Magnetic resonance stress tagging in ischemic heart disease

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Submitted 28 October 2003; accepted in final form 4 January 2005

Pharmacological stress testing with dobutamine is an established diagnostic method for the detection of stress-induced myocardial ischemia. High-dose dobutamine/atropine stress cardiac magnetic resonance (MR) imaging is safe and feasible (31), and its diagnostic use for the detection of coronary artery disease (CAD) is superior to echocardiography (22), especially in patients with limited echocardiographic image quality (14). However, the assessment of cine scans usually relies on visual interpretation and is, thus, somewhat subjective (e.g., influence of reader experience). Semiquantitative analysis is possible, although only wall thickening or endocardial inward motion can be determined, and components of myocardial deformation (such as rotation or circumferential shortening) are not considered. In addition, the through-plane motion of the heart during contraction and relaxation may result in visualization of different myocardial segments during systole and diastole.

Myocardial tagging may be advantageous: with this technique, the myocardium is labeled with grid or line tags at end diastole, e.g., by spatial periodic modulation of magnetization (SPAMM) (1, 33). The SPAMM technique was improved by achieving a tag contrast throughout the cardiac cycle (C-SPAMM) (6) and by compensating for through-plane motion of the heart (i.e., slice following) (7): the tag lines are “fixed” on the tissue and deform with the myocardium throughout the cardiac cycle. Consequently, quantification of grid deformation allows an exact and objective assessment of global and regional wall motion (21, 33): different components of myocardial motion, such as circumferential shortening, rotation, or strain along the myocardial fiber direction, can be determined. The use of myocardial tagging has provided new insights into the (patho)physiology of regional wall motion (3, 27), and several parameters have been described as being useful to identify an ischemic response of the myocardium (2, 26).

Rotation might be a sensitive marker for myocardial ischemia and may be advantageous, because it represents a measure of myocardial contractility that is, only to a minor degree, influenced by changes of pre- and afterload (13). Dong et al. (5) found that diastolic relaxation and untwisting correlate closely. Circumferential shortening has been shown to be the major component of myocardial strain at rest and during dobutamine treatment (8) and has been successfully used to detect viable myocardium during low- and medium-dose dobutamine stimulation (9, 17). Recently, Kuijpers et al. (18) reported that even the visual inspection of tagged images acquired during high-dose dobutamine stress was more sensitive for the detection of significant CAD than the visual inspection of conventional cine scans.

Thus the objective of the present study was to assess whether 1) myocardial tagging with slice following is feasible during a high-dose dobutamine stress protocol and 2) whether global quantitative parameters that may have the potential to distinguish patients with and without significant CAD during low-dose dobutamine stimulation can be identified.

METHODS

Study Population

Thirty-one consecutive patients (23 men and 8 women, age 59.0 ± 7.3 yr) with suspected CAD or suspected restenosis after prior

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percutaneous coronary intervention were examined with a standard dobutamine/atropine stress protocol before clinically indicated invasive coronary angiography. All patients had normal regional and global systolic left ventricular function at rest, as assessed by visual inspection and volumetry [area length ejection fraction = 60.6% (SD 3.6)]. Patients with a history or ECG signs of prior myocardial infarction, valvular disease, complete bundle branch block, or general contraindications to dobutamine or MRI were excluded. Twenty-two patients had arterial hypertension, 6 had diabetes mellitus, 15 had dyslipoproteinemia, 11 were active smokers, and 10 had a positive family history of CAD.

Written informed consent was obtained from all patients, and the research protocol was approved by the Committee on Clinical Investigation of our hospital.

The patient characteristics are summarized in Table 1.

MRI Examination

The examinations were performed with a 1.5-T whole body MR scanner (ACS NT, Philips Medical Systems, Best, The Netherlands) with the patient in the supine position. A five-element phased-array cardiac surface coil was used for signal acquisition. Images were acquired during end-expiratory breath holds; the ECG was continuously monitored, and blood pressure was measured at 1-min intervals.

After acquisition of two rapid localizer scans to identify the intrinsic axes of the heart, three conventional short-axis cine scans were performed at the basal, midventricular, and apical level (balanced gradient echo sequence as follows: echo time, repetition time, and flip = 1.9, 4, and 60, respectively); the scans were repeated at all stress levels and evaluated visually on the scanner console to check for inducible wall motion abnormalities. At rest and at each dobutamine stress level, a slice-following C-SPAMM-based tagging pulse sequence was performed at the apical short-axis level (segmented k-space, multishot FFE-EPI sequence as follows: repetition time, echo time, and flip = 25, 7.4, and 25, respectively) (30). The tagging sequences consisted of two sets of images with horizontally and vertically modulated stripes acquired within one breath hold. The heart phase interval was <40 ms in all data sets, and 15–25 heart phases were recorded depending on heart rate. Tagged images were acquired at rest, during treatment with dobutamine at 10 μg·kg⁻¹·min⁻¹, and during maximum dobutamine stress.

Stress Protocol

Dobutamine was infused at 10, 20, 30, and 40 μg·kg⁻¹·min⁻¹ at 3- to 5-min intervals. If target heart rate [defined as 85% of age-predicted heart rate (220 – age)] was not achieved at the maximum dobutamine level, additional atropine was applied (in 0.25-mg increments to a maximum of 1.5 mg). The stress protocol was terminated if target heart rate was reached or if the patient experienced progressive angina/dyspnea or significant side effects related to the dobutamine infusion or, in the case of visual detection, a new or worsening regional wall motion abnormality in at least one myocardial segment.

Image Analysis

After multiplication of the two images to obtain the grid, analysis of the apical short-axis slices was performed with semiautomatic software [MACAVA, ETH; the principles of this software application have been described in detail elsewhere (28)], which allows tracing of the intersection points of the tag lines in each phase image (Fig. 1). Epi- and endocardial borders of the left ventricle were defined manually in the first-phase image. By means of the tagging grid, the software determined the epi- and endocardial borders in all subsequent heart phases. As the basis for further analysis, 72 midmyocardial points were calculated: for definition of these points, a polar coordinate system was introduced, and points were distributed circumferentially every 5°; all quantitative parameters as given in Tables 2 and 3 represent the mean values of all segments of the apical slice. The end-diastolic and end-systolic phase images were defined as the first image acquired after the R-wave trigger and the phase image with the smallest left ventricular cavity area, respectively (28).

Definition of Terms

Parameters were normalized to values at rest. In addition, durations and velocities were normalized to percentage of the duration of systole to account for interindividual differences and stress-related changes in heart rate.

Circumferential shortening (CS) represents the relative shortening of the distance between two adjacent circumferential points, expressed as a percentage of the end-diastolic distance; mean CS was calculated using all 72 midmyocardial points. Diastolic lengthening is expressed as negative values of CS.

Maximal lengthening velocity is the first derivative of the CS curve, expressed as percent per second.

Rotation is the apical rotation of each midmyocardial point around the center of gravity of the left ventricle, expressed in degrees. For further analysis, mean rotation of all 72 midmyocardial points was considered. As viewed from the apex, counterclockwise rotation was defined as a positive angle and clockwise rotation as a negative angle.

Rotation velocity represents the rotational angle of a midmyocardial point between two heart phases divided by the interphase interval (1st derivation of the rotation curve; degrees/ %systole). For the analysis, all midmyocardial points were used.

Time to peak untwist is the time between end systole and peak diastolic rotation velocity, expressed as percentage of systole.

Statistics

Stress levels were compared with Student’s t-test for paired comparisons. Comparisons between patients with and without CAD were done with Wilcoxon’s test. Values are means (SD). Statistical significance was assumed for P < 0.05. Sensitivity, specificity, accuracy, and predictive values (positive and negative) were calculated according to standard definitions. For “time to peak untwist,” a receiver operating curve analysis was carried out to determine its ability to differentiate between patients with and patients without CAD, and the area under the curve was calculated.

RESULTS

Dobutamine stress testing was performed in 31 patients; 6 patients were excluded from the analysis because of poor

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Without (n = 12)</th>
<th>With (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62 (SD 7)</td>
<td>56 (SD 8)</td>
<td>0.45</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>66 (SD 9)</td>
<td>69 (SD 17)</td>
<td>0.32</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>125 (SD 20)</td>
<td>138 (SD 21)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>70 (SD 12)</td>
<td>73 (SD 9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Low stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>71 (SD 11)</td>
<td>71 (SD 17)</td>
<td>0.47</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122 (SD 21)</td>
<td>136 (SD 25)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>69 (SD 12)</td>
<td>74 (SD 11)</td>
<td>0.19</td>
</tr>
<tr>
<td>Maximum stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>138 (SD 20)</td>
<td>135 (SD 14)</td>
<td>0.32</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>148 (SD 28)</td>
<td>167 (SD 34)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74 (SD 13)</td>
<td>77 (SD 15)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are means (SD); n, number of patients. HR, heart rate; BP, blood pressure; CAD, coronary artery disease.
image quality. The remaining 25 patients formed the study population. Target heart rate was reached in 21 of 25 patients; reasons for premature termination of the stress test included severe angina, hypertensive dysregulation, severe headache/nausea, and atrial fibrillation (4 patients). Dobutamine and atropine doses were 34.1 μg·kg⁻¹·min⁻¹ (SD 8.9) and 0.5 mg (SD 0.5), respectively, with administration of atropine in 18 patients.

The quantitative analysis of stress MR tagging refers to 25 apical short-axis views at rest and under low-dose dobutamine (10 μg·kg⁻¹·min⁻¹) and to 21 apical short-axis views under maximum stress (4 patients failed to reach target heart rate).

Fig. 1. Representative end-diastolic and end-systolic apical images of a patient without significant coronary artery disease (CAD). A: rest. B: low-dose dobutamine stress. C: high-dose dobutamine stress. Note increase in systolic rotation and endocardial motion from rest to low-dose stress.

Angiographically, 13 of 25 patients had significant CAD (i.e., ≥1 epicardial vessel with >2 mm diameter had >50% luminal diameter reduction as assessed by quantitative coronary angiography).

Table 2. Quantitative parameters of systolic function during low-dose and maximum dobutamine stress in patients with and without significant CAD

<table>
<thead>
<tr>
<th>CAD</th>
<th>Without</th>
<th>With</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak CS</td>
<td>115 (SD 21)*</td>
<td>101 (SD 16)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak rotation</td>
<td>130 (SD 45)*</td>
<td>102 (SD 20)</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak CS</td>
<td>103 (SD 39)</td>
<td>96 (SD 18)</td>
<td>NS</td>
</tr>
<tr>
<td>Peak rotation</td>
<td>186 (SD 64)†</td>
<td>144 (SD 45)‡</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means (SD), expressed as percentage of rest. CS, circumferential shortening; NS, not significant. *P < 0.02 vs. rest. †P < 0.05; ‡P < 0.01 vs. low stress.

Table 3. Quantitative parameters of systolic and diastolic function during low-dose and maximum dobutamine stress in patients with and without significant CAD

<table>
<thead>
<tr>
<th>CAD</th>
<th>Without</th>
<th>With</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of peak CS</td>
<td>96 (SD 9)</td>
<td>101 (SD 12)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic rotation velocity</td>
<td>130 (SD 35)*</td>
<td>105 (SD 24)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Maximum stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of peak CS</td>
<td>87 (SD 11)†</td>
<td>100 (SD 13)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic rotation velocity</td>
<td>250 (SD 127)§</td>
<td>234 (SD 84)α</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity of CL</td>
<td>123 (SD 35)b</td>
<td>101 (SD 32)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak untwist</td>
<td>77 (SD 31)c</td>
<td>151 (SD 106)c</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic rotation velocity</td>
<td>130 (SD 30)c</td>
<td>102 (SD 44)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Maximum stress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Velocity of CL</td>
<td>76 (SD 35)c</td>
<td>110 (SD 43)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to peak untwist</td>
<td>88 (SD 80)</td>
<td>127 (SD 47)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic rotation velocity</td>
<td>225 (SD 155)</td>
<td>182 (SD 96)e</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means (SD), normalized to heart rate and expressed as percentage of rest values. CL, circumferential lengthening. *P < 0.05; bP < 0.02; cP < 0.01 vs. rest. dP < 0.05; eP < 0.01 vs. low stress.
Diastolic Cardiac Function

CS. In patients without CAD, CS increased at low-dose stress ($P < 0.05$) but returned to baseline values at maximum stress. In patients with CAD, neither low- nor high-dose stress significantly influenced peak CS, nor did time of peak CS (Table 3) change under low- or high-dose stress. Systolic rotation velocity was significantly reduced in patients with CAD.

Rotation. In accordance with previous studies, all patients showed a counterclockwise rotation of the apex in systole [13.5 degrees (SD 3.2) and 12.1 degrees (SD 3.6) in patients with and without CAD, respectively, $P = $ not significant] and a clockwise rotation in diastole at rest.

In patients without CAD, peak rotation and maximal systolic rotation velocity increased with increasing dobutamine stress (Table 2 and 3).

In contrast, patients with CAD showed neither an increase in peak rotation nor an increase in systolic rotation velocity during low-dose stress, although a significant increase was found during high-dose dobutamine stress. However, for low- and high-dose stress, the parameters did not significantly differ between the patient groups (without vs. with CAD).

Diastolic Cardiac Function

Diastolic lengthening. In patients without CAD, velocity of diastolic fiber lengthening first significantly increased at low-dose stress ($P < 0.02$ vs. rest) but then significantly decreased at maximum stress ($P < 0.01$ vs. low-dose stress).

In patients with CAD, no significant changes were found during stress. No significant difference was found between patients without and with CAD.

Time to peak untwist. Time to peak untwist significantly decreased at low-dose stress in patients without CAD but did not further change with high-dose stress. In contrast, in patients with CAD, time to peak untwist significantly increased from rest to low-dose stress ($P < 0.05$). Time to peak untwist was significantly different between patients with and without CAD ($P < 0.01$).

Diastolic rotation velocity. In patients without CAD, maximal diastolic rotation velocity increased with increasing stress; however, patients with CAD showed a significant increase at high-dose stress only (Fig. 2).

In addition, during low-dose stress, diastolic rotation velocity was significantly greater in patients without CAD than in those with CAD ($P < 0.05$).

Because time to peak untwist showed the largest effect for the comparison of patients with CAD vs. patients without CAD, this parameter was tested for its potential ability to detect patients with significant CAD. Thus a receiver operating curve analysis was carried out (Fig. 3): the results of using a cutoff value of 90% are shown in Table 4 and Fig. 4.

**DISCUSSION**

The major findings of our study are as follows. 1) Myocardial stress tagging was feasible using low- and high-dose dobutamine stress. 2) Under low-dose dobutamine stress, parameters of systolic (systolic rotation velocity) and diastolic function (time to peak untwist and diastolic rotation velocity) were significantly different between patients with and without CAD. 3) The most promising parameter for identification of patients with CAD was time to peak untwist.

The findings of our study are in agreement with the well-known concept of the ischemic cascade, which states that diastolic impairment is an early ischemic alteration. With stress tagging, we found significant differences between patients with and those without CAD mainly reflected in diastolic parameters (time to peak untwist and diastolic rotation velocity) but also in a single systolic parameter (systolic rotation velocity). It is noteworthy that the main effects occurred during low-dose stress, especially with regard to time to peak untwist. Thus quantitative stress MR tagging appears to be advantageous, because it might not be necessary to proceed to higher dobutamine levels to detect the presence of significant CAD.

Cardiac rotation resulting in a systolic wringing motion of the left ventricle is an energy-efficient means to achieve high intracavitary pressure with minimal fiber shortening. First, studies in animals and invasive studies in transplanted hearts...
demonstrated a pronounced rotation during dobutamine stress (2, 20, 26). In addition, a reduction of apical rotation was observed during myocardial ischemia. Gibbons Kroeker et al. (10) demonstrated a decreased apical rotation after left anterior descending coronary artery or left circumflex artery occlusion in dogs. Knudtson et al. (15) showed that apical rotation is a sensitive indicator of ischemia as assessed during percutaneous revascularization of the left anterior descending coronary artery in patients. Our results are in accordance with these previously published reports and indicate that, during low-dose dobutamine stress, systolic apical rotation is significantly reduced in patients with significant CAD. However, under high-dose dobutamine stress, the large interindividual variability between patients precluded the use of systolic rotation to differentiate between patients with and without CAD.

Diastolic dysfunction has been assessed in a variety of myocardial pathologies using invasive and noninvasive procedures: with myocardial tagging, it was possible to characterize diastolic dysfunction in patients with myocardial hypertrophy or infarction (23, 29). In particular, it was demonstrated that an impairment of the early filling period marked the onset of ischemia; in addition, the reduced velocity of peak diastolic pressure decay and postejction thickening of ischemic segments in early diastole were reported to be indicative of early ischemic reactions (19, 32).

Consequently, the value of diastolic parameters as measured with stress MR tagging for the detection of significant CAD has been examined. In an animal model, Rademakers et al. (26) demonstrated that maximal diastolic untwisting was accelerated during dobutamine infusion and further increased with its dose; these findings led to the hypothesis of an “energy storage” during systole that is subsequently released during diastole. The investigators reported that diastolic untwisting occurred before ventricular filling; this dissociation had been attributed to the dobutamine stimulation, and the authors could identify the energy-dependent early diastolic relaxation as a factor that is crucial for adequate ventricular filling. Our data support the idea that diastolic untwisting represents a promising parameter for the detection of patients with significant CAD.

**Limitations**

The time-consuming analysis of the tagged images renders stress MR tagging unsuitable for larger patient populations or in clinical routine. Recent software developments, such as HARP (24) and FastHARP (16), may provide a means to overcome this drawback.

Large interindividual differences of wall motion parameters have been reported at rest (25) and are further pronounced during dobutamine infusion (4); thus we decided to calculate and report the percent changes relative to the baseline values to account for the observed high interindividual variability.

In addition, the high number of patients with arterial hypertension (22 of 25) might have influenced our results, because in these patients the combined effects of dobutamine on (sub)clinical diastolic dysfunction and the presence of significant CAD were assessed. However, our aim was to study the feasibility of high- and low-dose dobutamine stress tagging and to identify those parameters that might be useful in future software applications to be displayed, e.g., on the console of the scanner.

It seems reasonable to compare the results of stress MR tagging with other functional methods for ischemia detection in future studies (rather than with invasive coronary angiography alone). We thought it useful, however, to first compare stress MR tagging with the clinical standard of reference to obtain a preliminary and raw estimate of its applicability as a gatekeeper for invasive testing.

Another limitation of our study is the restricted temporal resolution of the tagging technique applied especially compared with, e.g., the optical device technique used in previous invasive animal studies (11). This technique allowed online measurements of cardiac motion. The restricted temporal res-

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Table 4. Diagnostic performance of low-dose tagging using “time to peak untwist”

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>85</td>
</tr>
<tr>
<td>Specificity</td>
<td>67</td>
</tr>
<tr>
<td>Accuracy</td>
<td>76</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>73</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>80</td>
</tr>
</tbody>
</table>

Values are percentages. Receiver operating curve analysis for determination of cutoff value (90%) is shown in Fig. 3.
solution of MR tagging limits the evaluation of parameters of myocardial motion, which change rapidly over time. However, MR tagging is advantageous with regard to its noninvasiveness; thus our aim was to test in patients its ability to aid in the detection of significant CAD. In addition, with further technical refinements of the tagging sequences, a more detailed analysis of myocardial motion can be expected.

Load dependence has been shown to play an important role: the effects of load, contractility, and heart rate manipulations on left ventricular twist are manifested by changes in the amplitude and dynamics of torsion (12). In our patient study, we did not perform invasive assessment of the hemodynamic changes under dobutamine stress for ethical reasons; thus we cannot exclude a potential influence of the stress-induced hemodynamic changes on the parameters measured. However, heart rate and blood pressure did not significantly differ between patients with and without CAD, thereby minimizing the parameters’ potential influence.

Conclusion

MRI myocardial tagging at low-dose dobutamine stress is feasible and showed significant differences between patients with and without significant CAD. High-dose dobutamine stress MR tagging is feasible as well but, with the available MR techniques, was not superior to low-dose dobutamine stress MR tagging at low-dose dobutamine stress for the detection of CAD. Thus quantitative myocardial tagging may become a tool that reduces the need for high-dose dobutamine stress.

ACKNOWLEDGMENTS

We thank Gudrun Grosser, Heike Mueller, and Janina Rebakowski for assistance in performing the dobutamine stress MR examinations.

GRANTS

This research project was supported by the German Cardiac Society. D. Föll was supported by the German Cardiac Society. A. Wahl was supported by Swiss National Funds.

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