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Coronary Flow Reserve: Noninvasive Measurement in Humans with Breath-Hold Velocity-encoded Cine MR Imaging[1]

PURPOSE: **To measure coronary vasodilator reserve with breath-hold velocity-encoded cine magnetic resonance (MR) imaging.**

MATERIALS AND METHODS: **Eight healthy adult volunteers underwent 1.5-T MR imaging. Velocity-encoded cine images were acquired at seven to 13 temporal phases in 25 seconds, with k-space segmentation and view-sharing reconstruction (±1 m/sec velocity-encoding value) (repetition time msec/echo time msec = 16/9). Flow velocity in the left anterior descending (LAD) artery was measured twice before and twice after administration of dipyridamole (0.56 mg per kilogram of body weight).**

RESULTS: **Peak diastolic coronary flow velocity in the LAD artery was 14.8 cm/sec ± 1.9 (mean ± standard deviation) in the baseline state. It increased significantly ($P < .01$) to 46.3 cm/sec ± 10.2 after dipyridamole administration, with an average coronary reserve of 3.14 ± 0.59. Interstudy and interobserver reproducibilities for measurement of peak diastolic velocity were, respectively, 9.5% ± 1.6 and 7.0% ± .2.5 in the baseline state and 6.8% ± 2.2 and 3.4% ± 1.5 after dipyridamole administration.**

CONCLUSION: **Breath-hold velocity-encoded cine MR imaging provided reproducible assessment of coronary flow reserve in humans.**

Index terms: Coronary vessels, flow dynamics, 54.12144 • Coronary vessels, MR, 54.12144 • Magnetic resonance (MR), cine study, 54.12144 • Magnetic resonance (MR), phase imaging, 54.12144 • Magnetic resonance (MR), rapid imaging, 54.12144 • Magnetic resonance (MR), vascular studies, 54.12144

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X-RAY coronary angiography has been used for evaluation of the coronary arteries and findings are considered to be the standard of reference for determining the severity of coronary arterial stenoses. Visual inspection of the anatomic severity of a coronary stenosis, however, does not always adequately determine the functional significance of the lesion (1). The physiologic significance of coronary stenosis can be determined by measuring the coronary flow reserve—the ratio of hyperemic blood flow to resting blood flow (2). In recent years, the Doppler guide wire has been used to measure coronary blood flow velocity in humans (3–5), but this technique has several limitations, including its invasiveness, the exposure of the patient to additional radiation, and the superimposed obstruction of the vessel by the wire. Consequently, intravascular Doppler flow measurement is not suitable for sequential studies and is applied only in patients undergoing coronary angiography. Finding a noninvasive method for the evaluation of patients considered to be at risk for hemodynamically significant coronary artery lesions would be highly desirable.

The measurement of blood flow velocity in the coronary arteries with magnetic resonance (MR) imaging has been difficult because of the small diameter of these vessels, which exhibit considerable motion during cardiac pulsation and respiration. Recently, reports have appeared of the feasibility of measuring coronary flow velocity within a single breath hold with time-of-flight (6) and phase-velocity mapping methods (7–9). However, the MR imaging flow-measurement techniques used in these studies provided only a single time point in the cardiac cycle for each breath-hold data acquisition; therefore, peak flow velocity may not have been sampled. This problem may be exacerbated when coronary flow reserve is measured, because the heart rate sometimes increases after pharmacologic stress. A new technique, fast velocity-encoded cine MR imaging, with uniform repetition time and radio-frequency excitation and view-sharing reconstruction, can provide a phasic flow-velocity time curve for human coronary arteries by acquiring data during a single breath hold (10).

The purposes of this study were (*a*) to demonstrate the feasibility of breath-hold velocity-encoded cine MR imaging to display phasic coronary flow velocity in humans; (*b*) to measure the response of coronary flow velocity to the administration of dipyridamole, as a reflection of coronary flow reserve in humans; (*c*) to determine the interstudy and interobserver reproducibility values for the measurement of coronary blood flow velocity. The measurements were confined to the left anterior descending (LAD) artery, since this artery is most readily assessed in the cardiac short-axis plane and moves less during the cardiac cycle than does the right coronary artery.

MATERIALS AND METHODS

Eight healthy volunteers with no history of heart or lung diseases were included in this study (seven men and one woman, aged 22–32 years [mean, 25.8 years). Informed consent was obtained from each subject. The protocol and consent form were approved by the institutional committee for human research at our institution. The measurements were

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Abbreviation: LAD = left anterior descending.

performed with a 1.5-T clinical MR imaging unit (Signa Advantage; GE Medical Systems, Milwaukee, Wis). Subjects were placed supine, with a 7.5 cm receiving surface coil placed above the heart. Electrocardiographic leads were attached to the chest for cardiac gating.

To localize the LAD artery, breath-hold cine MR images were acquired as scout images by using a segmented k-space fast gradient-echo cine sequence with fat saturation (FASTCARD; GE Medical Systems). Conventional gradient configurations with maximum gradient strength of 10 T/m/sec and maximum gradient slew rate of 17 T/m/sec were used. Breath-hold cine MR images with seven to nine temporal phases in the cardiac cycle were obtained at consecutive transaxial imaging planes during a breath-hold period in shallow inspiration to show the left main coronary artery and the proximal portion of the LAD artery (11). With the transaxial image depicting the proximal LAD artery for orientation, breath-hold cine MR images were acquired on single oblique imaging planes that corresponded to the long-axis view of the left ventricle.

The pulse sequence employed for breath-hold flow measurements was a phase-contrast fast gradient-echo sequence with resonance-frequency phase spoiling (Fastcard-PC; GE Medical Systems) (10). Double oblique velocity-encoded cine MR images were acquired perpendicular to the LAD artery, with 5-mm-thick sections, 16-msec repetition time and 9-msec echo time, 96 phase-encoding steps, 24 × 18-cm field of view, 256 × 192 reconstructed image matrix, and 32-kHz receiver bandwidth. The phase-encoding direction was chosen so ghosting from ventricular chamber blood did not overlap the coronary artery. In this version of the fast, segmented k-space, gradient-echo technique, resonance-frequency excitation pulses are applied uniformly throughout the imaging period, even during the trigger window time, when no data are collected. The uniform excitation maintains the spins in the steady state, eliminates the need for dummy excitations before data collection, and enables the acquisition of data immediately after the electrocardiographic R wave trigger. In addition, by maintaining the steady state with uniform repetition time and resonance frequency excitation, this technique obviates the increased signal intensity in the first few temporal images that results from the longer T1 recovery period—the so-called "lighting flash" artifact. The view acquisition order is segmented by sequence rather than interleaved. Images with a sequential segmented order show fewer artifacts because the low spatial frequency views at the center of k space are acquired within a single RR interval. In addition, images obtained with a sequential segmented order have better edge definition, because adjacent spatial frequency data are acquired close in time (10).

Velocity-encoding gradients were applied in the section-select direction, with a velocity window of plus or minus 100 cm/sec. For each k-space view, positive and negative velocity-encoding data were acquired as a sequential pair. Four views of k-space data were collected in each segment for each RR interval. The true temporal resolution, defined as a data acquisi-

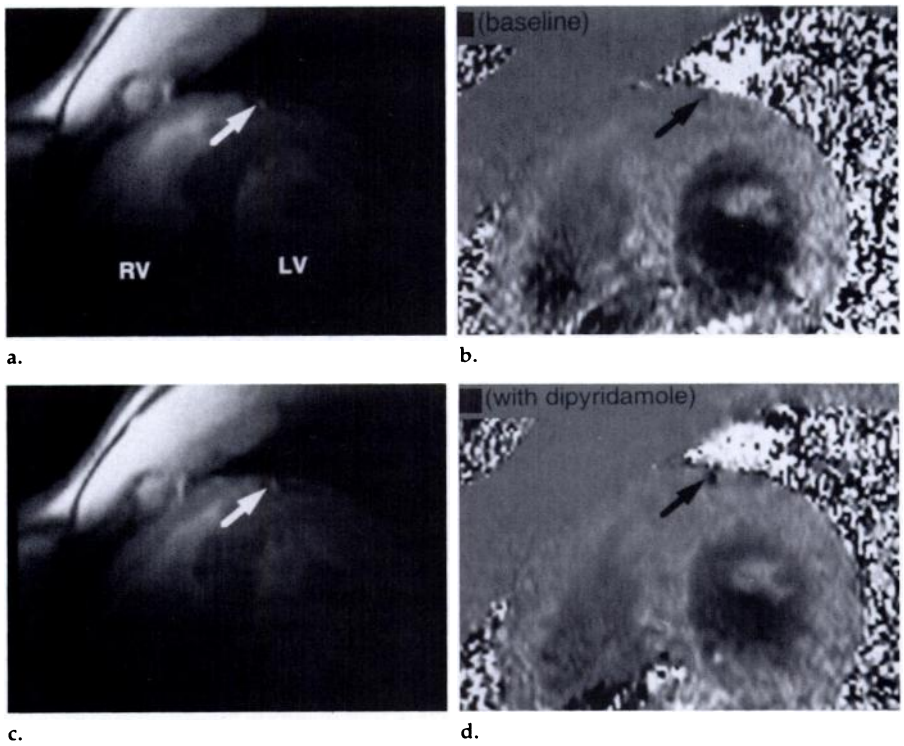

Figure 1. Subject 1. Breath-hold velocity-encoded cine MR images: unenhanced **(a)** magnitude and **(b)** phase images in early diastole and dipyridamole-enhanced **(c)** magnitude and **(d)** phase images. Increased blood flow velocity in the LAD artery after administration of dipyridamole is indicated by substantial darkening of the signal intensity in the vessel lumen (arrow) on **d** compared with **b**. In **a**, *LV* = left ventricle, *RV* = right ventricle.

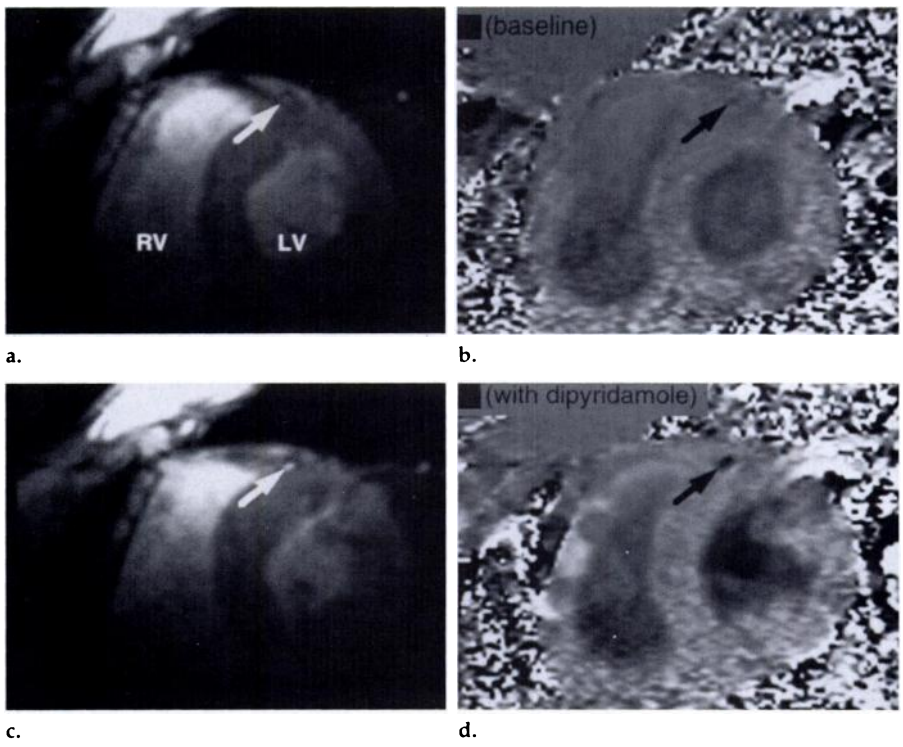

Figure 2. Subject 6. Breath-hold velocity-encoded cine MR images in early diastole in another subject: unenhanced **(a)** magnitude and **(b)** phase images and dipyridamole-enhanced **(c)** magnitude and **(d)** phase images. Arrow indicates the vessel lumen. In **a**, *LV* = left ventricle, *RV* = right ventricle.

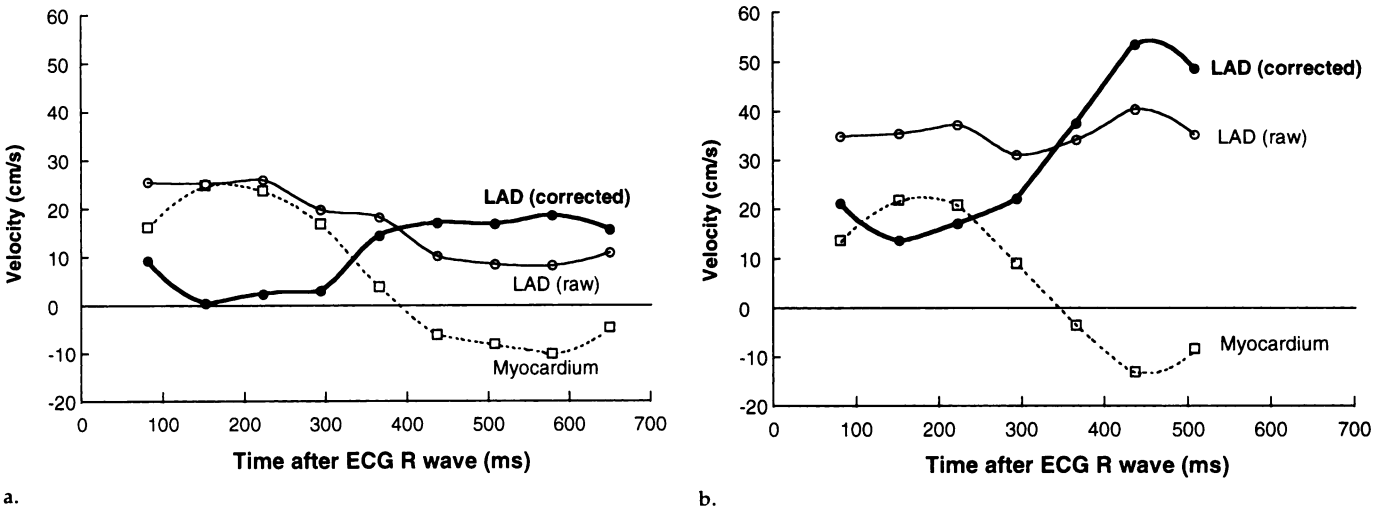

Figure 3. Subject 1. Blood flow velocity in the LAD artery and in the myocardium adjacent to the LAD artery is plotted as a function of time in the cardiac cycle **(a)** before and **(b)** after administration of dipyridamole. Corrected LAD flow velocity was obtained by subtracting the velocity in the adjacent myocardium from the uncorrected LAD flow velocity. Corrected peak diastolic flow velocity increased from 16.6 to 54.0 cm/sec with pharmacologic stress. The number of temporal phases in breath-hold velocity-encoded cine MR imaging decreased after dipyridamole administration, owing to the increased heart rate. *ECG* = electrocardiography.

tion window in which motion is averaged over the time, was 128 msec, which is expressed by $m \times n \times TR$, where m is the number of flow-encoding sequences for each k-space view, n is the number of views collected per segment, and TR is repetition time. View-sharing reconstruction was used to improve the effective temporal resolution. Images at intermediate temporal phases were generated by using the last $n/2$ views in each segment of one temporal-phase image with the first $n/2$ views in each segment of the succeeding temporal phase, where n is the number of views per segment (10). If m temporal-phase images were originally obtained with velocity-encoded cine MR imaging, this method increases the number of temporal-phase images to $2m - 1$. The true temporal resolution—that is, the time necessary to acquire data for all n views within a segment—is unchanged (128 msec). However, the effective temporal resolution—that is, the temporal separation between images—is halved (64 msec). Magnitude and phase cine images with seven to 13 temporal phases for an average cardiac cycle were reconstructed from the data acquired within a single breath-hold period.

After the subjects took a deep breath in and breath out, velocity-encoded cine imaging data were acquired for 24 heart beats, with suspended shallow inspiration. The short-axis imaging planes for flow measurements were determined by using long-axis breath-hold cine MR images of the left ventricle, which were parallel to the orientation of the LAD. Since the course of the LAD artery may be tortuous, the optimal imaging plane was chosen from three to five consecutive cardiac short-axis planes so that the orientation of the LAD artery was perpendicular to the imaging plane throughout the cardiac cycle. We chose the imaging plane on which the LAD artery was depicted as a small round vessel, and the adjacent imaging plane showed the LAD artery at a similar location.

To evaluate the interstudy reproducibility of coronary-flow-velocity measurements in humans, breath-hold velocity-encoded cine MR imaging was performed twice, with separate breath holds, in the baseline state. After the baseline measurements were obtained, 0.56 mg dipyridamole per kilogram of body weight was injected into the antecubital vein over 4 minutes. The subject's electrocardiograph and blood pressure were monitored during administration of dipyridamole, when the subject was not in a magnetic field. Then the table was advanced to the imaging position. Approximately 3–4 minutes after injection of dipyridamole, flow velocity in the LAD artery was measured with breath-hold velocity-encoded cine MR imaging to evaluate the augmentation of coronary blood flow velocity with this pharmacologic agent. The coronary-flow-velocity measurements were performed twice after pharmacologic stress to evaluate the interstudy reproducibility.

Flow velocities in the LAD arteries were measured independently by two observers. Reconstructed magnitude and phase images had pixel dimensions of approximately 1 × 1 mm. With use of a magnitude image, a track ball was used to place small regions of interest with pixel dimensions of 2 × 2 within the lumen of the LAD artery. Then the average velocity in the region of interest was measured on the corresponding phase image. The measurements were repeated for all cardiac phases, with the location of the region of interest modified for each frame. A region of interest with a relatively large area (30–50 pixels) was placed on the tissue adjacent to the LAD artery for each cardiac phase, and the relative blood flow velocity in the coronary artery was calculated in comparison with that in the surrounding tissue. Peak diastolic flow velocities in the baseline state and after dipyridamole administration were depicted from phasic time-velocity curves throughout the cardiac cycle. Coronary flow reserve was calculated as the ratio of hyperemic to baseline coronary blood flow velocity. The volume flow was not calculated, because the small diameter of the LAD artery in relation to the spatial resolution of the images made the accuracy of this measurement questionable. Moreover, the contrast of the LAD arterial edge in the basal and vasodilation states varied, because of the increased signal intensity in the artery associated with the increase in flow velocity.

All data were expressed as the mean plus or minus the standard deviation, except where noted. The peak diastolic flow velocities in the baseline and after stress were compared with a paired Student t test. Statistical significance was defined as a P value less than .05. Interstudy and interobserver variabilities were calculated as the absolute difference between the two measurements divided by the mean of the two measurements.

RESULTS

Measurements of phasic coronary blood flow velocity in the eight healthy volunteers were readily obtained in the baseline state and after dipyridamole administration with breath-hold velocity-encoded cine MR imaging (Figs 1, 2). Figures 3 and 4 show blood flow velocity plotted over time in the cardiac cycle before and after administration of dipyridamole. Table 1 summarizes diastolic peak velocities, blood pressure, and heart rates measured in the baseline state and after dipyridamole administration in the eight subjects. The average peak diastolic flow velocity in the LAD artery was 14.8 cm/sec ± 1.9 in

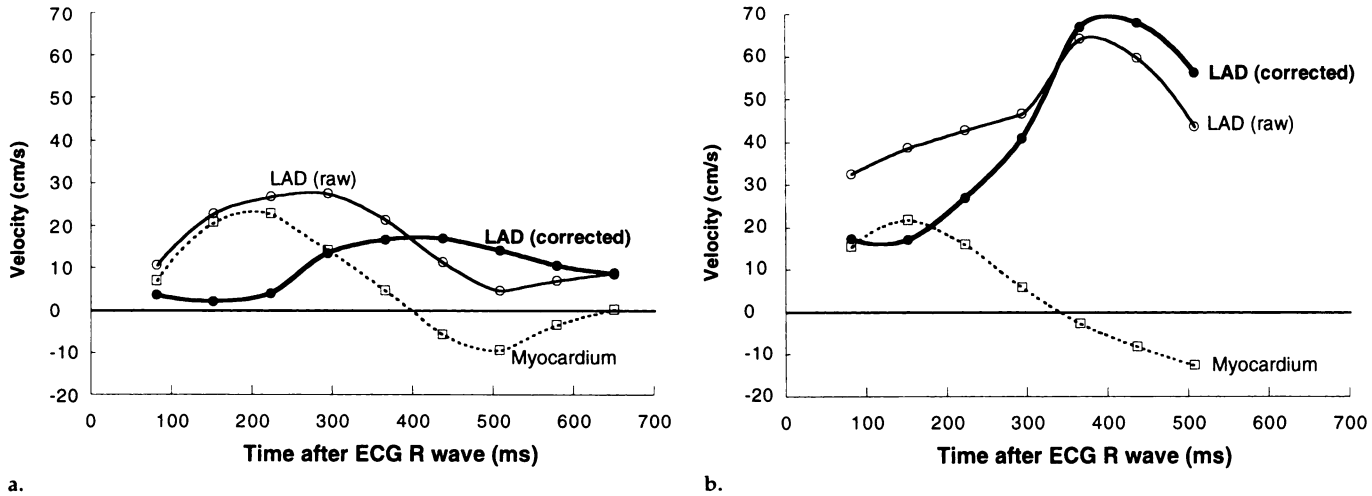

Figure 4. Subject 6. Blood flow velocity in the LAD artery and in the myocardium adjacent to the LAD artery is plotted as a function of time in the cardiac cycle **(a)** before and **(b)** after administration of dipyridamole. Peak diastolic flow velocity increased from 17.0 to 67.6 cm/sec with pharmacologic stress. *ECG* = electrocardiography.

Table 1
Individual Hemodynamic Parameters before and after Dipyridamole Administration

Subject No./ Age (y)†/Sex	Diastolic Peak Velocity*		Coronary Flow Reserve*‖	Blood Pressure		Heart Rate	
	Baseline (cm/sec)‡	Stress (cm/sec)§		Baseline (mm Hg)	Stress (mm Hg)	Baseline (beats/min)#	Stress (beats/min)**
1/32/M	16.6	54.0	3.25	129/86	129/77	75	90
2/29/M	14.9	43.8	2.94	114/62	110/64	68	88
3/27/M	15.8	35.9	2.28	116/68	101/48	52	60
4/24/F	16.3	42.1	2.59	120/74	128/65	82	93
5/27/M	11.6	43.9	3.80	113/63	110/72	60	60
6/22/M	17.0	67.6	3.98	129/71	127/67	70	89
7/22/M	13.5	46.1	3.44	109/56	121/66	73	72
8/23/M	13.2	37.4	2.84	101/58	100/50	53	60

* Expressed as mean of the two breath-hold flow velocity measurements.
† 25.8 ± 3.6 (mean ± standard deviation).
‡ 14.8 ± 1.9.
§ 46.3 ± 10.2.
‖ 3.14 ± 0.59.
66.6 ± 10.7.
** 76.5 ± 15.0.

the baseline state, and it increased significantly ($P < .01$) (Fig 5) to 46.3 cm/sec ± 10.2 after dipyridamole administration. The average coronary flow reserve was 3.14 ± 0.59.

The interstudy reproducibility for measurement of peak diastolic flow velocity—assessed as the mean percentage of the absolute differences in the measurements over the mean of the two measurements—was 9.5% ± 1.6 (mean ± standard error of the mean) in the baseline state and 6.8% ± 2.2 after dipyridamole administration (Table 2). Interobserver reproducibility was 7.0% ± 2.5 in the baseline state and 3.4% ± 1.5 after dipyridamole administration.

DISCUSSION

Coronary flow reserve has been previously evaluated with invasive techniques, such as intravascular Doppler ultrasonography (3–5) and quantitative digital angiography (12), which can measure blood flow or blood flow velocity in the baseline state and during vasodilation induced with pharmacologic stress. Although the functional severity of coronary artery stenosis can be assessed by measuring coronary flow reserve (1–2), use of invasive methods is not feasible to identify coronary artery disease in a large population of patients at risk for the disease or for the serial assessment of coronary function in response to therapy. Transesophageal echocardiography has been used to measure flow in the proximal portion of the LAD artery (13). Our results show that coronary blood flow velocities at multiple phases in the cardiac cycle can be assessed noninvasively with breath-hold velocity-encoded

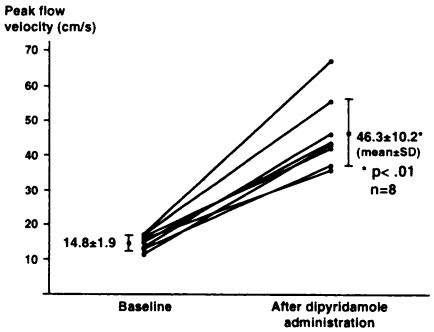

Figure 5. Peak diastolic velocities in the eight healthy subjects before (*Baseline*) and after administration of dipyridamole. *SD* = standard deviation.

cine MR imaging. The coronary flow reserve we measured in healthy subjects (3.14 ± 0.59) is consistent with that previously reported with transesophageal Doppler echocardiogra-

Table 2
Interstudy and Interobserver Variabilities for Diastolic Peak Velocity and Coronary Flow Reserve

Data	Interstudy Variability	Interobserver Variability
Diastolic peak velocity		
In baseline state	9.5 ± 1.6	7.0 ± 2.5
After dipyridamole administration	6.8 ± 2.2	3.4 ± 1.5
Coronary flow reserve	12.0 ± 1.8	9.5 ± 2.6

Note.—Numbers are percentages. Values are the mean of the absolute difference between the two measurements over the mean of the two measurements plus or minus the standard error of the mean.

phy (3.22 ± 0.96) (13). Interstudy and interobserver variabilities in our measurement of peak diastolic flow velocity with MR imaging were both satisfactory (less than 10%).

Flow Measurement with Breath-Hold Velocity-encoded Cine MR Imaging

The evaluation of coronary arterial anatomy and flow with MR imaging has been difficult because the arteries are small, tortuous, and move with the cardiac and respiratory cycles (14–15). Flow velocity quantification in the coronary artery with phase-contrast MR imaging was initially reported by Edelman et al (7) and Keegan et al (8). Although these two previous studies and our current study use the same approaches—namely, the use of velocity-encoded gradients and k-space segmentation—the sequence we employed incorporates several important improvements. In our study, cine data acquisition provided images at multiple temporal phases in the cardiac cycle during a single breath-hold period, but in the previous studies multiple breath holds were necessary because only one cardiac phase was depicted for each breath hold. Moreover, we used uniform repetition time and resonance frequency excitation to maintain spins at a dynamic equilibrium, which decreased artifacts and allowed acquisition of data immediately after the electrocardiographic R wave trigger. Finally, we used view-sharing reconstruction in our study to improve effective temporal resolution by shifting a virtual acquisition window by half the original temporal resolution, thereby providing better sampling for diastolic peak flow velocity.

A known error of velocity measurement with phase-contrast MR imaging is an offset in velocity caused by imperfection in the magnetic field gradient, due to eddy currents (9,16). Because the offset value in phase depends on spatial location, this imperfection can be corrected by measuring the offset value in the surrounding stationary tissue in static organs, such as the brain. Since the coronary arteries and their surrounding tissue undergo considerable motion due to cardiac contraction this offset is difficult to obtain. Consequently, the absolute flow velocity in coronary arteries measured with MR imaging may be imperfect. In our study, the relative velocity of blood flow in the coronary arterial lumen compared with that in the adjacent tissue was calculated. With this method, the flow velocity is determined with respect to the coronary vessel wall, not with respect to the stationary tissue.

Advantages of MR Imaging over Other Techniques

Measurement of flow velocity in the coronary artery with breath-hold velocity-encoded cine MR imaging is rapid and noninvasive. This method should be useful in sequential studies in patients. In addition, MR imaging can provide anatomic and functional information, such as ventricular wall motion and wall thickening, thus enabling the comprehensive assessment of ischemic heart disease within a single MR imaging examination.

A small intravascular Doppler probe has been used widely to measure coronary flow velocity and provide continuous measurement of phasic flow velocity, with good temporal resolution. The disadvantages of the intravascular Doppler probe include the following: (*a*) It is invasive and has a small, but proved, mortality risk to the patients, and (*b*) the increased radiation exposure to the patient may not be negligible if the time needed to position the Doppler probe is prolonged for a diagnostic procedure (8). Transesophageal echocardiography has also successfully depicted the coronary arteries and helped determine flow velocity in these vessels (13), but the method is semi-invasive.

Myocardial scintigraphy with thallium-201 or technetium-99m methoxyisobutyl isonitrile with exercise or pharmacologic stress can indicate the distribution of perfusion for the entire left ventricle and has been used widely to help detect myocardial ischemia. Although some similarities exist in what is being measured, the roles of myocardial scintigraphy and coronary flow measurement are different. MR imaging flow measurement demonstrates the functional severity of the stenosis at a specific site in the coronary artery, which directly relates to the indication for interventional procedures. Myocardial scintigraphy, on the other hand, shows the distribution of perfusion at peripheral myocardial tissue, which may be influenced by the collateral circulation. In MR flow imaging, data are acquired within a single breath hold, so the maximum effect of the stress can be detected. In contrast, myocardial scintigraphy depicts the averaged myocardial perfusion over several minutes after injection of the tracer. Tl-201 scintigraphy is also influenced by redistribution of the tracer.

Current Limitations of MR Imaging Flow Velocity Measurement

In current human studies, the absolute accuracy of the flow measurements in coronary arteries has not been demonstrated. Since the coronary arteries exhibit complex motions due to respiration and cardiac contraction, validation of MR imaging flow measurements with a small phantom tube is not sufficient to demonstrate the accuracy of the measurements. Further studies with animal models are necessary to compare MR imaging flow measurements with Doppler flow meter measurements.

Although flow volume measurement could be obtained, in principle, by integrating the flow velocity and the cross-sectional area of the coronary artery over the cardiac cycle, we calculated the coronary flow reserve as the ratio of resting-to-stress coronary blood flow velocity instead of the ratio of actual flow volume. The use of peak velocity and total flow volume may give different values for coronary flow reserve if the shape of the flow versus the time curve and diameter of the coronary artery are altered with stress. The accuracy of flow-volume measurement with phase-contrast MR imaging has been

shown for large vessels in several studies (17–19) in which a sufficient number of image pixels were included in the vessels. For small vessels, such as a coronary artery, however, the effects of partial volume averaging along the endothelial border of the coronary artery can be significant. The MR signals from blood flowing in the artery and those from the vessel wall and surrounding tissue are averaged in those marginal pixels. The current in-plane spatial resolution (approximately 1 × 1 mm) may not be sufficient to quantify volume flow accurately (20). The electrocardiographic trigger window during which no data are acquired also complicates the quantification of flow volume with phase-contrast cine MR imaging. Since we evaluated the peak flow velocity, it was not important to obtain the complete flow curve in the cardiac cycle.

Cardiac contraction generates two different components of motion in the coronary arteries, through-plane motion and in-plane motion. As mentioned previously, we corrected the effect of through-plane motion and of the offset error in phase by subtracting the velocity in the tissue surrounding the coronary artery. Large in-plane motion may blur the coronary artery during data acquisition in velocity-encoded cine MR imaging. Although we did not observe any noticeable blurring of the LAD artery throughout the cardiac cycle, the right coronary artery exhibited greater in-plane motion in the systolic phase than did the LAD artery. In contrast to the LAD artery, which generally has peak flow velocity in the diastolic phase, the right coronary artery may demonstrate peak flow velocity in the systolic phase. Thus, the evaluation of flow reserve in the right coronary artery necessitates flow measurement throughout the cardiac cycle. Measurement of flow velocity in the right coronary artery over the entire cardiac cycle necessitates use of better temporal resolution than we used (64 msec) or of a novel method to correct for coronary arterial motion (21). Spatial and temporal resolutions in current breath-hold velocity-encoded cine MR imaging are mainly limited by the performance of the gradient system in the MR imager. Use of a stronger gradient system, which is designed for nonresonant echo planar imaging, could improve both resolutions considerably.

Breath holding changes intrathoracic pressure, which can affect the rate of return blood flow to the heart and systemic blood pressure. Breath holding may affect the measurement of coronary flow velocity, but evaluation of the coronary flow reserve—the ratio of coronary flow in the baseline state to the flow during pharmacologic stress—should be less susceptible to changes in intrathoracic pressure, because both measurements are made during breath holds.

In conclusion, our results indicate that breath-hold velocity-encoded cine MR imaging is a noninvasive technique that can provide reproducible assessment of coronary flow reserve in humans. Further animal studies are needed to evaluate the absolute accuracy of the flow velocity and volume measurements obtained with MR imaging, by using an ultrasound flow probe. ■

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