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Limits of Detection of Regional Differences in Vasodilated Flow in Viable Myocardium by First-Pass Magnetic Resonance Perfusion Imaging

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Background—Perfusion imaging techniques intended to identify regional limitations in coronary flow reserve in viable myocardium need to identify 2-fold differences in regional flow during coronary vasodilation consistently. This study evaluated the suitability of current first-pass magnetic resonance approaches for evaluating such differences, which are 1 to 2 orders of magnitude less than in myocardial infarction.

Methods and Results—Graded regional differences in vasodilated flow were produced in chronically instrumented dogs with either left circumflex (LCx) infusion of adenosine or partial LCx occlusion during global coronary vasodilation. First-pass myocardial signal intensity-time curves were obtained after right atrial injection of gadoteridol (0.025 mmol/kg) with an MRI inversion recovery true-FISP sequence. The area under the initial portion of the LCx curve was compared with that of a curve from a remote area of the ventricle. Relative LCx and remote flows were assessed simultaneously with microspheres. The ratio of LCx and remote MRI curve areas and the ratio of LCx and remote microsphere concentrations were highly correlated and linearly related over a 5-fold range of flow differences ($y=0.96x\pm 0.07$, $P<0.0001$, $r^2=0.87$). The 95% confidence limits for individual MRI measurements were $\pm 35\%$. Regional differences of ≥ 2 -fold were consistently apparent in unprocessed MR images.

Conclusions—Clinically relevant regional reductions in vasodilated flow in viable myocardium can be detected with 95% confidence over the range of 1 to 5 times resting flow. This suggests that MRI can identify and quantify limitations in perfusion reserve that are expected to be produced by stenoses of $\geq 70\%$. (*Circulation*. 2001;104:2412-2416.)

Key Words: magnetic resonance imaging ■ regional blood flow ■ vasodilation

First-pass contrast-based MR perfusion imaging of the myocardium has received increasing attention as approaches providing improved temporal and spatial resolution and signal-to-noise ratio have become available. Clinical studies have focused on the identification of regional perfusion deficits indicating the presence of coronary artery disease. Because most studies have been performed during pharmacological coronary vasodilation, the perfusion deficits have included areas of both myocardial infarction and viable myocardium having limited coronary flow reserve.

The identification of a regional limitation in flow reserve in viable myocardium is based on the identification of a relative reduction in perfusion during coronary vasodilation. Pharmacological vasodilation can increase resting flow 4- to 8-fold in normally perfused viable tissue, whereas a lesser increase occurs in areas supplied by stenotic arteries.^{1,2} Because 70% diameter stenoses reduce vasodilated flow by only $\approx 50\%$,²⁻⁵

a clinically useful technique needs to identify 2-fold regional differences in vasodilated flow consistently. This is an appreciably more demanding requirement than when perfusion imaging is used to identify areas of myocardial infarction, ie, resting blood flow in infarcted tissue is no more than 10% to 20% of resting flow in adjacent viable tissue, and this 5- to 10-fold difference under resting conditions can increase to 20- to 50-fold during pharmacological vasodilation.

The present study was undertaken to define the limits of detection of regional differences in vasodilated coronary flow in viable myocardium with a first-pass MRI approach combining inversion recovery with a rapid-acquisition true-FISP (fast imaging with steady-state precision) sequence having an unusually favorable signal-to-noise ratio.^{6,7} Regional differences in first-pass MR curves were compared with the regional distribution of systemically administered microspheres in chronically instrumented dogs.

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Methods

Studies were conducted in mongrel dogs of both sexes by use of procedures and protocols approved by the Animal Care and Use Committee of Northwestern University Medical School.

Experimental Preparation

Twelve animals weighing 25 to 30 kg were instrumented after an overnight fast and a 3-week period of on-site conditioning. Details of the instrumentation procedure have been published previously.⁸ The proximal portion of the left circumflex artery (LCx) was instrumented with a 22-gauge infusion catheter and external Doppler flowmeter and, in 3 animals, an external hydraulic occluder. 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 being studied.

Study Procedures

Animals were brought to the MR scanner, anesthetized with methohexital sodium 11 mg/kg IV, intubated, and ventilated with a commercial anesthesia machine and an oxygen-isoflurane (1.5% to 2.5%) gas mixture. Systemic O₂ saturation and end-tidal PCO₂ were monitored continuously (model 3150 Physiological Monitor, Invivo Research, Inc), with ventilation adjusted to maintain end-tidal PCO₂ at 30 to 32 mm Hg. O₂ saturation always exceeded 95%. Heart rates averaged 109 ± 12 bpm (SD). Animals were studied in the right lateral decubitus position, with the heart located at the level of an in-table receiver coil. An additional 2-element quadrature array coil was positioned directly over the heart.

A single midventricular short axis or a longitudinal axis that included the posterior left ventricular wall was identified for study. A true-FISP inversion recovery sequence known to be very sensitive to changes in T1^{6,7} was used for first-pass imaging. Typical parameters included an 80×256 matrix, 150×300 mm field of view, TR 3.0, TE 1.5, inversion recovery TI 250 ms, 6-mm slice thickness, and 1 image per heartbeat. The requirement of complete rewinding on all 3 gradient axes caused the repetition time (TR) to be slightly longer than spoiled gradient echo sequences, eg, turbo-FLASH (fast low-angle shot). Single-slice imaging was performed to limit the application of the 180° inversion recovery preparation pulse to once per cardiac cycle to maintain adequate signal-to-noise ratio and contrast. A sequence diagram is shown in Figure 1.

Steady-state increases in regional LCx flow were produced with graded LCx infusion of adenosine (0.01 to 1.0 mg/min) in 9 animals. Three animals were studied during sustained generalized coronary vasodilation produced by carbocromen (5 mg/kg IV). In these latter cases, regional LCx flow limitations were produced by partial inflation of the LCx hydraulic occluder while the Doppler velocity signal was monitored (which always remained above its prevasodilation level). MR first-pass measurements were obtained, with ventilation interrupted at end expiration. Gd-HP-DO3A (gadoteridol) $0.025 \text{ mmol} \cdot \text{L}^{-1} \cdot \text{kg}^{-1}$ was injected into the right atrium over 4 seconds and followed by a 12-mL saline flush administered at 1 mL/s. This pattern of right-sided contrast injection was chosen to produce intensity-time curves in left ventricular blood similar to those seen in patients after central venous injection. The relatively low dose of contrast ($0.025 \text{ mmol} \cdot \text{L}^{-1} \cdot \text{kg}^{-1}$) ensured a linear response between myocardial signal and contrast concentration (Figure 2). Images were collected during each diastole for 40 to 60 beats. Fluorescent microspheres⁹ ($n=3 \times 10^6$) were injected into the left atrium immediately after each MR measurement. Up to 3 sets of MR and microsphere measurements were performed during a single study. After completion of the measurements, anesthesia was discontinued, and animals were returned to the vivarium after full recovery. Individual animals were studied on 1 to 3 occasions. When all studies had been completed, animals were euthanized with an overdose of pentobarbital, and the heart was retrieved for microsphere analysis.

After the most basal and apical 0.5-cm portions had been removed, the left ventricle and septum were divided into 4 or 5 short-axis slices for fluorescent microsphere analysis. Myocardial scarring was never

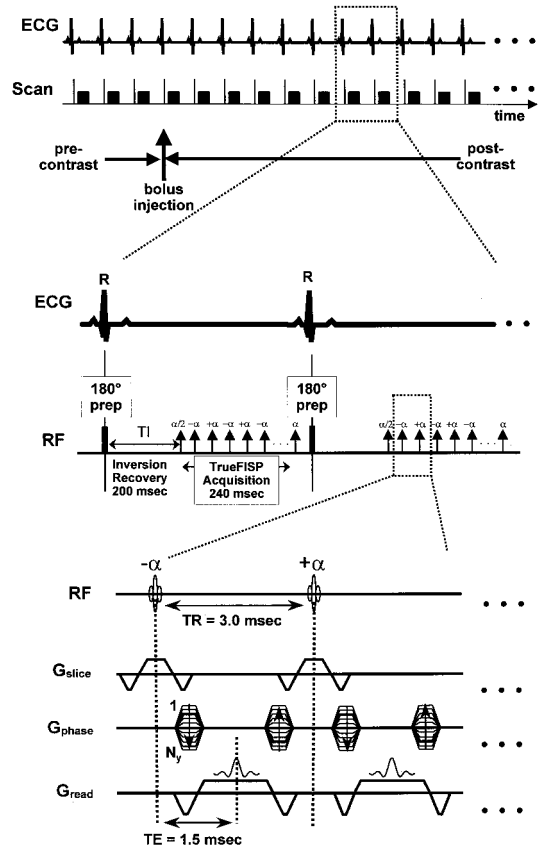


Figure 1. MRI sequence diagram for inversion recovery first-pass true-FISP perfusion imaging.

evident. Concentrations of microspheres in individual areas of each slice were assessed fluorometrically and expressed on a per gram basis.⁹

Data Analysis

Regional differences in flow were expected to produce differences in the initial portions of regional signal intensity–time curves. First-pass curves in an LCx region of interest were compared with simultaneous first-pass curves in a remote area of the ventricle, ie, the LAD bed or septum. Baseline signals measured before contrast

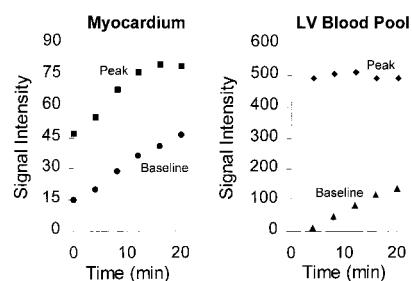


Figure 2. Baseline and peak myocardial and LV blood pool signal intensities for 6 successive $0.025\text{-mmol} \cdot \text{L}^{-1} \cdot \text{kg}^{-1}$ right atrial injections of gadoteridol administered at 4-minute intervals. Baseline myocardial and LV blood pool signals increase linearly throughout series of injections (myocardial signal = $1.63x + 15.0$, $r^2 = 0.99$; LV blood pool signal = $8.00x - 16.2$, $r^2 = 0.99$). Peak myocardial signals increase by similar amounts after first 5 injections but to a lesser degree after injection 6. Peak LV blood pool signals show a progressively ailinear response as injections proceed.

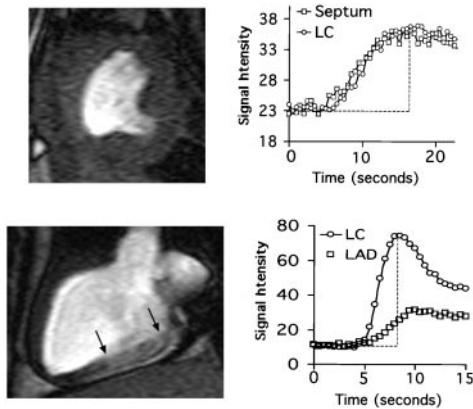


Figure 3. Signal intensity–time curves and representative MR images during upslope of first-pass curve. Dotted lines outline areas under curves from onset of contrast appearance to peak of curve showing more rapid upslope. Animal in top panels was studied under resting conditions. Ratio of areas under upslopes of LCx (LC) and septal first-pass curves was 0.86; corresponding microsphere flow ratio was 1.04. Animal in lower panels was studied during LCx adenosine infusion. The arrows outline vasodilated LCx area. Ratio of areas from onset of contrast appearance to peak of LCx curve was 5.00; corresponding microsphere flow ratio was 4.36.

administration were used to correct for any coil-induced differences in signal in the paired curves. These were present in $\approx 50\%$ of cases but rarely exceeded 15%. Areas under each pair of LCx and remote curves were measured from the onset of contrast appearance to the peak of the curve showing the more rapid upslope. The ratio of areas in the LCx and remote curves was then compared with the ratio of microsphere concentrations/g myocardium in the same areas of the ventricle. The reproducibility of measurements of MRI area ratios was assessed by triplicate determinations performed on 7 occasions. Ratios averaged 1.94; the SEM of measurement was 0.28.

Because the number of comparisons of MRI and microsphere flow ratios in an individual animal varied, the linear regression of MRI flow ratio on microsphere flow ratio was calculated with and without taking into account the structure of the data with regard to repeated measurements from the same dog.¹⁰ Because the results did not differ, the data values were treated as independent pairs. When subjected to linear regression, the slope of the linear model was consistent with unity, but the residual values showed a pattern of increasing variance as flow ratios increased ($P < 0.0002$). Accordingly, the data were fitted with a weighted linear regression model in

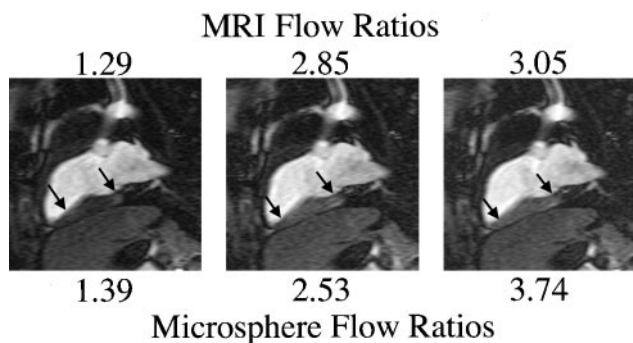


Figure 4. First-pass MR images from animal studied under basal conditions (left) and during 2 degrees of adenosine-induced LCx vasodilation (center and right). Arrows outline vasodilated LCx area. LCx/septal MRI curve area ratios and microsphere flow ratios are shown above and below images, respectively.

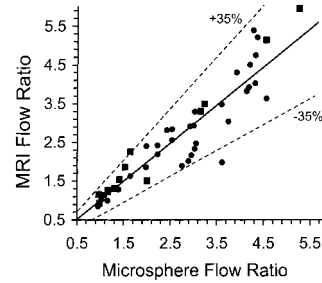


Figure 5. MRI vs microsphere flow ratios in all animals. Solid line is linear regression (MRI ratio = 0.96 microsphere ratio + 0.07); dotted lines indicate 95% confidence limits for individual values. ●, Ratios of LCx to remote MRI areas and relative microsphere flows during LCx adenosine infusion; ■, ratios of remote to LCx MRI areas and relative microsphere flows during LCx constriction in presence of global LV vasodilation.

which residual variance increases concomitantly with the independent variable.¹¹

Results

Figure 3 shows intensity-time curves and representative MR images during the upslopes of first-pass curves under basal conditions and during regional LCx vasodilation. Figure 4 shows MR images under basal conditions and during 2 degrees of regional vasodilation in a single animal. Figure 5 depicts the relationship between the ratio of MR curve area in the LCx and remote beds and the corresponding ratio of microsphere concentrations for all 12 animals. The linear regression is $y = 0.96x \pm 0.07$ ($P < 0.0001$, $r^2 = 0.87$). The 95% confidence limits for individual values are $\pm 35\%$ of the regression line value. Regional differences of ≥ 2 -fold were consistently apparent in the unprocessed MR images.

Discussion

Although the identification of regional limitations in coronary flow reserve remains a major goal in the evaluation of patients with known or suspected coronary artery disease, the minimum difference in flow required for identification of a relative perfusion deficit remains incompletely defined. The present study used microsphere measurements to define relative flows in vasodilated and nonvasodilated areas of the left ventricle. Because differences in flow were produced by selective regional vasodilation or by regional reductions in globally vasodilated flow, complicating effects of myocardial infarction were not an issue. Because perfusion in infarcted tissue is only 10% to 20% of resting flow, regional flow in normal myocardium is 5- to 10-fold greater than in areas of infarction under resting conditions and can be as much as 50-fold greater during vasodilation. This contrasts sharply with the situation in viable myocardium supplied by a stenotic coronary artery. Wilson et al² provided quantitative measurements of reductions in coronary flow reserve in patients with isolated stenoses supplying viable myocardium. On average, flow reserve in regions supplied by stenoses of 50%, 70%, and 80% diameter was reduced by 33%, 55%, and 67%, respectively. These reductions correspond closely with values in experimental studies reported by others.³⁻⁵

Thus, the identification of an area of viable myocardium supplied by an artery having a $\geq 70\%$ stenosis requires a flow

measurement technique that can consistently identify a 50% regional reduction in vasodilated flow. The data in Figure 5 indicate that the expected MRI flow ratio of 1.0 between 2 normally perfused territories is, at least in this experimental model, associated with 95% confidence limits of 0.65 to 1.35. An increase in this ratio to 2.0, as with a 50% reduction in vasodilated flow in a stenotic territory, is clearly beyond the limits of normal perfusion. The present findings further suggest that stenoses >70%, which are expected to produce larger regional differences in vasodilated flow, may be subdivided functionally on the basis of the relative reductions in the initial area of first-pass curves in the portions of the ventricle they supply.

The MRI area ratio "perfusion index" used in this study, like others reported in the literature, is arbitrary. Ratios of peak signal amplitudes and average curve upslopes (calculated as the quotient of the difference between baseline and peak signal values and time) were also linearly related to microsphere data. These showed poorer agreement, however ($r^2=0.62$ and 0.70 , respectively). The continued linearity of the relation between our MRI perfusion index and the corresponding microsphere perfusion index at vasodilated flows exceeding 2 to 3 times resting flows is in some respects surprising. Myocardial extraction of Gd-DTPA has been reported to vary inversely with flow,¹² as is known to be the case for ^{99m}Tc-sestamibi¹³ and, to a lesser degree, ²⁰¹Tl.^{14–16} In the case of ^{99m}Tc-sestamibi, the decreasing extraction causes the relation between tracer signal and flow to plateau as flow increases to more than 2 to 3 times its resting value. The MR signal has the additional complexity of resulting not from Gd directly but rather from reductions in proton relaxation times caused by the magnetic moment associated with Gd. Because most myocardial protons are located on water molecules, rates of water exchange among the intravascular, interstitial, and intracellular compartments influence the number of water molecules affected by Gd.^{17,18}

Most clinical studies that used first-pass perfusion imaging have focused on the identification of regional perfusion deficits indicating the presence of coronary artery disease. These have usually been observational studies in patients with already known or suspected coronary disease. A substantial portion of such patients may be expected to have had previous myocardial infarction, either silent or clinically apparent. Thus, in studies performed during pharmacological coronary vasodilation, the perfusion deficits identified have no doubt included areas of myocardial infarction as well as viable myocardium having limited coronary flow reserve. Wilke et al¹⁹ summarized studies through 1999. Of 21 studies (which included a total of more than 500 patients), 85% used coronary vasodilation with adenosine or dipyridamole. Values of sensitivity and specificity for the identification of coronary artery disease appeared comparable to those reported for radionuclide and angiographic modalities. More recently, Al-Saadi et al²⁰ reported that reductions in flow reserve in areas of >75% stenosis can be identified by upslope analyses of regional and left ventricular curves.

The Minnesota group developed sophisticated models for assessing myocardial flow quantitatively²¹ and used them to study absolute values of coronary flow reserve in a porcine

preparation in which marginal branches of the circumflex artery were ligated and vasodilation was produced by systemic infusion of adenosine.²² Microsphere flows in the anterior and septal regions averaged 430% of flow in the lateral wall at rest (1.16 versus 0.27 mL · min⁻¹ · g⁻¹) and 710% of flow in the lateral wall during adenosine-induced vasodilation (2.91 versus 0.41 mL · min⁻¹ · g⁻¹). The first-pass curves in the 2 areas were also used to derive a perfusion index similar to that reported here. The ratio of peak curve amplitudes was linearly related to the ratio of microsphere deposition in the same areas ($y=0.92x+0.098$, $r=0.88$). In view of the low absolute values of lateral wall flow and the paucity of native collateral vessels in the porcine heart, areas of the lateral wall may have included areas of infarction.

Although measurements of a perfusion index do not provide information about absolute values of coronary flow reserve, they may still prove quite useful clinically. If first-pass vasodilated imaging is combined with additional imaging 10 to 15 minutes after contrast administration, it should be possible to determine whether areas of relative perfusion deficit originate in viable or infarcted myocardium.^{23–25} Although quantitative determinations of flow reserve are of great value in studying pathophysiology, they require left ventricular blood pool as well as myocardial imaging, 2 sets rather than 1 of first-pass images, and relatively complex modeling.¹⁹ The interpretation of an individual value of flow reserve can also be problematic. Although absolute values of flow reserve are reduced locally beyond stenotic lesions, they are also reduced diffusely by processes seen commonly in coronary patients, eg, hypertrophy and small-vessel disease. Additional variability in absolute values of flow reserve that is unrelated to the degree of stenosis can be produced by hemodynamically induced variations in resting flow, reductions in vasodilated flow secondary to adenosine- or dipyridamole-induced reductions in blood pressure, and other factors.⁵

Although the inversion recovery true-FISP sequence provides improved image quality, it currently has significant limitations. Perhaps the most important of these is that only a single myocardial slice is imaged during each cardiac cycle. Other options, eg, imaging 2 slices every other beat, imaging 2 slices during different portions of each cardiac cycle, or 3D imaging may prove possible. Although multislice images can be obtained during individual beats if the true-FISP sequence is used with saturation recovery rather than inversion recovery, image quality is less satisfactory in our experience. Variations in cardiac cycle length that are sufficient to interrupt every-beat imaging present an additional problem, because they disturb the steady-state conditions required for inversion recovery true-FISP imaging.

In summary, with an inversion recovery true-FISP sequence having improved signal-to-noise characteristics, regional differences in flow in viable vasodilated myocardium were visually apparent in MR images obtained with a conventional contrast agent. Regional differences as small as 2-fold could be identified consistently in first-pass signal intensity-versus-time curves and were quantitatively related

to differences in the areas subtended by the early portion of the regional first-pass curves.

Acknowledgments

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