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Added Value of Rest to Stress Study for Recognition of Artifacts in Perfusion Cardiovascular Magnetic Resonance

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ABSTRACT

***Background*: The objective was to determine whether rest perfusion (RP) adds to stress perfusion (SP) and late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) for detection of impaired coronary flow reserve. *Methods:* We enrolled patients ($n = 45$) referred for myocardial perfusion SPECT (MPS) for adenosine CMR stress. SP, RP and LGE images were obtained with ^{99m}Tc sestamibi injection during a single adenosine infusion. Segmental perfusion and confidence scores were recorded for SP-LGE interpreted with and without RP. CMR agreement with MPS was determined. *Results:* MPS was normal in 653 and abnormal in 67 segments. SP-LGE CMR interpreted without RP was normal in 407, abnormal in 313 segments, and showed poor agreement with MPS (58%). Two hundred thirty-seven segments were changed to normal using data from RP, improving agreement (87%, $p < 0.0001$). Reader confidence was low in 33 patients with SP-LGE and improved in 26 patients using SP-RP-LGE, where 37/45 were read with high confidence. Artifact was present in 68% of SP CMR and accounted for false positive studies. *Conclusion:* Agreement between single stress adenosine CMR and MPS is optimized by combining RP, LGE and SP CMR. Addition of RP CMR to SP-LGE CMR improved agreement with MPS and reader confidence. Improved CMR pulse sequences may change the role of rest perfusion data.**

INTRODUCTION

Determination of myocardial perfusion is useful for management of patients with known or suspected coronary artery disease (CAD). Myocardial perfusion SPECT (MPS) is routinely used for detection of ischemia and has an established role in risk assessment. Stress first-pass (FP) cardiac magnetic resonance (CMR) has been used to detect impaired perfusion in patients referred for diagnostic coronary angiography (1–6). Adenosine FP CMR is accurate for detection of myocardial ischemia in animal models (7–9). Studies have compared FP CMR and MPS and have suggested that reduced CMR signal intensity correlates to perfusion deficits on stress MPS (5, 10).

There is uncertainty regarding the ideal FP CMR imaging protocol. While some centers use a rest-stress protocol (1–3), others acquire stress followed by rest (4, 5), and still others employ stress-only CMR (9). Studies have indicated that artifacts exist in FP CMR images that can mimic perfusion defects (11, 12). Distinguishing whether reduced signal intensity in FP CMR represents true hypoperfusion or artifact is critical to diagnosis.

The objective of the current study was to compare the results of CMR and MPS to determine whether agreement and/or reader confidence in interpretation of SP was improved by RP images. The hypothesis was that, in noninfarcted myocardium, regions of reduced image intensity present on both SP and RP CMR were unlikely to represent reversible ischemia on dual-isotope MPS.

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METHODS

We enrolled 45 patients (15 had known prior CAD) referred for rest ^{201}Tl - adenosine ^{99m}Tc MPS, who agreed to CMR examination. Studies were performed in compliance with the Institutional Review Board. Patients who had contraindications to CMR, asthma, 2nd or 3rd degree atrio-ventricular heart block, severe aortic stenosis, or severe emphysema were excluded.

For rest MPS, patients received 2.5 to 4 mCi ^{201}Tl IV and were imaged in supine position, using a dual-detector gamma camera (Forte, Philips-ADAC Laboratories, Milpitas, CA, USA or Siemens E Cam, Siemens Medical Systems, Hoffman Estates, IL, USA) (13). Rest imaging employed gating and the following parameters: 10% and 30% energy window centered over the 165 and 68–80 KeV peaks of ^{201}Tl, respectively, 64 × 64 matrix, 3° angular sampling over 180°, imaging time 35 seconds for each projection and elliptical orbit. No attenuation or scatter correction was used. After filtered back projection, short-, vertical long- and horizontal long-axis tomograms were generated.

Patients were then placed supine on a 1.5-T CMR scanner (Siemens Sonata, Erlangen, Germany) with a 32 × 46 cm flexible phased-array surface coil (CP Body Array Flex, Siemens Medical Systems, Erlangen, Germany) on the chest. Blood pressure, electrocardiogram, and pulse oxygenation were monitored (In Vivo, Philadelphia, PA, USA); heart rate and systolic blood pressure were used before, during, and after adenosine infusion to compute rate-pressure products. Following scouts, adenosine was administered (140 mcg/kg/min IV for 5 minutes). At 2 minutes into infusion, 25 to 40 mCi ^{99m}Tc sestamibi was injected followed by 0.1 mmol/kg gadolinium contrast (Gadodiamide, Omniscan, Amersham, Piscataway, NJ, USA) at 5 mL/sec (both via another IV catheter) followed by 30 mL saline at 5 mL/sec. FP CMR was acquired at end-expiration with breath-holding using a saturation recovery steady-state free precession (SSFP) pulse sequence that employed partial Fourier filling of k-space (either 6/8 or 7/8 factor) where images were acquired apex to base. Forty-two of the 45 subjects were able to hold their breath for the first-pass bolus of contrast through the myocardium; in the three patients who breathed during the first-pass bolus, image quality was still deemed acceptable by readers. FP CMR images were oriented such that distal, mid-, and basal short-axis views were acquired during each heartbeat using the following parameters: field of view 350 to 380 × 175 to 285 mm depending on patient size, 192 frequency encoding points, frequency encoding resolution 1.8–2.0 mm, 84 to 128 acquired phase encoding steps, slice thickness 8 mm, TE/TR 1.0/2.9 ms, bandwidth 1240 Hz/pixel, flip angle 50°, time between saturation pulse and center of k-space 90 ms, non-selective non-adiabatic saturation pulse, asymmetric echoes allowed, all slices acquired during each RR interval. Parallel imaging was not used.

Ten minutes after SP CMR, the same FP CMR sequence was used to acquire RP images. Ten minutes later, LGE images matched for field of view and slice position were acquired at mid to end diastole using segmented inversion-recovery SSFP with the following parameters: matrix 192 × 176 to 192, frequency encoding resolution 1.8–2.0 mm, slice thickness 8 mm, TE/TR 1.1/2.7 ms, bandwidth 1185 Hz/pixel, flip angle 50°, 5 to 9 phase encoding lines acquired per segment depending on heart rate, image data acquired every other RR interval, delay time adjusted to acquire image data at mid to end diastasis, and inversion time set to null normal myocardium, typically between 250 and 350 ms.

Following CMR, ^{99m}Tc MPS was performed as previously described (14). Supine post-stress images were acquired with 16-frame ECG gating. After filtered back projection, short- and long- -axis tomograms were generated.

MPS analysis

Semiquantitative interpretation was used to assess MPS images using a 5 point, 20 segment model. Initially, automatic segmental scores were obtained by comparison to gender-specific stress and rest normal limits (15). Computer-generated segments were adjusted by consensus of 2 nuclear cardiologists blinded to the CMR results using a 5-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction, 4 = absence of radiotracer in a segment versus remote). Scores were then converted into a 17 segment model using a previously published algorithm (16). Because a 2-chamber long-axis view could only be acquired by CMR in 19/45 patients studied, the apex of the left ventricle was not included yielding 16 segments per patient. Stress MPS was considered abnormal if ≥2 segments had a score ≥2. An increase in stress compared to rest score was considered indicative of segmental ischemia, provided the stress MPS score was ≥2.

CMR analysis

Visual scores for CMR were determined by consensus read of 3 observers employing the 16 segment model. CMR readers were blinded to the results of MPS. Studies were assigned a confidence using a 4 point system (high or low confidence normal, high or low confidence abnormal).

SP-LGE CMR

For each patient, SP was first viewed with corresponding LGE. SP images were read using a 5 point system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe decrease, and 4 = absence of gadolinium uptake in a segment versus remote). SP was considered abnormal (ie, indicative of hypoperfusion during stress) if a segment had a score ≥2. LGE images were scored using a 5 point system according to segmental transmurality of hyperenhancement (0 = no enhancement, 1 = 1 − 25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100% transmural) (17). Segments were considered abnormal if LGE score was ≥1. Perfusion within areas of LGE was not considered. In areas of subendocardial LGE, scoring took into account the perfusion pattern of the viable territory adjacent in the segment of interest. Perfusion scored by SP-LGE was considered abnormal (ie, indicative of hypoperfusion during stress) if a segment had a score ≥2. A segment with a perfusion defect or an LGE abnormality or both was considered abnormal. Ischemia was considered present if

SP was ≥2 and greater than LGE by ≥1 point. By patient, SP-LGE was considered abnormal if ≥2 segments had evidence of stress hypoperfusion or infarction.

SP-RP-LGE CMR

After analysis of stress data with LGE as described above, data sets were completely re-scored with stress, rest, and DE data six weeks later by the same three observers. The paired SP-RP images were viewed with corresponding LGE. The method for scoring was the same as that for SP-LGE and rest segmental perfusion scores were used to determine whether stress perfusion abnormalities were artifactual in noninfarcted segments. If the LGE score was ≥1, RP scores were not considered in determining whether ischemia was present or whether the segment was abnormal. However, if LGE score was 0 and the SP score was ≥2 and greater than RP, then a segment would be considered ischemic and abnormal. If the RP was ≥ SP and LGE was 0, the perfusion defect was considered artifactual. By patient, SP-RP-LGE was considered abnormal if ≥2 segments had evidence of ischemia or infarction. Regions with stress-rest change and no scar were considered ischemic, and regions with the same stress-rest score (both ≥2) with no scar were considered normal. Specifically, when similar regions of reduced signal intensity were observed at stress and rest perfusion CMR, these areas were considered artifactual rather than true hypoperfusion.

Statistical methods

Rate-pressure products were compared before, during, and after adenosine using repeated measures analysis of variance with Bonferronni correction. Kappa statistics were computed to determine whether a relationship existed between severity of MPS determined ischemia and SP CMR. Values are expressed as mean ± standard deviation throughout. Differences between the CMR and MPS examinations were compared using a student's paired t-test with $p < 0.05$ considered significant.

RESULTS

Patient characteristics are shown in Table 1. Anginal symptoms were present in all patients. All patients underwent the study without adverse events. The rate-pressure products were: 10,200 ± 3,400, 12,260 ± 3,300, and 1,0210 ± 3,700, before, during, and after adenosine administration, respectively ($p < 0.001$).

Table 1. Characteristics of the study population

Parameter	Patients ($n = 45$ total)
Gender: Male	23 (51%)
Mean Age (years)	70 ± 14
Diabetes	5 (9%)
Hyperlipidemia	23 (51%)
Prior Myocardial Infarction	4 (7%)
Prior revascularization	15 (35%)

Figure 1 shows CMR versus MPS in three patients. Fig. 1a reveals a lateral wall region judged as hypoperfusion using SP-LGE (score 2, low confidence) but was changed to normal (score 0, high confidence) after SP-RP-LGE. Fig. 1b reveals an inferior region judged as hypoperfusion (score 2, high confidence) using SP-LGE images and was unchanged after SP-RP-LGE. Fig.1c reveals stress CMR judged normal (score 0, low confidence) with 50–70% infarction by LGE; perfusion remained normal (score 0, high confidence) after SP-RP-LGE. MPS was abnormal with reversible defect in the anterior wall.

MPS

MPS was abnormal in 18/45 (40%) patients, where 16 (36%) had reversible defects, 7 (16%) had fixed defects, and 5 (11%) had both. By segment, MPS was abnormal in 68/720 (9%). Of these, 42/720 (6%) had reversible defects, 32 (4%) had fixed defects, and 6 (1%) segments demonstrated both.

SP-LGE

By patient, SP-LGE CMR was abnormal in 43/45 (96%) subjects. Forty-one (91%) demonstrated perfusion defects on SP-LGE, 13 (29%) had infarction, and 11 (24%) had both. Thirty-four were read with low confidence, while 11 were read with high confidence. By segment, SP-LGE CMR suggested 334/720 (46%) segments were abnormal. SP-LGE demonstrated hypoperfusion in 313/720 (43%), infarction in 54 (8%), and both in 33 (5%) segments.

SP-RP-LGE

By patient, SP-RP-LGE CMR was abnormal in 21/45 (47%) subjects. Sixteen (36%) demonstrated ischemia, 13 (29%) infarction, and 8 (18%) had both. By SP-RP-LGE CMR, 8 patients were read with low confidence, while 37 were judged with high confidence. Artifacts were noted in 30/45 (68%) SP CMR scans. By segment, SP-RP-LGE suggested 105/720 (15%) segments were abnormal. SP-RP-LGE showed ischemia in 76/720 (11%), infarction in 54 (8%), and both in 25 (3%) segments.

SP-RP-LGE resulted in a different score for SP in a total of 261 segments versus SP-LGE. Of these, 3/261 scores were increased (one from 1 to 2 and two from 2 to 3), and the remaining 258 values were decreased (13 from 3 to 0; 222 from 2 to 0; 20 from 1 to 0; and 3 from 2 to 1). The majority of score changes were attributed to identification of artifacts (Fig. 1a.)

Comparison by patient

A summary of CMR and MPS results by patient is shown in Table 2. Of 18 patients in whom MPS was abnormal, SP-LGE was abnormal in all 18. In the 7 patients with fixed defects by MPS, 5 (71%) had infarction by LGE CMR, while 2 patients had infarction by LGE that was not detected by MPS. SP-LGE was normal in only 2 of 27 patients (7%) who had a normal MPS. In contrast, SP-RP-LGE was abnormal in 14/18 (78%), who had abnormal MPS. Within the group of 16 patients with reversible

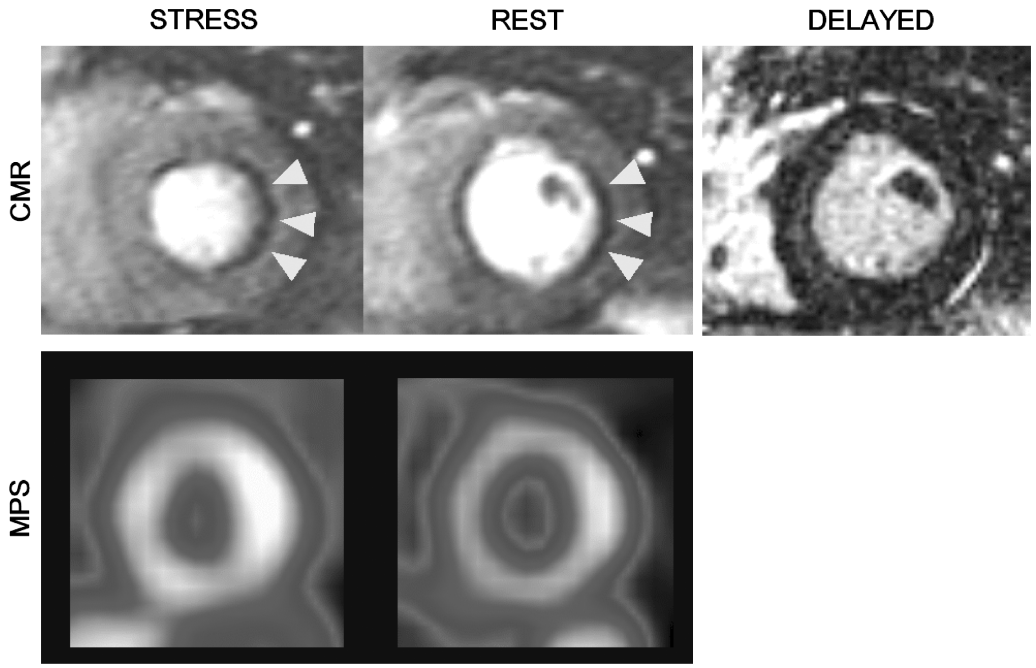

Figure 1a. CMR images–perfusion during adenosine (top left), perfusion at rest (top center), and late gadolinium enhancement (top right). A rim of decreased signal intensity was apparent in the subendocardial portion of the lateral wall during both stress and rest (arrowheads). Corresponding stress-rest MPS (bottom left and right) revealed no evidence of ischemia.

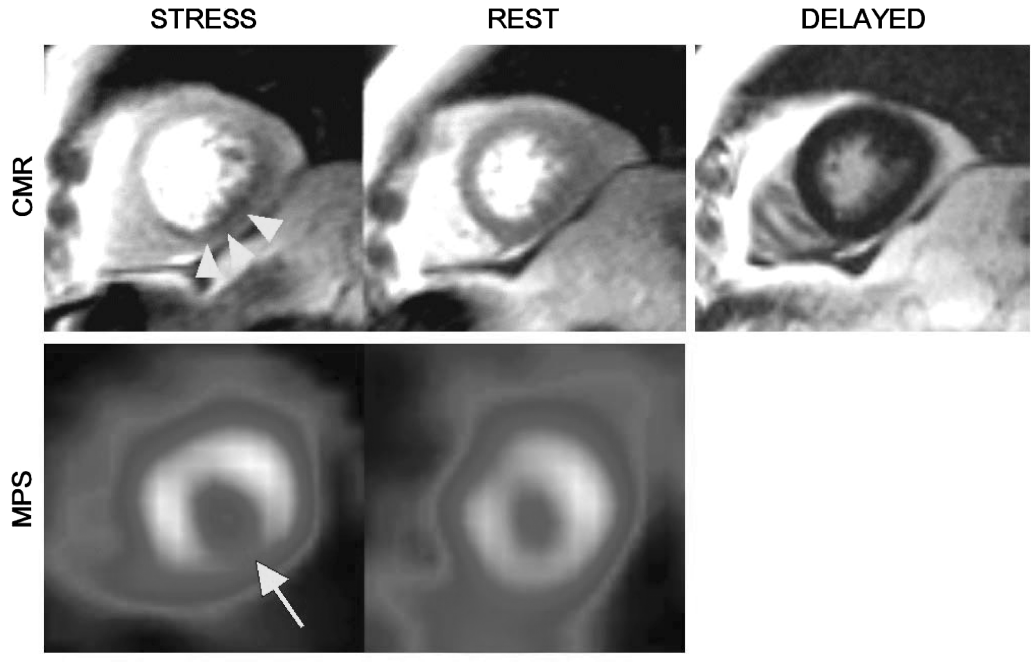

Figure 1b. CMR images–perfusion during adenosine (top left), perfusion at rest (top center), and late gadolinium enhancement (top right). Decreased image intensity was apparent in the inferior myocardium at stress (arrowheads) but not at rest with no evidence of late gadolinium enhancement. Corresponding stress-rest MPS (bottom left and right) revealed a reversible defect in the same myocardial region (arrow) suggestive of ischemia.

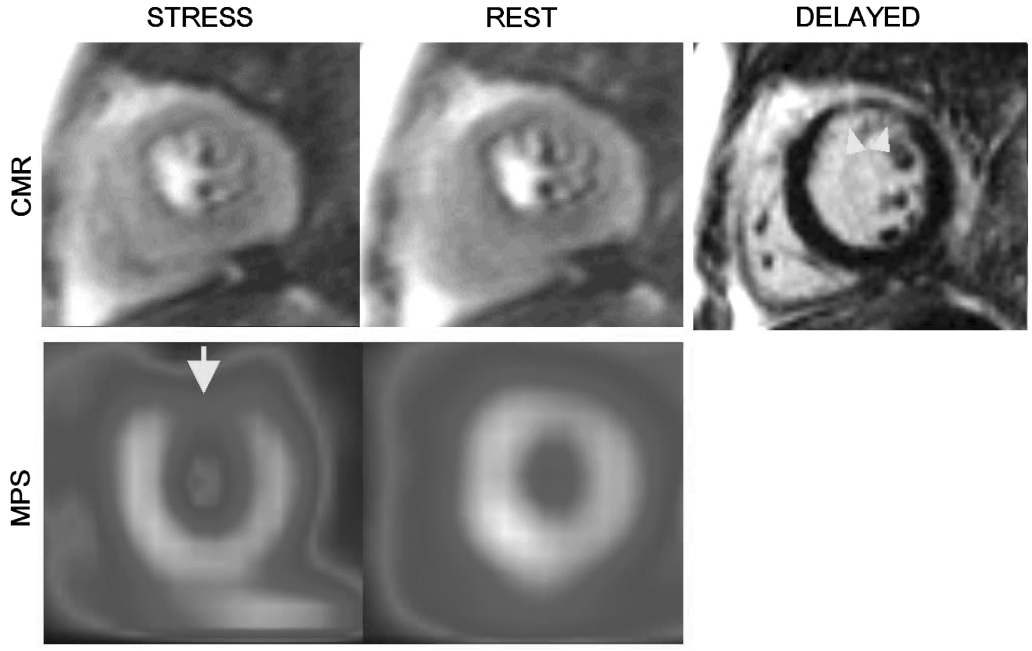

Figure 1c. CMR images–perfusion during adenosine (top left), perfusion at rest (top center), and late gadolinium enhancement (top right). CMR demonstrated no clear evidence of decreased signal intensity in the myocardium at stress or rest but definite late gadolinium enhancement (arrowheads). Corresponding stress-rest MPS (bottom left and right) revealed a reversible defect in the same myocardial region suggestive of ischemia.

MPS defects, 9 (56%) had ischemia seen with SP-RP-LGE. SP-RP-LGE was normal in 20 of the 27 (74%) patients who had normal MPS.

Comparison by segment

Comparison between CMR and MPS by segment is shown in Table 3. Of 68 segments abnormal by MPS, SP-LGE was abnormal in 40 (59%); of 652 normal segments by MPS, SP-LGE was normal in 369 (57%). Of 68 segments abnormal by MPS, SP-RP-LGE was abnormal in 41 (60%); of the 652 segments judged normal by MPS, SP-RP-LGE was normal in 588 (90%). SP-LGE CMR was concordant with MPS in 40/68 abnormal and 379/652 normal segments with 58% overall agreement. SP-RP-LGE was concordant with MPS in 41/68 abnormal and 600/652 normal segments by MPS with 87% overall agreement ($p < 0.0001$ versus SP-LGE). Variability of CMR adenosine perfusion scores by SP-RP-LGE demonstrated poor agreement compared with stress and rest MPS scores (kappa = 0.102, $p < 0.0001$.)

CMR LGE alone provided considerable information. By segment, LGE was abnormal in 36/68 abnormal MPS segments and was normal in 634/652 segments normal by MPS. Using CMR-detected scar as the comparative standard, MPS abnormalities were considered. Of 54/720 segments with LGE, stress MPS was abnormal in 36/54 and normal in 18/54 segments. In the 18 segments where MPS "missed" infarction, both stress and rest MPS scores were normal while LGE was scored as 1 in 7 segments, 2 in 5 segments, and 3 in 6 segments, suggesting that normal stress (not just rest) MPS may be seen in segments with significant subendocardial scar and occasionally in segments with nearly transmural irreversible injury.

Table 2. Sensitivity, specificity, accuracy of SP, RP, and LGE CMR reads versus MPS abnormality by patient

CMR Read	Sensitivity %	Specificity %	Agreement %
SP-LGE Abnormal	100	4	44
SP-RP-LGE Abnormal	78	74	76
SP Perfusion Alone	100	4	44
SP-RP Perfusion Alone	61	70	66
LGE Alone	72	96	86

"Perfusion alone" indicates whether CMR perfusion was abnormal; "LGE alone" indicates whether CMR LGE was abnormal.
CMR = cardiac magnetic resonance, MPS = myocardial perfusion SPECT, SP = stress perfusion, LGE = late gadolinium enhancement, RP = rest perfusion

DISCUSSION

The present study suggests that evaluation of adenosine FP CMR is improved when rest and LGE information is incorporated into stress images.

Artifacts on FP CMR

CMR perfusion images may contain artifacts that are difficult to distinguish from perfusion deficits (11, 12, 18, 19). These include susceptibility, motion, and ringing. Development of CMR pulse sequences with reduced artifacts is the focus of

Table 3. Summary of comparisons of SP, RP, and LGE CMR reads versus MPS abnormality by segment

		MPS				
CMR		Abnormal $n = 68$	Normal $n = 652$	Sens %	Spec %	Accuracy %
SP-LGE	+	40	273	59	58	58
Abnormal	−	28	379			
SP-RP-LGE	+	41	64	60	90	87
Abnormal	−	27	588			
SP	+	40	273	59	58	58
Perfusion alone	−	28	379			
SP-RP	+	24	52	35	92	86
Perfusion alone	−	44	600			
LGE alone	+	36	18	53	97	93
	−	32	634			

"Perfusion alone" indicates whether CMR perfusion was abnormal; "LGE alone" indicates whether CMR LGE was abnormal. CMR = cardiac magnetic resonance, MPS = myocardial perfusion SPECT, SP = stress perfusion, LGE = late gadolinium enhancement, RP = rest perfusion

ongoing research. In the present study, artifacts were present in at least one segment in 68% of patients. The results of this study suggest that the combination of rest and stress perfusion is useful in distinguishing artifacts from true perfusion defects. This finding is similar to that observed by Klem et al. (6), who found that myocardial areas with reduced image intensities during stress and rest FP CMR, termed "matched" defects, with no evidence of LGE corresponded to nonobstructive coronary arteries.

Utility of SP-RP-LGE CMR

When CMR was interpreted without RP, sensitivity was high (Table 3), but there was also high false positive rate. By combining stress-rest data and examining the qualitative change in myocardial contrast uptake, specificity and overall agreement improved compared to stress-only analysis. Quantitative assessment of CMR stress perfusion data may also improve image interpretation above that which may be possible using qualitative analyses (7–9, 12, 20).

Several studies have examined FP CMR at rest and during stress with comparison to cardiac catheterization (1–5, 21). These studies demonstrate that other pulse sequences and methodologies other than SSFP used in the present study have good sensitivities and specificities in these patient populations. A few studies have also compared radionuclide stress perfusion to CMR for detection of CAD and have suggested favorable CMR sensitivities and specificities (4, 5).

The findings of the present study with regard to LGE versus results obtained by MPS are of interest. While 4 (7%) patients had a history of MI, LGE was positive in 14/45 (31%) of patients. Subendocardial infarction detectable by CMR may be missed by rest myocardial perfusion SPECT (22). Extending this observation, our patient population demonstrated a strong relationship between the presence of subendocardial scar by LGE-CMR and segmental ischemia by MPS. Although testing algorithms incorporating CMR in the diagnosis and management of CAD are still evolving, our observation suggests that presence of subendocardial scar could be a useful predictor of vulnerable myocardium in patients at intermediate likelihood of disease.

The observed discordance between MPS and CMR perfusion on a segmental basis was largely due to disagreement in noninfarcted segments. In our study, 84/105 abnormal segments by SP-RP-LGE CMR had subendocardial scarring. In contrast, there were 32 segments judged abnormal by MPS (defined as resting score > 1) that had no evidence of LGE by CMR (defined as score $= 0$). Of these 32 segments without infarction (ie, LGE score $= 0$), only 4/32 also had first pass hypoperfusion by SP-RP-LGE CMR. Although the relationship between an area of perfusion (or hypoperfusion) within the myocardium and the absence (or presence) of infarction might seem straight forward, the present study suggested that LGE can occur in the setting of normal stress and rest MPS and that a majority of ischemic MPS studies have underlying subendocardial LGE.

Rest perfusion

Data from the present study suggest that RP aids in interpretation of SP-LGE by identifying artifacts. This finding follows the historical progression of MPS in that MPS can be performed either as a stress-only or as a rest-stress protocol (23–26). In addition to utility in interpretation of artifacts, rest MPS is useful for identification of resting ischemia (27). Similar to MPS, determination of resting myocardial perfusion may be possible using methods of quantitative CMR (12, 20).

Study limitations

The large number of artifacts observed in the stress perfusion images acquired in the present study employing the SSFP sequence and the 0.1 mmol/kg gadolinium dose with 5 mL/s injection may have accounted for the conclusion that rest perfusion helps to distinguish these areas from true perfusion deficits. An alternative approach would be to develop newer sequences with reduced artifacts. Other more recently available CMR SP pulse sequences may have fewer artifacts and may be more readily interpreted in the absence of rest perfusion imaging (6).

The conclusions stated in the present study apply to perfusion imaging using SSFP and a gadolinium dose of 0.1 mmol/kg. In addition, it is possible that residual gadolinium in the myocardium after the adenosine scan may have influenced the image intensities observed on RP imaging and, thus, the results of our study. A portion of our study population had no known coronary artery disease (30/45 patients), was referred for stress testing due to symptoms, and, thus, had an intermediate pretest probability of CAD. We elected to compare CMR stress to MPS. While established for risk assessment, the accuracy of MPS for CAD detection is imperfect. Ideally, the results of both CMR and MPS would have been compared to cardiac catheterization, but not all patients in our study underwent this procedure. We acquired only three short-axis slices by CMR so that all slices could be acquired every heartbeat during adenosine stress. Limited sampling of the left ventricle in this manner potentially leads to incorrect assessment of the extent of perfusion abnormalities. Also, the technique of scoring SP-LGE then SP-RP-LGE images did not allow for determination of whether rest perfusion, by itself, may have allowed for determination of image artifacts. Similarly, the scoring of RP along with SP-LGE did not allow for blinded assessment of RP images. In addition, changes in heart location, phase of the cardiac cycle acquired during perfusion versus LGE, and/or breath-hold position may affect registration of images and, hence, results of the present study. Finally, the visual scoring system used was chosen to emulate clinical practice; quantitative methods may improve ischemia detection (12, 20).

CONCLUSION

The combination of stress-rest perfusion imaging in the CMR environment with infarct imaging by LGE improves identification and characterization of patients with suspected CAD. In this patient population, RP aids in interpretation of SP-LGE CMR for determination of real versus artifactual perfusion defects during adenosine stress studies.

ABBREVIATIONS

CAD	Coronary artery disease
CMR	Cardiac magnetic resonance
LGE	Late gadolinium enhancement
FP	First-pass
IV	intravenous
MPS	Myocardial perfusion SPECT
RP	Rest perfusion
SP	Stress perfusion
SSFP	Steady-state free precession
^{99m}Tc	technetium-99-sestamibi
^{201}Tl	thallium-201

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