Relationship Between Regional Myocardial Oxygenation and Perfusion in Patients With Coronary Artery Disease
Insights From Cardiovascular Magnetic Resonance and Positron Emission Tomography

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Background—It is recognized that the interplay between myocardial ischemia, perfusion, and oxygenation in the setting of coronary artery disease (CAD) is complex and that myocardial oxygenation and perfusion may become dissociated. Blood oxygen level–dependent (BOLD) cardiovascular magnetic resonance (CMR) has the potential to noninvasively measure myocardial oxygenation, whereas positron emission tomography (PET) with oxygen-15 labeled water is the gold standard technique for myocardial blood flow quantification. Thus, we sought to apply BOLD CMR at 3 T and oxygen-15–labeled water PET in patients with CAD and normal volunteers to better understand the relationship between regional myocardial oxygenation and blood flow during vasodilator stress.

Methods and Results—Twenty-two patients (age, 62±8 years; 16 men) with CAD (at least 1 stenosis ≥50% on quantitative coronary angiography) and 10 normal volunteers (age, 58±6 years; 6 men) underwent 3-T BOLD CMR and PET. For BOLD CMR, 4 to 6 midventricular short-axis images were acquired at rest and during adenosine stress (140 μg/kg/min). Using PET with oxygen-15–labeled water, myocardial blood flow was measured at baseline and during adenosine in the same slices. BOLD images were divided into 6 segments, and mean signal intensities calculated. Taking ≥50% stenosis on quantitative coronary angiography as the gold standard, cutoff values for stress myocardial blood flow (<2.45 mL/min/g; AUC, 0.83) and BOLD signal intensity change (<3.74%; AUC, 0.78) were determined to define ischemic segments. BOLD CMR and PET agreed on the presence or absence of ischemia in 18 of the 22 patients (82%) and in all normal subjects. On a per-segment analysis, 40% of myocardial segments with stress myocardial blood flow below the cutoff of 2.45 mL/min/g did not show deoxygenation, whereas 88% of segments with normal perfusion also had normal oxygenation measurements.

Conclusions—Regional myocardial perfusion and oxygenation may be dissociated, indicating that in patients with CAD, reduced perfusion does not always lead to deoxygenation. (Circ Cardiovasc Imaging. 2010;3:32-40.)

Key Words: blood-oxygen level dependent ■ ischemia ■ myocardial blood flow ■ microvascular dysfunction

Positron emission tomography (PET) is the most extensively validated clinical modality for the absolute quantification of regional myocardial blood flow (MBF).1–4 Coronary flow reserve (CFR), defined as the ratio of MBF during near maximal vasodilation and basal MBF, has been proposed as a functional index of the severity of coronary artery stenosis.5 However, CFR can vary substantially in patients with coronary stenoses of apparent comparable severity.6,7

Moreover, myocardial oxygen demand can vary and may, for example, be downregulated in chronically ischemic myocardium along with a reduction in metabolism and ATP consumption.8 Cardiac tissue deoxygenation may be a useful complement to perfusion measurements, more closely reflecting the imbalance between oxygen demand and supply, which is characteristic of ischemic heart disease. The measurement of coronary sinus oxygen saturation has been used to detect...
global myocardial ischemia. However, this method is invasive, precludes serial assessment over time and, furthermore, does not allow direct comparison of regional myocardial oxygenation levels.

Clinical Perspective on p 40

Elevated deoxyhemoglobin seen downstream into a territory subented by a stenotic coronary artery can be assessed by blood oxygen level–dependent (BOLD) cardiovascular magnetic resonance (CMR). Deoxyhemoglobin is paramagnetic and acts as a natural contrast agent, leading to signal loss in T2- and T2*-weighted sequences. Previous animal and human BOLD studies at 1.5 T using T2*-weighted sequences were fundamentally limited by the relatively small signal differences between normal and deoxygenated myocardial regions. A new T2-prepared steady-state free precession (SSFP) BOLD sequence gave promising results in animal models at 1.5 T. Implementation of this sequence at the higher field strength of 3 T, with the expected increase in signal-to-noise and contrast-to-noise ratios, should further improve the detection of BOLD signal intensity (SI) changes. If feasible in the clinical setting, oxygenation assessment by BOLD 3-T CMR would be an important adjunctive test to perfusion imaging in the functional evaluation of patients with chest pain syndromes and dyspnea, potentially offering mechanistic insights into states of myocardial hibernation, hypertrophy, and diseases of the coronary macrovasculature and microvasculature. A greater pathophysiological understanding of the underlying disease processes might enable the development of new therapies aimed at symptom relief and reducing disease progression.

Thus, the aim of this study was 2-fold: the primary aim was to characterize the relationship between regional oxygenation and perfusion in normal volunteers and patients with coronary artery disease (CAD). Our secondary goals were to perform an initial comparison of BOLD versus PET for diagnosing CAD and to establish a T2 prepared BOLD technique at 3 T.

Methods

Study Population

We recruited 10 normal volunteers (normal 12-lead ECG, no chest pain, no known CAD, negative family history, and no risk factors for CAD) and 24 consecutive patients with 1- or 2-vessel CAD recently documented on invasive coronary angiography. We excluded patients with 3-vessel disease to study the BOLD effect in both the ischemic and “remote to ischemia” myocardium. Other exclusion criteria were medical instability (preclusion transfer between hospitals), myocardial infarction in the preceding 3 months, and contraindications to MRI (metallic implants such as pacemakers, defibrillators, cerebral aneurysm clips, ocular metallic deposits, severe claustrophobia) or adenosine (second- or third-degree atrioventricular block, history of asthma). Patients not in sinus rhythm were also excluded from the study. All subjects gave written informed consent before participation and underwent CMR and PET imaging within 4 weeks. The study protocol was approved by the Research Ethics Committee of the 2 participating hospitals (John Radcliffe Hospital, University of Oxford and Hammersmith Hospital, Imperial College) and by the UK Administration of Radioactive Substances Advisory Committee. The study was conducted according to the guidelines of the Declaration of Helsinki.

Coronary Angiography

Less than 8 weeks before the CMR or the PET examination, all patients underwent invasive coronary angiography using standard techniques. Images of the coronary arteries were obtained in multiple projections avoiding overlap of side branches and foreshortening of relevant coronary stenoses.

CMR Protocol

CMR was performed on a 3-T system (TIM Trio; Siemens Medical Solutions, Erlangen, Germany). All participants were instructed to refrain from caffeine-containing drinks and food in the 24 hours preceding the study. Images were acquired with the patient supine, using anterior and posterior phased-array surface coils. For cine CMR, from standard pilot images, short-axis cine images covering the entire left ventricle were acquired using a retrospectively ECG-gated SSFP sequence (echo time, 1.5 ms; repetition time, 3 ms; flip angle, 50°). For BOLD-CMR, a single midventricular slice was acquired at mid-diastole using a T2-prepared ECG-gated SSFP sequence with the following parameters: repetition time/echo time, 2.86/1.43 ms; T2 preparation time, 40 ms; matrix, 168×192; field of view, 340×340 mm; slice thickness, 8 mm; and flip angle, 44°. Each BOLD image was obtained during a single breath-hold over 6 heart beats. A set of 4 to 6 images was acquired at rest and during the infusion of adenosine (140 μg/kg/min). The acquisition of stress BOLD images commenced at peak stress approximately 90 seconds after the initiation of adenosine infusion. If necessary, shimming and center frequency adjustments were performed before BOLD imaging to generate images free of off-resonance artifacts.

For delayed enhancement CMR, a bolus of 0.1 mmol/kg of body weight of a gadolinium-based contrast agent (Gadodiamide, Omniscan; GE Healthcare, Amersham, United Kingdom) followed by a 10-mL saline flush were administered through an intravenous cannula inserted into the antecubital fossa. Electrocardiographically gated images were acquired in long- and short-axis planes identical to those of the cine images by using a breath-hold T1-weighted segmented inversion-recovery turbo fast low-angle shot sequence previously described. Blood pressure was recorded by a vital signs monitor machine at baseline and at 1-minute intervals during stress.

PET Protocol

On a separate day, the study subjects underwent PET scanning with oxygen-15-labeled water at rest and during adenosine stress to measure resting and peak MBF and CFR. Similar to the CMR scan, all participants were instructed to refrain from caffeine-containing drinks and food in the 24 hours preceding the study. The PET studies were performed in a 3D imaging mode using a 962 (HR +) scanner (Siemens, Knoxville, Tenn). The scanning protocol has been described in detail previously. Briefly, a 20-minute transmission scan was performed and used for subsequent attenuation correction of all emission scans. Commencing after the background frame, an intravenous bolus of oxygen-15-labeled water (2.18 MBq/kg) was infused at a rate of 10 mL/min over a period of 20 seconds to measure MBF. The venous line was then flushed for another 2 minutes, and the following acquisition frame times were used: 14×5 seconds, 3×10 seconds, 3×20 seconds, and 4×30 seconds for a total scanning time of 350 seconds. Adenosine infusion (140 μg/kg/min) was then given for 7 minutes, and repeat PET scanning was performed during pharmacological stress testing. Blood pressure was recorded by an automatic cuff sphygmomanometer (DINAMAP, GE Medical Systems, Milwaukee, Wis) at 1-minute intervals, the ECG was monitored continuously throughout the procedure, and a 12-lead ECG was obtained at baseline and at 1-minute intervals during the infusion of adenosine.

Angiographic Data Analysis

The diagnostic x-ray angiogram served as the reference standard in defining the degree of coronary stenosis. Each myocardial segment was ascribed a coronary artery territory according to standard criteria previously described. The distribution of blood supply (right/left/codominant) was taken into account in the matching of coronary and
myocardial segments. Diameters of reference and stenotic coronary arteries were measured by computerized quantitative methods using the Quantcor Coronary Analysis software (Siemens Medical Solutions). The contrast-filled catheter was used for image magnification calibration. Significant CAD was defined angiographically as the presence of at least 1 stenosis of ≥50% diameter in any of the main epicardial coronary arteries or their branches with a diameter of ≥2 mm. Coronary collaterals were graded according to the Cohen-Rentrop method as grade 0 (no filling of any collateral vessel), grade 1 (filling of side branches of the artery to be perfused by collateral vessels without visualization of epicardial segments), grade 2 (partial filling of an epicardial artery by collateral vessels), or grade 3 (complete filling of an epicardial artery by a collateral vessel). Collateral grading was classified as poor collateral development when the collateral grade was 0 to 1 and as good collateral development when the grade was 2 to 3. The examiner was blinded to the CMR and PET examinations.

CMR Data Analysis

For each patient, using Argus software (version V4.3.1, Siemens AG), left ventricular (LV) volumes, ejection fraction, and mass were calculated by manually tracing the endocardial and epicardial contours in end-diastolic and end-systolic images as previously described. For BOLD analysis, QMass software (version 6.2.3, Medis, Leiden, The Netherlands) was used. Myocardial SI was measured after manually tracing the endocardial and epicardial contours. Each midventricular short-axis BOLD image was divided into 6 segments (inferior septum, anterior septum, anterior, anterolateral, inferolateral, and inferior) according to the middle-slice 6 segments of the American Heart Association 17-segment model. Signal intensities were calculated for resting and stress conditions by averaging signal measurements from images during rest and adenosine stress, respectively. In this cardiac gated sequence, variations of heart rate also affect the SI due to its effect on T1 relaxation, and the following equation was used for correction:

\[ S = S_0 \left(1 - e^{-\frac{T_1}{T}}\right) \]

with T1 = 1220 ms and \( \beta = 0.59 \) (determined empirically for this sequence), where \( S_0 \) is the measured SI, \( S \) is the corrected SI, and \( T \) is the image-dependent time between acquisitions of sections of k-space, governed by the heart rate. \( T \) is replaced by the R-R interval. The relative SI change was calculated as follows:

\[ \Delta SI (\%) = \frac{\text{Mean SI (stress)} - \text{mean SI (rest)}}{\text{Mean SI (rest)}} \times 100 \]

for delayed enhancement, qualitative (visual) analysis was performed. Analysis of the CMR data was performed by 1 operator, blinded to the clinical information, the angiographic findings, and the PET data. A second operator blinded to the clinical, PET, and angiographic data graded image quality and the presence of susceptibility or respiratory artifacts in all of the obtained BOLD images during stress and at rest. A 0 to 3 scale system was used: 0=no artifacts, 1=minor artifacts, 2=moderate artifacts but the scan still considered analyzable, and 3=minor artifacts,scan not analyzable. This operator also analyzed half of the BOLD-CMR scans (11 CAD patients and 5 normal volunteers randomly selected) to assess interobserver reproducibility.

PET Data Analysis

All PET data were analyzed by an operator who was blinded to the clinical information and the angiographic and CMR findings. The sinograms were corrected for attenuation and reconstructed using standard algorithms. Factor images describing tissue and blood distributions were generated by iterative reconstruction and subsequently analyzed with dedicated software running in MATLAB programming language (MathWorks Inc, Natick, Mass) as previously described. Sixteen regions of interest were drawn within the LV myocardium and projected onto the dynamic oxygen-15 water images to obtain tissue activity curves. A separate set of regions of interest was defined for the right ventricular cavity and the left atrium. Myocardial and blood time-activity curves were then generated from the dynamic image and fitted to a single-tissue compartment tracer kinetic model to give values of MBF (mL/min/g). The mid LV slice for PET analysis was coregistered with the BOLD short-axis image using anatomic landmarks (eg, the distance from the LV apex on the vertical long-axis view). To account for cardiac work load, we corrected resting MBF for the rate-pressure product (RPP), an index of myocardial oxygen consumption: MBF = (MBF/RPP) \times 10^3. CFR was calculated as the ratio of MBF during adenosine-induced hyperemia to MBF at rest corrected for RPP.

Statistical Analysis

Data analysis was performed with commercially available software packages (SPSS version 15.0 for Windows; SPSS, Inc, Chicago, Ill; Medcalc version 9.6.4.0, Mariakerke, Belgium; and SAS version 9.1, SAS Institute, Cary, NC). The \( \chi^2 \) test or Fisher exact test were used to compare discrete data as appropriate. The measurements resulting from the PET and CMR scans were analyzed as continuous variables using PROC MIXED (mixed effects model) in SAS 9.1. The measurements of the 6 segments are repeated measurements within patients that are correlated, and this was taken into account in the analyses. The variables were assumed to be normally distributed. There is some evidence of the distributions being slightly skewed toward higher values, which could suggest a log transformation, but this is not possible where there were negative values (BOLD SI change). Paired \( t \) tests were used to compare the hemodynamic response of the patients during the CMR and the PET examinations. Receiver-operating characteristic (ROC) curve analyses were performed to define stress MBF and BOLD change in SI cutoff values that identify with the best combination of sensitivity and specificity the segments subtended by stenosed vessels. ROC curve analyses were also used to compare the diagnostic accuracy of BOLD CMR against PET and to define a stress MBF cutoff value below which deoxygenation occurs. Agreement for the identification of ischemic segments by BOLD CMR and PET was assessed by means of \( \kappa \) statistics. The relationship between the BOLD SI change, perfusion measurements, and the degree of coronary stenoses was investigated by calculation of Spearman rank correlation coefficient (\( r_s \)). Interobserver reproducibility of BOLD SI measurements was assessed by using the Bland-Altman method. Neither the ROC analyses nor the correlation analyses took into account multiple measurements (remote, stenosed regions) within patients. Statistical tests were 2-tailed, and a probability value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Study Population

Of the 24 CAD patients recruited, 22 completed the study protocol. One patient was claustrophobic and did not complete the CMR scan, and another patient could not tolerate the adenosine infusion during the PET scan. All 10 normal volunteers successfully completed the study protocol. Table 1 outlines the baseline characteristics of our study cohort. In the 22 patients with complete PET and CMR data, invasive coronary angiography demonstrated 18 patients with single-vessel and 4 patients with 2-vessel disease. Fourteen CAD patients had >70% stenoses on quantitative coronary angiography; 6 patients had totally occluded arteries but only 2 showed good collateral development. In terms of the anatomic location of the coronary stenoses, 12 (46%) were in the left anterior descending coronary artery, 4 (15%) in the left circumflex coronary artery, and 10 (39%) in the right coronary artery. Based on the coronary anatomy, of the 132 myocardial segments, 59 were subtended by significantly stenosed vessels (stenosed segments), whereas 73 segments were supplied by vessels with minimal or no disease (remote segments). A third group of myocardial segments (n=60) from normal volunteers was labeled as “normal” segments. Both
Table 1. Baseline Characteristics of the Cohort

<table>
<thead>
<tr>
<th>Risk factors for CAD</th>
<th>CAD Patients (n=22)</th>
<th>Normal Volunteers (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16 (73)</td>
<td>6 (60)</td>
<td>0.68</td>
</tr>
<tr>
<td>Age, y</td>
<td>62±8</td>
<td>58±6</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84±17</td>
<td>74±14</td>
<td>0.13</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170±10</td>
<td>174±9</td>
<td>0.34</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28±5</td>
<td>25±4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 2. Hemodynamic Data at Rest and During Adenosine Infusion for the Entire Population Studied (Normal Volunteers and CAD Patients)

<table>
<thead>
<tr>
<th>CMR Scan</th>
<th>PET Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest MBF</td>
<td>Stress MBF</td>
</tr>
<tr>
<td>1.05 (0.03)</td>
<td>0.94 (0.03)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. *P<0.05 for comparison between hemodynamic parameters at rest and stress (CMR scan).
†P<0.05 for comparison between hemodynamic parameters at rest and stress (PET scan).

MBF and CFR
Table 3 shows resting MBF, hyperemic MBF, and CFR (corrected for RPP) in the 3 groups of myocardial segments. The slight difference in resting MBF between normal, remote, and stenosed segments disappeared when correction for RPP was applied. Thus, corrected resting MBF measurements were similar in all 3 groups. In contrast, hyperemic (stress) blood flow was significantly reduced in segments subtended by stenosed arteries compared with normal segments. Remote segments had intermediate stress MBF measurements, falling

Table 3. Means and Differences (SEs) From the Mixed Model Analysis of the PET and CMR Measurements on 10 Normal Volunteers and 22 CAD Patients

<table>
<thead>
<tr>
<th>Type of segments</th>
<th>Normal Volunteers (n=60)</th>
<th>CAD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal MBF</td>
<td>0.11 (0.04)</td>
<td>-0.02 (0.04)</td>
</tr>
<tr>
<td>Remote MBF</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Stenosed MBF</td>
<td>-0.10 (0.06)</td>
<td>-0.01 (0.06)</td>
</tr>
<tr>
<td>Normal CFR</td>
<td>0.83 (0.15)</td>
<td>0.71 (0.15)</td>
</tr>
<tr>
<td>Remote CFR</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stenosed CFR</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Normal BOLD SI</td>
<td>7.07 (1.55)</td>
<td>6.52 (1.65)</td>
</tr>
<tr>
<td>Remote BOLD SI</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Stenosed BOLD SI</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CAD patients and normal volunteers had normal LV systolic function (Table 1). LV mass and maximal wall thickness showed no differences in CAD and normal volunteers. Although 4 CAD patients had a clinical history of myocardial infarction, only 2 had evidence of previous subendocardial infarction (25% to 50% transmural extent scar) on late gadolinium images in a total of 3 segments in the same midventricular slice corresponding to the BOLD image. Conversely, no patient without a clinical history of myocardial infarction had any evidence of scar on late gadolinium images.

Hemodynamic Measurements
Although the duration of adenosine infusion was significantly longer for the PET scan (420 seconds versus 300 seconds for the CMR scan, P<0.001), there was no difference between the 2 scans in the subsequent hemodynamic response (Table 2). ECG monitoring during the infusion of adenosine for the PET scan demonstrated significant ST depression in 11 CAD patients (50%) and in 1 normal volunteer (10%).
between those of the normal and stenosed groups (Figure 1). Similarly, CFR measurements differed significantly among the 3 groups of myocardial segments, with stenosed segments showing the lowest values and normal segments the highest.

**Changes in BOLD SI**

BOLD SI change values are presented in Table 3. The 3 groups of myocardial segments showed significant differences in the BOLD SI change (Figure 1). Segments subtended by significantly stenosed vessels showed essentially no change in SI during stress compared with segments in normal volunteers, which showed a significant mean 17% increase. Similar to hyperemic MBF and CFR, segments remote to ischemia had a significant BOLD SI change that was intermediate between those of the normal and stenosed groups. Figure 2 shows representative BOLD images from a patient with significant right CAD (dominant) and a normal volunteer. In the example shown, the normal volunteer demonstrated a BOLD SI rise of >10% in all segments. Similarly, all myocardial segments showed peak hyperemic blood flow values above 3.0 mL/min/g. In contrast, the patient had a drop in SI in the inferior, inferoseptal, and inferolateral segments of the left ventricle, but all other territories showed significantly increased BOLD signal. The deoxygenated regions had significantly impaired blood flow measurements as shown on the PET polar map.

**Relationship Between BOLD SI Changes and PET Myocardial Perfusion Measurements**

Taking quantitative coronary angiography as the gold standard, a cutoff value of stress MBF ≥2.45 mL/min/g identified segments subtended by significantly stenosed vessels with 79% sensitivity and 84% specificity (area under the ROC curve, 0.83±0.03, P<0.001). Similarly, a change in BOLD-SI after stress of <3.74% defined stenosed segments.
with 67% sensitivity and 88% specificity (area under the ROC curve, 0.78 ± 0.03, \( P < 0.001 \)). If at least 1 segment within the territory of a coronary artery was classified as ischemic according to these cutoff values, BOLD-CMR or PET was regarded as positive for that region. Per-subject analysis showed agreement between BOLD-CMR and PET regarding the presence or absence of CAD in 18 of the 22 patients (82%). The agreement was complete for normal volunteers (100%). Thus, overall, the 2 techniques showed good agreement on a per-subject basis. Per-segment analysis demonstrated that BOLD-CMR had very good specificity (88%) but moderate sensitivity (60%) to identify ischemic segments against PET as the gold standard. In other words, 40% (27 of 67) of myocardial segments with stress MBF below this cutoff value did not show deoxygenation. In contrast, 88% (110 of 125) of myocardial segments with normal perfusion (>2.45 mL/min/g) had also normal oxygenation. By applying a higher cutoff of >70% stenosis on quantitative coronary angiography, ROC analysis suggested a cutoff value of <2.45 mL/min/g for stress MBF (sensitivity, 89%; specificity, 85%) and <3.69% for BOLD SI change (sensitivity, 81%; specificity, 89%). In addition, segmental analysis with PET as the gold standard showed an improvement in sensitivity (69% for >70% stenosis versus 60% for >50% stenosis) and specificity (92% for >70% stenosis versus 88% for >50% stenosis) for BOLD. There was moderate agreement between BOLD-CMR and PET regarding the classification of myocardial segments as ischemic or not (κ = 0.50). A significant negative correlation was demonstrated between the severity of stenosis and either BOLD SI change \( (r_s = -0.52, P < 0.001) \) or stress MBF \( (r_s = -0.58, P < 0.001) \).

**BOLD CMR Image Quality and Interobserver Variability**

BOLD image quality was graded as very good with a mean score of 0.6 for rest images and 1.2 for stress (overall mean BOLD image quality score, 0.9). Minor off-resonance artifacts were reported in 9 subjects (7 CAD patients and 2 normal volunteers). The anterior wall (6 subjects) at the heart-lung interface was the most common place for these artifacts, whereas in 3 subjects, the artifact was present in the inferior wall. No scan was graded as nonanalyzable because of artifacts. Figure 4 shows an example of a BOLD CMR scan with a major off-resonance artifact in the anteroseptal wall that disappeared after shimming. The reproducibility of BOLD SI measurements was excellent, with a coefficient of variation of 3.3% for rest, 3.8% for stress images, and 3.0% for SI change measurements (Figure 5).

**Discussion**

The main findings of this study are: BOLD imaging with a T2-prepared SSFP sequence at 3 T is feasible, with good image quality in the clinical setting. Overall, perfusion and oxygenation assessment showed good agreement on a per-subject comparison. However, according to the cutoff value of stress MBF <2.45 mL/min/g, per-segment analysis revealed that regional myocardial perfusion and oxygenation...
were dissociated in a significant proportion of myocardial segments in patients with CAD. Interestingly, 40% of myocardial segments with impaired hyperemic blood flow demonstrated normal oxygenation measurements during stress. In contrast, most segments (88%) with peak hyperemic blood flow above the cutoff value of 2.45 mL/min/g also had normal oxygenation on BOLD imaging. This demonstrates that in CAD, reduced perfusion does not always lead to deoxygenation, whereas normal perfusion is usually associated with normal oxygenation.

It is tempting to speculate that the normal oxygenation measurements seen in 40% of segments with impaired perfusion indicate the absence of true ischemia in these territories despite reduced regional blood flow. An alternative explanation for the dissociation between perfusion and oxygenation seen in our study could be that this might reflect an impaired sensitivity of BOLD-CMR against PET as the gold standard to detect ischemia. However, it should be borne in mind that the relationship between regional MBF and epicardial CAD is multifaceted, and oxygenation may reflect ischemic changes better than perfusion. Our findings indicate that whereas conceptually, impairment of both perfusion and oxygenation occurs early in the ischemic cascade, it may not always occur simultaneously in the CAD cohort, and it is therefore conceivable that the addition of oxygenation assessment (using BOLD-CMR) to the noninvasive imaging armamentarium will better identify functionally significant coronary stenoses.

We chose to validate BOLD-CMR against PET with oxygen-15–labeled water, which is the ideal perfusion tracer because it is metabolically inert and freely diffusible across capillary and sarcolemmal membranes. Thus, it has a high time resolution and equilibrates rapidly between the vascular and extravascular spaces after intravenous injection, and its uptake by the myocardium does not vary despite wide variations in flow rate. The tracer kinetic model for quantification of MBF with oxygen-15–labeled water has been validated in animals against the radiolabeled microsphere gold standard over a wide flow range, and its reproducibility has been tested in humans.

Interestingly, the BOLD-CMR SI during hyperemia in “remote to ischemia” segments in CAD patients was “intermediate” compared with stenosed and normal segments. A similar behavior of hyperemic MBF was found using PET in our study and has also been described in previous PET studies on patients with single-vessel CAD, probably reflecting the presence of diffuse microvascular dysfunction. The ability of BOLD CMR to detect microcirculatory changes in noncardiac tissue is also supported by animal studies. Dharmakumar et al showed that BOLD-CMR is capable of detecting oxygen-sensitive SI changes in 2 microcirculation districts, the kidney cortex and the skeletal muscle of rabbits. One previous attempt to compare BOLD imaging with PET using nitrogen-13–labeled ammonia as flow tracer in patients with 3-vessel disease was fundamentally limited by the use of 0.95 T CMR, a very low magnetic field strength for this technique. Hence, differentiation between signal changes and noise levels proved problematic, and comparison with our results is difficult in the absence of an internal reference territory and of a normal control group.

It is likely that both MBF and myocardial blood volume affect the BOLD signal, although it is difficult to discriminate the individual effect of each component. Previously published animal studies have compared the BOLD effect with microsphere-measured blood flow and found a very good correlation between oxygenation and perfusion measurements. Similarly, we found a significant correlation between BOLD signal changes and stress MBF measurements by PET. As expected, the correlation was weaker because of the dissociation that we saw between oxygenation and perfusion in CAD patients. Moreover, animal studies had the advantage of a nearly simultaneous acquisition of BOLD and microsphere administration. In the clinical setting,
Friedrich et al\textsuperscript{12} compared BOLD T2* SI changes with thallium single-photon emission computed tomography in patients with CAD and found a modest but significant correlation between BOLD CMR and single-photon emission computed tomography data.

This is the first clinical study to report on the use of a T2-prepared SSFP sequence in humans (either CAD patients or volunteers) for BOLD imaging at 3 T, and, as such, we cannot compare our results directly with prior work. The mean 17% SI rise that we found in normal volunteers is smaller compared with that found by Fieno et al\textsuperscript{11} in the canine model (average 28% increase). However, the smaller increase found in our study, notwithstanding that we used a higher field strength, is probably explained by the fact that Fieno et al used selective intracoronary infusion of adenosine in sedated animals, with a higher effective dose of vasodilator and less reflex sympathetic activation. More recently, Dhar-makumar et al\textsuperscript{10} reported on an SSFP-based (but not T2 prepared) sequence in animal studies at both 1.5 T and 3 T. These experiments demonstrated that SSFP-based myocardial BOLD sensitivity is substantially greater at 3 T (2.5-fold increase compared with 1.5 T). Our study extends these observations to a clinical setting. With careful prescanning preparation (shimming and center frequency adjustments), we were able to generate good-quality images, and only a minority of our BOLD images had minor off-resonance artifacts.

This study was not designed to investigate the diagnostic performance of BOLD CMR compared with PET perfusion imaging. However, the recent concerns over gadolinium contrast safety and nephrogenic systemic fibrosis in patients with severe renal disease\textsuperscript{31} make any contrast-free CMR technique that is able to assess the functional status of CAD an attractive alternative to first-pass perfusion imaging for such patients. Our data indicate that BOLD-CMR has very good specificity but only moderate sensitivity compared with PET perfusion imaging. In other words, more than one third of myocardial segments with stress MBF below the cutoff of 2.45 mL/min/g show normal oxygenation, 40% of segments with impaired hyperemic blood flow show no evidence of deoxygenation. Additional studies are needed to establish the diagnostic performance of BOLD CMR in patients with suspected CAD and to determine whether deoxygenation or reduced perfusion are more powerful predictors of clinical events. BOLD CMR imaging with a T2 SSFP sequence at 3 T is feasible in the clinical setting with minor problems in image quality from off-resonance artifacts.

**Conclusions**

Regional myocardial perfusion and oxygenation are dissociated in a significant proportion of segments in patients with CAD: Although most myocardial segments with peak hyperemic blood flow above the cutoff of 2.45 mL/min/g show normal oxygenation, 40% of segments with impaired hyperemic blood flow show no evidence of deoxygenation. Additional studies are needed to establish the diagnostic performance of BOLD CMR in patients with suspected CAD and to determine whether deoxygenation or reduced perfusion are more powerful predictors of clinical events. BOLD CMR imaging with a T2 SSFP sequence at 3 T is feasible in the clinical setting with minor problems in image quality from off-resonance artifacts.

**Acknowledgments**

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This study was not designed to investigate the diagnostic performance of BOLD CMR compared with PET perfusion imaging. However, the recent concerns over gadolinium contrast safety and nephrogenic systemic fibrosis in patients with severe renal disease\textsuperscript{31} make any contrast-free CMR technique that is able to assess the functional status of CAD an attractive alternative to first-pass perfusion imaging for such patients. Our data indicate that BOLD-CMR has very good specificity but only moderate sensitivity compared with PET perfusion imaging. In other words, more than one third of myocardial segments with stress MBF below the cutoff of 2.45 mL/min/g did not show deoxygenation. In contrast, the specificity of BOLD CMR is high, which reflects the excellent image quality allowed by SSFP images, which, after shimming and frequency adjustments, can be relatively free from off-resonance artifacts at 3 T. An interesting question our study raises is whether deoxygenation or impaired perfusion during stress is the better predictor of prognosis/ischemic events in patients with suspected CAD. We speculate that deoxygenation reflects ischemia more directly than perfusion and might therefore be the more powerful index, but larger-scale clinical studies are needed to address this important issue.

**Limitations**

One of the main limitations to this study is that we only used a single midventricular short-axis slice for BOLD imaging. Thus, the myocardium was only partially visualized, and significant myocardial ischemia might have been missed. However, the principal aim of this study was to study the pathophysiological relationship between deoxygenation and perfusion and to validate the BOLD technique against an established method for quantification of myocardial perfusion such as PET, rather than to assess the diagnostic performance of BOLD CMR for detecting CAD. Another limitation is that we used quantitative coronary angiography to define the stenosed segments. However, angiography, if not accompanied by other measurements such as fractional flow reserve, provides only anatomic information, which is not always translated to functional significance. Moreover, it does not take into account disease of the microcirculation that can affect the BOLD signal, as demonstrated by the intermediate values of the remote segments in CAD patients. Last, the BOLD SI changes that we saw are not sufficient to be identified visually. Hence, quantitative assessment of SI with manual contouring of the myocardium is necessary, which is time and labor intensive.

**Disclosures**

None.

**References**

The impairment of myocardial oxygenation during stress has not been traditionally described as part of the continuum of events that characterize the ischemic cascade. However, ischemia is classically defined as the mismatch between oxygen supply and demand at stress. We used positron emission tomography to measure regional myocardial perfusion (absolute myocardial blood flow) and cardiovascular magnetic resonance to assess regional myocardial oxygenation in patients with known coronary artery disease and normal volunteers. Our findings indicate that whereas conceptually, impairment of both myocardial blood flow and myocardial oxygenation occurs early in the ischemic cascade, it may not always occur simultaneously in coronary artery disease. We therefore speculate that the addition of oxygenation assessment using blood oxygen level–dependent cardiovascular magnetic resonance to the noninvasive imaging armamentarium will better identify functionally significant coronary stenoses. Finally, given the recent concerns over gadolinium contrast safety in patients with severe renal disease, the assessment of myocardial oxygenation with blood oxygen level–dependent cardiovascular magnetic resonance might be an attractive alternative to first-pass perfusion imaging in such patients.
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