Quantification of Regional Myocardial Oxygenation by Magnetic Resonance Imaging
Validation With Positron Emission Tomography

Kyle S. McCommis, BS; Thomas A. Goldstein, MS; Dana R. Abendschein, PhD; Pilar Herrero, MS; Bernd Misselwitz, PhD; Robert J. Gropler, MD; Jie Zheng, PhD

Background—A comprehensive evaluation of myocardial ischemia requires measures of both oxygen supply and demand. Positron emission tomography (PET) is currently the gold standard for such evaluations, but its use is limited because of its ionizing radiation, limited availability, and high cost. A cardiac MRI method was developed for assessing myocardial oxygenation. The purpose of this study was to evaluate and validate this technique compared with PET during pharmacological stress in a canine model of coronary artery stenosis.

Methods and Results—Twenty-one beagles and small mongrel dogs without coronary artery stenosis (controls) or with moderate to severe acute coronary artery stenosis underwent MRI and PET imaging at rest and during dipyridamole vasodilation or dobutamine stress to induce a wide range of changes in cardiac perfusion and oxygenation. MRI first-pass perfusion imaging was performed to quantify myocardial blood flow and volume. The MRI blood oxygen level–dependent technique was used to determine the myocardial oxygen extraction fraction during pharmacological hyperemia. Myocardial oxygen consumption was determined by the Fick law. In the same dogs, $^{15}$O-water and $^{11}$C-acetate were used to measure myocardial blood flow and myocardial oxygen consumption, respectively, by PET. Regional assessments were performed for both MR and PET. MRI data correlated nicely with PET values for myocardial blood flow ($R^2=0.79$, $P<0.001$), myocardial oxygen consumption ($R^2=0.74$, $P<0.001$), and oxygen extraction fraction ($R^2=0.66$, $P<0.01$).

Conclusions—Cardiac MRI methods may provide an alternative to radionuclide imaging in settings of myocardial ischemia. Our newly developed quantitative MRI oxygenation imaging technique may be a valuable noninvasive tool to directly evaluate myocardial energetics and efficiency. (Circ Cardiovasc Imaging. 2010;3:41-46.)

Key Words: MRI ■ perfusion ■ ischemia ■ oxygen consumption

Adequate oxygenation is fundamental to myocardial health. The balance of oxygen supply (myocardial blood flow [MBF]) and oxygen demand (myocardial oxygen consumption [MVO$_2$]) is the central pathological tenet of myocardial ischemia. Conversely, luxuriant MVO$_2$ compared with level of cardiac work is indicative of reduced cardiac efficiency, a common finding in most forms of heart failure. Therefore, accurate measurements of the key components of myocardial oxygenation, including MBF, MVO$_2$, and fractional oxygen extraction (OEF), are needed to better understand the pathophysiology of these various disease processes. This knowledge may lead to new diagnostic strategies and could facilitate the evaluation of therapies designed to improve oxygen supply/demand imbalances or improve energy transduction.

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To date, positron emission tomography (PET) has been used to provide these measurements, with $^{15}$O-water to measure MBF and $^{11}$C-acetate to determine MVO$_2$. However, ionizing radiation, long scan times, limited availability, requirement of an on-site cyclotron, and high costs have limited the widespread use of PET for these purposes. Because of the physical half-life of the radiotracers and concerns about radiation exposure, measurements are typically limited to only 2 time points, such as rest and low-level catecholamine stress. Additionally, PET cannot assess myocardial blood volume (MBV), another important parameter of myocardial oxygen supply.

In contrast, MRI does not use ionizing radiation, requires relatively short scan times, is more readily available and at
lower cost, and is relatively fast and reproducible. Thus, it is optimal for serial assessments of myocardial oxygenation.

We have developed a variety of MRI techniques for evaluating MBF, MBV, OEF, and MVO2 through a combination of first-pass perfusion and blood oxygen level-dependent (BOLD) methods. In this study, we used these techniques to evaluate the regional changes in myocardial perfusion and oxygenation induced by an acute coronary artery stenosis at rest and during pharmacological hyperemia. The MRI measurements were validated against those obtained by PET imaging. Dipyridamole and dobutamine were used in dogs with or without moderate to severe coronary artery stenosis to induce a wide range of myocardial perfusion and oxygenation changes.

### Methods

#### Study Protocol

All animal protocols were approved by the Animal Studies Committee at Washington University. The study was performed in 21 beagle and small mongrel dogs (average weight, 9.4±1.9 kg), divided into 5 groups, as shown in the Table. The study protocol is shown in Figure 1. Pharmacological stress was performed with intravenous dipyridamole (Bedford Laboratories, Bedford, Ohio) or intravenous dobutamine (Abbott Labs, Chicago, Ill). Dipyridamole was infused at a rate of 0.14 mg·min⁻¹·kg⁻¹ body wt for 4 minutes. Dobutamine was started at a dose of 5 µg·min⁻¹·kg⁻¹ body wt and titrated at 5 µg·min⁻¹·kg⁻¹ intervals every 3 minutes until the rate-pressure product was approximately doubled compared with rest (maximum dose, 30 µg·min⁻¹·kg⁻¹ body wt). Dobutamine doses were typically the same during MR and PET scans but were occasionally optimized to retain similar hemodynamic states between the 2 imaging modalities; the average dobutamine dose was 20 µg·min⁻¹·kg⁻¹ during both MR and PET scans.

#### Animal Preparation and Surgery

Dogs were anesthetized with intravenous sodium thiopental (12.5 mg·kg⁻¹), intubated with an endotracheal tube, and then ventilated with 100% oxygen at a tidal volume of 12 mL·kg⁻¹ at a rate of 15 to 20 breaths/min. The animals were monitored continuously and anesthesia was maintained with ventilated 1% to 2% isoflurane.

**MRI Oxygenation Imaging**

Imaging of myocardial oxygenation was performed with a BOLD sequence that measures myocardial T₂ signals as described previously. The imaging sequence for this technique was a multicon-
trast 2D segmented turbo spin-echo sequence that collected T2-weighted images. To minimize flow artifacts in the LV, a double-inversion recovery preparation was used to yield black-blood images. The sequence was ECG-triggered with the segmented turbo spin-echo train placed in the motionless period of mid-diastole to minimize cardiac motion. Imaging parameters included field of view, 220×110 mm²; matrix size, 256×156; slice thickness, 8 mm; inversion time, 350 to 500 ms; segmentation number, 3, depending on the R-R interval; and data acquisition time, 24/R-R, or 14.4 seconds for a typical 600-ms R-R interval. Three echo times were used: TE1 = 24, TE2 = 48, and TE3 = 72. This sequence was executed twice at rest with 2 different echo spacings (8 and 12 ms) and multiple times at 8 ms during pharmacological vasodilation or hyperemia. Further information regarding the MR BOLD methods can be found in the online-only Data Supplement.

PET Methods
PET imaging was performed on a Focus 220 microPET scanner (Concorde Medical Systems, Knoxville, Tenn). A transmission scan was first performed with a rod source to ensure proper positioning and to correct for photon attenuation. ¹⁵O-water (average, 7.5±1.8 mCi) was administered intravenously, and dynamic PET data were acquired for 5 minutes. After 10 minutes, which allowed for decay of the ¹⁵O-water, ¹¹C-acetate (average 7.8±2.4 mCi) was injected intravenously and dynamic PET data were collected for 30 minutes. Approximately 40 minutes after the resting ¹¹C-acetate scan (to allow for radionuclide decay), the pharmacological stressor was started, set to the appropriate dose to approximately match the hemodynamics during MRI, and the ¹⁵O-water and ¹¹C-acetate protocols were repeated for stress imaging.

Image Analysis
MRI Analysis
First-pass perfusion images were first analyzed by a nonblinded reviewer with a JAVA program (Java V5.0, Sun Microsystems, Santa Clara, Calif) developed in our laboratory. Images were de-noised by a wavelet method and analyzed by a new model-independent perfusion algorithm validated in our laboratory. This algorithm rapidly generated both MBF and MBV maps, on which regions of interest (ROIs) could be drawn. For ease of representation, the fully regional data were averaged in 4 segments: LAD-perfused anterior, lateral, remote inferior, and septal myocardial regions. The anterior segment represents perfusion-defected myocardial tissue in stenotic dogs (Figure 2).

BOLD T₂-weighted images were analyzed with a MATLAB graphics program (MathWorks, Natick, Mass). Pixel-by-pixel maps of the myocardial T₂ decay constants were calculated from the T₂-weighted signal intensities. Then OEF maps during hyperemia were determined with our previously described model, on which ROIs similar to the first-pass perfusion map ROIs were drawn. The 2 T₂ maps with different echo spacings at rest were used to determine model parameters for the calculation of OEF during hyperemia. MBV values both at rest and stress, which are required inputs for the OEF calculation, were determined from the first-pass perfusion images. A resting OEF of 0.6 was assumed, which was based on our previous studies of arterial and coronary sinus blood sampling measurements in control dogs at rest (R²=0.90), as well as PET...
measurements in dogs with moderate stenosis ($R^2=0.75$). Resting and hyperemic MVO$_2$ were then estimated by the Fick law:

$$\text{MVO}_2 = \left[\text{O}_2\right]_a \cdot \text{MBF} \cdot \text{OEF}$$

The constant $\left[\text{O}_2\right]_a$ is defined as the total oxygen content of arterial blood, and a value of 7.99 mmol·mL$^{-1}$ was used. All images were analyzed in a fully regional manner with anterior, lateral, inferior, and septal ROIs assessed in the LV.

**PET Image Analysis**

The nongated, attenuation-corrected images were reconstructed with filtered back-projection and transferred to a Sun workstation (Sun Microsystems). Three image slices that approximately matched the MR slice were selected, and ROIs matching the MR image ROIs were drawn to generate blood and myocardial time-activity curves. MBF was determined by a previously validated compartmental modeling method. MVO$_2$ was then determined by a 1-compartment kinetic model to estimate the rate at which $^{11}$C-acetate was converted to $^{11}$CO$_2$. Regional OEF was then estimated by the Fick law (Equation 1). PET images were analyzed by a second nonblinded reviewer.

**Statistical Analysis**

Data are reported as mean±SD. Linear regressions were used to assess the accuracy of the MRI-determined values for MBF, MVO$_2$, and OEF measurements compared with those obtained with PET. The correlation data were pooled from data measured on all 4 myocardial segments. Bland-Altman plots were also used, and percentiles of differences (mean difference ±1.96 SD) were calculated. Unpaired $t$ tests were used to determine the significance of differences between MRI and PET measurements. Two-sided probability values <0.05 were considered statistically significant.

**Results**

**Interventions and Hemodynamics**

Surgical preparation of animals took an average of 1.5 hours. Hemodynamics at rest and stress appeared comparable for all dogs between the MR and PET imaging sessions (Figure 3). Strong correlation for heart rate was observed with moderate correlation in rate-pressure product, which reflects some physiological variations between PET and MRI scan sessions.

**Regional MBF**

Representative MRI and PET images from a control dog and a dog with a severe LAD stenosis are shown in Figure 2. As expected, increased stenosis severity progressively attenuated the MBF increase during pharmacologically induced hyperemia. With myocardial segment–based analysis, the correlation between MR and PET measurements was strong (slope, 0.88; intercept, 0.25; $r=0.90$, $P<0.001$; Figure 4). The Bland-Altman plot shows a mean difference of 0.006 mL/g/min (limits of agreement, −0.76 to 0.77). There was no systematical error in MRI MBF measurements.
Regional Myocardial Oxygenation (OEF and MVO$_2$)

The regional MVO$_2$ and OEF data included data during pharmacological stress only (Figure 4), due to the assumed resting OEF of 0.6 for MRI. The regression plot in MVO$_2$ demonstrated good correlation (slope, 0.83; intercept, 1.41; r = 0.86, P < 0.001). Bland-Altman analysis showed a mean difference of 0.42 μmol/g/min (limits of agreement, −3.6 to 4.5). For OEF measurements, moderate correlation was observed for MRI measurements in comparison with PET measurements (slope, 0.7; intercept, 0.14; r = 0.81, P < 0.01), although the relatively low slope indicates slightly systematic underestimation. Bland-Altman analysis showed a mean difference of −0.015 (limits of agreement: −0.28 to 0.25).

Discussion

This study evaluated several MRI techniques for the assessment of myocardial perfusion and oxygenation compared with PET quantification methods in a canine model of coronary artery stenosis. We found that the MR methods provided reasonable estimates of both oxygen supply and demand. With PET as the gold standard, MBF, OEF, and MVO$_2$ were quantified and validated with moderate to very good correlations by MRI methods.

The experimental design with various coronary artery stenoses and 2 pharmacological stressors provided a wide range of changes in MBF (0.74 to 4.3 mL/g/min), OEF (0.19 to 0.9), and MVO$_2$ (2.5 to 20.4 μmol/g/min). In general, the vasodilator dipyridamole can increase MBF 3- to 4-fold and can substantially reduce myocardial OEF in normal tissue, but it also produces a minimal effect on MVO$_2$. With increasing coronary artery stenosis, the impact of dipyridamole will be less pronounced and reduction of OEF will decline progressively. In contrast, the inotropic agent dobutamine increases MVO$_2$ by increasing cardiac work load, which in turn increases MBF. Small changes in MVO$_2$ with the vasodilator dipyridamole were also observed in our study, possibly due to slight systemic hypotension and reflex tachycardia, which have been reported previously. In this study, MBF shows the best correlation between MRI and PET measurements, followed by MVO$_2$ and OEF measurements. This probably was due to the robust measurement of MBF by our well-established perfusion quantification technique. The variation observed in MVO$_2$ measurement may be due to measurement errors in MBF and OEF but also may be partially related to hemodynamic differences in the dogs between MRI and PET sessions. Notably, Figure 3 shows a moderate correlation coefficient of rate-pressure product data between the 2 studies (r = 0.77), which matches well with the moderate correlation of MVO$_2$ in Figure 4 (r = 0.86).

Compared with MBF and MVO$_2$ measurements, OEF showed the greatest dissimilarities between MRI and PET measurements in this study. This probably was due to the assumed resting OEF of 0.6 for MRI, which was determined in an earlier study using arterial and coronary sinus blood gases in control dogs. In this study, OEF in the entire LV wall was 0.64 ± 0.17, measured by PET. The slightly lower resting OEF value of 0.6 would result in a lower calculated hyperemic OEF as well, which can be seen from the Bland-Altman analysis in Figure 4, showing that MRI slightly underestimated the hyperemic OEF determined by PET. Again, these differences were not significant, and MR and PET OEF measurements were reasonably well correlated. Additionally, if the MRI hyperemic OEF is calculated using the resting OEF value determined by PET (instead of the assumed 0.6), the calculated MRI hyperemic OEF is not significantly changed (slope, 1.01; intercept, 0.02; r = 0.81, P < 0.001; Figure 5).

Another issue is the possible interference of the first contrast injection with the pharmacological stress BOLD imaging. As noted, Gadomer has high renal retention and rapid clearance. With a half-life of 11 minutes in dogs as well as the low dosage of Gadomer, a lag time of 60 minutes before starting the stress BOLD imaging was found to be sufficient to minimize the effect of the first contrast injection. Based on the information from the previous report about the pharmacokinetics of Gadomer, it can be estimated that the change in myocardial T$_2$ value due to the contrast injection at 60 minutes was <1.1%, which is well within the myocardial T$_2$ measurement error range (≈3.5%). One limitation of the measurement of perfusion in stenotic dogs is the possible leakage of Gadomer into the extravascular space caused by capillary breakdown. We also performed late enhancement analyses in several dogs in groups 2 and 5, and no significant enhancement was observed at rest or during the pharmacologically induced stress, indicating that no infarction occurred in this animal ischemia model. It should be noted that our perfusion quantification method used a model-free deconvolution, which may be applicable to the extracellular contrast agent as well. Nevertheless, the effect of Gadomer leakage on the accuracy of the perfusion measurement should be investigated systematically in the future. It is also recognized that the PET scan was always performed after the MRI scan due to the minimal effect on MVO$_2$ production.
to the availability of the isotopes at the time of the PET scan and radiation safety issues. This experimental design sequence may introduce systematical errors because the physiological states of the dogs, such as resting MBF, may progressively change. Every effort was made to ensure stability of the heart rate and blood pressure of the dogs during and between the MRI and PET scans (Figure 3).

Conclusion
MRI quantification methods for myocardial oxygenation are promising alternatives to nuclear techniques because they could be used for serial assessments of perfusion and oxygenation in settings of regional or global myocardial ischemia. This repeatability could allow for dose-response studies necessary for the development of new therapies. In addition, these techniques could easily be coupled with other cardiac MRI methods, such as delayed enhancement and wall-motion analyses, thereby making MRI a valuable “1-stop shop” for imaging regional or global myocardial ischemia.

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Disclosures
Dr Misselwitz is an employee of Bayer Schering Pharma AG (Berlin, Germany). The remaining authors report no conflicts.

References

CLINICAL PERSPECTIVE
Myocardial ischemia manifests as an imbalance between myocardial oxygen supply and demand. Cardiac positron emission tomography is currently the only imaging modality for absolute quantification of regional myocardial perfusion with 15O-water and oxygen metabolism with 13C-carbon-acetate. However, the use of positron emission tomography in this setting is limited because of its low spatial resolution (not suitable for the detection of subendocardial perfusion defects), relatively long acquisition time, limited availability, relative high cost, and ionizing radiation. On the other hand, MRI is a noninvasive imaging modality that is widely available, provides excellent image spatial resolution and soft-tissue contrast, and does not require iodinated contrast media or ionizing radiation. In the present study, the technique for assessing myocardial oxygenation was validated against gold standard positron emission tomography measurements in a large animal model in a clinical 1.5-T MRI scanner. With the rapid image acquisition used in this study, it is possible to integrate our methods with other established cardiac MRI approaches, such as perfusion, myocardial cine, and even delayed enhancement for characterizing ischemic myocardial tissue. This nonradiation method also allows for consecutive monitoring of the myocardium’s dose responses to various therapeutic interventions. Although this MR technique was validated with altered myocardial oxygen status caused by upstream coronary artery stenosis, this method may potentially be used to assess change in myocardial oxygen consumption due to other generalized disease conditions such as hypertension, diabetes, cardiomyopathies, and valvular heart disease.
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SUPPLEMENTAL MATERIAL

Supplemental Methods

**MR Oxygenation Imaging**

We have established our theoretical modeling and experimental method to calculate regional myocardial OEF in vivo (1). In brief, myocardial magnetization in a voxel was described with a 2-compartment model: intravascular and extravascular. In T2-weighted images acquired by a turbo spin-echo (TSE) sequence with an interecho spacing τ (the time difference between two consecutive 180° pulses), the signal in a myocardial tissue voxel can be approximated in a biexponential form as follows:

\[
S_{\text{voxel}}(TE) = S_0 \times e^{-\frac{TE}{T_{2\text{app}}}} = MBV \times e^{-\frac{TE}{T_{2b}}} + (1 - MBV) \times e^{-\frac{TE}{T_{2t}}}
\]

where \( S_{\text{voxel}} \) is the mean signal intensity of the voxel at TE; \( S_0 \) is a variable related to the proton density of the voxel, receiver gain, and \( T_1 \) of the tissue; \( T_{2\text{app}} \) is apparent myocardial \( T_2 \); and \( MBV \) is the intravascular blood volume fraction. \( T_{2b} \) and \( T_{2t} \) are the \( T_2 \) values of blood and tissue, respectively. Because the TEs of 60 ms in our \( T_2 \) measurement were much less than the intracapillary residence time of water spins (>250 ms), a slow exchange was assumed in this model. Using the Van Zijl’s intravascular component model (2), intravascular \( T_2 \) can be derived:

\[
\frac{1}{T_{2b}} = A' \cdot OEF^2 + B' \cdot OEF + C'
\]

where \( A' \), \( B' \), and \( C' \) are the functions of magnetic susceptibilities, interecho spacing τ, oxygenation-dependent \( T_2 \) of erythrocytes and plasma, TE, arterial oxygen saturation (\( Y_a \)), and hematocrit. These constants can be derived with experimental data obtained at 1.5 T (3). The extravascular \( T_{2b} \) can be approximated using a diffusion model (4, 5):
where \( R_{20t} \) is the intrinsic myocardial tissue transverse relaxation rate, and \( R_{21t} \) is a function of the diffusion constant \( D \), susceptibility difference between blood vessel and surrounding tissue, geometry of the heart relative to the \( B_0 \) static field, and the size of capillary and venous vessels. Both parameters are subject-specific and need to be determined individually. With the application of at least two different \( \tau \), corresponding \( T_2 \) at rest can be calculated using Eq. [1]. If we assume the resting value of OEF at 0.6, using the measured resting MBV data from the first pass perfusion imaging, the subject-specific parameters \( R_{20t} \) and \( R_{21t} \), can be estimated at rest with Eq. [3] by acquiring MRI \( T_2 \) data in two different \( \tau \) values. With knowledge of \( R_{20t}, R_{21t} \), myocardial OEF during the hyperemia can be calculated through Eqs. [1–3] with apparent myocardial \( T_2 \) and measured MBV.

Imaging of myocardial oxygenation was performed with a BOLD sequence that measures myocardial \( T_2 \) signals as described previously (1). The imaging sequence for this technique was a multi-contrast 2D segmented turbo spin-echo (TSE) sequence that collected \( T_2 \)-weighted images. To minimize flow artifacts in the left ventricle, double-inversion-recovery preparation yielded black-blood images. The sequence was ECG-triggered with the segmented TSE train placed in the motionless period of mid-diastole to minimize cardiac motion. Imaging parameters included: FOV = 220 x 131 mm\(^2\); matrix size = 256 x 156; slice thickness = 8 mm; inversion time = 350-500 ms, segmentation number = 3, depending on the RR interval; and data acquisition time = 24 x RR, or 14.4 s for a typical 600 ms RR interval. Three echo times were used \( TE_1 = 24, TE_2 = 48, TE_3 = 72 \). This sequence was executed twice at rest with two different echo spacings \( (\tau = 8 \text{ and } \tau = 12 \text{ ms}) \) to calculate \( R_{20t}, R_{21t} \). During the hyperemia, BOLD sequence was run multiple times at \( \tau = 8 \text{ ms} \) only.
Supplemental References


