Noninvasive Diagnosis of Ischemia-Induced Wall Motion Abnormalities With the Use of High-Dose Dobutamine Stress MRI

Comparison With Dobutamine Stress Echocardiography

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Background—The analysis of wall motion abnormalities with dobutamine stress echocardiography (DSE) is an established method for the detection of myocardial ischemia. With ultrafast magnetic resonance tomography, identical stress protocols as used for echocardiography can be applied.

Methods and Results—In 208 consecutive patients (147 men, 61 women) with suspected coronary artery disease, DSE with harmonic imaging and dobutamine stress magnetic resonance (DSMR) (1.5 T) were performed before cardiac catheterization. DSMR images were acquired during short breath-holds in 3 short-axis views and a 4- and a 2-chamber view (gradient echo technique). Patients were examined at rest and during a standard dobutamine-atropine scheme until submaximal heart rate was reached. Regional wall motion was assessed in a 16-segment model. Significant coronary heart disease was defined as $\geq 50\%$ diameter stenosis. Eighteen patients could not be examined by DSMR (claustrophobia 11 and adipositas 6) and 18 patients by DSE (poor image quality). Four patients did not reach target heart rate. In 107 patients, coronary artery disease was found. With DSMR, sensitivity was increased from 74.3% to 86.2% and specificity from 69.8% to 85.7% (both $P<0.05$) compared with DSE. Analysis for women yielded similar results.

Conclusions—High-dose dobutamine magnetic resonance tomography can be performed with a standard dobutamine/atropine stress protocol. Detection of wall motion abnormalities by DSMR yields a significantly higher diagnostic accuracy in comparison to DSE. (Circulation. 1999;99:763-770.)

Key Words: magnetic resonance imaging ♦ echocardiography ♦ coronary artery disease

Although several noninvasive techniques are at hand for evaluating myocardial ischemia, many coronary angiograms yield negative results that may be explained by low diagnostic accuracy of most noninvasive tests. Single-photon emission computed tomography (SPECT) imaging and stress echocardiography yield the best results in clinical practice. Because many patients are unable to perform adequate exercise testing because of physical incapacity, dobutamine stress echo (DSE) has become a well-established modality for the diagnosis of myocardial ischemia. A recent review of 28 major DSE studies has reported sensitivity, specificity, and accuracy ranging from 54% to 96%, 60% to 100%, and 62% to 92%, respectively, depending on patient selection, study size, definition of coronary artery disease, and technical equipment. Dobutamine increases both contractility and rate-pressure product, thus increasing myocardial oxygen demand leading to ischemia in areas supplied by stenotic coronary arteries. Severe complications may be expected in 0.25% patients including infarction (0.07%), ventricular fibrillation (0.07%), and sustained ventricular tachycardia (0.1%). However, DSE has inherent disadvantages. Ten percent to 15% of patients yield suboptimal or nondiagnostic images. Mainly basal lateral and inferior segments show poor endocardial delineation. Optimal display and interpretation of segments require a long training period and remain user dependent. Thus accuracy largely depends on the experience of diagnostic centers and observers, and test reproducibility is low.

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Magnetic resonance (MR) imaging allows noninvasive cardiac visualization with high spatial and temporal resolution. Gradient echo techniques permit an accurate determination of left ventricular function and wall thickness. Complete tomographic cineloops can be imaged within short acquisition intervals (eg, 16 heartbeats). Therefore identical
pharmacological stress protocols can be implemented for DSE and MR imaging. At each stress level, several views can be acquired (Figure 1) that are highly reproducible because the coordinates rather than visual assessment are used for repetitive imaging. Gradient echo MR images provide high contrast between intracavitary blood and the endocardium without the use of contrast agents and allow an accurate delineation of the endocardium and epicardium. Thus regional wall motion and wall thickening is accessible.

To date, no reports exist on the comparison of DSE with dobutamine stress MR (DSMR). The aim of this study was to compare echocardiography and MR for the detection of stress-induced wall motion abnormalities in patients with suspected coronary artery disease.

**Methods**

**Patients**

In a pilot study of 30 patients, DSE, DSMR, and angiography were performed to define visual MR criteria for stress-induced wall motion behavior. Two hundred eight consecutive patients with suspected coronary artery disease then were prospectively studied after giving written informed consent. Patients with ECG signs or a history of previous myocardial infarction, unstable angina pectoris (Braunwald classification III), arterial hypertension (BP > 220/120 mm Hg), dilated or obstructive cardiomyopathy, ejection fraction < 20%, atrial flutter or fibrillation, ventricular premature beats (Lown class ≥ II), or significant valvular disease class ≥ II were excluded. To ensure an adequate heart rate response to dobutamine, patients receiving β-blockers were omitted. Calcium antagonists and nitrates were stopped 24 hours before stress examinations.

**Echocardiography**

Patients were positioned in the left lateral decubitus position. Heart rate was recorded continuously by ECG, and blood pressure was measured every 3 minutes. Commercially available equipment (SystemFive, Sonotron) was used, and ECG-triggered images were acquired with 2.25- to 3.5-MHz transducers in parasternal long- and short-axis and in apical 4-, 3-, and 2-chamber views and performed at rest and at each stress level without using contrast agents. Second harmonic imaging (1.75 to 3.5 MHz) was applied after becoming available to our institution (147 patients). Dobutamine was infused intravenously at 3-minute stages at doses of 5, 10, 20, 30, and 40 μg/kg per minute and stopped at the dose when ≥ 85% of age-predicted heart rate was reached, however continued and supplemented by 0.25-mg fractions of atropine (maximal dose 1 mg) if < 85% of age-predicted heart rate was achieved and the stress test was negative. Esmolol and nitroglycerin were administered when clinically indicated. Stress testing was discontinued on patient request, when new wall motion abnormalities, chest discomfort indicative of progressive or severe angina, dyspnea, decrease in systolic blood pressure > 40 mm Hg, arterial hypertension (BP ≥ 240/120 mm Hg), severe arrhythmias, or other serious adverse effects occurred. Rate-pressure product at rest and maximal stress was calculated from heart rate and systolic blood pressure.

**Magnetic Resonance Imaging**

MR imaging was performed within 14 days (median = 1 day) of DSE. Care was taken to examine patients during the same time of the day with both techniques to improve comparability. Patients were excluded from MR examination but not from the study population if contraindications (incompatible metallic implants, claustrophobia) were present or if significant side effects had occurred during DSE (intolerable angina pectoris 2, prolonged severe wall motion abnormalities after discontinuation of dobutamine 1, blood pressure drop > 60 mm Hg 3). All other patients were examined with a 1.5-T MR tomograph (ACS NT, Philips) with a phased array cardiac coil placed around the patient’s chest. After 2 rapid surveys to determine the exact heart axis, 3 short-axis planes (apical, equatorial, basal) and a 4- and 2-chamber views were acquired (Figure 1). A segmented k-space turbo-gradient echo technique (TE/TR/flip angle 2.15/5.9/25 degrees, turbo factor 8, spatial resolution 1.3×1.3 mm, slice thickness 8 mm, temporal resolution 40 ms) was used. At rest, 14 to 16 heartbeats were used for image acquisition; if heart rate reached 100 bpm, the number of beats for acquisition was increased to improve temporal resolution (30 ms, depending on patient compliance). Reduction of breathing artifacts was performed by breath-holding in end-expiration during scanning. ECG rhythm, blood pressure, and symptoms were continuously monitored. Images were displayed
20 seconds after acquisition for observation of new wall motion abnormalities. An identical dobutamine-atropine stress protocol as used for DSE was applied. Criteria for test cessation were identical to DSE.

Angiography
Biplane coronary angiography was performed within 14 days (median 2 days) after DSE and within 24 hours after DSMR in all patients. Coronary stenoses were filmed in multiple projections, minimizing overlap of side branches and foreshortening of relevant coronary stenoses.

Image Analysis
All digital echocardiographic and MR images were displayed as continuous cineloops by use of a quadscreen display for review with a 16-segment model for the analysis of regional left ventricular wall motion. Image quality, endocardial movement, and systolic wall thickening comparing rest, increasing stress levels, and peak stress images were evaluated off-line by 2 experienced observers (≥1000 stress echocardiograms each) blinded to the results of any other technique. If different classifications occurred between 2 observers, consensus was reached after joint review. Image quality was defined as very good (sharp delineation of the endocardial border in all segments), good (endocardial border visible in all segments), moderate (myocardial motion detectable in ≥13 segments but no clear endocardial border), and low (nondiagnostic). Patients with ≥4 nondiagnostic segments were excluded from the analysis. Segmental wall motion was graded as normokinesia, hypokinesia, akinesia, and dyskinesia. Echocardiographic and MR results were defined as positive and indicative of myocardial ischemia if new or worsening wall motion abnormalities in ≥1 segment developed (Figures 2, 3, and 4). If segments were visualized double in different views, wall motion abnormalities in 1 view were regarded as sufficient. Wall motion abnormalities observed at rest that improved during low-dose stress but deteriorated during peak stress were considered diagnostic of inducible myocardial ischemia. Wall motion abnormalities at rest, static during stress, and without deterioration at peak stress were considered negative. Other criteria were not stipulated.

Coronary angiograms were reviewed and interpreted by 2 experienced investigators blinded to the results of the noninvasive tests. Coronary artery disease was defined as a 50% narrowing of the luminal diameter with respect to prestenotic segment diameters in at least 1 major epicardial coronary artery or a major branch of 1 of these vessel distributions. Patients were classified as having 1-, 2-, or 3-vessel disease.

Statistical Analysis
Continuous variables are expressed as mean value±1 SD. Group differences were tested with a Student’s t test for continuous variables and the χ2 test or Fisher’s exact test for noncontinuous categorical variables. Results were considered significant if P<0.05. Sensitivity, specificity, accuracy, and predictive values (positive and negative) were calculated according to standard definitions and compared between groups (χ2 or Fisher’s exact test).

Results
Two hundred eight consecutive patients (147 men, 61 women 60±9 years of age, ejection fraction 62%±10%, body weight 66±34 kg) with suspected coronary artery disease were studied. In 186 (89.4%) patients, DSE was successfully performed (Table 1). Eighteen patients were excluded because of nondiagnostic image quality (emphysema 8, adipositas 10), and 4 had neither reached submaximal heart rate at maximal stress nor could wall motion abnormalities be observed. DSMR was successfully performed in 186 (89.4%) patients. Seventeen patients could not be examined because of claustrophobia (n=11), adipositas (>150 kg body weight; n=5), or retro-orbital metal (n=1). Three (1.4%) patients had nondiagnostic images caused by breathing artifacts, and 2 did...
not reach submaximal heart rate without traceable wall motion abnormalities.

For comparison, DSE and DSMR were obtained in a joint study population of 172 patients.

Table 2 lists the hemodynamic data. Maximal blood pressure was higher during peak stress with MR in comparison to echocardiography (P < 0.01), and heart rate was significantly lower (P < 0.01); however, no significant differences were found for rate-pressure product at rest or peak stress. Mean doses of dobutamine and atropine administration were similar for both modalities.

Image quality at target heart rate was very good in 40 (19.6%) of 204 patients with DSE and 131 (69%) of 189 patients with DSMR (P < 0.001), good in 63 (31%) and 25 (13%; P < 0.01), moderate in 83 (41%) and 30 (16%; P < 0.001), and nondiagnostic in 18 (8.8%) and 3 (1.6%; P < 0.001).

Figure 3. DSMR 4-chamber view in the same patient as Figure 2. Arrangement as in Figure 2. Clear definition of endocardial and epicardial border and clearly visible hypokinesia septal and apical-lateral as well as mid-lateral (arrows).

Figure 4. Short-axis view of the same patient as Figures 2 and 3. Septal hypokinesia is clearly demonstrated (arrows).
TABLE 1. Patient Exclusion From Dobutamine Stress Echocardiography and Dobutamine Stress Magnetic Resonance Tomography

<table>
<thead>
<tr>
<th></th>
<th>DSE</th>
<th>DSMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient image quality</td>
<td>18 (8.7%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Inadequate maximal heart rate</td>
<td>4 (1.9%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Severe obesity</td>
<td>...</td>
<td>5 (2.4%)</td>
</tr>
<tr>
<td>Claustrophobia</td>
<td>...</td>
<td>11 (5.3%)</td>
</tr>
<tr>
<td>Contraindication (metallic implants)</td>
<td>...</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>22 (10.6%)</td>
<td>22 (10.6%)</td>
</tr>
</tbody>
</table>

Coronary artery disease was present in 109 of 172 patients (prevalence: 63.4%; 1-vessel disease 39, 2-vessel disease 25, 3-vessel disease 45). The results of DSE compared with angiography are shown in Table 3. Table 4 lists the results of DSMR compared with angiography. In Table 5, diagnostic accuracy of DSE and DSMR are compared. Sensitivity increased from 74.3% for DSE to 86.2% for DSMR and specificity from 69.8% to 85.7%, respectively (both P<0.05). Test accuracy increased from 72.7% for DSE to 86.0% for DSMR (P<0.005).

Subgroup analysis for women revealed no significant differences in sensitivity, specificity, and test accuracy (data not shown).

Discussion

With DSMR, stress-induced wall motion abnormalities can be detected with a significantly higher diagnostic accuracy compared with DSE in patients with suspected coronary artery disease. Sensitivity increased from 74.3% to 86.2% and specificity from 69.8% to 85.7% (both P<0.05). Test accuracy increased from 72.7% for DSE to 86.0% for DSMR (P<0.005).

Subgroup analysis for women revealed no significant differences in sensitivity, specificity, and test accuracy (data not shown).

TABLE 2. Hemodynamic Data

<table>
<thead>
<tr>
<th></th>
<th>DSE</th>
<th>DSMR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting diastolic blood pressure, mm Hg</td>
<td>71±10</td>
<td>74±13</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal diastolic blood pressure, mm Hg</td>
<td>71±15</td>
<td>78±14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mm Hg</td>
<td>128±19</td>
<td>131±21</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal systolic blood pressure, mm Hg</td>
<td>155±33</td>
<td>167±31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart rate at rest, bpm</td>
<td>70±13</td>
<td>65±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Maximal heart rate, bpm</td>
<td>143±17</td>
<td>131±20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rate-pressure product (rest)</td>
<td>9017±2004</td>
<td>8474±2017</td>
<td>NS</td>
</tr>
<tr>
<td>Rate-pressure product (maximal)</td>
<td>22 180±5575</td>
<td>22 105±5522</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal dobutamine dose, μg · kg⁻¹ · min⁻¹</td>
<td>38±5</td>
<td>37±6</td>
<td>NS</td>
</tr>
<tr>
<td>Atropine dose, mg</td>
<td>0.69±0.29</td>
<td>0.53±0.33</td>
<td>NS</td>
</tr>
</tbody>
</table>

The same criteria as used for DSE to interrupt dobutamine infusion can be applied to MR. The guidelines released by the American Society of Echocardiography were adapted for the MR examination. The 16-segment model and the same visual criteria for detecting wall motion abnormalities were applied to DSMR.

Care was taken to include patients with moderate pretest likelihood of coronary artery disease into the study if they were sent from an outpatient basis. The results of the noninvasive stress tests had no impact on the decision to proceed to angiography. Thus the prevalence of coronary artery disease is relatively low (63.4%), which allows generalization of the results on an outpatient population.

A substantial group of women was included in the present study, and a subgroup analysis was performed to test differences of this group in comparison to the complete cohort. No significant differences in sensitivity, specificity, and test accuracy, as observed with other techniques, were found for DSE and DSMR.

Previous studies concerned with the detection of stress-induced wall motion abnormalities with MR applied medium doses of dobutamine only. Pennell et al.² and Baer et al.³ have shown that MR imaging may detect inducible wall motion abnormalities with a sensitivity of 91% and 85%, respectively, in 25 and 28 patients with 20 μg/kg per minute dobutamine. van Rugge et al.⁴ reported 91% sensitivity and 80% specificity in 39 patients at 20 μg/kg per minute dobutamine. These studies have shown that medium-dose dobutamine MR is feasible and yields very good results. However, medium-dose dobutamine is considered insufficient to induce myocardial ischemia in many patients (Figure 5). Even infusion rates of 40 μg/kg per minute dobutamine
may not be sufficient and has been shown to yield a high specificity with low sensitivity in previous DSE studies, leading to the addition of atropine to enhance sensitivity.\textsuperscript{15,16}

None of the above-mentioned MR studies correlated the results with DSE, which is clinically the most widely used pharmacological stress test to detect myocardial ischemia.

MR imaging has several advantages compared with echocardiography. Images can be acquired with good and reproducible image quality independent of the examiner and the patient’s condition (eg, emphysema, adipositas) because no imaging window is needed. The use of standardized procedures for determination of the heart axis and positioning of slices leads to reproducible results. Furthermore, each slice position can be accurately reproduced at different stress levels. The endocardial border can easily be detected and separated from intracavitary blood because a high natural contrast between flowing blood and the myocardium exists. Wall thickness and thickening can be accurately assessed because there is a clear demarcation of the epicardial border. Good spatial resolution, high signal-to-noise ratio, and sharp contour delineation in MR images meet the requirements for accurate quantitative analysis. Time for patient setup (placement, ECG tracing, coil connection) is only minimally longer than for DSE. The duration of the examination is mainly determined by the stress duration and thus similar to DSE. Image interpretation and report generation require minimally more time than for DSE because data handling is not yet as optimized as for DSE. However, the better delineation of the endocardial border allows a quicker interpretation of the images.

Currently, several disadvantages of DSMR must be accepted. Examination of patients with claustrophobia or metallic implants (pacemakers, cardioverter-defibrillators) is not feasible. In 0.5-T magnets, patients with pacemakers may be safely examined,\textsuperscript{17} which may be extended to 1.5-T magnets if new pacemakers are used.\textsuperscript{18} To suppress breathing artifacts and acquire high-quality images, breath-holding is used. Such breath-holds of \approx 16 seconds may be difficult to achieve in patients with reduced pulmonary reserve and influence hemodynamics. In addition, different breathing levels may cause different cardiac positions. The duration of breath-holding will be reduced by faster scanning with echo planar imaging techniques or real-time imaging,\textsuperscript{19,20} which is independent of ECG triggering and will allow correction for patient motion and changes of cardiac position during scanning.\textsuperscript{19,21} Temporal resolution of the MR sequence used was less than with DSE and needs to be increased, especially if other parameters such as ejection or filling times are to be assessed. With echo planar imaging techniques, a temporal resolution of \approx 20 ms is possible.

Patient monitoring is suboptimal compared with DSE. Diagnostic ECG cannot be obtained because ST segments are altered by the magnetic field. However, cardiac rhythm can be monitored, allowing an on-line assessment of stress-induced cardiac arrhythmias. Communication between the patient and the examiner is more complicated than with a bedside test. Frequent communication through the intercom between breath-holds was used to assess the patient’s symptoms. In addition, patients can be observed with a video monitor. Further technical developments are on their way to improve patient communication systems and ECG tracings.

The higher diagnostic accuracy of DSMR compared with DSE can mainly be explained by improvements of image quality. Eighty-three percent of all MR examinations yielded good or very good image quality in comparison to 50% with echocardiography. Sixty-eight percent of false-positive DSE results were attributed to the posterior circulation in basal inferior, posterior, and lateral segments and were analyzed from moderate quality images. A similar correlation between image quality and diagnostic accuracy has been observed for DSE, as most recent improvements were related to an improved endocardial contrast either using contrast agents or technical improvements such as harmonic imaging.\textsuperscript{22,23} Echocardiographic image quality depends largely on the distance of the transducer from the heart, the amount of air, or the presence of bone between the transducer and the object and the echogenicity of the myocardium. MR imaging is mainly influenced by the distance of the object from the receiver coil and the ability of the patient to hold his or her breath. Another possible source of error in MR imaging is the presence of blood and myocardium in the same voxel. Because slice thickness is 8 mm (depending on scan technique), this may occur, for example, in 4-chamber views when the inferior or anterior wall move into the image. These problems were avoided as much as possible by careful planning of the tomographic slices and correction of image position if the patient moved during scanning. Nevertheless, some of the differences between DSE and DSMR may be explained by the visualization of different myocardial segments.

The current study is limited by the exclusion of patients with myocardial infarction, unstable angina, low ejection fraction, frequent premature ventricular beats, and patients receiving β-blocker treatment. These patients form <10% of the outpatient basis evaluated for suspected coronary artery disease of our hospital. Patients with myocardial infarction were excluded to guarantee a homogeneous group not influenced by possible problems resulting from hibernating or

### TABLE 4. Sensitivity and Specificity of Dobutamine Stress Magnetic Resonance

<table>
<thead>
<tr>
<th></th>
<th>CA−</th>
<th>CA+</th>
<th>1VD</th>
<th>2VD</th>
<th>3VD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSMR+</td>
<td>9</td>
<td>94</td>
<td>29</td>
<td>21</td>
<td>44</td>
</tr>
<tr>
<td>DSMR−</td>
<td>54</td>
<td>15</td>
<td>10</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Correct</td>
<td>86%</td>
<td>86%</td>
<td>74%</td>
<td>84%</td>
<td>98%</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 3.

### TABLE 5. Results of Dobutamine Stress Echocardiography and Dobutamine Stress Magnetic Resonance Compared With Angiography

<table>
<thead>
<tr>
<th></th>
<th>DSE</th>
<th>DSMR</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>74.3%</td>
<td>86.2%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Specificity</td>
<td>69.8%</td>
<td>85.7%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Positive predicting value</td>
<td>81.0%</td>
<td>91.3%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Negative predicting value</td>
<td>61.1%</td>
<td>78.3%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Accuracy</td>
<td>72.7%</td>
<td>86.0%</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

\[ b \]-blocker treatment. These patients form 10% of
stunned myocardium. The diagnosis of viable myocardium was not aim of the current study. Patients with unstable angina (Braunwald classification III), low ejection fraction, or frequent premature ventricular complexes were not studied for safety reasons. Patients receiving β-blockers were excluded because most show no adequate heart rate response to dobutamine alone and thus significantly increase the number of nondiagnostic examinations with any stress test. All antianginal drugs were stopped 24 hours before all stress tests, which is routine at our institution to improve test accuracy.

A problem in validating noninvasive techniques for the detection of myocardial ischemia is the lack of an optimal gold standard. Possible sources of disagreements between angiography and DSMR or DSE may be explained by the different pathophysiology they detect. “Significant” coronary artery disease with a 50% diameter stenosis may not cause stress-induced ischemia, that is, if flow is still sufficient or collaterals are present. This may explain false-negative results. False-positive results may occur if ischemia is induced during stress without coronary artery disease, for example, as the result of small-vessel disease, reduced energy utilization, or coronary vasospasm.

Further studies must address possible improvements with quantitative wall motion analysis, which should further increase reproducibility and user independence. The analysis of complete volumes rather than tomographic slices should add to this goal. With such analysis tools, not only endocardial motion but also wall thickness and thickening must be quantitated. However, this will further reduce comparability with echocardiography.

This study is the first to compare DSE and high-dose dobutamine stress MR tomography. The results demonstrate that the detection of stress-induced wall motion abnormalities with dobutamine MR is superior to DSE. This difference can mainly be explained by the superior image quality of MR images with a sharp delineation of the endocardial and epicardial borders.

Acknowledgment
We thank Carola Roguhn for assistance in performing the MR stress examinations.

References


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_Circulation_. 1999;99:763-770
doi: 10.1161/01.CIR.99.6.763

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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