Magnetic Resonance Versus Radionuclide Pharmacological Stress Perfusion Imaging for Flow-Limiting Stenoses of Varying Severity

Daniel C. Lee, MD; Orlando P. Simonetti, PhD; Kathleen R. Harris, BA; Thomas A. Holly, MD; Robert M. Judd, PhD; Edwin Wu, MD; Francis J. Klocke, MD

Background—Although magnetic resonance first-pass imaging (MRFP) has potential advantages in pharmacological stress perfusion imaging, direct comparisons of current MRFP and established radionuclide techniques are not available.

Methods and Results—Graded regional differences in coronary flow were produced during global coronary vasodilation in chronically instrumented dogs by partially occluding the left circumflex artery. Regional differences in full-thickness flow quantified using microspheres were compared with regional differences obtained with MRFP and radionuclide SPECT imaging (99mTc-sestamibi and 201Tl). Relative regional flows (RRFs) derived from the initial areas under MRFP signal intensity-time curves were linearly related to reference microsphere RRFs over the full range of vasodilation (y = 0.93x + 4.3; r² = 0.77). Relationships between 99mTc-sestamibi and 201Tl RRFs and microsphere RRFs were curvilinear, plateauing as flows increased. The high spatial resolution of the MRI enabled transmural flow to be evaluated in 3 to 5 layers across the myocardial wall. Reductions in subendocardial flow were visually apparent in MRFP images for ≥50% reductions in full-thickness flow. Endocardial-to-epicardial gradients in MRFP flow increased progressively with stenosis severity, whereas transmural flow patterns in remote normally perfused myocardium remained normal. Flow reductions of ≥50% not identified by radionuclide imaging were apparent in MRFP full-thickness and transmural analyses.

Conclusions—High-resolution MRFP can identify regional reductions in full-thickness myocardial blood flow during global coronary vasodilation over a wider range than current SPECT imaging. Transmural flow gradients can also be identified; their magnitude increases progressively as flow limitations become more severe and endocardial flow is compromised increasingly. (Circulation. 2004;110:58-65.)

Key Words: magnetic resonance imaging • scintigraphy • regional blood flow • vasodilation

Radionuclide stress perfusion imaging now plays a major role in the noninvasive diagnosis of coronary artery disease. As the capabilities of magnetic resonance scanners have improved, the possibility has arisen that magnetic resonance first-pass perfusion (MRFP) imaging during pharmacological coronary vasodilation can provide similar information. Our laboratory has recently demonstrated that MRFP imaging can identify 2-fold regional differences in flow over the full range of coronary vasodilation.1 Because of the known plateau in radionuclide uptake at flow rates exceeding twice resting levels,2,3 this finding suggested that MRI may be able to identify limitations in regional flow reserve over a wider range of coronary stenoses than radionuclide imaging. The improved spatial resolution of MRIs also raises the possibility of identifying transmural differences in perfusion produced by stenotic lesions.

The present study was undertaken to compare MRFP and 99mTc-sestamibi and 201Tl SPECT imaging in the quantification of regional differences in full-thickness vasodilated blood flow in viable myocardium. Additionally, we tested the hypothesis that regional endocardial-to-epicardial differences in MRFP flow patterns can be helpful in identifying flow-limiting stenoses. Studies were conducted in a canine model in which high-resolution MR images could be obtained while regional differences in vasodilated flow were varied over a wide range and quantified independently using systemically administered microspheres.

Methods

Studies were conducted in 18 chronically instrumented dogs of both sexes (R&R Research, Howard City, Mich, and Covance Research Products, Denver, Pa) using procedures and protocols in accord with...
the Position of the American Heart Association on Research Animal Use.

Surgery and Anesthesia
Random and purpose-bred hounds weighing 17 to 27 kg were instrumented as reported previously.4 The proximal portion of the left circumflex artery (LC) was instrumented with an external hydraulic occluder and external cuff-type Doppler flowmeter. Left and right atrial catheters were placed for administration of fluorescent microspheres and MR contrast agent, respectively. Animals were allowed to recover for ≥7 days before study. On days of study, animals were brought to the MR laboratory or SPECT scanner, anesthetized with methohexital sodium (10 to 20 mg/kg IV), and ventilated with a commercial anesthesia machine and oxygen-isoflurane (1.5% to 2.5%) gas mixture. End tidal PCO₂ was maintained at 30 to 32 mm Hg. Systemic O₂ saturation always exceeded 95%. Heart rates varied between 80 and 110 bpm.

Magnetic Resonance Imaging
Fifty-three MRFP studies were performed using a 1.5T scanner (Sonata, Siemens Medical Systems) with animals in the right lateral decubitus position. To maximize spatial resolution and signal-to-noise ratios, we confined observations to a single 8-mm short-axis slice positioned in the mid-portion of the posterior papillary muscle and posterior attachments of the right ventricle (in-plane resolution, 2.3 mm²). Global coronary vasodilation was produced using carbocromen (5 to 10 mg/kg IV, n = 17) or adenosine (140 to 840 μg/kg per min IV, n = 36). The dose of adenosine was that producing the maximum LC Doppler velocity in a preliminary study. LC stenoses sufficient to produce regional flow limitations were produced by partially inflating the LC hydraulic occluder while monitoring the Doppler velocity signal. MRFP images were obtained with ventilation interrupted at end expiration. Using an automatic injection device (Medrad, Spectris), Gd-HP-DO3A (gadoteridol, n = 28) or Gd-DTPA (n = 25) 0.054±0.015 mmol/L per kg was injected into the right atrial catheter at a rate of 1 mL/s and followed by a 12-mL saline flush also at 1 mL/s. Images were obtained during each diastole during the first passage of contrast through the central circulation. MRFP image acquisition and regional flow analysis are depicted in Figure 1. A total of 3×10⁶ fluorescent microspheres5 were injected into the left atrium immediately after each MR measurement.

Radionuclide Imaging
Radionuclide perfusion tracers were administered either during or shortly after MR studies. In 18 studies, ⁹⁹mTc-sestamibi (25 mCi) was injected intravenously immediately after MRFP imaging under the same conditions of global coronary vasodilation and LC stenosis with the animal still in the MR scanner. Additional ⁹⁹mTc-sestamibi studies (n = 8) and ²⁰¹Tl studies (3 mCi, n = 12) were performed during global coronary vasodilation and similar degrees of flow reduction outside of the MR scanner, with additional concomitant microsphere flow measurements (including reference arterial blood sampling, which was ordinarily not possible in the scanner). Flows in normally perfused myocardium averaged 3.1±0.5 mL/min per g. ²⁰¹Tl SPECT images were acquired beginning 5 to 10 minutes after tracer injection. ⁹⁹mTc-sestamibi SPECT images were acquired in the first 2 hours after tracer injection and included any degree of tracer redistribution that occurred between the time of injection and the time of sampling.⁶ Images were obtained using a single crystal gamma camera (Siemens Orbiter) and high-resolution collimator interfaced with an ICON acquisition and processing system (64 views over 180 degrees, 40 seconds per view, 6.5-mm pixel size and slice thickness). When animals were studied on more than one occasion, at least 72 hours (>10 half lives of ⁹⁹mTc-sestamibi) were allowed between studies.

Postmortem Microsphere and Radionuclide Analyses
After completion of studies, animals were euthanized with an overdose of pentobarbital, and the heart was retrieved for additional analysis. Two contiguous 1-cm mid-left ventricular slices encompassing the posterior papillary muscle were positioned so that the papillary muscle and posterior attachments of the right ventricle matched the contour of MRI images. Each slice was then divided into 12 30-degree sectors. In 2 animals, hearts were fixed in formalin.
and individual sectors were additionally divided into 4 transmural layers. Concentrations of fluorescent microspheres in individual samples were quantified fluorometrically and expressed on a per-gram basis. Data from corresponding samples in the 2 slices were averaged for comparisons with MRI and SPECT data. In 9 animals in which a $^{99m}$Tc-sestamibi perfusion scan was obtained just before euthanasia, myocardial samples underwent well counting for $^{99m}$Tc-sestamibi measured using postmortem well counting.

### Data Analysis

**Full-Thickness Flow Analysis (MRI and SPECT)**

Left ventricle endocardial and epicardial borders were drawn manually, and MRI signal intensity-time curves were generated for each 30-degree full-thickness sector. Baseline values measured before contrast administration were used to correct for any coil-induced differences in signal, which rarely exceeded 15%. The initial areas under each curve were measured from the onset of contrast appearance to the peak of the curve showing the most rapid upstroke.1 These values were taken to represent relative regional flows. They were then normalized to the highest sector value and compared with relative regional concentrations of fluorescent microspheres normalized to their highest sector value.

For SPECT images, 3 contiguous short-axis midventricular images were similarly divided into 12 30-degree sectors. The average signal intensity of the 3 images for each sector was taken to represent relative regional flow. These values were then normalized to the highest sector value and compared with relative regional concentrations of fluorescent microspheres normalized to their highest sector value. In animals in which a $^{99m}$Tc-sestamibi perfusion scan was obtained just before euthanasia, SPECT intensities were also compared with values of $^{99m}$Tc-sestamibi measured using postmortem well counting.

**Transmural Flow Analysis (MRI)**

Transmural flow patterns across the myocardial wall in the inferior myocardium in the area of the posterior papillary muscle (distal LC bed) were compared with those in normally perfused anteroseptal myocardium. As outlined in Figure 2, MRFP signal intensity-time curves could be generated for 3 to 5 (and occasionally 6) transmural layers in the inferior myocardium and papillary muscle and 3 to 4 transmural layers in anteroseptal myocardium. The initial areas in the signal intensity-time curves across each wall were taken to represent relative flows. Areas were normalized to the peak value within the wall and subjected to linear regression. The endocardial-to-epicardial slope of the regression was taken to represent the transmural flow gradient across the wall.

### Results

**Full-Thickness Analyses**

Figure 3 illustrates MRFP images, regional MRFP signal-intensity curves, $^{99m}$Tc-sestamibi SPECT images, and regional microsphere concentrations in animals with normal and regionally reduced vasodilated flows. In the normal situation, regional microsphere concentrations show minimal variation, as do regional MRFP and $^{99m}$Tc-sestamibi SPECT signals, and MRFP signal-intensity curves have similar initial areas. When circumflex microsphere flow is reduced by $\geq$50%, a perfusion defect is apparent in MRFP images and signal-intensity curves but not the SPECT image. When microsphere flow is reduced by $\geq$85%, MRFP images, MRFP signal-intensity curves, and SPECT images all show marked abnormalities. A transmural gradient in flow reduction is visually apparent in MRFP images for both degrees of flow limitation.

Figure 4A shows the relationship between MRFP and microsphere relative regional flows (RRF [30-degree sectors]) in all MRFP studies. MRFP RRFs are linearly related to the reference microsphere RRFs over the full range of vasodilation ($y=0.93x+4.3$; $n=608$, $r^2=0.77$, SEE=13). Figures 4B and 4C show similar comparisons between in vivo $^{99m}$Tc-sestamibi and $^{201}$TI RRFs and microsphere RRFs. Both relationships are curvilinear, plateauing as flows increase ($y=23 \ln x-11$; $n=310$, $r^2=0.74$; $y=28 \ln x-35$; $n=142$, $r^2=0.70$). Figure 4D compares in vivo SPECT and ex vivo well counting values of $^{99m}$Tc-sestamibi with microsphere RRFs. The relationships agree closely.

**Transmural Analyses**

Figure 5 illustrates similar agreement between MRFP and microsphere flows in individual transmural layers to that in full-thickness analyses. Figure 6 shows representative analy-

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**Figure 2.** Transmural flow analysis. Using the plot profile feature of NIH Image and a self-designed macro, voxel-by-voxel signal intensities across the myocardial wall were serially measured in (1) the inferior myocardium and papillary muscle and (2) normally perfused anteroseptal myocardium throughout the first passage of contrast. Using a format similar to M-mode echocardiography, signal intensities were displayed as a function of time to facilitate subdivision of each myocardial wall in 2-voxel steps. Signal-intensity curves were then generated for each subdivision. Three to 5 (and occasionally 6) curves could be obtained in the area of the inferior myocardium, which included the posterior papillary muscle (6 to 12 voxels) and 3 to 4 curves in the anteroseptal area (6 to 8 voxels). The initial area under each curve was normalized to the highest value in that wall and taken to represent relative flow. Relative flow was plotted against step (layer) number, and the slope of the regression line was measured to quantify the transmural flow gradient.
ses of MRFP endocardial-to-epicardial flow gradients in normally perfused and stenotic myocardium. Figure 7 shows the relationship between inferior and anteroseptal transmural MRFP slopes and microsphere RRFs in all studies. Transmural gradients were apparent visually in regions of MRFP images in which full-thickness flow was reduced by ≥50%. MRFP slopes in these regions increased progressively with severity of stenosis but were unchanged in remote normally perfused myocardium.

Discussion

Although cardiac applications of MRI have increased substantially in recent years, the strengths and limitations of MRI in identifying regional limitations in coronary flow reserve in viable myocardium supplied by stenotic coronary arteries remain incompletely defined. Comparisons of MRFP with radionuclide stress perfusion imaging are especially pertinent because of the established clinical utility of the radionuclide modality. The present study examined entire short-axis slices as would be done in routine clinical examinations. The full-thickness MRI findings (Figure 4A) extend our earlier report that relative initial areas under MRFP curves in selected regions of interest are linearly related to relative regional flows determined with microspheres over the full range of coronary vasodilation.1 In contrast to MRFP findings, Figures 4B and 4C document the expected falloffs in 99mTc-sestamibi and 201Tl deposition at higher flow rates.2,3 In vivo SPECT and ex vivo well-counting data for 99mTc

Figure 3. MRFP, 99mTc-sestamibi SPECT, and microsphere data during pharmacological vasodilation in animals with no (top), moderate (middle), and severe (bottom) reductions in microsphere flow in the circumflex bed. Shown from left to right are (1) a single frame from the MRFP image stack; (2) MRFP signal-intensity curves for 12 30-degree sectors (beginning at the most cranial image point and proceeding clockwise); (3) the corresponding 99mTc-sestamibi SPECT image; and (4) relative MRFP curve areas, 99mTc-sestamibi count rates, and microsphere concentrations in each 30-degree sector. Peak flow reductions indicated by microspheres were ≥50% and 85%, respectively (lower 2 panels). MRFP images show homogeneous myocardial contrast enhancement in the absence of stenosis, moderately reduced enhancement in the circumflex bed with moderate flow reduction, and markedly reduced enhancement with severe flow reduction. A transmural gradient in flow is visually apparent in both cases of flow reduction. MRFP signal-intensity curves have nearly identical initial areas in the absence of stenosis. Areas in the circumflex distribution are reduced moderately and markedly with moderate and severe flow reductions, respectively. 99mTc-sestamibi SPECT images show a uniform signal intensity in the absence of flow reduction and in the presence of moderate flow reduction. A prominent perfusion defect is apparent with severe flow reduction. Relative MRFP curve areas and microsphere concentrations correspond closely in all cases. 99mTc-sestamibi count rates are homogeneous at rest and remain so with moderate flow reduction but show an approximately 50% peak reduction with severe flow reduction.
correspond closely (Figure 4D). Taken in context with Figure 4A, these data suggest that MRFP can be advantageous in the detection of stenoses producing moderate limitations in flow reserve.

The identification of regional flow limitations was additionally facilitated by the ability of MRFP to identify transmural differences in perfusion when high spatial resolution is achieved. When regional full-thickness flow was reduced by $\geq 50\%$, a transmural gradient in perfusion was consistently apparent in unprocessed images (Figures 3 and 6, middle and lower panels). Transmural analysis was aided by the development of an MRFP M-mode display to replace freehand drawing of regions of interest. The display allowed analysis of transmural layers in 2-voxel steps from endocardium to epicardium. Additionally, the ability to visualize regional signal intensity changes over time in a single frame (rather than a 30- to 40-frame cine loop) was helpful in recognizing motion-related artifacts and signal contamination originating outside the myocardium (eg, right ventricle and left ventricle cavity or pericardial structures). As illustrated in Figures 6 and 7, transmural MRFP slopes increased progressively with increasing stenosis severity, whereas transmural patterns in remote normally perfused myocardium remained unchanged.

The observed transmural MRFP slopes in normally perfused and stenotic beds are consonant with factors known to limit perfusion progressively from epicardium to endocardium. The pressure drop in arteries upstream of the microcirculation is intrinsically greater in arteries supplying the subendocardium than the subepicardium, presumably because of the longer intramural path of the vessels supplying the inner myocardial layers. Compressive effects of ventricular contraction narrow intramural arteries and other vessels, displacing a significant fraction of their contained blood and greatly increasing systolic inflow resistance. A finite period

Figure 4. Comparisons of MRI, radionuclide, and microsphere flows. A, Normalized MRFP and microsphere full-thickness RRFs in individual 30-degree sectors ($n=608$; $3.9\%$ [25 of 638] of sectors could not be analyzed because of MR artifacts; microspheres were lost during processing of 3 sectors). B, Normalized $^{99m}$Tc-sestamibi and full-thickness microsphere RRFs ($n=310$). C, Normalized $^{201}$TI and full-thickness microsphere RRFs ($n=142$). D, In vivo SPECT and ex vivo well counting values of $^{99m}$Tc-sestamibi versus microsphere RRFs ($n=108$).

Figure 5. A, MRFP areas versus absolute microsphere blood flows in individual transmural layers (30-degree sectors, $n=255$). Data are from 6 studies in 1 animal. MRFP values were normalized using the ratio of average microsphere flow to average MRFP area in each study. B, MRFP RRF versus microsphere RRF in individual transmural layers during vasodilation ($n=302$). Data are from 8 studies in 2 animals.
in early diastole is required for reexpansion and refilling of these vessels, thereby also delaying early diastolic microcirculatory perfusion. Finally, inner wall flow can be further limited if intraventricular diastolic pressure is elevated.9

Although these effects are normally counterbalanced by autoregulatory adjustments in transmural microvascular tone, they are unopposed when the coronary bed is maximally vasodilated. The resulting transmural gradients in flow are usually modest in normally perfused areas, as reflected in the present study by minimal transmural flow gradients in normally perfused myocardium (Figure 7). In stenotic areas, transmural flow limitations are magnified by the reductions in

Figure 6. Transmural flow gradients during pharmacological vasodilation in animals with no (top), moderate (middle), and severe (bottom) reductions in microsphere flow in the circumflex bed. Shown from left to right are (1) a single frame from the MRFP image stack with the plot profile window indicated; (2) the MRFP M-mode display generated from serial plot profiles; (3) signal intensity-time curves for 2-voxel steps from endocardium to epicardium in the anteroseptum (solid lines) and inferior wall (dotted lines); and (4) normalized areas plotted against step (layer) number and the slope of the resultant regression lines for the anteroseptum (open squares) and inferior wall (solid circles). In the absence of stenosis, signal intensity is uniform across all walls. An inferior transmural gradient is visually apparent with mild and severe stenoses. The MRFP M-mode display portrays the timing and pattern of contrast enhancement in the region of the plot profile. In the absence of stenosis, enhancement is uniform between anteroseptal and inferior walls, as well as within each wall. Subendocardial enhancement is delayed and diminished compared with adjacent epicardium in the presence of a moderate stenosis; these changes are accentuated with a severe stenosis. Although signal intensity-time curves in the normal myocardium are uniform, curves generated from stenotic myocardium demonstrate a diminished amplitude and delayed peak compared with normally perfused remote areas. Notably, differences are also demonstrated between endocardial and epicardial layers within a stenotic wall. The effect is more pronounced with a more severe stenosis. The slope of the regression line in the inferior wall increases with increasing stenosis severity. However, the gradient across the normally perfused remote anteroseptum remains low regardless of stenosis severity.
regional epicardial artery pressure that result from flow-related pressure gradients across the stenoses. These gradients increase exponentially with severity of stenosis, causing correspondingly larger reductions in distal coronary artery pressure. The resulting differences between left ventricular and distal coronary artery pressures progressively accentuate the transmural effects outlined above. Thus, even when absolute flows remain above resting values in all myocardial layers, regional gradients in transmural flow increase progressively with severity of stenosis. A regionally increased gradient can be helpful in interpreting the significance of a borderline reduction in full-thickness flow.

Radionuclide approaches for distinguishing viable myocardium with limited flow reserve from areas of myocardial infarction usually involve comparisons of perfusion images obtained at rest with those during vasodilation. Although a similar approach could be taken by performing MRFP at rest as well as during vasodilation, it is now possible to visualize areas of infarction directly by collecting contrast-enhanced inversion recovery images 10 to 15 minutes after MRFP. The high spatial resolution of MR facilitates the identification of small or nontransmural infarctions and can thereby more precisely define areas with limited vasodilator flow reserve, which represent viable myocardium. The ability to distinguish between viable and infarcted myocardium can also be useful in interpreting regional deficits in MRFP under resting conditions, eg, in the setting of acute ischemia or previous infarction.

Several limitations of this canine study need to be kept in mind when considering human clinical populations. We used an inversion recovery SSFP sequence to maximize signal-to-noise ratios as well as spatial resolution. However, inversion recovery sequences can image only a single myocardial slice during each cardiac cycle and require constant R-R intervals. Sequences using saturation recovery are insensitive to arrhythmia and capable of multislice imaging but involve significant tradeoffs in signal-to-noise and spatial resolution. The degree of resolution in the present study also benefited from a smaller field of view than is usually feasible in humans and did not have to contend with diaphragmatic instability during breath holds. These various limitations will need to be minimized or eliminated if the present findings are to be extended to the clinical setting.

Efforts to improve options in human first-pass imaging continue. Schreiber et al recently reported an in-plane resolution of 2.4×2.1 mm in single-slice imaging using a saturation recovery SSFP sequence. Using saturation recovery and a segmented echo-planar gradient echo readout, Kwong et al have achieved 3.0- to 3.3-mm in-plane resolution while imaging 7 to 9 locations every 2 heart beats. Using a similar sequence and readout, Nagel et al have reported a spatial resolution of 1.7 to 2.2×1.9 to 2.4 mm while imaging 5 8-mm slices each heart beat.

In summary, MRFP can identify regional reductions in full-thickness myocardial blood flow during pharmacological coronary vasodilation over a wider range than current SPECT imaging. The detection of flow-limiting stenoses is additionally facilitated by the ability of MRFP to quantify regional transmural gradients in flow that are accentuated as the severity of flow limitation increases.

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References


