Myocardial First-Pass Perfusion Magnetic Resonance Imaging

A Multicenter Dose-Ranging Study

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Background—MRI can identify patients with obstructive coronary artery disease by imaging the left ventricular myocardium during a first-pass contrast bolus in the presence and absence of pharmacologically induced myocardial hyperemia. The purpose of this multicenter dose-ranging study was to determine the minimally efficacious dose of gadopentetate dimeglumine injection (Magnevist Injection; Berlex Laboratories) for detecting obstructive coronary artery disease.

Method and Results—A total of 99 patients scheduled for coronary artery catheterization as part of their clinical evaluation were enrolled in this study. Patients were randomized to 1 of 3 doses of gadopentate dimeglumine: 0.05, 0.10, or 0.15 mmol/kg. First-pass perfusion imaging was performed during hyperemia (induced by a 4-minute infusion of adenosine at a rate of 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and then again in the absence of adenosine with otherwise identical imaging parameters and the same contrast dose. Perfusion defects were evaluated subjectively by 4 blinded reviewers. Receiver-operating curve analysis showed that the areas under the receiver-operating curve were 0.90, 0.72, and 0.83 for the low-, medium-, and high-contrast doses, respectively, compared with quantitative coronary angiography (diameter stenosis $\geq$70%). For the low-dose group, mean sensitivity was 93$\pm$0%, mean specificity was 75$\pm$7%, and mean accuracy was 85$\pm$3%.

Conclusions—First-pass perfusion MRI is a safe and accurate test for identifying patients with obstructive coronary artery disease. A low dose of 0.05 mmol/kg gadopentetate dimeglumine is at least as efficacious as higher doses. **(*Circulation*. 2004;110:732-737.)**

Key Words: adenosine ■ contrast media ■ ischemia ■ magnetic resonance imaging ■ perfusion

Myocardial perfusion imaging is an integral part of the assessment of patients with ischemic heart disease. Most patients today are evaluated by SPECT.[1] However, the accuracy of this technique is sometimes diminished by relatively low spatial resolution and the presence of artifacts from photon scatter and soft tissue attenuation.

MRI can produce higher-resolution perfusion images of the heart than SPECT without attenuation artifacts or the need to expose patients to radiation. Myocardial perfusion can be assessed by imaging the left ventricular myocardium during the first pass of a contrast bolus. Fast imaging methods have been developed so that the entire left ventricle can be imaged during the passage of the contrast bolus.[2,3] A number of studies have assessed myocardial perfusion at rest and during hyperemia. The validity of myocardial perfusion MRI has been shown by comparison to other techniques such as SPECT,[4–6] PET,[7] and coronary angiography.[8–16] Interestingly, the dose of gadolinium contrast administered in these studies varied 6-fold, with doses ranging from 0.025 to 0.15 mmol/kg. No systematic study has been performed to date to evaluate the optimal dose of contrast for cardiac perfusion. The purpose of the present study was to determine the minimally efficacious contrast dose for detecting obstructive coronary artery disease. To the best of our knowledge, this is the first controlled, dose-ranging, multicenter study to systematically evaluate the optimal dose of MR contrast agent in this application.

Methods

This prospective trial was performed at 3 clinical sites, each under institutional review board approval. Written, informed consent was

Received December 29, 2003; revision received March 10, 2004; accepted March 17, 2004.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000138106.84335.62**

obtained from all 99 patients who enrolled in this study. Patients were eligible to enroll if they had known or suspected coronary artery disease and were scheduled for cardiac catheterization as part of their clinical care. Patients were excluded if they were medically unstable, had a myocardial infarction <2 weeks earlier, or had any contraindication to MRI (eg, pacemaker, internal defibrillator). They were also excluded if they had a known allergy or contraindication to any paramagnetic or iodinated contrast agent. Patients were excluded from the study if they had a contraindication to adenosine (eg, asthma, heart block) or had ingested agents within 24 hours of the study that could potentiate (dipyridamole) or antagonize (eg, caffeine, methylxanthines) the effects of adenosine. Finally, for ease of determining the presence and extent of obstructive coronary artery disease, patients who had previously undergone CABG were excluded.

MRI Protocol

First-pass perfusion imaging was performed on 1.5-T Signa CV/i scanners (GE Medical Systems) using a segmented echo-planar imaging pulse sequence with a notched saturation pulse.[5] Perfusion pulse sequence parameters were as follows: repetition time, 6.6 to 15.8 ms; echo time, 1.3 to 2.2 ms; inversion time, 158 to 211 ms; echo train length, 4 to 8; field of view, 34 to 37×25 to 27 cm; matrix, 128×128; and slice thickness, 10 mm. All perfusion images were acquired in the short-axis orientation only. The maximum number of slices was limited by heart rate. At stress, the average heart rate was 80±17 bpm, and the average number of short-axis slices was 6.8±0.6. If the entire left ventricle could not be covered by contiguous slices, a small slice gap was introduced to allow complete coverage from the apex to base. The rest perfusion images were generally acquired with the same graphic prescription used for the stress study. At rest, the average heart rate was 65±9 bpm.

Patients were randomized to 1 of 3 doses of Magnevist Injection (Berlex Laboratories): 0.05 mmol/kg (low dose), 0.1 mmol/kg (medium dose), and 0.15 mmol/kg (high dose). For hyperemic perfusion imaging, contrast injection and image acquisition began 3 minutes after the initiation of adenosine infusion (Adenoscan, Fujisawa; dose, 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Contrast was injected at 5 mL/s and was followed with 25 mL saline flush at the same injection rate with an MRI-compatible power injector. The adenosine infusion was then stopped 4 minutes after it was initiated. Resting (nonhyperemic) perfusion images were acquired 20 minutes later with identical parameters but with no adenosine infusion. Because the protocol calls for 2 first-pass imaging studies, the cumulative dose of Magnevist Injection to the patient was 0.1, 0.2, or 0.3 mmol/kg for the low-, medium-, and high-dose groups, respectively.

MRI Analysis

Each patient study was reviewed by 4 independent blinded readers. Before interpreting cases for this trial, each blinded reader completed a training session that included a review of several MR perfusion studies (that were not from this trial) and their coronary catheterization results. Perfusion defects were determined solely by subjective visualization. Perfusion defects were defined as focal regions of myocardium that had diminished and/or delayed contrast enhancement compared with normal myocardium. Obstructive coronary artery disease was present if there was a myocardial perfusion defect during hyperemia that was not present at rest. For each patient study, each reader reported the likelihood of obstructive coronary artery disease on a scale of 1 to 5: 1=definitely normal, 2=probably normal, 3=possibly abnormal, 4=probably abnormal, and 5=definitely abnormal. A receiver-operating curve (ROC) analysis was performed for each reader at each dose level.

To quantify the effect of contrast dose on myocardial enhancement, the signal of the hyperemic myocardium at peak enhancement was compared with that before contrast arrival. Signal intensity was quantified within a small region of interest before contrast arrival and at peak enhancement. Care was taken to avoid myocardial regions where there was a suspected perfusion defect.

Quantitative Coronary Angiography

Cine angiography and quantitative coronary angiography were considered the gold standard for the purposes of this validation study. All cine angiograms were acquired with angiographic guidelines and had to be performed within 30 days of the perfusion study. A complete diagnostic catheterization was performed with at least 2 orthogonal views of every major coronary vessel and its side branches and submitted to an independent angiographic core laboratory (Cardiovascular Research Foundation, New York, NY) for independent and blinded analysis. An initial systematic screening evaluation of all major epicardial coronary Coronary Artery Surgery Study (CASS) segments and all significant side branches defined as >2 mm in diameter was performed quantitatively with handheld calipers. Any lesion with a diameter stenosis >40% by handheld caliper was subsequently analyzed by computerized quantitative methods using the CMS-GFT, MEDIS software.[17,18] The contrast-filled catheter was used for image calibration. The mean lumen diameter (MLD) and the interpolated reference diameter were used to calculate the percent diameter stenosis: (1−MLD/mean reference diameter)×100. A prespecified diameter stenosis ≥70% was considered positive for coronary artery disease for the purposes of the validation study.

Statistical Analysis

Continuous variables are expressed as mean±SD. Differences between groups were tested by use of Student's *t* test. A value of $P \leq 0.05$ was defined as statistically significant. ROC analyses were performed to evaluate the efficacy of MR perfusion imaging for each reader and each dose group. Cohen's κ test was used to assess for interreader agreement.

Results

Patient Population

A total of 99 patients were enrolled in this study. There were no serious adverse events reported. Of the 99 patients enrolled, 75 were evaluable. Reasons for patients not being evaluable included the following: incorrect MR imaging protocol (6 patients), off-resonance acquisition (5 patients), no quantitative coronary angiography (4 patients), no resting perfusion (4 patients), power injector failure (1 patient), MR images not archived (1 patient), poor ECG gating (1 patient), claustrophobia (1 patient), and atrioventricular block (1 patient). A total of 94 patients received Magnevist Injection. Clinical site 1 enrolled 40 patients, of whom 34 (85%) were evaluable; clinical site 2 enrolled 27 patients, of whom 23 (85%) were evaluable; and clinical site 3 enrolled 32 patients, of whom 18 (56%) were evaluable. Of the 75 evaluable patients, there were 26, 25, and 24 in the low-, medium-, and high-dose groups, respectively. Patient demographics and prevalence of coronary artery disease for the 3 dose groups were comparable (the Table).

MR Perfusion Imaging Versus Coronary Catheterization

Figure 1A shows an MR perfusion study from a patient with obstructive coronary artery disease. The top row contains images acquired during hyperemia; the bottom row contains images acquired at rest. Arrows point to regions of decreased signal intensity that represent delayed and diminished enhancement during hyperemia only, suggesting the presence of a flow-limiting stenosis. The coronary angiogram shown in Figure 1B shows that the mid portion of the left anterior descending artery is occluded (black arrow), and quantitative

Patient Characteristics and Baseline Data

	Low Dose	Medium Dose	High Dose
Sex, male/female	22/4	18/7	22/2
Age, y	59±8	56±9	57±9
Height, cm	171±7	170±9	173±9
Weight, kg	80±11	77±11	80±13
Obstructive coronary artery disease*			
None	12	15	11
1 Vessel	10	10	9
2 Vessel	4	0	4
3 Vessel	0	0	0

Values are expressed as a mean±SD.
*Defined as ≥70% stenosis on quantitative coronary artery angiography.

coronary angiography measured a 77% stenosis of the second obtuse marginal (white arrow).

Figure 2 shows an ROC analysis for each of the 4 readers at each of the 3 doses of Magnevist Injection. The average areas under the ROC were 0.90±0.04, 0.72±0.09, and 0.83±0.06 at doses of 0.05, 0.10, and 0.15 mmol/kg, respectively. Among the 3 doses, there is a statistically significant difference between the ROC areas of the low and medium doses ($P<0.02$). However, there is no statistically significant difference between the low and high or between the medium and high doses. For the low dose, Cohen's κ test shows substantial interreader agreement ($\kappa=0.74\pm0.06$). However, for the medium and high doses, the interreader agreement was only fair (medium dose, $\kappa=0.30\pm0.14$; high dose, $\kappa=0.35\pm0.39$). If one chooses a score of ≤2 as being normal and a score of ≥3 as being abnormal, the sensitivity, specificity, and accuracy for the low dose group are 93±0%, 75±7%, and 85±3%, respectively.

Effect of Contrast Dose on Myocardial Enhancement

Figure 3 shows the percent contrast enhancement as a function of contrast dose. Greater myocardial enhancement was achieved with higher contrast doses, but the incremental effect was less with the medium and high doses.

Discussion

The results of this study confirm that first-pass perfusion imaging with hyperemia can be performed safely in the MRI environment. Among the 99 patients enrolled, 94 received Magnevist Injection, and no serious adverse events were reported. In only 1 patient was the adenosine infusion terminated prematurely, and that was due to adenosine-induced atrioventricular block.

The results also show that first-pass perfusion MRI with subjective reader analysis is efficacious at a dose of 0.05 mmol/kg. The mean sensitivity, specificity, and accuracy were 93±0%, 75±7%, and 85±3%, respectively. The patient population in this study was quite challenging, given that most patients (78%) with coronary artery disease had single-vessel disease. Overall, the results are not dissimilar to those obtained from other studies that performed a semiquan-

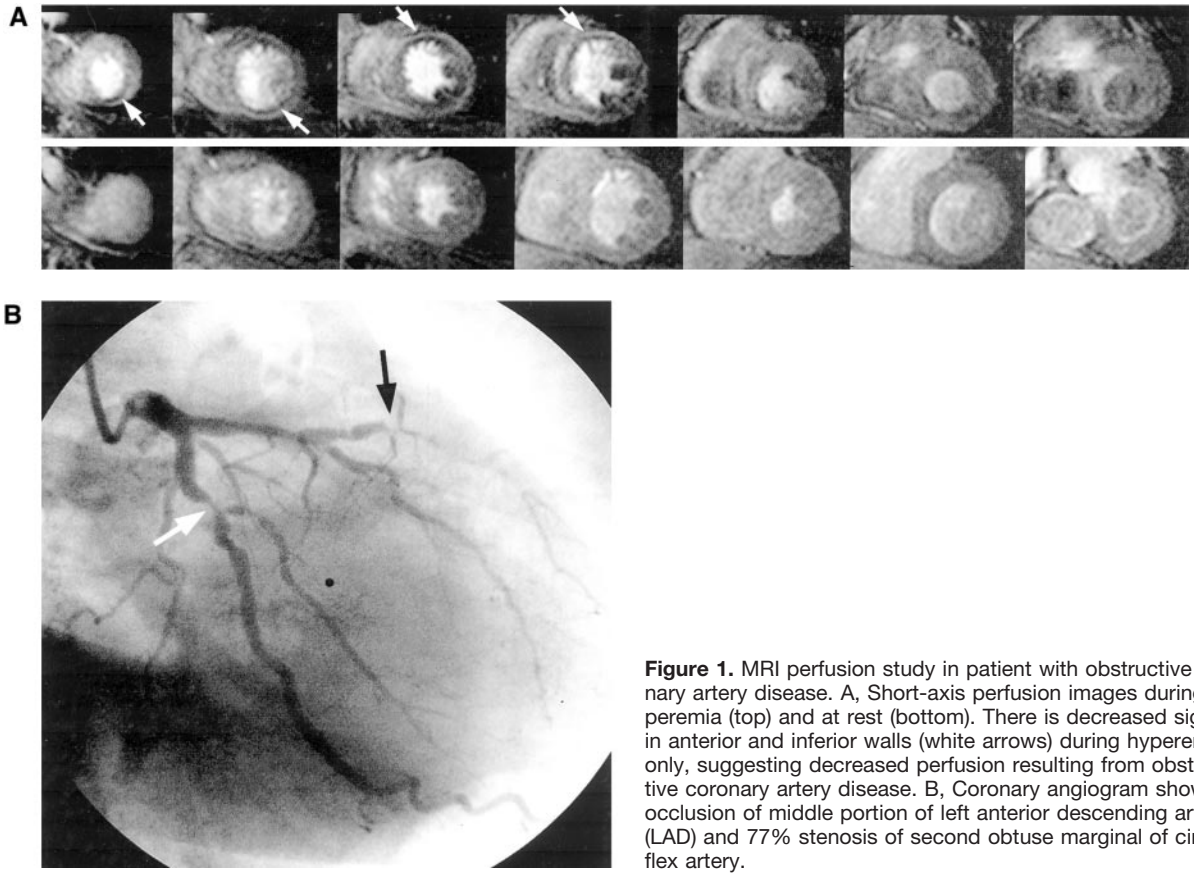

Figure 1. MRI perfusion study in patient with obstructive coronary artery disease. A, Short-axis perfusion images during hyperemia (top) and at rest (bottom). There is decreased signal in anterior and inferior walls (white arrows) during hyperemia only, suggesting decreased perfusion resulting from obstructive coronary artery disease. B, Coronary angiogram showing occlusion of middle portion of left anterior descending artery (LAD) and 77% stenosis of second obtuse marginal of circumflex artery.

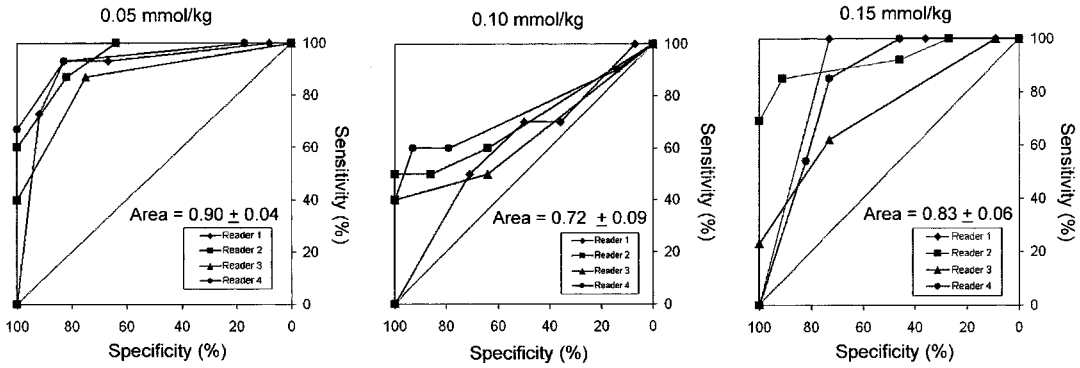

Figure 2. ROC analyses for each reader as function of contrast dose. Average areas under ROC curve were 0.90±0.04 for low dose, 0.72±0.09 for medium dose, and 0.83±0.09 for high dose.

titative analysis of the MRI data. One study of 90 patients using a gadolinium dose of 0.025 mmol/kg found a sensitivity and specificity of 88% and 90%, respectively.[16] Another study of 48 patients using a gadolinium dose of 0.1 mmol/kg found a sensitivity and specificity of 87% and 85%, respectively.[7] Unfortunately, differences in patient populations, gadolinium dose, imaging parameters, and methods of analysis make direct comparisons among the studies problematic.

In the present study, higher doses of gadolinium contrast yielded greater myocardial enhancement (Figure 3) but did not result in higher diagnostic accuracy. This result was unexpected because higher doses of contrast have been shown to improve diagnostic accuracy and confidence in other MRI applications such as in the cases of detecting brain metastases and for MR angiography of the abdomen.[19,20] Interestingly, the results of the present study suggest that doses of 0.1 and 0.15 mmol/kg are worse, although the difference was statistically significant ($P<0.02$) only for the medium-dose group compared with the low-dose group. We hypothesize that worse performance at higher contrast dose may be due to susceptibility artifacts that become more prominent at higher contrast doses. Susceptibility artifacts that can also cause a focal decrease in myocardial signal intensity could be mistaken by readers for real perfusion defects and thereby lead to an increase in the number of false-positives. Indeed, Figure 4 shows that the overall number of false-positives does increase with increasing dose. Also supporting the hypothesis that image quality is worse at higher contrast dose is the fact that the Cohen's κ test showed substantial interreader agreement for the low-dose group but only fair agreement for the medium- and high-dose groups. This observation is also supported by visual inspection of Figure 2, which shows a much greater separation between the individual reader ROC curves at the medium and high doses compared with the low dose.

Study Limitations

Perhaps the greatest study limitation is the use of quantitative coronary angiography as the standard of reference for perfusion imaging. Although there is a correlation between epicardial coronary stenoses and perfusion defects during hyperemia, clearly it is not perfect. For example, coronary stenoses may be underestimated if there is diffuse luminal narrowing or if the stenosis is eccentric and is not imaged precisely in profile. The impact of an epicardial stenosis on perfusion can be mitigated by the presence of an extensive collateral circulation. Epicardial coronary artery stenoses will be missed if the tissue they supply is completely infarcted. Finally, it is unclear what percent diameter stenosis should be considered significant. Figure 5 shows an example of a patient who had a 51% stenosis of a marginal branch of the circumflex coronary artery that presumably caused a perfu-

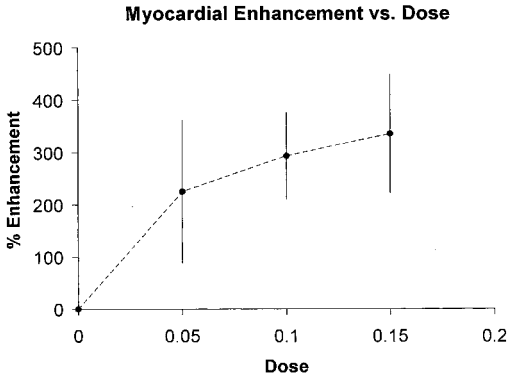

Figure 3. Percentage myocardial enhancement as function of contrast dose. Greater myocardial enhancement was achieved with higher contrast doses, but incremental effect was less with medium and high doses.

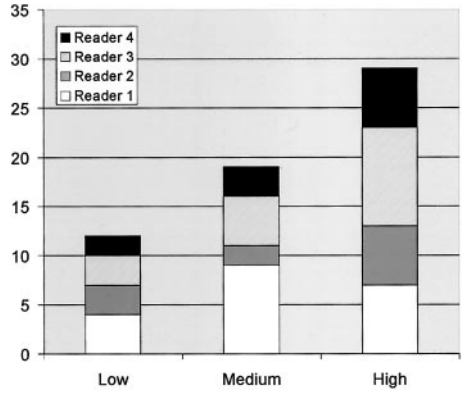

Figure 4. False-positives as function of contrast dose. Total number of false-positive readings increases approximately linearly with contrast dose.

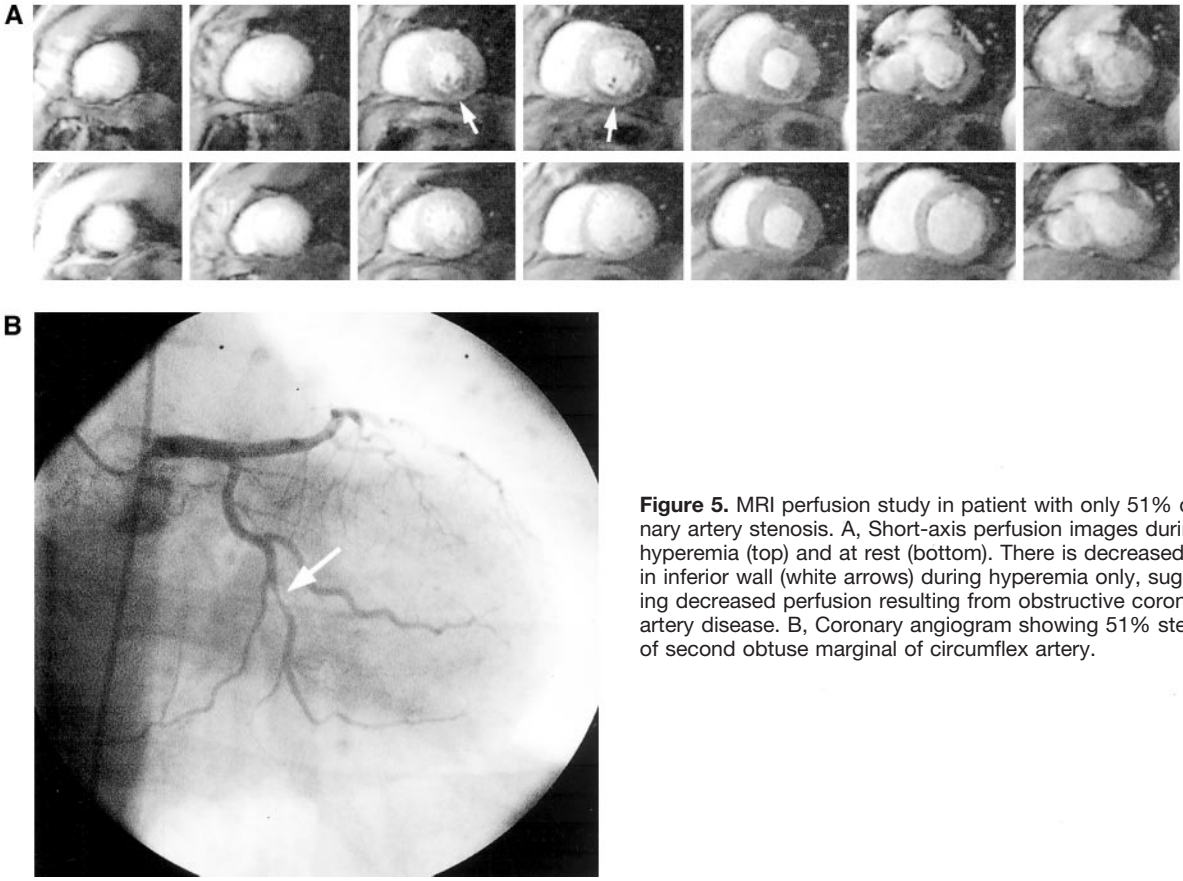

Figure 5. MRI perfusion study in patient with only 51% coronary artery stenosis. A, Short-axis perfusion images during hyperemia (top) and at rest (bottom). There is decreased signal in inferior wall (white arrows) during hyperemia only, suggesting decreased perfusion resulting from obstructive coronary artery disease. B, Coronary angiogram showing 51% stenosis of second obtuse marginal of circumflex artery.

sion defect in the inferior wall. All 4 readers believed this patient had obstructive coronary artery disease on that basis, yet because the stenosis was <70%, it was considered a false-positive case. Conversely, there were other patients with stenoses >70% in whom no perfusion defect was detected. Despite this limitation, perfusion imaging is used in clinical practice today as a noninvasive method of predicting those patients who are likely to have obstructive coronary artery disease and need coronary catheterization. The clinical imperative to predict the presence of epicardial coronary artery stenoses is a reason why many other perfusion studies have previously used coronary catheterization as a standard of reference.

A potential limitation of any technique is its ability to be successfully completed. Of the 99 patients enrolled in this study, 24 were unevaluable. However, 15 of these patients were unevaluable because sites did not complete the research protocol (ie, no quantitative coronary angiography, no resting perfusion images, incorrect MRI parameters, or failure to archive data). If these 15 patients are excluded from analysis, the success rates for sites 1, 2, and 3 are 94%, 92%, and 78%, respectively. Furthermore, had the sites simply verified that the scanner was on-resonance for perfusion imaging, presumably 95% of all patients would have been evaluable, indicating that perfusion MRI can be a robust technique.

A final limitation is that the dose evaluation is specific for the particular pulse sequence and method used in this study. Although one would expect a similar dose dependency for similar pulse sequences, this might not be the case for very different pulse sequences such as those having a very different repetition time, flip angle, and/or echo time, as in the case of steady-state free precession perfusion sequences, for example.[21] The advent of viability imaging and its exquisite ability to depict acute and chronic myocardial infarction may change the way perfusion studies are performed in the future. Namely, it is possible that hyperemic perfusion images will be directly compared with viability images, obviating the need for acquiring rest perfusion studies.

Conclusions

First-pass perfusion MRI is a safe and accurate test for identifying patients with obstructive coronary artery disease. A low dose of 0.05 mmol/kg Magnevist Injection is at least as efficacious as higher doses.

Disclosure

Drs Bluemke and Wolff have served as consultants for Berlex Laboratories and GE Medical Systems.

Acknowledgments

This study was supported in part by Berlex Laboratories and GE Medical Systems.

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