European Heart Journal (2007) **28**, 1242–1249
doi:10.1093/eurheartj/ehm113

The role of cardiovascular magnetic resonance in patients presenting with chest pain, raised troponin, and unobstructed coronary arteries

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Received 7 October 2006; revised 13 March 2007; accepted 22 March 2007; online publish-ahead-of-print 3 May 2007

See page 1175 for the editorial comment on this article (doi:10.1093/eurheartj/ehl567)

KEYWORDS
Magnetic resonance;
Acute coronary syndromes troponin;
Myocarditis;
Coronary angiography

Aims Troponin measurement is used in the assessment and risk stratification of patients presenting acutely with chest pain when the main cause of elevation is coronary artery disease. However, some patients have no coronary obstruction on angiography, leading to diagnostic uncertainty. We evaluated the incremental diagnostic value of cardiovascular magnetic resonance (CMR) in these patients.
Methods and results Sixty consecutive patients (mean age 44 years, 72% male) with a troponin-positive episode of chest pain and unobstructed coronary arteries were recruited within 3 months of initial presentation. All patients underwent CMR with cine imaging, T2-weighted imaging for detection of inflammation, and late gadolinium enhancement imaging for detection of infarction/fibrosis. An identifiable basis for troponin elevation was established in 65% of patients. The commonest underlying cause was myocarditis (50%), followed by myocardial infarction (11.6%) and cardiomyopathy (3.4%). In the 35% of patients where no clear diagnosis was identified by CMR, significant myocardial infarction/fibrosis was excluded.
Conclusion CMR is a valuable adjunct to conventional investigations in a diagnostically challenging and important group of patients with troponin-positive chest pain and unobstructed coronary arteries.

Introduction

Troponin measurement is used routinely in the assessment and risk stratification of patients presenting acutely with chest pain. It can accurately predict the presence of acute coronary syndromes (ACS) in coronary artery disease (CAD).[1,2] The magnitude of troponin elevation reflects the complexity of the atherosclerotic lesions and guides risk stratification for death and re-infarction.[3–6] However, in a small but important subgroup of patients presenting with chest pain and an elevated troponin, subsequent coronary angiography reveals normal or non-flow-limiting CAD.[7,8] These patients present a difficult diagnostic dilemma.[9,10] There are a number of potential causes of this scenario, including non-cardiac aetiologies, myocardial infarction with a recanalized coronary artery, and acute myocarditis.[7,11]

In patients with ACS, antithrombotic, antiplatelet, and interventional therapies are important, but no data support the role of these therapies in the management of patients with a non-thrombotic syndrome. For this reason, defining the underlying cause of the clinical presentation is important and further investigation is justified, as lack of an accurate diagnosis is likely to result in patients not receiving appropriate treatment and/or follow-up. The current lack of diagnostic certainty may in turn explain why this cohort of patients has been shown to have a poorer prognosis.[12,13]

In order to establish the underlying cause for the troponin elevation, cardiovascular magnetic resonance (CMR) offers a potential opportunity due to its ability to non-invasively identify areas of *in vivo* inflammation and replacement fibrosis with a high spatial resolution. Using a combination of available sequences, CMR is able to distinguish between different causative aetiologies including acute infarction, myocarditis, and other cardiomyopathies.[14–18] We therefore hypothesized that CMR would offer incremental value in determining the underlying aetiology.

Methods

Patient population

Sixty-four consecutive patients presenting with new-onset chest pain (present at rest, lasting for longer than 30 min), an elevated

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troponin, and unobstructed coronary arteries on X-ray angiography were prospectively recruited between December 2003 and February 2006. Consecutive patients were recruited from patients referred to the CMR unit at Royal Brompton Hospital. Referrals were made from 18 separate hospitals which regularly use the CMR facilities at Royal Brompton Hospital. No patients had undergone coronary intervention, and other initial investigations including transthoracic echocardiography had proved diagnostically inconclusive. Physicians referred patients for CMR to exclude myocardial infarction and to provide an alternative diagnosis which would explain the clinical presentation. All CMR scans were performed during the inpatient admission or within 3 months of initial presentation. Coronary angiograms were performed in all patients prior to enrolment and subsequent CMR scanning. Patients with a history of chronic troponin elevation were excluded, as were any patients with standard contraindications to CMR (one patient excluded due to severe claustrophobia). Any patients with a prior cardiac history, for example, of myocarditis, myocardial infarction, or impaired LV function (three patients), were also excluded. Following exclusions, the final cohort comprised 60 patients. The study was approved by the local Ethics Committee. Written consent was obtained from all patients.

Cardiovascular magnetic resonance

CMR (Siemens Sonata 1.5T, Erlangen, Germany) was performed using steady-state, free precession breath-hold cines echo time (TE)/repetition time (TR) (1.6/3.2 ms, flip angle 60°) in long-axis planes and sequential 7 mm short-axis slices (3 mm gap) from the atrioventricular ring to the apex. T2-weighted images (triple inversion recovery; TE: 60 ms, TR: 2× R–R interval, TI: 170 ms, slice thickness 7–15 mm, flip angle: 180°, pixel size 2.3 × 1.3 mm) were acquired in the same long- and short-axis planes. Finally, late gadolinium enhancement (LGE) images were acquired 10 min after intravenous gadolinium-DTPA (Schering; 0.1 mmol/kg) in identical short-axis planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically 320–440 ms; pixel size 1.7 × 1.4 mm). LGE images were phase-swapped to exclude artefact. Ventricular volumes and function were measured for both ventricles using standard techniques[19–21] and analysed using semi-automated software (CMRtools, Cardiovascular Imaging Solutions, London, UK). All volumes and masses were indexed for age, gender, and body surface area (BSA).[22]

Cardiovascular magnetic resonance analysis

CMR scans were analysed independently by two experienced interpreters who were blinded to clinical details. Scans were reviewed with assessment of ventricular volumes and function, review of T2-weighted images for areas of high signal suggesting myocardial inflammation, and by measuring the ratio of myocardial signal intensity to skeletal muscle.[23] Finally, the LGE images were assessed for subendocardial enhancement in the distribution of a coronary artery compatible with myocardial infarction[18] or for midwall/subepicardial enhancement which was compatible with myocarditis in this cohort. The myocarditis group was further subclassified into acute (T2 raised) or non-acute (T2 not raised) based on the corresponding T2-weighted signal in that territory or increased global ratio. Scans with increased normalized volumes and reduced systolic function but without evidence of LGE/T2 abnormalities were categorized as dilated cardiomyopathy (DCM). Scans with completely normal range volumes and function with no LGE/T2 abnormalities were considered non-diagnostic for cause by CMR. The incremental value of CMR was expressed as the proportion of cases where LGE-CMR scans yielded a new diagnosis.

Clinical data

Clinical data including history, examination findings, troponin levels, ECG recordings, transthoracic echocardiography, and coronary angiography were reviewed by a single experienced observer prior to enrolment into the study. The primary ECG abnormality was assigned using the Minnesota code.[24] ST-segment elevation was defined as the elevation of the ST-segment >1 mm in leads II, III, aVF, I, aVL, V5, and V6 or >2 mm in leads V1–V4. Readings were taken 60 ms after the J point. In addition, details of investigations for pulmonary emboli and serum electrolytes were recorded. Renal disease was defined as a reduced GFR (<90 mL/min/1.73 m^2).[25] Troponin assays differed between referring centres, and the recorded level was cross-checked with the upper limit of normal for the appropriate referring centre (typically 10–20% in excess of the 99th percentile value for a reference control group) to ensure they were elevated at a level to suggest significant myocardial injury. For each patient, the results of all troponin assays performed during the index admission were recorded. The peak troponin results for patients were also subdivided into categories depending on the extent of their elevation (<2 upper limit of normal (ULN), <5 ULN, <10 and >10 ULN). A 'false positive' troponin was considered a possibility in patients with a single troponin elevation, which was not repeated during the admission or if a single elevated troponin was followed by a second normal troponin level within 24 h.

Coronary angiograms were reviewed to ensure there were no epicardial stenoses (defined as $>50\%$ stenosis in the main- and side-branch arteries). The subsequent progress of patients was assessed by telephone contact with their primary care physician to establish whether subsequent investigations had uncovered any alternative diagnoses that were not evident on CMR.

Statistical analysis

Continuous data are expressed as a mean $\pm$ SD. Baseline characteristics were compared between subgroups using an independent sample *t*-test or Mann–Whitney test as appropriate. Fisher's or χ^2 tests were used for categorical variables. All tests were two-sided. A *P*-value of <0.05 was deemed significant and SPSS v12 (Chicago, USA) was used for all statistical analyses.

Results

Baseline characteristics

Group baseline characteristics are summarized in *Table 1*. The mean age of the cohort was 44 ± 17 years (71.7% male). None of the patients had a prior history of cardiac disease before presenting with acute chest pain. They had not required electrical cardioversion or undergone invasive cardiovascular investigations/treatment other than angiography. In addition, none of the recruited cohort had pre-existing renal impairment, prior exposure to cardiotoxic drugs, or prior chemotherapy/radiotherapy. At the time of the recorded troponin elevation, none of the patients had been treated for a prolonged episode of septicaemia. There was a low prevalence of cardiac risk factors. Fifty-five (91.7%) of the cohort had an abnormal ECG on presentation, with ST-segment elevation being the most commonly detected abnormality (40%). A few patients were on primary prevention therapy, with statins being the most commonly prescribed treatment. The median interval from presentation of chest pain to CMR was 14.5 days (range 1–90 days).

Incremental value of cardiovascular magnetic resonance

The range of diagnoses determined by CMR is summarized in *Table 2*. CMR provided a new diagnosis in 39 patients (65% of cohort). In the remaining patients, there was no detectable

Table 1 Baseline characteristics

Characteristics	Value ($n = 60$)
Mean age (SD), years	44.0 (17.0)
Male sex (%)	43 (71.7)
Family history of IHD (%)	9 (15.0)
Diabetes (%)	3 (5.0)
Hypertension (%)	10 (16.7)
History of smoking (%)	6 (10.0)
History of alcohol excess (%)	3 (5.0)
Dyslipidaemia (%)	19 (31.7)
Increased BMI (%)	12 (20.0)
Creatinine μmol/L (SD)	88.0 (20.9)
Median interval from troponin rise to CMR/days (range)	14.5 (1–90)
Primary ECG abnormality (%)	
Normal	5 (8.3)
T-wave changes	12 (20.0)
ST-elevation	24 (40.0)
ST-depression	9 (15.0)
SVT/VT	7 (11.7)
LBBB	2 (3.3)
Pathological Q-waves	1 (1.7)
Patients thrombolysed (%)	19 (31.7)
Medication on admission (%)	
ACE-I/AT-II blocker	2 (3.3)
Beta-blocker	2 (3.3)
Statins	5 (8.3)
CMR LV dimensions and function	
LVEDVI (SD), mL m^{-2}	85.6 (22.8)
LVESVI (SD), mL m^{-2}	37.5 (23.7)
LVEF (SD), %	59.4 (13.1)
LV mass index (SD), g^{-2}	81.2 (20.6)

IHD, ischaemic heart disease; BMI, body mass index; CMR, cardiovascular magnetic resonance; ECG, electrocardiogram; LBBB, left bundle branch abnormality; ACE-I, angiotensin-converting enzyme inhibitors; AT-II, angiotensin II; LV, left ventricular; LVEF, left ventricular ejection fraction; SVT, supraventricular tachycardia; VT, ventricular tachycardia; LVEDVI, left ventricular end diastolic volume index; LVESVI, left ventricular end systolic volume index.

Table 2 Cardiovascular magnetic resonance findings

CMR findings	*n* (%)
Myocarditis	30 (50.0)
Acute	19 (31.7)
Non-acute	11 (18.3)
Myocardial infarction	7 (11.6)
Takotsubo cardiomyopathy	1 (1.7)
Dilated cardiomyopathy	1 (1.7)
Normal CMR findings	21 (35)

Abbreviations as in *Table 1*.

infarction or inflammation and no additional new diagnosis was made. There was 100% concordance of diagnosis between the two observers. Myocarditis was the most common diagnosis, which was present in 50% of the patients (*Figure 1*). Myocardial infarction was found in seven (11.6%) patients (*Figure 1*). In one female patient with a history of recent stress, CMR revealed apical ballooning with preserved basal LV function and no LGE or T2 abnormalities. A diagnosis of Takotsubo cardiomyopathy was made, and repeat CMR 3 months later showed complete normalization of LV function (*Figure 2*).[26] In one patient, CMR revealed LV dilatation with moderate impairment of systolic function, with no evidence of detectable inflammation or fibrosis, and a diagnosis of DCM was made. Finally, one patient who presented with ECG evidence of inferior myocardial infarction had a CMR which confirmed transmural inferior myocardial infarction but also a patent foramen ovale (PFO) which was subsequently confirmed by contrast transoesophageal echocardiography (*Figure 3*). The infarct was presumed clinically to represent a paradoxical embolus through a PFO.

Diagnostic vs. non-diagnostic group

Patients with a non-diagnostic CMR were defined as patients in whom CMR did not reveal any structural or myocardial tissue abnormalities. None of these scans were suboptimal in the quality of images obtained. There was no significant difference in baseline LV parameters between the groups with and without a new CMR diagnosis, except for the baseline LVEF which was lower in the new diagnosis group (56.1 ± 14.7 vs. $65.5 \pm 5.6\%$, $P = 0.007$). A higher proportion of patients with a non-diagnostic CMR had a potential false-positive troponin (as defined previously) than those with a diagnosis confirmed by CMR (57 vs. 8%, $P < 0.001$). In addition, a significantly larger proportion of patients with a non-diagnostic CMR had troponin elevations <5 ULN when compared with those with a CMR-ascribed diagnosis (52 vs. 13%, $P < 0.001$).

ECG findings in the diagnostic and non-diagnostic groups are presented in *Table 3*. As can be seen, only tachyarrhythmias (SVT/VT) appeared to correlate with CMR findings. A significantly higher proportion of patients with a non-diagnostic CMR had a tachyarrhythmia at presentation (24 vs. 5%, $P = 0.045$).

On follow-up of both groups at a median of 398 (range 160–736) days, no new or alternative cardiac diagnosis has been made in any patient.

Diagnosis of inflammation in acute myocarditis

Of the 30 patients diagnosed with myocarditis by CMR, 19 had evidence of acute inflammation (31.7% of total cohort) with increased midwall/epicardial T2 signal and corresponding enhancement on LGE images. Eleven patients (18.3%) were ascribed a diagnosis of non-acute myocarditis without detectable active inflammation based on the presence of midwall/epicardial LGE abnormalities and normal intensity T2 images (*Table 4*). However, the median interval between troponin-positive chest pain and CMR scanning was significantly shorter in the acute myocarditis group [8 (range 1–88 days) vs. 41 days (range 6–83 days), $P = 0.005$]. In addition, patients with a diagnosis of acute myocarditis were significantly younger than those diagnosed with non-acute myocarditis (35.2 ± 14.9 vs. 48.5 ± 19.3 years, $P = 0.04$). No patients in the cohort had increased T2 signal intensity in the absence of midwall/epicardial LGE.

Validation of cardiovascular magnetic resonance findings

On the basis of improving clinical scenario, no patients required or underwent myocardial tissue biopsy. We

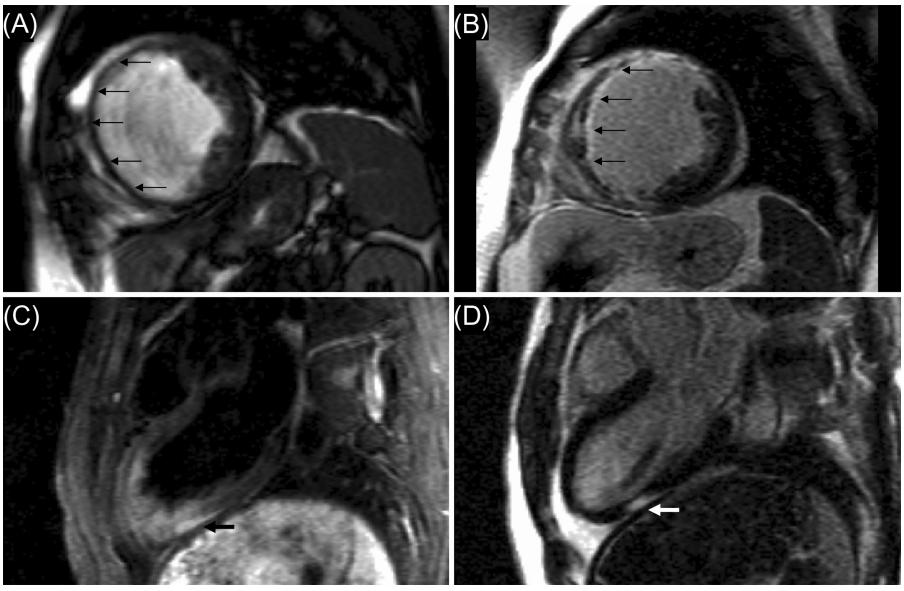

Figure 1 Late gadolinium enhancement-cardiovascular magnetic resonance appearances of myocardial infarction and myocarditis. (*A*) A cine sequence of mid-ventricular short-axis slice in a patient with classic features of myocardial infarction with anterior, inferior, and septal wall thinning (arrows). (*B*) The corresponding gadolinium-enhanced image demonstrating near-transmural late enhancement of the thinned region described (arrows). (*C*) A T2-weighted view of the left ventricular outflow tract, a focal area of increased signal in the inferolateral left ventricular wall indicating inflammation (arrows). A corresponding gadolinium-enhanced image (*D*) shows patchy, predominantly epicardial late enhancement indicating fibrosis (arrows). This pattern is typical of acute myocarditis.

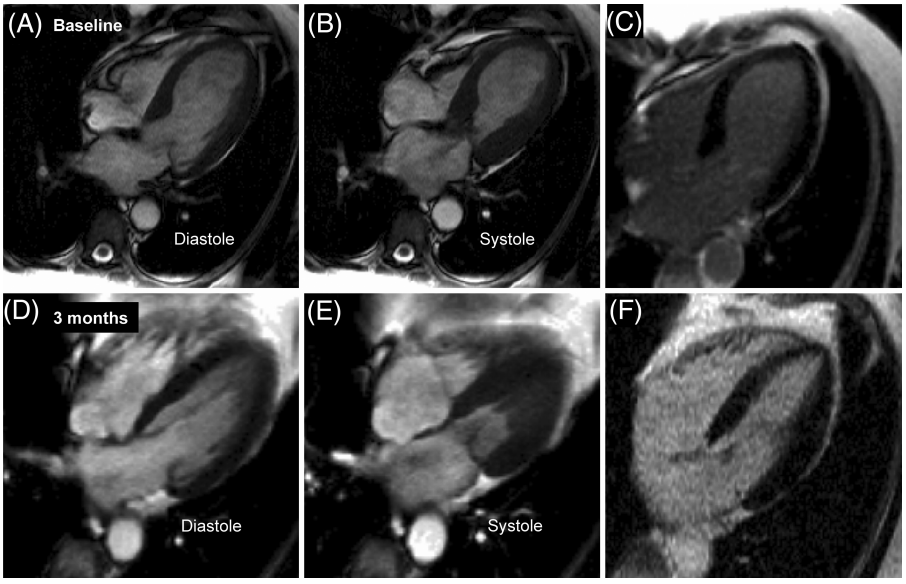

Figure 2 Serial late gadolinium enhancement-cardiovascular magnetic resonance in Takotsubo's cardiomyopathy. (*A–C*) Images acquired at baseline scanning demonstrate vigorous basal systolic function with apical hypokinesia (*A* and *B*) in the absence of late gadolinium enhancement (*C*). A repeat scan 3 months later shows complete normalization of ventricular function (*D* and *E*), with no late enhancement detectable (*F*).

rescanned four patients with a CMR diagnosis of active inflammatory myocarditis [median interscan time of 111 days (range 56–313 days)]. Repeat scans in all patients showed persistent fibrosis but diminished signal on T2 imaging (*Figure 4*), correlating with their clinical improvement.

Other clinical investigations

Depending on the clinical presentation and blood-gas profile, a small proportion of patients were additionally further investigated for pulmonary thromboembolism. CT pulmonary angiography was performed in three patients, all of whom did not show evidence of embolism. One patient was diagnosed with pulmonary embolism on the basis of a ventilation perfusion isotope scan.

Discussion

Raised troponin levels reflect myocardial necrosis. The vast majority of patients presenting with acute chest pain, troponin elevation, and abnormal ECGs are correctly diagnosed and treated for ACS. Subsequent coronary angiography usually reveals flow-limiting epicardial stenoses.[27]

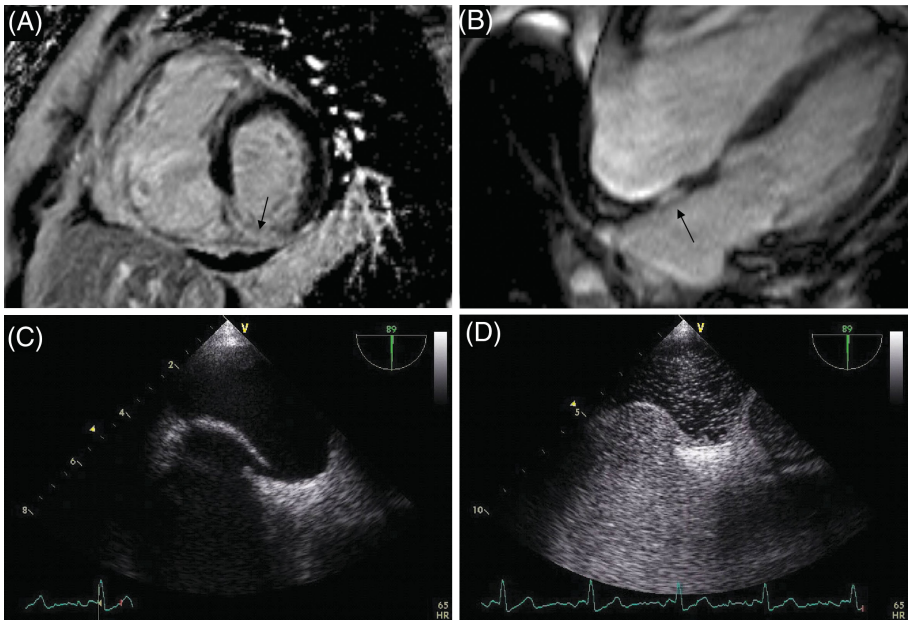

Figure 3 Myocardial infarction resulting from systemic embolism through a patent foramen ovale. (*A* and *B*) A gadolinium-enhanced short-axis view demonstrating transmural myocardial infarction (arrows). Cine imaging in the horizontal long axis (HLA) view shows a suspected patent foramen ovale in the inter-atrial septum (arrow), which is confirmed on bubble-contrast transoesophageal echocardiography (*C* and *D*).

Table 3 Electrocardiographic abnormalities in non-diagnostic vs. diagnostic cases

Primary ECG abnormality	Non-diagnostic CMR, $n = 21$ (%)	Diagnostic CMR, $n = 39$ (%)	Total, $n = 60$ (%)	*P*-value
Normal	3 (14.3)	2 (5.1)	5 (8.3)	0.22
T-wave changes	2 (9.5)	10 (25.6)	12 (20.0)	0.14
ST-elevation	6 (28.5)	18 (46.2)	24 (40.0)	0.19
ST-depression	4 (19.1)	5 (12.8)	9 (15.0)	0.52
SVT/VT	5 (23.8)	2 (5.1)	7 (11.7)	0.045
LBBB	1 (4.8)	1 (2.6)	2 (3.3)	0.54
Pathological Q-waves	0 (0)	1 (2.6)	1 (1.7)	0.65

Abbreviations as in *Table 1*.

Table 4 Acute vs. non-acute myocarditis

Characteristics	Acute ($n = 19$)	Non-acute ($n = 11$)	*P*-value
Mean age (SD), years	35.2 (14.9)	48.5 (19.3)	0.04
CMR LV dimensions and function			
LVEDVI (SD), mL m^{-2}	84.6 (17.0)	89.4 (29.4)	0.58
LVESVI (SD), mL m^{-2}	35.0 (17.5)	45.9 (29.9)	0.22
LVEF (SD), %	52.1 (15.3)	60.1 (11.4)	0.11
LV mass index (SD), g^{-2}	80.1 (23.8)	85.4 (29.0)	0.59
Median interval to scan days (range)	8 (1–88)	41 (6–83)	0.003

Abbreviations as in *Table 1*.

However, patients presenting with chest pain, an elevated troponin, and normal coronary angiography present a clinical dilemma. Further evaluation is required to establish a diagnosis and to direct treatment strategies. There are a large number of other causes of an elevated troponin in the absence of obstructive CAD, which include infarction, myocarditis, cardiomyopathy, cardiac contusion, congestive heart failure, and non-cardiac causes including pulmonary embolism, sepsis, and renal failure.

CMR is able to provide detailed information on myocardial tissue characteristics. It therefore has a potential role in evaluating the cause of troponin elevation. LGE-CMR has become the gold standard for *in vivo* detection of scarring associated with myocardial infarction and other non-ischaemic conditions.[11,14,15,28,29] The high spatial resolution and contrast of CMR allows very small areas of infarction to be identified, which are missed by SPECT.[30] Black-blood T2-weighted imaging delineates areas of myocardial oedema based on a water-excitation pulse. This sequence has been clinically used to detect oedema in acute infarction, sarcoid, myocarditis, and acute rejection following cardiac transplantation.[31–33] The application of excellent tissue characterization that is validated, non-invasive, and free from non-ionizing radiation makes LGE-CMR a safe and powerful tool.

Our study demonstrates that CMR can identify the basis for troponin elevation in 65% of patients presenting with ACS type symptoms but unobstructed coronary angiography.

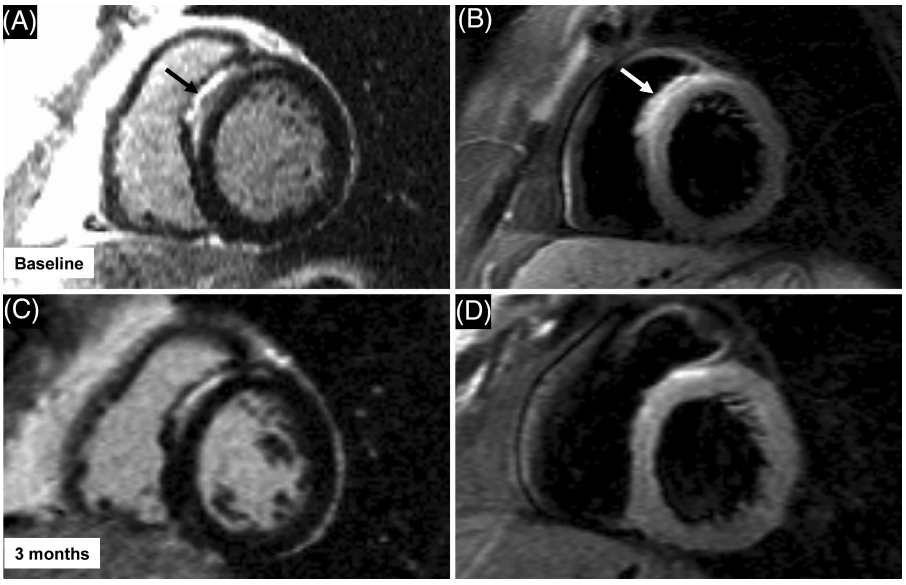

Figure 4 Resolution of myocardial inflammation but persistent fibrosis in myocarditis. (*A* and *B*) Gadolinium-enhanced and T2-weighted images at baseline, respectively. Epicardial late enhancement can be seen in the anteroseptal wall in (*A*) with corresponding increased signal on the T2-weighted image in (*B*) (arrows). A repeat scan 3 months later shows persisting fibrosis (*C*) but diminished signal on T2-weighted images, indicating resolving inflammation (*D*).

In this group, the commonest cause was myocarditis (50%), followed by myocardial infarction (11.6%). This finding is in keeping with studies using nuclear techniques identifying high rates of myocarditis in patients with troponin-positive chest pain and normal coronary arteries.[9] Also importantly, significant infarction, fibrosis, or active inflammation was excluded in the remaining 35% of patients. Several studies have confirmed that the elevation of troponin in patients with ACS correlates with evidence of infarction by LGE-CMR and furthermore that the extent of elevation predicts the size of infarct.[34,35] Unlike the present study, however, these studies excluded patients with normal coronaries and did not include patients with possible/suspected myocarditis.

In the subset with myocarditis, 63% of this group showed evidence of acute active inflammation as indicated by T2 imaging. These patients were scanned significantly sooner than those diagnosed with non-acute myocarditis. Previous work has demonstrated that the acute changes of oedema and fibrosis as detected by LGE-CMR correlate well with biopsy findings and increase the diagnostic yield of biopsies by guiding the site of tissue sampling.[17] Moreever, serial studies in such patients also demonstrate regression of these pathological changes over time in a proportion of patients.[36] In the present study, four patients who consented to a follow-up scan showed complete or partial resolution of myocardial inflammation on the repeat scanning using T2 after a period of 111 days. Therefore, if the extent of myocardial inflammation at baseline was limited, these changes may resolve following the acute period of inflammation. Failure to ensure early CMR scanning in these patients may miss any subtle changes that were present on acute admission.

Myocardial infarction was detected in 11.6% of patients, despite the presence of unobstructed coronary arteries. The mechanism of infarction in these patients may be explained by arterial recanalization, embolism, or coronary spasm. Five of these seven patients received thrombolytic therapy, which may have resulted in recanalization of the occluded vessel. In one patient, a clear source of potential embolism was identified in the form of a PFO which resulted in both systemic and pulmonary emboli highlighting the limitations of luminography. The example of Takotsubo cardiomyopathy demonstrates the additional role of CMR in characterizing a disease entity that is being increasingly recognized and where management based on the ECG and angiography alone may have resulted in the interpretation of recanalization rather than this reversible cardiomyopathy.[37]

CMR did not provide a clear diagnosis in 35% of patients. Patients with non-diagnostic CMR scans in this study were more likely to have a modest elevation of troponin (<5 ULN) when compared with patients with a diagnostic CMR scan. Moreover, we hypothesize that a proportion of these troponin elevations may also be biochemical false positives. Evidence for this is also provided by the fact that patients with a non-diagnostic CMR were more likely to have had a tachyarrhythmia at presentation, which had subsequently resulted in a troponin elevation which was (in retrospect) unlikely to be clinically significant.

In addition, a proportion of cases may be due to an underlying non-cardiac aetiology such as pulmonary embolism, although the confirmed incidence of this in our cohort was low. The delayed presentation for CMR scanning in part of our cohort may lead to a failure to diagnose mild inflammation without development of fibrosis in myocarditis, which was present on initial admission but subsequently resolved. Alternative explanations for troponin elevation, which do not involve tissue necrosis, have also been recently suggested.[38]

Limitations

Identical troponin assays were not used in this cohort, reflecting referral from different centres and hence meaningful comparisons between the extent of CMR scarring

and troponin levels could not easily be made. There was no histopathological correlation of the CMR diagnosis with biopsy findings for the diagnosis of myocarditis, which is currently a typical practice in the UK. However, several studies have already established the patterns of CMR findings with histology.[39,40] Finally, in patients with normal CMR scans, other important causes of a troponin elevation need to be considered, most importantly the diagnosis of pulmonary embolism, but our CMR scanning protocol was not designed for this possibility. This also has relevance in terms of potential referral bias for the CMR scan.

Conclusion

This study reveals a role for CMR as an adjunct to conventional investigations in patients with troponin-positive chest pain and unobstructed coronary arteries. In our cohort, LGE-CMR provided a new diagnosis in 65% of cases and excluded significant pathology in the remainder. Further studies are required to evaluate the prognostic implications of CMR abnormalities in this cohort of patients.

Acknowledgements

R.G.A. was supported by a Junior Fellowship Grant from The British Heart Foundation.

Conflict of interest: D.J.P. is a consultant to Siemens Medical Solutions and a Director of Cardiovascular Imaging Solutions.

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