Note: This copy is for your personal, non-commercial use only. To order presentation-ready copies for distribution to your colleagues or clients, contact us at www.rsna.org/rsnarights.

Purpose:

Materials and

Methods:

Results:

Heterogeneous Microinfarcts Caused by Coronary Microemboli: Evaluation with Multidetector CT and MR Imaging in a Swine Model¹

Marcus Carlsson, MD, PhD David Saloner, PhD Alastair J. Martin, PhD Philip C. Ursell, MD Maythem Saeed, DVM, PhD

¹ From the Department of Radiology and Biomedical Imaging (M.C., D.S., A.J.M., M.S.) and Department of Pathology (PC.U.), University of California, San Francisco, 185 Berry St, Suite 350, Campus Box 0946, San Francisco, CA 94107-5705. Received March 25, 2009; revision requested May 8; revision received June 24; accepted July 15; final version accepted August 10. Supported by a seed grant from the Department of Radiology and Biomedical Imaging, University of California San Francisco. Address correspondence to M.S. (e-mail: maythem.saeed@radiology.ucsf.edu).

© RSNA, 2010

Conclusion:

To directly compare the sensitivity of 64-section multidetector computed tomography (CT) with that of 1.5-T magnetic resonance (MR) imaging in the depiction and measurement of heterogeneous 7–8-week-old microinfarcts and the quantification of regional left ventricular (LV) function and perfusion in the territory of coronary intervention in a swine model.

Approval was obtained from the institutional animal committee. An x-ray/MR system was used to catheterize the left anterior descending (LAD) coronary artery with x-ray guidance and to delineate the perfusion territory. The vessel was selectively microembolized in six pigs with smalldiameter embolic material (40–120 μ m, 250000 count). At 7–8 weeks after microembolization, multidetector CT and MR imaging were used to assess LV function, first-pass perfusion, and delayed contrast enhancement in remote myocardium and microinfarct scars. Histochemical staining with triphenyltetrazolium chloride (TTC) was used to confirm and quantify heterogeneous microinfarct scars. The two-tailed Wilcoxon signed rank test was used to detect differences between modalities and myocardial regions.

The LAD territory was $32.4\% \pm 3.8$ (stadard error of the mean) of the LV mass. Multidetector CT and MR imaging have similar sensitivity in the detection of regional and global LV dysfunction and extent of microinfarct. The mean LV end-diastolic volume, end-systolic volume, and ejection fraction were 93 mL \pm 8, 46 mL \pm 4, and 50% \pm 3, respectively, on multidetector CT images and 92 mL \pm 8, 48 mL \pm 5, and 48% \pm 3, respectively, on MR images ($P \ge .05$). The extent of heterogeneous microinfarct was not significantly different between multidetector CT (6.3% \pm 0.8 of the LV mass), MR imaging (6.6% \pm 0.5 of the LV mass), and TTC staining $(7.0\% \pm 0.6 \text{ of the LV mass})$. First-pass multidetector CT and MR imaging demonstrated significant regional differences (P < .05) in time to peak between the heterogeneous microinfarct and remote myocardium (17.0 seconds \pm 0.3 and 12.4 seconds \pm 0.6, respectively, for multidetector CT and 17.2 seconds \pm 0.8 and 12.5 seconds \pm 1.0, respectively, for MR imaging).

Modern multidetector CT and MR imaging are sensitive modalities with which to depict heterogeneous microinfarcts and determine regional LV dysfunction and decreased perfusion in the territory of intervention.

[©] RSNA, 2010

Radiology

Percutaneous coronary intervention is commonly used to treat coronary artery disease. With the aging population in the United States and other countries, the number of these procedures has increased each year. In relatively recent studies, researchers have identified coronary microemboli as a compounding cause of regional myocardial contractile dysfunction and perfusion deficits in these patients (1–5). In fact, coronary microemboli have been documented at autopsy in patients after sudden death (4,6,7).

Noninvasive cardiac imaging is now key in the diagnosis and care of patients who are known to have or are suspected of having coronary artery disease. Myocardial viability imaging is performed with fluorine 18 fluorodeoxyglucose positron emission tomography, single photon emission computed tomography, magnetic resonance (MR) imaging, andrecently-64-section multidetector computed tomography (CT). Unlike imaging of homogeneous large infarcts, however, imaging of heterogeneous microinfarcts is challenging because of the limited spatial resolution and the fact that the microinfarcted area contains a mixture of viable and nonviable myocytes.

Microinfarcts are defined as bright heterogeneous subregions seen on delayed contrast material-enhanced MR images and pale unstained necrotic subregions seen on histochemically stained specimens (8–11). In several studies, researchers found heterogeneous microinfarcts in patients (2,5,12,13) and animals (8–11) on delayed contrastenhanced MR images. Experimental studies have shown that a heterogeneous microinfarct exceeding 5% of the re-

Advances in Knowledge

- Modern multidetector CT and MR imaging are sensitive modalities with which to visualize and measure heterogeneous microinfarcts.
- Multidetector CT and MR imaging can be used to detect regional myocardial perfusion deficits in the territory of intervention.

gion of interest could be detected with delayed contrast-enhanced MR imaging 6-8 hours after delivery of microemboli into the left anterior descending (LAD) coronary artery territory (10,11). The differential enhancement of heterogeneous microinfarct is related to the larger distribution volume and relatively slow wash-in and wash-out of extracellular contrast media (14-16). To the best of our knowledge, however, heterogeneous microinfarcts have not been previously studied with modern multidetector CT or a combination of multidetector CT and MR imaging. The aim of this study was to directly compare the sensitivity of 64-section multidetector CT with that of 1.5-T MR imaging in the depiction and measurement of heterogeneous 7-8-week-old microinfarcts and the quantification of regional left ventricular (LV) function and perfusion in the territory of coronary intervention in a swine model.

Materials and Methods

Study Protocol and Microemboli

This study was performed between November 30, 2007, and February 18, 2008, in accordance with the Guide for the Care and Use of Laboratory Animals (17) and with approval from our institutional committee on animal research. Eight adult healthy farm pigs (mean weight, 33 kg \pm 1 [standard error of the mean]) were anesthetized with a mixture of 2%-5% isoflurane and oxygen at a rate of 2-3 L/min, as described previously (8,9). Two animals died within 24 hours after delivery of the embolic materials. Coronary catheterization, intervention, and imaging were performed in a hybrid x-ray/MR suite that comprised an x-ray system (Integris V5000; Philips Medical Systems, Best, the Netherlands) and an

Implication for Patient Care

 Multidetector CT and MR imaging may be used to detect cardiac microinfarcts in patients with a wide range of diseases such as atherosclerosis, valvular disease, endocarditis, and arrhythmias—as well as after invasive coronary interventions. MR imager (Achieva I/T, Philips Medical Systems). The LAD coronary artery was catheterized with x-ray fluoroscopy, as described previously (18). The animals were brought to the MR imager after the 3-F infusion catheter (Cook, Chicago, III) was placed distal to the first diagonal branch of the LAD. First-pass perfusion MR images were acquired during intraarterial injection of 10 mL of 10% diluted gadoterate meglumine (Dotarem; Guerbet, Paris, France). The method of delineation of the LAD coronary artery territory has been described recently (18). Short-axis sections covering the LV were acquired to define the perfusion territory with a saturation-recovery gradient-echo sequence (repetition time msec/echo time msec, 4.5/2.2; section thickness, 10 mm; field of view, 26×26 cm; matrix, 128×128 ; flip angle, 20° ; acquisition time, three R-R intervals per dynamic acquisition). Thereafter, coronary microembolization was achieved with slow (60 sec) infusion of 250000 count of 40-120-µm-diameter embolic material (Embosphere; Biosphere Medical, Rockland, Mass) through the 3-F catheter. To enable us to confirm the presence of regional ischemia, additional first-pass perfusion MR imaging was performed 1 hour after microembolization with the same perfusion sequence

Published online

10.1148/radiol.09090527

Radiology 2010; 254:718-728

Abbreviations:

LAD = left anterior descending LV = left ventricle TTC = triphenyltetrazolium chloride

110 = unprietry tetrazonium chioride

Author contributions:

Guarantors of integrity of entire study, M.C., M.S.; study concepts/study design or data acquisition or data analysis/ interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.C., D.S., P.C.U., M.S.; experimental studies, M.C., A.J.M., P.C.U., M.S.; statistical analysis, M.C., M.S.; and manuscript editing, all authors

Funding:

This research was supported by the National Institutes of Health [grant R01HL072956].

Authors stated no financial relationship to disclose.

See also Science to Practice in this issue.

Radiology

described previously but with two R-R intervals per dynamic acquisition (9). A direct intraindividual comparison between 64-section multidetector CT and 1.5-T MR imaging was performed 7–8 weeks after microembolization. The rationale for using a time window of 7–8 weeks to study heterogeneous microinfarcts was based on the complete formation of scar tissue in homogeneous infarcts in swine, as shown in previous studies (19,20). Multidetector CT was performed 5 days \pm 1 (standard deviation) after the MR examination.

64-Section Multidetector CT

CT scanning was performed with a 64section multidetector unit (LightSpeed Ultra; GE Healthcare, Princeton, NJ) and with the animals in the supine position during an end-expiratory breath hold. After scout imaging was performed to localize the heart, cine imaging, first-pass perfusion, and delayed contrast-enhanced sequences were performed. Iodinated contrast media (300 mg of iodine per milliliter, Omnipaque; GE Healthcare) followed by a 40-mL saline chaser was administered during perfusion (1 mL per kilogram of body weight) and LV function (2 mL/kg) imaging. The following sequences were performed (21-25):

First-pass perfusion was performed with a tube voltage of 120 kV; a tube current of 100 mAs; and one full gantry rotation per heart beat, which was calculated by dividing the heart rate by 60 seconds to obtain images at approximately the same time during the R-R interval. Eight sections were acquired with 5-mm section thickness and an in-plane spatial resolution of 0.625 \times 0.625 mm. The injection rate of CT contrast media was 5 mL/sec.

Cine images were acquired to enable us to assess LV function and reconstruct every 5% of the cardiac cycle (tube voltage, 120 kV; tube current, 650 mAs; spatial resolution of reconstructed images, $0.625 \times 0.625 \times 0.625$ mm).

Delayed contrast-enhanced multidetector CT images were acquired to assess viability 3–5 minutes after the administration of contrast media for LV function (tube voltage, 120 kV; tube current, 650 mAs; spatial resolution of reconstructed images, $0.625 \times 0.625 \times$ 0.625 mm). The rationale for the time delay of 3-5 min between contrast material injection and imaging was based on the results of recent clinical and experimental multidetector CT studies on homogeneous infarcts (24-26). In these clinical and experimental studies, we found that an interval of 3-5 minutes between contrast material injection and multidetector CT scanning vielded the best contrast between homogenous infarcts, viable myocardium, and LV blood pool. A time delay of 5 minutes has been shown to yield the best differentiation of remote myocardium, infarcts, and LV blood pool in porcine models (27) and has been used previously (23). Multiplanar reformations of the cine and delayed contrast-enhanced images were reconstructed in 5-mm sections in the shortaxis view.

MR Imaging

The following MR sequences (19,28,29) were used to measure LV function, perfusion, and viability and to compare the data with multidetector CT.

Cine MR imaging was performed in the short-axis view, encompassing the LV, with a steady-state free precession sequence $(3.5/1.75, 70^{\circ} \text{ flip angle, 10-mm}$ section thickness, no section gap, 25×25 -cm field of view, 160×152 matrix, 16 heart phases).

First-pass perfusion MR images were acquired after administration of 0.1 mmol/kg gadoterate meglumine in four short-axis sections with a saturationrecovery gradient-echo sequence (4.5/2.2, 10-mm section thickness, 26×26 -cm field of view, 128×128 matrix, 20° flip angle, and two R-R intervals per dynamic acquisition). The injection rate of MR contrast media was 3 mL/sec.

Delayed contrast-enhanced MR images were acquired after injection of another 0.05 mmol/kg of gadoterate meglumine. These images were obtained 5–10 minutes after injection because the wash in and wash out of the contrast media from a heterogeneous microinfarct are faster than the wash in and wash out from a homogeneous infarct (8,9,16,30). We have previously shown that an imaging time of 6 minutes \pm 4 after contrast media administration yielded the best contrast between the microinfarct and the remote myocardium (9). Images were acquired in short- and long-axis views encompassing the LV with an inversionrecovery gradient-echo sequence (5/2; 15° flip angle; shot interval, two R-R intervals; 3-mm section thickness; no section gap; 26 × 26-cm field of view; 256 × 162 matrix). The inversion time was chosen to null normal myocardium.

Image Analysis

Two authors (M.S., M.C.; 21 and 9 years of experience, respectively) performed multidetector CT, MR imaging, and histochemical measurements in consensus at different times and in a random fashion. Multidetector CT and MR LV function, perfusion, and viability images were analyzed using Segment, version 1.7, software (Segment; http://segment.heiberg.se) (31,32). The method of image analysis used for multidetector CT did not differ from that used for MR. Cine images were used to measure the ejection fraction, end-diastolic volume, and end-systolic volume by delineating the endocardium in all short-axis sections at end diastole and end systole. The difference in epicardial and endocardial volumes was multiplied by 1.05 g/mL and used to determine LV mass. Systolic wall thickening was quantified in eight segments in three consecutive short-axis sections, as described previously (33). The mean wall thickening of the microinfarcted segments was calculated and compared with that of the remote segments of the same short-axis section. First-pass perfusion images were used to quantify maximuim upslope, peak signal intensity, and time to peak in the LV blood pool, LAD coronary artery territory with microinfarct scar, and remote myocardium (9,25). The total extent of heterogeneous microinfarct scar was measured on delayed contrast-enhanced images by thresholding and selecting subregions with a signal intensity or attenuation three standard deviations above the signal intensity or attenuation of remote myocardium (9). The attenuation (measured in Hounsfield units) and enhancement (measured in arbitrary units [au]) Figure 1



Figure 1: Multisection cine MR images acquired at (a) end-diastolic and (b) end-systolic phases used to measure LV regional and global function. Base = basal, Mid = middle.

of microinfarcts and remote myocardium obtained on delayed contrast-enhanced multidetector CT and delayed contrastenhanced MR images were compared.

Postmortem Analysis

a.

After completion of the imaging studies, the animals were euthanized with 40 mL of saturated KCl. The hearts were excised rapidly, cut into 10-mm-thick slices, and soaked for 30-45 minutes in 2% triphenyltetrazolium chloride (TTC). Histochemical staining served as the reference standard in the measurement of microinfarcts. Digital images of the TTC-stained slices were converted to black and white images with Adobe Photoshop CS2 software (Adobe; http://www.adobe.com/) and measured with ImageJ, version 1.30, software (National Institutes of Health; http: //rsb.info.nih.gov/ij/). For histopathologic analysis, representative tissue samples were taken from the microinfarcted region and remote myocardium (P.C.U.,





Figure 2: Multidetector contrast-enhanced cine CT images acquired at (a) end-diastolic and (b) end-systolic phases used to measure LV regional and global function. Note that contrast-enhanced multidetector CT images show better definition of LV and right ventricular walls and lack the interphase low signal intensity seen on unenhanced MR images (Fig 1). Base = basal, Mid = middle.

Table 1

Global Assessment of LV Function with Cine MR Imaging and Multidetector CT

Measurement	MR Imaging	Multidetector CT	P Value
Ejection fraction (%)	48 ± 3 (38–59)	50 ± 3 (38–56)	.16
End-diastolic volume (mL)	92 ± 8 (73–128)	93 ± 8 (73–127)	>.99
End-systolic volume (mL)	48 ± 5 (31–66)	46 ± 4 (36–58)	.69
Cardiac output (L/min)	3.8 ± 0.3 (2.7–4.7)	3.9 ± 0.4 (2.9–5.8)	.69
Left ventricular mass (g)	109 ± 5 (91–120)	102 ± 4 (85–114)	.06

Note.—Unless otherwise indicated, data are means ± standard errors of the mean. Data in parentheses are ranges.

more than 25 years of experience). The samples were dehydrated and embedded in paraffin in accordance with the standard procedure and cut into 5-µm-thick slices; adjacent slices were stained with hematoxylin-eosin and Masson trichrome stains (29). Postmortem analyses were performed without knowledge of the multidetector CT and MR imaging results.

Statistical Analyses

Continuous variables are presented as means \pm standard errors of the mean, unless otherwise stated. All statistical analyses were performed with Graph-Pad software (GraphPad Prism for Windows, version 5.00; GraphPad Software, San Diego, Calif). The two-tailed Wilcoxon test was used to determine if variables differed between imaging



Figure 3: Bar graphs show regional systolic wall thickening in (a) basal (*Base*), (b) middle (*Mid*), and (c) apical (*Apex*) sections on MR and multidetector CT (*MDCT*) images. Lines extending from the bars indicate standard errors of the mean. Note the impairment in systolic wall thickening in the microinfarcted LAD territory compared with remote myocardium 7–8 weeks after embolization with both methods. * = A significant difference (P < .05) was seen when comparing microinfarcted wall thickening with remote myocardium within each section.

modalities and between remote and microinfarcted myocardium. The parameters tested for differences between imaging modalities were LV volumes, ejection fraction, LV mass, cardiac output, microinfarction size, and signal intensity and attenuation of the myocardium. The variables tested to assess differences between remote and microinfarcted myocardium were systolic wall thickening for regional function and maximum upslope, maximum enhancement or attenuation, and time to peak for regional perfusion. Bias for microinfarct size on multidetector CT and MR images was determined with Bland-Altman analysis as the mean difference \pm standard deviation of the difference, with TTC staining serving as the reference standard. Bias was also calculated for the global LV function parameters by using the mean results of multidetector CT and MR imaging as a reference standard. A P value of less than .05 was considered indicative of a significant difference.

Results

X-ray MR Imaging in Defining LAD Coronary Artery Territory

The LAD coronary artery was successfully catheterized with x-ray guidance in all animals. With MR imaging, the LAD coronary artery territory was seen as a hyperenhanced region during an intraarterial bolus injection of MR contrast media (18). The extent of LAD coronary artery territory was $32.4\% \pm 3.8$ of the LV mass. Delivery of the embolic materials caused myocardial ischemia, as shown on electrocardiograms by ST-T wave changes. The presence of regional ischemia was confirmed on additional first-pass perfusion MR images as a hypoenhanced region in the LAD coronary artery territory. A transient (approximately 30minute) decline in mean heart rate (from 92 beats per minute \pm 5 to 82 beats per minute $\pm 2, P < .05$) was observed after delivery of the embolic material.

Multidetector CT and MR Imaging in the Assessment of Global and Regional LV Function

A direct (intraindividual) comparison between multidetector CT and MR imaging was performed 7–8 weeks after delivery of the embolic material. Figures 1 and 2 show MR and multidetector CT images acquired from the same animal. Both modalities yielded excellent contrast between the blood pool and the LV wall: The attenuation was $498\% \pm 50$ higher in the blood pool than in the LV wall on multidetector CT images, and the signal intensity was $485\% \pm 64$ higher in the blood pool on MR images. There was no significant difference between the multidetector CT and MR measurements of global LV function (ejection fraction, end-diastolic volume, end-systolic volume, and cardiac output) and LV mass (Table 1). The biases for functional parameters with multidetector CT compared with those with MR imaging were 2.6% \pm 3.6 for ejection fraction, 0.8 mL \pm 8.5 for end-diastolic volume, 1.9 mL \pm 6.5 for end-systolic volume, 0.2 L/min \pm 0.6 for cardiac output, and -6.7 g \pm 5.6 for LV mass.

Both multidetector CT and MR imaging revealed a decrease in systolic wall thickening in the microinfarcted LAD coronary artery territory compared with that of the remote myocardium (Fig 3).

Multidetector CT and MR Imaging in the Assessment of Regional Perfusion

The LAD coronary artery territory with heterogeneous microinfarcts could not be detected as differential enhancement with either modality at visual analysis. However, quantitative analysis of regions of interest revealed a minor difference in regional perfusion between the LAD coronary artery territory with heterogeneous microinfarcts and remote myocardium on both multidetector CT and MR images (Fig 4). MR estimates of perfusion in the LAD coronary artery territory with heterogeneous microinfarct scar showed a decrease in maximum upslope and time to peak (P = .03 for both) compared



a.

Figure 4: Plots show the quantitative analysis of first-pass perfusion on (a) multidetector CT and (b) MR images 7–8 weeks after microembolization. LAD territory with heterogeneous microinfarct scar showed perfusion deficit compared with remote myocardium on both CT and MR images. The results (mean ± standard error of the mean) from the myocardium are shown at a magnified scale for clarity. \Box = microinfarct, \triangle = LV blood pool, \diamondsuit = remote myocardium.

Table 2

Regional Assessment of Myocardial Perfusion with First-Pass MR Imaging and Multidetector CT

	MR Imaging			Multidetector CT		
Measurement	LV Blood	Remote Myocardium	LAD Territory	LV Blood	Remote Myocardium	LAD Territory
Maximum upslope (sec ⁻¹)	1780 ± 242	166 ± 26	$52\pm15^{*}$	88.8 ± 8.1	13.7 ± 3.2	12.6 ± 1.0
Maximum signal intensity (HU)	5471 ± 605	1627 ± 203	1314 ± 122	477 ± 36	74 ± 3	75 ± 2
Time to peak (sec)	7.5 ± 0.7	12.5 ± 1.0	$17.2\pm0.8^{*}$	8.9 ± 0.8	12.4 ± 0.6	$17.0\pm0.3^{*}$

Note.—Mean heart rate was 88 beats per minute ± 5 for MR imaging and 88 beats per minute ± 2 for multidetector CT. Data were obtained in six pigs. * P < .05 compared with remote myocardium

with remote myocardium (Table 2). Multidetector CT estimates differed only between the microinfarct and the remote myocardium for time to peak (P = .03). In remote myocardium, the increases in attenuation on multidetector CT images $(73\% \pm 10)$ and signal intensity on MR images $(150\% \pm 20)$ were significantly different (P = .03).

Multidetector CT and MR Imaging in the Detection of Heterogeneous Microinfarct Scar

At 7-8 weeks, heterogeneous microinfarct scars were clearly seen as hyperenhanced subregions in the LAD coronary artery territory on delayed contrast-enhanced multidetector CT and delayed contrast-enhanced MR images (Fig 5). Delayed contrast-enhanced multidetector CT and MR images obtained in the long-axis view also showed hyperenhanced stripes of microinfarct extending from the epicardium to the endocardium in the LAD coronary artery territory. Unlike homogeneous (20,34) infarcts caused by occlusion or reperfusion of major coronary arteries, the distribution of microinfarcts caused by microemboli was heterogeneous and covered the LAD coronary artery territory (8-11). The signal intensity of microinfarct scar on delayed contrastenhanced MR images was $843\% \pm 90$ higher than that of remote myocardium (1143 au \pm 51 vs 128 au \pm 15, P = .03). However, the attenuation of microinfarct scars on delayed contrastenhanced multidetector CT images was only $60\% \pm 4$ higher than that of remote myocardium (172 HU \pm 9 vs 107 HU \pm 6, P = .03). Thus, delayed contrast-enhanced MR images had a 15 ± 3 -fold higher signal intensity ratio between microinfarct scar and remote



c.

d.

Figure 5: (a, b) Short-axis delayed contrast-enhanced (a) multidetector CT and (b) MR images show heterogeneous microinfarct scars as high-attenuation or hyperintense subregions. (c, d) Long-axis views from delayed contrast-enhanced (c) multidetector CT and (d) MR images show high-attenuation or hyperintense stripes (arrows) that represent microinfarcts extending from the epicardium to the endocardium and indicating the path of occluded blood microvessels.





myocardium compared with multidetector CT (P = .03). The total extent of microinfarct measured with delayed contrast-enhanced multidetector CT, delayed contrast-enhanced MR imaging, and TTC staining with the semiautomatic method was $6.3\% \pm 0.8$, $6.6\% \pm$ 0.5, and 7.0% \pm 0.6, respectively. The results were not significantly different (multidetector CT vs MR imaging, P = .84; delayed contrast-enhanced multidetector CT vs TTC staining, P = .31; delayed contrast-enhanced MR imaging vs TTC staining, P = .69). Figure 6 shows the agreement between multidetector CT, MR imaging, and TTC staining with the Bland-Altman test. The bias for the extent of microinfarct on delayed contrast-enhanced multidetector CT and MR images was -0.6 ± 1.9 and -0.4 ± 1.3 , respectively, as compared with TTC staining. This suggested that both modalities have similar sensitivity in the measurement of heterogeneous microinfarct scars.

Histopathologic Analysis

TTC staining revealed a heterogeneous distribution of scarred microinfarcts in the LAD territory (Fig 7). The distribution and sizes of microinfarct varied from slice to slice and from animal to animal. Microscopic examination revealed the heterogeneous transmural distribution of the microinfarct scar 7-8 weeks after microembolization (Fig 7). Hematoxylin-eosin staining revealed the embolic material trapped in the scar tissue. Masson trichrome staining revealed the presence of stripes (tongues of fibrous tissue) extending from the epicardium to the endocardium mapping the territory of the occluded blood vessels. This staining enabled us to confirm the presence of stripes of the scar extending from the epicardium to the endocardium seen on delayed contrastenhanced multidetector CT and MR images (Fig 5).

Discussion

The main findings of this study are that (a) modern multidetector CT and MR imaging are sensitive modalities with which to visualize and measure heterogeneous microinfarcts and (b)

Figure 7



Figure 7: (a, b) Histochemical and (c, d) histopathologic staining show the transmural distribution of heterogeneous microinfarct scar. Arrowheads indicate the extent of LAD territory where heterogeneous microinfarct was detected. In c, the embolic material (arrows) is trapped in the core of scar tissue. (Hematoxylin-eosin stain; original magnification, $\times 100$.) In d, we confirmed the presence of stripes that extend from the epicardium to the endocardium, indicating the path of occluded blood vessels. (Masson trichrome stain; original magnification, $\times 40$.) F = tongues of fibrous tissue, V = viable myocardium.

multidetector CT and MR imaging can be used to detect regional perfusion deficits 7–8 weeks after coronary intervention.

We used multidetector CT and MR imaging to assess myocardial viability, perfusion, and LV function in microinfarcts 7–8 weeks after coronary intervention, simulating atheromatous microemboli in patients with coronary artery disease. Our findings suggest that either delayed contrast-enhanced multidetector CT or delayed contrastenhanced MR imaging can be used in patients to depict microinfarcts after percutaneous coronary intervention.

Myocardial microinfarcts resulting from showers of microemboli shed after coronary intervention are not limited to percutaneous coronary intervention for atherosclerosis but include a wide range of abnormalities, such as valvular disease, prosthetic valve placement, endocarditis, cardiomyopathy with mural thrombus, arrhythmias, and heart-lung bypass (35–41). This disease has also been reported in patients with hypertension, diabetes (3), systemic lupus erythematosus (42), and sickle cell disease; in these patients, abnormally shaped erythrocytes obstructing the capillaries and small arterioles may cause microinfarct (43).

The results of previous studies have shown that delayed contrast-enhanced MR imaging is able to depict acute heterogeneous microinfarcts in patients (2,5,12,13) and animals (9–11). Nassenstein and co-workers (10,11) found that a heterogeneous microinfarct exceeding 5% of myocardium per slice at histologic examination could be detected in vivo with delayed contrast-enhanced MR imaging in swine with a sensitivity of 83%. Our results have shown that delaved contrast-enhanced multidetector CT and delayed contrast-enhanced MR imaging can be used to depict and accurately quantify heterogeneous microinfarct scar 7-8 weeks after microembolization. Interestingly, both modalities vielded comparable data regarding the extent of heterogeneous microinfarct scar, and they were not significantly different from TTC staining microinfarct size. These findings are in line with those of clinical studies, in which delaved contrast-enhanced multidetector Radiology

CT and MR imaging yielded comparable sizes of homogeneous infarct (27,44). In a recent study, investigators compared multidetector CT with MR imaging in the definition of the periinfarct zone surrounding homogeneous infarct scars in swine (34). They suggested that delayed contrast-enhanced multidetector CT enables a more detailed assessment of the small periinfarct zone in scarred homogeneous infarcts and is less susceptible to the partial volume averaging effect than is MR imaging.

Study results have shown the potential of first pass multidetector CT (21-23,25) and MR imaging (28,45-47) in the detection of acute and subacute perfusion deficits in homogeneous infarcts. In the current study, we found a minor perfusion deficit in scarred microinfarcts compared with remote myocardium on first-pass multidetector CT and MR images. The differences were pronounced for maximum upslope and time to peak but were not visible on the images. The smaller standard error of the mean for multidetector CT compared with MR imaging seen in Figure 4 is inherent to the difference in the techniques. The signal intensity on MR images was measured in arbitrary units, while the attenuation on CT images was measured in Hounsfield units and was fairly constant between studies. Contrast-enhanced multidetector CT attenuation values are determined by the physical properties of the blood and myocardium (viable and nonviable) that result from direct x-ray attenuation by iodine. On the other hand, contrast-enhanced MR imaging values are based on gadolinium-induced alterations of water relaxivity and thus reflect indirect measurement of the amount and distribution of contrast media in the blood pool and myocardium (viable and nonviable) (34). This is reflected in the smaller increase in attenuation in the myocardium on multidetector CT images compared with the signal intensity increase on MR images after contrast media administration.

Both modalities yielded comparable regional and global data on LV function. MR imaging has emerged as the reference standard with which to evaluate LV function because of its threedimensional coverage, high spatial resolution, and excellent contrast between the myocardium and blood pool. Retrospectively, electrocardiographically gated multidetector CT has been used to quantify LV volumes, ejection fraction, and contractility (48). Our findings indicate that global LV functional measurements—namely, ejection fraction, end-diastolic volume, end-systolic volume, and cardiac output—quantified on multidetector CT images are comparable with those quantified on the reference standard MR images.

The ejection fraction in healthy swine with matched body weight is between 57.1% \pm 4.7 and 58.4% \pm 6.1 with MR imaging (49) and echocardiography (50), respectively. The ejection fraction in the animals in the current study was substantially lower (47.5% \pm 3.2) than that in our previous study in healthy swine (49). At the regional level, both imaging modalities depicted the decrease in regional wall thickening in the LAD coronary artery territory with microinfarct scars compared with that in remote myocardium.

The advantages of 64-section multidetector CT are the wide availability of CT scanners, their ease of use, and their high spatial resolution. On the other hand, the disadvantages of multidetector CT are the lower differential contrast between microinfarct and viable myocardium compared with MR imaging; the need for repeated injection of iodide-based contrast media, which may affect the use in patients with renal failure; and the relatively high radiation dose to patients. Recent studies, however, have shown that gadolinium-based contrast media may cause nephrogenic systemic fibrosis in patients with a reduced glomerular filtration rate (51). Finally, there is presently a larger body of published evidence on the diagnostic capabilities of MR imaging compared with those of multidetector CT in the measurement of perfusion, function, and viability of homogeneous infarcts (27.44).

This study comprised a small number of animals (a) because our institutional animal care and use committee imposed a restriction on all investigators, forcing them to use the minimum number of animals required to achieve significance, and (b) because of the high cost of imaging, surgery, and up to 8 weeks of animal husbandry. Thus, we did not perform a power calculation; instead, we based the number of animals in our study on the number of animals in previous studies. The number of animals in our study, however, was greater than or similar to the number of animals in relatively recently published reports (52–54). Another limitation was the use of a single injection and the limited range of embolic material (40-120 μm). However, the size range of the embolic materials used represented the common sizes of microemboli retrieved after placing distal protection devices (55). Additional multidetector CT, MR imaging, gross pathologic, and microscopic studies are needed to investigate the morphology, distribution, and pathophysiology of different sizes of microemboli. Future work will be needed to demonstrate the capability of multidetector CT to depict microinfarcts in patients.

Practical applications: This study has shown that multidetector CT and MR imaging are sensitive modalities with which to depict (a) heterogeneous microinfarcted scars resulting from microembolization and (b) the deleterious effect of microembolization on regional LV function and perfusion. These imaging modalities may be useful in depicting microinfarcts in other diseases, such as valvular disease, hypertension, diabetes, systemic lupus erythematosus, and sickle cell disease.

Acknowledgments: We gratefully acknowledge Carol Stillson, BA, Loi Do, BS, and Sammir Sullivan for their technical assistance.

References

 Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 2007;50:e1–e157.

- Porto I, Selvanayagam JB, Van Gaal WJ, et al. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. Circulation 2006;114:662–669.
- Erbel R. Spontaneous and interventional coronary microembolisation. Heart 2003; 89:986–989.
- 4. Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death: autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. Circulation 1985;71:699–708.
- Selvanayagam JB, Cheng AS, Jerosch-Herold M, et al. Effect of distal embolization on myocardial perfusion reserve after percutaneous coronary intervention: a quantitative magnetic resonance perfusion study. Circulation 2007;116:1458–1464.
- Davies MJ, Thomas AC. Plaque fissuring: the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363–373.
- Davies MJ, Thomas AC, Knapman PA, Hangartner JR. Intramyocardial platelet aggregation in patients with unstable angina suffering sudden ischemic cardiac death. Circulation 1986;73:418–427.
- Carlsson M, Martin AJ, Ursell PC, Saloner D, Saeed M. Magnetic resonance imaging quantification of left ventricular dysfunction following coronary microembolization. Magn Reson Med 2009;61:595–602.
- Carlsson M, Wilson M, Martin AJ, Saeed M. Myocardial microinfarction after coronary microembolization in swine: MR imaging characterization. Radiology 2009;250: 703–713.
- Nassenstein K, Breuckmann F, Bucher C, et al. How much myocardial damage is necessary to enable detection of focal late gadolinium enhancement at cardiac MR imaging? Radiology 2008;249: 829–835.

- Breuckmann F, Nassenstein K, Bucher C, et al. Systematic analysis of functional and structural changes after coronary microembolization: a cardiac magnetic resonance imaging study. J Am Coll Cardiol Cardiovasc Imaging 2009;2:121–130.
- Ricciardi MJ, Wu E, Davidson CJ, et al. Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. Circulation 2001;103:2780–2783.
- Selvanayagam JB, Porto I, Channon K, et al. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. Circulation 2005;111:1027-1032.
- 14. Arheden H, Saeed M, Higgins CB, et al. Measurement of the distribution volume of gadopentetate dimeglumine at echoplanar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats. Radiology 1999;211:698–708.
- 15. Arheden H, Saeed M, Higgins CB, et al. Reperfused rat myocardium subjected to various durations of ischemia: estimation of the distribution volume of contrast material with echo-planar MR imaging. Radiology 2000;215:520–528.
- 16. Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. Circulation 1996;94:3318–3326.
- National Research Council. Guide for the care and use of laboratory animals. 7th ed. Washington, DC: National Academy Press, 1996.
- Carlsson M, Saeed M. Intracoronary injection of contrast media maps the territory of the coronary artery: an MRI technique for assessing the effects of locally delivered angiogenic therapies. Acad Radiol 2008;15:1354–1359.
- 19. Saeed M, Lee RJ, Weber O, et al. Scarred myocardium imposes additional burden on remote viable myocardium despite a reduction in the extent of area with late contrast MR enhancement. Eur Radiol 2006;16:827–836.
- 20. Saeed M, Weber O, Lee R, et al. Discrimination of myocardial acute and chronic (scar) infarctions on delayed contrast enhanced magnetic resonance imaging with intravascular magnetic resonance contrast media. J Am Coll Cardiol 2006;48:1961– 1968.

- George RT, Jerosch-Herold M, Silva C, et al. Quantification of myocardial perfusion using dynamic 64-detector computed tomography. Invest Radiol 2007;42:815–822.
- 22. George RT, Silva C, Cordeiro MA, et al. Multidetector computed tomography myocardial perfusion imaging during adenosine stress. J Am Coll Cardiol 2006;48:153– 160.
- Lardo AC, Cordeiro MA, Silva C, et al. Contrast-enhanced multidetector computed tomography viability imaging after myocardial infarction: characterization of myocyte death, microvascular obstruction, and chronic scar. Circulation 2006;113:394–404.
- Carlsson M, Ursell PC, Saloner D, Saeed M. Multidetector computed tomography for characterization of calcium deposits in reperfused myocardial infarction. Acta Radiol 2009;50:396–405.
- 25. Furtado AD, Carlsson M, Wintermark M, Ordovas K, Saeed M. Identification of residual ischemia, infarction, and microvascular impairment in revascularized myocardial infarction using 64-slice MDCT. Contrast Media Mol Imaging 2008;3:198–206.
- 26. Jacquier A, Boussel L, Amabile N, et al. Multidetector computed tomography in reperfused acute myocardial infarction: assessment of infarct size and no-reflow in comparison with cardiac magnetic resonance imaging. Invest Radiol 2008;43:773–781.
- 27. Gerber BL, Belge B, Legros GJ, et al. Characterization of acute and chronic myocardial infarcts by multidetector computed tomography: comparison with contrastenhanced magnetic resonance. Circulation 2006;113:823–833.
- 28. Saeed M, Martin A, Ursell P, et al. MR assessment of myocardial perfusion, viability, and function after intramyocardial transfer of VM202, a new plasmid human hepatocyte growth factor in ischemic swine myocardium. Radiology 2008;249:107–118.
- 29. Saeed M, Saloner D, Martin A, et al. Adenoassociated viral vector-encoding vascular endothelial growth factor gene: effect on cardiovascular MR perfusion and infarct resorption measurements in swine. Radiology 2007;243:451–460.
- Judd RM, Wagner A, Rehwald WG, Albert T, Kim RJ. Technology insight: assessment of myocardial viability by delayed-enhancement magnetic resonance imaging. Nat Clin Pract Cardiovasc Med 2005;2:150–158.
- Heiberg E, Engblom H, Engvall J, Hedstrom E, Ugander M, Arheden H. Semiautomatic quantification of myocardial infarction from delayed contrast enhanced

magnetic resonance imaging. Scand Cardiovasc J 2005;39:267–275.

- Heiberg E, Wigström L, Carlsson M, Bolger AF, Karlsson M. Time resolved threedimensional automated segmentation of the left ventricle. In: Proceedings of IEEE Computers in Cardiology. 2005;32:599–602.
- 33. Carlsson M, Osman NF, Ursell PC, Martin AJ, Saeed M. Quantitative MR measurements of regional and global left ventricular function and strain after intramyocardial transfer of VM202 into infarcted swine myocardium. Am J Physiol Heart Circ Physiol 2008;295:H522-H532.
- 34. Schuleri KH, Centola M, George RT, et al. Characterization of peri-infarct zone heterogeneity by contrast-enhanced multidetector computed tomography: a comparison with magnetic resonance imaging. J Am Coll Cardiol 2009;53:1699–1707.
- Caraballo V. Fatal myocardial infarction resulting from coronary artery septic embolism after abortion: unusual cause and complication of endocarditis. Ann Emerg Med 1997;29:175–177.
- Charles RG, Epstein EJ, Holt S, Coulshed N. Coronary embolism in valvular heart disease. Q J Med 1982;51:147–161.
- Garg RK, Jolly N. Acute myocardial infarction secondary to thromboembolism in a patient with atrial fibrillation. Int J Cardiol 2007;123:e18–e20.
- Kitts D, Bongard FS, Klein SR. Septic embolism complicating infective endocarditis. J Vasc Surg 1991;14:480–485, discussion 485–487.
- 39. Quinn EG, Fergusson DJ. Coronary embolism following aortic and mitral valve replacement: successful management with

abciximab and urokinase. Cathet Cardiovasc Diagn 1998;43:457–459.

- 40. Takenaka T, Horimoto M, Igarashi K, Yoshie H, Tsujino I, Morihira M. Multiple coronary thromboemboli complicating valvular heart disease and atrial fibrillation. Am Heart J 1996;131:194–196.
- Yutani C, Imakita M, Ueda-Ishibashi H, Katsuragi M, Fujita H. Coronary artery embolism with special reference to invasive procedures as the source. Mod Pathol 1992;5:244–249.
- Mandell BF. Cardiovascular involvement in systemic lupus erythematosus. Semin Arthritis Rheum 1987;17:126–141.
- 43. Westwood MA, Shah F, Anderson LJ, et al. Myocardial tissue characterization and the role of chronic anemia in sickle cell cardiomyopathy. J Magn Reson Imaging 2007;26:564–568.
- 44. Nieman K, Shapiro MD, Ferencik M, et al. Reperfused myocardial infarction: contrastenhanced 64-section CT in comparison to MR imaging. Radiology 2008;247:49–56.
- 45. Al-Saadi N, Nagel E, Gross M, et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. Circulation 2000;101:1379–1383.
- 46. Al-Saadi N, Nagel E, Gross M, et al. Improvement of myocardial perfusion reserve early after coronary intervention: assessment with cardiac magnetic resonance imaging. J Am Coll Cardiol 2000;36:1557–1564.
- 47. Schwitter J, Nanz D, Kneifel S, et al. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission to-mography and coronary angiography. Circulation 2001;103:2230–2235.

- Mahnken AH, Bruners P, Katoh M, Wildberger JE, Gunther RW, Buecker A. Dynamic multi-section CT imaging in acute myocardial infarction: preliminary animal experience. Eur Radiol 2006;16:746–752.
- 49. Kuehne T, Saeed M, Gleason K, et al. Effects of pulmonary insufficiency on biventricular function in the developing heart of growing swine. Circulation 2003;108:2007–2013.
- 50. Dib N, Diethrich EB, Campbell A, Gahremanpour A, McGarry M, Opie SR. A percutaneous swine model of myocardial infarction. J Pharmacol Toxicol Methods 2006;53:256–263.
- Perez-Rodriguez J, Lai S, Ehst BD, Fine DM, Bluemke DA. Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment—report of 33 cases. Radiology 2009;250:371–377.
- Kraitchman DL, Heldman AW, Atalar E, et al. In vivo magnetic resonance imaging of mesenchymal stem cells in myocardial infarction. Circulation 2003;107:2290–2293.
- 53. Ferrarini M, Arsic N, Recchia FA, et al. Adeno-associated virus-mediated transduction of VEGF165 improves cardiac tissue viability and functional recovery after permanent coronary occlusion in conscious dogs. Circ Res 2006;98:954–961.
- 54. Saeed M, Martin A, Jacquier A, et al. Permanent coronary artery occlusion: cardiovascular MR imaging is platform for percutaneous transendocardial delivery and assessment of gene therapy in canine model. Radiology 2008;249:560–571.
- 55. Angelini A, Rubartelli P, Mistrorigo F, et al. Distal protection with a filter device during coronary stenting in patients with stable and unstable angina. Circulation 2004;110:515–521.