Assessment of Myocardial Viability With Contrast-Enhanced Magnetic Resonance Imaging
Comparison With Positron Emission Tomography

Christoph Klein, MD; Stephan G. Nekolla, PhD; Frank M. Bengel, MD; Mitsuru Momose, MD; Andrea Sammer, MD; Felix Haas, MD; Bernhard Schnackenburg, PhD; Wolfram Delius, MD; Harald Mudra, MD; Dieter Wolfram, MD; Markus Schwaiger, MD

Background—Recent studies indicate that MRI, after administration of gadolinium-diethylenetriamine pentaacetic acid, can identify nonviable areas in dysfunctional myocardium. We compared MRI hyperenhancement with PET as a gold standard for detection and quantification of myocardial scar tissue.

Methods and Results—Thirty-one patients with ischemic heart failure (ejection fraction, 28±9%) were imaged with PET and MRI. Scar was defined as regionally increased MRI signal intensity 20 minutes after injection of 0.2 mmol/kg gadolinium-diethylenetriamine pentaacetic acid and as concordantly reduced perfusion and glucose metabolism as defined by PET. Sensitivity and specificity of MRI in identifying patients and segments (n=1023) with matched flow/metabolism defects was 0.96 of 1.0 and 0.86 of 0.94, respectively. Eleven percent of segments defined as viable by PET showed some degree of MRI hyperenhancement. Defect severity score based on visual analysis was 44.3±9.1 for PET and 47.6±11.1 for MRI (r=0.91, P<0.0001). Quantitatively assessed relative MRI infarct mass correlated well with PET infarct size (r=0.81, P<0.0001). Furthermore, MRI hyperenhancement was a better predictor of scar tissue than end-diastolic and end-systolic wall thickness or thickening.

Conclusions—In severe ischemic heart failure, MRI hyperenhancement as a marker of myocardial scar closely agrees with PET data. Although hyperenhancement correlated with areas of decreased flow and metabolism, it seems to identify scar tissue more frequently than PET, reflecting the higher spatial resolution. Additional functional studies after revascularization are required to define the significance of small islands of scar detected by MRI. (Circulation. 2002; 105:162-167.)

Key Words: magnetic resonance ■ coronary disease ■ heart failure ■ hibernation

It is well established that impaired left ventricular (LV) function does not necessarily represent irreversible tissue injury, because contractile performance can improve after revascularization.1 Correct assessment of the extent of viable and nonviable myocardium in patients with severely reduced LV ejection fraction (EF) and chronic coronary artery disease (CAD) is important for clinical decision making, because perioperative mortality and morbidity of these patients are increased. However, it has been shown that patients with dysfunctional but viable myocardium profit most from revascularization.2 Detection of viability based on assessment of myocardial perfusion and glucose metabolism by PET is presently considered by many as the reference method.3 The extent of viable myocardium correlates with improved contractile performance after revascularization4,5 and affects both short-term6 and long-term7,8 prognosis.

MRI, using gadolinium-based contrast agents, delineates irreversibly damaged myocardium9 and predicts areas that will not recover functionally after revascularisation.9 The aim of this study was to compare extent and location of hyperenhancement with nonviable tissue defined by PET in patients with chronic ischemic heart failure.

Methods

Patients
Thirty-one patients (26 men; 59±10 years of age) with CAD (angiography) and reduced LV function (EF<35%), assessed by echocardiography or contrast ventriculography and scheduled for a diagnostic PET study, were included in the study after giving informed consent. Twenty-six patients had documented (history, Q-waves, or elevated enzymes) myocardial infarction (14 anterior and 15 inferior). Twenty patients had 3-vessel, 7 had...
2-vessel, and 4 had 1-vessel disease. Patients suffering a myocardial infarction within 6 weeks before PET or MRI or with contraindication to MRI, unstable angina pectoris, or advanced heart failure (NYHA IV) were excluded. PET and MRI were performed within 1 week, with none of the patients having a change in clinical status. Local ethics committee approval was obtained.

Imaging Protocols

MRI

All patients were examined in supine position using a 1.5-T scanner (ACS NT, INCA software, Philips) equipped with fast gradients (23-mT/m amplitude, 105-mT/m per msec slew rate) and a dedicated cardiac phased-array surface coil. For evaluation of LV function, consecutive cine short-axis views were acquired to cover the left ventricle using breath hold and steady-state free-precession technique (echo-time, 1.4 ms; recovery time, 2.9 ms; slice thickness, 8 mm; spatial resolution, 1.4×1.2 mm²; flip angle, 60 degrees; and temporal resolution, 42 ms). To assess the apex, one vertical and one horizontal long-axis view were obtained. To evaluate myocardial distribution of hyperenhancement, data were acquired using short-axis images 20 minutes after bolus injection of 0.2 mmol gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) per kg body weight (bw) (Magnevist) in end diastole. An inversion-recovery three-dimensional turbo-gradient echo technique with echo planar readout (echo-time, 3.3 ms; recovery time, 5.4 ms; EPI factor, 11; slice thickness, 5 mm; spatial resolution, 1.2×1.2 mm²; flip angle, 15 degrees; acquisition time, 284 ms; and prepulse delay, 225 to 300 ms) was used.

PET

All patients were studied in postprandial state receiving glucose and insulin before and during imaging, according to a standardized protocol.10 After initial transmission scanning for attenuation correction, rest myocardial perfusion imaging with ¹⁸F-N-ammonia (NH₃) (740 MBq) was performed. After allowing for NH₃ decay, ¹⁸F-fluorodeoxyglucose (FDG) (370 MBq) was injected, and data acquisition was initiated 40 minutes after tracer injection. Transaxial planes were obtained using a whole-body PET (ECAT EXACT or HR+/H₁₁₀₀₁ planes were obtained using a whole-body PET (ECAT EXACT or Siemens/CTI). Attenuation-corrected transaxial images were generated from NH₃ and FDG data. Data were realigned to generate short- and long-axis views for visual analysis.¹¹

Image Analysis

The left ventricle was divided into 33 segments using the apex and a representative apical (8 segments), equatorial (12 segments), and basal (12 segments) short-axis view, yielding a total of 1023 segments in 31 patients. The inferior interception of the ventricles served as landmark. Images were assessed in both modalities within each segment by 2 independent observers, blinded to the results of the other modality.

Viability

MRI

Nonviable tissue (scar) was defined as increased signal intensity 20 minutes after administration of Gd-DTPA. The extent of hyperenhancement was divided into transmural and subendocardial. Additionally, LV mass was calculated using commercially available software (Medis). Areas of hyperenhancement were delineated manually, mass calculated, and normalized to total LV mass.

PET

Two different viability criteria combining interpretation of perfusion and metabolism were used: (1) normal blood flow with normal or increased FDG uptake (normal), and (2) reduced blood flow with preserved or increased FDG uptake (mismatch). Reduced blood flow with reduced metabolism (matched defect) was divided into mild (nontransmural) or severe (transmural) defect and considered scar tissue.¹⁰ In addition, an automated, semiquantitative image analysis was performed using a previously validated software (MunchHeart) on the basis of volumetric sampling of tracer uptake.⁶¹² Areas of normal, mismatched, and matched defects were calculated.

Extent of scar tissue was estimated using a 3-point scoring system, where −1 indicated viable tissue, −2 indicated nontransmural defect, and −3 indicated transmural defect. For each patient, the 33 segments were scored and the sum was calculated (minimum possible score, 33; maximum possible score, 99). Interobserver variability for MRI and PET was low (r=0.95, slope=0.80, P<0.0001 and r=0.94, slope=0.82, P<0.0001, respectively).

Global and Regional LV Function

LV volumes, mass, EF, and regional wall thickness in end diastole/end systole were calculated from MRI cine short-axis views. Regional wall motion was visually assessed within each of the 33 segments by 2 observers. It was graded as normokinetic, moderate hypokinetic, severe hypokinetic, and akinetic or dyskinetic.

Statistics

Mean and standard deviation (SD) are given for all continuous data. Using PET as the gold standard, sensitivity and specificity of detecting scar tissue were determined for MRI. Linear regression/Bland-Altman analysis was used for comparison of defect extent.¹³ One-way ANOVA and post hoc Bonferroni-corrected t test, as well as receiver operating characteristic (ROC) analysis (SPSS Inc), was applied for assessment of hyperenhancement and wall thickness/thickening in differentiating scar from viable tissue. P<0.05 was considered statistically significant.

Results

MRI

LV EF averaged 28±9%, mean LV mass was 135±31 g, end-diastolic volume was 258±78 mL, and end-systolic volume was 190±74 mL.

Enhanced MRI and PET

Five patients (16%) had transmural and 4 patients (13%) had subendocardial hyperenhancement only, whereas 18 patients (58%) had a combination of both. Four patients (13%) showed no hyperenhancement. Eleven patients (35%) had a severe-matched and 7 patients (23%) had a mild-matched PET defect only. Ten patients (32%) showed a combination of both, and 3 patients (10%) were normal. Individual patient data are shown in Table 1. Sensitivity and specificity of MRI in detecting patients with scar tissue, defined by PET, were 0.96 and 1, respectively. In the single patient who did not show hyperenhancement, 1 segment had a severe and 2 segments had a mild-matched defect in PET. Figures 1 and 2 show patient examples of MRI hyperenhancement compared with PET results.

Location of Scar Tissue

Sensitivity and specificity for detecting transmural defects only were 0.86 and 0.94, respectively, and for detecting any defect (transmural or nontransmural) were 0.83 and 0.88, respectively. In 11% of segments defined as normal by PET, MRI showed hyperenhancement, whereas only 5% with a matched PET defect showed no hyperenhancement (Table 2). Fifty-five percent of segments with subendocardial hyperenhancement were classified as normal by PET. Of 34 segments showing a mismatch, reflecting hibernating myocardium in PET, 3 showed transmural, 8 showed nontransmural, and 23 showed no hyperenhancement.

The number of segments with scar tissue increased with the level of dysfunction. In segments with normokinesia, there...
were 17 of 249; with moderate hypokinesia, there were 16 of 248; in severe hypokinesia, there were 44 of 277; and with dyskinesia and akinesia, there were 128 of 249 segments with scar tissue as assessed with PET. To assess influence of contractile performance, the results in akinetic and dyskinetic segments and severely and moderately hypokinetic segments were determined separately (Table 3). In normokinesia, of 6 segments with a transmural defect in PET, only 2 were detected by hyperenhancement, and of 11 segments with a nontransmural defect, only 2 were detected by hyperenhancement.

### Extent of Scar Tissue

Visual scar score averaged 44.3±9.1 for PET and 47.6±11.1 for MRI, with a mean difference of 9%. A close correlation between both estimates was found ($r=0.91$, slope=1.1, $P<0.0001$, Figure 3).

Mean LV mass, derived from contrast MR images, was 135±31 g compared with the value of 132±28 g obtained from cine images ($r=0.94$ with a mean difference of 7% and a slope of 0.84, $P<0.0001$). Relative infarct size expressed as percent LV mass was 18±16%, which correlated well ($r=0.81$, slope=0.70, $P<0.0001$) with quantitative measurements of 20±18% by PET expressed as percent defect of LV surface (Figure 3).

### Viability and Cardiac Function

The extent of scar tissue showed a weak inverse correlation ($P=0.05$) with EF ($r=-0.42$) and with end-diastolic and end-systolic volumes ($r=0.32$ and $r=0.41$, respectively). As shown in Table 4, there was a significant difference between

### Table 1. Original Data of Visual (Number of Segments) and Quantitative (Percent Scar) Assessment for Each Patient

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$v$ indicates viable tissue; $nt$, nontransmural defect; $t$, transmural defect; and $m$, mismatch.

*Quantitatively calculated extent of scar tissue.

Figure 1. Typical example of the MRI hyperenhancement technique (top) and PET viability study (bottom) covering the complete heart. Hyperenhancement and matched defect (reduced perfusion [NH3] in the middle row and reduced metabolism [FDG] in the bottom row) are seen at similar location in PET, as indicated by arrows.

Figure 2. Top, Three short-axis views (apical, equatorial, and basal) of a PET viability study with assessment of rest perfusion (NH3) and glucose metabolism (FDG). Below, MRI images in corresponding slices showing hyperenhancement. Note that in segments with reduced perfusion and metabolism, there is an increased signal in MRI. Because of better spatial resolution in MRI, distinction between transmural, subendocardial, and papillary defects can be made. The border between enhanced and normal areas is distinct.
end-diastolic and end-systolic wall thickness and wall thick-
ening in viable segments compared with segments with transmural scar in PET ($P<0.001$). However, ROC analysis
(Figure 4) revealed smaller area under the curve for wall
thickness and thickening compared with hyperenhancement.

**Discussion**

The present study indicates that in patients with chronic CAD and severely reduced LV function, the MRI hyperen-
chancement technique is able to identify location and extent of nonviable tissue in close agreement with PET measurements
provided by comparison of flow and glucose metabolism. Dysfunctional but viable areas have a high likelihood of
improving contractile performance after restoration of flow. Estimation of perfusion and glucose metabolism by PET has
been reported to accurately differentiate between viable and nonviable myocardial tissue in many studies and, thus, was
used as reference method. Myocardial regions graded viable by PET are expected to improve contractile performance in
78% to 92% of cases. A recent comparison of various imaging modalities suggested that nuclear techniques, including
PET, tend to overestimate tissue viability on the basis of functional recovery after revascularization, yielding lower
specificity compared with techniques assessing contractile reserve. In cases of nontransmural scar formation, regional
function may not recover despite the presence of residual tissue viability in the affected territory. Therefore, functional
recovery may not be the only valid endpoint for evaluation of tissue viability. Prognosis may be altered without changing
LV function by improving LV remodeling processes, thus preventing additional LV dilatation, promoting electrical
stability, and reducing risk of subsequent fatal ischemic events. Besides scintigraphic and echocardiographic meth-
ods, MRI offers various parameters of tissue viability, such as wall thickness and wall thickening, and hyperenhancement. This study is, to our knowledge,
and compared them with their PET findings. They found a significantly higher proportion of fibrosis in areas with a matched defect than in normal areas evidencing scar formation. This may lead to altered kinetic behavior and partition coefficient of Gd-DTPA as extracellular space increases. In our study, segments with hyperenhancement agreed closely with segments with matched defects. This is in concordance with the above studies.

Compared with 201TI imaging, a reduced accuracy of hyperenhancement in hypokinetic segments compared with akinetic segments for detecting scar tissue was found. As shown in Table 3, diagnostic accuracy of MRI did not change with the degree of dysfunction in our study when compared with PET. Different sequence parameters, such as an inversion prepulse as described by Simonetti et al and the higher dose of Gd-DTPA (0.1 vs 0.2 mmol/kg bw), may be important for signal intensity in areas with smaller proportion of scar tissue, which is suspected in segments with preserved wall motion. In normokinesia, a reduced sensitivity compared with PET was found. However, in these areas, scar tissue is not expected, and, therefore, defects in these segments might represent false-positive results by PET.

Visual assessment of MRI data tends to overestimate scar tissue compared with PET (Figure 2). Several reasons may account for this observation. First, MRI can delineate segments more accurately, because the border between hyperenhanced and normal areas is distinct, whereas in nongated PET images, the border between normal and defect areas is less well defined (Figure 2). Fifty-five percent of segments showing a subendocardial enhancement by MRI were classified as normal by PET. Because the assessment of wall thickness is limited by the spatial resolution of nongated PET, epicardial tracer activity may mask small subendocardial defects. Therefore, MRI might provide, with its better spatial resolution, a more subtle delineation of scar tissue than PET. Second, FDG is a marker for viability, whereas Gd-DTPA is considered a marker for scar tissue. Thus, a relatively small number of viable cells may show increased FDG uptake, indicating viability, whereas structural changes may already coexist and alter Gd-DTPA kinetics. Therefore, PET imaging may show viability in segments with hyperenhancement, depending on the relative contribution of viable and fibrotic tissue. Third, an increase in regional signal intensity (Gd-DTPA) may be easier to interpret than a regional comparison of flow and metabolism by PET. And, finally, all comparative studies have the potential for anatomical misalignment. Although short-axis views were used in both modalities, the visualization of the inferior interception of the ventricles is especially difficult in patients with extensive scar tissue, because regions are not always clearly definable in PET.

Viability and Myocardial Function
As expected, the proportion of segments with scar increased with severity of dysfunction. However, parameters like EF and end-diastolic and end-systolic volumes showed only a weak correlation with extent of scar. Regional wall thickness or thickening is reduced significantly with increasing myocardial damage. However, these wall-thickness parameters had only limited diagnostic value for differentiation between viable and scar tissue (Figure 4). In contrast to previous investigations, remodeling processes may have altered LV geometry in our patient population with severely dilated ventricles, so that these parameters did not allow the detection of viable myocardium.

Study Limitations
An improved contractile performance is commonly considered the gold-standard for assessing viable myocardium. We did not examine patients after revascularization. However, several clinical studies exist demonstrating the diagnostic value of PET criteria in predicting functional recovery and clinical outcome. In addition, a recent study by Kim et al showed the predictive value of MRI for functional recovery. It was the purpose of this study to compare results of the most sensitive technique presently available for assessing viability with extent and location of MRI hyperenhancement as a specific marker for scar tissue.

Only a few segments showed a mismatch in PET (hibernating myocardium, 34 of 1023). Therefore, we were not confident evaluating MRI findings in these segments. It is interesting to note that 68% of these segments showed no hyperenhancement, whereas transmural enhancement occurred in only 8% (Table 2). This suggests that hibernating myocardium was diagnosed correctly by MRI as viable in most cases. However, patients with higher incidence of
hibernation have to be examined before final conclusions can be drawn.

Conclusions
In patients with chronic CAD and severely reduced LV function, hyperenhancement 20 minutes after application of 0.2 mmol Gd-DTPA/kg bw correlated closely concerning location and extent with scintigraphically assessed infarct size using PET with NH3 for perfusion and FDG as a metabolic tracer. Results were independent of the severity of contractile dysfunction. Thus, the MRI hyperenhancement technique seems to be a promising diagnostic tool for detecting nonviable tissue in patients with advanced CAD.

Acknowledgments
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References
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