The Salvaged Area at Risk in Reperfused Acute Myocardial Infarction as Visualized by Cardiovascular Magnetic Resonance

Matthias G. Friedrich, MD,* Hassan Abdel-Aty, MD,*† Andrew Taylor, MD,‡ Jeanette Schulz-Menger, MD,† Daniel Messroghli, MD,† Rainer Dietz, MD†

Calgary, Alberta, Canada; Berlin, Germany; and Melbourne, Australia

Objectives
We aimed to characterize the tissue changes within the perfusion bed of infarct-related vessels in patients with acutely reperfused myocardial infarction (MI) using cardiovascular magnetic resonance (CMR).

Background
Even in successful early revascularization, intermittent coronary artery occlusion affects the entire perfusion bed, also referred to as the area at risk. The extent of the salvaged area at risk contains prognostic information and may serve as a therapeutic target. Cardiovascular magnetic resonance can visualize the area at risk; yet, clinical data have been lacking.

Methods
We studied 92 patients with acute MI and successful reperfusion 3 ± 3 days after the event and 18 healthy control subjects. Breath-hold T2-weighted and contrast-enhanced ("late enhancement") CMR were used to visualize the reversible and the irreversible myocardial injury, respectively.

Results
All reperfused infarcts consistently revealed a pattern with both reversibly and irreversibly injured tissue. In contrast to the infarcted area, reversible damage was always transmural, exceeding the infarct in its maximal extent by 16 ± 11% (absolute difference of the area of maximal infarct expansion 38 ± 15% vs. 22 ± 10%; p < 0.0001). None of the controls had significant T2 signal intensity abnormalities.

Conclusions
In patients with reperfused MI, CMR visualizes both reversible and irreversible injury. This allows for quantifying the extent of the salvaged area after revascularization as an important parameter for clinical decision-making and research. (J Am Coll Cardiol 2008;51:1581–7) © 2008 by the American College of Cardiology Foundation

From the *Stephenson Cardiovascular Magnetic Resonance Centre at the Libin Cardiovascular Institute of Alberta, Departments of Cardiac Sciences and Radiology, University of Calgary, Calgary, Alberta, Canada; †Franz-Volhard-Klinik, Helios-Klinikum Berlin-Buch, Humboldt-Universität zu Berlin, Berlin, Germany; and the ‡Baker Heart Research Institute, Melbourne, Australia.

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between the reversible and the irreversible injury within the area at risk has not been described in patients.

We hypothesized that CMR allows for clinical imaging of both the salvaged and the irreversibly injured tissue within the area at risk.

Methods

Subjects

PATIENTS. In total, 92 patients with acute myocardial infarction (MI) were studied. Sixty-nine patients were recruited from center 1 (Stephenson CMR Centre, Calgary, Alberta, Canada). Forty-eight of the patients from center 1 participated in a previously published study (16), whereas all center 2 patients were recruited exclusively for this study. Myocardial infarction was defined by clinical history of persistent typical chest pain, characteristic electrocardiogram (ECG) changes, and a 2-fold elevation of creatine kinase levels or a positive troponin-T level. Patients were not enrolled if they were clinically unstable, presented with severe arrhythmia, or had known contraindications to CMR (claustrophobia, pacemakers, or implantable defibrillator devices). To ensure that CMR imaging findings reflected an acute myocardial injury, patients were not enrolled if they had previous MI.

CONTROL GROUP. Eighteen subjects (11 men and 7 women, mean age 36 ± 12 years, age range 22 to 62 years) with no previous or current evidence of cardiovascular disorders as revealed by clinical examination and a conventional ECG served as the control group. Subjects in the control group were not examined by post-contrast CMR and did not undergo coronary angiography.

The Charité ethics committee approved this study; written informed consent was obtained.

Methods

IMAGE ACQUISITION. The CMR studies were performed using a 1.5 T system optimized for cardiovascular applications (Signa CV/i, GE Medical Systems, Milwaukee, Wisconsin). The patients were continuously monitored during the examination with a single-lead ECG, repeated blood pressure measurements, and pulse oximetry. With the patient in the supine position, a series of real-time images to localize the short axis of the heart were acquired. We then applied a breath-hold short-T1 inversion recovery pulse sequence (TR 2 R-to-R intervals, TE 65 ms, TI 140 ms, slice thickness 15 mm, field of view 34 to 38 μm, matrix 256 × 256) in 3 short-axis slices (basal, midventricular, and apical) using a body coil. Each slice was obtained during an end-expiratory breath-hold of 12 to 15 s depending on the patient’s heart rate.

We acquired LE images in the slice location with the maximum extent of T2 signal abnormality 10 to 15 min after an intravenous Gd-DTPA (0.2 mmol/kg body weight Magnevist; Schering, Berlin, Germany) injection using a mechanical injector (Medrad, Indianola, Pennsylvania). We used an inversion recovery gradient echo technique (TR 7.1 ms, TE 3.1 ms, TI individually determined, range 200 to 275 ms, slice thickness 15 mm, matrix 256 × 192), and images were obtained during an end-expiratory breath-hold.

IMAGE ANALYSIS. Images were stored on magnetic optical disks and were then transferred for a blinded evaluation to a dedicated workstation as provided by the manufacturer (Advantage Windows 4.0; GE Medical Systems). A myocardial region was regarded as affected when at least 10 connected pixels of the myocardium revealed an SI of more than mean +2 SD of remote myocardium in T2 images and +5 SD in LE images (19). Remote myocardium was defined by visually normal myocardium in contralateral segments.

Regions of interest of the same size were then manually drawn within infarcted and remote myocardial regions as well as within the background noise to measure SI. We calculated the signal-to-noise ratio (SNR) by the formula:

\[
\text{SNR} = \frac{\text{SI}_\text{ROI}}{\text{SI}_\text{noise}}
\]

with SI_{ROI} being measured in the region of interest (ROI) and SI_{noise} in background air.

Contrast-to-noise ratio (CNR) was calculated by:

\[
\text{CNR} = \frac{(\text{SI}_\text{ROI} - \text{SI}_\text{remote})}{\text{SI}_\text{noise}}
\]

with SI_{ROI} being measured in the ROI, SI_{remote} in contralateral segments within the same slice, and SI_{noise} in background air.

The area of abnormal SI was measured in the T2-weighted image and in the corresponding LE image. Then the total slice area was measured and the area of signal abnormality in the T2-weighted and corresponding LE image was expressed as a percentage of the total slice area using the formula:

\[
\text{Transmural extent of abnormal signal} = \frac{(\text{area of high signal}/\text{total slice area}) \times 100}{100}
\]

Transmural extent of abnormal signal in both sequences was visually quantified using the maximal extent of the infarcted area. When the extension of the enhancing myocardium was 75% or more of the transmural distance, we designated the signal abnormality as transmural. The mean myocardial SNR in T2-weighted images was calculated for each patient.

For comparing results to normal subjects, we assembled a group of 18 healthy volunteers and 4 patients with infarcts. Two blinded observers performed a visual analysis of the T2-weighted images of this group. If visual assessment did
not allow for a definite result, a quantitative analysis was performed. For quantitative analysis, ROIs of equal size were drawn in the visually abnormal segment as well as within the remote myocardium. An area of at least 10 connected pixels including the subendocardial region was regarded as indicative for MI.

Kappa values were calculated for interobserver variability and for intraobserver variability after repeating the analysis by the same readers.

Another observer blinded to CMR data evaluated coronary angiographic examinations. Assignment of myocardial segments to coronary arterial territories was performed according to the imaging guidelines of the American Society of Nuclear Cardiology (20), except for the apical segment (segment 17), which was not included in our analysis.

Statistics. All values are presented as mean ± SD. Statistical analysis was performed using commercially available software (SPSS 11.0 for Macintosh, SPSS, Chicago, Illinois). Continuous variables were compared using the Student t test or the Mann-Whitney U test depending on their distribution. Correlation of continuous variables was calculated using a Spearman or Pearson correlation test, depending on the data distribution pattern, which was tested using the 1-sample Kolmogorov-Smirnov (K-S) test. A Bland-Altman analysis comparing the size of the signal abnormalities in LE and T2-weighted images was performed. A p value of < 0.05 was considered to be significant.

Results

Table 1 summarizes the patients' characteristics.

Angiographic data. In 16 patients, pre-hospital thrombolysis was performed; success was defined as relief of clinical symptoms or normalization of ST-segment elevation. One patient did not show a relevant coronary artery stenosis on the acutely performed coronary angiography and did not undergo further revascularization. Ninety-one patients underwent acute percutaneous coronary intervention (right coronary artery [RCA] in 45 cases, left anterior descending artery in 32 cases, and left circumflex artery in 14 cases). Reperfusion was not successful in 1 patient. There were no clinical events suggesting reoclusion/stenosis in the period between the angiographic and CMR examinations.

Patients. Patient-related data are listed in Table 1. All patients were studied within 12 days of the acute event, with 62 of 92 patients (67%) being studied within 3 days after the infarct. As for the remaining 30 patients, 13 were studied on day 4; 6 on day 5; 1 each on days 6, 8, 9, and 10; 3 on day 11; and 2 on day 12.

CMR data. All images were considered to be diagnostic. For analyzing 18 healthy subjects plus 4 infarcts, the interobserver agreement between the 2 readers was 0.95 with a kappa value of 0.86 (95% confidence interval [CI] 0.60 to 1.0). Intraobserver agreement for the 2 readers was 0.91 with a kappa value of 0.74 (95% CI 0.42 to 1.0) and 0.95 with a kappa value of 0.86 (95% CI 0.60 to 1.0), respectively.

In all 92 patients, a high T2 signal abnormality was observed in the infarct region (Fig. 1, right), yielding a sensitivity of 100% for visualizing injured myocardium.

Predictably, the area of high signal intensity had a mean SNR (normally distributed, K-S test; p = 0.113 for SNR infarct; p = 0.177 for SNR remote) significantly higher than that of the remote myocardium (12.1 ± 3.9 vs. 6.5 ± 2.8; p < 0.0001), with a CNR of 5.6 ± 1.9. Figure 2 shows an example of an acutely occluded RCA with a corresponding high signal in the inferior left and right ventricular walls. The localization of LE matched that of high T2 signal in all cases. The CNR between infarcted and remote myocardium was 6.2 ± 4.3.

In the slice with maximum infarct extension, the proportion of the area with high T2 signal was 38 ± 15% of the myocardial slice compared with 22 ± 10% in LE images (average difference 12 ± 8%), corresponding to the reversible injury being 16 ± 11% larger (absolute value) compared with the irreversible injury. In relative terms, the edematous yet not necrotic area exceeded the scar by 85 ± 75%. Examples for the difference of the infarct extent compared with that of edema are given in Figure 3.

Control group. None of the healthy subjects were classified as having MI. Sixteen of the 18 control subjects exhibited visually homogeneous low T2 signal intensity in the myocardium (Fig. 1, left). However, 2 volunteers showed a localized (inferior in one and septal in the other) area of high T2 signal that, albeit atypical for MI, did not allow for ruling out acute injury. Therefore, the specificity of visual interpretation of T2 high signal to rule out acute MI in volunteers was 89%. Quantitative evaluation of the suspicious segments, however, was negative for both readers in both cases. Thus, the specificity was 100% for a combined visual and—in equivocal cases added—quantitative SI analysis.

Correlation between CMR and clinical criteria. There was a significant correlation (Pearson correlation 0.50; p < 0.0001) between the extent of LE (normally distributed, K-S test; p = 0.532) and maximum creatine kinase (normally distributed, K-S test; p = 0.189); this correlation was
weaker between creatine kinase and extent of T2 signal abnormality (0.36; \( p < 0.0001 \)).

Ejection fraction (normally distributed, K-S test; \( p = 0.583 \)) correlated inversely with the spatial extent of T2 SI abnormality (normally distributed, K-S test; \( p = 0.985 \); Pearson correlation \(-0.44; p < 0.0001\)) and LE (\(-0.47; p < 0.0001\)). The difference between T2 and LE (normally distributed, K-S test; \( p = 0.270 \)), reflecting salvaged myocardium, correlated inversely with the time between onset of symptoms and reperfusion (not normally distributed, K-S test; \( p < 0.0001 \); Spearman correlation \(-0.37; p < 0.0001\)) and infarct age (not normally distributed, K-S test; \( p < 0.0001 \); Spearman correlation \(-0.44; p < 0.0001\)). None of the CMR variables differed between type of MI or gender.

**Discussion**

Our study shows that CMR techniques reveal a uniform pattern of the peri-infarct region, also referred to as the area at risk in reperfused acute MI. It consists of the infarcted core and a surrounding zone with myocardial edema. Reperfusion leads to an inflammatory-like response with intracellular and extracellular myocardial edema (21) and subsequent prolongation of the T2 relaxation time and high T2 signal intensities (22). Thus, the high T2 signal intensity in acute MI most likely reflects the increased free water content in the area of reversible injury (23, 24). Earlier studies in animal models of acute MI demonstrated a linear correlation between myocardial free water content of the infarcted region and prolongation of its T2 relaxation time.

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**Figure 1** T2-Weighted CMR Images (Short-Axis View)

*(Left)* T2-weighted cardiovascular magnetic resonance (CMR) image of a healthy subject with a homogeneous low signal intensity of the myocardium. *(Right)* T2-weighted CMR image of a patient with an acutely reperfused inferior infarction. The infarct-related injury is visually apparent by a thickened myocardium with high signal (arrows). Apparent extension into the inferior wall of the right ventricle is visible (arrowhead).

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**Figure 2** CMR Findings in a Patient With Inferior Myocardial Infarction

*(Left)* T2-weighted image. There is high signal intensity involving the posterior and the inferior and inferoseptal wall of the left ventricle (arrows) and the right ventricle (arrowhead). *(Right)* Right coronary angiogram of the same patient before revascularization revealing total occlusion of the right coronary artery. CMR = cardiovascular magnetic resonance.
which encouraged subsequent reports to use T2-weighted CMR to visualize acute MI (14,26,27). A recent study showed that edema imaging accurately allows for differentiating acute from chronic MI (16).

The finding that in acute MI the area with high T2 signal exceeds that of irreversible injury agrees with recent animal data (28,29). In a pig model, Choi et al. (30) showed that the high signal intensity in T2-weighted CMR reflects both irreversibly and reversibly injured, but essentially viable, peri-infarct zone. One study related this area to preserved LV function (31). In contrast, LE is only observed in areas of irreversible myocardial injury (10). Persisting Gd-DTPA accumulation late after bolus injection most likely is based on an increased volume of distribution secondary to loss of cell membrane integrity (32–34) and abnormally prolonged wash-out kinetics related to decreased functional capillary density in the irreversibly injured myocardium (35).

Based on the first mechanism, LE and T2-weighted CMR should agree in terms of infarct extent, because interstitial edema results in increased Gd-DTPA volume of distribution. However, certain pathophysiological factors may render the peri-infarct zone “T2 positive” but “LE negative.” First, the functional capillary density of the reversibly injured myocardium may not be significantly compromised in the area at risk, and Gd-DTPA washout kinetics would not be significantly altered. Second, myocardial edema in the peri-infarct zone is mainly interstitial without cell membrane disruption (30). Therefore, intact membranes may prevent the intracellular accumulation of Gd-DTPA (36). In a recent study by Rehwald et al. (37), Gd-DTPA concentration was not significantly increased in reversibly injured ischemic myocardium.

Clinical implications. Clinically, quantitatively assessing reversible and irreversible injury in acutely reperfused infarctions could substantially enhance our view of infarct-related tissue injury. One may extend the “dead or alive” concept to “dead,” “alive but sick,” or “alive” based on this combined approach. Animal data by Garcia-Dorado et al. (38) and Aletras et al. (17) support this conclusion. Both found that the area of high T2 signal abnormality closely matched the pathologically-determined myocardial area at risk.

In the setting of acutely reperfused infarction, the relation of myocardial edema to irreversible myocardial injury provides additional information on the salvaged myocardium within the area at risk. The information could also be used to guide therapy focused on the vulnerable “battlefield” of viable yet injured myocardium surrounding the necrosis, with infarct expansion being a main therapeutic target.

Recent studies suggest that reduction of myocardial edema is a novel target to reduce irreversible injury and improve left ventricular remodeling (39). Edema imaging using T2-weighted CMR could therefore act as powerful tool to monitor the effect of emerging antiedema reperfusion strategies.

Study limitations. Because we do not have follow-up data for the early post-infarction period, we cannot exclude that the extent of abnormalities was at least in part defined by the elapsed time from the event.

Because the limited SNR due to the sequence and the body coil necessitated thick slices, we did not generate volumetric data and used the area of the largest extent of the infarct instead. The observed difference in size may have been underestimated, because the relative extent of the
surrounding edema is likely to be larger in the outer portions of the area at risk. However, the finding that the area of edema exceeded that of irreversible injury was consistent in the vast majority of patients; therefore, we do not believe that volume analysis would have altered our results or conclusion. Extrapolating our results to patients with non-reperfused infarcts should be taken with caution. We have previously shown, however, that high T2 signal is a feature of nonreperfused infarcts (16).

Conclusions

In patients with reperfused MI, CMR visualizes both reversible and irreversible injury with very high sensitivity and specificity. This allows for quantifying the extent of the salvaged area after revascularization as an important parameter for clinical decision making and research.

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Reprint requests and correspondence: Dr. Matthias G. Friedrich, Stephenson CMR Centre at the Libin Cardiovascular Institute of Alberta, Departments of Cardiac Sciences and Radiology, University of Calgary, 1403 29th Street NW, Calgary, Alberta T2N 2T9, Canada. E-mail: matthias.friedrich@ucalgary.ca.

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