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FULL PAPER

Peri-infarct ischaemia assessed by cardiovascular MRI: comparison with quantitative perfusion single photon emission CT imaging

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Objective: To develop a new method for the cardiac MR (CMR) quantification of peri-infarct ischaemia using fused perfusion and delayed-enhanced images and to evaluate this method using quantitative single photon emission CT (SPECT) imaging as a reference.

Methods: 40 patients presenting with peri-infarct ischaemia on a routine stress ^{99m}Tc-SPECT imaging were recruited. Within 8 days of the SPECT study, myocardial perfusion was evaluated using stress adenosine CMR. Using fused perfusion and delayed-enhanced images, peri-infarct ischaemia was quantified as the percentage of myocardium with stress-induced perfusion defect that was adjacent to and larger than a scar. This parameter was compared with both the percent myocardium ischaemia (SD%) and the ischaemic total perfusion deficit (TPD). The diagnostic performance of CMR in detection of significant coronary artery stenosis (of $\geq 70\%$) was also determined.

Results: On SPECT imaging, in addition to peri-infarct ischaemia, reversible perfusion abnormalities were

detected in a remote zone in seven patients. In the 33 patients presenting with only peri-infarct ischaemia, the agreement between CMR peri-infarct ischaemia and both SD% and ischaemic TPD was excellent [intraclass coefficient of correlation (ICC) = 0.969 and ICC = 0.877, respectively]. CMR-defined peri-infarct ischaemia for the detection of a significant coronary artery stenosis showed an areas under receiver-operating characteristic curve of 0.856 (95% confidence interval, 0.680–0.939). The best cut-off value was 8.1% and allowed a 72% sensitivity, 96% specificity, 60% negative predictive value and 97% positive predictive value.

Conclusion: This proof-of-concept study shows that CMR imaging has the potential as a test for quantification of peri-infarct ischaemia.

Advances in knowledge: This study demonstrates the proof of concept of a commonly known intuitive idea, that is, evaluating the peri-infarct ischaemic burden by subtracting delayed enhancement from first-pass perfusion imaging on CMR.

Stress ^{99m}Tc myocardial perfusion imaging is a clinically useful tool for assessment of ischaemia, particularly including peri-infarction ischaemia.¹ Peri-infarction ischaemia detected on quantitative perfusion single photon emission CT (SPECT) imaging is associated with restenosis 6 months after acute myocardial infarction (AMI).² Peri-infarction ischaemia is also associated with a greater risk of cardiac death than remote ischaemia.³ In addition, peri-infarction ischaemia is a trigger of ventricular arrhythmias.⁴

The assessment of segmental viability after AMI is possible using cardiac MR (CMR) imaging of contractile reserve,

microvascular obstruction and delayed enhancement extent.⁵ Furthermore, myocardial perfusion can be reliably assessed with CMR at both rest and stress.⁶ Only a few studies^{7,8} have evaluated CMR in the detection of peri-infarction ischaemia. However, no method is currently available to quantify the extent of peri-infarction ischaemia using CMR. Therefore, the main objective of this study was to develop a CMR method for the quantification of peri-infarct ischaemia using fused perfusion and delayed-enhanced images and to examine the agreement between CMR and SPECT imaging for the quantification of peri-infarct ischaemia. The second aim of the study was to determine the value of CMR measured

peri-infarct ischaemia in the detection of significant coronary artery disease, as defined by coronary angiography.

METHODS AND MATERIALS

Patients

This prospective study was approved by our institutional review board. All patients gave their written informed consent before inclusion. 40 consecutive Caucasian patients [35 males; mean age $\pm$ standard deviation (SD), 62.1 ± 11.6 years; range, 36–81 years] referred for routine exercise stress SPECT imaging were included between October 2010 and September 2012. The inclusion criterion was the presence of peri-infarction ischaemia as determined by one expert observer on visual interpretation of SPECT studies. Segments with reversible perfusion defects were considered ischaemic, while segments with fixed perfusion defects during stress and at rest were considered necrotic. Peri-infarction ischaemia was defined as a partly reversible perfusion abnormality in at least one segment in the territory of an infarct-related artery. Exclusion criteria were acute coronary syndrome, atrial fibrillation, contraindications to gadolinium-enhanced CMR (*e.g.* pacemaker) or adenosine infusion (*e.g.* reversible airway disease and atrioventricular block) and a glomerular filtration rate of 30 ml min^{-1} per 1.73 m^2 or less. Stress adenosine CMR was performed within 8 days of the SPECT study. All anti-ischaemic medications were interrupted at least 48 h before each study. In addition, no patient consumed beverages containing caffeine within 24 h of each cardiac study. Coronary angiography was performed within 2 weeks of SPECT studies.

Gated myocardial perfusion single photon emission CT acquisition and analysis

All patients underwent a 1-day $^{99\text{m}}\text{Tc}$ -tetrofosmin rest/stress imaging protocol using a hybrid SPECT/CT scanner (DiscoveryTM NM/CT 570c; GE Healthcare, Haifa, Israel) integrating a cadmium-zinc-telluride (CZT) gamma camera and a 64-slice CT device. Electrocardiogram (ECG)-gated rest images were acquired in prone position during 7 min, 45 min after the injection of 250–370 MBq of $^{99\text{m}}\text{Tc}$ -tetrofosmin, depending on the patients' weight. A symptom-limited exercise treadmill test using the Bruce protocol was employed for all patients. A three times higher dose of $^{99\text{m}}\text{Tc}$ -tetrofosmin was administered at near-maximal exercise, which was continued at a maximal workload for 1 min and, at one stage, lower for 2 additional minutes whenever possible. ECG-gated stress images were acquired in prone position over 4 min, 15–30 min after a radiopharmaceutical injection. Maximum-penalized-likelihood iterative reconstruction was performed on all gates using a dedicated iterative algorithm with integrated collimator geometry modelling. A Butterworth post-processing filter was applied (cut-off frequency, 0.37 cycle per centimetre; order, 7) to the reconstructed slices. For attenuation correction, a prospectively triggered CT scan was acquired at inspiratory breath hold (2.5-mm section thickness, 0.35-s gantry rotation time, 120 kV and 200–250 mAs, depending on the patients' size). Central, radial and tangential resolutions were 4.9, 4.3 and 4.3 mm, respectively.

Images were analysed with a commercially available software package (quantitative perfusion SPECT (QPS)/quantitative gated SPECT (QGS); Cedars-Sinai[®] Medical Centre, Los Angeles, CA). Image analysis was performed by one observer (EB) (10 years'

experience in nuclear cardiology) blinded to CMR results and clinical data. In each patient, two parameters were measured. Automatic processing was performed in all cases, with the option of manual correction in the case of inadequate anatomical delineation. A computer-derived maximum severity score was quantified using a 17-segment model.⁹ Each segment was scored using a five-point scale, as previously described.² A summed stress score (SSS) was computed by adding the scores obtained on each of the 17 segments on stress images and a summed rest score (SRS) by adding the scores obtained on the rest images. To assess defect reversibility, a summed difference score (SDS) was calculated by subtracting SRS from SSS, reflecting the severity and extent of ischaemia. The conversion of SDS to percent ischaemic myocardium (SD%) was accomplished by dividing the SDS by the worst segmental score possible for the 17 segments of the model used (*i.e.* 68 for 17 segments) and multiplying by 100. SD% was the first parameter measured. Peri-infarction ischaemia was defined as ischaemia that was adjacent to a necrosis area and located in the same vessel territory, as previously determined.² Remote ischaemia was defined as reversible perfusion abnormalities in coronary artery distributions other than an infarct-related artery. We also computed the total perfusion deficit (TPD), which is a validated computer-derived analogue of the percent myocardium abnormal by visual analysis,⁹ representing both the extent and severity of a perfusion defect. The TPD was calculated as the percentage of the total surface area of the left ventricle below the pre-defined uniform average deviation threshold using the QPS software. The TPD was measured at stress (stress TPD) and rest (rest TPD). The ischaemic TPD, the second parameter used for the study, was calculated by subtracting rest TPD from stress TPD and was considered to represent myocardial ischaemia in these patients with known coronary artery disease. Thus, in each patient, the SD% and ischaemic TPD were measured.

Cardiac MR acquisition

CMR studies were performed on a 1.5-T clinical scanner equipped with a 32-channel cardiac coil (MAGNETOM[®] Avanto; Siemens Medical Solutions, Forchheim, Germany). Following a low-resolution survey scan and localizers to define the cardiac long and short axes, intravenous adenosine was administered for 5 min at $140 \mu\text{g kg}^{-1} \text{ min}^{-1}$, during which the first-pass stress perfusion imaging was assessed with a $0.05 \text{ mmol kg}^{-1}$ intravenous bolus of gadoterate meglumine (Dotarem[®]; Laboratoire Guerbet, Villepinte, France) followed by a 20-ml flush of saline solution injected at a rate of 5 ml s^{-1} using an automated device (Accutron MR; Medtron AG, Saarbrücken, Germany). The heart rate and blood pressure were monitored during adenosine infusion. During bolus arrival, three short-axis views were acquired at every heart beat at one-quarter, half, and three-quarters of the left ventricular long axis using a T_1 weighted multishot TurboFLASH inversion recovery sequence [repetition time (TR), 6.6 ms; echo time (TE), 1.3 ms; TI, 240 ms; flip angle, 25°; and matrix, 128×128 pixels]. This two-dimensional gradient echo pulse sequence used for perfusion imaging was preceded by a saturation recovery preparation. The in-plane resolution was $2.0625 \times 2.0625 \text{ mm}$. The slice thickness was 10 mm. Perfusion images were acquired at each RR interval during 50 heart beats. Patients were asked to hold their breath on full expiration for the duration of the first pass of the gadolinium bolus. Rest perfusion imaging was undertaken for a minimum of 10 min after stress perfusion, with

a further injection of $0.05 \text{ mmol kg}^{-1}$ gadoterate meglumine. A final injection of 0.1 mmol kg^{-1} gadoterate meglumine was given after this sequence, bringing the overall gadolinium dose to 0.2 mmol kg^{-1} . Cine imaging was then performed to acquire a stack of short-axis slices covering the whole left ventricle from base to apex, using an ECG-gated balanced steady state free precession breath-hold sequence with the following parameters: TR/TE, 20/30 per 1.4 ms; flip angle, 60° ; slice thickness, 6 mm; pixel size, 1.6×1.6 – $1.8 \times 1.8 \text{ mm}$; and 20 frames per cardiac cycle. 15 min after the last injection of gadolinium, delayed-enhanced imaging was performed to acquire a stack of short-axis slices covering the whole left ventricle (LV) from base to apex using an inversion–recovery prepared three-dimensional (3D) turbo fast low-angle-shot breath-hold sequence with the following parameters: TR/TE, 700/1.4 ms; flip angle, 10° ; slice thickness, 6 mm; pixel size, $1.8 \times 1.4 \text{ mm}$. The slice orientation was identical to the one used for the three short-axis perfusion images. Inversion time was optimized on a previously acquired TI scouting sequence.

Cardiac MR image interpretation

CMR data were analysed on a stand-alone computer workstation using the open-source software OsiriX v. 3.9.4 (OsiriX Foundation, Geneva, Switzerland).¹⁰ Perfusion scans were analysed by two observers (HC and CR) (10 and 2 years' experience in CMR, respectively) who were blinded from the results of the SPECT study and clinical data. On adenosine perfusion scans, a perfusion deficit was defined as abnormal if it was darker than the surrounding myocardium and if it persisted more than five images beyond the initial peak enhancement of the segment that appeared most normal. Diffuse sub-endocardial perfusion defects not assignable to a specific coronary supply territory were defined as unspecific. Transient dark rim artefact was not regarded as a perfusion deficit. On delayed-enhanced images, endo- and epicardial contours were manually traced and myocardial scar was automatically segmented with a threshold set at 50% maximal signal intensity using the full width at half maximum technique, as previously described.¹¹

Cardiac MR image fusion technique

Adenosine perfusion images and delayed enhancement images were also matched by the same observers (HC and CR) using the same software OsiriX 3.9.4. The selection of the three delayed enhancement images (basal, mid and apical) for registration to the three perfusion images was done by selecting the appropriate slice location in the image digital imaging and communications in medicine fields. To minimize registration errors, the registration was performed manually aiming at aligning abnormal LV segments first. Adenosine perfusion images were registered to the corresponding delayed-enhanced images to produce a fused image.

Cardiac MR peri-infarct ischaemia analysis

On the resulting image displaying fused delayed-enhanced and stress perfusion data, peri-infarct ischaemia was defined as a stress-induced perfusion defect adjacent to and larger than a scar (Figure 1). Transmural inducible ischaemia in the presence of a sub-endocardial infarct and inducible ischaemia adjacent to the lateral margins of the infarct were included. Both abnormalities were considered as the expression of peri-infarct ischaemia. The area of peri-infarct ischaemia was quantified by manual planimetry and expressed as a percentage using the

Figure 1. An example of region-of-interest drawings in the cardiac MR (CMR) definition of peri-infarct ischaemia. This patient shows a perfusion deficit (arrows) on CMR stress perfusion (a). The same patient has delayed enhancement (arrowhead) in the inferolateral wall (b). The myocardial scar was determined using the full width at half maximum technique (area in green, c). Adenosine perfusion images presenting with significant abnormalities were fused (d and e) with the corresponding sections of delayed enhancement (area in white). On each fused section, peri-infarct ischaemia (region outlined in green) was defined as a stress-induced perfusion deficit area adjacent to and larger than the scar area. For colour image please see online www.birpublications.org/doi/full/10.1259/bjr.20130774.

following formula: the sum of the combined peri-infarct ischaemic areas/the sum of the combined left ventricular myocardial cross-sectional areas over the three short-axis slices. Additionally, on each fused image, remote ischaemia was defined as a stress-induced perfusion defect distinct from the scar. This area was also quantified by manual planimetry. For each patient, global ischaemia was expressed as a percentage using the following formula: the sum of the combined peri-infarct and remote ischaemic areas/the sum of the combined left ventricular myocardial cross-sectional areas over the three short-axis slices.

Coronary angiography

All coronary angiograms were analysed with online quantitative coronary angiography software (ACA; Philips Medical Systems, Eindhoven, Netherlands) by two cardiologists blinded to clinical

Table 1. Baseline characteristics and X-ray angiographic findings

Characteristics	Values (<i>n</i> = 40)
Mean age (years)	62.1 ± 11.6
Male gender, <i>n</i> (%)	35 (87.5)
Family history of pre-mature heart disease, <i>n</i> (%)	16 (40.0)
Hypertension, <i>n</i> (%) ^a	27 (67.5)
Smoking status	
Never smoked, <i>n</i> (%)	4 (10.0)
Ex-smoker, <i>n</i> (%)	23 (57.5)
Current smoker, <i>n</i> (%)	13 (32.5)
Hyperlipidaemia, <i>n</i> (%) ^b	26 (65.0)
Body mass index, <i>n</i> ^c	27.4 (3.6) (24.4–29.4)
Diabetes mellitus, <i>n</i> (%)	8 (20.0)
Previous hospital admission for acute myocardial infarction or acute coronary syndrome, <i>n</i> (%)	36 (90.0)
Previous percutaneous coronary intervention, <i>n</i> (%)	35 (87.5)
Previous CABG, <i>n</i> (%)	3 (7.5)
Medication	
Aspirin or clopidogrel or prasugrel, <i>n</i> (%)	39 (97.5)
Anticoagulant, <i>n</i> (%)	4 (10.0)
Statins, <i>n</i> (%)	37 (92.5)
Angiotensin-converting enzyme or angiotensin II receptor blockers, <i>n</i> (%)	28 (70.0)
β-blocker, <i>n</i> (%)	33 (82.5)
Angina pectoris class	
CCS I, <i>n</i> (%)	8 (20.0)
CCS II, <i>n</i> (%)	20 (50.0)
CCS III, <i>n</i> (%)	10 (25.0)
CCS IV, <i>n</i> (%)	2 (5.0)
Patients undergoing X-ray angiography, <i>n</i> (%)	39 (97.5)
Any significant stenosis, <i>n</i> (%) ^d	26 (65.0)
Triple-vessel disease, <i>n</i> (%) ^d	8 (20.0)
Double-vessel disease, <i>n</i> (%) ^d	6 (15.0)
Single-vessel disease, <i>n</i> (%) ^d	12 (30.0)
Left main stem artery disease, <i>n</i> (%) ^d	3 (7.5)
Left anterior descending artery disease, <i>n</i> (%) ^d	18 (45.0)
Left circumflex artery disease, <i>n</i> (%) ^d	15 (37.5)
Right coronary artery disease, <i>n</i> (%) ^d	15 (37.5)
CABG disease, <i>n</i> (%) ^d	2 (5.0)

CABG, coronary artery bypass grafting surgery; CCS, Canadian Cardiovascular Society grading of angina pectoris.

Patients' characteristics on admission.

Values are number (*n*) of patients (percentages), means ± standard deviation or medians (interquartile ranges).

^aHypertension was defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

^bHyperlipidaemia was defined by total cholesterol >6.5 mmol l⁻¹, low density lipoprotein (LDL) cholesterol >4.0 mmol l⁻¹ or high density lipoprotein (HDL) cholesterol <1.2 mmol l⁻¹.

^cBody mass index was expressed in kg m⁻².

^dA reduction in the luminal diameter of 70% was considered as a significant stenosis.

data (PC and EG) (20 and 8 years' experience in coronary angiography, respectively) to confirm the presence of significant epicardial stenosis. A reduction in the luminal diameter of 70% was considered as significant stenosis (70% cut-off value). The two cardiologists (PC and EG) determined for each patient the dominance of the coronary arteries. The coronary tree was considered right dominant when the posterior descending artery and posterolateral branches originated from the right coronary artery (RCA) and left dominant when they both originated from the left circumflex artery (LCX). A balanced coronary circulation was defined when the posterior descending artery originated from the RCA and all posterolateral branches from the LCX. The two cardiologists (PC and EG) also determined for each patient the coronary arterial supply for the more variably supplied segments. Consequently, all myocardial segments (American Heart Association 17 segment model) have been correctly assigned to the appropriate coronary artery.¹² Then, CMR data were retrospectively analysed in view of arteriographic findings to determine the diagnostic performance of CMR in detection of significant coronary artery stenosis (of $\geq 70\%$).

Statistical analysis

Continuous data are expressed as mean $\pm$ standard deviation, or median (interquartile range) when appropriate. The Shapiro–Wilk test of normality and z-scores for skewness and kurtosis were used to assess whether quantitative data conformed to the normal distribution. Heart rate and blood pressure variations during adenosine infusion were analysed using Student's paired *t*-test or

Wilcoxon signed-rank test, depending on data distribution. Interobserver and intra-observer variability was determined as mean absolute difference (bias) and 95% confidence interval (CI) of the mean difference (limits of agreement) according to the methods of Bland and Altman. Furthermore, the agreement between methods was evaluated using intraclass coefficient of correlation (ICC) and Bland and Altman analysis. The diagnostic performance of the peri-infarct ischaemia percentage at CMR for detecting a significant stenosis in the distribution of an infarct-related artery was assessed using receiver–operating characteristic (ROC) curve analysis. Areas under ROC curves (AUC) were compared using Z-statistics. All statistical tests were two-tailed. Analyses were performed using NCSS 2001 (NCSS Statistical Software, Kaysville, UT) except Bland and Altman analysis (Excel®; Microsoft Corporation, Redmond, WA). *p*-values < 0.05 were considered to indicate statistical significance.

RESULTS

Population

Between October 2010 and September 2012, 1946 patients were referred for routine exercise stress SPECT imaging using a hybrid SPECT/CT scanner (Discovery NM/CT 570c; GE Healthcare) in our centre (Hôpital du Haut Lévêque, Pessac, France). In this population, 212 (10.9%) had peri-infarct ischaemia on visual interpretation of SPECT studies. Among them, 45 patients had atrial fibrillation; 60 patients had contraindications to gadolinium-enhanced CMR or adenosine infusion; 30 patients presented a glomerular filtration rate of 30 ml min^{-1} per 1.73 m^2

Table 2. The quantification of ischaemia, values of left ventricular end-diastolic volume (EDV), left ventricular end-systolic volume (ESV) and left ventricular ejection fraction from single photon emission CT (SPECT) and cardiac MR (CMR)

Patients	Peri-infarct ischaemia (<i>n</i> = 33)	Global ischaemia (<i>n</i> = 40)
Summed stress score	14.0 (8.0–24.0)	13.5 (8.0–24.0)
Summed rest score	8.0 (3.0–12.0)	7.0 (2.0–10.2)
Summed difference score	5.0 (4.0–8.0)	5.0 (4.0–9.0)
Percent myocardium ischaemia (SD%)	7.0 (6.0–12.0)	7.0 (6.0–13.0)
TPD stress (%)	22.0 (11.0–32.0)	21.5 (11.7–31.2)
TPD rest (%)	12.0 (6.0–16.0)	11.0 (5.0–16.0)
Ischaemic TPD (%)	7.0 (4.0–12.0)	7.5 (3.7–12.2)
CMR stress perfusion defect (%)	21.5 (16.8–30.0)	21.0 (15.7–29.0)
CMR scar (%)	14.6 (7.2–18.3)	13.8 (7.1–18.2)
CMR ischaemia percentage (%)	7.5 (5.0–10.7)	7.7 (5.2–11.8)
Left ventricular values from SPECT		
Median EDV (ml)	92.0 (25.0)	91.0 (25.0)
Median ESV (ml)	41.0 (24.0)	39.0 (23.0)
Mean ejection fraction (%) $\pm$ SD	54.0 $\pm$ 10.1	56.0 $\pm$ 10.5
Left ventricular values from CMR		
Median EDV (ml)	121.0 (34.0)	118.0 (33.0)
Median ESV (ml)	51.0 (28.0)	48.0 (27.0)
Mean ejection fraction (%) $\pm$ SD	56.9 $\pm$ 10.0	58.7 $\pm$ 10.4

SD, standard deviation; SD%, conversion of summed difference score to percent myocardium ischaemia; TPD, total perfusion deficit. Data are medians (interquartile ranges).

or less and 37 patients declined participation to this study. Consequently, the study included 40 patients whose characteristics are reported in Table 1. Of these patients, 36 had previous myocardial infarction of ≥ 6 months and 3 had previous coronary artery bypass of ≥ 3 years. 88% ($\pm 8.0\%$) of the maximum age-predicted heart rate was obtained during symptom-limited exercise treadmill test. The mean achieved workload with exercise was 147 ± 31 W. During adenosine infusion, the heart rate

increased significantly (64 ± 10 vs 92 ± 13 beats per minute; $p < 0.001$) and the systolic blood pressure decreased (161 ± 23 vs 147 ± 25 mmHg; $p = 0.009$).

Cardiac MR and single photon emission CT ischaemia quantification

The results of ischaemia quantification using the two techniques are presented in Table 2. In addition to peri-infarct ischaemia, reversible

Figure 2. The agreement between cardiac MR (CMR) peri-infarct and global ischaemia and SD%. The correlation analysis and Bland and Altman plots are shown for the measurement of peri-infarct and global ischaemia. d, mean difference; ICC, intraclass coefficient of correlation; SD, standard deviation; SD%, conversion of summed difference score to percent myocardium ischaemia.

perfusion abnormalities were also detected in a remote zone in seven patients on SPECT imaging. On the 40 patients, intra-observer and interobserver variability for CMR peri-infarct ischaemia was low with a mean bias of 0.1% (limits of agreement $\pm 2.1\%$) and -0.4% (limits of agreement $\pm 3.6\%$), respectively. In addition, intra-observer and interobserver variability for CMR global ischaemia was low with a mean bias of 0.15% (limits of agreement $\pm 2.6\%$) and -0.5% (limits of agreement $\pm 3.9\%$), respectively.

Agreement between cardiac MR and single photon emission CT

The agreement between the CMR peri-infarct ischaemia percentage and the SD% was excellent for the 33 patients presenting with only peri-infarct ischaemia on SPECT imaging (ICC = 0.969, Figure 2). The agreement between the CMR global ischaemia percentage and the SD% was excellent when considering the whole population (ICC = 0.963, Figure 2).

Figure 3. The agreement between cardiac MR (CMR) peri-infarct and global ischaemia and ischaemic total perfusion deficit (TPD). Correlation analysis and Bland and Altman plots are shown for the measurement of peri-infarct and global ischaemia. d, mean difference; ICC, intraclass coefficient of correlation; SD, standard deviation; SD%, conversion of summed difference score to percent myocardium ischaemia.

However, a weak but significantly positive correlation was found between the standard deviation and the mean of measurements [Spearman coefficient of correlation (ρ) was 0.4 (0.011) and 0.369 (0.034) for total and peri-infarction ischaemia, respectively], indicating that the agreement between both methods depended on the extent of peri-infarct or remote ischaemia.

The agreement between CMR peri-infarct ischaemia percentage and the ischaemic TPD was excellent for the 33 patients presenting with only peri-infarct ischaemia on SPECT imaging

(ICC = 0.877, [Figure 3](#)). In the whole population, the agreement between global ischaemia percentage and the ischaemic TPD was also excellent ($R = 0.806$, [Figure 3](#)). Using TPD, no correlation was found between the standard deviation of measurements and their mean.

An example of peri-infarct ischaemia using CMR and SPECT is presented in [Figure 4](#). In one case, there was a disagreement between CMR and SPECT findings. In this patient, stress CMR did not detect any significant peri-infarct ischaemia ([Figure 5](#)).

Figure 4. An example of peri-infarct ischaemia in a 64-year-old male revealing a severe stenosis of the mid segment of the right coronary artery (RCA). 1 year earlier, the patient presented an inferior ST-elevated myocardial infarction. He underwent direct stenting of the RCA with a drug-eluting stent. The patient recently presented with angina during strenuous effort. Stress and rest single photon emission CT (a) suggested a reversible perfusion defect in the mid and distal inferolateral wall. Myocardial scintigraphy also detected hypo-uptake in the distal inferior wall at rest. Stress cardiac MR (b) confirmed a myocardial perfusion defect adjacent to and larger than the sub-endocardial inferior scar. Coronary angiography (c) confirmed a severe restenosis in the proximal edge of the first stent. Consequently, another drug-eluting stent was implanted with a good final result.

Coronary angiography

One patient declined to undergo coronary angiography. 27 out of 39 patients presented significant coronary artery disease in the peri-infarct ischaemia area determined by CMR and SPECT. Among them, three patients had a significant stenosis in a remote ischaemic area determined by CMR and SPECT. 20 out of 39 patients underwent a coronary angioplasty. 11 patients had a significant restenosis in the infarct-related coronary artery. Two patients had a significant stenosis in collateral arteries

supplying the persisting viable myocardium of an occluded artery. Four out of seven patients had a successful recanalization of the occluded coronary artery. The number of treated lesions per patient was 1.4 ± 0.8 . The number of stents per patient was 1.8 ± 1.0 . Two patients underwent coronary artery bypass grafting surgery, and one patient refused coronary artery bypass grafting surgery. 16 patients continued medical treatment, with an intensification in 4 of them.

Figure 5. An example of false-negative stress cardiac MR (CMR) for the detection of peri-infarct ischaemia. A 55-year-old female patient underwent a stress-rest gated myocardial perfusion single photon emission CT (SPECT) as part of a complete health check-up. She was a smoker with hyperlipidaemia, Type 2 diabetes and hypertension. She was asymptomatic. Stress-rest gated myocardial perfusion SPECT (a) showed a small area of necrosis in the inferior wall. This examination also detected myocardial ischaemia in the right coronary artery (RCA) vascular territory. Stress CMR (b) showed a perfusion defect in the inferior wall, which was superimposable to the scar on delayed enhancement imaging. This examination did not detect any significant peri-infarct ischaemia. However, coronary angiography (c) determined a chronic total occlusion of the right coronary artery. This patient had a successful recanalization of the right coronary artery with two drug-eluting stents.

Comparison of cardiac MR with quantitative coronary angiography

The ROC analysis for the detection of significant stenosis (*i.e.* $\geq 70\%$) was performed on the 32 patients presenting with peri-infarct ischaemia only (Figure 6). CMR-defined peri-infarct ischaemia showed an AUC of 0.856 (95% CI, 0.680–0.939). The best cut-off value was 8.1% of peri-infarct ischaemia and allowed a 72% sensitivity, 96% specificity, 60% negative-predictive value and 97% positive-predictive value.

DISCUSSION

This study introduces a new method for the quantification of peri-infarct ischaemia based on combined delayed-enhanced and stress perfusion CMR data. Studying 33 patients with a large range of peri-infarct ischaemia on SPECT imaging, we observed that (1) CMR quantification of peri-infarct ischaemia is feasible, (2) the agreement between SPECT and CMR for the quantification of peri-infarct ischaemia is excellent, and (3) CMR-derived peri-infarct ischaemia with a cut-off value of 8.1% accurately detects significant coronary artery disease.

Agreement between cardiac MR and single photon emission CT

Peri-infarction ischaemia is a trigger of ventricular arrhythmias and is associated with adverse left ventricular remodelling. The determination of peri-infarction ischaemia using CMR is important in routine adenosine stress CMR practice. However, a direct quantitative comparison of the CMR pattern with SPECT imaging as a reference has not been reported. Recently, two major studies, CE-MARC¹³ and MR-IMPACT II,¹⁴ demonstrated that CMR is a valuable alternative to SPECT to detect significant coronary artery stenosis, but these two studies did not evaluate specifically the accuracy of CMR in quantifying peri-infarct ischaemia. Thus, only a few studies have evaluated CMR in the detection of peri-infarction ischaemia. The definition of

peri-infarct ischaemia using CMR may be debatable. However, all previous studies^{7,8} have used the same criteria. The extent of the inducible perfusion defect under adenosine stress was compared in the corresponding delayed-enhanced images to see whether the perfusion defect overlaps the extent of the infarcted myocardial tissue or not. This was achieved by direct comparison of the corresponding images with respect to their sub-endocardial or transmural extent. In our study, the agreement between peri-infarct myocardial ischaemia defined by CMR using fused perfusion and delayed-enhanced images and two SPECT parameters, that is, SD% and ischaemic TPD, was excellent. The TPD measure was designed to be equivalent to the commonly used summed segmental scoring, but it has a continuous character and does not require arbitrary segmental definition.⁹ TPD and SD methods evaluate combined defect severity and extent, whereas no severity component is used for the CMR method except a mural penetration threshold. Even if stress CMR analysis of peri-infarct ischaemia is only performed on three short-axis views in our study, we hypothesize that we would obtain similar results using dynamic 3D whole-heart MR myocardial perfusion imaging.¹⁵

Comparison of cardiac MR with quantitative coronary angiography

In this study, the diagnostic performance of CMR in detection of a significant stenosis (*i.e.* $\geq 70\%$) was excellent. The best cut-off value of CMR-defined peri-infarct ischaemia was 8.1% in our population including 80% of symptomatic patients. This value is very close to the cut-off value of 10% found in the COURAGE trial nuclear substudy that assessed global ischaemia in a large population.¹⁶ However, Hachamovitch et al¹⁷ observed, in 3216 patients with prior AMI who underwent SPECT, that therapeutic benefit of revascularization was relatively independent of the level of ischaemia. Consequently, they suggested that both the absence of significant ischaemia, and the presence of extensive AMI, identifies patients who are unlikely to benefit from revascularization. Unfortunately, our study was not designed to determine whether quantification of peri-infarct ischaemia using CMR could help to predict future cardiovascular events in a high-risk patient population. Moreover, it is likely that the diagnostic performance of CMR to detect severe coronary stenosis will be significantly affected by test referral bias, since all patients had evidence of peri-infarct ischaemia on SPECT in order to be enrolled in the study. Consequently, statements regarding sensitivity and specificity for the detection of peri-infarct ischaemia using CMR should be treated with caution.

Limitations

Firstly, our study included a small number of patients. Secondly, as we included only patients with ^{99m}Tc-SPECT-defined peri-infarct ischaemia as a reference for the adenosine stress CMR, the current evaluation is accurate only for this population. ^{99m}Tc-SPECT may not be the ideal reference standard against which to compare CMR-determined peri-infarct ischaemia. As described by Wagner et al,¹⁸ SPECT cannot detect a significant number of sub-endocardial myocardial infarctions. The inability to accurately detect smaller myocardial infarctions may affect the measurement of peri-infarct ischaemia. Thirdly, the present

Figure 6. Receiver-operating characteristic curves for the detection of a significant coronary artery stenosis using cardiac MR peri-infarct ischaemia.

study did not compare CMR and SPECT with a standard invasive functional assessment such as fractional flow reserve. Fourthly, we acknowledge that LV motion throughout the cardiac cycle during the acquisition of the three perfusion slices led to differences in LV shape between delayed enhancement and perfusion images. However, as outlined in the CMR image fusion technique section, to minimize registration errors, registration was performed manually aiming at aligning abnormal LV segments first. Thus, most registration errors were located in normal LV segments therefore minimizing the impact of misregistration on the quantification of peri-infarct ischaemia. Finally, the ^{99m}Tc -SPECT

study employed symptom-limited exercise treadmill test using the Bruce protocol, whereas stress CMR applied adenosine infusion.

CONCLUSION

The main finding of our study was the excellent agreement between peri-infarct myocardial ischaemia defined by CMR and the two SPECT imaging parameters, SD% and ischaemic TPD. This proof-of-concept study shows that CMR imaging has potential as a test for the quantification of peri-infarct ischaemia. Consequently, CMR imaging may be an alternative to SPECT to quantify peri-infarct ischaemia.

REFERENCES

- Elhendy A, Soozy FB, van Domburg RT, Bax JJ, Geleijnse ME, Valkema R, et al. Accuracy of exercise stress technetium 99m sestamibi SPECT imaging in the evaluation of the extent and location of coronary artery disease in patients with an earlier myocardial infarction. *J Nucl Cardiol* 2000; **7**: 432–8. doi: [10.1067/mnc.2000.107426](https://doi.org/10.1067/mnc.2000.107426)
- Zellweger MJ, Weinbacher M, Zutter AW, Jeger RV, Mueller-Brand J, Kaiser C, et al. Long-term outcome of patients with silent versus symptomatic ischemia six months after percutaneous intervention and stenting. *J Am Coll Cardiol* 2003; **42**: 33–40.
- Elhendy A, Schinkel AFL, van Domburg RT, Bax JJ, Poldermans D. Differential prognostic significance of peri-infarction versus remote myocardial ischemia on stress technetium-99m sestamibi tomography in patients with healed myocardial infarction. *Am J Cardiol* 2004; **94**: 289–93.
- John Sutton M, Lee D, Rouleau JL, Goldman S, Plappert T, Braunwald E, et al. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. *Circulation* 2003; **107**: 2577–82.
- Nijveldt R, Beek AM, Hirsch A, Stoel MG, Hofman MB, Umans VA, et al. Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury. *J Am Coll Cardiol* 2008; **52**: 181–9.
- Al-Saadi N, Nagel E, Gross M, Bornstedt A, Schnackenburg B, Klein C, et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. *Circulation* 2000; **101**: 1379–83.
- Tsukiji M, Nguyen P, Narayan G, Hellinger J, Chan F, Herfkens R, et al. Peri-infarct ischemia determined by cardiovascular magnetic resonance evaluation of myocardial viability and stress perfusion predicts future cardiovascular events in patients with severe ischemic cardiomyopathy. *J Cardiovasc Magn Reson* 2006; **8**: 773–9.
- Vincenti G, Nkoulou R, Steiner C, Imperiano H, Ambrosio G, Mach F, et al. Noninvasive stress testing of myocardial perfusion defects: head-to-head comparison of thallium-201 SPECT to MRI perfusion. *J Nucl Cardiol* 2009; **16**: 549–61.
- Germano G, Kavanagh PB, Slomka PJ, Van Kriekinge SD, Pollard G, Berman SD. Quantitation in gated perfusion SPECT imaging: the Cedars-Sinai approach. *J Nucl Cardiol* 2007; **14**: 433–54.
- Rosset A, Spadola L, Ratib O. OsiriX: an open-source software for navigating in multidimensional DICOM images. *J Digit Imaging* 2004; **17**: 205–16. doi: [10.1007/s10278-004-1014-6](https://doi.org/10.1007/s10278-004-1014-6)
- Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2011; **4**: 150–6. doi: [10.1016/j.jcmg.2010.11.015](https://doi.org/10.1016/j.jcmg.2010.11.015)
- Pereztol-Valdes O, Candell-Riera J, Santana-Boado C, Angel J, Aguade-Bruix S, Castell-Conesa J, et al. Correspondence between left ventricular 17 myocardial segments and coronary arteries. *Eur Heart J* 2005; **26**: 2637–43.
- Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet* 2012; **379**: 453–60.
- Schwittler J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettler K, et al. MR-IMPACT II: magnetic resonance imaging for myocardial perfusion assessment in coronary artery disease trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. *Eur Heart J* 2013; **34**: 775–81.
- Jogiya R, Kozerke S, Morton G, De Silva K, Redwood S, Perera D, et al. Validation of dynamic 3-dimensional whole heart magnetic resonance myocardial perfusion imaging against fractional flow reserve for the detection of significant coronary artery disease. *J Am Coll Cardiol* 2012; **60**: 756–65.
- Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the clinical outcomes utilizing revascularization and aggressive drug evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008; **117**: 1283–91. doi: [10.1161/CIRCULATIONAHA.107.743963](https://doi.org/10.1161/CIRCULATIONAHA.107.743963)
- Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LEJ, Friedman JD, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; **32**: 1012–24.
- Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003; **361**: 374–9.