Int J Cardiovasc Imaging (2014) 30:1097–1103
DOI 10.1007/s10554-014-0435-7

ORIGINAL PAPER

Evidence of myocardial scarring and microvascular obstruction on cardiac magnetic resonance imaging in a series of patients presenting with myocardial infarction without obstructed coronary arteries

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Received: 15 January 2014 / Accepted: 26 April 2014 / Published online: 3 May 2014

Abstract Patients with acute chest pain, electrocardiographic ST-elevation and significant elevation of cardiac troponin but without obstructive coronary artery disease represent a diagnostic and therapeutic dilemma. Cardiac magnetic resonance imaging (CMR) can elucidate underlying alternative causes of troponin elevation including detection of (minor) myocardial infarction (MI) by identifying myocardial scarring as delayed enhancement. Of 77 patients, who were admitted between March 2009 and December 2012 with electrocardiographic (ECG) and biochemical evidence of acute MI without obstructive coronary artery disease, 45 patients underwent CMR that showed in 11/77 (14 %) late gadolinium enhancement (LGE), compatible with myocardial scarring. We analyzed clinical, echocardiographic, and CMR data of these patients. Elevated troponin I levels were observed in all patients (median 1.3 ng/l, IQR 0.44–187) with median peak creatinine phosphokinase of 485 U/l (IQR 234–618). Echocardiographic wall motion abnormalities were detected in 8/11 (73 %) patients; in 75 % of these segments, ECG abnormalities were observed in corresponding leads. CMR detected LGE in the inferior (4/11), the inferolateral (5/11), the inferoseptal (2/11), the anterior (3/11), apical (3/11) and in the lateral segments (2/11). In addition, in all but two patients, these segments matched ECG abnormalities in corresponding leads. CMR identified microvascular obstruction in 4/11 (36 %) patients. Patients with clinical, ECG, and biochemical signs of acute MI but unobstructed coronary arteries may have CMR-detectable myocardial scars. Information on myocardial scarring may help to make the diagnosis and draw therapeutic consequences. This case series underlines the value of contrast-enhanced CMR for myocardial tissue characterization.

Keywords Myocardial infarction · Non-obstructed coronary arteries · Cardiac MR delayed enhancement · Myocardial scarring

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Introduction

Patients presenting in the emergency room with acute onset of chest pain, ST-elevation on ECG and significantly elevated cardiac troponin levels in the absence of obstructive coronary artery disease comprise a diagnostic dilemma [1]. Cardiac magnetic resonance imaging (CMR) provides accurate, non-invasive myocardial tissue characterization, which can be used to diagnose causes of troponin elevation other than obstructive coronary artery disease. Previous studies showed that, using CMR, in 65 % of all cases, an alternative cause could be determined (peri-myocarditis in 50 %, cardiomyopathy in 11.6 %). In a small subset of patients however, there was evidence of myocardial necrosis, indicating myocardial infarction [2, 3].

Using CMR, different aspects of acute myocardial infarction can be assessed accurately: wall motion

abnormalities (WMA), ejection fraction, T2 weighted detection of edema and T1 weighted late-enhancement after Gadolinium contrast administration (LGE), indicative for myocardial damage. In addition, temporary coronary occlusion followed by reperfusion may lead to microvascular obstruction by red blood cells and necrotic debris. This can be visualized on CMR after gadolinium contrast administration as dark, subendocardial zones surrounded by hyperenhanced infarcted myocardium indicating necrosis of myocytes and capillary occlusion in the infarct core despite restoration of epicardial blood flow [4]. Microvascular obstruction is independently associated with adverse left ventricular (LV) remodeling and prognosis [5, 6]. Therefore, proper identification of myocardial necrosis and appropriate medical treatment in these patients is very important.

In this study we describe in detail both clinical and imaging characteristics in series of patients with clinical, ECG and biochemical signs of acute MI but unobstructed coronary arteries, and CMR-based evidence of myocardial necrosis (some with microvascular obstruction).

Patients and methods

Patient characteristics

From the patients admitted between 1 March 1, 2009 and December 30, 2012 with the diagnosis of an MI at Thoraxcentrum Twente (Enschede, The Netherlands) but without significant coronary artery obstruction on emergency coronary angiography, we retrospectively identified patients with evidence of CMR–LGE, compatible with MI.

Myocardial infarction was defined as follows. (1) Typical new-onset chest pain (present at rest, lasting for longer than 30 min); (2) Electrocardiographic (ECG) abnormalities consistent with ST-elevation; ST-elevation was defined as the elevation of the ST segment >1 mm in leads II, III and AVF, I, AVL, V5 and V6 or >2 mm in leads V1–V4, according to the Minnesota code [7]; 3. Increased cardiac enzymes; Troponin I levels where considered elevated >0.5 ng/l (local laboratory threshold of myocardial infarction). Creatinine phosphokinase (CPK) elevation was considered significant >170 U/l.

All patients were treated with aspirin, clopidogrel, beta blockers and lipid-lowering drugs according to current guidelines [8] and all patients were treated with an intravenous bolus of unfractionated heparin (5,000 IU). Emergency coronary angiography revealed the absence of obstructive coronary artery disease; which means that the coronary arteries were normal or showed no more than mild vessel wall changes with a maximum lumen diameter stenosis of <50 % (visually determined) in the absence of irregular lumen contours, intraluminal thrombus, or other features of complex coronary lesion.

Patients with a history of previous myocardial infarction, cardiac surgery or percutaneous intervention, myocarditis, or impaired LV function were not included. In addition, we excluded all patients in whom a disorder other than myocardial infarction was identified as cause of symptoms, ECG changes, and laboratory findings (e.g., peri-myocarditis, Takotsubo cardiomyopathy, pulmonary embolism, sepsis, or shock). Echocardiography and/or LV angiography were performed in all patients. In majority of patients, CMR was performed to elucidate the underlying cause of troponin elevation. Only patients with CMR–LGE, compatible with myocardial necrosis, were included in the present case series.

CMR data acquisition

All CMR studies were performed on a 1.5-Tesla whole body scanner (Achieva Scan, Philips Medical System, Best, The Netherlands) using CMR software. For signal reception a five-element cardiac synergy coil was used. ECG triggering was performed with a vector-ECG setup and subjects were examined in the supine position. Morphological images in the multislice cardiac short axis, single slice 4-chamber, 3-chamber two-chamber long-axis, and LV outflow tract views were acquired by using fast field echo cine images (slice thickness 8.0 mm, repetition time 3.4 ms; echo time 1.7 ms; flip angle 60°; matrix 256 × 256). Increased myocardial signal intensity depicted by T2-weighted imaging (T2 TSE Black blood with SPIR fat suppression (TR 2beats, TE 80 ms. Mid diastole, 1 slice per breathhold, 8 mm slice thickness, resolution 0.68 mm/0.68 mm)). Myocardial scar was assessed on multislice short-axis, long-axis, and 4-chamber views, obtained approximately 10 min after intravenous bolus injection of 0.2 mmol Dotarem/kg body weight (Guerbet Asia Pacific, Hong Kong) A three dimensional turbo field echo-inversion recovery T1-weighted sequence was used with the following parameters: repetition time 4.0 ms; echo time 1.3 ms; flip angle 15°; inversion time individually optimized to null myocardial signal (usually between 180 and 250 ms); matrix 157; and slice thickness 8 mm.

CMR data analysis and definitions

Two expert image interpreters independently analyzed the CMR data on a workstation, using dedicated software for cardiac analysis (Philips MR workspace, Release 2.5.3.0 2007-12-03; Philips, The Netherlands). Scans were reviewed with assessment of LV volume and function. In addition, WMA were assessed according to a standardized myocardial segmentation model with recognition of 17 different LV wall regions [9].

Definitions and tissue characteristics

Black-blood T2-weighted images were reviewed for the presence of areas of high signal intensity, compatible with increased water content, representing myocardial inflammation and edema. These images were visually assessed. In addition, the presence of myocardial necrosis (i.e., in general LGE) was reviewed on T1-weighted imaging; all patients with subendocardial and/or transmural contrast enhancement were diagnosed with myocardial infarction.

Microvascular obstruction was defined as the appearance of dark, subendocardial zones surrounded by hyperenhanced infarcted or injured myocardium.

Statistical analysis

Normally distributed continuous variables were expressed as mean values and SD. Continuous variables that were not normally distributed were expressed as median values with an interquartile range (IQR).

Results

From March 1, 2009 to December 30, 2012, a total of 2065 patients were admitted at Thoraxcentrum Twente in Enschede with the diagnosis of MI; 1715 patients (83 %) had ST elevated myocardial infarction. In 77 of these patients coronary angiography revealed no significant coronary obstruction; 45 of these patients (58 %) underwent CMR assessment. In 11/77 patients (14 %), LGE–CMR revealed tissue characteristics compatible with myocardial necrosis. The characteristics of the 11 study patients are described in detail below.

Clinical and echocardiographic findings

Table 1 summarizes both patients and imaging characteristics. Median age was 54.0 years (IQR 44–60) and 3/11 (27 %) patients were men. None of the patients had a history of previous cardiac disease. Troponin I (median 1.3 ng/l, IQR 0.44–187) and peak creatine kinase levels (median 485 U/l, IQR 234–618) were elevated in all patients. All patients presented with a normal renal function, infection parameters were within normal range and there where no signs of hypercoagulable state". All patients included in this cases series had normal sinus rhythm at admission; no rhythm disorders where observed during admission.

The most frequent ECG changes were ST-segment elevations in the inferior region (6/11 patients) and ST-segment depression in the lateral segments (4/11).

Echocardiography revealed WMA in all but three patients; WMA were observed in the inferior and lateral (7/11) and in the anterior LV segments (4/11). The location of the WMA matched in 6/11 (55 %) patients with the infarct localization based on the ST-segment deviations on ECG. In 3 patients echocardiography revealed no WMA.

Findings of cardiac magnetic resonance imaging

The median interval from presentation with acute chest pain to CMR was 6 days (IQR 3–9). Mean LV ejection fraction was 58 ± 10 %. On the T2-weighted images, edema was present in 7/11 (64 %) patients.

Late gadolinium enhancement was located in the inferior segments (4/11), the inferolateral segments (5/11), the inferoseptal segments (2/11), the anterior segments (3/11), apical segments (3/11) and in the lateral segments (2/11). In addition, in all but two patients (patients J, and K), the localization of myocardial damage was consistent with localization of ECG-abnormalities at admission.

In four patients we observed perfusion defects typical of microvascular obstruction. Figure 1 illustrates CMR and angiographic images of patient E, showing subendocardial delayed enhancement in the inferolateral LV region with typical characteristics of microvascular obstruction. Figure 2 demonstrates images of patient F, showing delayed enhancement in the mid-lateral LV region.

All 11 patients were discharged with long term treatment with aspirin and a statin.

Discussion

In the present study, we found CMR-detectable myocardial scars in 11 out of 45 patients who presented with clinical, ECG, and biochemical signs of an acute MI despite lack of obstructive coronary artery disease. In 4 out of these 11 patients, there was also CMR-based evidence of microvascular obstruction. This case series underlines the importance of performing CMR in as many as possible patients with unexplained ECG and biochemical evidence of MI, as knowledge on the presence of myocardial scarring (especially in combination with microvascular obstruction) is important in both treatment strategies and determining long term prognosis. The detection of scar in all these 11 patients helped us to better treat these patients meaning all 11 patients were discharged with long-term treatment with at least aspirin and a statin.

During the past 4 years, 4 % of our patients referred for acute MI showed unobstructed coronary arteries on urgent coronary angiography. This relatively low rate may be partly explained by the experience of nurses and physicians who are involved in the triage by the emergency

Table 1 Patient and imaging characteristics

Patient ID	Sex	Age	Smoking	HT	HC	FH	DM	ECG abnormality	Troponin-I high sensitive admission	Troponin I-high sensitive max	CK max	Echo WMA	CMR on day	CMR EF (%)	CMR DE area	MVO
A	M	54	N	Y	Y		Y	ST↑ II, III, AvF, V2–V6; ST↓ AvL	0.88	1.3	825	Anterior and Inferior (d) WMA 4	9	50	I, IL(d), apical	N
B	F	80	N	N	N	Y	N	ST↑ V1–V5	0.16	2.19	422	Inferoseptal (d) and Inferolateral (d) WMA 1	3	67	AS (d)	Y
C	M	62	N	N	N	Y	N	ST↑ II, III, AVF	0.49	0.49	119	Inferolateral WMA 1	14	61	IL (m)	Y
D	M	57	Y	N	N	Y	N	ST↑ II, III, AVF, V5–V6	0.02	0.36	322	Lateral WMA 1	6	58	IL (d)	Y
E	F	47	N	Y	N	N	N	ST↑ II, III, AVF ST↓ I, AVL	2.01	2.95	1,155	Anterior WMA 4 Inferior (d) WMA 4	3	39	Infero apical, I (d), IL (d), IS (d), IS (m)	Y
F	F	44	N	N	N	N	N	ST↑ I, AVL, V6; ST↓ III, AVF	0.04	1.07	494	Inferolateral (m) WMA1	9	68	L (m)	N
G	F	42	N	N	N	N	N	ST↑ III, AVF	0.36	0.44	618	Anterior WMA 1 and inferior WMA 1	2	55	I (m + d), IL (m + d)	N
H	F	42	Y	N	N	N	N	Negative T: I, AVL, biphasic T: V3–V6	<0.01	0.25	197	Inferoseptal (m) WMA 1, Anteroseptal WMA 1	2	46	IS (d)	N
I	F	58	N	N	N	N	N	ST↑ I, II, AVL, V4–V6	<0.01	668	501	No WMA	7	63	AL (d), apical, L (d)	N
J	F	45	Y	N	N	Y	N	ST↑ II, III, AVF	62	187	234	No WMA	49	61	AL (d)	N
K	F	60	Y	N	N	Y	N	ST↑ all leads, ST↓ AVR	<9	619	485	No WMA	5	72	I (m + b)	N

HT hypertension, *HC* hypercholesterolemia, *FH* family history, *DM* diabetes mellitus, *MVO* micro vascular obstruction, *CK* creatinine phospokinase, *OHCA* out of hospital cardiac arrest, *AL* anterolateral, *AS* anteroseptal, *b* basal, *DE* delayed enhancement, *d* distal, *EF* ejection fraction, *I* inferior, *IL* inferolateral, *IS* inferoseptal, *L* lateral, *m* mid, *MVO* microvascular obstruction, *WMA* wall motion abnormalities

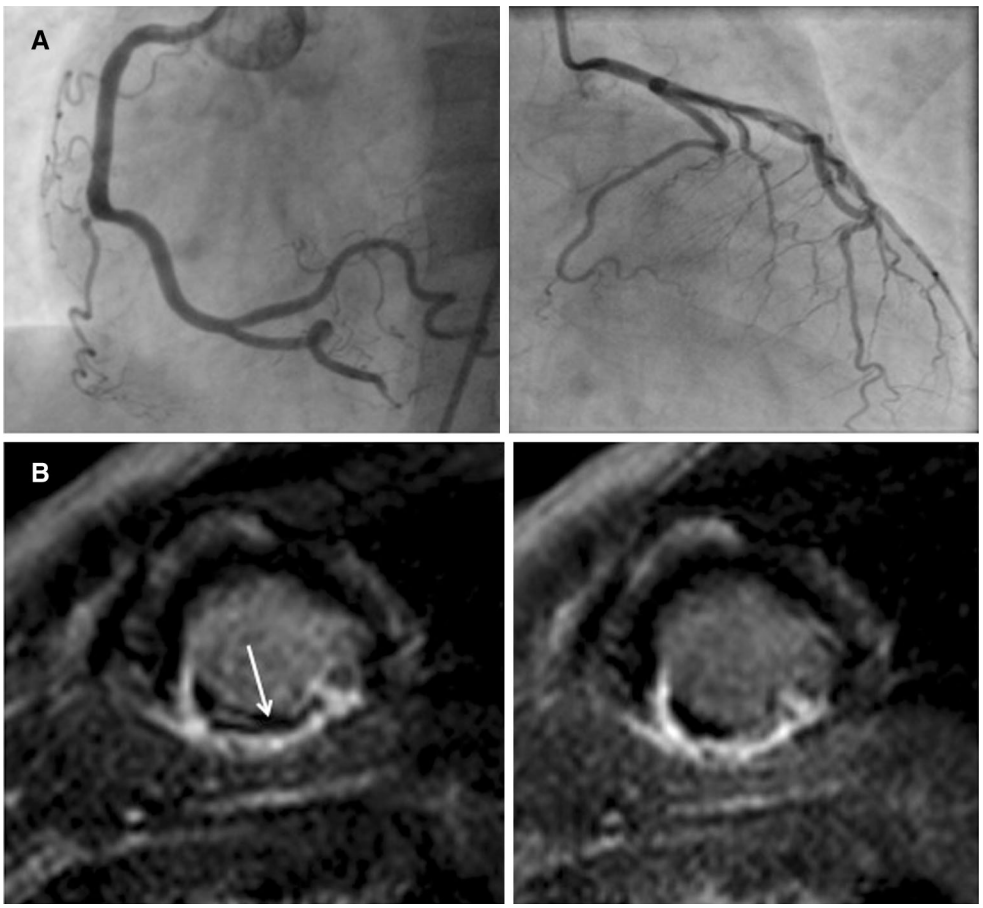

Fig. 1 Coronary angiography and delayed enhancement CMR images (patient E). Coronary angiography (**a**) demonstrated absence of obstructive coronary disease in the right (*left upper panel*) and left (*right upper panel*) coronary arteries. Delayed enhancement CMR images in the short axis view (**b**) showed early after the administration of gadolinium (*left lower panel*) a dark subendocardial zone (*arrowhead*) surrounded by hyperenhanced infarcted myocardium in the inferior myocardial wall, indicating necrosis of myocytes and capillary occlusion in the infarct core. The *right lower panel* shows the extension of hyper-enhanced myocardium late after the administration of contrast

department, and the comprehensive training of ambulance teams and paramedics regarding both clinical assessment of patients with acute chest pain and ECG interpretation. Previous studies have reported rates as high as 10 % [1]. In patients with acute coronary syndromes, in 9–31 % of female and 4–14 % of male patients were reported to have angiographically normal coronary arteries [10]. Lack of an accurate diagnosis might lead to improper treatment and a less stringent secondary prevention. Therefore, lack of diagnostic certainty in MI patients without obstructive coronary artery disease may contribute to a poorer prognosis in such patients [11].

Cardiac magnetic resonance imaging increases the diagnostic certainty in MI patients without obstructive coronary artery disease. LGE–CMR provides detailed information on the characteristics of myocardial tissue and allows detection of even very small areas of myocardial scarring due to its high spatial resolution and contrast. Previous studies revealed that CMR identified the actual diagnosis in two-thirds of patients who were referred with signs of an MI but unobstructed coronary arteries: myocarditis was the cause in the majority in 50 % of cases, followed by myocardial infarction (12–15 %) and (Takotsubo-) cardiomyopathies (3 %) [2, 3].

In our present study, we report the clinical characteristics and findings of cardiac imaging of 11 patients who showed LGE–CMR characteristics compatible with myocardial scarring. Comprising a period of almost 4 years, this population represents 0.6 % of all patients referred for an acute MI to our center. Other studies reported 12 % (7/60) and 15 % (12/80) of patients with an MI to have unobstructed coronary arteries but myocardial scarring on CMR [3, 12]. Christiansen et al. [16] even diagnosed 30 % of these patients with myocardial necrosis.

In our relatively small patient population, WMA on echocardiography were consistent with ECG abnormalities

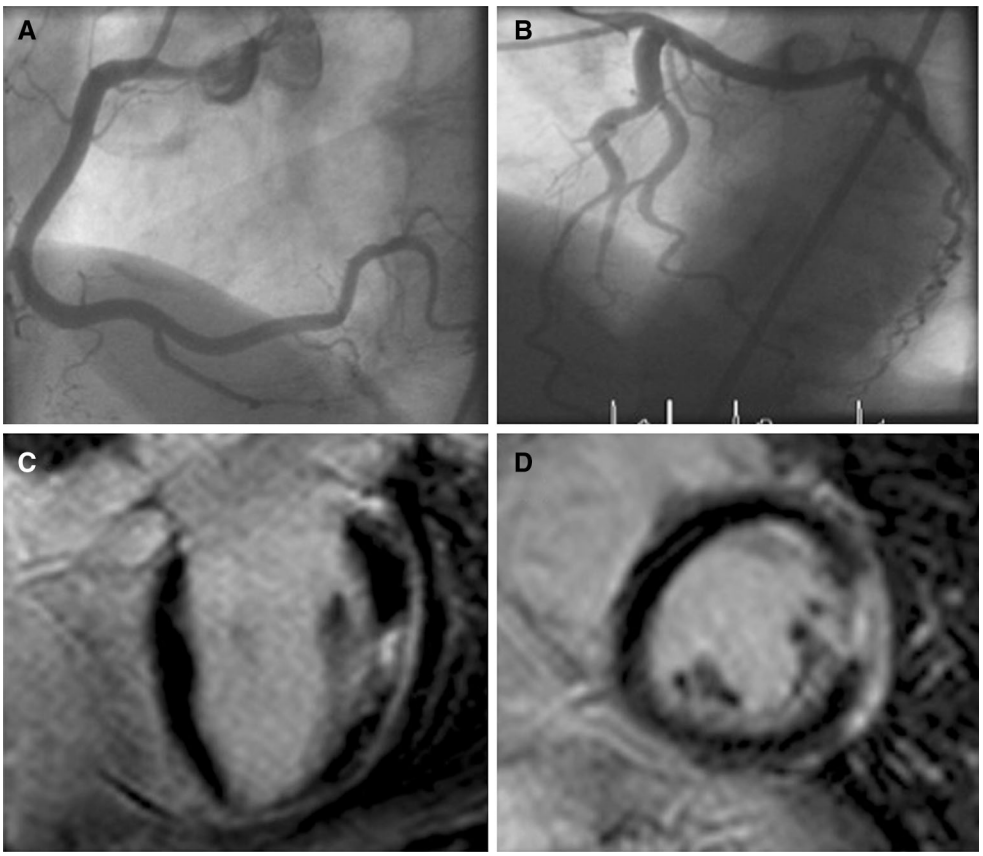

Fig. 2 Coronary angiography and delayed enhancement CMR images (patient F). Coronary angiography demonstrated absence of significant obstructive coronary disease in the right coronary artery (**a**) and the left coronary artery (**b**). LGE-CMR images in the long axis view (**c**) and short axis view (**d**) illustrating LGE in a small portion of the left mid-lateral myocardial wall, indicating myocardial necrosis

in 6 out of 11 patients, while three patients showed no WMA at all. The localization of myocardial scars on CMR matched in 9 out of 11 patients with ECG abnormalities in the corresponding leads, which may indicate that CMR detects the presence of myocardial scarring with greater accuracy than echocardiography, especially if these areas are small.

While the exact pathophysiology of MI in our patients remains uncertain, several hypotheses have been postulated. For instance, MI could have been caused by transient thrombotic obstruction at the site of a disrupted, angiographically non-obstructive atherosclerotic plaque [13.] Moreover, distal embolization of material from the atheroma core might be involved [14, 15]. Other mechanisms comprise coronary embolism or coronary spasm [16]. In our study, all patients received prior to hospital admission two anti-platelet drugs and heparin (according to the routine protocol of the ambulance in our region), which might have supported a rapid dissolution of temporarily occlusive coronary thrombi. By identifying these patients with certainty on the presence of myocardial scarring (which might otherwise have been missed on echocardiography only), there are more clinical arguments for life long treatment with aspirin and a statin in order to reduce the risk of future (thrombo-embolic) events.

Limitations

Although our cases series was accumulated during almost 4 years, the population remained relatively small. Therefore, findings should be interpreted with care. Referral of patients with MI and unobstructed coronary arteries for CMR assessment was left to the discretion of the individual cardiologists, and—as a result—CMR was performed in only 58 % of all possible cases. That, as well as the retrospective character of the analysis, implies potential selection bias. Although patients with a history of previous myocardial infarction were excluded from the analysis, we cannot be entirely sure that all cases of LGE–CMR were related to the clinical event that triggered CMR assessment.

Conclusion

Patients with clinical, ECG, and biochemical signs of acute MI but unobstructed coronary arteries may have CMR-

detectable myocardial scars. Information on myocardial scarring may help to make the correct diagnosis and draw important therapeutic consequences which is important for long term prognosis. The present case series underlines the value of contrast-enhanced CMR for myocardial tissue characterization in this special group of patients.

Conflict of interest None.

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