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# **Head-to-Head Comparison of a 2 day Myocardial Perfusion Gated SPECT protocol and Cardiac Magnetic Resonance Late Gadolinium Enhancement for the Detection of Myocardial Infarction**

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**Running title:** SPECT and CMR for myocardial infarction

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## ABSTRACT

**Background:** The aim was to determine the sensitivity and specificity of gated myocardial perfusion SPECT (MPS) with a technetium-labelled (Tc) perfusion tracer to detect myocardial infarction (MI) in a clinical population referred for assessment of stress induced ischemia using late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) as reference method.

**Methods:** 119 patients referred for evaluation of stress induced ischemia with MPS were included. 108 patients (age  $62 \pm 10$  years, 39% females) completed MPS and CMR. A 2-day protocol for MPS were used for most patients ( $n=105$ ).

**Results:** MI was found in 31 patients (29%) using MPS and 30 patients using CMR (28%). The sensitivity and specificity on a patient basis were 93% and 96%, respectively. Positive predictive value (PPV) was 90% and negative predictive value (NPV) was 97%. Per territory, the sensitivity and specificity for LAD-infarcts were 83% and 97%, respectively. PPV was 77% and NPV was 98% for LAD-infarcts. The sensitivity and specificity for RCA/LCx-infarcts were 95% and 95%, respectively. PPV was 84% and NPV was 99% for RCA/LCx-infarcts. The MI size on CMR was  $12.0 \pm 7.3\%$  of the LV and mean transmuralitity was  $66.3 \pm 12.0\%$ . All  $MI > 3\%$  were detected on gated SPECT.

**Conclusion:** This study has demonstrated high sensitivity and specificity for gated Tc-MPS detecting subendocardial and transmural MI.

**Key Words:** Technetium, gated SPECT, MRI, coronary artery disease, myocardial infarction

## BACKGROUND

The detection of myocardial infarction (MI) is important in clinical cardiology and myocardial perfusion scintigraphy with single-photon emission computed tomography (SPECT) is widely used for this purpose (1). Decreased perfusion tracer uptake at rest indicates a loss of viability and hypoperfusion and therefore indicates MI.

Cardiac magnetic resonance imaging (CMR) using late gadolinium contrast enhancement (LGE) has emerged as the reference imaging method for MI (2) with high spatial resolution and an ability to detect MI as small as a few grams (3-5). LGE-CMR can be used both in the acute and chronic stages of MI and demonstrates hyper-enhancement in MI due to an increased distribution volume for the contrast media in both necrosis (acute MI) and fibrous tissue (chronic MI) (6-7). Infarct size on CMR correlates to that on myocardial perfusion SPECT (MPS) using technetium (Tc) (8) or thallium (9). Studies comparing LGE-CMR to MPS have raised concerns regarding the sensitivity and specificity of MPS for infarct detection (10-13). However, some of these studies were performed using thallium as perfusion tracer and did not use gated SPECT. Technetium-labelled tracers yield superior image quality for MPS and gated SPECT helps in the diagnosis of MI showing decreased regional function in areas of MI and this approach has been used in two previous studies (12, 14). The specificity of MPS is also increased when using gated SPECT (15). Therefore, the aim of this study was to determine the sensitivity and specificity of gated Tc-MPS to detect myocardial infarction in a clinical population referred for assessment of stress induced ischemia using LGE-CMR as reference method.

## MATERIALS AND METHODS

**Study population and design.** The local medical ethics committee approved the study.

Patients referred for elective MPS because of suspected coronary artery disease (CAD) or

detection of ischemia in cases of known heart disease were asked to participate. Patients were excluded in cases of atrial fibrillation, cardiac pacemaker or claustrophobia. Presence of previous MI was not taken into account when considering a patient for inclusion. CMR and stress MPS were performed the same day. Rest MPS was performed within 5 days of stress MPS and CMR. In total, 119 patients were included in the study. Pharmacological stress was performed during CMR with adenosine (n=111) or dobutamine (n=8) according to standard protocols (16). Isotope was injected in a peripheral vein at peak stress immediately followed by MR contrast media. Adenosine stress had to be suspended in one patient due to arrhythmia but LGE images could be obtained. Out of 119 included patients, 108 patients (age  $62 \pm 10$  years, 42 females) could be used for image analysis with both CMR and gated SPECT. The patient characteristics are listed in Table 1. Seven patients were excluded due to inability to perform CMR (claustrophobia or arrhythmia), 3 due to loss of CMR-images during archiving and one patient due to inadequate CMR image quality. No patients were excluded due to reasons pertaining to SPECT

**MPS:** A body weight adjusted dose (500-700 MBq) of  $^{99m}\text{Tc}$ -tetrofosmin (GE Healthcare) was used for MPS at rest and stress using a 2-day protocol in 105 patients. The remaining 3 patients underwent a 1-day rest-stress protocol for logistical reasons. The doses for the 1 day-protocol were 350-370 MBq at rest and 1000-1080 MBq at stress. MPS acquisition was performed using a dual-head gamma camera (Vertex, ADAC Corporation, Milpitas, CA, USA) equipped with high-resolution, parallel-hole collimators as previously described (17-19). Data were collected at 32 projections over a  $180^\circ$  orbit, 40 seconds per projection, and  $64 \times 64$  matrix zoomed to a pixel size of 5 mm. Image acquisition time was approximately 15 min. Iterative reconstruction using maximum-likelihood expectation maximization was performed, with a low-resolution Butterworth filter and a cutoff frequency set to 0.5 of

Nyquist and an order of 5.0. ECG gated SPECT acquisition was performed in eight phases at rest and stress. Attenuation correction was not used.

**CMR:** A 1.5 T system (Philips Intera CV, Philips, Best, The Netherlands) with a cardiac synergy coil was used to acquire short- and long-axis LGE-CMR images covering the left ventricle 15 minutes after administration of a total of 0.2 mmol/kg of an extra-cellular gadolinium-based contrast agent (gadopentetate dimeglumine or gadoteric acid) as previously described (20-21). Images were acquired during end-expiratory breath-hold, using an ECG-triggered segmented 3D inversion-recovery gradient echo sequence. Typical sequence parameters were: repetition time 4.2 ms, echo time 1.3 ms, flip angle 15° with acquisition at every heartbeat. In-plane image resolution 1.5x1.5 mm with slice thickness reconstructed to 8 mm without slice gap. Inversion time was manually set to null the myocardium and was for most patients from 220-280 ms.

**Image analysis:** Two experienced physicians evaluated the MPS and CMR data in consensus blinded to patient data. An additional 23 patients with ischemic and non-ischemic cardiomyopathy were added to the CMR images to avoid bias of knowing how many infarcts were found in the MPS data. MIs were located in the LAD-territory (anterior, septal and/or apical parts) or in the RCA/LCx territory (lateral and/or inferior parts). A perfusion defect on the resting MPS detected by visual analysis with decreased wall thickening in the systolic frames was considered as MI. If the perfusion defect was not present at stress, the resting defect was interpreted as an artefact. On CMR, hyper-enhanced regions extending from the endocardium in the left ventricle visualized in two perpendicular imaging planes were reported as MI. Myocardial infarct size was quantified using a previously described semi-automatic quantification method (22) and expressed as a percentage of the left ventricle. Infarct transmuralty was quantified as previously described (23) by assessing the radial extent of hyperenhancement between the endocardial and epicardial borders of the

myocardial wall at 4.5° intervals around the circumference of LV short-axis DE-MR images.

The mean transmural extent of the entire MI was then determined. All image analysis was performed using Segment v1.8 (22) (<http://segment.heiberg.se/>).

**Statistical analysis.** Statistical data analysis was performed using GraphPad Prism 5.02.

Continuous variables are expressed as mean  $\pm$ SD. The results from SPECT and CMR imaging are presented in a 2 $\times$ 2 frequency table. Sensitivity, specificity and negative and positive predictive values with corresponding 95% confidence interval (CI) were calculated using standard definitions. Two-tailed *t*-test was used to test statistical significance of differences between continuous variables. Differences with *p*-values below 0.05 were considered statistically significant.

## RESULTS

Infarcts were found in 31 patients (29%) using MPS and 30 patients using CMR (28%) (Table 2). Four patients had MI in both the LAD and RCA/LCx territories on CMR compared to seven on MPS. CMR and MPS found 12 vs 13 LAD-infarcts and 22 vs 25 infarcts in the RCA/LCx-territory, respectively. The sensitivity and specificity on a patient basis were 93% (CI 78-99%) and 96% (CI 89-99%), respectively (Table 2). PPV was 90% (CI 74-98%) and NPV was 97% (CI 91-100%). When dividing MI per territory, the sensitivity and specificity for LAD-infarcts were 83% (CI 52-98%) and 97% (CI 91-99%), respectively (Table 3). PPV was 77% (CI 46-95%) and NPV was 98% (CI 93-100%) for LAD-infarcts. The sensitivity and specificity for RCA/LCx-infarcts were 95% (CI 77-100%) and 95% (CI 89-99%), respectively (Table 4). PPV was 84% (CI 64-95%) and NPV was 99% (CI 93-100%) for RCA/LCx-infarcts. The mean MI size on CMR was 16.2 $\pm$ 10.2 ml or 12.0 $\pm$ 7.3% of the LV (range 2-33%) and mean transmural extent was 44 $\pm$ 10% (range 18-58%). Sixteen patients had infarcts <11% of the LV and of these 13 (81%) patients were accurately diagnosed with



infarction. The three false negative gated SPECT studies corresponded to the smallest infarcts with infarct sizes of 2.3, 1.9 and 1.8 % of the LV mass, respectively. In one of these patients SPECT detected infarction in the LCx/RCA territory but missed a small infarction in the LAD-territory. Therefore there are three infarcts missed on a vessel basis but only two missed infarcts on a patient basis. Notably, all infarcts >3% of LV mass were detected on gated SPECT. The number of segments with varying degree of transmuralities are shown in Figure 1. 16 patients had subendocardial infarcts, i.e. segmental infarct transmuralities <50% (13). Of these, 2 were false negative on MPS (16% and 26% maximum transmuralities respectively) but the remaining 14 infarcts were accurately detected on MPS, corresponding to a sensitivity of 88%.

Six vessel territories (in 5 patients) showed false positive gated SPECT studies, of which three infarcts were found in 2 patients with LBBB and dyssynchrony and three with normal wall motion on CMR. On a patient basis only 3 patients of these were false positive as the other patients had infarcts in another vessel territory on CMR. Mean EF was 55% (range 20-80%), Table 1. Eleven patients had EF below 40% (range 20-38%) and in 10 of those patients the results from MR and SPECT agreed. In the remaining patient with 20% EF and LBBB there were SPECT defects that were falsely read as infarcts.

Of the 35 patients with a history of MI, 28 showed LGE on CMR. Two of the seven patients with a history of MI and no LGE had Q-waves on ECG. One of the seven patients with a history of MI and no LGE showed signs of MI on MPS, this was a patient with a reported peri-procedural MI during CABG. The remaining six patients had clinically documented small subendocardial MI and normal MPS. One patient with extensive LGE (29%) in the LAD-territory had no history of MI but was found to have an occluded LAD on subsequent angiography. Three patient examples are shown in Figures 2-4.

## DISCUSSION

This study has demonstrated high sensitivity and specificity for myocardial perfusion SPECT even in the detection of subendocardial myocardial infarcts when using technetium-labelled perfusion tracers and gated SPECT. All infarcts >3% of left ventricular mass were detected on gated SPECT. This is important as MPS is widely used in clinical routine and the diagnosis of MI can transfer patients to correct treatment.

### *Comparison with earlier studies*

A study comparing CMR and non-gated technetium-tetrofosmin MPS in patients routinely referred to SPECT showed an agreement of 79% of methods (11). Using their results with CMR as reference method, the sensitivity and specificity of MPS for infarct was 93% (CI 83-98%) and 63% (CI 47-76%), respectively. Thus, the main difference is that our study shows a markedly higher specificity which is probably explained by the use of gated SPECT. Our results also show higher sensitivity and specificity compared to a study in patients with end-stage renal disease without known MI (67% and 87%, respectively) even though infarct sizes were similar ( $17\pm 11$  vs.  $16\pm 8$  g) (10).

In our study population 7 patients with a previous MI showed negative LGE. This can be compared to a previous study by Ibrahim *et al* who investigated the sensitivity of gated Tc-MPS and CMR early after an acute MI (12). They found a lower sensitivity (87%) of MPS compared to CMR (97%) and false negatives on MPS were mainly seen in non-Q wave infarctions and non-anterior locations.

The interpretation of the MPS was made without knowledge of the clinical status and ECG and 3 of the 6 false positive findings were found in patients with LBBB. Therefore, in the clinical setting with knowledge of the ECG the specificity may in fact be even higher as resting perfusion defects in patients with LBBB is clinically not interpreted as infarcts.

Earlier studies have shown that infarcts with transmuralities below 50% do not always show wall motion abnormalities (24) and a sensitivity of only 50% for small infarcts (<11% of LV) (13). However, in this study we found a sensitivity of 81% for small infarcts and 88% for subendocardial infarcts when using gated SPECT and tetrofosmin at rest and stress in a 2-day protocol. The differences in protocol probably explain the higher sensitivity compared to the study of Wagner et al where infarct detection was based on non-gated resting thallium images.

Distinguishing an infarct from attenuation is particularly challenging in dilated ventricles and in non-ischemic cardiomyopathy regional wall thickening is decreased even without infarction. In this study we included patients with a wide range of ejection fraction (20-80%) and did not exclude patients with non-ischemic cardiomyopathy but still found high specificity values.

#### *Limitations of the study*

Infarct detection was performed per vessel territory and not on a segmental basis. We did not perform segmental comparison because of difficulties to accurately divide the left ventricle into the same segments with both modalities. On the other hand, for patient care the primary interest is to know if there is an infarct or not and in cases when guiding invasive treatment correspondence to the vessel territory is important. Therefore, in this study we divided the analysis in a per patient and a vessel territory analysis. Vessel territory was divided into LAD and non-LAD (RCA and LCx) because of the low specificity in determining vessel territory between the RCA and LCx (25). MPS and CMR were interpreted by the same observers and this may introduce a bias. To decrease this risk a population of 23 extra CMR patients examined for detection of MI was added to the blinded reading. The perfusion defects on MPS was detected by visual reading and not objectively quantified. The percentage of

patients with infarct (28%) was higher in this cohort compared to recently presented data on the decreasing number of abnormal SPECT studies over the recent decades (26).

This study was performed using a 2-day protocol in order to comply with the maximum radiation doses allowed by the national radiation safety agency with good image quality. However, with the new SPECT cameras, and the CZT-technology in particular, a 1-day protocol is possible with radiation doses well below the maximum limits. The present study was performed using a conventional gamma camera. New digital detector technology is now available with higher spatial resolution and improved image quality (27). Studies examining the sensitivity and specificity with this new detector technology and 1-day protocols are warranted.

## **CONCLUSION**

MPS using technetium-labelled tracer and gated SPECT with a 2-day protocol has a high sensitivity and specificity for detection of myocardial infarction. In the present study, all infarcts >3% of left ventricular mass were detected on gated SPECT.

**Competing interests** The authors declare that they have no competing interests.

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## **FIGURE LEGENDS**

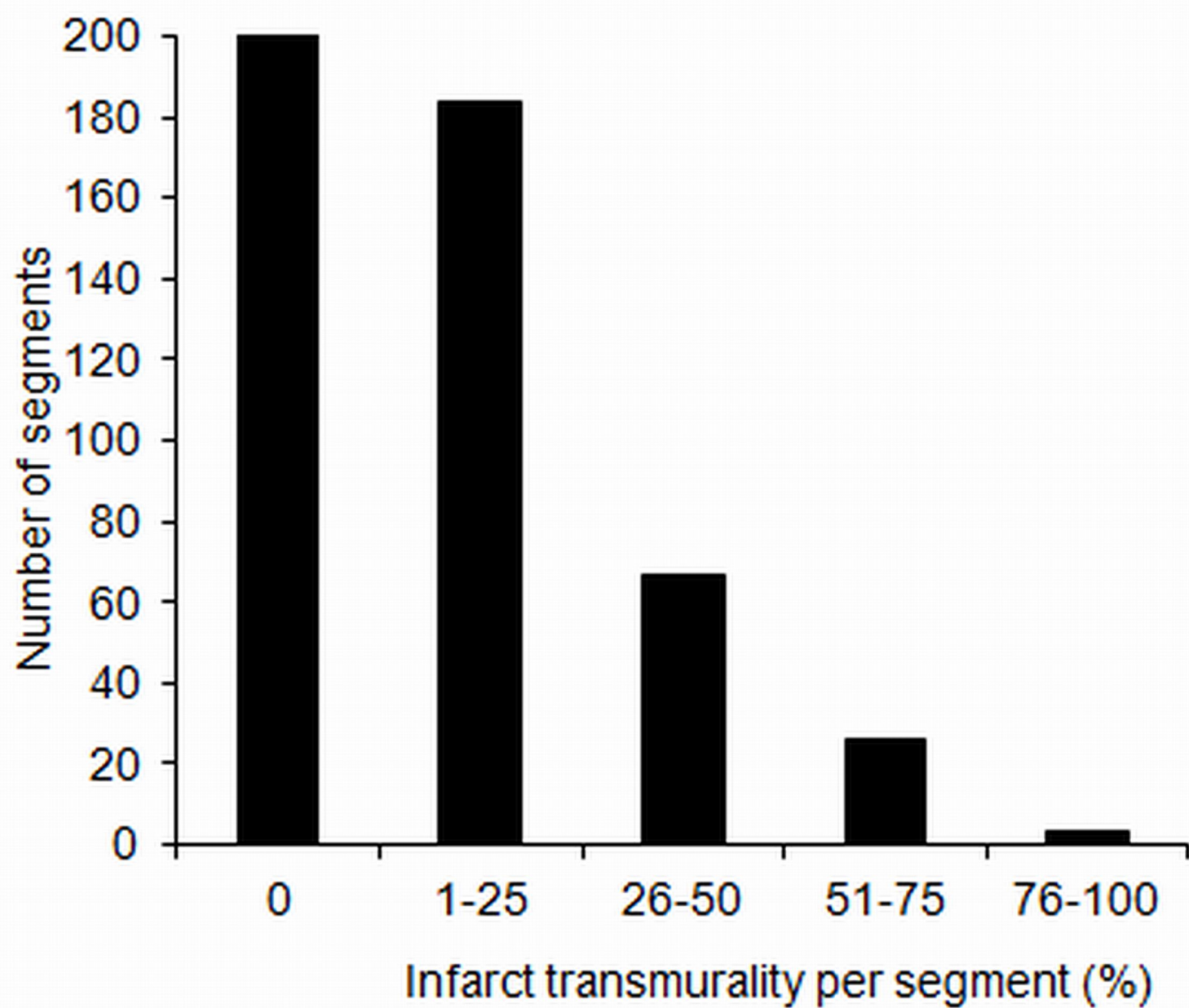
**FIGURE 1.** Histogram of the number of segments with varying degree of transmural injury in patients with infarcts on CMR.

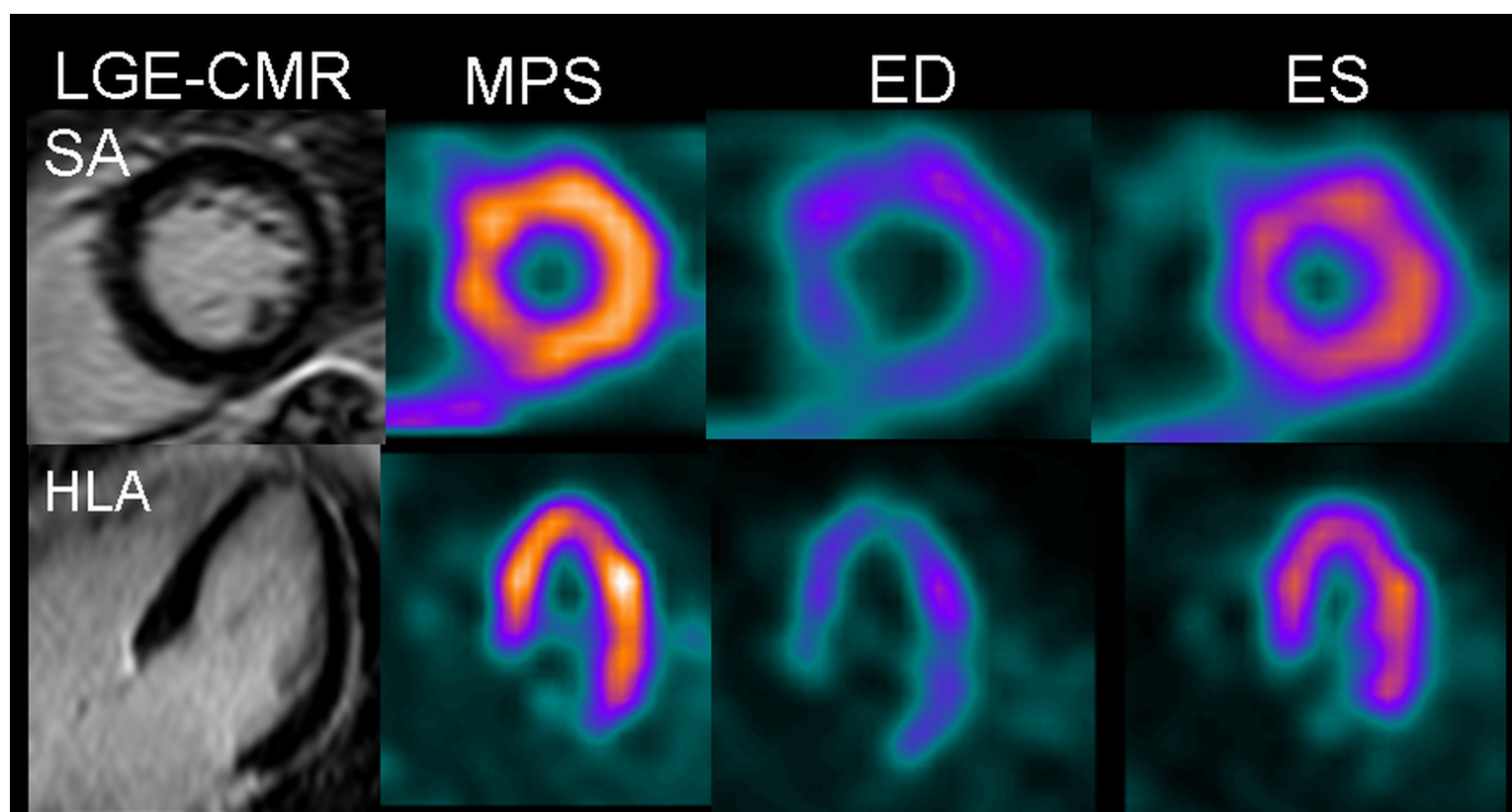
**FIGURE 2.** True negative myocardial perfusion SPECT (MPS). CMR excludes infarct. MPS shows no perfusion defect and normal function at gated SPECT. ED end-diastole, ES end-systole, SA short-axis, HLA horizontal long-axis.

**FIGURE 3.** True positive myocardial perfusion SPECT (MPS). Arrows indicate one apical/anterior and one inferior infarct, both of which are detected on MPS. VLA vertical long axis.

**FIGURE 4.** False negative myocardial perfusion SPECT (MPS). Arrows indicate anterolateral contrast enhancement with both endocardial and midmural pattern. This pattern may correspond to infarct or myocarditis. MPS does not show a perfusion defect or abnormal function.





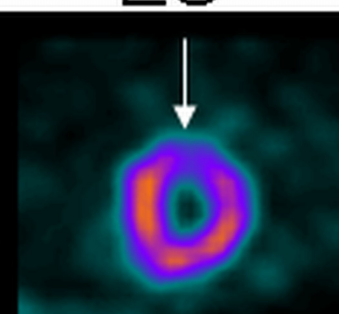
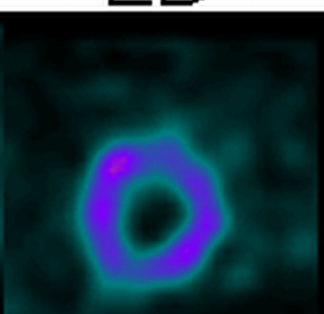
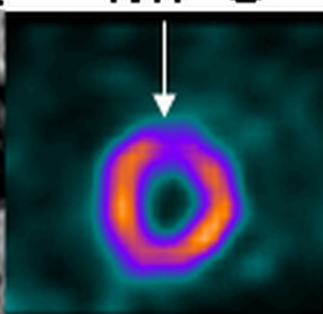
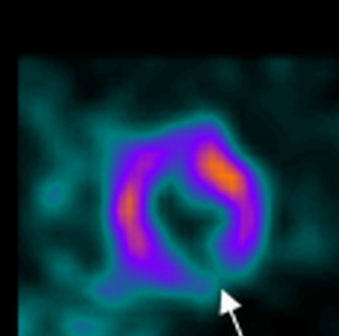
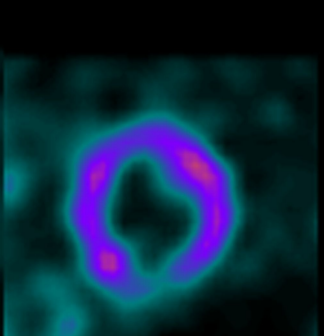
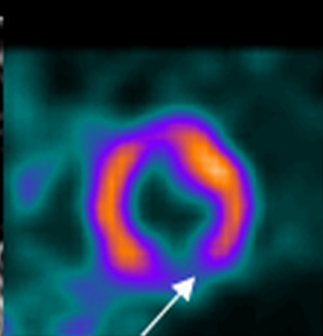
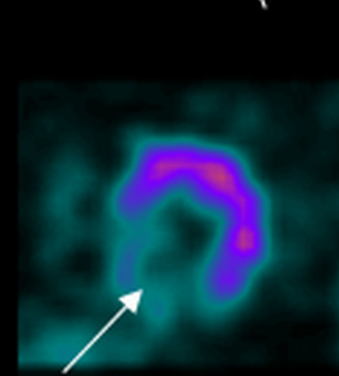
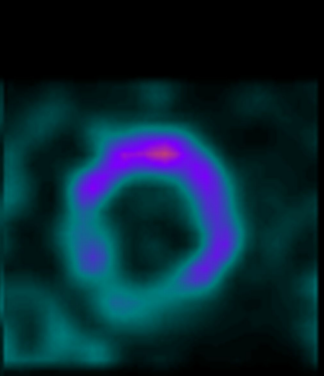
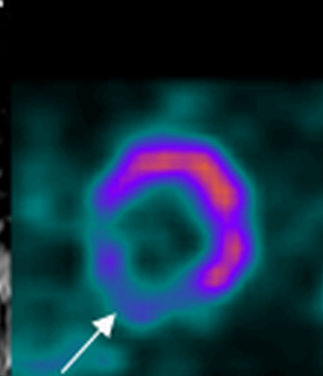
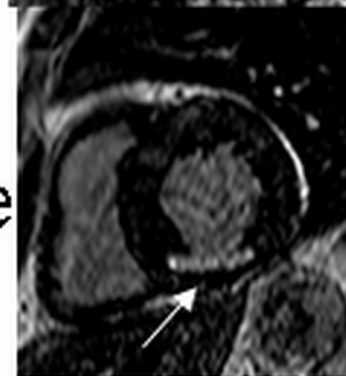


LGE-CMR

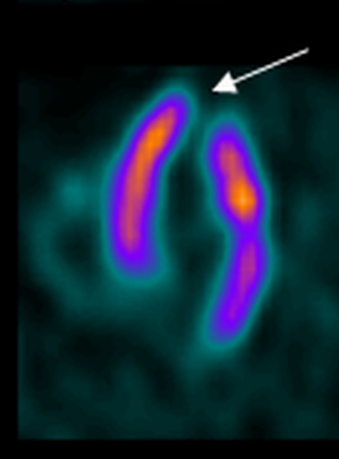
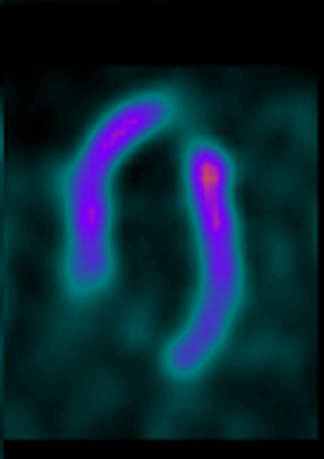
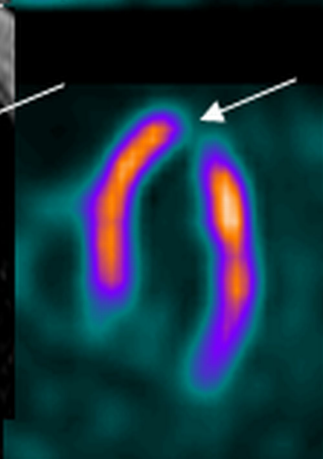
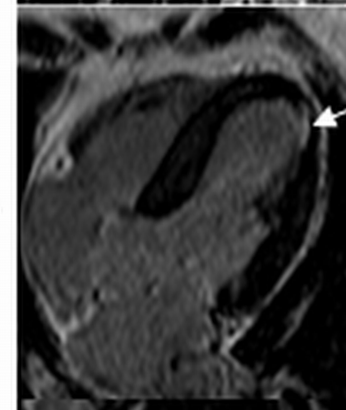
MPS

ED

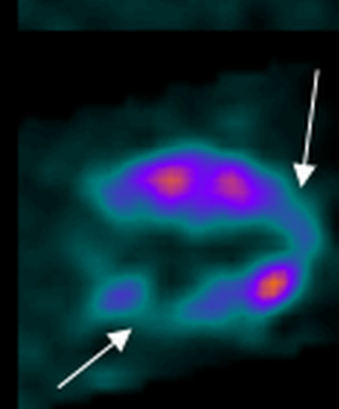
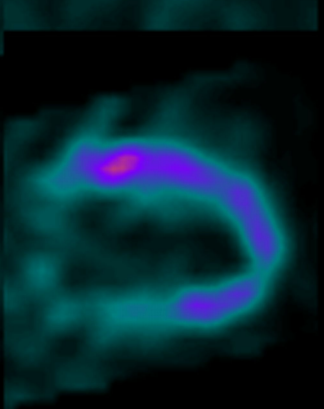
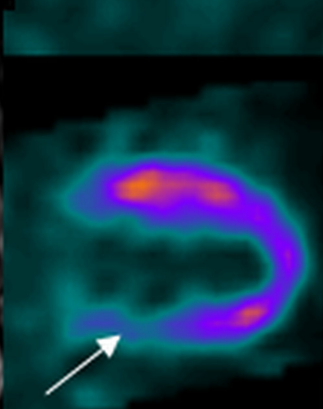
ES

SA  
apexSA  
midSA  
base

HLA



VLA





LGE-CMR

MPS

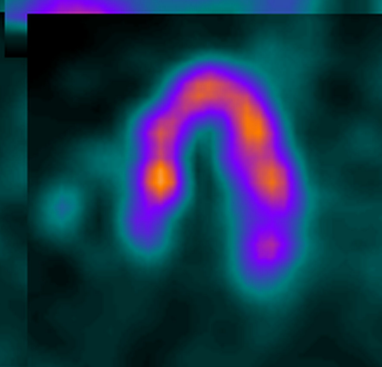
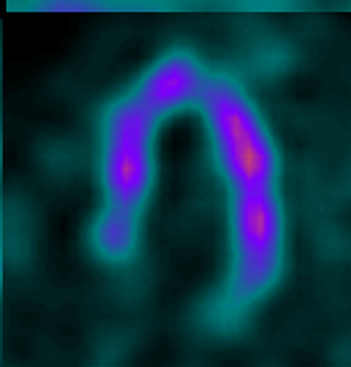
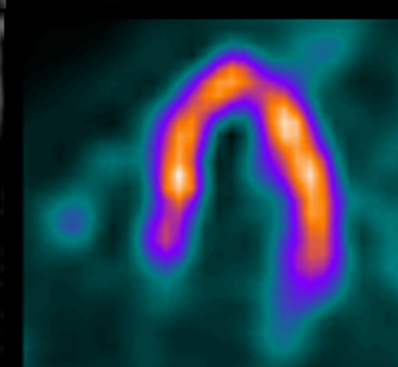
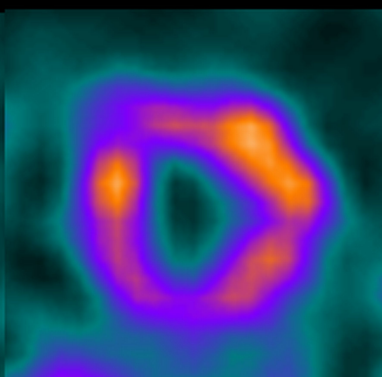
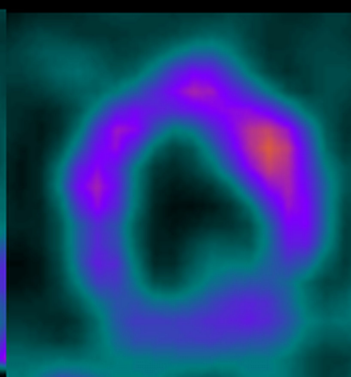
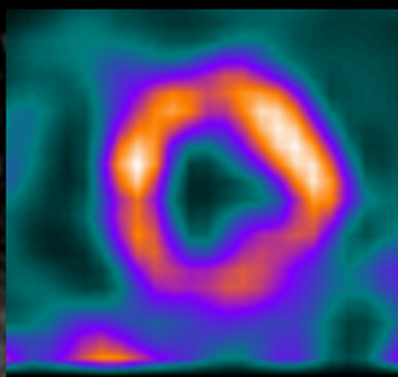
ED

ES

SA



HLA



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**TABLE 1**Patient clinical characteristics

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Age, years	62±12
Female	42 (39%)
Body surface area (m <sup>2</sup> ) female	1.8±0.2
Body surface area (m <sup>2</sup> ) male	2.0±0.2
Weight (kg) female	73±14
Weight (kg) male	85±14
Risk factors	
Hypertension	57 (53%)
Diabetes mellitus	19 (18%)
Hyperlipidemia	57 (53%)
Current smoker	9 (8%)
Family history of CAD	36 (33%)
Previous MI	35 (32%)
Previous coronary artery bypass surgery	16 (15%)
Previous percutaneous coronary intervention	27 (25%)
1-vessel CAD on coronary angiography	17 (16)
2 or 3-vessel CAD on coronary angiography	29 (27%)
ECG	
Q-waves	23 (21%)
Atrial fibrillation	2 (2%)
LBBB	8 (7%)

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Medications

Acetylsalicylic acid	69 (64%)
Beta-blockers	64 (59%)
ACE/ARBs	44 (40%)
Statins	52 (48%)
Ejection fraction	55±12% (range 20-80 %)

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Values are mean±SD and n (%). CAD= Coronary artery disease; MI= myocardial infarction; LBBB= left bundle branch block; ACE/ARB= angiotensin-converting enzyme/angiotensin II receptor blocker.

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**TABLE 2**

Number of myocardial infarctions (MI) on CMR and MPS on a patient basis

	MI on CMR	No MI on CMR
MI present on MPS	28	3
No MI on MPS	2	75

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MPS: Myocardial perfusion SPECT.

CMR: Cardiac Magnetic Resonance imaging,

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**TABLE 3**

Number of myocardial infarctions (MI) on CMR and MPS in the LAD-territory

	MI on CMR	No MI on CMR
MI present on MPS	10	3
No MI on MPS	2	93

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MPS: Myocardial perfusion SPECT.

CMR: Cardiac Magnetic Resonance imaging,



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**TABLE 4**

Number of myocardial infarctions (MI) on CMR and MPS in the LCx or RCA-territory

	MI on CMR	No MI on CMR
MI present on MPS	21	4
No MI on MPS	1	82

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MPS: Myocardial perfusion SPECT.

CMR: Cardiac Magnetic Resonance imaging