

Diagnostic Performance of Myocardial Perfusion MR at 3 T in Patients with Coronary Artery Disease¹

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Purpose:

To prospectively determine the diagnostic performance of myocardial perfusion magnetic resonance (MR) imaging at 3 T for helping depict clinically relevant coronary artery stenosis ($\geq 50\%$ diameter) in patients with suspected or known coronary artery disease (CAD), with coronary angiography as the reference standard.

Materials and Methods:

The study was approved by the local ethics committee; written informed consent was obtained. Vasodilator stress perfusion imaging by using a turbo field-echo sequence was obtained in 101 patients (71 men, 30 women; mean age, 62 years \pm 7.7 [standard deviation]) scheduled for coronary angiography. Myocardial ischemia was defined as stress-inducible perfusion deficit in arterial territories without delayed enhancement (DE) or additional stress-inducible perfusion deficit in territories with nontransmural DE. Images were evaluated in consensus by two blinded readers. Diagnostic performance was determined on per-patient and per-coronary artery territory bases. The number of dark rim artifacts in patients without DE was determined in a second read. Interobserver variability was assessed in 40 randomly selected patients.

Results:

One hundred one patients underwent MR examinations. Coronary angiography depicted relevant stenosis in 70 (69%) patients. Patient-based sensitivity and specificity were 90% and 71%, respectively. Sensitivity, specificity, and diagnostic accuracy for the detection of coronary stenosis in a specific territory were 76%, 89%, and 86%, respectively. In 24% of patients without DE, dark rim artifacts were detected, mostly in the left anterior descending artery territory (56%). Among 40 randomly selected patients, there was agreement in the determination of myocardial perfusion deficits in 37 (93%, $\kappa = 0.79$) patients.

Conclusion:

Myocardial perfusion MR imaging by using saturation-recovery spoiled gradient-echo imaging at 3 T has an accuracy of 84% for depicting hemodynamically relevant coronary artery stenosis in patients with suspected and known CAD.

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Given the pathophysiologic events during the ischemic cascade, the assessment of myocardial perfusion appears to be the most promising concept for a noninvasive test to help detect hemodynamically relevant coronary artery disease (CAD) (1). Myocardial perfusion assessment is frequently performed by using stress and rest single photon emission computed tomography (SPECT) or positron emission tomography (PET). However, both modalities expose patients to radiation, SPECT is limited by attenuation artifacts and reduced spatial resolution, and PET is limited by its reduced availability.

Myocardial perfusion magnetic resonance (MR) imaging has been developed extensively over the past decade. So far, clinical trials have mostly been performed with 1.5-T scanners and have shown that MR perfusion yields diagnostic results for the detection of CAD comparable to those of clinically established nuclear techniques such as SPECT or PET (2–4). When using coronary angiography as the reference standard (5–9), MR perfusion imaging is associated with good diagnostic accuracy (sensitivity, 88%–93%; specificity, 75%–90%). Recently, MR imaging at 3 T has become available and potentially provides a substantial improvement of tissue contrast in T1-weighted imaging techniques relying on gadolinium-based contrast material enhancement. Yet, 3-T systems in general are known to be prone to imaging artifacts (eg, susceptibility artifacts) (10).

Advances in Knowledge

- Myocardial stress perfusion imaging at 3 T has an accuracy of 84%–86% to detect relevant coronary artery stenoses.
- Dark rim artifacts represented by matched perfusion defects between stress and rest imaging occur in almost one-fourth of patients without evidence of delayed enhancement.
- There is high interobserver agreement ($\kappa = 0.79$) for the detection of perfusion deficits.

We hypothesized that by using a combined MR imaging approach with stress-rest first-pass perfusion imaging, followed by delayed-enhancement (DE) imaging at 3 T, it is possible to detect relevant coronary stenosis in patients with clinically suspected or known CAD. Thus, the purpose of our study was to prospectively determine the diagnostic performance of myocardial perfusion MR imaging at 3 T for depicting clinically relevant coronary artery stenosis ($\geq 50\%$ diameter stenosis) in patients with suspected or known CAD, with coronary angiography as the reference standard.

Materials and Methods

Patients

The study was approved by the Charité and Virchow-Klinikum Ethics Committee. Written informed consent was given by all patients. One hundred four patients (72 men, 32 women; mean age, 62 years \pm 7.7 [standard deviation]) scheduled for clinically indicated coronary angiography were examined between August 2005 and July 2006.

Patients with contraindications to either MR imaging (noncompatible biometallic implants or claustrophobia) or adenosine-related side effects (atrioventricular node block grade $> I$, acute coronary syndrome, severe hypertension, asthma) and patients with arrhythmia were not considered for study inclusion. All patients were instructed to refrain from any beverages or foods containing caffeine within 24 hours before the MR study. The pertinent medical history of the patients was recorded at the time of the examination by one of three authors (R.G., C.J., or I.P.).

Three of 104 patients could not be evaluated owing to (a) adverse ade-

nosine-related side effects ($n = 2$) and (b) poor-quality MR images ($n = 1$) (Fig 1). Of the patients with adverse side effects, one developed severe dyspnea and requested termination of the examination; the dyspnea resolved after 30 seconds without the administration of theophylline (Bronchoparat; Astellas Pharma, Munich, Germany). The other patient developed bradycardia of 30 beats per minute, with atrioventricular node block being the most likely cause; 15 seconds after the termination of the adenosine infusion, heart rate returned to normal. Thus, a total of 101 patients were evaluated in our study (Table 1).

MR Examination

MR sequence design.—All patients were examined in the supine position by using a 3-T whole-body imager (Achieva 3T; Philips, Best, the Netherlands) equipped with a dual gradient system (Quasar; Philips) by using gradient strength of 80 mT/m and slew rate of 200 T/m/sec. A six-element cardiac synergy coil was used for signal detection. Cardiac synchronization was performed by using a four-electrode vector electrocardiogram, and image acquisitions were triggered on the R wave (11).

For cine imaging, a balanced steady-state free precession sequence was used (repetition time msec/echo time msec, 3/1.5; flip angle, 40°). A saturation pre-

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Abbreviations:

CAD = coronary artery disease
DE = delayed enhancement
LAD = left anterior descending artery
LCX = left circumflex artery
RCA = right coronary artery

Author contributions:

Guarantors of integrity of entire study, R.G., E.N.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, R.G., I.P., B.S., E.F., E.N.; clinical studies, R.G., C.J., I.P., S.K.; statistical analysis, R.G.; and manuscript editing, all authors

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Implication for Patient Care

- Myocardial perfusion MR imaging at 3 T is an option for patients with suspected or known coronary artery disease to help depict hemodynamically relevant coronary stenosis in patients.

pared (prepulse delay, 95 msec) single-shot spoiled gradient-echo sequence was used for perfusion imaging. The acquisition parameters were as follows: 2.8/0.9; flip angle, 18°; field of view, 380 × 380 mm; turbo factor, 59; and matrix, 128 × 128. For 60 consecutive cardiac cycles, three short-axis sections with a spatial resolution of 2.9 × 2.9 × 8 mm recorded every heartbeat up to a heart rate of 110 beats per minute. DE imaging was performed by using an inversion-prepared three-dimensional spoiled gradient-echo sequence (1.5 × 1.7 × 5 mm).

Imaging protocol.—All patients received two 18-gauge intravenous lines to allow separate administration of adenosine and the contrast agent to prevent high-grade atrioventricular blockade during the injection of the bolus. The patients underwent a standard MR examination that included the following steps:

1. Standardized planning to determine the actual short axis of the left ventricle.

2. Cine imaging of three short-axis views and three long-axis views (four-, two-, and three-chamber views). The three short-axis views were distributed to cover the heart at the basal, equatorial, and apical positions by adjusting the gap between the sections. The distance between the apical section and the apex, as well as the basal section and the mitral valve, were identical.

3. Perfusion test imaging by using geometry identical to that of the short-axis cine views to carefully exclude any wraparound or trigger artifacts before starting the actual index test.

4. Stress perfusion imaging by using the described perfusion sequence. Adenosine (140 µg/min/kg) was given for a total of 4 minutes. Scanning was started in the last minute of vasodilator stress by using an intravenous bolus of 0.025 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at an injection rate of 4 mL/sec followed by a flush of 20 mL of saline solution at the same rate. Blood pressure and heart rate were monitored during the administration of adenosine and the contrast agent. Patients were instructed to hold

their breath as long as possible during imaging and to continue breathing shallowly when they could no longer hold their breath.

5. Rest perfusion imaging by using geometry identical to the short-axis cine views and giving a bolus of contrast agent identical to that given during stress imaging after 15 minutes to allow for myocardial washout.

6. An additional bolus of 0.15 mmol/kg gadopentetate dimeglumine immediately after the rest perfusion scan and standard DE gadolinium-based imaging performed 10 minutes later.

MR Image Analysis

Images were evaluated in consensus by two experienced readers (C.J. and R.G., both with 5 years experience in cardiac MR) who were blinded to the patients' history and angiographic results. The readers were presented with anonymous MR cases, including perfusion at stress, at rest, and DE. Perfusion

defects were determined qualitatively by using subjective visualization. Ischemia was defined as (a) territories without DE that showed a perfusion deficit

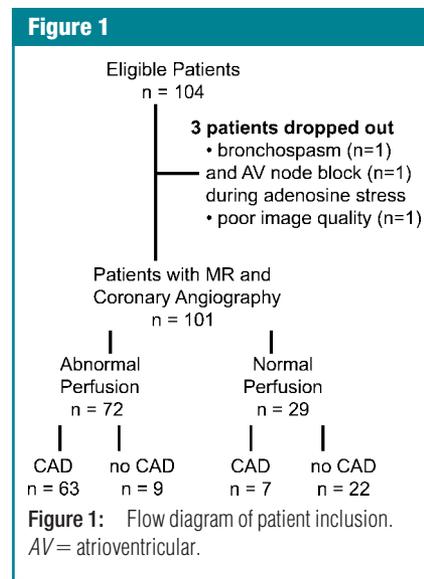


Table 1

Patient Demographics

Characteristic	No. of Patients
Age (y)	62 ± 7.6 (44–80)*†
Sex (male/female)	71/30
Body mass index	27 ± 4*
Risk factors and patient history	
Hypertension	87 (86)
Hypercholesterolemia	70 (69)
Smoking	42 (42)
Diabetes mellitus	26 (26)
Family history	27 (27)
Suspected CAD	45 (45)
Known CAD	56 (55)
Prior myocardial infarction	35 (35)
Prior percutaneous coronary intervention	53 (52)
Prior coronary artery bypass graft	9 (9)
CAD classification	
One vessel	25 (36)
Two vessel	32 (46)
Three vessel	13 (19)
None	31 (31)
Therapy following MR	
Percutaneous coronary intervention	62 (61)
Coronary artery bypass graft	7 (7)

Note.—Numbers in parentheses are percentages, except where noted.

* Data are the mean ± standard deviation.

† Numbers in parentheses are the range.

of 25% or more of the transmural extent during stress perfusion, but not at rest (stress-inducible deficit), for three or more consecutive image frames and (b) territories with nontransmural DE demonstrating additional stress-inducible perfusion deficits. Myocardial territories were assigned to the three major coronary arteries according to standard definitions (12). The readers were instructed to consider defects as artifacts if they had an identical extent during stress and rest in territories without DE, if defects appeared in a nonphysiologic pattern in the epicardium, if defects occurred in less than 25% of the transmural extent of the myocardium during maximum signal intensity of the left ventricular blood pool before maximum signal intensity in the myocardium was reached, or if they appeared only briefly (less than three consecutive frames). The studies were analyzed on a per-patient and per-territory basis.

As a measure of image quality, we determined the amount of dark rim artifacts in the subendocardium associated with 3-T perfusion imaging, which can pose a substantial challenge to making a diagnosis. The blinded perfusion images of those patients without evidence of DE were analyzed again in a second read 4 weeks after the first session by two readers (C.J. and R.G.) in consensus to determine cases that showed territories with perfusion defects that had similar intensity and extent during stress and rest (matched perfusion deficit). In the absence of DE, these cases were considered to represent artifacts. The territory distribution of these artifacts was noted.

To assess interobserver variability for interpretation of perfusion imaging, two independent observers (I.P. and E.N., with 9 and 11 years experience in cardiac MR, respectively) scored perfusion imaging qualitatively on the basis of reading criteria mentioned above in a randomly selected sample of 40 studies.

Coronary Angiography: Reference Standard

All patients underwent conventional coronary catheterization within 24–48 hours after the MR examination by using a standard Judkins technique. A reduction of the luminal diameter 50% or more in a major epicardial coronary artery or the major branches (≥ 2.5 mm) was considered to be a relevant stenosis. The angiographic results were classified as one-, two-, or three-vessel disease or exclusion of relevant CAD. In patients with CAD, the most severe stenosis was defined by an experienced blinded interventionalist (one of three treating physicians with 8–25 years experience in coronary angiography) and assigned to a coronary artery territory (left anterior descending artery [LAD], left circumflex artery [LCX], or right coronary artery [RCA]) deemed responsible for the occurrence of a perfusion defect. Similarly, in patients with bypass grafts, relevant arterial or vein graft stenoses were considered responsible for ischemia in the myocardial territory supplied by the recipient native coronary vessel.

Relevant coronary artery stenoses were present in 69% (70 of 101) of patients; one-, two-, and three-vessel dis-

ease was found in 25% (25 of 101), 32% (32 of 101), and 13% (13 of 101) of patients, respectively. The most severe stenosis was assigned to the LAD in 41% (29 of 70), to the LCX in 23% (16 of 70), and to the RCA in 36% (25 of 70) of patients with CAD.

Statistical Analysis

Statistical analysis was performed by using computer software (SPSS, release 12.0.1; SPSS, Chicago, Ill). For all continuous parameters, mean \pm standard deviation is given. Student *t* test was used to assess significance of continuous variables. κ values were calculated to compare interobserver agreement on a per-patient basis for myocardial territories. Sensitivity, specificity, diagnostic accuracy, and negative and positive predictive values were calculated according to standard definitions. A *P* value of less than .05 was considered to indicate a significant difference.

Results

Patient Group

In the 101 patients (303 coronary territories) available for comparison between coronary angiography and MR perfusion imaging, hemodynamic responses were appropriate, such as an increase in heart rate of 30% and a mild decrease in systolic and diastolic blood pressure (Table 2).

Diagnostic Performance of MR

Per-patient analysis.—The overall patient-based sensitivity, specificity, and diagnostic accuracy for the detection of coronary artery stenosis ($\geq 50\%$) were 90% (63 of 70), 71% (22 of 31), and 84%, respectively (Figs 2 and 3; Table 3). Negative and positive predictive values were 76% and 88%, respectively.

In patients with one-vessel disease, patient-based sensitivity was 88% (22 of 25); in two-vessel disease, sensitivity was 88% (28 of 32); and in three-vessel disease, sensitivity was 100% (13 of 13). In patients with prior myocardial infarction, sensitivity was 89% (31 of 35).

Per-territory analysis.—In a per-

Table 2

Hemodynamic Data

Characteristic	Rest	Stress
Heart rate (beats per minute)	66 \pm 9	88 \pm 11*
Blood pressure		
Systolic (mm Hg)	139 \pm 23	137 \pm 23
Diastolic (mm Hg)	76 \pm 9	73 \pm 11*
Pulse pressure product [†]	9020 \pm 2512	11 800 \pm 2966*

Note.—Data are the mean \pm standard deviation.

* *P* < .001.

[†] Measured as beats per minute times millimeters of mercury.

territory analysis, respective sensitivity and specificity for the LAD were 83% (24 of 29) and 86% (62 of 72); for the LCX, 75% (12 of 16) and 91% (77 of 85); and for the RCA, 68% (17 of 25) and 91% (69 of 76) (Table 3). Respective negative and positive predictive values for LAD were 93% and 71%; LCX, 95% and 60%; and RCA, 90% and 71%. Sensitivity, specificity, and diagnostic accuracy for the detection of relevant coronary stenosis for all coronary arterial territories were 76% (53 of 70), 89% (208 of 233), and 86%, respectively.

In patients with one-vessel disease, the sensitivity for the detection of an ischemic territory was 84% (21 of 25).

Of 74 patients suspected of having relevant CAD with no history of myocardial infarction and no electrocardiographic changes suggesting myocardial infarction, eight patients had evidence of DE.

Artifacts

In 24% (16 of 66) of patients without evidence of DE, territories with a matched perfusion defect during stress and rest were detected, thus representing artifacts (Fig 4). In a per-territory analysis, 56% (nine of 16) of the artifacts were located in the LAD territory, 13% (two of 16) in the LCX territory, and 31% (five of 16) in the RCA territory. In 94% (15 of 16) of patients, no substantial stenosis was detected in the territory of these vessels during coronary angiography.

Interobserver Agreement

Of 40 randomly selected patients, there was agreement in the determination of myocardial perfusion deficits in 37 (93%, $\kappa = 0.79$) on a per-patient basis. For coronary territories, there was concordance in 34 (85%, $\kappa = 0.63$) patients for the LAD, 34 (85%, $\kappa = 0.67$) patients for the LCX, and 33 (83%, $\kappa = 0.63$) patients for the RCA.

Discussion

In our study, we evaluated myocardial perfusion MR imaging at 3 T in a population with suspected and known CAD.

Figure 2

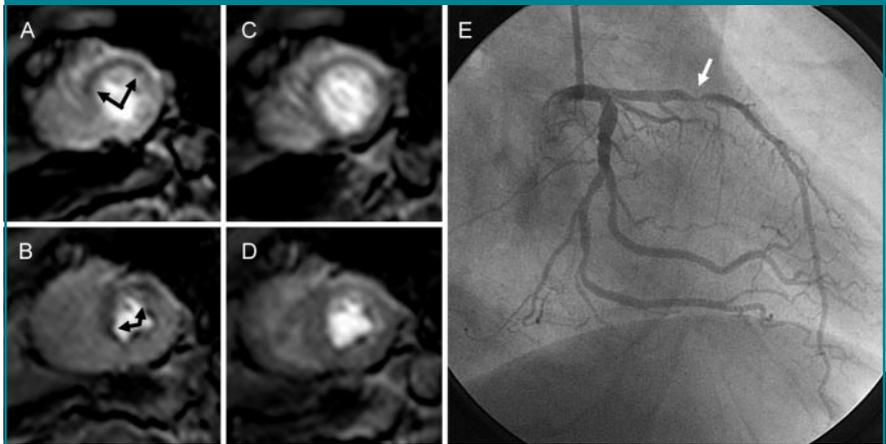


Figure 2: Patient with stress-inducible anterior and anteroseptal perfusion defect (black arrows). Scans show *A*, apical and *B*, equatorial short-axis views during stress; *C* and *D* show perfusion images at rest (2.8/0.9; flip angle, 18°). *E*, Coronary angiography shows 90% stenosis (white arrow) of proximal LAD.

Figure 3

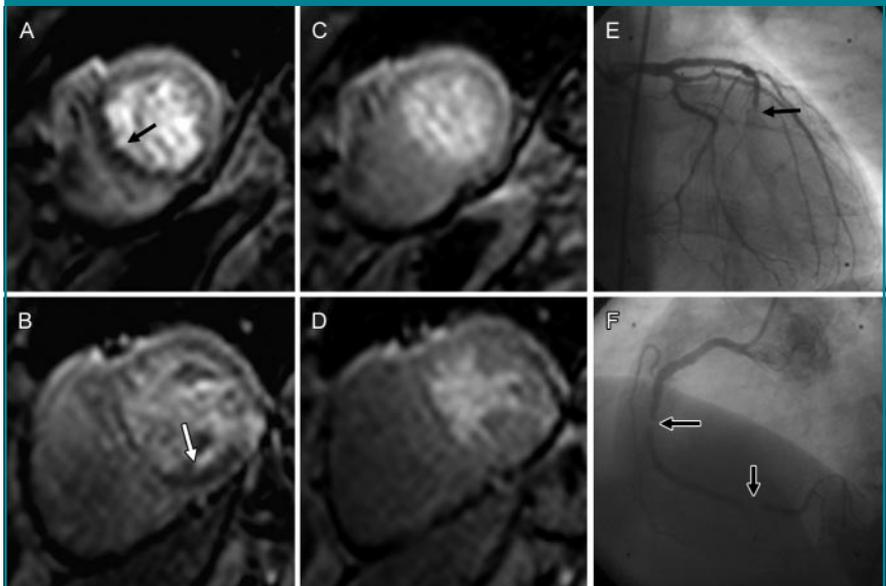


Figure 3: Short-axis views of patient with stress-inducible perfusion defect show apical septum (*A*, black arrow) and basal inferior wall (*B*, white arrow); images during rest (*C*, *D*) do not (2.8/0.9; flip angle, 18°). Coronary angiograms shows distal occlusion of LAD (*E*, black arrow) and two subtotal stenoses (*F*, black arrows) of mid and distal RCA.

The principal findings of our study are that (a) myocardial stress perfusion imaging at 3 T has an accuracy of 84%–86% to help detect relevant coronary artery stenoses; (b) dark rim artifacts represented by matched perfusion de-

fects between stress and rest imaging occur in almost one-fourth of patients without evidence of DE; and (c) there is high interobserver agreement for the detection of perfusion deficits.

Myocardial perfusion imaging with

1.5-T MR has evolved into a clinically useful technique to help detect myocardial ischemia while still experiencing a low signal-to-noise ratio. Thus, the 3-T platform is attractive for its immediate increase in magnetization by a factor of two, a higher signal-to-noise ratio, and better tissue contrast (13). Cardiac imaging at 3 T, however, is substantially different from imaging at 1.5 T because of increased susceptibility artifacts, differences in tissue relaxation, and radio-frequency homogeneity issues. Because findings in initial small studies (14,15) have shown that MR perfusion at 3 T provides improved contrast over a range of gadopentetate dimeglumine doses and improved diagnostic accuracy compared with perfusion imaging at 1.5 T, we aimed to demonstrate its diagnostic performance in a larger patient cohort that is typical for a tertiary center (including an analysis of dark rim artifacts, which play an important role in image analysis).

We found that adenosine vasodilator MR perfusion imaging is a feasible and safe stress test in the 3-T environment. Only two of 104 patients could not be evaluated owing to adenosine-related side effects, including self-limiting dyspnea and bradycardia, which occurred probably owing to transient atrioventricular node block. Both patients recovered within seconds after discontinuation of the adenosine infusion. This is in accordance with previously reported tolerance levels and safety profile of adenosine MR perfusion studies at 1.5 T (16). Poor-quality MR images led to the exclusion of only one patient. Although our overall patient-based diagnostic accuracy of 84% is comparable to previously reported results from perfusion studies at 1.5 T (8,9), our specificity was lower at 71%. There might be several reasons for this finding. First, our patient population consisted of a cohort with a high number of hypertensive patients, patients

with previous interventions, and prior myocardial infarction, while in previous studies, these patient groups have often been excluded, resulting in a higher specificity (5,8). Second, the number of patients with artifacts, represented by matching stress-rest defects in patients without evidence of DE, was relatively high. When performing visual assessment, perfusion defects must be differentiated from dark rim artifacts, which may appear in the subendocardial layer of the myocardium.

Recently, Klem et al (17) have shown that by combining stress and rest perfusion imaging with DE imaging, the diagnostic value significantly improves compared with perfusion imaging alone in a population with a low prevalence of CAD. This improvement was most pronounced in dark rim artifact spoiled perfusion images. The results of our study confirmed that the incorporation of a rest perfusion scan and DE is helpful in distinguishing potential perfusion defects from artifacts. A number of possible causes for the appearance of dark rim artifacts have been discussed, including susceptibility effects of the highly concentrated contrast agent bolus during the first pass (18). We anticipated this issue and lowered the contrast agent dose from 0.05 mmol/kg at 1.5 T to 0.025 mmol/kg for our study at 3 T. Nevertheless, the amount of these artifacts in our study was higher compared with the results (24% vs 18%) reported by Klem et al (17). This might reflect the stronger susceptibility effects caused by larger B_0 inhomogeneities at 3 T when compared with 1.5 T, as previously reported. Most of the dark rim artifacts (56%) in our study were found in the LAD territory, which might be related to partial volume effects and susceptibility affecting the septum, as it is located between the right and left ventricular cavities, both of which have high concentrations of gadopentetate dimeglumine during the first pass of the contrast agent.

Our study had limitations. The per-territory analysis does not take into account the correlation owing to territories being clustered within patients. We did not perform quantitative or semi-quantitative measurements, which have been reported to lead to increased spec-

Table 3

Diagnostic Performance of Myocardial Perfusion Imaging According to the Extent and Location of Coronary Stenosis

Coronary Stenosis \geq 50%	Sensitivity (%)	Specificity (%)	Accuracy (%)
Patient-based total	90 (63/70)	71 (22/31)	84
Coronary artery			
LAD	83 (24/29)	86 (62/72)	85
LCX	75 (12/16)	91 (77/85)	88
RCA	68 (17/25)	91 (69/76)	85

Note.—Numbers in parentheses are raw data.

Figure 4

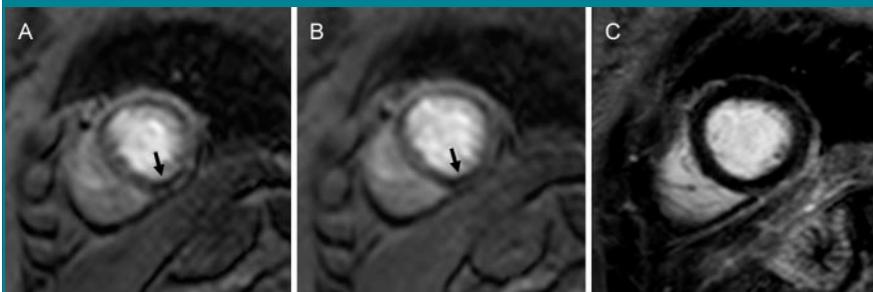


Figure 4: Short-axis views of patient with suspected CAD show subendocardial perfusion defect (arrow) during *A*, stress and *B*, rest (2.8/0.9; flip angle, 18°) in absence of scar (*C*) at DE, representing typical dark rim imaging artifact. Patient had no relevant stenosis at coronary angiography.

ificity of myocardial perfusion imaging (8). The drawback of quantitative analysis is that it is time consuming and not ideal for day-to-day clinical purposes. Our aim, however, was to establish a clinically robust approach for myocardial perfusion imaging at 3 T.

Myocardial perfusion MR imaging by using saturation-recovery spoiled gradient-echo imaging at 3 T has an accuracy of 84%–86% for depicting hemodynamically relevant coronary stenosis in patients with suspected or known CAD. Recent studies on the causes of dark rim artifacts have pointed out that low spatial and temporal resolutions are both associated with more pronounced artifacts (19,20). Future efforts should thus be directed at improving both spatial and temporal resolution in an attempt to optimize image quality at 3-T perfusion imaging. Multicenter trials incorporating a multimodality approach are needed to establish the clinical role of cardiac MR with 3 T for the detection of relevant myocardial ischemia.

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