Commentary

Pitfalls and problems of relying on serum troponin

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Summary

Cardiac troponin (cT) is released after myocardial damage. In the appropriate clinical setting, a measured elevation of cT can increase the diagnostic rate of myocardial infarction and acute coronary syndrome. Elevations of cT, however, can occur in a wide variety of other clinical situations. Failure to recognize this can lead to an over-diagnosis of myocardial infarction (MI). We present clinical cases from our institution that illustrate this diagnostic problem, and review similar cases in the literature. We also discuss the implications of an erroneous diagnosis of myocardial infarction, for the patient and for the health services.

Introduction

The introduction of measures of cardiac troponin (cT) has revolutionized the diagnosis and management of the acute coronary syndromes (ACS). Release of cT occurs after irreversible cardiac myocyte injury, along with a number of other proteins (e.g. myoglobin, lactate dehydrogenase and creatine kinase). The troponin complex comprises three subunits. Each subunit is a protein, and together they regulate the calcium-dependent interactions between actin and myosin, which result in contraction and relaxation of striated muscle. Whereas the identical troponin C is expressed by both skeletal and cardiac muscle, the amino acid sequences of cardiac troponins I (cTI) and T (cTT) differ from the sequences in skeletal muscle. This has allowed monoclonal antibodies to be formed against cTI and cTT that have very little cross-reactivity to the skeletal isoforms.1 Both are very sensitive markers for the detection of myocardial damage and powerful prognostic indicators of future adverse cardiac events.2–5

The sensitivity of cT as a diagnostic tool has led to an increased rate of diagnosis of MI. A recent study by Ferguson et al.6 considered 80 patients who presented with a history suggestive of ischaemic chest pain (excluding those who had ECG changes indicating ‘obvious’ MI) and used both the new cT and conventional cardiac enzymes (creatine kinase and CK-MB) to diagnose MI. When the cT I level was measured 12 to 24 h after the onset of typical cardiac symptoms, then an elevated level became ‘a highly specific diagnostic indicator of myocardial damage’. It was concluded that cT could be used in preference to the conventional cardiac enzyme criteria. Forty percent of patients fulfilled the cT criteria for MI, compared to 29% using conventional cardiac enzymes alone. Although this may at first be considered to imply that the diagnosis of acute MI was previously missed due to inadequate diagnostic techniques, it is becoming increasingly apparent that false positive results can occur with cT, which can lead to over-diagnosis of MI, with
subsequent implications for patients and the health service.

There is increasing evidence that false positives also occur in a wide range of other conditions without significant coronary disease. Bakshi et al. reported 21 patients with elevated cTII who had normal coronary angiograms. The diagnoses in this group included tachycardia (6), physical exertion (2), pericarditis (2), severe congestive cardiac failure (2) and unknown (10). They concluded that a rise in cTI may have a cause other than ACS.

This article describes a number of cases and reviews the literature that illustrates raised cT in disease states other than unstable acute coronary syndromes. The cases described have all occurred recently within the practice of our institution. The initial clinical scenarios show that a reliance on troponin alone to diagnose myocardial infarction may deflect the physician away from correct treatment of the underlying condition.

Heart failure
Case
A 75-year-old woman presented with a 2-day history of increasing breathlessness, and marked orthopnoea. She had a previous history of atrial fibrillation, asthma and hypertension. On examination, she had clinical signs of fluid overload with pulmonary and ankle oedema and raised central venous pressure. She had functional mitral incompetence. ECG showed left bundle branch block, and the cTT level was 0.23 µg/l. CK was within normal limits, leading the physician to make a diagnosis of acute myocardial infarction in association with left ventricular failure. She had been investigated previously by cardiac catheterization and found to have normal coronary angiograms and a dilated cardiomyopathy.

Comment
Other sources have observed raised cT in cardiac failure and speculated about the mechanism responsible. In severe heart failure, raised levels of cT have been detected during symptom-limited exercise (compared to normal levels at rest) in 27 patients with NYHA II-III. There may also be a difference between cT levels in patients with left-sided and those with right-sided cardiac failure—Guler et al. found that levels were comparable between patients with right-sided failure and controls, but were significantly increased in left-sided failure. They postulated that small areas of myocardial cell death were responsible for this phenomena. Interestingly, CK-MB and thyroglobulin (previously popular as markers of myocardial injury) remained unchanged between the three groups. It is possible that the increase in wall stress that occurs in heart failure syndrome may result in some myocyte damage and troponin release. It is only the high sensitivity of the troponin assays that detect this, compared to the sensitivities of previous markers. To date, any additional prognostic significance of troponin detection in a patient with diagnosed heart failure has not been determined.

Thromboembolic disease
Cases
A 74-year-old man presented with a 10-day history of progressive shortage of breath with central chest discomfort. He had undergone a left knee hemiarthroplasty 10 weeks earlier. Examination revealed a normal blood pressure, a clear chest and normal heart sounds. However, pulse oximetry revealed a low blood oxygen saturation. His ECG showed a dominant R wave in V1 with right axis deviation. Blood gases revealed marked hypoxia (pO2 = 7.4 kPa, pCO2 and pH normal). Chest X-ray showed an area of oligaemia at the right mid zone with no evidence of pulmonary congestion. Troponin T on admission was 1.2 µg/l, although the first CK sample was not elevated. The initial differential diagnosis included myocardial infarction, and he was treated with high-dose aspirin and low-molecular-weight heparin. Subsequent investigations revealed a massive pulmonary embolism with right ventricular dysfunction. He received thrombolysis with alteplase, with a prompt improvement in symptoms.

A 69-year-old man presented with four episodes of acute dyspnoea, which occurred at rest and resolved spontaneously. He had a past history of polymyositis and paroxysmal atrial fibrillation and was receiving treatment with oral prednisolone 50 mg daily and sotalol 40 mg bd. On examination he was desaturated on air (SaO2 95%), had a heart rate of 72 bpm and no other abnormal clinical findings. The resting 12-lead ECG showed T-wave inversion in leads V1–V3, lead III and AVF. Troponin I was 42.9 (normal <0.03) µg/l. Creatinine kinase was normal on admission and remained so. A diagnosis of non-Q-wave myocardial infarction was made, and he was treated with aspirin and clopidogrel prior to transfer for angiography. This was deferred because of an acute urinary tract infection, and his symptoms subsided on medical therapy. Six weeks later, he was readmitted with
increasing breathlessness. A CT pulmonary angiogram showed multiple bilateral thrombo-emboli. Doppler examination revealed a left popliteal deep vein thrombosis.

Comment

There have been several reports of positive cT assays in patients with pulmonary embolism as described above. Gibson and Hanchard reported the case of an elderly woman who died with the diagnosis of MI shortly after a raised cTI was measured. At post-mortem, she was found to have small-cell lung cancer complicated by pulmonary embolism. There was no evidence of myocardial injury.\textsuperscript{10} Dieter et al. explored the diagnostic utility of this finding but found no significant difference between those with positive or negative ventilation-perfusion scan results.\textsuperscript{11} This would seem to suggest that cT is not a reliable marker for use in the diagnosis of pulmonary embolism. However a number of studies have now shown that patients with a positive cT have larger, more clinically significant pulmonary embolisms. This is best explained by the hypothesis that cT is raised in pulmonary embolism when there is myocardial injury with a degree of right ventricular dysfunction. One multi-centre study found that high cT was strongly correlated with increased mortality, complications and recurrent embolism.\textsuperscript{12} Another German group\textsuperscript{13} found that patients with high cT levels had more ventilation-perfusion defects, and claimed that raised cT indicates a degree of RV dysfunction.

Pulmonary embolism has a significant mortality, even when correctly diagnosed and treated,\textsuperscript{14} and the mortality in cases where the diagnosis is missed is even higher. It is therefore important to recognize that although a raised cT does not diagnose pulmonary embolism, elevations can occur in association with a pulmonary embolism and possibly reflect larger thromboembolic load.

Renal failure

Case

A 34-year-old man with dialysis-dependent diabetic nephropathy presented with typical anginal chest pain at the time of dialysis. He had many other cardiovascular complications related to his diabetes, with peripheral vascular disease and a previous clinical diagnosis of ischaemic heart disease. He was registered blind secondary to retinopathy, and was taking treatment for hypertension. The ECG showed voltage criteria for left ventricular hypertrophy with widespread repolarization changes through the lateral chest leads, the cT was elevated at 0.44 μg/l. He was referred for a cardiology opinion, with a view to cardiac catheterization. It was noted that the cT elevation could be due to the chronic renal failure and ECG changes consistent with his hypertension. Nevertheless angiography was performed, and demonstrated remarkably little coronary atheroma with no flow-limiting lesions. Treatment was not altered as a result.

Comment

It remains unclear why cT elevations are detected in chronic renal failure. It has been suggested that uraemic muscle may express fetal muscle that contains cTT.\textsuperscript{15} Renal dysfunction may also reduce the clearance of cT, causing a false-positive result. There is a poor correlation between cT-positive samples and cardiac events in patients on intermittent haemodialysis.\textsuperscript{16} Furthermore, in this situation cT levels may have a limited prognostic role for future cardiac events.\textsuperscript{17} The sensitivity and specificity of cTT and cTI for cardiac events in patients on intermittent haemodialysis are lower, compared to studies involving people with normal renal function.\textsuperscript{18,19} However, for patients with other evidence of acute coronary syndrome (chest pain and ECG ST depression), and the finding of a raised troponin may still be independently predictive of adverse short-term outcomes.\textsuperscript{20} Overall, cT should be considered as an imperfect marker in patients with renal dysfunction who present with symptoms suggestive of an acute coronary syndrome.\textsuperscript{21}

Arrhythmias and DC shock

Cases

A 62-year-old jogger developed chest pain and collapsed during a 5 mile run. On arrival, he had a tachycardia of 230 bpm with a broad complex appearance on the ECG, BP was 87/68 mmHg. The arrhythmia spontaneously reverted to sinus rhythm. Troponin I was 7.6 μg/l and CK normal. He had a history of an inferior myocardial infarction in 1995 and coronary surgery in 1997, but had experienced no symptoms with exercise until this episode. Subsequent exercise test revealed no evidence of inducible ischaemia into stage 4 of the BRUCE protocol.

A 45-year-old woman presented with a narrow complex tachycardia with a rate of 170 bpm. This reverted to sinus rhythm with a bolus of intravenous adenosine. cT was subsequently measured and
found to be raised at 1.3 μg/l. This was the 13th admission in the previous 18 months, and on three previous occasions myocardial infarction had been diagnosed on the basis of the elevated troponin. Resting 12-lead ECG remained normal.

Comment
The cT elevations in both cases reflect myocardial damage resulting from rapid heart rates. There was no evidence of an acute coronary syndrome or myocardial ischaemia as the underlying aetiology. Cardioversion of atrial flutter or fibrillation has been reported not to be associated with increases in cT levels.22 There is one other published case report of elevated cT with supraventricular arrhythmia, in an 11-year-old with a diagnosis of hypertrophic cardiomyopathy, who had two episodes of supraventricular tachycardia but no electrocardiographic evidence of ischaemia.23 When increased levels are found in ventricular tachycardia (VT) or ventricular fibrillation (VF), it is unclear whether this is due to underlying myocardial ischaemia, dysfunction or haemodynamic deterioration.

Sepsis
Case
A 63-year-old woman was admitted confused, agitated and breathless following a ‘gradual deterioration’ at home. She had a history of hypertension, but not of ischaemic heart disease. On examination, she looked ill with pyrexia of 39.5°C, hypotension and widespread crackles on chest auscultation. She had tender hepatomegaly. Blood gases showed hypoxia (pO2 = 6.0 kPa on 4 lO2/min and pCO2 = 6.22 kPa, pH = 7.6). She was alkalotic and hypokalaemic. cTT was elevated at 1.6 μg/l. Resting electrocardiograph was normal. Abdominal ultrasound showed acute cholecystitis. She died from Gram-negative septicaemia.

Comment
Various sources have reported raised cT levels in lobar pneumonia with no evidence of renal failure or acute coronary syndrome.24,25 One study reported elevated cT in 85% of patients with sepsis, septic shock or systemic inflammatory response syndrome.26 Many of these patients were infected with *Streptococcus pneumoniae*. The mechanism by which infection causes cT release is not yet understood.

Inflammatory conditions and trauma
Endogenous antibodies can interfere with the immunoassay measurement of cT. Raised levels have been reported in seropositive rheumatoid arthritis,27 acute rheumatic fever,28 and in the presence of heterophile antibody.29,30

In polymyositis and dermatomyositis, raised cT has also been documented.31 The levels were related to the severity of disease, and also to markers of skeletal muscle damage. The skeletal isoform of troponin (sTI) is a myofibrillar protein, which is very specific for musculoskeletal injury.12 In the assessment of 20 patients with soft tissue injury and 16 orthopaedic patients, raised sTI levels with normal cTI were found. This suggests that a raised cT in the presence of musculoskeletal disease occurs for a reason other than simple muscle damage.

A rise in cTI has been shown to occur during acute idiopathic pericarditis.33 Cardiac amyloidosis has also been associated with raised cTI levels.34 In both of these conditions, cardiac damage occurs, but by a mechanism other than thrombo-occlusive coronary artery disease. Loss of integrity of cardiac myocyte membranes allows release of troponin and other macromolecules into the cardiac interstitium and eventually the peripheral circulation.

Chemotherapy
High-dose cyclophosphamide is used in patients with breast cancer, and is associated with cardiac toxicity and fatality in a minority of patients.35 However, high-dose chemotherapy was associated with raised plasma cTI in one third of patients.36 Furthermore, these were the patients who progressed to reduction in LV ejection fraction during the following 12 months.36 It seems that in this context, cT can be used as a sensitive and reliable marker of myocardial damage, and this may have a prognostic role in selecting patients susceptible to subsequent overt LV dysfunction.

Animal attacks
In a patient stung by a jellyfish37 in tropical waters, and in eight young children with signs and symptoms of severe scorpion envenoming,38 cTI levels were increased. These levels met the diagnostic criteria for the diagnosis of MI, but normalized rapidly. The venom of these creatures may well cause a degree of transient myocyte toxicity in the absence of underlying coronary disease. In this
Conclusions

Although the use of troponin in the diagnosis and risk assessment of patients presenting with chest pain should be welcomed, the practicing physician must always interpret an abnormal test result in the clinical context (Bayes' theorem in practice). This series of case reports illustrates how an abnormal serum cT can occur as a result of a number of different pathogeneses. The test has a high sensitivity for the detection of myocardial damage, and the negative predictive value of the test is very useful in facilitating the early discharge of patients. However, it must be remembered that an elevated cT level simply means ‘cardiac damage’. The detection of cT reflects a loss of integrity of cardiac myocyte membranes which can be due to a variety of pathological processes, and is not specific to ischaemic damage alone. Thus, an elevated cT alone does not imply the presence of an acute coronary thrombo-occlusive event. The test must be interpreted in the light of a thorough clinical evaluation in order to make best use of the result. Without this, the current emphasis on aggressive management of the acute coronary syndrome, with the use of anti-platelet drugs and referral for invasive investigations and treatment, will lead to inappropriate referrals to Regional Cardiac Centres. Furthermore, the acute clinical management may be inappropriate and fail to properly treat the underlying pathology.

The main problem for the clinician, therefore, is to decide the level of emphasis that an elevated troponin level should carry in managing an individual patient. The upper limit of the normal reference range is defined as two standard deviations (97.5 percentile) from the mean value of the control population. Jaffe et al. proposed that in order to further improve specificity, the upper limit should be extended to three standard deviations above the mean for the normal range (99th percentile). More importantly, the authors recommend that an increased cT level is recognized as not synonymous with an ischaemic mechanism of cardiac injury, and does not mandate a diagnosis of myocardial infarction. It is suggested that this term is used only when there is evidence of cardiac injury (as detected by marker proteins) in a setting consistent with myocardial ischaemia.

Implications for the patient

When a doctor makes a diagnosis of acute myocardial infarction then there are ramifications for the patient. A period of rehabilitation and recovery is required, and most patients would not return to work until 4–6 weeks had elapsed. Moreover, this diagnosis may have a direct impact on work for example, if the patient is a vocational driver. The diagnosis restricts travel by air, and may affect the ability to obtain life insurance. The psychological impact of the diagnosis is significant, with up to a third of patients suffering depression. The doctor therefore has a duty to get it right. An ischaemic aetiology may be suggested by typical pain, risk factors for ischaemic heart disease and appropriate ECG changes. However, if this is not the case, additional tests may be required to determine the nature of the troponin release. A diagnosis of myocardial infarction should not be made solely on the presence of increased biochemical marker values.

Implications for public health

The Government has set targets for the reduction in mortality from coronary heart disease (CHD) and the National Service Framework includes guidelines and targets for the provision of rehabilitation programmes and secondary prevention. These targets are audited continually on the basis of hospital and diagnostic coding. A diagnosis of myocardial infarction has implications for the Trust and achieving targets. In all Western countries, the incidence of coronary events is falling, but these data rely on the standard WHO definitions. Redefining myocardial infarction on the basis of a cT elevation alone may introduce inaccuracy in the diagnosis, and affect the ability of secondary prevention programmes to target the most appropriate population.

References

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