Characterization of Dysfunctional Myocardium by Positron Emission Tomography and Magnetic Resonance Relation to Functional Outcome After Revascularization

Patrick R. Knuesel, MD; Daniel Nanz, PhD; Christophe Wyss, MD; Martin Buechi, MD; Philip A. Kaufmann, MD; Gustav K. von Schulthess, MD, PhD; Thomas F. Lüscher, MD; Juerg Schwitter, MD

Background—Metabolic assessment of dysfunctional myocardium by PET allows prediction of functional recovery after revascularization. Contrast-enhanced MR (ce-MR) discriminates transmural distribution of viable and scar tissue with excellent spatial resolution. Both techniques were applied in ischemic chronic left ventricular dysfunction to relate metabolism and tissue composition to changes of contractile function after revascularization.

Methods and Results—Nineteen patients with myocardial infarctions (>3 months) were studied by MR and PET, and 10 patients were followed by MR 11 ± 2 months after revascularization. In 56 to 64 segments/heart, systolic wall thickening, viable mass, and thickness of viable rim tissue were determined by MR (inversion-recovery MR with 0.25 mmol/kg Gd-chelate). [18 F]Fluorodeoxyglucose (FDG) uptake and resting perfusion ([13]N-ammonia) were determined by PET. Viable tissue per segment on ce-MR correlated with FDG uptake per segment (r = 0.62 and 0.82 for segments with and without flow metabolism mismatch, P < 0.0001). FDG uptake ≥50% (a predictor of functional recovery) corresponded to a viable rim thickness of 4.5 mm on ce-MR. Thick (>4.5 mm) and metabolically viable segments (≥50% FDG uptake) showed functional recovery in 85%, whereas thin metabolically nonviable segments improved function in 13% (P < 0.0005). Metabolically viable segments with a thin viable rim and thick segments with reduced FDG uptake improved function in only 36% and 23% of segments, respectively (NS versus thin metabolically nonviable). In these 2 classes of segments, scar per segment was higher than in thick viable segments (P < 0.0001).

Conclusions—Metabolism and tissue composition discriminate various classes of dysfunctional myocardium. Most metabolically viable segments with a thick viable rim on ce-MR recover function after revascularization, whereas all other classes showed low recovery rates of contractile function. (Circulation. 2003;108:1095-1100.)

Key Words: magnetic resonance imaging ■ scintigraphy ■ metabolism ■ hibernation

In patients with ischemic cardiomyopathy and chronic left ventricular (LV) dysfunction, the extent of viable myocardium relates to prognosis1 and also predicts outcome after revascularization.2-5 Up to 83% to 95%6-9 of segments with inotropic reserve on β1-adrenergic stimulation recover function after revascularization. Although scintigraphic techniques appear more sensitive for detection of viability, their specificity to predict functional recovery is in general somewhat lower, ranging from 48% to 82%.8,10 One might reason that some myocardial segments classified metabolically viable by PET imaging may lack a sufficient amount of viable tissue to contract even with adequate blood supply after revascularization. In advanced stages of hibernation with still preserved [18 F]fluorodeoxyglucose (FDG) uptake on PET, investigators reported an increase in interstitial fibrosis11 whereas others showed a loss of myofibrils in hibernating myocytes that correlated with an impaired inotropic reserve on low-dose dobutamine stress.12-14

Contrast-enhanced MR (ce-MR) is able to detect myocardial scar with high spatial resolution.15-18 Therefore, in patients with chronic LV dysfunction, myocardial metabolism and resting flow were determined by PET and tissue composition, ie, viable and scar tissue content were determined by MR. Based on PET and MR data, several classes of dysfunctional myocardial segments were defined and change in contractile function after revascularization was related to metabolism and tissue composition in these subsets of myocardial segments.

Study Population

Nineteen patients (age 58 ± 8 years) with known coronary artery disease on x-ray coronary angiography and hypokinetic/akinetic regions on echocardiography or LV angiography were studied with MR and PET in random
order within 4 weeks (without interventions or complications between studies). Patients with insulin-dependent diabetes were excluded from the study. In case of revascularization, patients were reexamined by MR 9 to 12 months later for assessment of functional recovery. Study protocols were approved by the local ethics committees, and written informed consent was obtained from all patients.

**MR Examination**

LV function was assessed on short-axis slices (thickness/gap, 8/0.5 mm) covering the entire LV (1.5T system, CV/i, GE Medical Systems). Twenty minutes after administration of 0.25 mmol/kg of the extravascular contrast medium Gd-DTPA-BMA (Omniscan, Amersham Health), a breath-hold inversion recovery pulse sequence (TR/TE, 6.4/1.6 ms, inversion time nulling normal myocardium) was used to cover the entire LV with short-axis slices (thickness/gap, 8/0.5 mm; spatial resolution, 1.3×1.8 to 2.1 mm²; central slice of stack at center of end-diastolic LV long axis). Endocardial and epicardial borders and enhancing myocardium were traced manually (excluding papillary muscles). Eight equiangular segments per slice were generated automatically (using the anterior septal insertion of the right ventricle as reference), and mass of hyperenhancing and nonenhancing tissue per segment as well as total mass of viable and scar tissue per heart were calculated. Mean thickness of viable rim was calculated for each segment by dividing the area of nonenhancing tissue by the length of its segmental perimeter. Scar per viable tissue was also determined automatically using a threshold 2 SD above a reference region (drawn remote of the infarcted territory).

For comparison with PET data and for assessment of segmental systolic function, 7 to 8 slices were analyzed depending on heart size (with slice 1 representing the most basal slice and slice 4 being located at the midpoint of LV diastolic long axis). Segmental systolic wall thickening was measured by the centerline method (Mass software v4.0), applying thresholds reported elsewhere. A scoring system is often used for visual assessment of contractile function differentiating 5 grades from dyskinetic to normal function (ie, 4 grades differentiate changes from akinetic to normal). Because postrevascularization systolic wall thickening in normal segments (metabolically viable and without scar formation on ce-MR) was 57%, an increase of ≥15% systolic wall thickening was used to define improvement of postoperative contractile function.

**PET Examination**

PET imaging was performed to assess uptake of FDG by a whole-body scanner (Advance, GE Medical Systems). After oral glucose loading (50 g), blood glucose was kept <6 mmol/L during the examination by intravenous administration of insulin (Actrapid HM; mean dose, 6.4±3.3 U). After measurement of resting perfusion by 13N-ammonia (400 to 600 MBq IV), FDG was injected (250 MBq IV), and 30 minutes later image acquisition (12×5 minutes) was initiated. On reformatted short-axis images (slice thickness 4.25 mm, no gap), FDG uptake was measured in 8 segments per slice (using same reference as in MR). To obtain a slice thickness as in MR, neighboring PET slices were averaged and 7 to 8 slice pairs were analyzed as described for the MR data sets.

The segmental FDG uptake and the segmental amount of unenhanced tissue on MR were expressed as fraction of the same segment demonstrating highest resting flow on PET (yielding FDG uptake corr, and MR viable tissue corr, respectively). Furthermore, in each segment the flow metabolism relationship was expressed as ratio of FDG uptake per gram of tissue (relative to the FDG uptake per gram of the reference segment) divided by blood flow in milliliter per minute per gram in the corresponding segment. In segments with preserved myocardial blood flow of ≥0.8 mL/min per gram and normal systolic wall thickening, this ratio was 0.8±0.3 min/g per milliliter. Therefore, a threshold value of ≥1.4 (mean±2 SD) was used to identify mismatch segments.

To relate the absolute thickness of viable rim on MR (in millimeters) with FDG uptake in that segment, rim thickness was related to FDG uptake per gram of tissue (expressed as percentage of the FDG uptake per gram of the reference segment), which is thought to reflect the fraction of viable tissue in a given segment.

**Statistical Analysis**

Values are given as mean±SD. Correlations between the amount of viable tissue or viable rim thickness on ce-MR and FDG uptake on PET were sought using regression analyses. To compare scar tissue per segment in the various classes of myocardial segments, ANOVA was performed followed by Scheffé post hoc testing. Comparisons of proportions (mismatch or match segment distribution and distribution of segment classes with or without functional recovery) were performed using χ² analyses (in cases of n comparisons, a probability value of P/n <0.05 was considered statistically significant). Intraobserver and interobserver variabilities of MR viability data are reported as mean±SD of differences of paired analyses. P<0.05 was considered statistically significant.

**Results**

Nineteen patients were studied at baseline by MR and PET. For demographics, see the Table. Of these patients, 10 underwent revascularization (coronary artery bypass graft surgery [CABG] in 8 and percutaneous coronary intervention in 2), whereas 9 were considered high-risk patients and obtained medical treatment only. Revascularization was performed 31±21 and 30±27 days after the MR and PET studies, respectively, and follow-up MR was performed 11±2 months after intervention (without clinical evidence of myocardial infarction during follow-up). One patient with medical treatment died during the follow-up period, and 1...
patient received heart transplantation. During the 55 studies (19 PET and 36 MR), 1 complication occurred in a patient with medical treatment (sustained ventricular tachycardia at the end of MR study that necessitated cardioversion).

**Baseline Viability Data: MR and PET Comparison**

In 1176 segments from 19 patients, the amount of viable tissue on MR and segmental FDG uptake (both normalized to the segment with highest resting flow) correlated positively (FDG uptake_{\text{PET}} = 0.85 MR viable tissue_{\text{MR}} + 0.21, r = 0.79, P<0.0001). Segments with flow metabolism mismatch substantially contributed to the scatter of data (r=0.62 versus r=0.83 for segments with flow metabolism match). The correlation between viable rim thickness and FDG uptake in dysfunctional segments (Figure 1) demonstrates that the threshold value of 50% FDG uptake often used to predict functional recovery\textsuperscript{22,23,25} corresponds to a rim thickness of \(\approx 4.5\) mm. Application of these PET and MR criteria for functional recovery\textsuperscript{22,23,25} corresponds to a viable rim thickness on MR of \(\approx 4.5\) mm. These findings allow the subdivision of dysfunctional myocardial segments into various classes meeting both MR and PET criteria for recovery of function, only 1 criterion (intermediate segments), or none of these criteria.

**Follow-Up Data: Recovery of Function in Various Segment Classes**

In the dysfunctional segments (Figure 3; \(n=331\)), 77% fulfilled criteria of viability in PET (\( \geq 50\% \) FDG uptake) along with a rim thickness of viable tissue \(>4.5\) mm on MR, whereas 10% of dysfunctional segments were classified as scar (\(<50\% \) FDG uptake) with a thin viable rim on MR (\(\leq 4.5\) mm). Of viable segments (\( \geq 50\% \) FDG uptake, rim thickness \(>4.5\) mm; PET/MR+/-), 85% recovered function after revascularization, yielding 93% of all segments with functional recovery (\(P<0.0005\)).

**Figure 1.** In dysfunctional segments, viable rim thickness on contrast-enhanced MR correlates with FDG uptake on PET. Mismatch segments explain partly the scatter observed in this relationship, which indicates that viable tissue as defined by ce-MR may differ with respect to flow-metabolism balance. The PET threshold of \(\geq 50\% \) FDG uptake (predicting functional recovery\textsuperscript{22,23,25}) corresponds to a viable rim thickness on MR of \(\approx 4.5\) mm. These findings allow the subdivision of dysfunctional myocardial segments into various classes meeting both MR and PET criteria for recovery of function, only 1 criterion (intermediate segments), or none of these criteria.

**Figure 2.** Scar content and proportions of mismatch and match segments are shown for the various classes of myocardial segments meeting both MR and PET criteria for functional recovery (PET/MR+/-), meeting only 1 (PET/MR-/+ and PET/MR-/-), or meeting none of these criteria (PET/MR-/-). Scar percentage per segment was highest in those segments meeting no recovery criteria. Intermediate segments also contained higher scar percentage per segment than segments fulfilling both PET and MR criteria for functional recovery. The highest portion of mismatch segments was found in the segments with preserved FDG uptake but a thin viable rim on MR (\(\leq 4.5\) mm). Error bars represent SEM.

**Figure 3.** The distribution of various classes of myocardial segments at baseline and after revascularization is shown. Viability predicting functional recovery was defined for PET as FDG uptake \(\geq 50\% \) (PET+) and for MR as viable rim thickness \(>4.5\) mm (MR+, see also Figure 1). At baseline, 77% of all dysfunctional segments fulfilled viability criteria of both techniques (PET/MR+/-), and 85% of these segments improved function after revascularization (upper right). In contrast, only 13% of segments fulfilling none of these criteria improved function. Metabolically viable segments with a thin viable rim on MR (PET/MR-/-) recovered function in only 36% and segments with thick viable rim but reduced FDG uptake (PET/MR-/-) recovered function in only 24%. In this latter class of segments, considerable amount of scar tissue was present (see Figure 2). Thus, in a subset of segments, insufficient amount of viable tissue (PET/MR-/-) and metabolic alterations or considerable scar content (PET/MR-/-) may limit the ability of these segments to recover function after revascularization.
versus 38% of segments without functional recovery). On the other hand, 87% of all scar segments (<50% FDG uptake, rim thickness ≤4.5 mm; PET/MR−/+−) showed no change of function after revascularization, yielding 28% of all segments without functional recovery (P<0.0005 versus 2% of segments with functional recovery). A typical example of a patient with thick metabolically viable segments and postoperative improvement of contractile function is shown in Figure 4.

A total of 13.5% of dysfunctional segments fell within either category of MR and PET classes (intermediate segments): ie, the segments were metabolically viable but thickness of viable rim was small (<4.5 mm; PET/MR−/+−) or segments showed a thick viable rim with a reduced FDG uptake (PET/MR−/+; Figure 3). These 2 classes showed no change in postoperative function in 64% and 77%, respectively, which is similar to scar segments (87% had no change in function; NS). Figure 2 demonstrates the relatively high scar percentage in these intermediate segments (28±29% in thin metabolically viable segments; 41±29% in thick metabolically nonviable segments, P<0.01 and P<0.0001 versus thick viable segments, respectively). Figure 5 demonstrates metabolic viability in a thin rim of viable tissue. After revascularization, no improvement in contractile function occurred in these segments.

In the patients with revascularization, LV ejection fraction at baseline was 41.6±10.9% and increased insignificantly to 45.3±9.8% (P=0.08). In patients without revascularization, LV ejection fraction was 30.0±12.8% at baseline and did not change at follow-up (29.8±11.1%, NS).

Reproducibility of MR Viability Data
On MR, scar mass was 23.2±17.3 g and total LV mass was 168.8±41.3 g (calculated from 1537 segments covering the entire LV in all patients). Intraobserver and interobserver variability for quantification of viable myocardium was −1.8±11.0 g (−0.8±8.1%) and 2.7±9.2 g (2.0±6.8%), respectively (mean difference±SD). Mean difference between manual and automatic analysis was 3.8±7.3 g (2.6±5.1%).

Discussion
The major findings of this study are as follows. First, a correlation between the amount of viable tissue on MR and FDG uptake is observed that is modulated by the presence of mismatch segments. Second, 85% of segments with preserved FDG uptake and a thick rim of viable tissue on MR recover function after revascularization, whereas 87% of metabolically nonviable segments (FDG uptake <50%) with a thin rim of viable tissue on MR do not recover function. Third, segments with either reduced FDG uptake or a thin rim of viable tissue on MR show a reduced probability for functional recovery (36% and 24%, respectively).

Detection of Viability by FDG-PET and ce-MR
The amount of viable tissue per segment on ce-MR positively correlated with this segment’s metabolic activity, ie, its myocardial FDG uptake. Both PET and MR techniques probe the integrity of myocyte membranes and are therefore related to the amount of viable tissue.11,12,15,17,18,26,27 The correlation observed between the amount of viable tissue as measured by MR and PET explains the high sensitivity and specificity of ce-MR to detect viability, which is in line with recently reported data.18 The present data indicate that this relationship is modulated by the flow metabolism relationship. Thus, MR provides information on the amount of viable tissue, whereas...
FDG uptake on PET may additionally reflect the severity of myocyte metabolic alterations. A 50% FDG uptake (a cut off value often used to predict functional recovery) corresponded to a viable rim thickness on MR of ≈4.5 mm. Although segments above and below these thresholds are expected to recover function with high and low probability, the fate of intermediate segments (fulfilling only 1 criterion for functional recovery) is of particular interest.

Recovery of Function in the Various Classes of Myocardial Segments

The follow-up data in the 331 dysfunctional segments for which a revascularization was performed demonstrate that thick metabolically viable segments are highly likely to recover function after revascularization (85% of these segments). Conversely, very few thin metabolically nonviable segments (13%) did improve function after revascularization. These findings are in line with ce-MR data on functional recovery reported by others.

A smaller portion of dysfunctional segments demonstrated preserved FDG uptake but a thin rim of viable tissue on ce-MR (≈4.5 mm). In this class of segments, a high portion of mismatch segments was found that are generally associated with a high likelihood of functional recovery. However, only one third of these segments improved in postoperative function. This finding of metabolically viable myocardium that does not recover function after revascularization might be explained by a loss of contractile material in these segments that precludes contractile recovery. A reduction in wall thickness <5.5 mm or a fibrous content exceeding 35% predicted lack of functional recovery and translates into a rim of viable tissue of ≈4 mm (>65% of 5.5-mm wall thickness) necessary for contractile function. A severe alteration of metabolism was a common finding in PET-viable segments with a thin rim of viable tissue (≈4.5 mm), as indicated by the high portion of mismatch segments of 59% in this class. These findings are in keeping with histological data of hibernating tissue that demonstrated severe ultrastructural changes of myocytes with intact cell membranes.

Conversely, in approximately half of segments with an impaired FDG uptake (predicting lack of functional recovery), the thickness of viable tissue on MR exceeded 4.5 mm. Despite this thick rim of viable tissue, 77% of these segments did not improve postoperative function. The low portion of mismatch segments in this class (10%) indicates that the amount of viable tissue as measured by MR is not the only predictor for functional recovery. In addition, scar percentage per segment was high in this class (41% per segment), suggesting a role for tethering in postoperative dysfunction. This possible explanation is supported by a recent study where scar as measured by PET was a strong predictor of postoperative function.

As demonstrated in many previous studies, ce-MR is an excellent tool for quantification of scar tissue. In the present study, ce-MR data analysis focused on quantification of viable tissue. This analysis takes advantage of the fact that viable myocardium (signal nulled) yields high contrast versus blood (unlike scar tissue exhibiting high signal similar to blood) and consequently allowed for automatic and reproducible quantification of viable myocardium.

Figure 5. In this 48-year-old female patient, 3 years after a lateral myocardial infarction, a small subendocardial scar in the lateral segments 3 and 4 is demonstrated (A) with a thin rim of viable tissue. These segments show preserved FDG uptake (B) with a reduced perfusion (D), thus exhibiting the pattern predictive for recovery of function (see also schematic C). Although these segments were hypocontractile at baseline (E and F), 11 months after bypass surgery these segments did not improve function (G and H). Conversely, segments 5 and 6 were not infarcted (A), had a thick rim of viable tissue (A), and fulfilled metabolic viability criteria (B and D). Follow-up MR demonstrates substantial improvement of contractile function (G and H) compared with baseline function in these segments (E and F).
Limitations

It is a drawback of this study that FDG uptake\textsuperscript{22,23} was not determined during euglycemic clamp conditions. However, after glucose loading, the level of blood glucose was kept <6 mmol/L by intravenous insulin administrations to maximize glucose uptake by myocytes. The fact that scar in metabolically negative segments averaged 54\%, which is close to values obtained in biopsies of scar regions (49±20\%\textsuperscript{11}), indicates that the portion of false-negative PET segments was low with this technique.

Complete revascularization was attempted in all patients undergoing CABG surgery. Percutaneous coronary intervention was performed in 2 patients with 2-vessel disease to revascularize 1 perfusion territory (whereas the other territory showed no viability on PET). Therefore, adequate revascularization of viable territories was most likely achieved in all patients by CABG or percutaneous interventions. However, PET perfusion studies at follow-up were not performed to document completeness of revascularization.

Conclusions

Combined assessment of metabolism and tissue composition discriminates various classes of dysfunctional myocardium. Most metabolically viable segments with a thick viable rim on ce-MR recover function after revascularization, whereas all other classes showed low recovery rates of function. The low portion of recovery of metabolically viable but thin segments suggests that the amount of viable tissue impacts on functional recovery. In a smaller class of segments with impaired FDG uptake and an increased scar content, functional recovery was also rare despite a thick viable rim on ce-MR, indicating that metabolic alterations or tethering may influence the likelihood of functional recovery. Larger longitudinal studies are warranted to relate classes of myocardial segments not only to functional parameters but also to clinical outcome after revascularization.

Acknowledgments

This study was supported in part by the Swiss National Science Foundation, Swiss Heart Foundation, and Amersham Health, Norway.

References


Characterization of Dysfunctional Myocardium by Positron Emission Tomography and Magnetic Resonance: Relation to Functional Outcome After Revascularization

Patrick R. Knuesel, Daniel Nanz, Christophe Wyss, Martin Buechi, Philip A. Kaufmann, Gustav K. von Schulthess, Thomas F. Lüscher and Juerg Schwitter

_Circulation_. 2003;108:1095-1100; originally published online August 25, 2003;
doi: 10.1161/01.CIR.0000085993.93936.BA

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/9/1095

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/