

# Comparison of Dobutamine Stress Magnetic Resonance, Adenosine Stress Magnetic Resonance, and Adenosine Stress Magnetic Resonance Perfusion

I. Paetsch, MD; C. Jahnke, MD; A. Wahl, MD; R. Gebker, MD; M. Neuss, MD;  
E. Fleck, MD; E. Nagel, MD

**Background**—Dobutamine stress MR (DSMR) is highly accurate for the detection of inducible wall motion abnormalities (IWMA). Adenosine has a more favorable safety profile and is well established for the assessment of myocardial perfusion. We evaluated the diagnostic value of IWMA during dobutamine and adenosine stress MR and adenosine MR perfusion compared with invasive coronary angiography.

**Methods and Results**—Seventy-nine consecutive patients (suspected or known coronary disease, no history of prior myocardial infarction) scheduled for cardiac catheterization underwent cardiac MR (1.5 T). After 4 minutes of adenosine infusion ( $140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 6 minutes), wall motion was assessed (steady-state free precession), and subsequently perfusion scans (3-slice turbo field echo-echo planar imaging;  $0.05 \text{ mmol/kg Gd-BOPTA}$ ) were performed. After a 15-minute break, rest perfusion was imaged, followed by standard DSMR/atropine stress MR. Wall motion was classified as pathological if  $\geq 1$  segment showed IWMA. The transmural extent of inducible perfusion deficits ( $<25\%$ ,  $25\%$  to  $50\%$ ,  $51\%$  to  $75\%$ , and  $>75\%$ ) was used to grade segmental perfusion. Quantitative coronary angiography was performed with significant stenosis defined as  $>50\%$  diameter stenosis. Fifty-three patients (67%) had coronary artery stenoses  $>50\%$ ; sensitivity and specificity for detection by dobutamine and adenosine stress and adenosine perfusion were 89% and 80%, 40% and 96%, and 91% and 62%, respectively. Adenosine IWMA were seen only in segments with  $>75\%$  transmural perfusion deficit.

**Conclusions**—DSMR is superior to adenosine stress for the induction of IWMA in patients with significant coronary artery disease. Visual assessment of adenosine stress perfusion is sensitive with a low specificity, whereas adenosine stress MR wall motion is highly specific because it identifies only patients with high-grade perfusion deficits. Thus, DSMR is the method of choice for current state-of-the-art treatment regimens to detect ischemia in patients with suspected or known coronary artery disease but no history of prior myocardial infarction. (*Circulation*. 2004;110:835-842.)

**Key Words:** adenosine stress ■ dobutamine stress ■ magnetic resonance imaging ■ perfusion ■ ischemia

In recent years, pharmacological stress testing has evolved as an alternative to physical exercise for the detection of inducible myocardial ischemia. The diagnostic performance of the stress tests may vary considerably, depending on the imaging modality (echocardiography, MRI, nuclear techniques) or stress agent used. Routinely used pharmacological stress agents are adenosine or dipyridamole and the synthetic  $\beta$ -adrenergic agent dobutamine. There is controversy regarding the “optimal” pharmacological stress agent; according to guidelines, adenosine should be used mainly for myocardial perfusion measurements, whereas dobutamine is advised for the detection of stress-inducible wall motion abnormalities (IWMA). A

large number of studies are available on the relative value of different stressors for different imaging modalities. However, the value of such studies may be reduced by performing the test on different days, which may significantly influence results, or by different physicians based in different departments. In addition, each modality has different advantages and disadvantages; thus, the resulting information describes the value of the modality rather than the stressor.<sup>1-4</sup> To determine the diagnostic value of the stress agents, it seems reasonable to directly compare adenosine and dobutamine stress for wall motion analysis using the same imaging modality and, if possible, to concomitantly assess segmental myocardial perfusion un-

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From the Department of Internal Medicine/Cardiology, German Heart Institute, Berlin, Germany (I.P., R.G., M.N., E.F., E.N.); Department of Internal Medicine/Cardiology, University of Freiburg, Freiburg, Germany (C.J.); and Department of Cardiology, Swiss Cardiovascular Center, Bern, Switzerland (A.W.).

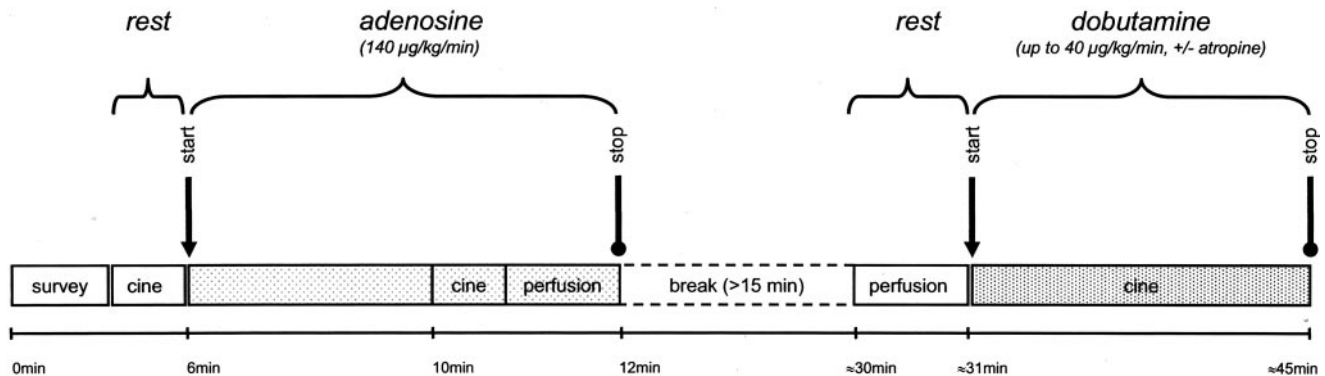
The online-only Data Supplement is available at <http://www.circulationaha.org>.

Correspondence to Ingo Paetsch, MD, Internal Medicine/Cardiology, German Heart Institute Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail [paetsch@dhzb.de](mailto:paetsch@dhzb.de)

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**Figure 1.** Time course of stress testing (adenosine and dobutamine administration) and corresponding MRI (cine and perfusion scans).

der adenosine stress. Cardiac MR is favorable regarding both functional measurements: It allows assessment of even subtle wall motion disturbances resulting from the consistently high endocardial border definition, and the measurement of myocardial perfusion can be integrated into the same examination, with the high spatial resolution of the scans facilitating the determination of the transmural extent of a regional perfusion deficit.

Thus, the present study sought to determine the diagnostic performance of MRI for the assessment of IWMA under dobutamine and adenosine stress and to determine the extent of concomitantly occurring adenosine-inducible perfusion abnormalities.

## Methods

### Study Population

The study was conducted in accordance with the standards of the Charité and Virchow-Klinikum Ethics Committee. Seventy-nine consecutive patients referred to our hospital for cardiac catheterization who were complaining of chest pain were prospectively enrolled after written informed consent was obtained. Patients were eligible if they had suspected or known coronary artery disease (CAD; with or without prior percutaneous revascularization) but no prior history of myocardial infarction, no significant Q waves in the admittance ECG, and no prior coronary surgery. Patients were excluded if they had typical contraindications for MRI or administration of dobutamine and adenosine. All patients were instructed to refrain from cigarettes, tea, coffee,  $\beta$ -blockers, and antianginal medication for at least 24 hours before the MR study.

### MR Study

MR was performed with the patient in the supine position with a 1.5-T MR scanner (Philips Intera CV) equipped with a Power-Trak6000 gradient system (23 mT/m; 219- $\mu$ s rise time) and software package release 9. Cardiac synchronization was performed with 4 electrodes placed on the left anterior hemithorax (Vector-ECG).

Figure 1 shows the course of the examination. After acquisition of rest cine scans in the standard views (apical, mid, and basal short-axis views; 4-, 2-, and 3-chamber views), the adenosine infusion ( $140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ; total duration, 6 minutes) was started, and the standard cine scans were repeated after 4 minutes of adenosine infusion. Within the last minute of the infusion, the adenosine stress MR perfusion scan was performed to visualize the identical 3 short-axis geometries using 60 dynamic acquisitions during the administration of a gadolinium-BOPTA intravenous bolus (dosage, 0.05 mmol/kg; infusion rate, 4 mL/s) and applying a previously described breathhold scheme.<sup>5</sup>

A 15-minute waiting period allowed equilibration of the contrast agent within the myocardium while the patient remained in position. After the break, the examination was continued, repeating the identical MR perfusion scan at rest.

Directly afterward, a DSMR examination was carried out following a standard high-dose regimen (up to  $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) plus atropine (up to 2 mg) if needed to reach target heart rate defined as age-predicted submaximal heart rate [ $(220 - \text{age}) \times 0.85$ ]. Termination criteria were as previously published.<sup>6</sup>

### MRI Technique

For cine imaging, a steady-state free precession sequence with retrospective gating [25 phases per cardiac cycle; repetition time (TR), 2.7 ms; echo time (TE), 1.4 ms; flip angle,  $60^\circ$ ] during an end-expiratory breathhold of 4 to 6 seconds was used. Typical in-plane spatial resolution was  $1.8 \times 1.8$  mm with a slice thickness of 8 mm.

For perfusion imaging, a 3-slice turbo field echo-echo planar imaging sequence (TR, 9.3 ms; TE, 3.3 ms; flip angle,  $30^\circ$ ) was used with 1 saturation prepulse per slice before data readout (prepulse delay, 130 ms; typical spatial resolution,  $2.4 \times 2.4 \times 8$  mm).

### Image Analysis

#### Cine Scans

Segmental analysis of the cine scans was performed by the consensus of 2 observers (I.P., C.J.) blinded to the perfusion scans and invasive coronary angiography using a synchronized quad-screen image display and applying the standard scoring system (1=normokinesis, 2=hypokinesis, 3=akinesis, 4=dyskinesis).<sup>7,8</sup> To adequately compare segmental wall motion with the short-axis perfusion scan, the apical segment (number 17) was not considered. For dobutamine scans, ischemia was defined as  $\geq 1$  segments showing IWMA (ie, an increase in the segmental wall motion score of  $\geq 1$ ); a biphasic response was considered to indicate ischemia. Adenosine stress MR scans were analyzed twice: once using identical criteria as for dobutamine (analysis A, see above) and once using the additional criterion of segmental absence of a hyperkinetic response as an indicator of IWMA (analysis B).<sup>2,9,10</sup> In patients with WMA at rest, all segments with resting akinesis were not considered for further analysis.

#### Perfusion Scans

Similarly, perfusion scans were interpreted by 2 different observers (R.G., M.N.) who were blinded to the findings of wall motion analysis and coronary angiography. For visual grading of perfusion deficits, adenosine stress and rest perfusion scans were magnified 2-fold and displayed simultaneously. The transmural extent of an inducible perfusion deficit was determined from the single dynamic image showing the maximum extent of regional hypoenhancement (identical 16 myocardial segments). Hypoenhancement (perfusion deficit) was graded visually with regard to its transmural extent: 0=no regional hypoenhancement, 1=transmural extent  $< 25\%$ ,

TABLE 1. Patient Demographics

Patient characteristics	
Sex, F/M	27/52
Age, y	61±9
Range	38–81
BMI, kg/m <sup>2</sup>	27.5±3
BMI >25 kg/m <sup>2</sup> , n	57
Historical information, n (%)	
Hypertension	62 (78)
Diabetes mellitus	19 (24)
Hyperlipoproteinemia	66 (84)
History of smoking	47 (59)
CAD in family	31 (39)
Suspected CAD	38 (48)
Known CAD	41 (52)
Previous PCI	38 (48)
Vessel disease, n (%)	
Single	7 (13.2)
Double	23 (43.4)
Triple	23 (43.4)

BMI indicates body mass index; PCI, percutaneous coronary intervention.

2=transmural extent 25% to 50%, 3=transmural extent 51% to 75%, and 4=transmural extent >75%. A regional hypoenhancement ≥25% in any segment was considered to be pathological (inducible perfusion deficit). As a global measure for the transmural perfusion deficit of the myocardium per patient, a transmural perfusion deficit index (TPDI) was calculated as the sum of all segmental transmural scores divided by 16.

### Quantitative Coronary Angiography

Quantitative coronary angiography (Philips Inturis Suite software) was performed with the observer unaware of the results of MRI. A significant coronary stenosis was defined as >50% stenosis (percent luminal diameter narrowing). Significant left main coronary stenosis was considered double-vessel disease.

### Statistical Analysis

For all continuous parameters, mean±SD is given. The paired Student's *t* test or repeated-measures ANOVA was used to assess statistical significance of continuous variables. Group differences for categorical variables were tested with the  $\chi^2$ - or Fisher's exact test. All tests were 2 tailed; *P*<0.05 was considered significant.

Sensitivity, specificity, accuracy, and predictive values (positive and negative) were calculated according to standard definitions and compared between groups ( $\chi^2$  or Fisher's exact test).

To determine the relationship of IWMA's with the degree of coronary stenosis and the TPDI, receiver-operating curve (ROC) analysis was performed, and the area under the curves was calculated.<sup>11</sup>

All data analysis was performed with SPSS for Windows 11.0.1 (SPSS Inc).

## Results

### Patient Characteristics and Hemodynamic Data

Tables 1 and 2 summarize the clinical and hemodynamic data. The average dosages of dobutamine and atropine leading to development of IWMA's was  $36.2\pm 5.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and  $0.3\pm 0.4 \text{ mg}$ , respectively.

TABLE 2. Left Ventricular Function at Rest and Hemodynamic Data

Left ventricular function (at rest)	
LVEF, %	58±6
LVEDV, mL	143±33
LVESV, mL	60±18
Heart rate, bpm	
Adenosine	
At rest	69±13
Maximum stress	89±14*
Dobutamine	
At rest	70±12
Maximum stress	137±14*†
Systolic blood pressure	
Adenosine, mm Hg	
At rest	136±22
Maximum stress	128±17*
Dobutamine	
At rest	136±19
Maximum stress	144±34*†
Heart rate–pressure product, bpm×mm Hg	
Adenosine	
At rest	9608±2695
Maximum stress	11535±2672*
Dobutamine	
At rest	9466±2213
Maximum stress	19820±5330*†

LVEF indicates left ventricular ejection fraction at rest; LVEDV, left ventricular end-diastolic volume at rest; and LVESV, left ventricular end-systolic volume at rest. Values are expressed as mean±SD. Heart rate–pressure product is heart rate times systolic blood pressure.

\**P*<0.01 rest vs stress (dobutamine or adenosine); †*P*<0.01 dobutamine vs adenosine.

### Segmental Analysis

All segments showing resting akinesis (23 of 1264 segments) were excluded from further analysis. The remaining 1241 segments (1204 with normokinesis, 37 with hypokinesis) were used to assess the diagnostic value of each of the stress tests.

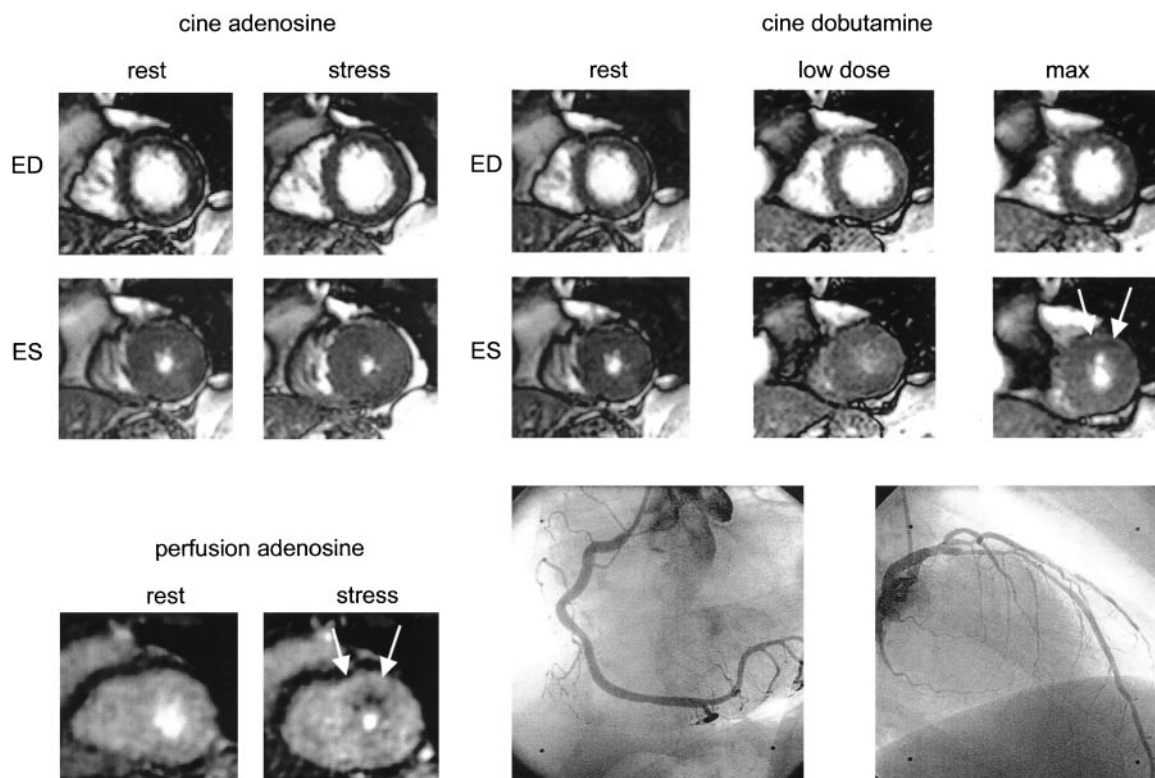
### Diagnostic Performance

Table 3 shows the diagnostic value of each stress test for the detection of epicardial coronary stenoses using analysis

TABLE 3. Diagnostic Performance of DSMR, Adenosine Stress MR (Analysis B), and Adenosine Stress MR Perfusion

	DSMR	Adenosine Stress MR	Adenosine Stress MR perfusion
Sensitivity, %	89*	40	91
Specificity, %	80	96	62
Accuracy, %	86*	58	81
Positive predictive value, %	91	95	83
Negative predictive value, %	77*	44	76

\**P*<0.01 for dobutamine vs adenosine stress MR.



**Figure 2.** False-negative adenosine stress MR (for analysis A and B) but true-positive results of adenosine stress MR perfusion and dobutamine stress MR in patient with significant in-stent left anterior descending artery (LAD) stenosis (58% diameter reduction). Adenosine stress MR: normal segmental contraction at rest and normal hypercontractile response in all segments; adenosine stress MR perfusion: inducible perfusion deficit of anterior segment (<50% transmural); dobutamine stress MR: newly developed WMA of anterior segment at maximum stress.

B for adenosine stress MR. Using analysis A for adenosine stress MR, 7 additional patients showed no IWMA (6 patients with false-negative and 1 patient with true-negative result), yielding a sensitivity of 30%, specificity of 100%, and diagnostic accuracy of 52%. One imaging example is shown in Figure 2; 2 additional examples can be downloaded at <http://www.circulationaha.org> (Figure 2A and Figure 2B).

### Distribution of Perfusion Deficits in Segments With or Without IWMA

Myocardial segments with dobutamine IWMA showed perfusion abnormalities with varying transmural extent (Figure 3A), whereas adenosine IWMA occurred in the presence of perfusion deficits with >75% transmural extent only. Interestingly, in 57 of 257 segments (22.2%) with dobutamine IWMA, no perfusion deficit could be detected. On a per-patient basis, 26 of 53 patients (49%) who were "test-positive" for dobutamine IWMA showed  $\geq 1$  segment without adenosine-inducible perfusion deficit (segmental mismatch) but were correctly classified as test-positive by the adenosine perfusion because they all showed  $\geq 1$  segment(s) with an inducible perfusion deficit in another segment.

Myocardial segments without IWMA showed a large variability of transmural extent of perfusion deficits for both stress agents (Figure 3B): 19% of segments without dobutamine IWMA and 23% of segments without adenosine

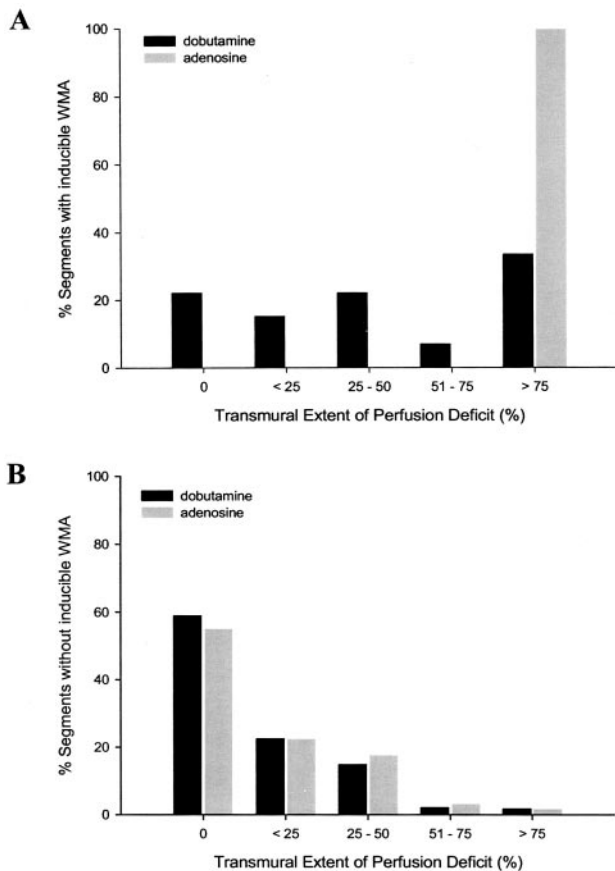
IWMA showed perfusion deficits  $\geq 25\%$ . For segments without dobutamine IWMA, 3.7% had perfusion abnormalities with >50% transmural extent (1.7% with >75% transmural extent). A similar distribution was found for segments without adenosine IWMA (5.0% with >50% and 1.7% with >75% transmural extent).

### Relationship Between IWMA and Severity of Coronary Stenosis

Figure 4A and 4B shows the results of the ROC analysis performed to determine the degree of coronary stenosis being related to a dobutamine or adenosine IWMA. For dobutamine IWMA, the highest accuracy values were found for coronary stenoses >50% (cutoff, 47%), whereas for adenosine IWMA, the highest accuracy values were found for coronary stenoses >75% (cutoff, 77%). The area under the curve was nearly identical for both stress agents.

### Relationship Between IWMA and Perfusion Deficit

Figure 5A and 5B shows the results of the ROC analysis carried out to determine the cutoff value for the TPDI to predict the occurrence of an IWMA under dobutamine or adenosine. The TPDI cutoff of 1.35 resulted in a high sensitivity and specificity for its ability to predict an adenosine IWMA. For dobutamine, a TPDI cutoff of 0.6 showed the highest sensitivity and specificity. The area under the



**Figure 3.** Results of perfusion analysis in segments with (A) and without (B) IWMA for dobutamine and adenosine stress MR. A, Segments with dobutamine IWMA showed varying transmural extent of perfusion deficits, whereas adenosine IWMA were found only in segments with perfusion deficits of >75% transmural extent. B, During dobutamine or adenosine stress, 59% and 55% of myocardial segments had no perfusion deficit and no IWMA. However, 3.7% and 5.0% of segments exhibited adenosine-inducible perfusion deficits with >50% transmural extent.

curve for the prediction of an IWMA from the TPDI was greater for adenosine.

### Discussion

The main findings of our study are as follows. First, DSMR is superior to adenosine stress MR for the detection of IWMA in the presence of significant epicardial coronary stenoses defined as >50% luminal narrowing. Second, coronary stenoses >50% are highly predictive of a dobutamine IWMA, whereas high-grade coronary stenoses >75% are associated with adenosine IWMA. Third, visual assessment of adenosine stress-inducible perfusion deficits is sensitive with a low specificity. Fourth, adenosine IWMA rather than dobutamine IWMA are related to more extensive transmural perfusion deficits (TPDI cutoff, 1.35 versus 0.6; respectively). Fifth, myocardial segments with dobutamine IWMA show varying degrees of perfusion deficits, whereas IWMA under adenosine stress are found exclusively in the presence of concomitant high-grade segmental perfusion deficits (>75% transmural extent). Finally, myocardial segments without dobutamine or adenosine IWMA show varying degrees of

perfusion deficits, which may have >50% transmural extent in some cases.

The diagnostic accuracy reached for all 3 tests is within the range of previously published data on DSMR,<sup>6,12</sup> adenosine stress echo,<sup>2</sup> and adenosine stress MR perfusion using visual criteria.<sup>13</sup> The higher sensitivity for DSMR found in the present study compared with previously published literature<sup>6</sup> is probably related to the recent technical improvements in MR cine imaging; steady-state free precession sequences further improved endocardial border definition<sup>14</sup> and, combined with parallel imaging techniques (SENSE) and retrospective ECG gating, allowed consistent acquisition of 25 phases per cardiac cycle during short breathholds. The lower specificity of DSMR is most likely due to the high proportion of patients with known CAD (52%) and prior percutaneous revascularization (48%).

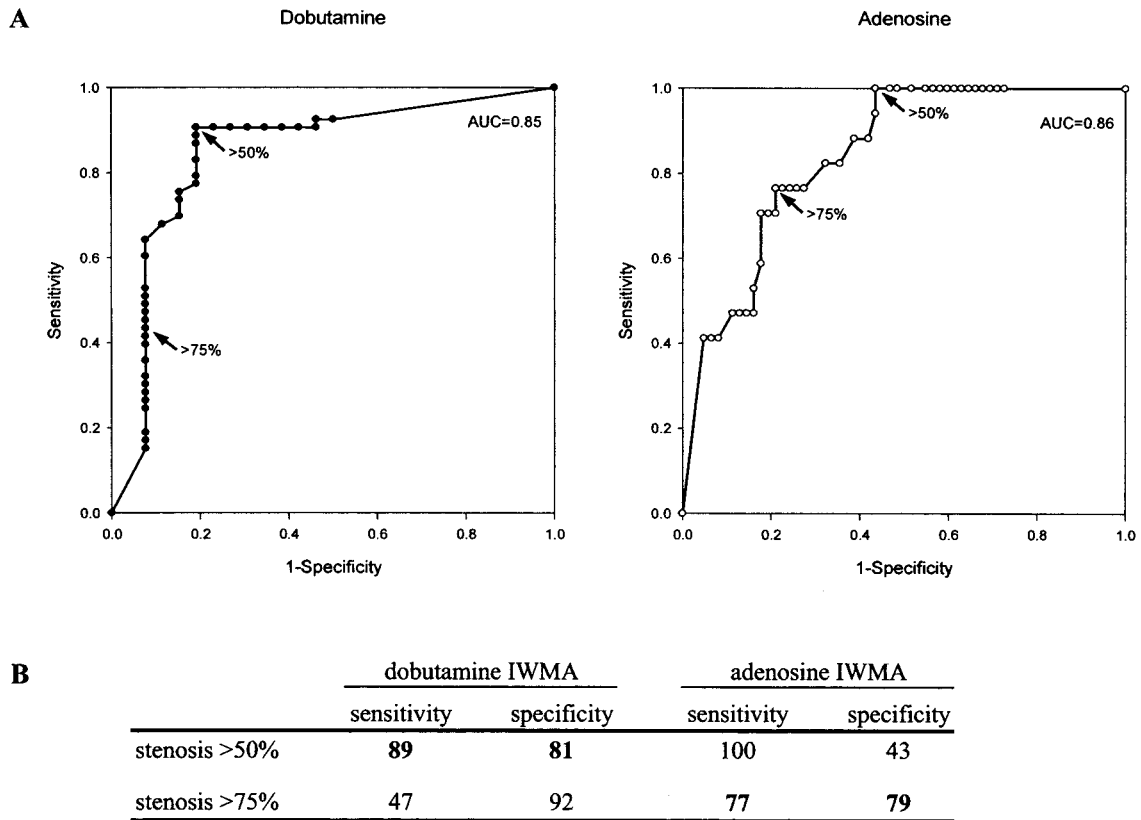
To the best of our knowledge, no data on adenosine stress MR have been reported so far. Even though adenosine stress MR had a higher specificity compared with DSMR, the low sensitivity led to a significantly lower diagnostic accuracy. This may be due to 2 major reasons: (1) Adenosine IWMA are inducible only in the fraction of patients with high-grade stenosis (>75%), or (2) adenosine is an insufficient stressor for the induction of “true” ischemia (relative ischemia resulting from an imbalance of myocardial oxygen demand and supply), which is a prerequisite for the development of IWMA.

ROC analysis was done to determine the relationship between dobutamine and adenosine IWMA and degree of coronary stenosis, demonstrating that the presence of a coronary stenosis >50% yielded high accuracy values for dobutamine IWMA, whereas >75% diameter stenosis was required for adenosine IWMA.

Examining the relationship of IWMA with the transmural extent of perfusion deficits, ROC analysis again showed a lower cutoff value for dobutamine versus adenosine IWMA (TPDI of 0.6 versus 1.35, respectively), thus indicating that dobutamine IWMA occur at lesser degrees of a global perfusion deficit. The higher cutoff and greater area under the curve for adenosine IWMA underline the close relationship with the presence of extensive perfusion deficits. Additionally, adenosine IWMA occurred exclusively in segments with >75% transmural perfusion deficit.

These findings further corroborate the concept of relative versus absolute ischemia.<sup>10</sup> Adenosine is known to cause absolute reductions in myocardial blood flow, which, according to our results, have to comprise >75% of the transmural extent of the respective segment to cause a WMA. Adenosine-inducible WMA, together with such extensive blood flow maldistribution, were related to the presence of high-grade epicardial stenosis. Thus, adenosine has to be considered an insufficient stressor for detection of IWMA resulting from coronary stenoses <75%.

Adenosine mainly induces myocardial blood flow inhomogeneities by vasodilatation and steal effects that do not necessarily result in WMA. Previous studies found a clear disparity between scintigraphically detected perfusion abnormalities and IWMA under adenosine stress.<sup>1,15</sup> In the present study, MR perfusion imaging with its higher spatial resolu-



**Figure 4.** A, ROC analysis to determine degree of coronary stenosis being predictive of dobutamine or adenosine IWMA. B, Sensitivity and specificity derived from ROC analysis for occurrence of dobutamine or adenosine IWMA in presence of coronary stenosis >50% and >75%. AUC indicates area under the curve.

tion allowed us to identify the degree of transmuralty of the perfusion deficit as a strong predictor of adenosine IWMA. This observation fully supports the view that the alteration of blood flow induced by adenosine is insufficient to induce WMA in less severe CAD (stenoses <75%).

Our study showed that with dobutamine stress there is also a disparity between the perfusion status and the induction of WMA in a substantial number of segments: 59% of the segments without a dobutamine IWMA did not have a perfusion deficit, yet 19% had perfusion deficits with  $\geq 25\%$  transmuralty, and 1.7% showed even >75% transmuralty.

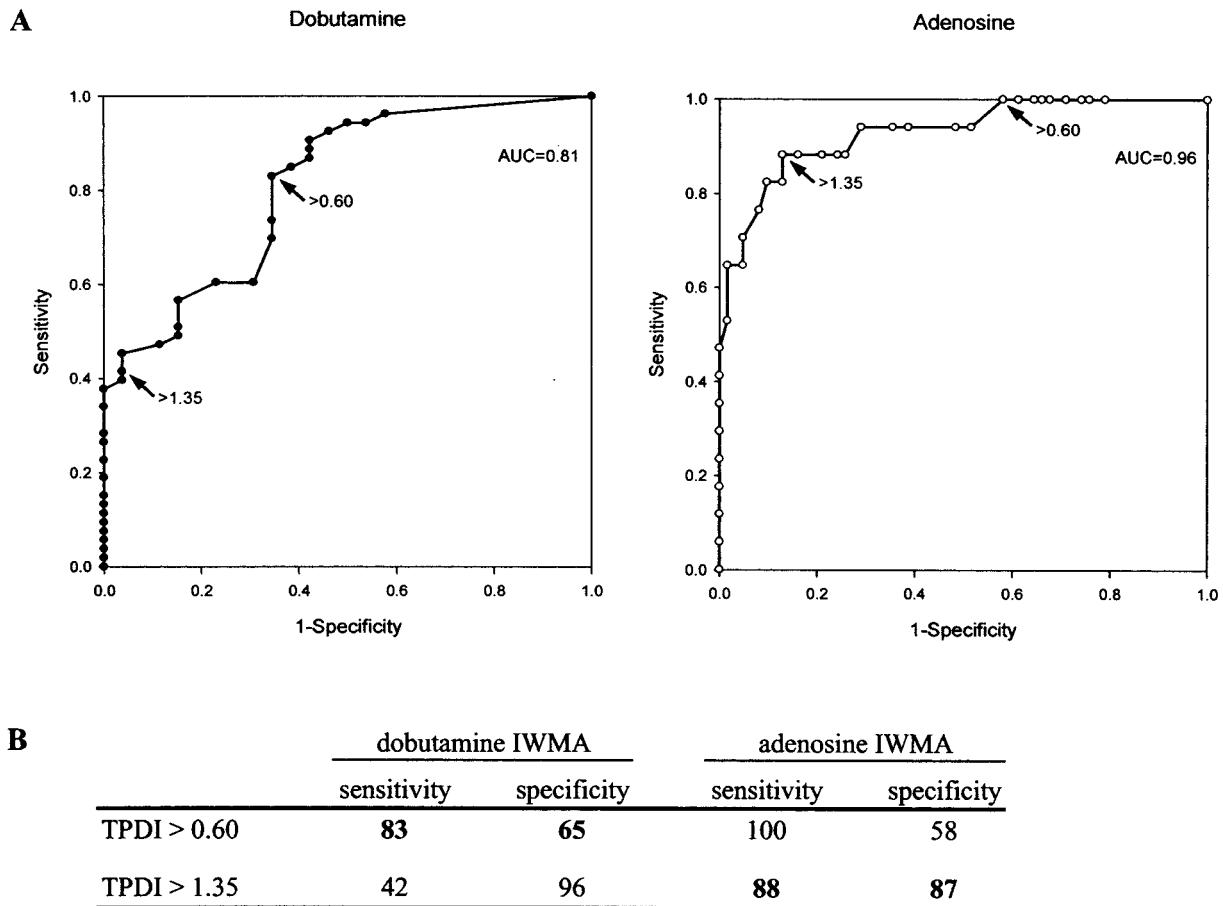
Additionally, we found adenosine IWMA only in segments with a >75% transmural perfusion deficit, demonstrating that these patients suffer from extensive myocardial perfusion abnormalities. Consequently, our results emphasize that adenosine/dipyridamole IWMA are useful only for identifying patients with high-grade perfusion deficits who are at high risk for future cardiac events.<sup>16,17</sup>

Yet, it should be stressed that assessment of patient prognosis alone does not sufficiently aid the cardiologist in clinical decision making. When aiming to follow the guidelines and apply current state-of-the-art treatment regimens of CAD,<sup>18</sup> it is important to evaluate the hemodynamic impact of coronary lesions with 50% to 75% diameter reduction. Regarding this, DSMR represents the more powerful noninvasive diagnostic tool.

### Study Limitations

Approximately 20% of those segments developing dobutamine IWMA did not show a visually assessable perfusion deficit. In our experience, such a segmental mismatch of dobutamine IWMA and adenosine inducible perfusion deficits is quite frequent. However, all patients with a segmental mismatch were correctly classified as test-positive by the adenosine perfusion because they all showed  $\geq 1$  segment(s) with an inducible perfusion deficit in a different segment. The reasons may be as follows. First, "tethering effects" concomitantly occurring with dobutamine IWMA might represent a possible explanation for visually more extensive segmental wall motion disturbances. Second, dobutamine may represent the stronger ischemic stimulus, ie, more extensive impairment of contractile function resulting from pronounced relative ischemia compared with the redistribution of myocardial blood flow as seen with adenosine.

The perfusion sequence, contrast agent (gadolinium-BOPTA), and its dosage were optimized for visual evaluation of MR perfusion. Previous publications reporting on semiquantitative analysis mainly used lower doses of gadolinium-DTPA for the quantitative approach<sup>5,19,20</sup> because quantification but not visual assessment suffers from nonlinearity between contrast agent concentration and signal intensity. Thus, the present data do not allow for semiquantification, and we do not know whether it would produce the same results. Yet, for practical reasons, we deem the assessment of



**Figure 5.** A, ROC analysis to determine extent of perfusion deficit (TPDI) being predictive of dobutamine or adenosine IWMA. B, Sensitivity and specificity derived from ROC analysis for occurrence of dobutamine or adenosine IWMA in presence of TPDI >0.60 and >1.35. AUC indicates area under the curve.

the transmural extent of a perfusion deficit to be a clinically applicable and relevant approach.

### Conclusions

DSMR proved highly accurate for the detection of IWMA in patients with suspected or known CAD but no history of prior myocardial infarction. IWMA during adenosine stress MR are strictly linked to high-grade perfusion deficits, thereby corroborating the role of vasodilator-inducible WMA as a prognostic tool to identify patients at high risk for future cardiac events. Yet, adenosine stress MR cannot be recommended for the detection of IWMA related to epicardial coronary stenoses.

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