Prognostic Value of Cardiac Magnetic Resonance Stress Tests
Adenosine Stress Perfusion and Dobutamine Stress Wall Motion Imaging

Cosima Jahnke, MD; Eike Nagel, MD; Rolf Gebker, MD; Thomas Kokocinski, MD; Sebastian Kelle, MD; Robert Manka, MD; Eckart Fleck, MD; Ingo Paetsch, MD

Background—Adenosine stress magnetic resonance perfusion (MRP) and dobutamine stress magnetic resonance (DSMR) wall motion analyses are highly accurate for the detection of myocardial ischemia. However, knowledge about the prognostic value of stress MR examinations is limited. We sought to determine the value of MRP and DSMR, as assessed during a single-session examination, in predicting the outcome of patients with known or suspected coronary artery disease.

Methods and Results—In 513 patients (with known or suspected coronary disease, prior coronary artery bypass graft, or percutaneous coronary intervention), a combined single-session magnetic resonance stress examination (MRP and DSMR) was performed at 1.5 T. For first-pass perfusion imaging, the standard adenosine stress imaging protocol (140μg·kg\(^{-1}\)·min\(^{-1}\) for 6 minutes, 3-slice turbo field echo–echo-planar imaging or steady-state free precession sequence, 0.05 mmol/kg Gd-DTPA) was applied, and for DSMR, the standard high-dose dobutamine/atropine protocol (steady-state free-precession cine sequence) was applied. Stress testing was classified as pathological if at MRP ≥1 segment showed an inducible perfusion deficit >25% transmurality or if at DSMR ≥1 segment showed an inducible wall motion abnormality. During a median follow-up of 2.3 years (range, 0.06 to 4.55 years), 19 cardiac events occurred (4.1%; 9 cardiac deaths, 10 nonfatal myocardial infarctions). The 3-year event-free survival was 99.2% for patients with normal MRP and DSMR and 83.5% for those with abnormal MRP and DSMR. Univariate analysis showed ischemia identified by MRP and DSMR to be predictive of cardiac events (hazard ratio, 12.51; 95% confidence interval, 3.64 to 43.03; and hazard ratio, 5.42; 95% confidence interval, 2.18 to 13.50; \(P<0.001\), respectively); other predictors were diabetes mellitus, known coronary artery disease, and the presence of resting wall motion abnormality. By multivariate analysis, ischemia on magnetic resonance stress testing (MRP or DSMR) was an independent predictor of cardiac events. In a stepwise multivariate model (Cox regression), an abnormal magnetic resonance stress test result had significant incremental value over clinical risk factors and resting wall motion abnormality (\(P<0.001\)).

Conclusions—In patients with known or suspected coronary artery disease, myocardial ischemia detected by MRP and DSMR can be used to identify patients at high risk for subsequent cardiac death or nonfatal myocardial infarction. For patients with normal MRP and DSMR, the 3-year event-free survival was 99.2%. MR stress testing provides important incremental information over clinical risk factors and resting wall motion abnormalities. (Circulation. 2007;115:1769-1776.)

Key Words: adenosine ■ coronary disease ■ dobutamine ■ magnetic resonance imaging ■ perfusion ■ prognosis

Cardiac magnetic resonance (MR) stress testing has been intensely researched in recent years, and its high diagnostic accuracy for the detection of significant coronary disease has been demonstrated.\(^1\)\(^-\)\(^7\) In limited patient populations, dobutamine stress MR (DSMR) has been used successfully for cardiac prognostication. Hundley et al\(^8\) provided the first data on determination of cardiac prognosis in patients with poor echocardiographic image quality and showed its value for forecasting myocardial infarction and cardiac death. Similarly, the value of DSMR for the assessment of preoperative cardiac risk in patients undergoing noncardiac surgery has been examined. In a subgroup of patients with intermediate clinical risk of future cardiac events, a positive DSMR test proved to be an independent factor for predicting myocardial infarction, cardiac death, or congestive heart failure during or after the surgery.\(^9\)

Clinical Perspective p 1776

More recent literature indicated a possible role of adenosine stress MR perfusion (MRP) imaging in identifying patients at high risk for future cardiac events; however, as for DSMR, those studies dealt with specific subsets of patient
populations (eg, presenting with acute chest pain) and examined primarily the ability of MRP to predict composite adverse outcome that would include “soft” cardiac end points (eg, a diagnosis of correlative myocardial ischemia on subsequent nuclear studies or the interval diagnosis of >50% stenosis on x-ray coronary angiography).10

Cardiac MR imaging offers the advantage of conducting myocardial perfusion and wall motion measurements at rest and under stress conditions during a single-session examination, thereby ensuring superb comparability of test results.4 Thus, we sought to determine the value of MRP measurements during adenosine stress and wall motion imaging during dobutamine stress in predicting cardiac death and nonfatal myocardial infarction in a large patient population with known or suspected coronary artery disease (CAD). In addition, the incremental value of the results of MR stress testing, after consideration of clinical risk factors and wall motion at rest, was assessed.

Methods

Study Population

The study was conducted in accordance with the standards of the Charité and Virchow-Klinikum Ethics Committee. From April 2001 through October 2005, we prospectively studied 597 consecutive patients referred to our hospital for evaluation of chest pain or dyspnea; written informed consent was obtained from all patients before the MR examination. Patients were eligible if they had typical contraindications for MR imaging or surgical revascularization (thereby altering the subsequent event rate), those patients who underwent a revascularization procedure (thereby altering the subsequent event rate), and those patients who underwent a revascularization procedure within 3 months of MR stress testing were excluded (n=84 patients). Figure 1 illustrates the composition of the final study population; 473 patients had a complete combined stress MR examination, but 12 patients (2.5%) could not be followed up. Thus, 461 patients had complete combined stress MR and follow-up information.

MR Study

MR was performed with the patient in the supine position with a 1.5-T MR scanner (Philips Intera CV, Best, the Netherlands) equipped with a PowerTrak6000 gradient system (23 mT/m, 219-μs rise time; Philips Intera) and software package releases 9 and 10. Cardiac synchronization was performed with 4 electrodes placed on the left anterior hemithorax (vector ECG).

The MR imaging protocol followed the previously published approach for a combined, single-session examination of adenosine stress MRP and DSMR wall motion analyses (see Figure 2). Briefly, after acquisition of rest cine scans in the standard views (apical, mid, and basal short-axis views; 4-, 2-, and 3-chamber views), MR first-pass perfusion scanning during adenosine infusion (140 μg · kg⁻¹ · min⁻¹; total duration: 6 minutes) was performed using identical short-axis geometries. After a 10- to 15-minute waiting period for equilibration of the contrast agent within the myocardium, an identical MRP scan was repeated at rest.

Immediately afterward, a DSMR examination was carried out using the standard high-dose regimen (up to 40 μg · kg⁻¹ · min⁻¹) plus atropine (up to 2 mg) if needed to reach the target heart rate, defined as age-predicted submaximal heart rate: (220−age)×0.85. Termination criteria were as previously published.4,11

MR Imaging Technique

For perfusion imaging, a 3-slice turbo field echo–echo-planar imaging sequence (repetition time, 9.3 ms; echo time, 3.3 ms; flip angle, 30°) or a steady-state free-precession sequence (repetition time, 2.8 ms; echo time, 1.4 ms; flip angle, 50°) was used with 1 saturation prepulse per slice before data readout (prepulse delay, 130 and 100 ms, respectively); typical spatial resolution was 2.4×2.4×8 mm.

For cine imaging, a steady-state free-precession sequence with retrospective gating combined with sensitivity encoding was used (>25 phases/cardiac cycle; repetition time, 2.7 ms; echo time, 1.4 ms; flip angle, 60°) during an end-expiratory breathhold of ~5 seconds. Typical in-plane spatial resolution was 1.8×1.8 mm with a slice thickness of 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 patient history, MRP, and follow-up data, using a synchronized quad-screen image display and applying the standard scoring system (1 = normokinesis, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis). 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 1 or more segments showing inducible wall motion abnormality (WMA; i.e., an increase in the segmental wall motion score of ≥1); a biphasic response was considered to indicate ischemia. Left ventricular ejection fraction was determined with the combined triplane model.15

**Perfusion Scans**
Similarly, perfusion scans were interpreted by 2 different observers (R.G., E.N.) who were blinded to patient history, the findings of wall motion analysis, and follow-up data. For visual assessment of inducible perfusion deficits, adenosine stress and rest perfusion scans were magnified and displayed simultaneously. The transmurality of a perfusion deficit was determined from the single dynamic image showing the maximum extent of regional hypoenhancement (identical 16 myocardial segments). A regional hypoenhancement ≥25% in

---

**TABLE 1. Baseline Characteristics of Patients With and Without Cardiac Events**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients Without Events (n=442)</th>
<th>Patients With Events (n=19)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, male, n (%)</td>
<td>295 (66.7)</td>
<td>16 (84.2)</td>
<td>0.112</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±9</td>
<td>64±9</td>
<td>0.113</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9±3.6</td>
<td>26.8±3.1</td>
<td>0.849</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>334 (75.6)</td>
<td>16 (84.2)</td>
<td>0.388</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>82 (18.6)</td>
<td>7 (36.8)</td>
<td>0.048</td>
</tr>
<tr>
<td>Hyperlipoproteinemia, n (%)</td>
<td>306 (69.2)</td>
<td>17 (89.5)</td>
<td>0.059</td>
</tr>
<tr>
<td>Known CAD, n (%)</td>
<td>225 (50.9)</td>
<td>15 (78.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>89 (20.1)</td>
<td>12 (63.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>168 (38.0)</td>
<td>9 (47.4)</td>
<td>0.410</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>87 (19.7)</td>
<td>9 (47.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>57.0±8.2</td>
<td>49.5±13.7</td>
<td>0.028</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>11 (2.5)</td>
<td>4 (21.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Framingham risk score, %</td>
<td>12.5±8.2</td>
<td>16.6±6.6</td>
<td>0.070</td>
</tr>
<tr>
<td>Total risk factors, n</td>
<td>3.7±1.4</td>
<td>4.6±1.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>279 (63.1)</td>
<td>13 (68.4)</td>
<td>0.640</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>241 (54.5)</td>
<td>14 (73.7)</td>
<td>0.100</td>
</tr>
<tr>
<td>Sartanes</td>
<td>47 (10.6)</td>
<td>4 (21.1)</td>
<td>0.156</td>
</tr>
<tr>
<td>Statins</td>
<td>243 (55.0)</td>
<td>10 (52.6)</td>
<td>0.841</td>
</tr>
</tbody>
</table>

Data are mean±SD when appropriate.
BMI indicates body mass index; PCI percutaneous coronary intervention; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; and ACE, angiotensin-converting enzyme.

*Framingham risk score calculated in 273 patients who had all relevant blood tests within 3 days of MR stress testing.
Patients who underwent coronary artery bypass grafting and development of new ECG changes (ie, transient ST-segment elevation was defined by an increase in cardiac-specific enzymes and/or occurring without another explanation; nonfatal myocardial infarction were registered as cardiac events. Cardiac death was defined as death from any cardiac cause (eg, lethal arrhythmia, infarction) or the treating hospital. Cardiac death and nonfatal myocardial clinical events were confirmed by contact with the general practitioner and telephone interviews with the patient or a close relative; reported patients’ interviews at the outpatient clinic, hospital chart reviews, collected from a standardized questionnaire and determined from

Follow-Up

Follow-up was completed in February 2006. Outcome data were collected from a standardized questionnaire and determined from patients’ interviews at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient or a close relative; reported clinical events were confirmed by contact with the general practitioner or the treating hospital. Cardiac death and nonfatal myocardial infarction were registered as cardiac events. Cardiac death was defined as death from any cardiac cause (eg, lethal arrhythmia, myocardial infarction, or pump failure) or sudden unexpected death occurring without another explanation; nonfatal myocardial infarction was defined by an increase in cardiac-specific enzymes and/or development of new ECG changes (ie, transient ST-segment elevation). Patients who underwent coronary artery bypass grafting and percutaneous coronary intervention >3 months after MR stress testing were censored at the time of revascularization.

Statistical Analysis

Continuous variables are expressed as mean and SD; categorical variables are expressed as proportions. Unpaired Student 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 exact test. All tests were 2 tailed; values of $P<0.05$ were considered significant. Concordance of wall motion and perfusion analyses was calculated as the percentage of agreement, Spearman correlation coefficient, and $\kappa$ statistics.

Clinical variables considered for both univariate and multivariate analyses were defined according to the Framingham Risk Score assessment. For multivariate analysis, the total number of cardiac risk factors at the time of MR stress testing was used. Kaplan-Meier curves were used to estimate the distribution of time to cardiac events (death or nonfatal myocardial infarction). Differences between time-to-event curves were compared with the log-rank test.

The association of clinical and MR imaging findings with outcomes was investigated with a Cox proportional-hazards model using univariate and stepwise multivariate procedures. The Cox model was used to estimate the risk of a given variable as expressed by a hazard ratio with corresponding 95% confidence interval (CI). In addition, to investigate the prognostic value of stress MR imaging incremental to clinical data, a 3-step modeling procedure was performed, with variables included in the model in the same order as in clinical practice. First, only clinical data were analyzed, and the global $\chi^2$ value was calculated. Subsequently, a second step was created after adding MR cine imaging results (ie, resting left ventricular ejection fraction and WMA at rest). A third analysis was conducted by adding DSMR or stress MRP data to the multivariate predictors in the second step. The incremental prognostic value of the added variables was determined by comparison of the global $\chi^2$. At each step, entry and removal were set at a significance level of $P<0.1$ and $P>0.05$, respectively. Sensitivity and specificity were calculated according to standard definitions. All data analysis was performed with SPSS for Windows 12.0.1 (SPSS Corp, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### TABLE 2. Hemodynamic Parameters During Dobutamine and Adenosine Stress Testing in Patients With and Without Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients Without Events (n=442)</th>
<th>Patients With Events (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dobutamine dose, $\mu g \cdot kg^{-1} \cdot min^{-1}$</td>
<td>35.2±7.2</td>
<td>33.2±10.0</td>
</tr>
<tr>
<td>Atropine dose, mg</td>
<td>0.3±0.4</td>
<td>0.4±0.5</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±12</td>
<td>72±15</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134±20</td>
<td>132±24</td>
</tr>
<tr>
<td>Heart rate–pressure product, bpm×mm Hg</td>
<td>9578±2359</td>
<td>9477±2525</td>
</tr>
<tr>
<td>Peak stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>138±17</td>
<td>135±27</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>150±32</td>
<td>146±34</td>
</tr>
<tr>
<td>Heart rate–pressure product, bpm×mm Hg</td>
<td>20 710±4968</td>
<td>19 298±4979</td>
</tr>
<tr>
<td>Adenosine stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±13</td>
<td>70±11</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±21</td>
<td>127±19</td>
</tr>
<tr>
<td>Heart rate–pressure product, bpm×mm Hg</td>
<td>9799±2525</td>
<td>8913±1973</td>
</tr>
<tr>
<td>Peak stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>91±16</td>
<td>87±8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>133±22</td>
<td>129±23</td>
</tr>
<tr>
<td>Heart rate–pressure product, bpm×mm Hg</td>
<td>12 018±3034</td>
<td>11 207±2122</td>
</tr>
</tbody>
</table>

Data are mean±SD. No statistically significant differences were found between groups ($P>0.05$ for all parameters).

Determination of Interobserver Variability

In a random sample of 55 studies, DSMR and MRP scans were independently evaluated by 2 observers (I.P. and C.J. or R.G. and E.N.) who scored regional wall motion at rest and during stress or assessed regional hypoenhancement of MRP scans at rest and during stress, respectively.

Follow-Up

Follow-up was completed in February 2006. Outcome data were collected from a standardized questionnaire and determined from patients’ interviews at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient or a close relative; reported clinical events were confirmed by contact with the general practitioner or the treating hospital. Cardiac death and nonfatal myocardial infarction were registered as cardiac events. Cardiac death was defined as death from any cardiac cause (eg, lethal arrhythmia, myocardial infarction, or pump failure) or sudden unexpected death occurring without another explanation; nonfatal myocardial infarction was defined by an increase in cardiac-specific enzymes and/or development of new ECG changes (ie, transient ST-segment elevation). Patients who underwent coronary artery bypass grafting and percutaneous coronary intervention >3 months after MR stress testing were censored at the time of revascularization.

Statistical Analysis

Continuous variables are expressed as mean and SD; categorical variables are expressed as proportions. Unpaired Student 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 exact test. All tests were 2 tailed; values of $P<0.05$ were considered significant. Concordance of wall motion and perfusion analyses was calculated as the percentage of agreement, Spearman correlation coefficient, and $\kappa$ statistics.

Clinical variables considered for both univariate and multivariate analyses were defined according to the Framingham Risk Score assessment. For multivariate analysis, the total number of cardiac risk factors at the time of MR stress testing was used.

Kaplan-Meier curves were used to estimate the distribution of time to cardiac events (death or nonfatal myocardial infarction). Differences between time-to-event curves were compared with the log-rank test.

The association of clinical and MR imaging findings with outcomes was investigated with a Cox proportional-hazards model using univariate and stepwise multivariate procedures. The Cox model was used to estimate the risk of a given variable as expressed by a hazard ratio with corresponding 95% confidence interval (CI). In addition, to investigate the prognostic value of stress MR imaging incremental to clinical data, a 3-step modeling procedure was performed, with variables included in the model in the same order as in clinical practice. First, only clinical data were analyzed, and the global $\chi^2$ value was calculated. Subsequently, a second step was created after adding MR cine imaging results (ie, resting left ventricular ejection fraction and WMA at rest). A third analysis was conducted by adding DSMR or stress MRP data to the multivariate predictors in the second step. The incremental prognostic value of the added variables was determined by comparison of the global $\chi^2$. At each step, entry and removal were set at a significance level of $P<0.1$ and $P>0.05$, respectively. Sensitivity and specificity were calculated according to standard definitions. All data analysis was performed with SPSS for Windows 12.0.1 (SPSS Corp, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
Results

Patient Characteristics and Hemodynamic Response During Pharmacological Stress

Table 1 provides the clinical baseline characteristics of patients with and without events. Differences between groups were statistically significant for the presence of diabetes mellitus, known CAD, a history of heart failure, and the total number of cardiac risk factors.

Table 2 summarizes the hemodynamic data during MRP and DSMR imaging in patients with and without cardiac events; no statistically significant differences between groups were observed. During DSMR testing, target heart rate was achieved in 380 of 461 patients (82.4%).

Interobserver Variability

In 55 patients randomly selected from the study population, the interobserver agreement (ie, agreement on test positivity or negativity) of MRP and DSMR in our laboratory was 87% (k value, 0.73) and 91% (k value, 0.78), respectively.

Relationship Between MRP and DSMR Results

Agreement of both stress tests on test positivity and negativity was found in 372 of 461 patients (k value, 0.54; Spearman correlation coefficient, 0.56; P<0.0001 for both).

Outcomes

Mean follow-up time was 2.26±1.03 years (median, 2.30 years; range, 0.06 to 4.55 years). Coronary revascularization was performed in 60 patients (13 coronary bypass grafts, 47 percutaneous coronary interventions) >3 months after MR stress testing. Of these patients, 45 (75%) had abnormal MRP results, and 38 (63%) had abnormal DSMR test results. These patients were censored at the time of revascularization. Noncardiac death occurred in 2 patients (0.4%; 1 patient died of prostate cancer, and the other died of gastrointestinal bleeding and liver failure). These patients were censored at the time of death. Nineteen cardiac events were observed (4.1%; 9 cardiac deaths, 10 nonfatal myocardial infarctions).

Predictors of Cardiac Death or Nonfatal Myocardial Infarction

The univariate predictors of hard cardiac events (cardiac death and nonfatal myocardial infarction) are listed in Table 3. A significant association was found for diabetes mellitus, known CAD, or total number of cardiac risk factors >4 as clinical variables and for the presence of WMA at rest, left ventricular ejection fraction, and inducible WMA or MRP deficits as MR imaging results.

With a multivariate procedure, an abnormal result of either MRP (hazard ratio, 10.57; 95% CI, 2.86 to 39.07; P<0.001) or DSMR (hazard ratio, 4.72; 95% CI, 1.76 to 12.64; P=0.002) was the only covariate independently associated with hard cardiac events. Variables that were not significant were age, sex, current or prior cigarette smoking, hypertension, diabetes mellitus, hyperlipoproteinemia, known CAD, WMA at rest, and left ventricular ejection fraction.

Outcome With Normal and Abnormal MRP and DSMR Testing

The Kaplan-Meier curves of event-free survival according to the results of MRP and DSMR testing are illustrated in Figure 3. Table 4 shows the cumulative event rates at 1-, 2- and 3-year follow-up intervals; the 3-year event-free survival was 99.2% for patients with normal MRP and DSMR and 83.5% for those with abnormal MRP and DSMR. A combined analysis of the results of MR stress testing (ie, the combined test is considered normal if either test showed an abnormality) was not superior for the prediction of event-free survival compared with each MR stress test alone (log-rank P=0.18).

Incremental Value of MR Stress Testing

Sequential Cox regression models were fit to test the incremental value of MRP and DSMR over clinical variables (total number of cardiac risk factors >4) and assessment of wall motion at rest, respectively. The presence of WMA at rest increased the likelihood of death or nonfatal infarction over the analysis of clinical risk factors (χ2, 16.0 versus 10.6; P<0.001). An abnormal result of MRP or DSMR further increased the χ2 from 16.0 to 34.3 or 29.5, respectively (both P<0.001).

Discussion

The present study is the first to assess the prognostic value of adenosine stress MRP and DSMR wall motion imaging in patients with known or suspected CAD in a relatively large group of patients and to directly compare the predictive value
of perfusion with functional abnormality within the same patient group. The principal findings of our study are that (1) MRP and DSMR can be used to identify patients at risk for future cardiac events (ie, cardiac death and nonfatal myocardial infarction), (2) a normal MRP or DSMR result identified a low-risk patient group, and (3) MRP and DSMR are superior to clinical data and wall motion assessment at rest to predict cardiac outcome.

Our data show that a patient with ischemia detected by MRP or DSMR has a 12- or 5-fold increased risk, respectively, for experiencing a subsequent cardiac event. For both tests, however, a wide 95% CI must be taken into consideration (see Table 3). Importantly, in multivariate analysis, an abnormal MR stress test result (MRP or DSMR) remained the only independent predictor of cardiac events and provided significant incremental value over clinical variables and rest wall motion analysis.

An important goal of any stress modality is not only to identify those patients at high risk but also to separate those patients with a low cardiac event rate. For this purpose, the

**TABLE 4. Cumulative Event Rate During 3-Year Follow-Up According to the Results of MRP and DSMR Testing**

<table>
<thead>
<tr>
<th>Result of MR Stress Testing</th>
<th>Cumulative Event Rate at Follow-Up Intervals, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 y</td>
</tr>
<tr>
<td>Normal DSMR</td>
<td>1.2</td>
</tr>
<tr>
<td>Abnormal DSMR</td>
<td>7.3</td>
</tr>
<tr>
<td>Normal MRP</td>
<td>0.7</td>
</tr>
<tr>
<td>Abnormal MRP</td>
<td>6.2</td>
</tr>
<tr>
<td>Normal DSMR and MRP</td>
<td>0.8</td>
</tr>
<tr>
<td>Abnormal DSMR and MRP</td>
<td>9.0</td>
</tr>
</tbody>
</table>

**Figure 3.** A, Kaplan-Meier curves based on the results of DSMR and MRP testing. Differences between curves are statistically significant ($P<0.001$ by log-rank test). B, Kaplan-Meier curves for the comparison of normal and abnormal results of DSMR and MRP testing. Differences between curves are statistically not significant ($P=0.20$ and 0.97 by log-rank test, respectively).
short-, medium- and long-term prognostic value of nuclear myocardial perfusion imaging is well established. After a normal nuclear scan, the major cardiac event rate is ~1% per year during the 1 to 3 years after examination.\textsuperscript{16,17} Our results indicate that stress MRP testing conveys a similar prognostic value and thus may be used interchangeably for identifying a low-risk patient group.

With regard to stress MR wall motion analysis, we found the predictive power of DSMR to be comparable to that of dobutamine stress echocardiography. Numerous studies have proved that a normal dobutamine stress echocardiography results in a low annual cardiac event rate in the range of 1% to 3%.\textsuperscript{18} With DSMR, we found identical event rates; thus, prognostic stratification can be done similarly.

Cardiac MR imaging offers the possibility to integrate MRP and wall motion analysis into the same examination, which ensures superb comparability of the results of stress testing. Taking advantage of such a combined examination approach, we demonstrated that stress MRP data and stress MR wall motion analysis are equally valuable in predicting cardiac outcome. This finding is in agreement with previous studies reporting head-to-head comparisons of stress echocardiography and perfusion scintigraphy, with the limited study data available indicating that the techniques were comparable and that one does not provide additive data to the other.\textsuperscript{19}

However, the value of such studies may be reduced by performing the test on different days, which may significantly influence results. In addition, advantages and disadvantages inherent to the different imaging modalities may severely limit the comparability of data (eg, limiting acquisition windows/near-field artifacts on echocardiography or diaphragmatic attenuation on scintigraphy). Using a combined single-session stress MR examination, we showed that prognostication of cardiac outcome can be done with either technique.

However, the detection of ischemia in the setting of resting WMAs may be difficult for less experienced readers because recognizing worsening wall motion is more demanding. In such a setting, MRP imaging may be better suited to detect the presence of ischemia defined as an inducible regional inhomogeneity of myocardial blood flow.

As with other stress imaging modalities, we found that the “warranty period” of noninvasive stress testing using MRP and DSMR may be set at a 2-year level (eg, for MRP, the 2-year cumulative event rate was 0.7% and escalated to 2.3% at 3 years). Interestingly, in patients with normal MRP and normal DSMR results, the warranty period of event-free survival appeared to be prolonged as indicated by a constantly low event rate of 0.8% at 1-, 2- and 3-year follow-up intervals. Long-term studies are needed to define whether the “hard” criterion of a normal MRP result and a normal DSMR result is predictive of a constantly prolonged low event rate.

Study Limitations

Some limitations apply to our study. First, our study population arises from a referral population at a tertiary care center; thus, our findings may be applicable only to a similar scenario. Second, clinicians had full access to the results of MR stress testing; however, when the study was begun in 2001, stress MR imaging was not widely recognized by cardiologists/general practitioners as part of a routine diagnostic workup for the detection of myocardial ischemia. Because this has been acknowledged only recently in respective guidelines,\textsuperscript{20} some minor bias with regard to revascularization might be present in our study. In addition, to minimize such bias, we excluded all patients with early revascularization (<3 months after stress MR testing) from further analysis. Third, because the number of hard cardiac events (ie, cardiac death and nonfatal myocardial infarction) in our study is limited, small differences in the prognostic value of parameters (ie, <20% for less common events) may not be detectable with this sample size. Hence, verification of our single-center experience in large-scale, randomized, multicenter trials dealing with more general populations is desirable.

Conclusions

In patients with known or suspected CAD, myocardial ischemia detected by MRP and DSMR can be used to identify patients at high risk for subsequent cardiac death or nonfatal myocardial infarction, whereas normal MR stress test results are associated with a very low event rate. In addition, MR stress testing provides important incremental information over clinical risk factors and wall motion assessment at rest.

Acknowledgments

We acknowledge our technologists, Corinna Else, RN, MSN, and Gudrun Grosser, RN, for quality cardiac stress MR examinations and dedicated work in completing the patient follow-up.

Disclosures

Dr Nagel received a research grant from Phillips Medical Systems. The other authors report no conflicts.

References


Disclosures

Dr Nagel received a research grant from Phillips Medical Systems. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Studies have shown that cardiac magnetic resonance stress testing is a useful modality for detecting significant coronary artery disease. However, an important goal of any stress modality is the ability not only to distinguish the presence from the absence of obstructive stenoses but also to discriminate those patients at high risk for future cardiac events from those with a low cardiac event rate. The present study is the first to assess and directly compare the prognostic value of adenosine stress magnetic resonance perfusion and dobutamine stress magnetic resonance wall motion imaging in a relatively large group of patients. We found that both magnetic resonance stress tests are superior to clinical data and wall motion assessment at rest in predicting cardiac outcome and allowed the identification of a very low-risk patient group given a normal stress imaging study. Thus, this work further contributes to the information base for cardiac magnetic resonance stress testing in its evolving role as an arbitrer for clinical decision making in patients with known or suspected coronary artery disease.
Prognostic Value of Cardiac Magnetic Resonance Stress Tests: Adenosine Stress Perfusion and Dobutamine Stress Wall Motion Imaging
Cosima Jahnke, Eike Nagel, Rolf Gebker, Thomas Kokocinski, Sebastian Kelle, Robert Manka, Eckart Fleck and Ingo Paetsch

_Circulation_. 2007;115:1769-1776; originally published online March 12, 2007; doi: 10.1161/CIRCULATIONAHA.106.652016

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/115/13/1769

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/