Prognostic Value of High-Dose Dobutamine Stress Magnetic Resonance Imaging in 1,493 Consecutive Patients

Assessment of Myocardial Wall Motion and Perfusion

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Objectives
This study sought to determine the prognostic value of wall motion and perfusion assessment during high-dose dobutamine stress (DS) cardiac magnetic resonance imaging (MRI) in a large patient cohort.

Background
DS-MRI offers the possibility to integrate myocardial perfusion and wall motion analysis in a single examination for the detection of coronary artery disease (CAD).

Methods
A total of 1,493 consecutive patients with suspected or known CAD underwent DS-MRI, using a standard protocol in a 1.5-T magnetic resonance scanner. Wall motion and perfusion were assessed at baseline and during stress, and outcome data including cardiac death, nonfatal myocardial infarction (“hard events”), and “late” revascularization performed >90 days after the MR scans were collected during a 2-year follow-up period.

Results
Fifty-three hard events, including 14 cardiac deaths and 39 nonfatal infarctions, occurred during the follow-up period, whereas 85 patients underwent “late” revascularization. Using multivariable regression analysis, an abnormal result for wall motion or perfusion during stress yielded the strongest independent prognostic value for both hard events and late revascularization, clearly surpassing that of clinical and baseline magnetic resonance parameters (for wall motion: adjusted hazard ratio [HR] of 5.9 [95% confidence interval [CI]: 2.5 to 13.6] for hard events and of 3.1 [95% CI: 1.7 to 5.6] for late revascularization, and for perfusion: adjusted HR of 5.4 [95% CI: 2.3 to 12.9] for hard events and of 6.2 [95% CI: 3.3 to 11.3] for late revascularization, p < 0.001 for all).

Conclusions
DS-MRI can accurately identify patients who are at increased risk for cardiac death and myocardial infarction, separating them from those with normal findings, who have very low risk for future cardiac events. (Prognostic Value of High Dose Dobutamine Stress Magnetic Resonance Imaging; NCT00837005) (J Am Coll Cardiol 2010;56:1225–34) © 2010 by the American College of Cardiology Foundation

High-dose dobutamine/atropine stress (DS) cardiac magnetic resonance imaging (MRI) is incorporated into daily clinical practice for the detection of coronary artery disease (CAD). This technique offers the possibility to integrate myocardial perfusion and wall motion analysis in a single examination. In this regard, recent data suggest that the assessment of myocardial wall motion and perfusion during a single dobutamine stress session may enhance the sensitivity of the technique for ischemia detection (1).

However, to date, limited data are available on the prognostic value of high-dose DS-MRI in large patient cohorts receiving optimal medical therapy (2). Assessment of long-term outcome of DS-MRI is important because this test may identify both high-risk patients who would benefit from invasive diagnostic and therapy, and lower-risk patients in whom additional procedures and intensive medical follow-up are not required.

In the present study, we sought to determine the association between DS-MRI findings with future cardiac events in a large
due to suspected or known CAD. Written informed consent was obtained from all patients before the magnetic resonance examination. Patients with nonsinus rhythm, unstable angina, severe arterial hypertension (>200/120 mm Hg), moderate or severe valvular disease, and general contraindications to MRI (implanted pacemakers or defibrillators) were excluded.

A total of 1,784 patients were screened, and diagnostic stress examinations (positive for ischemia or negative but with achievement of ≥85% of the age-predicted heart rate) were obtained in 1,510 patients. Reasons for discontinuation of the stress procedures included claustrophobia, large body habitus, arrhythmias, failure to achieve the target heart rate, and side effects. Furthermore, during the follow-up period, 17 of 1,510 patients (1.1%) were lost, so that 1,493 patients had complete stress MRI and follow-up information, and constituted our patient population (Fig. 1).

Methods

Study population. The study was conducted in accordance with the standards of our local ethics committee. From December 2004 through January 2008, consecutive patients (n = 1,787) were referred to our institution for clinically indicated DS-MRI.

A total of 1,784 consecutive patients were screened for clinically indicated dobutamine stress magnetic resonance imaging (DS-MRI), and diagnostic stress examinations (positive for ischemia or negative but with achievement of ≥85% of the age-predicted heart rate [HR]) were obtained in 1,510 patients. During the follow-up period, 17 patients were lost, so that 1,493 patients had complete stress MRI and follow-up data, and constituted our patient population.

Traditional risk factors for CAD, including advanced age (≥45 years for men, ≥55 years for women), arterial hypertension, hyperlipidemia, current or prior smoking, diabetes mellitus, history of CAD, and a family history of CAD were recorded at the time of imaging. Furthermore, the total number of cardiovascular risk factors (range 0 to 7) and the Duke Clinical Score, which incorporates clinical presentation of chest pain, age, sex, and atherogenic risk factors (3) were calculated. Hereby, patients were categorized into a low (<30%), intermediate (30% to 70%), or high (≥70%) pre-test probability group for CAD, as reported previously (4). Subsequently, patients were separated into 2 major groups for further analysis, including those with low or intermediate risk for CAD and those with high pre-test probability or known CAD. In addition, renal function, which is a major determinant of cardiac-related outcomes in patients with CAD (5), was calculated using the Modified Diet in Renal Disease (MDRD) equation (6).

Cardiovascular MR examination. Patients were examined in a clinical 1.5-T whole-body MR scanner Achieva system (Philips Medical Systems, Best, the Netherlands) using a 5-element cardiac phased-array receiver coil. The 4-, 2-, and 3-chamber and 3 short-axis views (apical, midventricular, and basal) were used for wall motion assessment at baseline and at peak stress. Dobutamine was infused intravenously during 3-min stages, at incremental doses of 10, 20, 30, and 40 μg/kg of body weight per minute until at least 85% of the age-predicted heart rate was reached (Online Fig. 1). If, at the peak dose of dobutamine infusion, the target heart rate was not achieved, atropine was administered in 0.25-mg increments up to a maximal dose of 2.0 mg. Stress testing was discontinued when the target heart rate was achieved, or when 1 of the following occurred: new or worsening wall motion abnormalities (WMA), severe chest pain or dyspnea, decrease in systolic blood pressure of ≥40 mm Hg,
severe arterial hypertension (≥240/130 mm Hg), or severe arrhythmias.

CINE AND PERFUSION IMAGING. A steady-state free precession sequence was used to obtain the cine images of the 4-, 2-, and 3-chamber views and the 3 short-axis planes (apical, mid-ventricular, and basal) with an 8-mm slice thickness. For perfusion imaging, a single-shot, segmented k-space, turbo gradient echo/echo planar imaging sequence was used with a 10-mm slice thickness. Images were acquired during the first pass of 0.05 mmol/kg of body weight gadolinium-DTPA (Magnevist, Bayer, Germany).

INTERPRETATION OF MYOCARDIAL WALL MOTION AND PERFUSION. For interpretation of wall motion, corresponding rest and peak stress cine images were displayed using View Forum software (Philips Medical Systems). Seventeen myocardial segments were evaluated according to American Heart Association guidelines (7), and wall motion was graded semiquantitatively using a 3-point scale (0 = normal wall motion, 1 = hypokinesia, 2 = akinesia or dyskinesia) (8–10). Inducible ischemia was considered present in cases of new or worsening WMA of ≥1 grade during stress. Both short- and long-axis views were considered, and WMA in 1 view was regarded sufficient for the detection of inducible ischemia. For the evaluation of myocardial perfusion, the transmural extent of a perfusion deficit was determined from the single dynamic image showing the maximum extent of regional hypoenhancement. The transmural extent of perfusion deficits was evaluated visually (0 = no defect; 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; and 4 = 76% to 100%) both at baseline and during stress. A regional worsening of the transmural score during stress by ≥1 in any segment, which persisted for >5 consecutive image frames beyond peak myocardial enhancement of the remote myocardium, which appeared most normal, was considered indicative of myocardial ischemia. When uncertainty existed, signal intensity curves from a remote myocardial region were derived over time to determine the time frame of peak myocardial enhancement. Perfusion defects that were present at baseline and did not increase during stress (i.e., fixed defects associated with prior infarction) were not considered. In Online Figure 2, 3 examples are provided of studies with: 1) normal findings; 2) a subendocardial inducible perfusion abnormality but without inducible WMA; and 3) inducible WMA and perfusion defects.

Follow-up data and definition of study endpoints. Personnel unaware of the stress results contacted each subject or an immediate family member, and the date of this contact was used for calculating the follow-up time duration. Outcome data were collected from a standardized questionnaire and determined from patient interviews at the outpatient clinic or by telephone interviews. Reported clinical events were confirmed by review of the corresponding medical records in our electronic Hospital Information System, contact with the general practitioner, referring cardiologist, or the treating hospital. Cardiac death and nonfatal myocardial infarction were registered as “hard events.” Other events included clinically indicated revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Because the results of the MR examination may have triggered revascularization procedures (thereby altering the subsequent event rate), “early” revascularization procedures within 90 days of MRI were not considered (n = 158 patients), and patients were censored at the time of revascularization.

Statistical analysis. Continuous variables are expressed as mean ± SD, whereas categorical variables are expressed as proportions. Unpaired Student t tests or repeated-measures ANOVA with Bonferroni correction for multiple comparisons were used to compare continuous variables. Group differences between ordinal variables were tested using the exact Mann-Whitney test, and differences between nominal variables were assessed using Fisher exact tests. All tests were 2-tailed. In a random sample of 40 studies, wall motion and perfusion data were independently evaluated by 2 observers (H.S. and G.K.), and agreement was calculated using κ statistics. Kaplan-Meier curves were used to estimate the distribution of cardiac events as a function of the follow-up duration, and the association of baseline and MR findings with outcomes was investigated using Cox proportional hazards models and univariate and multivariable procedures. For multivariable analysis, combined assessment studies were considered abnormal, according to pre-specified criteria, if either WMA or perfusion defects were present; and normal if both modalities yielded normal findings. In order to investigate the complementary value of wall motion and perfusion analysis, the value of WMA for the assessment of hard events was tested in the presence and absence of perfusion deficits. Furthermore, subgroup analysis was conducted in this context in patients with known CAD, resting WMA, and left ventricular hypertrophy. A p value of <0.05 was considered statistically significant.

Results

Outcomes

Data were prospectively collected at least 6 months after the MR examination (2.0 ± 1.0 years, range 0.5 to 4.0 years). Fifty-three hard events, including 14 cardiac deaths and 39 nonfatal myocardial infarctions, occurred during the follow-up period. In 158 patients, early revascularization was performed within 90 days after the MR examination (137 by PCI and 21 by CABG), and 85 patients underwent late revascularization (68 by PCI and 17 by CABG).

The baseline characteristics and hemodynamic data of patients with (n = 53) and without hard events (n = 1,440) are illustrated in Table 1. Furthermore, data including
Univariate and Multivariable Analyses

By univariate analysis, significant associations were observed between several clinical parameters, including renal function and stress MRI findings for hard events and late revascularization (Fig. 2). Using multivariable analysis, renal function and baseline ejection fraction were independently associated with hard events, whereas the total number of risk factors was associated with late revascularization procedures. In both models, an abnormal result for myocardial wall motion or perfusion was most strongly associated with outcome (Fig. 3).

Survival Analysis

Complementary value of wall motion and perfusion analysis. Kaplan-Meier curves based on stress MR findings can be appreciated in Figure 4. The presence of inducible WMA and perfusion deficits was associated with a markedly higher rate of hard events (Figs. 4A and 4B) and revascularization procedures (Figs. 4C and 4D). Conversely, patients with normal DS-MRI (n = 1,193) yielded a very low event rate for hard events (1 cardiac death; 4 myocardial infarctions) and for revascularization procedures over the following 4 years (4 by CABG and 11 by PCI).

The presence of inducible WMA added value to risk stratification of patients with and without diagnosed inducible perfusion deficits, contributing to significantly poorer outcome in both cases (blue arrows in Figs. 4E and 4F). Conversely, perfusion deficits added value to the risk stratification only in the absence of inducible WMA (red arrow in Fig. 4G). In patients with diagnosed inducible WMA on the other hand, the presence of additional perfusion deficits contributed to significantly poorer outcome only in patient subgroups with resting WMA, whereas a trend was noted in this context for subgroups with known CAD and LV hypertrophy (red arrows in Fig. 5).
Division into subgroups. PRE-TEST PROBABILITY FOR CAD. Both in patients with low or intermediate risk and in those with high risk, the presence of inducible WMA was associated with hard events (Figs. 6A and 6B). Furthermore, the presence of inducible WMA was associated with an equally adverse outcome in both groups (Fig 6C). Conversely, the absence of WMA was associated with excellent hard events–free survival (99.5%) only in the patients with low or intermediate risk, whereas patients without WMA but high risk still showed a significant number of subsequent hard events during follow-up (~5%) (Fig. 6D).

BASELINE EJECTION FRACTION. Excluding patients with baseline ejection fraction <35% (n = 58), an excellent outcome was observed in 1,149 patients with normal DS-MRI (no cardiac deaths and only 1 nonfatal infarction) (Fig. 6E). Conversely, patients with ejection fraction <35% had an increased rate of hard events irrespective of stress MR findings (Fig. 6F).

INFLUENCE OF DIURETIC THERAPY AND HEMODYNAMIC RESPONSE. In patients who received treatment with diuretics, WMA showed a trend for less robust assessment of future events...
compared with those who did not receive diuretics ($p = 0.06$ for interaction), whereas no interaction was observed for perfusion analysis in this context. On the other hand, assessment of subsequent hard events was similar in patients with blood pressure increase during DS-MRI compared with those with decrease of systemic blood pressure due to systemic vasodilatation.

**Observer Variability**

Agreement between observers interpreting wall motion and myocardial perfusion was 90% ($\kappa = 0.73$) and 93% ($\kappa = 0.76$), respectively for test positivity versus test negativity on a patient level.

**Discussion**

The MR findings presented in our study, in what we believe to be the largest cohort so far, of 1,493 patients who underwent high-dose DS-MRI indicate that: 1) inducible ischemia diagnosed by DS-MRI identifies patients at increased risk for hard events and for late revascularization procedures independent of conventional atherogenic risk factors and of baseline MR findings; 2) myocardial wall motion and perfusion assessment yielded complementary diagnostic characteristics. The presence of inducible WMA was of incremental value for the risk stratification of patients with and without diagnosed inducible perfusion deficits, whereas perfusion deficits contributed to poorer outcome only in the absence of inducible WMA; and 3) a normal...
stress MRI is prognostically most valuable in patients with low or intermediate risk, because patients at high risk still exhibit a non-negligible rate of subsequent hard events even in the absence of inducible ischemia.

**Previous studies.** Several findings of our study are consistent with those reported in previous stress studies. Thus, using a combined protocol with 2 stressors (adenosine and dobutamine) Jahnke et al. (11) previously reported on the incremental prognostic value of stress MRI over clinical parameters. In another interesting study, dipyridamole stress MRI also yielded independent information for the assessment of cardiac outcome (12). Furthermore, our patients with inducible WMA exhibited a cardiac event rate (7% to 9% annual rate for cardiac death/nonfatal infarction), which is very similar to those previously reported by stress echocardiography and nuclear scintigraphy (13,14).

**Methodological aspects and complementary value of perfusion and wall motion.** Previous MR studies used 2 stressors in the same patient, making the test less feasible and more time-consuming than stress echocardiography. In our study, a single stressor (dobutamine) was used both for the evaluation of wall motion and perfusion. This protocol may be more useful in the clinical routine, particularly with high-volume MR laboratories, due to reduced complexity and lower time spent (~25 to 30 min for single stress vs. ~45 min for dual stress).

Based on the ischemic cascade, perfusion assessment is expected to perform better in ischemia detection, preceding the development of WMA (1). However, in agreement with previous studies, the assessment of wall motion during stress was the most powerful index, yielding the highest hazard ratio for subsequent hard events. Furthermore, the presence of inducible WMA added value to risk stratification of patients with and without inducible perfusion deficits. Conversely, the consideration of myocardial perfusion test results was useful mainly in the absence of inducible WMA. Implementing our results in the clinical work flow, the following algorithm is proposed: if an inducible WMA is not seen during a diagnostic DS-MRI procedure, the administration of contrast for the evaluation of myocardial perfusion is recommended. If an inducible WMA is already detected by cine imaging on the other hand, the value of additional perfusion assessment may be limited to patients with resting WMA and possibly to those with known CAD and LV hypertrophy, where the detection of true positive inducible WMA may be more challenging (15,16).

Certainly, technical limitations with myocardial perfusion MR imaging, such as motion artifacts and lower resolution...
with increasing heart rates during stress testing, should be considered when interpreting our results. Furthermore, with our current perfusion protocol, less myocardium is visualized, so that ischemia in regions like the apical cap (segment 17) or the true basal inferior wall may be missed. These shortcomings, however, may be circumvented in future studies by the recent availability of multichannel cardiac coils, which may allow for 3D first-pass perfusion scans.

Clinical aspects of survival analysis. By dividing our patients into those at high risk versus those at low or intermediate risk (3), we found that all groups with inducible WMA had a high post-test probability for hard events. On the other hand, in the absence of inducible WMA, only patients with low or intermediate risk showed an excellent long-term outcome (event-free survival of $>99.5\%$), whereas patients with high risk still yielded a significant number of subsequent hard events ($\sim 5\%$). Thus, the value of a negative stress MR examination may be higher in patients with low or intermediate risk than in those with high risk, which may still experience a considerable rate of cardiac events despite negative test results. However, even in patients with known CAD, stress MRI examinations may be clinically valuable in order to guide revascularization procedures in patients with ischemic myocardium (17), as recently proposed by the COURAGE (Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation) trial substudy (2) (Online Fig. 3).

In addition, in patients without severely impaired LV function, no cardiac deaths and only 1 nonfatal myocardial infarction were recorded in the latter, in the presence of normal DS-MRI, which represents an excellent outcome. Conversely, in patients with severely impaired LV function, DS-MRI test results did not predict outcome beyond the assessment of resting LV ejection fraction, which is in agreement with previous observations (18). Simultaneously, this patient group exhibited increased risk for life-threatening complications during imaging.

Interestingly, in patients who received diuretics, WMA showed a trend for less robust assessment of future events compared with those without treatment. Possibly, reduced LV volume in patients treated with diuretics may result in reduced wall stress, diminishing myocardial oxygen consumption associated with any given heart rate. This may prevent the development of inducible WMA, weakening the diagnostic capability of DS-MRI in this patient subgroup.
Furthermore, it must be noted that since stress test results were used to structure treatment, and a great number of patients underwent early revascularization, the discriminative power of DS-MRI may be overall underestimated in our study.

**Safety and feasibility aspects.** The number of side effects during imaging in our study was relatively high, especially in patients with reduced LV function. This may be attributed to the high proportion of high-risk patients that were included. However, the safety profile reported in our study is similar to that reported in other MR studies and by other methodologies using dobutamine infusions (19,20). Furthermore, the real success rate of DS-MRI was relatively low (only in 1,510 of 1,784 patients initially screened). However, in the absence of general contraindications to MRI or to dobutamine, diagnostic stress examinations were obtained in 1,510 of 1,658 patients (91%). These numbers are comparable to those reported in previous MRI (19) and echocardiography (21) studies, where around 10% of patients will have nondiagnostic results because of an insufficient hemodynamic response or limiting side effects.

**Study limitations.** Our study population arises from a referral population at a tertiary care university hospital so that a high proportion of high-risk patients was included. This may limit the extrapolation of our findings to ambulatory settings with lower-risk cohorts. Furthermore, wall motion and perfusion of the myocardium were assessed visually, which is subjective and depends on the expertise of the observers. Given the association between myocardial strain response during stress and cardiac outcome (22), and the ability of strain-encoded MRI techniques to quantify myocardial strain during stress procedures (23), it would be useful to investigate the incremental value of strain quantification with DS-MRI in future trials. Increased LV mass and concentric remodeling of the left ventricle were shown to be important predictors of increased cardiovascular risk in previous echocardiographic studies (24,25). Furthermore, late gadolinium enhancement is a clinically established technique for the detection of myocardial infarction and was recently shown to predict adverse outcome independent of segmental WMA (26) or inducible perfusion defects during stress testing (27). In our study, patterns of LV geometric remodeling and the presence of delayed enhancement were not systematically analyzed, which is a limitation. Such conditions may have influenced cardiac outcome of individuals with high pre-test probability, even in the absence of positive stress test results, and merit further investigation in future studies. Furthermore, clinicians had access to the results of stress testing, which obviously triggered early revascularization in the majority of patients with inducible ischemia.

**Conclusions**

DS-MRI is diagnostic procedure that allows for risk stratification and guides revascularization procedures in patients with ischemic heart disease. The assessment of wall motion and perfusion during stress testing can accurately identify patients with positive findings who are at increased risk for cardiac events, and separate them from those with normal findings who are at much lower risk. Furthermore, myocardial wall motion and perfusion assessment yielded complementary values for the prediction of hard cardiac events, whereas a normal stress test was prognostically most valuable in patients with low or intermediate pre-test probability and in those with nonseverely impaired baseline LV function.

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**REFERENCES**


Key Words: combined assessment • coronary artery disease • high-dose dobutamine stress testing • inducible ischemia • myocardial perfusion • wall motion.

APPENDIX

For additional figures and tables, please see the online version of this article.