The Significance of Perfusion Defect at Myocardial Perfusion MR Imaging in a Cat Model of Acute Reperfused Myocardial Infarction

Hyun Woo Goo, MD
Dong Hun Kim, MD
Seoung Soo Lee, MD
Sung Bin Park, MD
Tae-Hwan Lim, MD

Objective: To determine whether the size of a perfusion defect seen at myocardial perfusion MR imaging represents the extent of irreversibly damaged myocardium in acute reperfused myocardial infarction.

Materials and Methods: In nine cats, reperfused myocardial infarction was induced by occlusion of the left anterior descending coronary artery for 90 minutes and subsequent reperfusion for 90 minutes. At single-slice myocardial perfusion MR imaging at the midventricular level using a turbo-FLASH sequence, 60 short-axis images were sequentially obtained with every heart beat after bolus injection of gadomer-17. The size of the perfusion defect was measured and compared with both the corresponding unstained area seen at triphenyl tetrazolium chloride (TTC) staining and the hyperenhanced area seen at gadophrin-2-enhanced MR imaging performed in the same cat six hours after myocardial perfusion MR imaging.

Results: The sizes of perfusion defects seen at gadomer-17-enhanced perfusion MR imaging, unstained areas at TTC staining, and hyperenhanced areas at gadophrin-2-enhanced MR imaging were 20.4 ± 4.3%, 29.0 ± 9.7%, and 30.7 ± 10.6% of the left ventricular myocardium, respectively. The perfusion defects seen at myocardial perfusion MR imaging were significantly smaller than the unstained areas at TTC staining and hyperenhanced areas at gadophrin-2-enhanced MR imaging (p < .01). The sizes of both the perfusion defect at myocardial perfusion MR imaging and the hyperenhanced area at gadophrin-2-enhanced MR imaging correlated well with the sizes of unstained areas at TTC staining (r = .64, p = .062 and r = .70, p = .035, respectively).

Conclusion: In this cat model, the perfusion defect revealed by myocardial perfusion MR imaging underestimated the true size of acute reperfused myocardial infarction. The defect may represent a more severely damaged area of infarction and probably has prognostic significance.

Determination of myocardial infarction size is important for initial prognostic assessment of clinical outcome, and is also a prerequisite for prediction of the extent of salvageable myocardium around myocardial infarction. MR imaging has been used for this purpose and is regarded as a promising approach, providing excellent tissue contrast as well as high spatial and temporal resolution (1).

The high signal intensity of myocardial infarction at T2-weighted MR imaging has a linear relationship with increased water content of the myocardium (2). However, the size of myocardial infarction at T2-weighted MR imaging has been reported as larger than infarct size measured at triphenyl tetrazolium chloride (TTC) histochemical staining (3, 4), and the overestimation of infarct size is therefore unavoidable.

Contrast-enhanced MR imaging of myocardial infarction may, on the other hand, re-
reflect different physiological information according to the
time after administration of contrast agents, e.g. early ver-
sus delayed. Early enhancement is due, in part, to the pa-
tency of the large epicardial artery and microvessels in the
myocardium, and is thought to reflect myocardial perfu-
sion (5, 6). Reports have shown that the perfusion defects
seen at myocardial perfusion MR imaging were smaller
than the hyperenhanced areas revealed by gadolinium-di-
ethylene triamine penta-acetic acid (Gd-DTPA)-enhanced
MR imaging, and correlated well with the infarcted areas
seen at TTC staining (3). Although the matter is still con-
troversial, delayed enhancement after the use of Gd-DTPA
seems to overestimate the size of myocardial infarction by
approximately 10–20% (6–8). A necrosis-avid MR con-
tраст agent, bis-gadolinium mosoporphins (Gadophrin-2;
Schering, Berlin, Germany), has become available for ex-
perimental purposes and appears to have a high affinity for
necrotic tissue. The hyperenhanced areas revealed by
gadophrin-2-enhanced MR imaging correlate well with the
infarcted areas seen at TTC staining (4, 9).

Using combined MR imaging, other investigators have
recently attempted to distinguish between reversibly and
irreversibly damaged myocardium. Saeed et al. (10) sug-
gested that differences in the size of the hyperenhanced re-
dion demarcated by gadophrin-2 and Gd-DTPA might pro-
vide an estimation of salvageable myocardium. In contrast,
Rogers et al. (11) found that combined assessment of early
and delayed enhancement patterns using only Gd-DTPA
might predict late functional recovery after reperfused my-
ocardial infarction.

For accurate evaluation of viable myocardium, a stan-
dard MR imaging method depicting irreversibly damaged
myocardium should first be determined. To the best of our
knowledge, the perfusion defect seen at myocardial perfu-
sion MR imaging has not been compared with true infarct
size. The purpose of this study was, therefore, to deter-
mine whether, in acute reperfused myocardial infarction,
the perfusion defect seen at myocardial perfusion MR
imaging can be considered as irreversibly damaged my-
ocardium.

MATERIALS AND METHODS

This experimental study was approved by the institution-
al committee for animal research. In 14 adult cats, the left
anterior descending (LAD) coronary artery just distal to the
first diagonal branch was occluded for 90 minutes, prior to
reperfusion for 90 minutes. The animal preparation meth-
ods employed have previously been described in detail (9).

For MR imaging, a 1.5-T imager (Magnetom Vision;
Siemens Medical Systems, Erlangen, Germany) with a 27-
cm-diameter circularly polarized head array coil was used. During the procedure, heart rates were kept between 140
and 170 beats per minute, and with every beat, 60 short-
axis myocardial perfusion images were sequentially ob-
tained at the left midventricular level using an electrocar-
diography (ECG)-triggered turbo fast low-angle shot
(FLASH) sequence. In order to allow magnetization to
reach a steady state, five images were acquired prior to a
bolus injection of 0.05 mmol/kg of gadomer-17 via the
femoral vein. The acquisition parameters for the inversion-
recovery turbo-FLASH imaging sequence were as follows:
repetition time, 2.5 msec; echo time, 1.2 msec; inversion
time, 200 msec; flip angle, 8°; field of view, 306 × 350 mm;
matrix, 90 × 128; slice thickness, 10 mm; and acquisition
time, 45–55 seconds. At the same slice position, ECG-trig-
gered breath-hold T1-weighted turbo spin-echo images
were then obtained 60, 90, and 120 minutes after admin-
istration of 0.025 mmol/kg of gadophrin-2, also via the
femoral vein. This enhanced imaging was performed six
hours after myocardial perfusion MR imaging and with the
following parameters: repetition time, 400–600 msec (ac-
cording to the heart rate); echo time, 30 msec (with 13
echo trains); field of view, 210 × 280 mm; matrix, 130 ×
256; slice thickness, 5 mm; and acquisition time, 9–12
seconds. Since the plasma half-life of gadomer-17 is ap-
proximately 0.5–1.5 hours and the interval was thus at
least 4–5 times the half-life, six hours was regarded as
long enough to nullify the effect of previously-injected
gadomer-17. Five cats died before the completion of image
acquisition, and nine, weighing 3.5–5.1 (mean, 4.38) kg,
were therefore included in this study.

After imaging studies were complete, the cats were sacri-
ficed. Their excised hearts were cut into five or six consec-
tutive, 5-mm-thick slices in the same plane as that in which
the MR images were obtained. The specimens were then
immersed in 1.5% TTC solution at 36 °C for 15 minutes,
and after staining were stored in 10% formalin solution for
12 hours. The area of infarction was defined as a TTC-un-
stained area, and was used as a reference for determining
true infarct size.

In all nine cats, perfusion defects were present at the ante-
rior and septal wall of the left ventricle, and to verify this,
time-signal intensity curves were obtained at the left ven-
tricular cavity, the site of the defect, and the posterior wall
of the left ventricle (normal myocardium) (Fig. 1A). The
time-signal intensity curves demonstrated a characteristic
pattern of myocardial enhancement (Figs. 1B, C). There
was rapid wash-in and wash-out of contrast agent at normal
myocardium, but a slow wash-in and disturbed wash-out at
the perfusion defect led to a gradual increase in signal inten-
sity. We measured the size of the defect in the image in
which it was best visualized, and then measured the hyper-
enhanced areas in the gadophrin-2-enhanced image which
showed maximal enhancement. This was performed manu-
ally, twice, and averaged without knowledge of the TTC
staining results. The sizes of the perfusion defects, hyperen-
hanced areas, and TTC-unstained areas were expressed as a
percentage of the corresponding left ventricular myocardial
(LVM) area, calculated by subtracting the area outlined by
the endocardial surface of the left ventricle from that out-
lined by its epicardial surface.

Using paired Student t tests, the size of the perfusion de-
fect was compared with the corresponding unstained area
seen at TTC staining and the hyperenhanced area at
gadophrin-2-enhanced MR imaging. Correlation between
the sizes of abnormal areas seen at MR (myocardial perfu-
sion and gadophrin-2-enhanced) imaging and true infarct
sizes, at TTC staining, were analyzed using Spearman’s
correlation coefficient. A p value of less than 0.05 was con-
sidered significant.

RESULTS

At both MR imaging and TTC staining, all nine cats
showed evidence of myocardial infarction in LAD territory.
Although myocardial perfusion MR imaging showed lower
spatial resolution, perfusion defects were also obvious and
measurable. The sizes of these at gadomer-17-enhanced
perfusion MR imaging, and of unstained areas at TTC stain-
ing and hyperenhanced areas at gadophrin-2-enhanced MR
imaging were 20.4 ±4.3%, 29.0 ±9.7%, and 30.7 ±10.6%
of the LVM area, respectively (Fig. 2). The perfusion defects
seen at myocardial perfusion MR imaging were significantly
smaller than unstained areas at TTC staining and hyperen-
hanced areas at gadophrin-2-enhanced MR imaging (p <
.01). The sizes of both the perfusion defect at myocardial
perfusion MR imaging and the hyperenhanced area at
gadophrin-2-enhanced MR imaging correlated well with the
sizes of unstained areas at TTC staining (r = .64, p = .062
and \( r = .70, p = .035 \), respectively) (Fig. 3), though the statistical significance of this correlation was marginal.

**DISCUSSION**

In the present study, the perfusion defects seen at myocardial perfusion MR imaging were significantly smaller than unstained areas at TTC staining and hyperenhanced areas at gadophrin-2-enhanced MR imaging. According to some researchers (3, 12), however, this defect matched the TTC-unstained area. Similar correlation was observed in our study, though the defect was obviously smaller than the TTC-unstained area. As far as we are aware, these results have not been previously reported, and probably indicate that in acute reperfused myocardial infarction, an area of reperfused but necrotic myocardium is present. The findings that time-signal intensity curves showed a characteristic pattern of myocardial enhancement and all perfusion defects were smaller than areas at risk served as verification of the perfusion defect seen at myocardial perfusion MR imaging.

This defect may represent the area where the microvasculature was occluded, and has therefore been described as a “no reflow phenomenon” (13, 14). The defect might not simply be an area of irreversibly injured myocardium, but may represent greater myocardial damage. This assumption is supported by the finding that all perfusion defects in our study were located in the central or endocardial portion of acute reperfused myocardial infarction. Previous studies also indicated that the presence of the perfusion defect at MR imaging correlated with poorer global ventricular function during the early post-infarction phase (15) and indicated that more frequent long-term cardiovascular complications would arise (16). Moreover, the defect remained a strong prognostic marker even after control of infarct size (16). Like infarct size, the size (as well as the presence) of perfusion defect is prognostically significant.

![Fig. 2. Comparison of the size of perfusion defects at myocardial perfusion MR imaging (20.4 ±4.3% of the area of the left ventricular myocardium [LVM]), hyperenhanced areas at gadophrin-2-enhanced MR imaging (30.7 ±10.6%), and unstained areas at TTC staining (*) (29.0 ±9.7%). The first mentioned was significantly smaller than the second and last (\( p < .01 \)).](image)

![Fig. 3. Correlation between the sizes of abnormal areas at MR (myocardial perfusion and gadophrin-2-enhanced) imaging and true infarct sizes at TTC staining. Spearman’s correlation coefficients (\( r \)) were 0.64 (A) between myocardial perfusion MR imaging and TTC staining and 0.70 (B) between gadophrin-2-enhanced MR imaging and TTC staining.](image)
Because we used gadomer-17, an intermediate-sized contrast agent which acts like a blood pool contrast agent during the first pass, the perfusion defect could be more accurately delineated in this study than where Gd-DTPA was used. A blood pool contrast agent limits contrast agent diffusion through the endothelial membrane (17).

Although little is known about the mechanism of gadophrin-2 accumulation in necrotic tissue, initial studies showed that gadophrin-2 has a peculiar affinity for necrotic tissue (18, 19). In experimental studies involving reperfused myocardial infarction, gadophrin-2-enhanced MR imaging accurately indicated the extent of irreversibly damaged myocardium, showing strong and persistent hyperenhancement (4, 9). Our results, in which the extent of hyperenhanced areas at gadophrin-2-enhanced imaging was somewhat similar to that of unstained areas at TTC staining, were in accordance with those obtained previously.

Correlation between the findings of MR imaging and TTC staining in our study was relatively weak compared with that of earlier reports (4, 9), and this may be because we did not analyze the whole LVM but only a single slice. Previous studies found that the limits of agreement between MR imaging- and TTC-based measurements of infarct size were wider in single-slice comparison than in whole-LVM comparison (4). In addition, some change in slice position and anatomical distortion is inevitable when preparing heart specimens for TTC staining.

The present study suffers certain limitations. First, follow-up was not performed after acute myocardial infarction, and functional recovery in reperfused myocardial infarction could thus not be evaluated. We do, however, focus on measurement of the perfusion defect at myocardial perfusion MR imaging during the acute stage. Second, the difference in slice thickness (myocardial perfusion MR imaging: 10mm; gadophrin-2-enhanced MRI: 5 mm; and TTC-stained specimen: surface) could affect the precision of the match. Compared to heart specimens, MR imaging could overestimate infarct sizes due to the partial-volume effect. Because the infarct sizes we encountered are considered sufficiently large, this concern may, however, be trivial. In small infarctions, on the other hand, infarct sizes can be greatly affected by slice thickness and the partial-volume effect.

In conclusion, a perfusion defect seen at myocardial perfusion MR imaging underestimates the true size of acute reperfused myocardial infarction in a cat model. It may represent a more severely damaged area of infarction and is probably prognostically significant.

References
1. Lim TH, Hong MK, Lee JS, et al. Novel application of breath-hold turbo spin-echo T2 MRI for detection of acute myocardial infarction. J Magn Reson Imaging 1997;7:996-1001
2. Higgins CB, Herfkens R, Lipton MJ, et al. Nuclear magnetic resonance imaging of acute myocardial infarction in dogs: alterations in magnetic relaxation times. Am J Cardiol 1983;52:184-188
3. Choi SI, Jiang CZ, Lim KH, et al. Application of breath-hold T2-weighted, first-pass perfusion and gadolinium-enhanced T1-weighted MR imaging for assessment of myocardial viability in a pig model. J Magn Reson Imaging 2000;11:476-480
4. Pilsaru SV, Ni Y, Pilsaru C, et al. Noninvasive measurements of infarct size after thrombolysis with a necrosis-avid MRI contrast agent. Circulation 1999;99:690-696
5. Wilke N, Simm C, Zhang J, et al. Contrast-enhanced first pass myocardial perfusion imaging. Magn Reson Med 1993;29:485-497
6. Judd RM, Lugo-Olivieri CH, Ariai M, et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. Circulation 1995;92:1902-1910
7. Saeed M, Wendland MF, Matusi T, Higgins CB. Reperfused myocardial infarctions on T1- and susceptibility-enhanced MRI: evidence for loss of compartmentalization of contrast media. Magn Reson Med 1994;31:31-39
8. Lim TH, Lee JG, Lee TK, Mun CW. Comparison of gadolinium polylysine and gadopentetate in contrast-enhanced MR imaging of myocardial ischemia-reperfusion in cats. J Korean Radiol Soc 1995;33:59-65
9. Choi SI, Choi SH, Kim ST, et al. Irreversibly damaged myocardium at MR imaging with a necrotic tissue-specific contrast agent in a cat model. Radiology 2000;215:863-868
10. Saeed M, Bremerich J, Wendland MF, Wyittenbach R, Weinmann HJ, Higgins CB. Reperfused myocardial infarction as seen with use of necrosis-specific versus standard extracellular MR contrast media in rats. Radiology 1999;213:247-257
11. Rogers WJ, Kramer CM, Geskin G, et al. Early contrast-enhanced MRI predicts late functional recovery after reperfused myocardial infarction. Circulation 1999;99:744-750
12. Stillman AE, Wilke N, Jerosch-Herold M. Myocardial viability. Radiol Clin North Am 1999;37:361-378
13. Lim T-H, Choi SI. MRI of myocardial infarction. J Magn Reson Imaging 1999;10:686-693
14. Ambrosio G, Weisman HF, Mannisi JA, Becker LC. Progressive impairment of regional myocardial perfusion after initial restoration of postischemic blood flow. Circulation 1989;80:1846-1861
15. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the ‘no-reflow’ phenomenon: a predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation 1996;93:223-228
16. Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765-772
17. Kroft LJN, de Roos A. Blood pool contrast agents for cardiovascular MR imaging. J Magn Reson Imaging 1999;10:395-403
18. Ni Y, Marchal G, Yu J, et al. Localization of metalloporphyrins: ‘specific’ enhancement in experimental liver tumors: comparison of magnetic resonance imaging, microangiographic, and histologic findings. Acad Radiol 1995;2:687-699
19. Marchal G, Ni Y, Herijgers P, et al. Paramagnetic metalloporphyrins: infarct-avid contrast agents for diagnosis of acute myocardial infarction by MRI. Eur Radiol 1996;6:2-8