of 'at risk' myocardium are included under the definition. Recruitment and outcomes from clinical trials are similarly affected by this change in criteria. Epidemiologists and the organisers of trials are well equipped to accommodate new definitions, and perhaps the most important effect of redefining MI is the increased number of patients who will face the social and psychological effects of being diagnosed as having had a 'heart attack'. McKenna has highlighted the importance of further qualification of the diagnosis of MI, using the new definition, in terms of magnitude of muscle damage and impairment of cardiac function both for case records and as part of the information communicated to the patient about their illness.[5] This may not be straightforward in clinical practice compared to using a diagnostic label such as unstable angina and may be one reason why terms such as 'non-Q-wave MI' and 'troponin-positive acute coronary syndrome' remain popular phrases to describe patients with certain clinical features.

RISK STRATIFICATION OF PATIENTS PRESENTING WITH ISCHAEMIC CHEST PAIN

Patients presenting with symptoms of MI have varying levels of risk for suffering unfavourable outcomes, including MI and death. Targeting intensive therapies to those patients at higher risk of adverse events should be the goal of assessment, and troponin measurement has greatly facilitated this process.

The link between elevated troponin levels and adverse outcomes in patients with both ST-elevation and non-ST-elevation MI has been confirmed repeatedly.[6,7] In a meta-analysis of cohort studies measuring Troponin I, a positive value was associated with a mean death rate of 8·4% over a median follow-up of eight weeks as compared to a death rate of 0·7% in troponin-negative patients.[8] Other important clinical variables help identify this high-risk subset including, in particular, the presence of ST segment shift on the ECG,[9] age and the presence of cardiac risk factors. Patients presenting with ischaemic chest pain who are troponin positive have a reduced mortality and a decrease in incidence of further cardiac event rates if they receive antiplatelet therapy, including aspirin and clopidogrel,[10] β-blockers, low molecular weight heparin,[11] and aggressive risk factor control including the prescription of statins.[12] Depending on their response to these treatments and the presence of other indicators of clinical risk, they should be considered for coronary angiography ideally within 48 hours of admission.[13,14] A further use of troponin testing has been to identify low-risk patients presenting with chest pain who can be discharged home from emergency departments.[15]

TROPONIN ELEVATIONS IN PATIENTS WITHOUT ACUTE CORONARY SYNDROMES

The success of the troponin assay has led to its widespread use in patients presenting to acute medical admission units. Its strong association in the literature with acute coronary syndromes can lead, in our experience, to a misguided belief that an elevated result always reflects myocardial necrosis secondary to atheromatous plaque rupture and epicardial coronary artery occlusion. Detectable myocardial troponin release occurs in a wide range of clinical situations (summarised in Table 2). Percutaneous intervention produces troponin elevations through transient vessel occlusion, plaque rupture and microembolisation.[16] Similarly, coronary vasospasm with or without cocaine use produces levels of myonecrosis that may have previously gone undetected by conventional cardiac enzyme analysis.[17] The importance of the clinical scenario must be emphasised in reaching a final diagnosis, and clinicians should be aware of not relying too heavily on the troponin level, particularly when the history is not typical for angina.

Significant troponin release from the myocardium occurs in a variety of conditions that may present with chest pain and dyspnoea.[18] Right ventricular strain or pulmonary infarction following pulmonary embolism,[19] and inflammatory changes associated with pericarditis and myocarditis lead to cardiomyocyte disruption and necrosis with ensuing troponin release.[20] Patients with septicaemia may also have troponin elevations.[21] Concluding that an elevated troponin reflects an underlying acute coronary syndrome can lead to inappropriate investigation, including coronary angiography and treatment.

TABLE 2

Conditions that may be associated with detectable myocardial troponin release.

1	**Coronary artery occlusion**
	Plaque rupture, coronary occlusion, platelet-thrombin microemboli and microvascular obstruction
	Coronary spasm
	Coronary dissection
	Coronary embolism (from vegetation)
2	**Inflammation**
	Pericarditis
	Myocarditis
3	**Direct myocardial damage**
	Chest wall trauma
	Surgical manipulation
	Radiofrequency ablation
	Drug toxicity (adriamycin, 5-fluorouracil)
4	**Miscellaneous**
	Tachyarrhythmias
	Acute congestive cardiac failure
	Severe pulmonary embolism
	Severe exacerbation of chronic obstructive airways disease
	Renal failure
	Sepsis, particularly septic shock
	Ischaemic stroke or subarachnoid haemorrhage
	Gastrointestinal haemorrhage

Patients with elevated troponin levels who have no clear history of chest pain present a further source of confusion. The use of troponin assays as part of a 'biochemical screen' in patients presenting with conditions that may have a cardiac basis should perhaps be discouraged. One study examined the final diagnoses in patients presenting to an emergency unit with troponin elevation, a normal creatine kinase MB fraction and no history of chest pain. The diagnoses ranged through exacerbation of congestive heart failure, stroke, respiratory failure, cirrhosis, gastrointestinal bleeding, renal failure, to atrial fibrillation.[22] This particular study failed to detect an association between troponin elevation and mortality at one year, although subsequent studies have suggested that an association with adverse outcome remains for pulmonary embolus[23] and other non-cardiac conditions including stroke[24] and renal failure.[25, 26]

Finally, routine troponin analysis has not yet been validated in other common cardiac conditions. Slight elevations in troponin levels have been observed in high endurance athletes.[18] It is also not surprising that the stress on the heart during decompensated left ventricular failure[27] and tachyarrhythmias may be associated with elevated troponin levels in the absence of ischaemic chest pain. Whereas these conditions may often be associated with coronary artery disease and troponin elevations may prove again to be a further indicator of outcome,[28] there are currently no large studies from which to draw information on the meaning of an elevated troponin result in terms of prognosis or patient management.

A NEGATIVE TROPONIN DOES NOT EXCLUDE THE POSSIBILITY OF SIGNIFICANT CORONARY ARTERY DISEASE

Troponins are excellent discriminators of high risk in patients presenting with ischaemic chest pain. Unfortunately, the converse is not true in that a normal troponin does not necessarily exclude significant coronary artery disease. The recent guidelines highlight the importance of further testing in selected higher risk patients with convincing histories.[1] Clinicians may erroneously misplace trust in normal troponin levels. Excellent sensitivity for myocyte necrosis has been demonstrated if the investigation is carried out 12 hours from the time of presentation to the medical unit. Earlier testing or samples timed on the patient's own estimation of when chest pain started may miss the troponin peak.

The underlying mechanism of ischaemic chest pain is also an important determinant of troponin release. Patients with fixed coronary artery stenoses may have troublesome angina and prognostically significant coronary artery disease. However, myonecrosis and troponin elevation are more closely associated with plaque rupture, fresh thrombus formation and associated distal embolisation. The combination of a normal troponin and an exercise stress test greatly reduce the likelihood of either type of lesion and are therefore very reassuring.[1]

Troponin assays have revolutionised the management of patients presenting with ischaemic chest pain by facilitating early discharge of low-risk patients and targeting expensive treatments to those who are more likely to benefit from them. Cardiac troponin release occurs in many other diseases and the significance of this is still a matter for research. Clinicians should remain wary of misinterpreting an elevated level when the clinical presentation and ECG changes do not fit with MI. The consequences in terms of incorrect diagnosis and inappropriate investigation or treatment may be severe.

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