Blood Oxygen Level–Dependent Magnetic Resonance Imaging in Patients with Stress-Induced Angina

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Background—Blood oxygen level–dependent (BOLD) MRI reflects tissue oxygenation and may be useful for the detection of myocardial ischemia in patients with suspected coronary artery disease.

Methods and Results—We studied 25 patients with stress-induced angina using a T2*-sensitive echo planar imaging sequence before and during adenosine in a single-slice approach. BOLD-MRI results were compared with quantitative angiography and adenosine thallium single-photon emission computed tomography (SPECT). Although image quality was variable because of artifacts, no data were excluded from the analysis. During adenosine, a mean signal intensity decrease was observed for myocardial segments related to coronary stenoses >75%. On average, a nonsignificant increase was observed in the other segments. The angiographically determined stenosis was correlated with BOLD-MRI results. Including all segments and using BOLD-MRI signal intensity increase cutoff value of 1.2%, BOLD-MRI had a sensitivity of 88% and a specificity of 47% to correctly classify severe stenoses. Adenosine thallium SPECT data from distal segments of the same coronary territory were also correlated with BOLD-MRI. However, variability was substantial.

Conclusions—In patients with stress-induced angina, adenosine BOLD-MRI detects myocardial ischemia in myocardial segments related to severe coronary stenoses. Its potential will increase with additional improvement of spatial coverage and image quality. (Circulation. 2003;108:●●●●●●.)

Key Words: magnetic resonance imaging ■ perfusion ■ adenosine ■ coronary heart disease ■ ischemia

The noninvasive assessment of the hemodynamic relevance of a suspected or known stenotic coronary artery remains a challenge. Routine techniques such as echocardiography and imaging techniques like echocardiography, nuclear medicine, and first-pass perfusion MRI, however, are limited to repolarization abnormalities, functional consequences, or tracer kinetics as surrogate parameters.

Blood oxygenation level–dependent (BOLD) MRI may overcome these limitations by observing changes of tissue oxygenation directly. Ogawa et al1 first related BOLD signal intensity (SI) changes obtained in T2*-weighted imaging to fractional blood deoxygenation attributable to paramagnetic properties of deoxygenated hemoglobin. BOLD imaging is capable of mapping small changes in cerebral tissue oxygenation, a process termed functional MR imaging.2 Toussaint et al3 applied the BOLD-MRI technique to visualize changes in muscle perfusion. Li et al4 have shown that T2* reflects changes of myocardial oxygenation independent of coronary flow, and Niemi et al5 detected significant changes of myocardial SI in T2*-weighted images after the administration of dipyridamole. Wacker et al6 applied the method to detect perfusion-related changes of T2* relaxation time induced by dipyridamole in healthy volunteers and coronary patients.7,8 The purpose of our study was to test the feasibility and sensitivity of BOLD-MRI to detect coronary perfusion defects. We assessed the relationship between adenosine-induced changes in SI with T2*-weighted images to angiography and thallium single-photon emission computed tomography (SPECT) studies in patients with coronary disease.

Methods

We studied 25 patients with exercise-induced angina pectoris. Six patients had had myocardial infarction, 2 patients had a bypass graft, and 8 patients had an implanted coronary stent.

MRI Protocol

MRI was performed on a 1.5-Tesla system (GE Medical Systems) with a whole-body gradient coil (switching capacity, 40 mTm-1 within 268 μs). For BOLD-MRI, a single-slice interleaved T2*-sensitized gradient-echo planar imaging (EPI) pulse sequence was used for BOLD with the following parameters: data matrix, 128×128; number of shots, 2; flip angle, 15 degrees; FOV, 280 mm; slice thickness, 8 mm; number of slices, 1. ECG gating was applied (trigger delay, 300 ms), resulting in a repetition time of a single R-R interval. The echo time was fixed at 17.4 ms to attain T2* sensitivity.
and an appropriate signal-to-noise ratio. Ramp sampling was used to reduce image distortion.

A set of 4 images was obtained every 60 seconds. Each set was acquired during a single breath hold over 12 heart beats (2 beats per image), including 4 dummy scans to drive the magnetization to steady state. Images were acquired in a true short-axis view through the mid left ventricle.

**Rest and Stress Protocol**

After 3 baseline image sets, 1 set was acquired in each of the 6 minutes of a stress period with infusion of 140 μg/kg per min body weight adenosine. This was followed by 4 sets during recovery, starting 1 minute after stop of adenosine infusion.

**Single-Photon Emission Computed Tomography**

SPECT was done on a MB 9200 gamma camera (Gamma Mivek) with the same adenosine stress protocol. The studies were done, on the average, 4 hours later. Segmentation was based on built-in algorithms.

**Data Analysis**

Images were transferred to a workstation (Advantage Windows, GE Medical Systems). SI was measured after manually tracing the entire myocardial segment in each of the images. The observers were not aware of the data from angiography or SPECT analyses. To observe steady state, we selected the fourth image of each set. The cross-sectional short-axis view was divided into 6 segments (anterior, lateral, posterior, inferior, septal-inferior, and septal-anterior). Because of heart-rate variations, the repetition time (TR) was not constant. To minimize saturation effects associated with these TR variations, a small flip angle (15 degrees) was used for excitation. Data were corrected for heart rate–dependent saturation effects. The correction factor for a train of RF pulses was as follows for a given flip angle and a given linear relationship of the TR/T1 ratio in heart rates between 50 and 130 beats per minute,10 whereby T1 was assumed to be 1004 ms for healthy myocardium at 1.5 T:

\[
M_{sy} = \frac{1 - \exp(-\frac{TR}{T1})}{1 - \cos \alpha \exp(-\frac{TR}{T1})} \sin \alpha.
\]

The corrected mean SI was calculated for resting conditions by averaging all 7 SI values from images during rest and recovery. The results were compared with the mean corrected SI of the 6 images obtained after adenosine. The relative SI change was calculated by:

\[
\text{mean SI (stress) - mean SI (rest + recovery)} \times 100.
\]

SPECT data were used to calculate the percent SI change (analogous to the BOLD quantification) in 4 slices, namely basal, mid, apical, and supra-apical.

For the comparison of SPECT data with the BOLD-MRI results, the following data sets were generated from the quantitative SPECT evaluation. The first was a pooled data set averaging the results of all 4 SPECT slices in that segment (for competing with a clinical standard). This was used for the comparison of the diagnostic accuracy. The second was a single-slice data set of each of the 4 slices for a slice-to-slice comparison to the single slice of the BOLD-MRI technique. This was used in an additional analysis comparing the slice-selective results between SPECT and BOLD-MRI (see Results).

Angiography was done on a standard system (HICOR, Siemens Medical Solutions). Conventional methods and evaluation software (CAAS II, PIE Medical System) were used. For comparison to angiography, the segments were assigned to coronary territories as shown in Figure 1. A right dominant was assumed when the right coronary artery supplied the inferior parts of the ventricular septum and at least 1 posterolateral branch to the diaphragm wall of the left ventricle. Left dominant was determined when the right coronary artery did not exceed the crux cordis and the left branches supplied the inferior septum. A balanced type requested a posterior interventricular branch supplied by the right coronary artery but posterolateral branches with a left circumflex coronary artery offspring. All data were analyzed in a blinded manner.

**Statistical Analysis**

All segments were incorporated. The primary variable of the stress-induced BOLD-MRI SI change was evaluated prospectively. A post-hoc analysis was performed to compare the segmental changes to the SPECT results. To compare the BOLD-MRI results to an accepted clinical standard, the SPECT results of all slices were averaged for the ROC analysis. The Spearman-Rho correlation was calculated to examine continuous variables. ANOVA was used to test continuous variables. A contingency analysis with Fisher’s exact test was used. P<0.05 was considered significant. We analyzed data with StataView (Abacus Concepts) for the Spearman-Rho correlation, and for the ROC analysis we used SPSS for Windows 10.0.7 (SPSS Inc). For the comparison of the area under the curve, we applied the method described by deLong, deLong, and Clarke-Pearson using STATA 7.0 (Stata Corporation).

**Results**

Twenty-four of the 25 patients (96%) had coronary artery disease as defined by visible coronary artery stenoses. One patient had no significant stenoses at all, whereas 23 had coronary stenoses ≥50%, of whom 10 patients had severe (>75%) stenoses. One hundred twenty-five of 150 segments were supplied by visually altered vessels, and 25 of 150 (16.7%) segments were related to a severe stenosis or to an occluded artery, 6 of them inferoseptal, none anteroseptal, 1 anterior, 3 lateral, 7 posterior, and 8 inferior.

BOLD-MRI with adenosine infusion was feasible in all 25 patients. Eleven patients developed angina during the infusion. In 1 patient, the session was stopped after 4 minutes.
because of severe angina. This patient’s data were nonetheless included.

Figure 2 shows representative BOLD-MR images from 3 patients. The image quality was good in 64 segments (43%), moderate in 50 segments (33%), poor in 24 segments, and very poor in 12 segments (8%). With a standard deviation of noise of 6% (ie, of segment means), the signal-to-noise ratio was 59.8 for the stress images and 64.6 for the rest and recovery data. Ghosting artifacts (n/H110054), image distortion (n/H110057), respiratory motion (n/H110058), and susceptibility artifacts were limiting factors for image quality. Susceptibility artifacts were encountered in all 8 patients with coronary stents; however, they were also observed in 4 other patients, mostly located in the posterior and lateral myocardium. Nevertheless, we measured the SI of the remaining parts of the myocardium and included all 150 segments in the analysis. No systematic difference in the mean SI or in intensity changes was observed between various coronary artery regions. However, the posterior-lateral segment was most prone to signal attenuation caused by susceptibility artifacts.

Figure 3 shows the relationship between the SI change (percent compared with rest/recovery) in BOLD-MRI during adenosine and coronary artery stenosis severity related to the segments. The mean SI change during adenosine was +0.94±0.67% (P=NS) for segments without stenosis, +0.27±0.63% (P=NS) for segments related to a stenosis of <50%, and +0.84±0.76% (P=NS) for segments related to a stenosis of 50% to 75%. In contrast, for segments related to
Comparison to SPECT Results/Slice-Selective

Interestingly, a correlation was found in the slice-selective comparison. This was significant when BOLD-MRI data were compared with the apical (correlation coefficient, 0.22; \( P < 0.01 \)) and the supra-apical (0.184; \( P < 0.05 \)) 201 Tl-SPECT segments. Again, the comparison of the area under the ROC curves for all 3 slices did not show any difference for the overall diagnostic accuracy.

Discussion

We found that we could identify severe coronary stenoses with BOLD-MRI about as well as with thallium SPECT analysis. BOLD-MRI detects SI changes, representing changes in the ratio between deoxygenated and oxygenated hemoglobin in myocardial territories subtended by stenosed coronary arteries. The phenomenon is an example of coronary steal induced by adenosine with a resultant shift of blood toward normal or near-normal areas of myocardium. The signal increase in normally perfused segments represents increased perfusion on a microvascular level.

Our data extend the observations of Wacker and colleagues, who showed that dipyridamole was associated with an increase of \( T_2^* \) in healthy volunteers but with a decrease in patients with stenotic coronary arteries. A decrease of \( T_2^* \) leads to a concomitant decrease of SI changes in \( T_2^* \)-sensitive images such as we used; however, SI changes were not addressed in these studies. Thus, when comparing the data, our results have to be translated into \( T_2^* \) changes. This is possible by (1) assuming that the SI changes are exclusively attributable to \( T_2^* \) changes and (2) taking into account a value of \( T_2^* \) of 35 ms for healthy myocardium. This results in a \( T_2^* \) change of approximately 5% for segments related to a stenosis \( > 75\% \) under adenosine stress conditions. For comparison, relative \( T_2^* \) changes of 40% were recently reported by Wacker et al.\(^6\) using a dipyridamole stress protocol. It remains unclear why the \( T_2^* \) changes observed in our study were smaller than those found by Wacker et al. One reason might be that our data were averaged over the entire stress period, whereas Wacker et al. obtained their measurements under maximal stress. Another possible reason might be associated with the longer acquisition time used in the multiecho approach by Wacker et al. An acquisition window length of 300 ms per cardiac cycle induces motion sensitivity, especially for high heart rates, where the cardiac rest period is \(< 100\) ms. This might cause motion-related dephasing, which results in a T2* change of approximately 5% for healthy myocardium.

Like in our study, SI changes instead of \( T_2^* \) values were assessed by Niemi et al., who described a significant SI increase during dipyridamole administration. When compared with our study, the SI increase was higher (14% vs. 0.94% for SPECT in their subjects. However, the data of Niemi et al. were obtained in healthy volunteers and ours were obtained in patients with coronary artery disease (except for a stenosis of \( > 75\% \), the SI change was \(-2.33 \pm 0.99\% \) (\( P < 0.05 \) compared with no stenosis) and \(-2.15 \pm 1.18\% \) for occluded vessels (\( P < 0.05 \) compared with no stenosis, see Figure 3).

The correlation coefficient for the relationship between SI change and degree of stenosis was \(-0.219 \) (\( P < 0.01 \)). The mean SI change was \(+0.52 \pm 0.43\% \) for all segments related to normal coronary artery lumen or stenoses \(< 75\% \). For those segments related to coronary artery stenoses \( > 75\% \), the mean SI change was \(-2.29 \pm 0.77\% \) (\( P < 0.05 \) compared with segments with coronary artery lumen reduction of \(< 75\% \)). Using the prospectively defined criteria negative \( \Delta S_I \) as a marker for significantly reduced perfusion, the sensitivity and specificity of BOLD-MRI was 73% and 56%, respectively. The positive predictive value was 26%, whereas the negative predictive value was 91%. The ROC analysis revealed an optimal cutoff value for the SI change of 1.2% to discriminate between segments related to coronary arteries with \(< 75\% \) or \( \geq 75\% \) stenosis. Using this cutoff value, the following accuracy values were calculated: sensitivity, 88%; specificity, 47%; positive predictive value, 26%; and negative predictive value, 95%.

Comparison to SPECT Results/Nonselective

A similar pattern of SI change was observed in the pooled (mean of all 4 slices) adenosine 201 Tl-SPECT results, with a significant difference for segments with a degree of stenoses of \( > 75\% \) compared with all other segments (\(-8.34 \pm 3.81\% \) versus \(-0.16 \pm 1.01\%; \( P < 0.01 \)). The cutoff \( \delta \) of the ROC analysis for 201 Tl-SPECT was \(-5.4 \) and revealed a sensitivity of 72% and a specificity of 78%. The correlation coefficient to quantitative coronary angiography was \(-0.232 \) (\( P < 0.01 \)). There was no significant correlation between the observed SI changes in BOLD-MRI (\( \Delta S_I_{BOLD} \)) and those of 201 Tl-SPECT (%\( \Delta S_I_{Tl} \)) in this comparison (\( \Delta S_I_{BOLD} = 0.12 + 0.12 \times %\Delta S_I_{Tl}; R = 0.019; P = 0.14 \)). Figure 4 shows the ROC analysis of both BOLD-MRI related to quantitative coronary angiography and thallium SPECT related to quantitative angiography. The area under the curve for BOLD-MRI was 0.66, whereas that for SPECT was 0.73 (\( P = 0.61 \). NS). Visually, the curve shape may indicate a slightly higher sensitivity but lower specificity for BOLD-MRI to identify that high-grade stenosis is present, but the ROC analysis itself does not show any difference of diagnostic accuracy between BOLD-MRI and 201 Tl-SPECT.

Figure 4. ROC analysis of both BOLD-MRI and thallium SPECT as related to quantitative coronary angiography. The area under the curve was 0.66 for BOLD-MRI and 0.73 for thallium SPECT (\( P = \text{NS} \)).
Thus, our findings could be explained by an abnormality of microvascular myocardial perfusion, which is known in segments of patients with coronary heart disease even in the absence of any relevant stenoses of subepicardial coronary arteries.11,12 This could also explain the low specificity we encountered. This may only be relevant for detecting severe stenoses and not for detecting coronary artery disease. Furthermore, a higher specificity profile is expected, with technical developments aiming at reducing artifacts related to local field homogeneity that could be mistaken for myocardial ischemia. Nevertheless, even with its current diagnostic performance of limited specificity but high sensitivity, BOLD-MRI would be helpful in excluding coronary artery disease in certain clinical settings, such as in patients with a low or moderate pretest probability, for example, to justify pharmacological primary prevention in yet asymptomatic patients.

BOLD SI is not only altered by blood volume and hemoglobin oxygenation but also by blood flow.5,13,14 Thus, analyzing SI without simultaneous measurements of blood flow and volume does not render specific information on the relevance of each of these factors influencing SI. The underlying physiology of myocardial ischemia, however, goes along with a parallel drop of blood flow, volume, and tissue oxygenation.15 Thus, from a clinical point of view, the multifactorial pattern of the SI change does not affect the conclusion.

We found that BOLD-MRI compared favorably with thallium SPECT in our patients. The techniques, however, differ in what they show. BOLD-MRI reflects blood flow, blood volume, and hemoglobin oxygenation on a microvascular level, whereas thallium SPECT counts the actual entry of thallium atoms into the cells. The shape of their ROC curves differed slightly, suggesting that the techniques may show different aspects of ischemic pathology. Given the direct character of the BOLD-MRI observation of tissue oxygenation and the fact that BOLD-MRI would be far less intricate and less expensive than nuclear medicine techniques, this approach may develop to a useful clinical tool.

Study Limitations

Our observations are preliminary and are meant to show the feasibility of the technique. The prevalence of relevant coronary lesions in these patients was very high, and we did not correlate our findings with healthy control subjects. We used a single-slice approach, which seems inadequate for the detection of regional perfusion deficits; future studies using multiple slices should generate more robust results. When comparing SPECT to BOLD-MRI data, no correction for rotational shifts was performed; this may have increased the agreement between both methods. Standardized algorithms, however, are not available, and thus we decided not to additionally process the original data. Quantitative coronary angiography was our standard of truth, although this method only gives information on the lumen of the vessels and not on perfusion abnormalities of the related myocardium. We selected patients with exercise-induced angina with the reasoning that we were identifying stenoses of pathogenic significance in terms of producing angina pectoris. Thus, results may not apply to patients without overt symptoms.

We conclude that BOLD-MRI is a promising tool with sufficient sensitivity to detect significant coronary artery disease. To meet clinical needs, an enhanced spatial coverage, a more robust image quality, and additional validation are needed.

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