How Much Myocardial Damage Is Necessary to Enable Detection of Focal Late Gadolinium Enhancement at Cardiac MR Imaging?[1]

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Purpose: To assess the visibility of small myocardial lesions at magnetic resonance (MR) imaging and to estimate how much myocardial damage is necessary to enable detection of late gadolinium enhancement (LGE) in vivo.

Materials and Methods: The study was approved by the local bioethics committee. Coronary microembolization was performed by injecting 300 000 microspheres into the distal portion of the left anterior descending artery in 18 anesthetized minipigs to create multifocal areas of myocardial damage. In vivo MR imaging was performed a mean of 6 hours after microembolization by using an inversion-recovery spoiled gradient-echo sequence (repetition time msec/echo time msec, 8/4; inversion time, 240–320 msec; flip angle, 20°; spatial resolution, $1.3 \times 1.7 \times 5.0$ mm^3) after injection of 0.2 mmol gadopentetate dimeglumine per kilogram of body weight. High-spatial-resolution imaging of the explanted heart was performed by using the same sequence with a higher spatial resolution ($0.5 \times 0.5 \times 2.0$ mm^3). Imaging results were verified with histologic examination. Signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of in vivo and ex vivo images were calculated, and a *t* test was used to analyze observed differences.

Results: Multifocal myocardial damage was successfully induced in all animals. Areas of LGE with low SNR (mean, 36.3 ± 29.4 [standard deviation]) and CNR (23.7 ± 19.8) were observed in vivo in 12 (67%) of 18 animals, whereas ex vivo imaging revealed spotted to streaky areas of LGE with higher SNR (91.4 ± 27.8, $P < .0001$) and CNR (72.1 ± 25.4, $P < .0001$) among normal-appearing myocardium in all cases (100%). Focal myocardial lesions exceeding 5% of myocardium per slice at histologic examination were detected in vivo with a sensitivity of 83%.

Conclusion: Focal myocardial damage exceeding 5% of myocardium within the region of interest seems to be necessary for detection of LGE in vivo in an experimental model of coronary microembolization.

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Within the past decade, the concept of late gadolinium enhancement (LGE) in cardiac magnetic resonance (MR) imaging has been established for the assessment of different myocardial diseases (1,2). Initially, basic and clinical research focused on the detection of acute or chronic myocardial infarction by using LGE. Because myocardial infarction typically affects larger areas of myocardium, it can be reliably visualized with cardiac MR imaging in vivo. However, several studies (1,3) recently focused on different nonischemic causes of LGE. In contrast to myocardial infarction, nonischemic diseases (eg, myocarditis, cardiomyopathies) frequently show patchy areas of myocardial damage, rather than large areas of myocardial necrosis (4–6). Thus, the detection of structural myocardial abnormalities in nonischemic diseases by using LGE is more challenging because the areas of myocardial damage are smaller and may not appear that bright because of partial volume effects or a lower contrast material concentration in cases of incomplete myocardial damage.

Advances in Knowledge

- Small multifocal myocardial lesions result in blurred, patchy areas of late gadolinium enhancement (LGE) with low contrast compared with normal myocardium at in vivo MR imaging.
- Focal myocardial damage exceeding 5% of myocardium within the region of interest seems to be necessary for the detection of in vivo LGE in an experimental model of coronary microembolization.
- Multifocal myocardial lesions result in small, streaky areas of LGE among normal-appearing myocardium at high-spatial-resolution ex vivo MR imaging.
- High-spatial-resolution MR imaging with high signal-to-noise and contrast-to-noise ratios seems to be key for a more detailed characterization of these lesions.

Owing to the limited spatial resolution of in vivo MR imaging, combined with potential respiratory and cardiac motion artifacts, the detection of these non–myocardial infarction lesions is challenging in clinical studies. Additionally, the inability to obtain large myocardial samples for a detailed histologic analysis hampers a systematic analysis of these lesions. However, experimental coronary microembolization may be an interesting animal model for the analysis of small areas of myocardial damage. Experimental microembolization leads to multifocal inflammatory reactions and microinfarcts, which are remarkably similar in morphologic and hemodynamic features to the clinical situation in patients with coronary artery disease in which microembolization occurs either spontaneously or during coronary interventions (7–11). Cardiac MR imaging should be able to depict these lesions because inflammatory reactions, as well as focal infarcts, result in an increased distribution volume for low-molecular-weight contrast agents, which is the pathophysiologic background of LGE (12).

Experimental microembolization can reliably be performed in laboratory animals (10), and, on the basis of this model, our study aimed *(a)* to assess whether cardiac MR imaging is able to depict small focal myocardial lesions ex vivo and in vivo and *(b)* to estimate how much myocardial damage is necessary to enable detection of LGE in vivo.

Materials and Methods

This study was conducted in full accordance with the U.S. National Institutes of Health guidelines for the care and use of laboratory animals and was approved by the Bioethics Committee of the District of Düsseldorf, Germany.

Experimental Preparation

Experiments were performed in 18 male 23–41-kg minipigs (Göttingen Minipig; Ellegaard, Dalmose, Denmark). Endotracheal intubation was performed after initial sedation was achieved by using intramuscular injection of ketamine (30 mg per kilogram of body weight), azaprone (2 mg/kg), and atropine (0.025 mg/kg) and after initiation of anesthesia by intravenous injection of fentanyl (0.005 mg/kg), midazolam (0.15 mg/kg), and thiopental (12.5 mg/kg). Anesthesia was achieved with continuous intravenous injection of thiopental (10 mg/kg/h) and repetitive intravenous bolus injection of fentanyl (0.0025 mg/kg) and midazolam (0.25 mg/kg). Vital parameters were monitored during the entire experiment with electrocardiography, a peripheral oxygen sensor, temperature measurements, and repetitive arterial blood gas analysis. A 6-F catheter sheath was implanted in the left common carotid artery for coronary catheterization. After the catheter sheath was implanted, the pigs were given heparin.

Coronary Catheterization and Microembolization

All coronary interventions were performed by experienced cardiologists

Implication for Patient Care

- The color gray (intermediate signal intensity) is important at in vivo LGE MR imaging in patients with nonischemic diseases because it may result from a mixture of damaged and normal myocardium.

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Abbreviations:
CNR = contrast-to-noise ratio
LGE = late gadolinium enhancement
SNR = signal-to-noise ratio

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(including T.K., with 6 years of experience in interventional cardiology). The left anterior descending artery was intubated with a coronary catheter (XB-3; Cordis, Miami, Fla). Thereafter, a 2.3-F microcatheter (Prowler Plus; Cordis) was inserted coaxially and placed in the distal portion of the left anterior descending artery by using a guidewire (Guidant, Santa Clara, Calif) under fluoroscopic guidance. Microembolization was performed with slow manual injection of 300 000 white-stained 42-μm microspheres (Dynospheres; Dyno Particles, Lillstrom, Norway) to induce multiple focal lesions (13).

In Vivo MR Imaging

All examinations were performed with a 1.5-T MR imaging unit (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany) equipped with high-performance gradients. Inversion-recovery spoiled gradient-echo images (two-dimensional turbo fast low-angle shot; repetition time msec/echo time msec, 8/4; inversion time, 240–320 msec; flip angle, 20°; section thickness, 5 mm; in-plane resolution, 1.3 × 1.7 mm^2) were acquired 15 minutes after intravenous injection of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) a mean of 6 hours (range, 4–8 hours) after microembolization. For all studies, the optimal inversion time to null the signal of normal myocardium was determined by using an inversion-recovery steady-state free precession sequence with incrementally increasing inversion times (2.4/1.1; flip angle, 50°; section thickness, 8 mm).

Laboratory Analysis

Venous blood samples were obtained prior to euthanasia, and troponin I serum levels (in nanograms per milliliter) were determined with routine laboratory tests (Dade Behring, Eschborn, Germany).

Ex Vivo MR Imaging

Immediately after in vivo imaging, the animals were euthanized with intravenous injection of pentobarbital (80 mg/kg), and the heart was explanted without any delay. Residual blood was washed out of the cardiac cavities to avoid artifacts from contrast material–enhanced blood clots, and the heart was cut into five to six slices parallel to the mitral valve. Each slice was placed between two phased-array surface coils (Machnet, Eelde, the Netherlands), and high-spatial-resolution inversion recovery–prepared spoiled gradient-echo images (two-dimensional turbo fast low-angle shot; 8/4; inversion time, 240–320 msec; section thickness, 2 mm; in-plane resolution, 0.5 × 0.5 mm^2; number of signals acquired, 15) were acquired by using an imaging unit–generated dummy electrocardiogram with a heart rate of 60 beats per minute. For all studies, the optimal inversion time to null the signal of normal myocardium was determined by using a scout inversion-recovery steady-state free precession sequence with incrementally increasing inversion times (2.4/1.1; flip angle, 50°; section thickness, 8 mm).

Figure 1

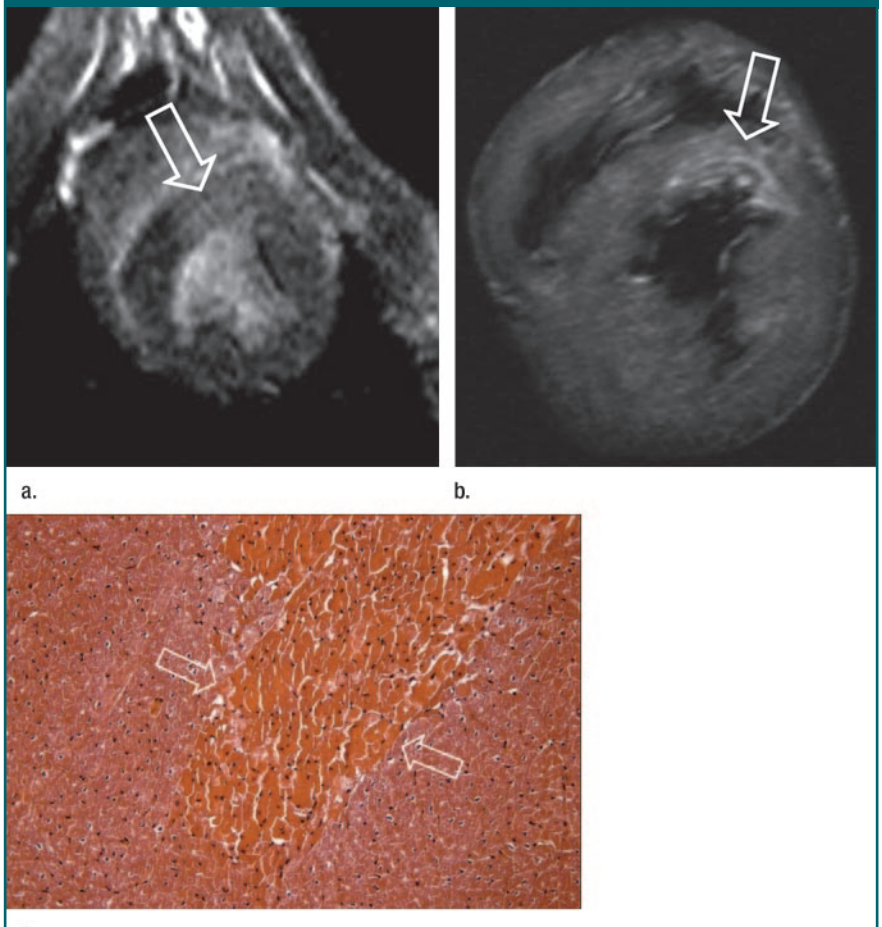

Figure 1: **(a)** In vivo and **(b)** ex vivo MR images in animal with a maximum extent of myocardial damage of more than 5% per slice at **(c)** histologic examination. Whereas **a** shows a blurred area of LGE (arrow) after coronary microembolization, streaky areas of high signal intensity (arrow) within normal myocardium were observed at **(b)** high-spatial-resolution ex vivo imaging. **(c)** Histologic slice obtained from target area of coronary microembolization shows focal myocardial damage (arrows) surrounded by normal myocardium. (Note that exact mapping of histologic slices and MR images was impossible owing to a lack of landmarks at histologic examination.) (Hematoxylin-eosin stain; original magnification, ×200.)

Image Evaluation

Each study was evaluated by a radiologist (K.N., with 5 years of experience in cardiac MR imaging) and a cardiologist (F.B., with 4 years of experience in cardiac MR imaging) in consensus, and the pattern of LGE was visually assessed. The total area of LGE (in square millimeters) was calculated by automated counting of pixels with a signal intensity (SI) greater than 2 standard deviations above the mean SI in a remote myocardial region, as previously described (14,15). Signal-to-noise ratios (SNRs) and contrast-to-noise ratios (CNRs) were calculated on the basis of SI measurements in manually drawn regions of interest. Regions of interest were placed by two observers (K.N. and F.B.) in consensus in areas of LGE, normal myocardium, and the air outside the object. Noise *(N)* was defined as the standard deviation of the SI within air. SNR and CNR values were calculated with the following equations: SNR = SI_{LGE}/N and CNR = $(SI_{LGE} - SI_{myo})/N$, where SI_{LGE} is SI in the area of LGE and SI_{myo} is SI in the myocardium.

Figure 2

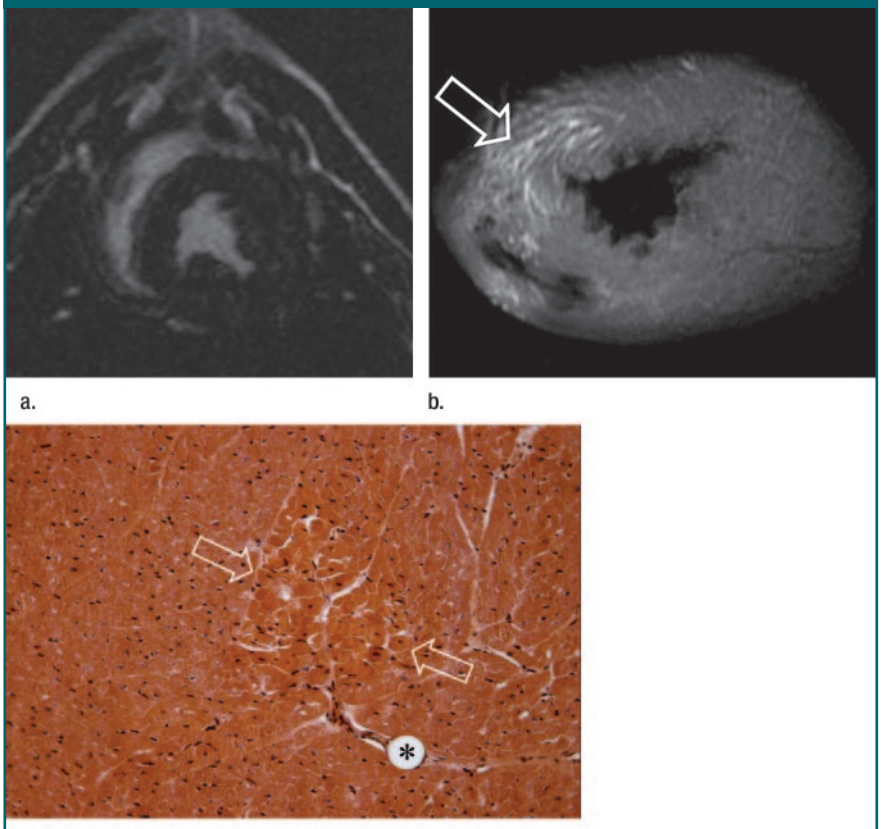

Figure 2: Whereas **(a)** in vivo MR imaging showed no LGE, **(b)** high-spatial-resolution ex vivo MR imaging revealed streaky enhancement (arrow) in normal myocardium within the perfusion area of the left anterior descending artery in a minipig. **(c)** Histologic slice obtained from target area of coronary microembolization shows focal areas of myocardial infarction (arrows) with, in all, a maximum extent of myocardial damage of less than 5% per slice. A microsphere (*) is also shown. (Note that exact mapping of histologic slices and MR images was impossible owing to a lack of landmarks at histologic examination.) (Hematoxylin-eosin stain; original magnification, ×200.)

Table 1

Results of SNR and CNR Calculation at In Vivo and Ex Vivo MR Imaging

Parameter	In Vivo Imaging	Ex Vivo Imaging	*P* Value*
Signal intensity in area of LGE	112.0 ± 85.8	420.5 ± 113.8	<.0001
Signal intensity in normal-appearing myocardium	40.5 ± 37.0	79.1 ± 46.4	<.001
Noise	3.4 ± 1.0	4.6 ± 1.1	<.001
SNR in area of LGE	36.3 ± 29.4	91.4 ± 27.8	<.0001
CNR between area of LGE and normal-appearing myocardium	23.7 ± 19.8	72.1 ± 25.4	<.0001

Note.—Unless otherwise specified, data are means ± standard deviations.

* Calculated with *t* test.

Histologic Examination

Specimens fixed in 4% formaldehyde from the anterior, anteroseptal, and septal myocardium (target area) and from the posterior wall (control area) were embedded in paraffin, sliced into 5-μm-thick slices, and stained with hematoxylin-eosin. Histologic analysis, including phase-contrast microscopy, aimed to detect focal inflammatory infiltration, necrotic myocardium, and microspheres. The total extent of myocardial damage within the target area was determined with planimetry and was expressed as a percentage of the entire target area, as described elsewhere in detail (16).

Statistical Analysis

Statistical analysis was performed by using software (SPSS, version 15.0 for Windows; SPSS, Chicago, Ill). Data are given as means ± standard deviations. A *t* test was used to analyze observed differences, and $P < .05$ was regarded as indicating a statistically significant difference. Pearson correlation coefficients were calculated to analyze associations.

Results

At histologic examination, focal areas of myocardial infarction with infiltrating leukocytes were detected within the tar-

Figure 3

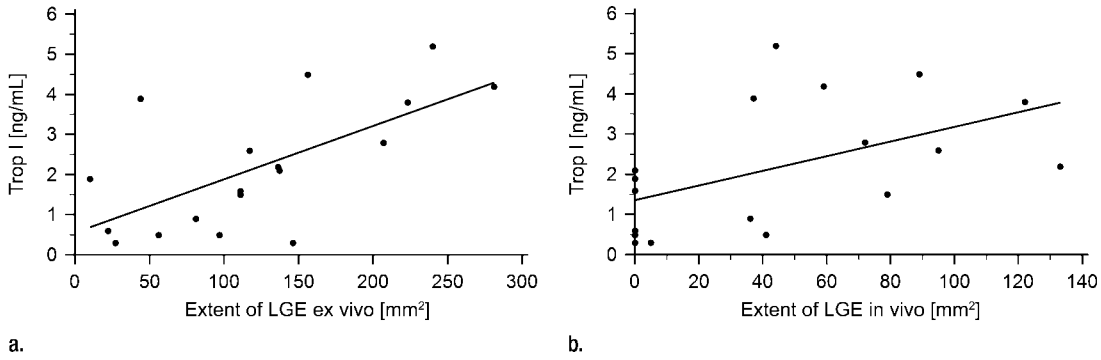

Figure 3: **(a, b)** Scatterplots of extent of LGE at **(a)** ex vivo MR imaging and **(b)** in vivo MR imaging versus troponin I *(Trop I)* values.

get area in all 18 animals (Figs 1c, 2c). The maximum extent of myocardial damage per slice at histologic examination was 2% or less in one animal, 2%–5% in four animals, 5%–8% in six animals, 8%–10% in three animals, and greater than 10% in three animals. Estimation of focal myocardial damage at histologic examination was impossible in one animal because of autolysis. Normal myocardium was observed within all control areas at histologic examination.

Blurred midmyocardial or transmural areas of contrast enhancement with low signal intensity (mean SNR, 36.3 ± 29.4 [standard deviation]) were observed within the target area in vivo in 12 (67%) of 18 animals after experimental microembolization (Fig 1a). Ex vivo imaging revealed spotted to streaky subendocardial or transmural areas of contrast enhancement with high signal intensity (SNR, 91.4 ± 27.8) among normal-appearing myocardium in all (100%) animals (Figs 1b, 2b). CNR measurements demonstrated a significantly higher contrast between areas of focal myocardial damage and normal-appearing myocardium at ex vivo imaging compared with in vivo imaging (72.1 ± 25.4 vs 23.7 ± 19.8, $P < .0001$, t test) (Table 1). No areas of LGE were observed outside the target area at either in vivo or ex vivo imaging.

The mean extent of LGE was 110.2 mm^2 ± 78.3 at ex vivo imaging and 45.1 mm^2 ± 44.8 at planimetry based on in vivo images ($P = .0001$, t test). Laboratory analysis showed a mean troponin I level of 2.20 ng/mL ± 1.6 after microembolization. Troponin I values correlated with the extent of LGE ex vivo (Pearson correlation coefficient: $r = 0.66$, $P = .03$) (Fig 3a) and in vivo (Pearson correlation coefficient: $r = 0.52$, $P = .028$) (Fig 3b). Animals with areas of LGE at in vivo imaging showed a significantly higher troponin I level than animals without LGE (2.7 ng/mL ± 1.6 vs 1.2 ng/mL ± 0.8, $P = .48$, t test).

Ten animals with areas of LGE at in vivo imaging, as well as two animals without LGE at in vivo imaging, showed a maximum extent of myocardial damage per slice of more than 5% in at least one slice of the target area. Four animals without areas of LGE at in vivo imaging and one animal with areas of LGE at in vivo imaging showed a maximum extent of myocardial damage per slice of 5% or less. Estimation of focal myocardial damage was impossible in one animal because of autolysis. Therefore, in vivo LGE imaging showed a sensitivity of 83% for the detection of focal myocardial damage with an extent of more than 5% within the region of interest (Table 2). Animals with a maximum extent of myocardial damage per slice of greater than 5% showed significantly higher SNRs (99.9 ± 24.4 vs 58.1 ± 14.9, $P = .0002$, t test) and CNRs (81.8 ± 21.7 vs 32.0 ± 6.5, $P < .0001$, t test) between LGE and remote myocardium ex vivo.

Table 2

Maximum Extent of Myocardial Damage per Slice at Histologic Examination in Animals with and Those without Areas of LGE at In Vivo MR Imaging after Coronary Microembolization

Maximum Extent of Myocardial Damage (%)	No. of Animals with Areas of LGE	No. of Animals without Areas of LGE
≤5	1	14
>5	10	2

Note.—Estimation of focal myocardial damage at histologic examination was impossible in one of the 18 study animals because of autolysis.

Discussion

Within the past decade, cardiac MR imaging has emerged as the standard of reference for the assessment of functional and structural myocardial abnormalities in different cardiac diseases (1–3). Whereas structural abnormalities affecting larger areas of myocardium can reliably be detected by means of LGE, the visualization of small multifocal lesions remains challenging.

In our study, high-spatial-resolution ex vivo MR imaging showed focal areas of LGE in all animals after experimental microembolization. In correspondence with the histologic findings, ex vivo MR imaging allowed visualization of small, streaky areas of LGE among normal-

appearing myocardium in all cases, whereas in vivo imaging depicted blurred areas of LGE with moderately increased signal intensity in only 12 of 18 animals. Thus, in principle, cardiac MR imaging can feasibly depict even small myocardial lesions by means of LGE. However, in the daily clinical routine, the detection of small myocardial lesions like focal inflammatory spots in myocarditis, focal fibrosis in the cardiomyopathies, and necrotic foci in coronary microembolization remains challenging. This problem poses the question of which factors influence the accuracy of cardiac MR imaging in the detection of small areas of LGE.

The ex vivo images in our study show that high-spatial-resolution imaging is able to depict multifocal areas of LGE with high signal intensity among normal-appearing myocardium after experimental microembolization. Obviously, high-spatial-resolution images with improved SNR and CNR are necessary for visualizing small structural changes in multifocal myocardial diseases. This assumption is supported by our data, which show that planimetry of LGE in vivo underestimates the extent of myocardial damage compared with high-spatial-resolution ex vivo imaging.

Although the lack of motion artifacts during ex vivo imaging may aggravate the difference, our data show that partial volume effects due to the low spatial resolution of in vivo images result in a significantly reduced contrast between normal-appearing myocardium and areas of focal myocardial damage. Therefore, LGE after inversion-recovery sequences does not allow for binary decisions, defining black as normal and white as damaged myocardium, because small areas of myocardial damage adjacent to normal myocardium may result in gray areas at in vivo imaging.

These findings are clinically important because mixtures of focal damaged and normal myocardium can frequently be detected in different myocardial diseases at histologic examination (4,5, 17,18). For example, focal inflammatory spots among normal-appearing myocardium are typical histologic findings in viral myocarditis (5), as well as in idiopathic congestive cardiomyopathy (17). Moreover, small multifocal areas of replacement fibrosis can be observed at histologic examination in different cardiac diseases like scleroderma heart disease (18) and hypertrophic cardiomyopathy (4).

Although compared with myocardial infarction, only a small amount of myocardium is affected in multifocal myocardial diseases, it is well known from clinical and experimental studies that small, multifocal myocardial lesions have a major impact on cardiac function (19). Thus, the direct visualization and quantification of multifocal myocardial damage in vivo may have a great clinical impact, especially in risk stratification of patients with nonischemic diseases.

To detect these focal myocardial diseases with in vivo LGE imaging, a correct setting of the inversion time is required, because a too-short inversion time may result in a midmyocardial layer of increased signal intensity. Look-Locker or inversion time scout sequences can be helpful in optimizing the inversion time, and renewed acquisitions with a slightly increased inversion time (10–20 msec) can be helpful in distinguishing true lesions from artifacts.

Beyond the correct setting of the imaging parameters, high-spatial-resolution imaging with high SNR and CNR seems to be the key to improving the detection of structural myocardial changes in diseases that predominantly affect focal areas of the myocardium. However, patient breath-hold capabilities limit improvements in spatial resolution and the use of multiple signal averages to improve SNR and CNR. Therefore, navigator-gated motion-corrected free-breathing sequences (20) or imaging at higher field strengths may be attractive options to improve spatial resolution, as well as SNR and CNR.

The outlined study was not without limitations. The most crucial one was that histologic quantification of myocardial damage within the first 8 hours after experimental microembolization is difficult because of limited contrast between necrotic and nonnecrotic myocytes. Furthermore, an exact mapping of histologic slices and MR imaging voxels is naturally impossible. Thus, our results represent only estimates for myocardial damage necessary for the detection of LGE in vivo. However, the good correlation between LGE and levels of troponin I as a serum marker of myocardial damage supports our finding that larger areas of myocardial damage result in larger areas of LGE ex vivo and an improved detection rate of LGE in vivo. Additionally, multifocal myocardial lesions in our animal model consisted of inflammatory reactions and microinfarcts, which limits the extension of our results to other (eg, chronic) conditions.

In summary, our study demonstrated that cardiac MR imaging is able to depict even small multifocal areas of myocardial damage; focal myocardial lesions exceeding approximately 5% of myocardium per histologic slice can be detected as blurred areas of moderately increased signal intensity in vivo. High-spatial-resolution imaging with high SNR and CNR seems to be the key to a more detailed characterization of multifocal myocardial lesions.

References

1. Lim RP, Srichai MB, Lee VS. Non-ischemic causes of delayed myocardial hyperenhancement on MRI. AJR Am J Roentgenol 2007; 188:1675–1681.

2. Sakuma H. Magnetic resonance imaging for ischemic heart disease. J Magn Reson Imaging 2007;26:3–13.

3. Hunold P, Schlosser T, Vogt FM, et al. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. AJR Am J Roentgenol 2005;184:1420–1426.

4. Cardiomyopathies. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1984;697:7–64.

5. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis: a histopathologic definition and classification. Am J Cardiovasc Pathol 1987;1:3–14.

6. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation 2006;113:876–890.

7. 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.

8. 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.

9. Herrmann J, Haude M, Lerman A, et al. Abnormal coronary flow velocity reserve after coronary intervention is associated with cardiac marker elevation. Circulation 2001;103:2339–2345.

10. Skyschally A, Erbel R, Heusch G. Coronary microembolization. Circ J 2003;67:279–286.

11. Heusch G, Schulz R, Haude M, Erbel R. Coronary microembolization. J Mol Cell Cardiol 2004;37:23–31.

12. Mahrholdt H, Wagner A, Judd RM, Sechtem U. Assessment of myocardial viability by cardiovascular magnetic resonance imaging. Eur Heart J 2002;23:602–619.

13. Dorge H, Neumann T, Behrends M, et al. Perfusion-contraction mismatch with coronary microvascular obstruction: role of inflammation. Am J Physiol Heart Circ Physiol 2000;279:H2587–H2592.

14. Mahrholdt H, Wagner A, Holly TA, et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. Circulation 2002;106:2322–2327.

15. Amado LC, Gerber BL, Gupta SN, et al. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. J Am Coll Cardiol 2004;44:2383–2389.

16. Neumann T, Konietzka I, van de Sand A, Aker S, Schulz R, Heusch G. Identification of necrotic tissue by phase-contrast microscopy at an early stage of acute myocardial infarction. Lab Invest 2000;80:981–982.

17. Zee-Cheng CS, Tsai CC, Palmer DC, Codd JE, Pennington DG, Williams GA. High incidence of myocarditis by endomyocardial biopsy in patients with idiopathic congestive cardiomyopathy. J Am Coll Cardiol 1984;3:63–70.

18. Fernandes F, Ramires FJ, Arteaga E, Ianni BM, Bonfa ES, Mady C. Cardiac remodeling in patients with systemic sclerosis with no signs or symptoms of heart failure: an endomyocardial biopsy study. J Card Fail 2003;9:311–317.

19. Skyschally A, Leineweber K, Gres P, Haude M, Erbel R, Heusch G. Coronary microembolization. Basic Res Cardiol 2006;101:373–382.

20. Spuentrup E, Buecker A, Karassimos E, Gunther RW, Stuber M. Navigator-gated and real-time motion corrected free-breathing MR imaging of myocardial late enhancement. Rofo 2002;174:562–567.