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Noninvasive Assessment of Coronary Vasodilation Using Magnetic Resonance Angiography

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OBJECTIVES The purpose of this study was to investigate the use of coronary magnetic resonance angiography (MRA) for assessing human epicardial coronary artery vasodilation.

BACKGROUND Coronary vasodilation plays a vital role in the human coronary circulation. Previous studies of epicardial coronary vasodilation have used invasive coronary angiography. Coronary MRA may provide an alternative noninvasive method to directly assess changes in coronary size.

METHODS Thirty-two subjects were studied: 12 patients (age 55 ± 18 years) and 20 healthy subjects (age 34 ± 4 years). High-resolution multi-slice spiral coronary MRA (in-plane resolution of 0.52 to 0.75 mm) was performed before and after sublingual nitroglycerin (NTG). Quantitative analysis of coronary vasodilation was performed on cross-sectional images of the right coronary artery (RCA). A time-course analysis of coronary vasodilation was performed in a subset of eight subjects for 30 min after NTG. Signal-to-noise ratio was also measured on the in-plane RCA images.

RESULTS Coronary MRA demonstrated a 23% increase in cross-sectional area after NTG (16.9 ± 7.8 mm^2 to 20.8 ± 8.9 mm^2, $p < 0.0001$), with significant vasodilation between 3 and 15 min after NTG on time-course analysis. The MRA measurements had low interobserver variability (≤5%) and good correlation with X-ray angiography ($r = 0.98$). The magnitude of vasodilation correlated with baseline cross-sectional area ($r = 0.52$, $p = 0.03$) and age ($r = 0.40$, $p = 0.019$). Post-NTG images also demonstrated a 31% improvement in coronary signal-to-noise ratio ($p = 0.002$).

CONCLUSIONS Nitroglycerin-enhanced coronary MRA can noninvasively measure coronary artery vasodilation and is a promising noninvasive technique to study coronary vasomotor function. (J Am Coll Cardiol 2005;45:104–10) © 2005 by the American College of Cardiology Foundation

Impaired coronary vasodilation, as measured by changes in epicardial coronary artery size in response to vasoactive stimuli, is an early feature of coronary atherosclerosis (1–4). Coronary endothelium-*dependent* vasodilation, in particular, has been shown to predict long-term atherosclerotic disease progression and cardiovascular events (4–8). Impaired coronary vasodilation to nitroglycerin (NTG), an endothelium-*independent* vasodilator, has also been found in patients who have coronary risk factors (9) and has also been associated with an increased risk of future cardiac events (7). However, previous studies have required either invasive X-ray coronary angiography (XRA) (1,4–8) or intravascular ultrasound (10) to measure epicardial coronary vasodilator responses. A noninvasive technique for measuring human epicardial coronary vasodilation directly would allow more widespread study of coronary vasoreactivity in patients with, or at risk for, coronary artery disease (CAD).

Coronary magnetic resonance angiography (MRA) has developed rapidly over the past decade. High-resolution coronary MRA can now achieve sub-millimeter spatial resolution by a variety of breath-hold and non–breath-hold techniques (11,12), making measurement of coronary vasodilation feasible. It also does not require ionizing radiation or contrast agents, making it particularly safe for serial measurements.

This study tested the hypothesis that high-resolution coronary MRA can quantify changes in epicardial coronary artery size in response to an easily administered vasodilator, sublingual NTG, in both patients and healthy subjects.

METHODS

Subjects. A total of 32 subjects without contraindications to magnetic resonance imaging (MRI) were studied. This included 20 healthy subjects (age 33 ± 5 years, 18 male/2 female) who had no known cardiovascular disease. In addition, to validate the technique in patients, 12 subjects (age 53 ± 18 years, 9 male/3 female) who had previously undergone XRA were also evaluated. This included six patients with native CAD, ranging from one- to three-vessel disease, as well as six patients averaging 5 ± 3 years after heart transplant (Tx). All participants provided written informed consent approved by the Human Subjects Committee at Stanford University.

MRI. A 1.5-T Signa MRI scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with high-performance gradients (40 mT/m, 150 mT/m/ms) and a real-time interactive workstation was used. A commercial surface

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Abbreviations and Acronyms

CAD = coronary artery disease
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NTG = nitroglycerin
RCA = right coronary artery
ROI = region of interest
SNR = signal-to-noise ratio
Tx = post-transplant
XRA = X-ray coronary angiography

coil provided signal reception (5-inch General Purpose Coil, Model #2127316, GE Healthcare, Milwaukee, Wisconsin). A real-time interactive MRI system, reported previously (13,14), was used for coronary localization (sequence parameters: 16 frames/s, recovery time (TR) = 30 ms, echo time (TE) = 4.6 ms, flip angle = 30°, slice thickness = 7 mm, field of view = 24 cm, in-plane spatial resolution = 2.7 mm).

High-resolution coronary MRA was performed using a multi-slice spiral sequence, as previously reported (15,16), with cardiac gating, breath-holding, and acquisition during diastole (field of view = 20 to 22 cm, in-plane spatial resolution = 0.52 to 0.75 mm, slice thickness = 5 mm, 5 slices, TR = 1 heart beat, TE = 7 ms, 14 to 20 interleaves, flip angle = 60°). Images were reconstructed onto a 512 × 512 matrix, yielding a pixel size of 0.39 to 0.43 mm.

Study protocol. Vasoactive medications were discontinued 24 h before the examination. Subjects were placed supine in the magnet with the surface coil placed over the anterior chest. Noninvasive blood pressure and heart rate monitoring were performed throughout the study (Omega 1400, Invivo Research Inc., Orlando, Florida). Real-time interactive MRI was used to prescribe in-plane views of the right and left coronary arteries. For quantitative analysis, a cross-sectional view of a linear portion of the proximal to mid-right coronary artery (RCA) was also prescribed, avoiding a site of stenosis or stent in the patients. Then, in-plane and cross-sectional high-resolution coronary MRA scans were acquired before and then 3 to 5 min after 0.4 mg sublingual NTG was given to the subject while in the magnet. For time-course analysis, we performed cross-sectional coronary MRA in a subset of eight healthy subjects before and then every minute up to 5, 7, 10, 15, 20, and 30 min after sublingual NTG.

Image analysis. VASODILATION. For quantitative analysis of coronary vasodilation, the cross-sectional RCA images were used. The slice with the most circular cross-section was identified on the pre-NTG images. The corresponding post-NTG slice was carefully matched according to the surrounding cardiac and chest wall structures. These images were all pooled and then randomized, with no patient information provided on the images. Using Scion Image (PC version of NIH Image from Scion Corporation, Frederick, Maryland), all MRA images were analyzed independently by two observers, blinded to patient and NTG information. Images were magnified two-fold, and a circular region-of-interest (ROI) tool was used to trace around the RCA, yielding cross-sectional area (Fig. 1). The pre- and post-NTG measurements from all 30 subjects were also analyzed for intraobserver and interobserver variability.

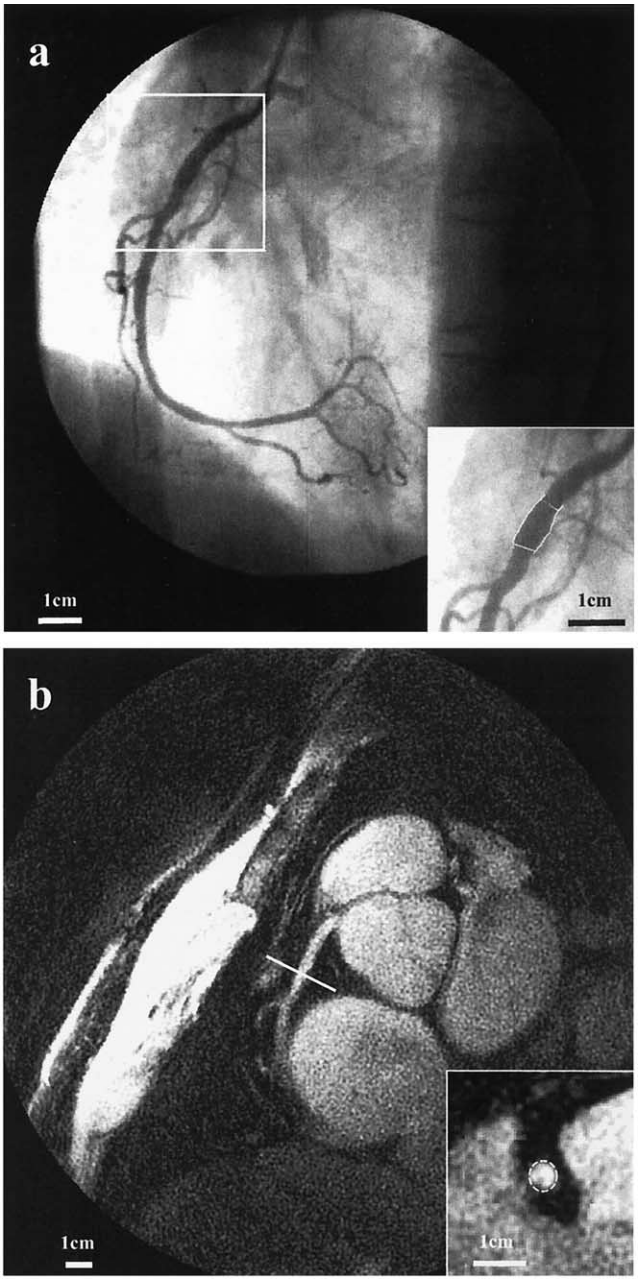

Figure 1. Quantitative analysis of corresponding X-ray coronary angiography **(a)** and coronary magnetic resonance angiography (MRA) **(b)** images of the right coronary artery showing the quantitative measurements of coronary size (X-ray: mean diameter = 4.1 mm; MRA: cross-sectional area = 19.8 mm^2, diameter = 5.0 mm).

SIGNAL-TO-NOISE RATIO (SNR). Because the slice thickness of in-plane images (typically used to assess coronary anatomy) is often on the order of the coronary diameter, vasodilation may be expected to increase the coronary SNR.

JACC Vol. 45, No. 1, 2005
January 4, 2005:104–10

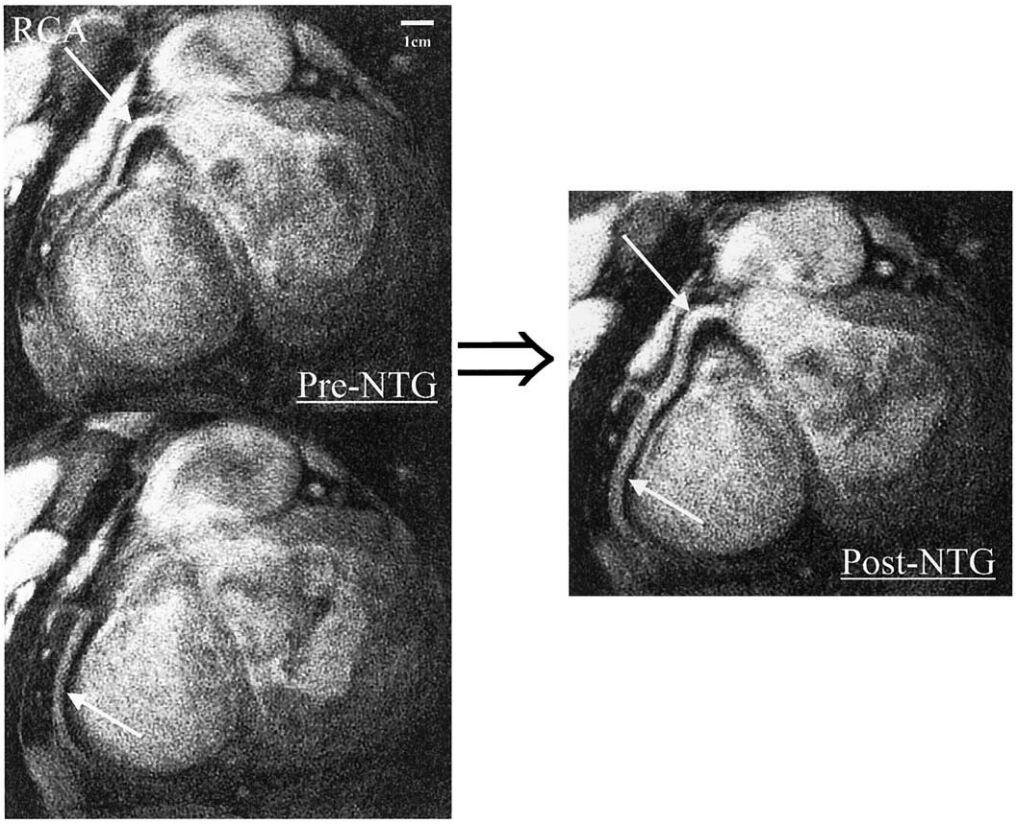

Figure 2. Right coronary artery (RCA) vasodilation with nitroglycerin (NTG). **(Left)** Coronary magnetic resonance angiography (MRA) images pre-NTG showing the proximal and mid-RCA **(arrows)** over two slices. **(Right)** Coronary MRA image after NTG showing clear vasodilation of both the proximal and mid-vessel.

The SNR of coronary MRA before and after NTG was compared on in-plane RCA images using one ROI drawn inside the coronary lumen and a second ROI drawn outside the heart, with SNR calculated as the signal intensity of the coronary artery divided by the standard deviation of the artifact-free noise.

XRA CORRELATION. A subset of seven patients had XRA performed within one month of their MRI study. This allowed a comparison of baseline coronary diameter between XRA and MRI. Using XRA images in diastole (as the MRA acquisition was in diastole), a 10-mm length of the RCA was analyzed by quantitative coronary angiography (QCA plus, Sanders Data Systems, Palo Alto, California) to calculate the mean diameter (Fig. 1); MRA diameter was calculated from the cross-sectional area of the RCA using the formula:

$$\text{lumen diameter} = 2 \times \sqrt{[\text{lumen area} / \pi]}$$

Statistical analysis. Data were expressed as mean values ± SD. StatView (version 5, SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses. The difference in coronary size before and after NTG was compared by the paired *t* test. Differences in subject groups were tested using a one-way analysis of variance (ANOVA) followed by post-hoc Fisher protected least significant differences test (PLSD). Correlation between coronary vasodilation and baseline cross-sectional area and age was tested by non-linear (logarithmic) regression analysis. Intra- and interobserver variability were analyzed by calculating both the percentage of the absolute difference between the two measurements divided by the mean of the measurements as well as the correlation coefficient. The comparison between MRA and XRA was performed by linear regression analysis. For time-course analysis, we performed one-way repeated-measures ANOVA with Fisher PLSD. Statistical significance was assumed as a two-tailed p value <0.05.

RESULTS

All subjects completed the study without any complications. Nitroglycerin caused a small but significant systemic effect. There was a 5% decrease in systolic blood pressure (from 112 ± 12 mm Hg to 107 ± 8 mm Hg), 8% decrease in diastolic blood pressure (from 72 ± 8 mm Hg to 66 ± 8 mm Hg), and 6% increase in heart rate (from 72 ± 18 beats/min to 77 ± 17 beats/min). Two subjects were excluded from quantitative analysis—one healthy subject had a diminutive RCA, presumably non-dominant, whereas one patient had taken long-acting nitrates on the day of the study.

Coronary vasodilation. Coronary vasodilation was evident on in-plane and through-plane coronary images of both the

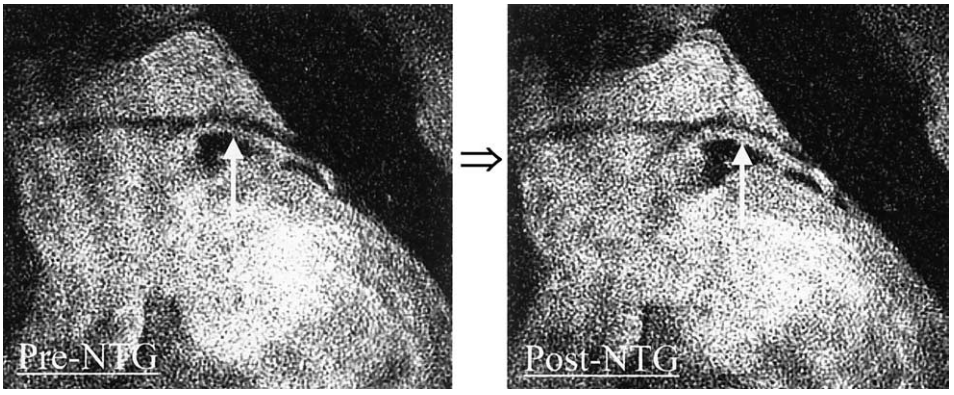

Figure 3. Left anterior descending coronary artery (LAD) vasodilation with nitroglycerin (NTG). Coronary magnetic resonance angiography images of the proximal LAD **(arrow)** before **(left)** and after NTG **(right)**.

right and left coronary arteries (Figs. 2 to 4). On quantitative analysis (n = 30), coronary cross-sectional area increased 23.1% (16.9 ± 7.8 mm^2 to 20.8 ± 8.9 mm^2, $p < 0.001$) after NTG (Fig. 5). There were moderate yet significant correlations between the magnitude of vasodilation and the baseline cross-sectional area ($r = 0.52$, $p = 0.03$), and age ($r = 0.40$, $p = 0.019$) (Fig. 6). On subgroup analysis, significant vasodilation was demonstrated for both healthy subjects (24.0%, $p < 0.001$) and patients (22.2%, $p = 0.003$). However, with this endothelial-independent vasodilator, the difference in vasodilation between healthy subjects and patients was not significant ($p > 0.05$ for subjects vs. patients and for CAD vs. Tx patients). The coronary area measurements had an intraobserver variability of 3 ± 2%, with a correlation of 0.99, and an interobserver variability of 5 ± 5%, with a correlation of 0.96.

Time course of coronary vasodilation. Time course analysis (n = 8) demonstrated significant vasodilation from baseline to 3 min (16.9 ± 5.9 mm^2 vs. 20.8 ± 4.6 mm^2, $p = 0.002$) with minimal change from 5 min (21.4 ± 4.6 mm^2, $p = 0.001$) to 15 min (20.5 ± 8.1 mm^2, $p = 0.03$) (Fig. 7). The degree of vasodilation was no longer significant at 20 and 30 min (19.3 ± 5.0 mm^2, $p = 0.06$ and 19.3 ± 6.5 mm^2, $p = 0.14$).

SNR improvement. Clinical coronary MRA studies typically use in-plane rather than cross-sectional coronary views.

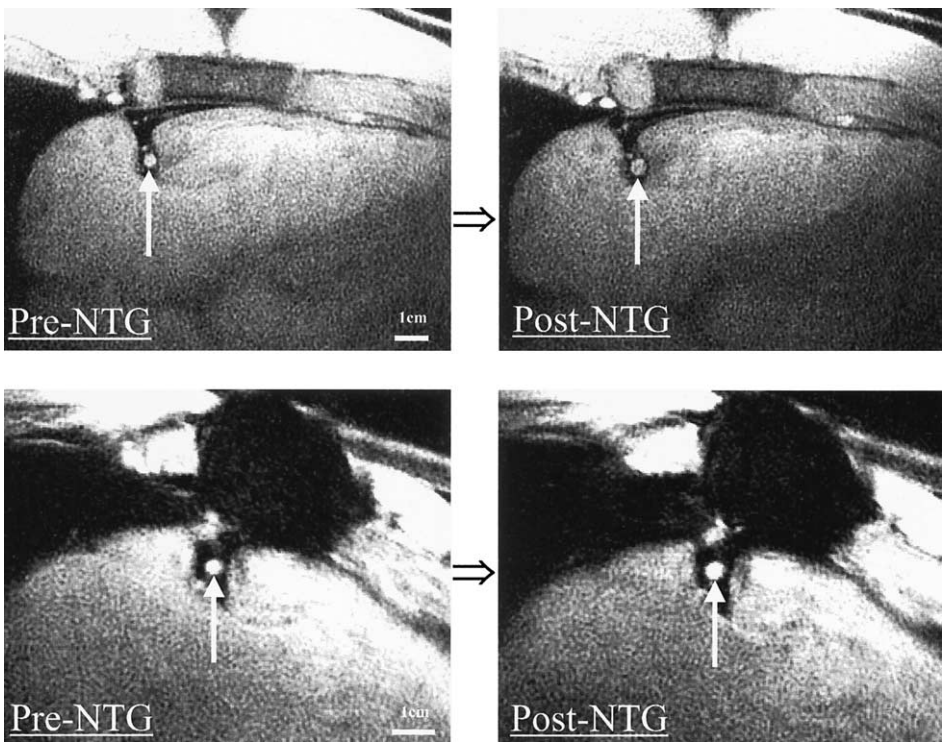

Figure 4. Cross-sectional magnetic resonance angiography images of the right coronary artery (RCA) **(arrows)** before **(left)** and after **(right)** nitroglycerin (NTG), showing vasodilation in a healthy volunteer (RCA area increased from 12.0 to 17.0 mm^2) **(top)** and a heart transplant patient (RCA area increased from 12.6 to 15.5 mm^2) **(bottom)**. Note the multiple similarities in the shape/features of the adjacent atrioventricular groove, right atrium and ventricle, and chest wall on the pre- and post-NTG images, indicating good spatial correspondence.

JACC Vol. 45, No. 1, 2005
January 4, 2005:104–10

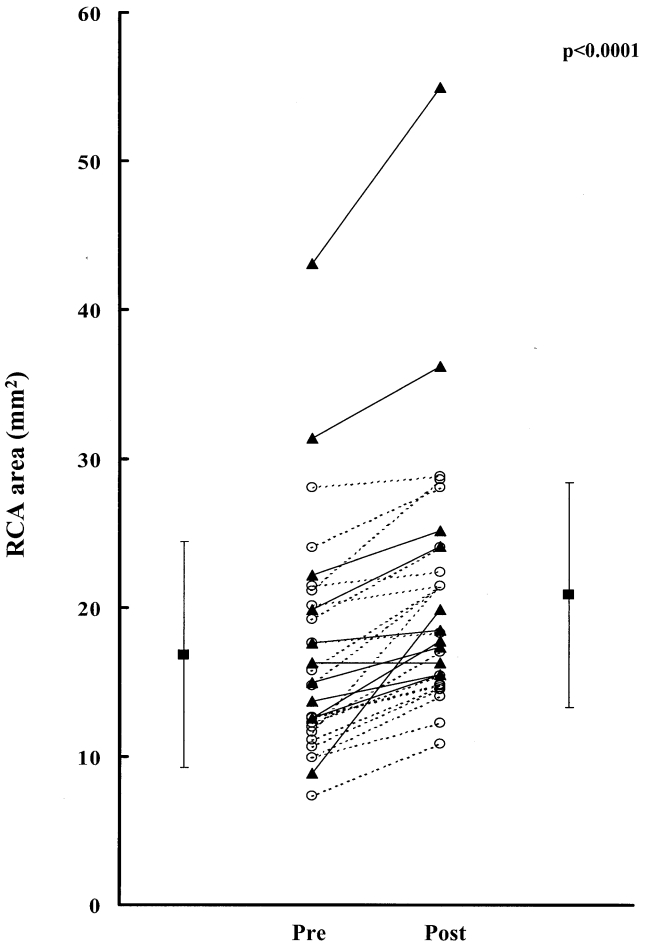

Figure 5. Quantitative analysis of nitroglycerin-induced coronary vasodilation with coronary magnetic resonance angiography showing the significant increase in right coronary artery (RCA) cross-sectional area. **Open circles** = healthy subjects; **closed triangles** = patients. **Filled squares** and **error bars** indicate mean ± SD.

With NTG-induced coronary dilation, improved coronary SNR was seen on the in-plane images, increasing 31% (11.3 ± 5.5 vs. 14.8 ± 6.8, p = 0.002).

Coronary MRA vs. X-ray angiography. For the subset of patients with recent XRA (n = 7), there was good correlation of baseline coronary artery diameter measurements between MRA and XRA (r = 0.98, p < 0.0001). There was an offset in the regression line (Y = 1.05X + 0.72 mm), with MRA overestimating XRA by an amount similar to the MRA spatial resolution (0.52 to 0.75 mm).

DISCUSSION

The present study demonstrates that coronary MRA can noninvasively detect and quantify coronary vasodilation in both healthy subjects and patients. Coronary cross-sectional area increased 23% overall, and measurements had low interobserver variability; NTG also increased the SNR of coronary MRA by 31%.

Coronary vasomotor function. Coronary vasodilation plays a pivotal role in the human coronary circulation's response to varying demand. Although NTG typically has been used to demonstrate endothelium-independent vasodilation as a positive control to endothelium-dependent vasodilation, some previous studies have shown that an impaired vasodilatory response to NTG is associated with risk factors for CAD (9) and with an increase in future clinical events (7). However, direct measurement of epicardial coronary vasodilation has typically required invasive techniques, which limit coronary vasodilation testing to patients already undergoing XRA and make serial or follow-up measurements impractical.

Several groups have used M-mode or transesophageal echocardiography to image the left main coronary artery (17,18). However, the left main trunk is well visualized in only a subset of patients by transthoracic echocardiography, and transesophageal echocardiography is semi-invasive. A large number of studies have directly imaged brachial artery vasodilation by high-resolution ultrasound based on the concept that peripheral vascular function parallels that of the coronary arteries because of the systemic nature of atherosclerosis (2,19,20). Although there is a reasonable overall correlation between coronary and brachial vasomotor function (21,22), Hirooka et al. (23) demonstrated divergent effects of L-arginine on these two vascular beds. It is, thus, unknown if brachial vasomotor function is as predictive as coronary function on an individual basis.

There are other noninvasive approaches to assess coronary microvascular vasodilatory function indirectly by measuring coronary flow or perfusion reserve, including contrast-enhanced transthoracic echocardiography (24,25), positron emission tomography (26), and MRI (27,28). Future MRI studies may be able to combine measurements of epicardial coronary vasodilation with coronary flow reserve.

Coronary vasodilation by NTG. According to previous reports, sublingual NTG, at a dose of 0.4 mg, typically elicits a vasodilatory response within 2 to 5 min with maximal effects at 3 to 15 min and little residual activity by 20 to 30 min (29–31). Our time-course data were consistent with these published data, demonstrating significant coronary vasodilation over 3 to 15 min but not at 20 to 30 min. Whereas most coronary vasodilation studies have used intracoronary NTG, a study of sublingual NTG demonstrated an 18% increase in cross-sectional area calculated by XRA in patients with CAD (32). Correlations between the degree of vasodilator responses to NTG and the baseline cross-sectional area and age were also seen in our study (Fig. 6), which has been noted in previous studies (10,32,33). Interestingly, even in the healthy subjects, those with lower vasodilation (<20% area change, n = 7) had a higher mean age (38 ± 2 years) compared to those with >20% area vasodilation (mean age 30 ± 3 years, n = 12).

This study included a group of different types of patients in order to validate that coronary MRA detection of coronary vasodilation was not limited to healthy subjects. Many coronary MRA techniques initially demonstrated in healthy subjects are more difficult to demonstrate in patients, due to body habitus, breath-holding ability, surgical

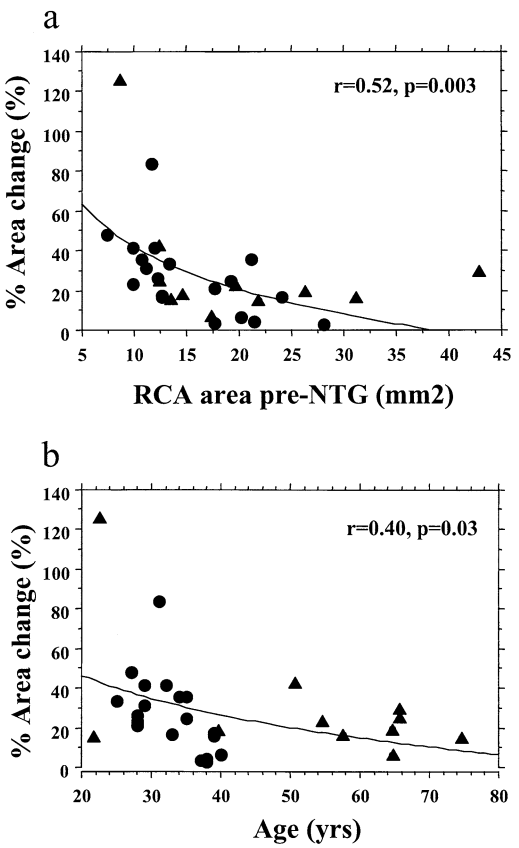

Figure 6. Non-linear (logarithmic) correlations of coronary vasodilator response to baseline cross-sectional area **(a)**, and patient age **(b)**. **Circles** = healthy subjects; **triangles** = patients. NTG = nitroglycerin; RCA = right coronary artery.

artifacts, and the like. Although we were able to show significant coronary vasodilation for the patient group, the study was not sufficiently powered to demonstrate differences between the study groups, particularly using an endothelium-independent stimulus. The use of endothelium-dependent stimuli would be expected to show greater differences between study groups, but is challenging in the MRI environment. Typical intra-arterial agents, such as acetylcholine, cannot safely be given systemically. Non-pharmacologic approaches, such as the cold-pressor test (4) and mental stress (34), offer promise and warrant further study.

Improved SNR of Coronary MRA. We demonstrated that sublingual NTG improved coronary SNR on in-plane imaging, as an additional benefit of coronary vasodilation. Higher SNR may improve image quality, allow for higher spatial/temporal resolution, or improve visualization of branch vessels. Given that sublingual NTG was well-tolerated, it has the potential to improve the diagnostic accuracy of clinical coronary MRA studies. Of note, long-acting nitrates were used as part of the first multicenter clinical coronary MRA trial (35).

Study limitations. As mentioned, a major limitation to the current study is that we assessed only endothelium-independent coronary vasodilation using NTG, as endothelium-dependent coronary stimuli have practical limitations and the primary goal was to demonstrate that coronary MRA can quantitate coronary vasodilation in both healthy subjects and patients. A substantially larger clinical study would be needed in order to be sufficiently powered to show significant differences in coronary vasodilation between study groups.

Quantitative analysis was performed exclusively on the RCA because it has the highest SNR, allowing higher spatial resolution for more precise quantification; RCA measurements by MRA have also been shown to be very reproducible (36). Further improvements in coronary MRA should allow quantitative analysis of both the RCA and left coronary system.

The XRA data were limited to the subset of patients who had a recent angiogram and provides only baseline data (not pre-/post-NTG). The data are consistent with previous studies showing both good correlation between coronary MRA and XRA, as well as the overestimation by MRA (37–39). The amount of overestimation by MRA is due to partial volume effects related to the spatial resolution of the imaging sequence, the pixel width of the image, as well as the window/level settings of the image and how the ROI is placed (37). Improvements in spatial resolution and quantitative image analysis software may help to minimize this overestimation (36,37). The time between XRA and MRA studies and that holding vasoactive medications for 24 h was not part of the instructions before XRA may have further contributed to differences between the XRA and MRA measurements.

Clinical implications. Coronary vasodilation by MRA may have clinical applications in addition to the potential for improved SNR and image quality of clinical coronary MRA studies. A noninvasive method to assess coronary vasodilation avoids the small, but non-zero risk of XRA. Coronary MRA could, thus, be used to assess vasodilatory drugs, as well as to assess serial changes of coronary function in response to therapeutic interventions. To be most useful, an endothelium-dependent stimulus needs to be incorporated. Moreover, combining coronary vasodilation with MR techniques for the study of coronary anatomy, coronary

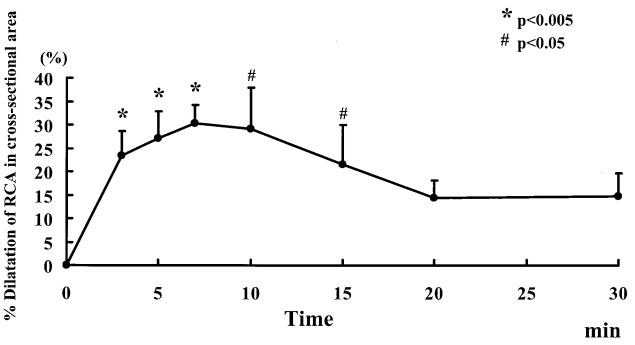

Figure 7. Time course of coronary vasodilation. Significant coronary vasodilation was seen starting at 3 min after nitroglycerin and persisting up to 15 min. RCA = right coronary artery.

flow, and the coronary wall may provide a comprehensive noninvasive structural and functional evaluation of CAD.

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