Noninvasive imaging approaches that can rapidly assess an ongoing ischemia can be of great value in managing patients with clinically significant coronary artery disease. Although several imaging approaches exist for the identification of myocardial territories supplied by stenotic coronary arteries, generally all available imaging methods require provocative stress and most also require exogenous contrast media. The most desirable imaging approach is one that can noninvasively and rapidly identify ischemic territories before the onset of tissue-specific changes (development of edema or necrosis) and can permit the assessment of functional/volumetric status while minimizing patient discomfort.

Methods and Results—CP-BOLD, standard cine, and T2-weighted images were acquired in canines (n=11) at baseline and within 20 minutes of ischemia induction (severe left anterior descending stenosis) at rest. After 3 hours of ischemia, left anterior descending stenosis was removed, and T2-weighted and late-gadolinium-enhancement images were acquired. From standard cine and CP-BOLD images, end-systolic and end-diastolic myocardium was segmented. Affected and remote sections of the myocardium were identified from postperfusion late-gadolinium-enhancement images. Systolic-to-diastolic ratio (S/D), quotient of mean end-systolic and end-diastolic signal intensities (on CP-BOLD and standard cine), was computed for affected and remote segments at baseline and ischemia. Ejection fraction and segmental wall thickening were derived from CP-BOLD images at baseline and ischemia. On CP-BOLD images, S/D was >1 (remote and affected territories) at baseline; S/D was diminished only in affected territories during ischemia, and the findings were statistically significant (ANOVA, post hoc P<0.01). The dependence of S/D on ischemia was not observed in standard cine images. Computer simulations confirmed the experimental findings. Receiver-operating characteristic analysis showed that S/D identifies affected regions with performance (area under the curve, 0.87) similar to ejection fraction (area under the curve, 0.89) and segmental wall thickening (area under the curve, 0.75).

Conclusions—Preclinical studies and computer simulations showed that CP-BOLD cardiovascular magnetic resonance could be useful in detecting myocardial ischemia at rest. Patient studies are needed for clinical translation. (Circ Cardiovasc Imaging. 2013;6:311-319.)

Key Words: acute coronary syndrome ■ BOLD MRI ■ coronary artery disease ■ ischemia

Previous studies have shown that an ongoing ischemia may be detected with cardiovascular magnetic resonance (CMR) on the basis of stress perfusion and changes in functional indexes. More recently, it has been shown that myocardial edema may be used as a marker of ongoing ischemia using animal models1 and patients.2 Although the edema approach eliminates the need for provocative stress, both approaches require separate acquisitions for accurate assessment of functional indexes. In this work, we propose and test a new CMR approach for the rapid assessment of myocardial ischemia. The proposed method is based on cardiac phase (CP)–resolved steady-state free-precession (SSFP) magnetic resonance signal changes originating primarily from alterations in blood oxygen saturation (%HbO2) and secondarily...
from changes in regional myocardial blood volume (MBV) in the myocardial territory supplied by a stenotic artery. Because the proposed approach can generate functional and tissue-specific indexes in 1 acquisition, the proposed approach can provide opportunities to rapidly determine the presence and territory of myocardial ischemia.

It is known that MBV is a function of CP, increasing during diastole and decreasing during systole, and that MBV directly determines the oxygen extraction by cardiomyocytes. Thus, MBV and %HbO2 are expected to be different between systole and diastole. Hence, under normal (healthy) conditions, one expects the MBV and oxygen extraction to be maximal during diastole and minimal during systole. In addition to these effects, as MBV increases, each unit volume of ventricle (ie, each voxel in a myocardial image) contains a slightly higher proportion of blood and a correspondingly smaller proportion of myocardial tissue. Thus, even at a stable level of %HbO2, the number of deoxygenated hemoglobin molecules within a voxel increases as MBV increases. Furthermore, several studies have shown that with increasing grade of coronary stenosis, MBV in the myocardial territory supplied by a stenotic artery increases in systole, which is known that T1 of myocardium is dependent on blood volume and that T2 is dependent on blood oxygenation saturation. Because BOLD SSFP signals are approximately T1/T2 fraction (EF), wall thickening, and myocardial edema.

Investigate the effects of acute coronary occlusion on ejection fraction (EF), wall thickening, and myocardial edema. In addition, we hypothesized that the BOLD SSFP method can be used to detect the presence of coronary stenosis even at rest (ie, without pharmacological stress). Under conditions of coronary stenosis, the physiological changes in basal MBV and %HbO2 are expected to work synergistically to enhance the SSFP-based detection capacity of myocardial territories supplied by stenotic arteries. In this work, we test these hypotheses using a canine animal model of severe coronary artery stenosis and computer/numeric simulations. In particular, we examine whether the systolic-to-diastolic myocardial SSFP signal intensity ratio (S/D) is >1 in health and is diminished during ischemia. In addition, we investigate the effects of acute coronary occlusion on ejection fraction (EF), wall thickening, and myocardial edema.

Methods

Numeric Computer Simulations

To establish the theoretical foundation and to lend additional support to our hypothesis that MBV and %HbO2 synergistically contribute to CP-dependent myocardial BOLD SSFP signal changes, numeric simulations were performed with a 2-pool exchange model, with T2/1-weighted, it may be possible to capture the changes in MBV and %HbO2, changes between systole and diastole are expected to be different between myocardial territories supplied by healthy and stenotic coronary arteries.

CP-resolved blood oxygen level–dependent (BOLD) SSFP CMR might provide a unique opportunity to capture these physiological changes and hence assess ongoing ischemia. It is known that T1 of myocardium is dependent on blood volume and that T2 is dependent on blood oxygenation saturation.11 Because BOLD SSFP signals are approximately T2/1-weighted, it may be possible to capture the changes in MBV (via T1) and %HbO2 (via T2) in 1 acquisition. In particular, because coronary artery stenosis leads to an increased systolic MBV that is expected to be accompanied by decreases in %HbO2 (because of increased oxygen extraction), we hypothesized that the BOLD SSFP method can be used to detect the presence of coronary stenosis even at rest (ie, without pharmacological stress). Under conditions of coronary stenosis, the physiological changes in basal MBV and %HbO2 are expected to work synergistically to enhance the SSFP-based detection capacity of myocardial territories supplied by stenotic arteries. In this work, we test these hypotheses using a canine animal model of severe coronary artery stenosis and computer/numeric simulations. In particular, we examine whether the systolic-to-diastolic myocardial SSFP signal intensity ratio (S/D) is >1 in health and is diminished during ischemia. In addition, we investigate the effects of acute coronary occlusion on ejection fraction (EF), wall thickening, and myocardial edema.

Animal Protocol

Mongrel dogs (n=14; 5 female; weight, 20–25 kg) were studied under the protocols approved by the Institutional Animal Care and Usage Committee. Animals were acclimated for 7 days and were premedicated with buprenex (0.01–0.02 mg/kg IM or SQ), anesthetized with propofol (3.5–7.0 mg/kg IV), intubated, and placed on gas anesthesia with isoflurane (2%–5%) and oxygen (1 L/min) before surgery. Subsequently, dogs were ventilated with a Drager Narkomed 2A Anesthesia machine (Drager, Lubeck, Germany), and a left lateral thoracotomy was performed. Catheters were inserted into the descending aorta and the right and left atria and were routed so that they exited the body via the chest cavity. A magnetic resonance–compatible hydraulic occluder was placed around the left anterior descending (LAD) artery. An intercostal block was performed with bupivacaine (0.5%, 3 mg/kg SQ) and buprenex (0.01–0.02 mg/kg IM). The ribs, muscle, and subcutaneous layers were closed with sutures and were allowed to recover for 7 days before CMR studies. On the day of the CMR studies, dogs were fasted, sedated with innovar (fentanyl 0.4 mg/mL and droperidol 20 mg/mL IM), and anesthetized using propofol (3.5–7.0 mg/kg IV). Animals were intubated, placed on the CMR scanner table, and ventilated with a Narkomed Anesthesia machine, isoflurane (2%–3%), and oxygen (1 L/min at a rate of 12 to 15 breaths per minute). ECG, SpO2, end-tidal CO2, invasive blood pressure, and coronary Doppler flow monitoring were established. Severe LAD stenosis was created at the time of CMR studies by inflating the hydraulic occluder to reduce Doppler signals by 90% to 95% of baseline values, and the constancy of the Doppler signals was evaluated every 30 minutes. This stenosis was maintained for 3 hours, followed by reperfusion. After the final CMR studies, animals were euthanized with euthasol (1 cm3 /5 kg IV), hearts were excised, and myocardial slices were stained with triphenyltetrazolium chloride.

Imaging Protocol

All imaging studies were performed on a clinical 1.5-T MRI system (MAGNETOM Espree; Siemens Healthcare, Germany). Animals were positioned in feet-first right-anterior oblique position, and a surface coil was placed over the chest for signal reception. The study protocol is shown in Figure 1. After scout scans to localize the axes of the heart, whole-heart shimming was performed, and the shim values were held constant throughout the study. No imaging acceleration schemes were used, and built-in coil normalizations were performed to ensure signal homogeneity within the myocardium. In addition, breath-holds (mechanical suspension of the ventilator) were limited to no more than 25 seconds to avoid spontaneous breathing of the animals during the acquisition.

CP-BOLD SSFP Imaging

After scout scans, a breath-held, retrospectively gated, flow and motion-compensated 2-dimensional short-axis cine BOLD SSFP sequence was prescribed over the midventricle at rest (without and with severe LAD stenosis). Scan parameters were as follows: field of view 32 × 32 cm, matrix 256 × 256, slice thickness 7 mm, echo train length 12, temporal resolution 10 ms, spatial resolution 1.25 × 1.25 × 7 mm, and TR = 200 ms. Flow compensation was enabled, and the SSFP and BOLD SSFP images were acquired in a single breath-hold sequence. After the final CMR studies, animals were euthanized with euthasol (1 cm3 /5 kg IV), hearts were excised, and myocardial slices were stained with triphenyltetrazolium chloride.
of view, 240×145 mm²; spatial resolution, 1.2×1.2×8 mm³; readout bandwidth, 930 Hz per pixel; flip angle, 70°; TR/echo time (TE), 6.2/3.1 milliseconds; and temporal resolution, 37.5 milliseconds.

**Standard Cine SSFP Imaging**

Animals were also scanned under the same physiological conditions at rest with and without stenosis using a standard retrospectively gated, 2-dimensional cine SSFP sequence immediately before or after BOLD imaging. Scan parameters were as follows: field of view, 240×145 mm²; spatial resolution, 1.2×1.2×8 mm³; readout bandwidth, 930 Hz per pixel; flip angle, 70°; TR/TE, 2.5/1.3 milliseconds; and temporal resolution, 37.5 milliseconds. No parallel imaging was used, and coil normalization and shimming were performed as above.

**Edema Imaging**

T2 short-t inversion recovery images (matched to the BOLD imaging slices) were acquired at baseline, under LAD stenosis (<20 minutes of ischemia induction), and subsequent to reperfusion after 3 hours of ischemia with the following imaging parameters: TE of 64 milliseconds; TR, 2 R-R intervals (synchronized with every other heartbeat); TI, 170 milliseconds; echo train length, 15; echo spacing, 7.1 milliseconds; readout bandwidth, 235 Hz per pixel; and spatial resolution, 1.2×1.2×8.0 mm³. Edema images were acquired immediately after the cine acquisitions (12±2 minutes after stenosis) and after 3 hours of ischemia.

**Late-Gadolinium-Enhancement Imaging**

Late-gadolinium-enhancement (LGE) scans (matched to the BOLD imaging slice) were performed within 20 minutes of the induction of ischemia and 3 hours after the infliction of stenosis to determine the site of myocardial injury. The imaging protocol for LGE MRI is as follows: phase-sensitive inversion-recovery reconstruction with TurboFLASH readout²⁶; spatial resolution, 1.3×1.3×8 mm³; TE/TR, 3.9/8.2 milliseconds; TI, 200 to 220 milliseconds; flip angle, 25°; and readout bandwidth, 140 Hz per pixel.

**Image Analysis**

All SSFP studies were analyzed with custom MATLAB (The Mathworks, Inc) software developed in our laboratory. Endocardial and epicardial borders were manually traced for an image in systole, and the right ventricular groove was manually identified. The borders were propagated (tracked) automatically in all images of the cardiac cycle with a myocardial border tracking method.²⁴ Subsequently, the myocardium was further segmented automatically into 6 segments per image according to standard practice.²³ From the automatically estimated blood volume in the ventricular cavity over the full cine stack, end systole (ES) and end diastole (ED) were automatically identified as those having the minimum and maximum blood volumes, respectively. Using postreperfusion LGE images, a remote (noninfarcted territory) was identified on the edema-weighted images and used to determine edematous territories using a 2 standard deviation threshold criterion as before.²⁶

**S/D Ratios**

On the basis of presence of tissue damage on the LGE images acquired 3 hours after reperfusion, 2 regions of myocardial segments were identified on the BOLD SSFP and cine SSFP images: affected, that is, those affected by the LAD stenosis, and remote, typically in the left circumflex territory. The same regions (myocardial segments) were used to evaluate BOLD and cine SSFP signal changes under baseline or stenosis conditions. The average pixel intensity of a region was measured for each CP and recorded as a time series, which was subsequently smoothed by the use of a moving average filter of length 3. On the basis of the smoothed time series, the S/D of a region was defined as:

\[
\text{S/D} = \frac{\text{Regional average pixel intensity at ES}}{\text{Regional average pixel intensity at ED}},
\]

where ES and ED are as defined above. This process was repeated for the remote and affected regions under baseline and stenosis conditions on BOLD and standard cine images.

**Cardiac Function**

EF was estimated from BOLD SSFP images with the endocardial delineations used in the analysis described above. Myocardial wall thickening (WT) was estimated again from BOLD SSFP images using the myocardial delineations from the analysis described above by excluding papillary muscles and measuring the transmural length of the myocardium using 360 equally spaced radial chords in ES (WT at ES) and ED (WT at ED). For each of the 6 myocardial segments, the segmental WT (sWT), defined as the per-segment average of 100% [(WT at ES)−(WT at ED)]/(WT at ED), was computed.

**Statistical Analysis**

Data are reported as mean±SE. One-tailed t tests were used to test the null hypothesis that S/D was ≤1 for any region independently of condition. A 2-way repeated measures ANOVA was used to test the within-subject effects of region (2 categories: remote and affected) and condition (2 categories: baseline and ischemia), and their interaction on S/D, as derived from either BOLD or standard cine studies. The same test was used to assess the effects of region and condition on sWT measurements derived from BOLD studies. The identity of the canine used was as a fixed effect. Bonferroni post hoc tests were used when appropriate. A paired t test was used to test the null hypothesis that EFs at baseline and ischemia are equal. Receiver-operating characteristic analyses were performed to determine the diagnostic power of the proposed biomarker (S/D) in relation to EF and sWT using groupings of positive and negative diagnoses. Differences in area under the curve between receiver-operating characteristic curves were compared by use of the critical z ratio.²⁷ Normality of study data was tested by the Shapiro–Wilks and Kolmogorov–Smirnov tests to indicate the appropriateness of parametric testing. The significance level for all tests was set at P≤0.05. All analyses were performed with OriginPro (OriginLab Corp, version 8, Northampton, MA).

**Results**

Of the 14 animals, insufficient occluder fidelity (variable Doppler flow throughout the ischemia period) was evident in 3 animals, and results of these animals were excluded from further analysis. Overall, 11 animals were studied, and 22 BOLD and cine (baseline and ischemia), 33 edema-weighted (baseline, ischemia, reperfusion), and 22 LGE (during ischemia and after reperfusion) images were available for analysis. LGE studies (during ischemia) showed that no animal experienced infarction, whereas all LGE studies after reperfusion showed myocardial injury. All study data were found to follow normal distribution and are reported as mean±SE. For post hoc tests, least-square means and SEs of the comparison are shown when appropriate.

Figure 2 shows representative regional mean BOLD signal intensities from remote and affected regions under baseline (Figure 2A) and ischemia (Figure 2B), normalized to ED.
values, obtained from a canine study. During baseline conditions (Figure 2A), both regions have S/Ds >1 (1.1 and 1.07 for remote and affected, respectively). Under ischemia (Figure 2B), however, in this animal, the remote territory exhibited an S/D >1 (1.17). Conversely, the S/D for the affected (LAD) region was <1 (0.93), in line with the hypothesis that S/D values are diminished during ischemia. For the same animal (and corresponding myocardial territories), Figure 2C and 2D shows that the normalized regional mean signal intensities from a standard cine SSFP acquisition (which has minimal or no sensitivity to the BOLD effect) do not exhibit the same variation in S/D, as observed in Figure 2A and 2B.

Figure 3 shows ES and ED BOLD images and bull’s-eye plots of S/Ds derived from the ES and ED BOLD images, as well as the sWT of the myocardium at baseline and ischemia from the same animal in Figure 2. Observe that under baseline conditions, all regions of the myocardium exhibit high S/D (green). However, under ischemia, the affected regions corresponding to the LAD territory exhibit lower S/D (red), whereas all other regions remain green (S/D >1). Also note that the baseline sWT varies among regions and that, in the presence of ischemia, sWT is reduced. However, this reduction is not confined to the affected region, and in fact, remote regions also exhibit large deviations compared with their baseline values.

In Figure 4, edema-weighted and LGE images, as well as a gross histology (triphenyltetrazolium chloride) image acquired from the same animal in Figures 2 and 3, are shown. Note that edema seems to be absent at baseline and during early ischemia but is clearly present after reperfusion after a 3-hour ischemic period. Similarly, LGE images show that no enhancement is present in the early ischemic phase of the study but is clearly present after the 3-hour ischemic period followed by reperfusion and is confirmed by the gross histological triphenyltetrazolium chloride staining.

Our statistical analysis showed that EF was markedly reduced during ischemia compared with baseline (0.25±0.03 [ischemia] versus 0.45±0.03 [baseline]; P<0.001; Figure 5A). sWT measurements (Figure 5B) showed region to have a statistically significant effect (remote versus affected: 0.58 [remote] versus 0.43 [affected]; P<0.009) but not condition (0.58 [baseline] versus 0.42 [ischemia]; P=0.07). The interaction term and all post hoc statistical comparisons were not significant (remote: 0.66±0.08 [remote] versus 0.51±0.08 [affected]; ischemia: 0.51±0.08 [remote] versus 0.34±0.08 [affected]; remote: 0.66±0.08 [baseline] versus 0.51±0.08 [ischemia]; affected: 0.51±0.08 [baseline] versus 0.34±0.08 [ischemia]; all P=NS), indicating that wall thickness may vary across regions and that regional ischemia may affect sWT measurements in a global fashion. Subject effects were not statistically significant (P=1).

Figure 6 shows both simulated and experimental SSFP signal variations between ES and ED at baseline and ischemia.

Figure 2. Normalized regional mean steady-state free precession (SSFP) intensities obtained with cardiac phase–resolved blood oxygen level–dependent (CP-BOLD) and standard cine acquisitions. Regional mean SSFP intensities obtained with CP-BOLD acquisitions from affected and remote regions under baseline (A) and ischemia (severe left anterior descending [LAD] stenosis; B), normalized by the regional mean intensities at end diastole (shown with red circles) as a function of a nominal percentage of cardiac cycle. Similar signal profile from standard cine, under baseline (C) and ischemia (severe LAD stenosis; D), is also shown. In A through D, green circles indicate end systole. A line of identity (systolic-to-diastolic ratio=1) is also shown for reference.
under BOLD (Figure 6A) and standard cine acquisitions (Figure 6B). Simulations showed that during baseline S/D >1 and in the presence of ischemia S/D <1 (Figure 6A, theory). Statistical analysis (Figure 6A, experiments) showed that mean S/D values obtained from remote (1.13±0.025) and affected (1.05±0.016) regions under baseline conditions or from remote regions during ischemia (1.11±0.02) were likely >1 (P<0.05, t test). However, the same test showed that this did not hold for S/D values obtained from affected regions during ischemia (1.01±0.017). Furthermore, controlling for repeated measures, the ANOVA test found region to be a significant factor (1.12 [remote] versus 1.03 [affected]; P=0.001), whereas condition (1.09 [baseline] versus 1.06 [ischemia]) and interaction were not significant.

Post hoc tests found statistically significant differences in S/D between remote and affected (LAD) regions under ischemia (1.11±0.026 [remote] versus 1.01±0.026 [affected]; P=0.03) but not for other comparisons (baseline: 1.13±0.026 [remote] versus 1.05±0.026 [affected]; P=0.13; remote: 1.13±0.03 [baseline] versus 1.11±0.03 [ischemia]; P=1; and affected: 1.05±0.03 [baseline] versus 1.01±0.03 [ischemia]; P=1). Subject effects were not statistically significant (P≈1).

If a standard cine acquisition is used (Figure 6B, theory), in which the BOLD effect is expected to be minimal, simulations showed that ES and ED SSFP signal intensities are approximately equal at baseline and ischemia (ie, S/D ≈1).

The ANOVA test (Figure 6B, experiments) did not find any statistically significant effect for region (1.04 [remote] versus 1.02 [affected]; P=0.12), whereas condition (1.09 [baseline] versus 1.06 [ischemia]) and interaction were not significant.

Figure 3. Blood oxygen level–dependent end-systolic and end-diastolic images, circumferential polar plots (bull’s-eye) of systolic-to-diastolic ratios, and segmental wall thickening from a representative animal under baseline and ischemia (severe left anterior descending stenosis) are shown.

Figure 4. Edema-weighted (T2 short-τ inversion recovery [STIR]) and late-gadolinium-enhancement (LGE) images from the same animal as in Figure 3, obtained within 20 minutes of ischemia induction and 3 hours after reperfusion, and triphenyltetrazolium chloride (TTC) image confirming the infarct territory are shown. No edema (absence of elevation in T2-weighted signal) or infarction was observed within the 20 minutes of ischemia induction (left); after reperfusion (preceded by 3-hour ischemia), both edema and infarction were readily apparent in regions where systolic-to-diastolic ratio changes were observed during the early ischemic phase (Figure 3).
EF may be capable of discriminating between baseline and ischemia at rest (Figure 7A). The proposed method based on S/D achieves comparable performance with EF (area under the curve=0.87 versus 0.89) and is able to identify the affected territory solely through the use of BOLD images acquired during ischemia (Figure 7B). sWT (area under the curve=0.75) seems to underperform S/D; however, this difference was not statistically significant (z ratio=0.96; P=0.33).

Discussion

Recently, the use of CMR for evaluating myocardial ischemia has received significant attention.\(^{28,29}\) Several noninvasive imaging approaches have been proposed for the identification of ischemic territories, although these methods typically require provocative (exercise or pharmacological) stress.\(^{30,31}\) Although the edema approach is appealing, given that it is performed at rest and does not require contrast injections, it requires the appearance of edema within the ischemic period, which may be related to the time of onset of ischemia and may be limited by the lack of specificity of an ongoing ischemia or a recent reversible injury. In this work, we demonstrated a contrast-free CMR approach for rapidly assessing myocardial ischemia without provocative stress before the evolution of edema. The proposed method relies on the differences between systolic and diastolic BOLD SSFP signal intensities, attributable to changes in MBV and %HbO\(_2\), to determine the ischemic territory. In particular, we demonstrated that with ischemia, regional S/D values are significantly reduced, which may allow the detection of ischemic territories at rest. We also showed that the proposed approach could complement standard functional indexes, EF, and segmental WT for localizing ischemic territories. Hence, the deployment of cine BOLD MRI in place of standard cine MRI provides incremental improvement for the assessment of myocardial ischemia without resorting to provocative stress or the appearance of edema.

Our simulations and experimental findings demonstrate the capability of the proposed method to identify ischemic territories on the basis of CP-dependent BOLD signal changes under rest. These findings confirm our hypothesis that systolic and diastolic BOLD SSFP signal intensities should be different in the absence of ischemia and that such differences are marginalized in the presence of ischemia. In addition, consistent with the theoretical prediction, we found that when the BOLD effect is minimized (minimal TR, standard cine SSFP), the S/D of SSFP signal intensities was indifferent in the presence or absence of coronary artery stenosis. Because T1 effects are equally present in standard SSFP and BOLD SSFP acquisitions, it appears that the T2 effect (which is sensitive to changes in TR and is affected by changes in %HbO\(_2\)) is the dominant source of the observed effect.

More recently, it was shown that myocardial edema could be useful in identifying ischemic territories before the appearance of myocardial necrosis.\(^{30,32}\) Using canines, Abdel-Aty et al\(^{32}\) showed that the appearance of edema may be observed as early as 30 minutes after ischemic insult to the myocardium. In this study, we showed that S/D changes in the affected territories are apparent even before the appearance of edema. This suggests that the alterations in MBV and %HbO\(_2\), in response to coronary obstruction, precede intracellular edema, making the proposed approach more attractive as a very early marker of myocardial ischemia.

Although we observed the S/D to be significantly reduced of specificity of an ongoing ischemia or a recent reversible injury. In this work, we demonstrated a contrast-free CMR approach for rapidly assessing myocardial ischemia without provocative stress before the evolution of edema. The proposed method relies on the differences between systolic and diastolic BOLD SSFP signal intensities, attributable to changes in MBV and %HbO\(_2\), to determine the ischemic territory. In particular, we demonstrated that with ischemia, regional S/D values are significantly reduced, which may allow the detection of ischemic territories at rest. We also showed that the proposed approach could complement standard functional indexes, EF, and segmental WT for localizing ischemic territories. Hence, the deployment of cine BOLD MRI in place of standard cine MRI provides incremental improvement for the assessment of myocardial ischemia without resorting to provocative stress or the appearance of edema.

Our simulations and experimental findings demonstrate the capability of the proposed method to identify ischemic territories on the basis of CP-dependent BOLD signal changes under rest. These findings confirm our hypothesis that systolic and diastolic BOLD SSFP signal intensities should be different in the absence of ischemia and that such differences are marginalized in the presence of ischemia. In addition, consistent with the theoretical prediction, we found that when the BOLD effect is minimized (minimal TR, standard cine SSFP), the S/D of SSFP signal intensities was indifferent in the presence or absence of coronary artery stenosis. Because T1 effects are equally present in standard SSFP and BOLD SSFP acquisitions, it appears that the T2 effect (which is sensitive to changes in TR and is affected by changes in %HbO\(_2\)) is the dominant source of the observed effect.

More recently, it was shown that myocardial edema could be useful in identifying ischemic territories before the appearance of myocardial necrosis.\(^{30,32}\) Using canines, Abdel-Aty et al\(^{32}\) showed that the appearance of edema may be observed as early as 30 minutes after ischemic insult to the myocardium. In this study, we showed that S/D changes in the affected territories are apparent even before the appearance of edema. This suggests that the alterations in MBV and %HbO\(_2\), in response to coronary obstruction, precede intracellular edema, making the proposed approach more attractive as a very early marker of myocardial ischemia.

Although we observed the S/D to be significantly reduced in the setting of ischemia, it seems that the baseline S/D values vary throughout the myocardium and may not be uniform, as shown in Figure 6. These variations may be explained on the basis of phasic differences in coronary blood flow.\(^{33}\) Additional
Because the differences in S/Ds between nonischemic and ischemic segments from this study were ≥15%, additional improvements in sensitivity are expected to be necessary to extend this approach to investigate stable but significant coronary artery disease. Because 3-T BOLD SSFP is expected to yield an ≥3-fold increase in sensitivity to changes in myocardial %HbO₂, we anticipate further studies at 3 T to be of great value. In addition, it is expected that more advanced image registration and myocardial tracking methods that operate at the pixel level would further increase sensitivity and specificity.

The present study examined only the CP-resolved BOLD SSFP signal changes under severe (flow-limiting) acute stenosis. It would be useful to examine whether appreciable S/D signal differences can also be detected in the setting of clinically significant but stable (non–flow-limiting) coronary artery stenosis. We anticipate that S/Ds may be directly related to stenosis extent and that with increased sensitivity (eg, by imaging at 3 T), it may be possible to detect critically significant coronary artery disease, even when left ventricular function is within normal limits, without resorting to provocative stress. Should such changes be detectable, they could provide a truly noninvasive imaging paradigm for diagnosing ischemic heart disease.

Limitations
This is a pilot study investigating S/D changes using an oxygen-sensitive imaging sequence in the presence of coronary artery stenosis under rest in 11 animals. The proposed method remains to be validated in patients. Image processing methods that can rapidly and automatically segment and analyze CP-dependent myocardial BOLD images are also expected to be useful for the effective translation of the proposed approach into the clinical arena.

Because this study used a 2-dimensional flow-compensated CP-BOLD SSFP sequence, it is possible that through-plane motion of the heart may have an effect on the results. However, to limit the effect of through-plane motion on phase-dependent signal and to accurately segment the left ventricular myocardial wall, we only considered the midventricular section of the myocardium, where it is expected that such motion is significantly lower than the basal slices. In fact, standard cine imaging of the same animal under the same physiological conditions, typically

---

**Table. Grouping of Positive and Negative Diagnoses for the Different ROC Analysis**

<table>
<thead>
<tr>
<th>ROC Comparison</th>
<th>Imaging Biomarkers</th>
<th>Positive (+)</th>
<th>Negative (−)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ejection fraction</td>
<td>Ischemia</td>
<td>Baseline</td>
</tr>
<tr>
<td>B</td>
<td>Systolic-to-diastolic ratio, segmental wall thickening</td>
<td>Affected region during ischemia</td>
<td>Remote region during ischemia</td>
</tr>
</tbody>
</table>

ROC indicates receiver-operating characteristic.
acquired within 5 minutes of the CP-BOLD acquisition, did not show any statistically significant effects on systolic-to-diastolic differences between regions, lending further support that the contribution to signal changes from through-plane motion effects is insignificant. It is expected that with further pulse sequence development to extend the image acquisitions to 3 dimension, along with flow and motion compensation, potential through-plane effects can be minimized and would facilitate a smooth clinical translation of the proposed approach.

The 2-compartment model is expected to provide a reasonable approximation for the myocardial system, as demonstrated previously. Nevertheless, there may be some limitation to this model because it assumes that the spin exchange between the vascular and extravascular space is fast, which may not be fully accurate. Bauer et al.23 have suggested that the spin exchange in the myocardium may conform to the intermediate exchange regime, which can be a source that underestimates the T2 values and ultimately underestimates the S/D contrast between ischemic and nonischemic territories. In addition, the simulations do not use the actual MBV or myocardial %HbO2. In this work, simulations were performed to lend a mechanistic insight into the direction of signal changes in conventional and BOLD cine acquisitions as a result of modulations in systolic and diastolic MBV and myocardial %HbO2. A more accurate model would require one to take into account the random motion of spins (via Monte Carlo simulation), along with measured values for MBV and myocardial %HbO2. However, such details on the physical parameters that elucidate the CP-resolved changes in MBV and %HbO2 in disease and health are currently unavailable because of the lack of direct measurement tools.

In addition, this study did not evaluate the changes in S/D values in chronic infarcts. From the biophysical mechanisms and our simulation results, we anticipate that in the chronic phase, S/D will be 1 and will vary minimally across the cardiac cycle because the infarcted tissue would be replaced by fibrotic tissue. To the extent that fibrotic tissue receives blood from residual (spared from ischemia) or neovascular capillary beds, there would be some variation between systolic and diastolic signal intensities; however, such variations would be expected to be significantly lower than that in healthy myocardium. Hence, it is possible that S/D measurements alone cannot identify acute ischemic territories and that, in addition to estimating S/Ds, it may be important to rule out previous myocardial infarctions. Further studies are necessary to investigate the difference in S/D values between acute and chronic infarction.

Conclusions

Using a controlled canine model, we have provided the first evidence that it is possible to identify ischemic territories secondary to severe coronary artery stenosis on the basis of CP-resolved myocardial BOLD CMR without exogenous contrast agents or provocative stress before the evolution of myocardial edema. The proposed method may be valuable in determining the presence of ongoing ischemia in patients.

Sources of Funding

This work was supported by grants from National Institutes of Health/National Heart, Lung and Blood Institute (HL091898) and the American Heart Association (SDG 0735099 N).

Disclosures

Drs Dharmakumar and Li hold research grants from the National Institutes of Health/the National Heart, Lung and Blood Institute and receive research support from Siemens Healthcare. Dr Dharmakumar also holds a research grant from the American Heart Association. The other authors have no conflicts to report.

References

Detecting Myocardial Ischemia at Rest With CP-BOLD

The diagnosis of myocardial ischemia secondary to clinically significant coronary artery stenosis is typically performed with the induction of provocative (exercise or pharmacological) stress. However, provocative stress generally imparts discomfort to the patient, is associated with a small but significant number of adverse events, and is contraindicated in people with lung disorders and atrioventricular block. Hence, approaches that can provide diagnostic information without additional stress to the vulnerable patient are of great interest. Recent studies have shown that provocative stress may be obviated in cases of acute ischemia because the ensuing myocardial edema can be used as a marker of ischemia before tissue necrosis. In this study, using state-of-the-art cardiac phase–resolved blood oxygen level–dependent cardiovascular magnetic resonance and a controlled animal model, we demonstrate that it may be possible to detect an ongoing ischemia at rest even before the appearance of tissue-specific changes (eg, edema, necrosis), which typically occur downstream of the ischemic cascade. The proposed cardiovascular magnetic resonance method relies on the pathological alterations in the phasic changes of myocardial oxygenation and blood volume within the myocardial segments subtended by the stenotic coronary artery. Because our approach is capable of generating functional and tissue-specific indexes in 1 acquisition without requiring exogenous contrast media, we anticipate that cardiac phase–resolved blood oxygen level–dependent cardiovascular magnetic resonance can provide opportunities to rapidly and noninvasively assess myocardial ischemia at rest. Detecting the ischemic cascade at a very early stage can be of critical importance because it can facilitate successful patient management before the appearance of myocardial tissue damage.
Detecting Myocardial Ischemia at Rest With Cardiac Phase–Resolved Blood Oxygen Level–Dependent Cardiovascular Magnetic Resonance
Sotirios A. Tsaktaris, Xiangzhi Zhou, Richard Tang, Debiao Li and Rohan Dharmakumar

*Circ Cardiovasc Imaging*. 2013;6:311-319; originally published online December 18, 2012;
doi: 10.1161/CIRCIMAGING.112.976076

*Circulation: Cardiovascular Imaging* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/6/2/311

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

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

**Subscriptions:** Information about subscribing to *Circulation: Cardiovascular Imaging* is online at:
http://circimaging.ahajournals.org//subscriptions/