

False positive or true positive troponin in patients presenting with chest pain but 'normal' coronary arteries: lessons from cardiac MRI

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This editorial refers to 'The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin and unobstructed coronary arteries'[†] by R.G. Assomull *et al.*, on page 1242

Cardiac magnetic resonance imaging (MRI), particularly when enhanced with commonly available gadolinium-based contrast agents, is a powerful clinical tool for characterizing myocardial abnormalities. One of the best-known applications of this relatively new technology has been the detection of myocardial infarction. It is also possible to image myocardial scarring or fibrosis in other disease states such as myocarditis and infiltrative cardiomyopathies. Assomull *et al.*¹ from the Royal Brompton Hospital document the adjunctive diagnostic value of late gadolinium enhancement imaging in patients who present with chest pain, elevated troponin but unexpectedly 'normal' appearing coronary angiograms.

The introduction of troponin assays revolutionized the diagnosis of acute myocardial infarction. This was largely based on the high sensitivity and specificity for acute myocardial injury. Elevated troponin was associated with adverse prognosis before we came to a consensus that it must be a marker of cardiac necrosis. On the basis of this work and a much wider range of literature than can be quoted in this brief article, the very definition of myocardial infarction was revised in 2000.²

The revised definition of myocardial infarction required either pathological evidence of acute myocardial infarction or a new set of clinical criteria based largely on serum markers of myocardial necrosis. Acute myocardial infarction can be diagnosed by a typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: (i) ischaemic symptoms, (ii) development of pathological Q-waves on ECG, (iii) ECG changes indicative of ischaemia

(ST-elevation or ST-depression), or (iv) percutaneous coronary intervention.²

Although overall a substantial advance in our understanding of acute myocardial infarction, the revised definition of myocardial infarction introduced vulnerability to lack of specificity for a number of mechanisms. Specifically, there is more than one way to kill a cardiomyocyte, so there is more than one way for troponin to be released into the blood stream. In addition, symptoms compatible with myocardial ischaemia are notoriously common and lead to use of serum markers of ischaemia in a wide range of patients with low pre-test probability of acute myocardial infarction. 'Possible ischaemic symptoms include chest, epigastric, arm, wrist or jaw discomfort with exertion or at rest. The discomfort associated with acute MI usually lasts at least 20 min, but may be shorter in duration. The discomfort may develop in the central or left chest and then radiate to the arm, jaw, back or shoulder. The discomfort is usually not sharp or highly localized and may be associated with dyspnea, diaphoresis, nausea, vomiting or lightheadedness. The discomfort can develop in the epigastrium (often confused with indigestion), arm, shoulder, wrist, jaw or back, without occurring in the chest, but such a pattern is atypical. The discomfort is not affected by moving the muscles of the region where the discomfort is localized, nor is it worsened by deep inspiration. The discomfort is not positional in nature. Symptoms can also include unexplained nausea and vomiting, persistent shortness of breath secondary to left ventricular failure and unexplained weakness, dizziness, lightheadedness or syncope, or a combination of these. These symptoms may be noted in association with chest discomfort or they may occur in the absence of chest symptoms'.² The variability of possible ischaemic symptoms includes symptoms possibly due to many other conditions. As a result, there is substantial likelihood of false positive diagnoses of acute myocardial infarction based only on symptoms and biomarkers. However, the ECG criteria or performance of a percutaneous coronary intervention in the current definition of acute MI is highly specific for acute myocardial infarction when combined with biochemical markers of myocardial necrosis.

Furthermore, recent work has pushed the field to accept that lower and lower thresholds of abnormalities on troponin

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Table 1 Differential diagnosis of elevated serum troponin (adopted from Korff *et al.*¹⁰)

Clinical conditions associated with elevated serum troponin	MRI possibly helpful
Acute myocardial infarction	
Acute coronary syndrome	Yes
After percutaneous coronary intervention	Yes
After coronary bypass surgery	Yes
Troponin elevation not due to acute myocardial infarction	
Acute heart failure	Yes
Acute pulmonary embolism	Not yet
Aortic dissection Stanford A	Not yet
Asymptomatic patients with end stage renal disease	Yes
Cardiac contusion after blunt chest wall trauma	Yes
Cardiac infiltrative disorders (amyloidosis)	Yes
Cardiotoxic chemotherapy	Yes
Cardioversion/defibrillation	No
Chronic heart failure	Yes
Heart transplant	Yes
High frequency ablation	Yes
Pericarditis/myocarditis	Yes
Rhabdomyolysis	Not yet
Sepsis/critically ill patients	Not yet
Strenuous exercise/ultra-endurance athletes	Yes
Valvular heart disease	Yes
Biochemical false positive	?

assays are prognostically important³ and represent important heart disease.⁴ The change in phraseology to 'heart disease' rather than acute myocardial infarction is important. Many conditions can cause myocardial injuries that are now detectable with troponin assays (*Table 1*). The range of clinical diagnoses encompassed on this list indicates that there is substantial latitude for the possibility that a troponin elevation in a given patient may represent something other than acute myocardial infarction. Of note, cardiac MRI is capable of providing clinically useful information in the majority of conditions that cause troponin elevations.

Extensive work over the past decade has validated contrast-enhanced MRI as an accurate and sensitive way of detecting myocardial infarction.⁵ Subendocardial vulnerability to ischaemia was a concept originally developed in laboratories by studying the pathophysiology of myocardial ischaemia.⁶ Owing to a complex interplay among haemodynamic stresses, transmural distribution of coronary perfusion, and subendocardial energy requirements, many investigators helped prove that myocardial infarction starts near the endocardial surface of the left ventricle and progresses towards a more transmural infarction depending on the duration of coronary occlusion prior to reperfusion. This subendocardial initiation of infarction offered unique diagnostic opportunities when MRI techniques became good enough to resolve the transmural extent of infarction in patients.

Just as myocardial infarction is not the only cause of troponin release from the heart, myocardial infarction is not the only condition leading to contrast late gadolinium enhancement on a cardiac MRI. Myocarditis frequently

causes enough myocardial injury and scarring to result in troponin release and late gadolinium enhancement on MRI. Myocardial biopsies targeted to areas with late gadolinium enhancement show histological evidence of myocarditis in patients.⁷ Non-viral causes of myocarditis replicate many of the patterns seen in community acquired myocarditis and also correlate with histology. Some patients may have less severe forms of myocarditis that do not cause enough permanent injury to be detectable by current gadolinium enhancement techniques, but can be detected using T2-weighted MRI. MRI can detect regions of myocardial infarction that involve <1 g of myocardium and is capable of detecting small islands of abnormal gadolinium accumulation in patients with myocarditis. In the light of the entry criteria for the study by Assomull *et al.*¹ it seems that myocarditis is the most likely non-coronary artery disease-related cause of abnormal troponin elevations.

Late gadolinium enhancement may also be present in patients with other diagnoses.⁸ Localization of gadolinium contrast agents to parts of the heart other than the subendocardium or in distributions that cannot be explained by the distribution of coronary arteries raises the possibility of non-ischaemic aetiologies.^{5,8} It is the high resolution of MRI that allows the transmural extent and transmural pattern of abnormalities—critical factors to differentiating the clinical syndromes that may cause elevations of troponin in the absence of acute myocardial infarction.

In summary, the work of Assomull *et al.*¹ highlights a practical validation of how MRI technology can be used to solve clinically relevant problems in troponin-positive patients. The scenario of a troponin elevation in a patient with no significant obstructions on coronary angiograms is common enough that many clinicians simply assume that these represent biochemical false positive assays. It is impressive that the investigators come to just the opposite conclusion. In fact, ~65% of troponin elevations in patients with negative coronary angiograms represent true positive for heart disease, although most of these patients do not have acute myocardial infarctions. As noted by Hamm *et al.*⁹ 'A constellation like this should not be used to discredit troponins as helpful markers but to remind us that troponin measurements, like all other laboratory results, should be seen as pieces in the diagnostic puzzle'. We can conclude that a contrast-enhanced MRI scan of the heart is indicated in the patient with chest pain, positive troponin, but no significant obstructions on coronary angiography as MRI is capable of differentiating so many of the conditions that lead to this frustrating clinical scenario.

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Clinical vignette

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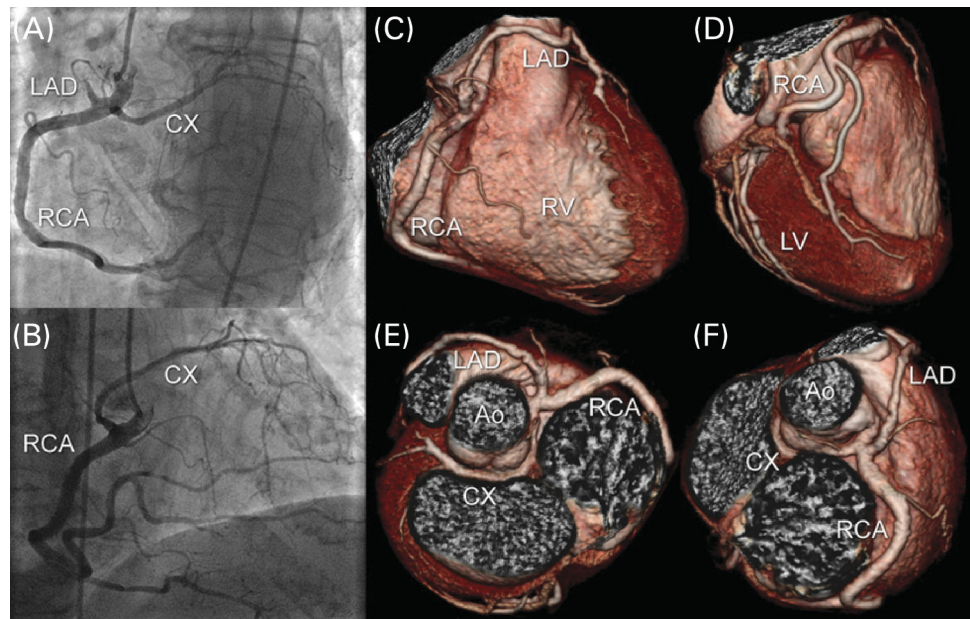
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Spontaneous recanalization of an anomalous left anterior descending coronary artery after acute myocardial infarction demonstrated by computed tomography

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We describe the case of an 80-year-old woman who came to our attention with a diagnosis of sub-acute antero-lateral myocardial infarction. She underwent coronary angiography, which revealed the presence of a rare anomaly of the left coronary artery (type R-III C according to Yamanaka's classification) in which the left anterior descending (LAD) and left circumflex artery (CX) arise separately from the proximal part of a normal right coronary artery (RCA) and run in a 'combined' manner (Panels A and B). In our patient, the proximal segment of the LAD showed an acute thrombotic occlusion, and percutaneous revascularization could not be completed because of the anomalous anatomy. From the coronary angiogram it was not possible to determine the LAD course. When discharged, the patient was receiving aspirin, clopidogrel, ramipril, simvastatin, and metoprolol.



Fifteen days after the acute coronary syndrome, a computed tomography (CT) (Sensation 64 Cardiac, Siemens, Germany) scan showed (Panels C–F) the course of the patent LAD anterior to the left ventricle outflow tract (Panels C, E, and F), as well as the course of the large RCA (Panels C and D). The spider (Panel E) and posterior views (Panel F) show the trifurcation of the proximal RCA with the CX running posteriorly to the aortic root, and the LAD running anteriorly to the right ventricle outflow tract. The CT images show coronary walls irregularities with calcific and non-calcific components at the level of the proximal segments of the three main vessels (i.e. RCA, LAD, CX). These features, with the exception of the acute thrombosis of the LAD, are less evident on conventional coronary angiography.

The use of CT, in our case, was a means of following-up a recanalized thrombosis after an acute coronary syndrome, and assessing the anomalous course of the left coronary artery.

Supplementary movies are available at *European Heart Journal* online.

Panel A and B Coronary angiogram. Coronary angiogram showing the common origin of the RCA, LAD, and CX. The LAD is occluded immediately after its origin and reperused by the collateral circulation.

Panel C–F Four-dimensional computed tomography. Volume rendered multiphase reconstruction of the CT dataset showing all of the anatomical features of the coronary artery anomaly.