Additional Value of Myocardial Perfusion Imaging During Dobutamine Stress Magnetic Resonance for the Assessment of Coronary Artery Disease

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Background—Dobutamine stress magnetic resonance (DSMR) imaging has emerged as a valuable tool for the detection of inducible wall motion abnormalities. The role of perfusion imaging during DSMR is not well defined. We examined whether the addition of myocardial perfusion imaging during DSMR provides incremental benefit for the evaluation of coronary artery disease.

Methods and Results—DSMR was combined with perfusion imaging in 455 consecutive patients who were scheduled for clinically indicated invasive coronary angiography. Perfusion images were acquired in 3 standard short-views at rest and during maximum dobutamine-atropine stress. Wall motion and perfusion images were interpreted sequentially, blinded to other data. Significant (≥70%) stenoses were present in 285 patients on invasive coronary angiography. The use of DSMR combined with perfusion imaging versus DSMR increased sensitivity (91% versus 85%, \(P<0.001\)), but not specificity (70% versus 82%, \(P=0.001\)), resulting in identical overall diagnostic accuracy (84% versus 84%, \(P=NS\); Youden index 0.61 versus 0.67). DSMR combined with perfusion imaging enabled the correct diagnosis of coronary artery disease in an additional 13% of DSMR-negative patients at the cost of 11% more false-positive cases.

Conclusion—The addition of perfusion imaging during DSMR improves sensitivity for the diagnosis of coronary artery disease but does not enhance overall diagnostic accuracy because of a concomitant decrease in specificity. (Circ Cardiovasc Imaging. 2008;1:122-130.)

Key Words: magnetic resonance imaging • coronary disease • myocardium • perfusion • dobutamine • ischemia

Dobutamine stress magnetic resonance (DSMR) wall motion imaging is an established clinical method with high diagnostic and prognostic value for the evaluation of coronary artery disease (CAD).1–4 Because of a high intrinsic contrast between intracavitary blood and the endocardium DSMR allows an accurate delineation of the endocardial border and thus compares favorably with stress echocardiography.5,6 Nevertheless, wall motion studies during dobutamine have a number of inherent limitations, eg, interobserver variability of qualitative wall motion scoring.7 In addition, the presence of left ventricular hypertrophy (LVH)8 and resting wall motion abnormalities (WMAs)9 are known to reduce diagnostic accuracy and may impair the ability of DSMR to detect CAD.

The capability of cardiovascular magnetic resonance (CMR) to evaluate myocardial perfusion has been demonstrated in several studies as well.10–12 Although vasodilators such as adenosine are usually applied to perform perfusion studies, dobutamine may cause enough myocardial blood flow heterogeneity to detect perfusion deficits in myocardial territories supplied by a coronary artery with a critical stenosis.13,14 In nuclear and echocardiographic studies,15,16 dobutamine proved to be a useful stress agent for the induction of myocardial perfusion deficits. Recent advances in magnetic resonance gradient performance and innovative pulse sequence design led to a substantial increase in acquisition speed of CMR first pass perfusion imaging thereby allowing multislice imaging at higher heart rates.17

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Thus, we sought to determine whether CMR perfusion imaging during high-dose dobutamine stress (DSMRP) adds additional diagnostic value to DSMR for the detection of ischemia in patients with known and suspected CAD, as defined by invasive coronary angiography.

Materials and Methods

Patient population
The study was conducted in accordance with the standards of the Charité Ethics Committee. Written informed consent was given by all patients. DSMRP was performed prospectively in 455 consecu-
tive patients who were scheduled for a clinically indicated coronary angiography with suspected and known CAD. Patients with contraindications to either magnetic resonance imaging (noncompatible biometallic implants or claustrophobia) or dobutamine (acute coronary syndrome, severe hypertension, significant aortic stenosis, myocarditis, endocarditis, pericarditis), and patients with arrhythmias were not considered for study inclusion. All patients were instructed to refrain from any β-blockers or nitrates 24 hours before the MRI.

Magnetic Resonance Imaging

Imaging Protocol

MRI was performed with the patient in supine position with a 1.5-T MR scanner (Philips Intera CV, Best, The Netherlands) equipped with a Nova gradient system (33 mT/m; 160 mT/m/ms) based on Philips release 11. A 5-element cardiac synergy coil was used for signal reception. Cardiac synchronization was performed by using 4 electrodes placed on the left anterior hemithorax (vector electrocardiography), and scans were triggered on the R wave of the ECG.

Figure 1 shows the course of the examination. The patients underwent a standardized CMR examination including the following steps. First, fast survey images were acquired in 3 standard planes (transversal, sagittal and coronal) for localization of the heart. Second, single-angulated, single-slice cine scan of the left ventricle was performed on a transverse view. Third, a double-angulated, single slice cine scan of the left ventricle was planned on the previous view. Fourth, cine-imaging of 3 short-axis views and 3 long-axis views (4-chamber, 2-chamber and 3-chamber view) were acquired. The 3 short-axis views were distributed to cover the heart at the basal, equatorial, and apical position by adjusting the gap between the sections. The distance between the apical slice and the apex on the one hand and the basal slice and the mitral valve on the other hand were identical. Fifth, perfusion test scans using an identical geometry as the 3 short-axis cine views were conducted to carefully exclude any wrap around or trigger artifacts before starting the actual index test. Sixth, rest perfusion imaging was performed using 60 dynamic acquisitions during the administration of an intravenous bolus of 0.1 mmol/kg gadolinium-diethylenetriamine-pentaacetic acid (Magnevist, Bayer, Berlin, Germany) at an injection rate of 4 mL/s followed by a flush of 20 mL of saline solution at the same rate. 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. Seventh, a standard DSMR examination18 was performed following a high-dose regimen (up to 40 μg/(kgmin)) plus atropine (up to 2 mg) if needed to reach target heart rate defined as age-predicted submaximal heart rate [(220 – age) × 0.85]. Eighth, during maximum dobutamine stress perfusion imaging was performed using the same geometry and giving an identical bolus of contrast agent as during rest imaging. Blood pressure and heart rate were monitored continuously during the administration of dobutamine and the contrast agent. Termination criteria were severe chest pain, significant arrhythmia, hypertension (blood pressure ≥240/120 mm Hg), systolic blood pressure drop of >40 mm Hg, and any intolerable side effect regarded as associated with dobutamine.9 If chest pain or arrhythmias did not resolve after termination of dobutamine infusion esmolol (50 to 100 mg) was given intravenously. Ninth, standard delayed enhancement imaging was performed 10 minutes after the termination of dobutamine infusion.

MR Sequence Design

For cine-imaging, a balanced steady-state free precession sequence in combination with parallel imaging (SENsitivety Encoding, SENSE-factor 2.0) and retrospective gating (50 phases per cardiac cycle) was used during an end-expiratory breath hold of 9 s (repetition time, 3.4 ms; echo time, 1.7 ms; flip angle, 60°). In-plane spatial resolution was 1.8×1.8 mm with a slice thickness of 8 mm.

For perfusion imaging, the balanced steady-state free precession sequence parameters were as follows: repetition time 2.8 ms, echo time 1.4 ms, flip angle 50°. SENSE-factor 3.0, raw data matrix 160×143, rectangular field of view 450×428 cm², and voxel size 2.8×3×10 mm³. Three short-axis views (1 basal, midventricular, and apical slice) were acquired every second heart beat during dobutamine stress with 2 slices being acquired during the first heart beat and the remaining slice being acquired during the second heart beat. A separate saturation pulse was applied to each slice (delay 100 ms). A half a/half repetition time startup mode with additional 8 startup echoes had been applied before real data acquisition started in order for the steady-state free precession magnetization to reach equilibrium. The acquisition time per image was 145 ms.

Delayed enhancement imaging was performed using an inversion prepared 3D-spoiled-gradient-echo-sequence (repetition time3.6 ms, echo time 1.7 ms, flip angle 15°, voxel size 1.5×1.7×10 mm³, interpolated to 1.5×1.7×5 mm³) with an individually adapted infrared-delay (200 to 250 ms).

MR Image Analysis

Measurements of left ventricular wall thickness were performed immediately basal to the tips of the papillary muscles during end-diastole on the basal short-axis view. LVH was defined as an interventricular septum thickness ≥12 mm.19 Isolated basal septal hypertrophy was accounted for by carefully double-checking our measurements in the short-axis view with the 4- and 3-chamber long-axis views. Left ventricular ejection fraction was determined with the combined triplane model.20

Segmental analysis of wall motion was performed in consensus by 2 observers blinded to patients’ identities and results of the perfusion study and coronary angiography using a synchronized quad-screen image display and applying a standard 16-segment scoring system (1=normal, 2=hypokinetic, 3=akinetik, or 4=dysskinetic). A positive DSMR was defined as a new or worsening WMA in ≥1 segments.

Perfusion scans were interpreted in consensus by 2 observers blinded to the results of DSMR and invasive coronary angiography. The readers were presented with anonymized magnetic resonance imaging studies including perfusion at stress and rest and delayed enhancement. For visual grading of perfusion deficits, stress and rest perfusion scans were magnified 2-fold and displayed simultaneously. Ischemia was considered present when segments without delayed enhancement showed a perfusion deficit of ≥25% of the transmural extent during stress perfusion but not at rest (stress-inducible deficit) for ≥3 consecutive image frames or when segments with nontransmural delayed enhancement demonstrated additional stress-inducible perfusion deficits.
For the overall assessment, patients were judged to have CAD if inducible WMAs or inducible perfusion deficits were evident. These overall results were compared with those from DSMR assessment.

To assess interobserver variability for interpretation of DSMRP, 2 independent observers scored perfusion imaging qualitatively based on the reading criteria mentioned earlier in a randomly selected sample of 50 studies. The interobserver agreement in our laboratory is 91% for DSMR.21

Coronary angiography
All 455 patients underwent coronary x-ray angiography within 1 month after magnetic resonance imaging. Conventional coronary x-ray angiography was performed using the transfemoral Judkins approach with selective catheterization of the left and right coronary artery system in multiple projections. The classification of patients into those with and without obstructive CAD was based on their current coronary status as assessed by invasive angiography. The angiograms were evaluated visually for the presence of significant stenoses (ie, ≥50% and ≥70% luminal diameter reduction) in major epicardial coronary arteries and their branches (vessel diameter ≥2.0 mm) by highly experienced interventionalists; all readers were blinded to the MR data. In patients with bypass grafts, significant arterial or vein graft stenoses were assigned to the recipient native coronary vessel. The angiographic results were then classified as 1-, 2- and 3-vessel disease or exclusion of significant obstructive CAD.

Statistical Analysis
Statistical analysis was performed using the SPSS software package release 15.0.1 (Chicago, Ill). For all continuous parameters, mean ± standard deviation is given. Comparisons were made with 2 sample t tests for continuous data and χ² tests for discrete. McNemar’s test was used to compare the diagnostic accuracy of techniques. Sensitivity, specificity, and diagnostic accuracy were calculated according to standard definitions. The Youden index, defined as sensitivity plus specificity minus 1, was applied to compare the 2 tests.22 The Wilcoxon test was applied to paired samples. Agreement between the 2 methods and between observers was assessed with κ statistics.23 Statistical tests were two-tailed; significance was considered if P<0.05.

Results

Dobutamine Stress Test
Assessment of wall motion at rest was feasible in all patients. Table 1 summarizes the reasons for nondiagnostic tests. Technical difficulties like poor ECG-triggering and insufficient image quality during stress precluded interpretation of wall motion and perfusion images in 12 (3%) patients. In 29 (6%) patients, target heart rate was not achieved either because of a maximum infusion of dobutamine-atropine (13 patients) or because of early termination of the examination as a result of limiting side effects (16 patients); thus, DSMRP was feasible in 414 patients (91%). The clinical data of the final population of the study are presented in Table 2.

The mean dosages of dobutamine and atropine given were $34±7.4 \mu g/(kg\cdot min)$ and $0.3±0.4 \mu g$, respectively. Atropine was administered in 217 (52%) patients. Table 3 summarizes the hemodynamic data. Most patients (62%) experienced side effects during the infusion like chest pain (54%) or dyspnea (32%). One patient had self-limiting ventricular tachycardia during dobutamine infusion. No death, myocardial infarction, or ventricular fibrillation occurred. Target heart rate was achieved in 388 (94%) patients and 26 patients (6%) developed new WMAs before reaching target heart rate; in these cases, stress perfusion imaging was performed at this stress level and the dobutamine infusion was terminated.

Table 1. Reasons for Nondiagnostic Tests

<table>
<thead>
<tr>
<th>Reasons for Nondiagnostic Tests</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Nondiagnostic tests</td>
<td>41 (9)</td>
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<tr>
<td>Technical reasons (insufficient ECG-triggering)</td>
<td>5 (1)</td>
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<tr>
<td>Insufficient image quality</td>
<td>7 (2)</td>
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<tr>
<td>Maximum infusion in submaximal negative</td>
<td>13 (3)</td>
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<tr>
<td>Limiting side effects</td>
<td>16 (3)</td>
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<tr>
<td>Patient request</td>
<td>2</td>
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<tr>
<td>Severe chest pain</td>
<td>4</td>
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<tr>
<td>Severe dyspnea</td>
<td>3</td>
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<tr>
<td>Severe increase in blood pressure (≥240/120 mm Hg)</td>
<td>2</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>4</td>
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<tr>
<td>Ventricular tachycardia (self-limiting)</td>
<td>1</td>
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</tbody>
</table>

Values are n (%) unless otherwise noted.

Table 2. Patient Demographics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Age, yr</th>
<th>Range</th>
<th>Gender, M/F</th>
<th>BMI, kg/m²</th>
<th>Risk factors and patient history, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63±9</td>
<td>32–85</td>
<td>297/117</td>
<td>27±4</td>
<td>Hypertension 290 (70)</td>
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<td></td>
<td>Hypercholesterolemia 276 (67)</td>
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<td></td>
<td>Smoking 121 (29)</td>
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<td>Diabetes mellitus 114 (28)</td>
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<td>Family history 94 (23)</td>
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<td>LVEF, % 56±8</td>
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<td></td>
<td>Patients with LVH 126 (30)</td>
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<td></td>
<td>Resting wall motion abnormalities 190 (46)</td>
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<td>Prior CAD 267 (64)</td>
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<td></td>
<td>Prior Myocardial infarction 197 (48)</td>
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<td>Prior PCI 232 (56)</td>
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<td>Prior CABG 92 (22)</td>
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<td></td>
<td>Serum creatinine, mg/dL 0.99±0.25</td>
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<td>GFR, mL/min 89±27</td>
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</table>

Vessel disease (coronary stenosis ≥70%), n (%)

<table>
<thead>
<tr>
<th>1-CAD</th>
<th>2-CAD</th>
<th>3-CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>167 (40)</td>
<td>99 (24)</td>
<td>19 (5)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy (septum ≥12 mm); CABG, coronary artery bypass graft surgery; GFR, glomerular filtration rate estimated using Cockcroft equation; Values are n (%) unless otherwise noted and expressed as mean±SD.
Coronary Angiography
CAD (≥70% stenosis) was present in 285 (69%) patients. Among these patients, 167 (59%) had single-vessel, 99 (35%) had 2-vessel, and 19 (7%) had 3-vessel CAD. The remaining 129 (31%) patients had no significant CAD.

Table 3. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Stress</th>
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<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>72±14</td>
<td>137±15*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132±23</td>
<td>142±31*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>71±12</td>
<td>70±15</td>
</tr>
<tr>
<td>Pulse pressure product, bpm×mm Hg</td>
<td>9539±2773</td>
<td>19463±4737*</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. *P<0.001.

Results of DSMR and DSMRP
New or worsening WMAs occurred in 264 (64%) patients. DSMR had a sensitivity of 85% for the detection of CAD, as defined by ≥70% stenosis by coronary angiography and a specificity of 82%. Stress-inducible perfusion deficits were detected in 269 (65%) patients. A stress-inducible WMA or perfusion deficit occurred in 299 patients (72%). Perfusion deficits occurred in the presence of inducible WMAs in 234 of 264 patients (89%) and in the absence of inducible WMAs in 35 of 150 patients (13%).

The use of DSMRP versus DSMR to detect CAD as defined by ≥70% luminal narrowing increased sensitivity (91% versus 85%, P=0.001, Table 4), whereas specificity decreased (70% versus 82%, P=0.001) resulting in identical overall diagnostic accuracy (84% versus 84%, P n.s.). When defining CAD as ≥50% luminal narrowing, diagnostic accuracy increased significantly for DSMR versus DSMRP from 82% to 85%, respectively (P<0.001). The Youden index suggested that DSMRP did not provide a measurable diagnostic advantage in the overall study cohort (Table 4). However, in those 150 patients without inducible WMAs, we found that adding DSMRP enabled the correct diagnosis in an additional 13% (19/150, ≥70% stenosis) or 15% (23/150, for ≥50% stenosis) of patients. In 68% (13/19) of these patients, the number of ischemic segments was ≥3; 42% (8/19) had multivessel CAD (ie, 2- or 3-vessel CAD). This advantage in sensitivity came at the cost of 11% (16/150, ≥70% stenosis) or 8% (12/150, for ≥50% stenosis) more false-positive cases.

Subgroup Analysis
DSMR led to a significant increase in sensitivity and diagnostic accuracy in patients with LVH from 79% to 91% (P<0.001) and from 80% to 87% (P<0.001, Table 4), respectively, without significant reduction in specificity from 85% to 74% (P=0.25). The Youden index was similar for DSMR versus DSMR (0.65 versus 0.64) when defining CAD as ≥70% stenosis. With DSMR alone, sensitivity decreased in patients with LVH versus patients without LVH (79% versus 88%, P=0.52), whereas specificity increased (85% versus 81%, P=0.63).

In patients with resting WMAs, the use of DSMRP compared with DSMR also led to a significant increment in sensitivity from 82% to 89% (P=0.002) with a nonsignificant reduction in specificity from 73% to 61% (P=0.125) and a significant increase in diagnostic accuracy from 80% to 84% (P<0.001). However, the Youden index implied that DSMR was superior to DSMRP in patients with resting WMAs (see Table 4). With DSMR alone sensitivity and specificity decreased for patients with resting WMAs versus patients without resting WMAs (82% versus 88%, P=0.53; and 73% versus 85%, P<0.001, respectively). The results for using ≥50% luminal narrowing for the definition of CAD can be found in Table 4. Representative imaging examples are given in Figures 2 and 3.

In patients with prior CAD the use of DSMRP led to a significant increment in sensitivity from 83% to 90% (P<0.001) with a significant decline in specificity from 75% to 65% (P=0.03) and a significant increase in diagnostic accuracy from 82% to 85% (P<0.001). In patients without prior CAD DSMRP was associated with a significant increase in sensitivity from 87% to 95% (P<0.001) as well. However, the decrease in specificity from 88% to 74% (P<0.001) led to a decrease in overall diagnostic accuracy from 87% to 84% compared with DSMR alone when CAD was defined as ≥70% luminal narrowing.

In patients with single-vessel CAD, the use of DSMR significantly improved sensitivity from 84% to 91% (P=0.001).

In patients with no LVH, no resting WMAs, no prior CAD, and no single-vessel CAD, the use of DSMR compared with DSMRP led to a nonsignificant increase in sensitivity from 88% to 94% (P=0.125) and a significant decrease in specificity from 87% to 72% (P=0.02) resulting in a significant decrease in diagnostic accuracy from 87% to 78% (P=0.008, Table 4).

The application of the Youden index suggested that DSMRP was not associated with a measurable diagnostic advantage in most patient subgroups (Table 4).

Segmental Analysis
The number of segments exhibiting inducible WMAs in the absence of perfusion deficits was 318 (4.8%). The number of segments experiencing perfusion deficits in the absence of inducible WMAs was 516 (7.8%). The total number of mismatched segments was thus 12.6%. In 132 patients, perfusion deficits involved more segments; in 83 patients, less segments were involved than WMAs; and in 84 patients, the number of ischemic segments was identical. The mean number of ischemic segments in patients with perfusion deficits versus patients with inducible WMAs was 3.6±1.9 versus 2.9±1.5 (P<0.001), respectively.

Delayed enhancement was present in 197 patients with a mean number of 3.1±1.8 segments. In 162 of these 197 patients, perfusion deficits or inducible WMAs were present. In 64 patients, perfusion deficits were more extensive than WMAs, in 60 patients WMAs were less extensive than perfusion deficits, and in 38 patients identical. The mean number of ischemic segments in patients with perfusion deficits versus patients with inducible WMAs was 3.1±2.1 versus 2.8±1.5, P=0.12.
Table 4. Diagnostic Performance of DSMRP and DSMR

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>DSMR</th>
<th>DSMRP</th>
<th>P</th>
<th>DSMR</th>
<th>DSMRP</th>
<th>P</th>
<th>DSMR</th>
<th>DSMRP</th>
<th>P</th>
<th>DSMR</th>
<th>DSMRP</th>
<th>P</th>
<th>Youden-Index</th>
</tr>
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<tbody>
<tr>
<td>Coronary Stenosis:=70%</td>
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<tr>
<td>All patients</td>
<td>241/285 (85)</td>
<td>260/285 (91)</td>
<td>0.001</td>
<td>106/129 (82)</td>
<td>90/129 (70)</td>
<td>0.001</td>
<td>347/414 (84)</td>
<td>350/414 (84)</td>
<td>n.s.</td>
<td>0.67</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with LVH*</td>
<td>78/99 (79)</td>
<td>90/99 (91)</td>
<td>&lt;0.001</td>
<td>23/27 (85)</td>
<td>20/27 (74)</td>
<td>0.25</td>
<td>101/126 (80)</td>
<td>110/126 (87)</td>
<td>&lt;0.001</td>
<td>0.64</td>
<td>0.65</td>
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<tr>
<td>Resting WMAs</td>
<td>128/157 (82)</td>
<td>139/157 (89)</td>
<td>0.001</td>
<td>24/33 (73)</td>
<td>20/33 (61)</td>
<td>0.125</td>
<td>152/190 (80)</td>
<td>159/190 (84)</td>
<td>&lt;0.001</td>
<td>0.55</td>
<td>0.5</td>
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<tr>
<td>Prior CAD</td>
<td>176/210 (83)</td>
<td>189/210 (90)</td>
<td>&lt;0.001</td>
<td>43/57 (75)</td>
<td>37/57 (65)</td>
<td>0.03</td>
<td>219/267 (82)</td>
<td>226/267 (85)</td>
<td>&lt;0.001</td>
<td>0.58</td>
<td>0.55</td>
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<tr>
<td>No prior CAD</td>
<td>65/75 (87)</td>
<td>71/75 (95)</td>
<td>&lt;0.001</td>
<td>63/72 (88)</td>
<td>53/72 (74)</td>
<td>&lt;0.001</td>
<td>128/147 (87)</td>
<td>124/147 (84)</td>
<td>&lt;0.001</td>
<td>0.75</td>
<td>0.69</td>
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<tr>
<td>Single-vessel CAD</td>
<td>141/167 (84)</td>
<td>152/167 (91)</td>
<td>0.001</td>
<td>41/47 (87)</td>
<td>34/47 (72)</td>
<td>0.02</td>
<td>55/63 (87)</td>
<td>49/63 (78)</td>
<td>0.008</td>
<td>0.75</td>
<td>0.66</td>
<td></td>
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<tr>
<td>No LVH, no resting WMAs, no prior CAD, no single-vessel CAD</td>
<td>14/16 (88)</td>
<td>15/16 (94)</td>
<td>0.125</td>
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<tr>
<td>Coronary Stenosis:=50%</td>
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<tr>
<td>All patients</td>
<td>252/315 (80)</td>
<td>275/315 (87)</td>
<td>&lt;0.001</td>
<td>87/99 (88)</td>
<td>75/99 (76)</td>
<td>&lt;0.001</td>
<td>339/414 (82)</td>
<td>350/414 (85)</td>
<td>&lt;0.001</td>
<td>0.68</td>
<td>0.63</td>
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<tr>
<td>Patients with LVH*</td>
<td>80/106 (76)</td>
<td>92/106 (87)</td>
<td>&lt;0.001</td>
<td>18/20 (90)</td>
<td>15/20 (75)</td>
<td>0.05</td>
<td>98/126 (78)</td>
<td>107/126 (85)</td>
<td>&lt;0.001</td>
<td>0.66</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting WMAs</td>
<td>134/170 (79)</td>
<td>146/170 (86)</td>
<td>&lt;0.001</td>
<td>17/20 (85)</td>
<td>14/20 (70)</td>
<td>0.018</td>
<td>151/190 (79)</td>
<td>160/190 (84)</td>
<td>&lt;0.001</td>
<td>0.64</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CAD</td>
<td>184/234 (79)</td>
<td>199/234 (85)</td>
<td>&lt;0.001</td>
<td>27/33 (82)</td>
<td>23/33 (70)</td>
<td>&lt;0.001</td>
<td>211/267 (79)</td>
<td>222/267 (83)</td>
<td>&lt;0.001</td>
<td>0.61</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior CAD</td>
<td>68/81 (84)</td>
<td>76/81 (94)</td>
<td>0.008</td>
<td>60/66 (91)</td>
<td>52/66 (79)</td>
<td>0.008</td>
<td>128/147 (87)</td>
<td>128/147 (87)</td>
<td>n.s.</td>
<td>0.75</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-vessel CAD</td>
<td>100/126 (79)</td>
<td>106/126 (84)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No LVH, no resting WMAs, no prior CAD, no single-vessel CAD</td>
<td>15/21 (71)</td>
<td>18/21 (86)</td>
<td>0.02</td>
<td>37/42 (88)</td>
<td>32/42 (76)</td>
<td>&lt;0.001</td>
<td>52/63 (83)</td>
<td>50/63 (79)</td>
<td>0.008</td>
<td>0.59</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise noted. Abbreviations are as defined in text.
*End-diastolic wall-thickness of interventricular septum >=12 mm.
Interobserver Agreement
In 50 randomly selected patients from the study population, the interobserver agreement (ie, agreement on test positivity or negativity) of DSMRP was 88% ($\kappa=0.67$).

Discussion
We found that DSMRP provided good diagnostic accuracy for the detection of CAD. However, though DSMRP improved sensitivity compared with DSMR, no gain in overall diagnostic accuracy was detectable because of a concomitant decrease in specificity for the overall population and all subgroups.

Cardiac Stress Testing With CMR
CMR has been shown to be a clinically useful and versatile technique for the detection of myocardial ischemia. Both the detection of stress-inducible WMAs as well as the depiction of inducible perfusion deficits have been established as independent techniques to diagnose myocardial ischemia. However, the clinical usefulness of combined wall motion and perfusion assessment during application of dobutamine is less well defined, and it is unknown whether high-dose dobutamine-atropine perfusion imaging provides incremental diagnostic information. Several clinical studies applying echocardiography or nuclear imaging techniques provided evidence that dobutamine can effectively induce perfusion deficits. The induction of myocardial ischemia during dobutamine stress testing is largely attributed to an increase in myocardial oxygen demand with subsequent worsening of left ventricular wall motion in areas subtended by coronary arteries with relevant stenoses. Besides an increase in contractility and rate-pressure product, dobutamine may also exert a direct vasodilative effect on coronary vessels.

CMR is regarded the standard of reference for the assessment of left ventricular function and regional wall motion at rest. Compared with echocardiography, CMR has been shown to be diagnostically superior for the detection of WMAs because of a consistently high endocardial border delineation. Although additional diagnostic value was ascribed to dobutamine perfusion imaging with echocardiography, it is unclear whether the same applies to CMR. Furthermore, diagnostic accuracy of dobutamine stress wall motion studies for the detection of CAD is impaired in patients with LVH and resting WMAs.

Delayed enhancement imaging has been demonstrated to be a highly sensitive and specific technique to diagnose myocardial scar tissue and has become part of a routine CMR examination today. Because the administration of an extracellular contrast agent is mandatory for delayed enhancement, total examination duration with additional perfusion imaging during dobutamine stress is only marginally prolonged (~3 minutes).

Diagnostic Accuracy of DSMRP
DSMRP yielded a high number of diagnostic examinations, as 91% were either positive for ischemia or negative after reaching target heart rate. Main reasons for early termination of the examination were insufficient hemodynamic response to dobutamine-atropine administration or limiting cardiac side effects such as chest pain, dyspnea, hypertension, and atrial fibrillation and were comparable to studies using dobutamine stress perfusion scintigraphy and echocardiography. Noncardiac side effects such as nausea, headache, and anxiety were not uncommon but usually well tolerated without the need to terminate the examination. Only a minority of patients had to be excluded because of insufficient image quality or technical failure of DSMRP. In addition, the interobserver agreement for DSMRP is good despite the heterogeneity of our patient population.

Our study showed that inducible myocardial perfusion deficits could be detected by DSMRP. Furthermore, DSMRP is significantly more sensitive than DSMR for the detection...
of CAD in the overall population of our study. This finding is in line with the ischemic cascade theory, which states that perfusion deficits precede WMAs and electrocardiographic changes.\textsuperscript{31} Our study also showed that the sensitivity in identifying patients with single-vessel CAD is significantly higher for DSMRP compared with DSMR, which further supports the aforementioned theory. Animal studies have confirmed this phenomenon by demonstrating that dobutamine causes a reduction in coronary flow distal to a noncritical coronary stenosis whereas wall thickening remains normal.\textsuperscript{32} Our results regarding diagnostic accuracy of DSMR were within the range of previously published data,\textsuperscript{3,6,7} thereby reflecting its reliability in detecting significant CAD. However, the observed increase in sensitivity for DSMRP in our study did not translate into an improved diagnostic accuracy because of a significant decrease in specificity. Other studies using dobutamine perfusion imaging have reported lower values for specificity either.\textsuperscript{28,33} This might be explained by several factors. Half of the patients responsible for false-positives during DSMRP were diabetic, and 75% of them had arterial hypertension. Both of these risk factors are known to cause impaired coronary vasoreactivity even in the absence of a significant epicardial coronary arterial narrowing.\textsuperscript{34,35} In addition, the decline in specificity of DSMRP might be attributed to CMR specific artifacts (mainly susceptibility), which arise from gadolinium bolus administration, motion, or limited spatial resolution, and are known to reduce specificity in CMR perfusion studies.\textsuperscript{36}

Our study showed that DSMRP exhibited a higher sensitivity for the detection of CAD in patients with LVH. A possible explanation for this might be inherent to the perfusion imaging approach, because it depicts inducible regional inhomogeneities of myocardial blood flow rather than their functional consequences. Moreover, in patients with LVH left ventricular obliteration during dobutamine stress and diastolic dysfunction associated with increased myocardial stiffness are known phenomena, which can interfere with the identification of WMAs.\textsuperscript{37,38} However, the recognition of a perfusion deficit in a largely obliterated left ventricle should be less demanding and might further serve as an explanation as to why DSMRP might be a better test than DSMR to detect ischemia in patients with LVH. The fact that in our study the differences in specificity did not reach statistical significance in patients with LVH was somewhat surprising taking into account that patients with hypertrophy have a high probability of microvascular coronary disease and impaired coronary flow reserve\textsuperscript{39} and was most likely because of the small number of patients with negative invasive angiograms.

In patients with prior CAD the use of DSMRP also led to a significant increase in sensitivity. Conversely, in patients with no LVH, no resting WMAs, no prior CAD, and no single-vessel CAD, DSMRP was associated with a lower diagnostic accuracy because of a significant decrease in specificity. Thus, our results indicate that DSMRP is not necessarily justified in all patients but may be advantageous in those in whom a high sensitivity is desirable.

The Youden index gives equal weight to sensitivity and specificity without reflecting CAD prevalence. Although it is generally desirable to choose a test that has high values for both, sensitivity and specificity may not be equally important in clinical practice. Patients who are at high risk for future cardiac events may benefit from a test with high sensitivity. In the present study, DSMRP enabled the correct diagnosis in an additional 13% of DSMR-negative patients: 68% (13/19) demonstrated ischemia in ≤3 segments with multivessel CAD in 42% (8/19), and thus, these patients are at considerable risk for future cardiac events.\textsuperscript{2,40} In addition, more accurate detection of disease extent with DSRMP may facilitate better risk stratification.

### Study Limitations
Catheterization results were based on visual analysis and not on quantitative coronary angiography. A common problem in validating noninvasive techniques for the detection of myocardial ischemia is the lack of an optimal standard of reference.\textsuperscript{41} The present study documents the diagnostic accuracy of DSMRP in patient population typically referred to a tertiary care hospital, and many patients had prior CAD and myocardial infarctions. Thus, our results may be applicable only to a similar clinical setting. Multicenter studies are required before the clinical role of DSMRP for the assessment of myocardial perfusion can be determined. The perfusion sequence, contrast agent (gadolinium-diethylenetriaminepentaacetic acid), and its dosage were optimized for visual evaluation of MR perfusion. Previous publications reporting on (semi)quantitative analysis mainly used lower doses of gadolinium-diethylenetriaminepentaacetic acid because quantification, but not visual assessment, suffers from nonlinearity between contrast agent concentration and signal intensity. Thus, the present data set does not allow for quantification, and we cannot assure whether it would produce similar results.

### Summary and Conclusions
DSMRP is a safe noninvasive stress modality and is useful to assess patients with suspected and known CAD. Compared with DSMR the addition of perfusion imaging during high-dose dobutamine stress is associated with a significant increase in sensitivity which is offset by a decrease in specificity for the overall population and the subgroups of our study. In patients with a negative DSMR result, DSMRP enabled the correct diagnosis of CAD in an additional 13% (≥70% stenosis) of patients at the cost of 11% more false-negative cases. The findings of our study suggest that DSMRP might be helpful in identifying patients in whom the benefit of very high sensitivity outweighs the disadvantage of lower specificity. Future studies are needed to determine whether DSMRP may provide incremental prognostic value.

### Disclosures
None.

### References


The assessment of regional wall motion during dobutamine stress magnetic resonance (DSMR) is an established clinical method with high diagnostic and prognostic value for the evaluation of coronary artery disease (CAD); however, the role of dobutamine stress MR perfusion imaging (DSMRP) is unclear. Thus, the present study assessed the diagnostic information derived from additional perfusion imaging during high-dose dobutamine-atropine stress in a large referral population. Compared with DSMR alone, DSMRP generally resulted in an increase in sensitivity and a decrease in specificity for the detection of significant CAD. Overall DSMRP enabled the correct diagnosis of CAD in an additional 13% of DSMR negative patients at the cost of 11% more false-positive studies. DSMRP might be considered a useful diagnostic test for CAD detection in patients in whom the benefit of very high sensitivity outweighs the disadvantage of lower specificity.
Additional Value of Myocardial Perfusion Imaging During Dobutamine Stress Magnetic Resonance for the Assessment of Coronary Artery Disease

Rolf Gebker, Cosima Jahnke, Robert Manka, Ashraf Hamdan, Bernhard Schnackenburg, Eckart Fleck and Ingo Paetsch

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