Detection of Acutely Impaired Microvascular Reperfusion After Infarct Angioplasty With Magnetic Resonance Imaging

Andrew J. Taylor, PhD; Nidal Al-Saadi, MD; Hassan Abdel-Aty, MD; Jeanette Schulz-Menger, MD; Daniel R. Messroghli, MD; Matthias G. Friedrich, MD

Background—Despite the reopening of the infarct-related artery (IRA) with infarct angioplasty, complete microvascular reperfusion does not always ensue.

Methods and Results—We performed cardiovascular MRI (CMR) in 20 acute myocardial infarction (AMI) patients within 24 hours of successful infarct angioplasty and 10 control patients without obstructive coronary artery disease on a clinical 1.5-T CMR scanner. Three-month follow-up CMR in AMI patients evaluated the impact of abnormal reperfusion on recovery of function. Infarction was localized by delayed contrast hyperenhancement and impaired systolic thickening. Microvascular perfusion was assessed at rest by first-pass perfusion CMR after a bolus of gadolinium-DTPA by use of the time to 50% maximum myocardial enhancement. Whereas contrast wash-in was homogeneous in control patients, AMI patients exhibited delays in the hypokinetic region subtended by the IRA compared with remote segments in 19 of 20 patients, with a mean contrast delay of 0.9 ± 0.1 seconds (95% CI, 0.6 to 1.2 seconds). At follow-up, the mean recovery of systolic thickening was lower in segments with a contrast delay of 2 seconds or more (10 ± 7% versus 39 ± 4%, P < 0.001). A contrast delay ≥ 2 seconds and infarction > 75% transmurally were independent predictors of impaired left ventricular systolic thickening at 3 months (P = 0.002 for severe contrast delay, P = 0.048 for > 75% for transmural infarction).

Conclusions—CMR detects impaired microvascular reperfusion in AMI patients despite successful infarct angioplasty, which when severe is associated with a lack of recovery of wall motion. (Circulation. 2004;109:2080-2085.)

Key Words: imaging ■ microcirculation ■ reperfusion ■ infarction

The cornerstone of treatment for acute myocardial infarction (AMI) is the restoration of perfusion in the infarct-related artery (IRA). Although restoring patency to the IRA with percutaneous coronary intervention (PCI) is of proven benefit, this alone does not guarantee restoration of adequate perfusion to the ischemic myocardium. In many cases, reperfusion is impaired even with successful reopening of the IRA, characterized by the “no-reflow” phenomenon, which can occur in up to 40% of all successful infarct angioplasty cases and is associated with a higher incidence of heart failure.

Despite its prognostic importance, accurate assessment of microvascular reperfusion in AMI and its consequences is difficult. The ideal modality would combine information on microvascular flow, along with defining regional wall motion abnormality and areas of myocardial viability. Angiography is an insensitive tool for the assessment of microvascular perfusion, and even with the measurement of coronary flow with TIMI frame counts or Doppler wire, no information on myocardial viability can be attained. Myocardial contrast echocardiography and single-photon emission computed tomography also assess microvascular perfusion; however, they too have limitations. Single-photon emission computed tomography may also delineate areas of infarcted myocardium from viable regions, but assessment of regional myocardial function is not possible, whereas myocardial contrast echocardiography provides data on local myocardial function but cannot differentiate myocardial infarction from stunning without repeated examinations or the administration of pharmacological stressors such as dobutamine.

A promising modality for the assessment of microvascular reperfusion in AMI is cardiac MRI (CMR), because it is capable of obtaining data about microvascular flow, regional myocardial wall motion, and viability in one single examination and without the administration of a pharmacological stress. The application of CMR is highly accurate in assessing left ventricular (LV) function, and techniques incorporating the administration of gadolinium-DTPA contrast with rapid acquisition of sequential images demonstrate myocardial perfusion both at rest and with stress in the assessment of coronary artery disease. Furthermore, delayed hyperenhancement after contrast enables accurate delineation be-
tween infarcted and viable myocardium, allowing prediction of recovery of myocardial function.

In the present prospective study, we assessed the incidence of impaired microvascular reperfusion after AMI treated with emergency PCI and its association with recovery of myocardial function. We performed CMR on 20 patients within 24 hours of emergency PCI performed for AMI to assess acute LV dysfunction, myocardial perfusion, and viability. CMR was then repeated 3 months after AMI to assess the relation of acute myocardial reperfusion patterns to recovery of wall motion. CMR was also performed on a control group of 10 patients without obstructive coronary artery disease for comparison with normal perfusion patterns.

Methods

Patient Selection
All subjects were enrolled through the Department of Cardiology, Humboldt-University, Charité, Campus Buch, Franz Volhard Klinik, Berlin, Germany. Patients with AMI were considered for enrollment if they had undergone successful emergency PCI within the preceding 24 hours, with AMI defined either by diagnostic ECG changes or an acutely rising serum creatinine kinase of twice the upper limit of normal. Only those who had undergone emergency PCI within 12 hours of the onset of chest pain were included. Control subjects were patients without significant coronary obstruction, as confirmed by angiography before enrollment. Patients were excluded if they suffered from claustrophobia or atrial or ventricular tachyarrhythmias or had a history of a metallic prosthetic implant that contraindicated CMR. In addition, patients who were hemodynamically unstable were also excluded. Informed consent was obtained before CMR, and the study was performed under the guidelines of the Franz Volhard Klinik Ethics Committee.

Coronary Angiography and Angioplasty Procedure
All patients underwent coronary angiography on a Siemens angiography suite (Hicor). Obstructive coronary artery disease was defined as a >50% stenosis in a coronary artery or major sub-branch, which was calculated by dividing the diameter at maximum stenosis by a proximal reference segment. All AMI patients received combined oral antiplatelet therapy with aspirin (100 mg/d) and clopidogrel (75 mg/d after an oral bolus of 300 mg) for a minimum of 1 month after PCI. The administration of intravenous antiplatelet agents, such as abciximab or tirofiban, was at the proceduralist’s discretion. Heparin was administered as an intravenous bolus during PCI to attain an activated clotting time of 200 seconds. Procedural success in AMI patients was defined by successful emergency PCI and in 10 control patients on a clinical indication. Heparin was administered as an intravenous antiplatelet agent, such as abciximab or tirofiban, as at the proceduralist’s discretion. Heparin was administered as an intravenous bolus during PCI to attain an activated clotting time >300 seconds. Procedural success in AMI patients was defined by an open coronary artery with <30% residual stenosis.

CMR Protocol

MRI Sequences
We performed CMR in 20 AMI subjects within 24 hours of successful emergency PCI and in 10 control patients on a clinical 1.5-T CMR scanner (General Electric CV/i, Milwaukee, Wis). Microvascular perfusion was assessed at rest by first-pass perfusion CMR (saturation recovery, gradient echo/echo planar-readout sequence, TR/TE 113 to 134 ms/1.3 to 1.7 ms, flip angle 25°, slice thickness 15 mm) after a bolus of gadolinium-DTPA (0.1 mmol/kg body weight; Magnevist, Schering). This permitted reliable analysis of perfusion and also delayed hyperenhancement imaging with a single contrast dose, thus keeping the scan time to a minimum (~40 minutes total). LV function was assessed by a steady-state free precession pulse sequence (TR 3.8 ms, TE 1.6 ms, 30 phases, slice thickness 15 mm), and percent myocardial thickening was calculated. Delayed hyperenhancement was evaluated 10 minutes after gadolinium-DTPA administration to identify the infarct region by use of an inversion-recovery gradient echo technique (TR 7.1 ms, TE 3.1 ms, TI individually determined to null the myocardial signal, range 180 to 250 ms, slice thickness 15 mm, matrix 256×192, number of acquisitions 2). All sequences except perfusion were acquired during a breath-hold of 10 to 15 seconds. Because the perfusion sequence ran for 60 heartbeats, patients were instructed to hold their breath for as long as was comfortable, taking a further breath when required and then breath-holding again. All CMR sequences were performed in 3 standard short-axis slices (apical, mid, and basal), kept identical for each sequence throughout the CMR examination. From a 4-chamber long-axis view, 5 equally spaced slices were planned, so that the 2 outer slices lined up exactly with either the tip of the apex or the mitral annulus. The 2 outer slices were then deleted, leaving 3 slices corresponding to typical basal, mid, and apical short-axis views. The slice thickness and separation were recorded to permit accurate reproducibility of views in subsequent studies.

Evaluation of Myocardial Perfusion, LV Wall Motion, and Myocardial Infarction in AMI and Control Subjects
Regional perfusion and wall thickening were evaluated from the 3 standard short-axis slices by use of a 16-segment LV model. Semi-quantitative perfusion analysis was performed by calculating the time to 50% maximum myocardial enhancement (T50%max) during the first pass of contrast in each myocardial segment (Figure 1) by use of a specialized software package (MASS 6.0, Medis). The contrast delay in AMI segments was then calculated by subtracting the T50%max of these segments from that of a remote myocardial segment. The criteria for the selection of the remote segment were the complete absence of infarction (as assessed by delayed hyperenhancement) and uniform wash-in over all 3 slices in that myocardial segment. LV wall motion was assessed on a segmental basis by calculating the percent systolic thickening and using Simpson’s biplane method globally in 2- and 4-chamber long-axis views.

Myocardial infarction was identified by delayed hyperenhancement within the myocardium, defined quantitatively by myocardial postcontrast signal intensity >2 SD above that with a reference region of remote noninfarcted myocardium within the same slice.

Clinical Information and Follow-Up
Baseline clinical data were obtained before enrollment, including coronary risk factors and other relevant medical history and medications. In AMI subjects, patients were also assessed during their hospital admission and 3 months after their AMI for a number of adverse clinical outcomes, including recurrent chest pain, cardiac failure, reinfarction, and death.

Statistics
All data are expressed as mean±SEM except where otherwise stated. Comparisons between groups were made by use of paired or unpaired Student’s t tests. When comparisons between groups involved proportionality, the χ2 test or Fisher’s exact test was applied. The Pearson product moment was calculated to assess
TABLE 1. Clinical and Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>AMI (n=20)</th>
<th>Control (n=10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.9±2.8</td>
<td>61.3±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>16 (80)</td>
<td>6 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (55)</td>
<td>8 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (50)</td>
<td>6 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (15)</td>
<td>3 (30)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Smoking</td>
<td>9 (45)</td>
<td>2 (20)</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>18 (90)</td>
<td>8 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>18 (90)</td>
<td>8 (80)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73.0±1.9</td>
<td>64.6±2.5</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>95.2±2.9</td>
<td>97.9±6.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are n (%) or mean±SEM.
*Fisher’s exact test.
†Unpaired t test.

correlation, and multiple linear regression evaluated the independence of multiple variables. Statistical power of the correlation between acute perfusion delay and recovery of LV function was >0.8, given an α value of 0.05 and an estimated correlation coefficient of 0.6 and a sample size of 20 subjects. A computerized statistical program, (SPSS for Windows, Release 9.0.1, SPSS Inc) was used for all analyses.

Results

Clinical and Demographic Data

AMI subjects underwent emergency angiography and PCI within a mean time of 8.1±1.2 hours of the onset of chest pain. Compared with control subjects, AMI subjects had a lower incidence of diabetes mellitus and a higher resting heart rate but were otherwise similar with regard to cardiac risk factors and medications (Table 1).

Coronary Angiography and PCI

The majority of AMI patients had TIMI 0 flow at angiography, with the remainder having either TIMI I or II flow (Table 2). The mean diameter of the IRA was 3.0±0.1 mm.

Of the 10 control patients, 5 (50%) had angiographically normal coronary arteries, with the remainder having a maximal stenosis in any vessel of 50% or less (mean 30±5%).

PCI was successful in all AMI patients, with TIMI III flow being restored in all but 2 patients. Adjunctive antiplatelet therapy with intravenous glycoprotein IIb/IIIa blocking agents was administered in 13 of 20 patients (65%). In addition, thrombolysis was administered before the PCI in 4 (20%). One patient received both thrombolysis and intravenous IIb/IIIa blockade in conjunction with PCI. Coronary stents were deployed in 17 of 20 patients (85%).

Perfusion Patterns in AMI and Control Subjects

The area of myocardium affected by the AMI was defined as all segments with impaired (<40%) systolic thickening13 corresponding to the area subtended by the IRA. Despite the restoration of TIMI III flow in almost all AMI patients, there was delayed wash-in of gadolinium-DTPA on the first pass of contrast in 19 of 20 patients (95%). In all patients, this extended beyond the infarcted zone (Figure 2). There was no correlation between the corrected angiographic TIMI frame count immediately after PCI and the mean contrast wash-in delay assessed by CMR perfusion within 24 hours of PCI.

In total, 124 segments within the perfusion region of the IRA had impaired systolic thickening, with a mean delay of wash-in during the first pass of contrast of 0.9±0.1 seconds (95% CI, 0.6 to 1.2 seconds). Of these 124 segments, 24 (19%) had severely delayed contrast wash-in, defined by a delayed first-pass contrast wash-in ≥2 seconds. Of the 24 AMI segments with severely delayed contrast wash-in, 8 (33%) had >75% transmural infarction indicated by delayed contrast hyperenhancement, compared with 24 of 100 (24%) of AMI segments without severely delayed contrast wash-in (P=NS, χ²). In contrast to AMI patients, control subjects had largely homogeneous wash-in of contrast during the first pass, with a severe delay of contrast wash-in observed in only 2 of 160 segments (<2%).

Relationship of Abnormal Reperfusion Patterns to Recovery of Myocardial Function

Follow-up CMR was performed in 16 patients 3 months after AMI. A cutoff value of 2 seconds for severe delay of contrast wash-in on the acute scan was based on receiver operating characteristic analysis of its ability to predict failure of segmental recovery, yielding a sensitivity of 53% and a specificity of 87%. Acutely, there was no difference in the mean systolic thickening in segments with severely delayed contrast wash-in compared with the remainder of the hypokinetic segments (21±4% versus 19±2%, P=NS). However, at follow-up, systolic thickening was markedly worse in those initially hypokinetic segments with a severe delay of contrast wash-in within 24 hours of reperfusion (31±6% versus 56±4%, P<0.001). This corresponded to an almost 4-fold reduction in absolute recovery of systolic thickening in segments with severe delays of contrast wash-in (10±7% versus 38±4%, P<0.001; Figure 3). Perfusion scanning at 3 months in AMI subjects demonstrated improved contrast wash-in in segments with severe contrast delays on their acute scan (mean contrast delay of 3.0±0.2 seconds acutely versus 1.9±0.3 seconds at follow-up, P<0.01). In contrast,

TABLE 2. Angiographic and PCI Data

<table>
<thead>
<tr>
<th></th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
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</thead>
<tbody>
<tr>
<td>TIMI flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (50)</td>
<td>...</td>
</tr>
<tr>
<td>I</td>
<td>9 (45)</td>
<td>...</td>
</tr>
<tr>
<td>II</td>
<td>1 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>III</td>
<td>...</td>
<td>18 (90)</td>
</tr>
<tr>
<td>Infarct artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>12 (60)</td>
<td>...</td>
</tr>
<tr>
<td>Right coronary</td>
<td>3 (15)</td>
<td>...</td>
</tr>
<tr>
<td>Circumflex</td>
<td>5 (25)</td>
<td>...</td>
</tr>
<tr>
<td>Lesion grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A or B1</td>
<td>4 (20)</td>
<td>...</td>
</tr>
<tr>
<td>B2 or C</td>
<td>16 (80)</td>
<td>...</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>5 (25)</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are n (%).
there was no change in contrast wash-in over the 3-month period in segments without severe delays of contrast wash-in (mean contrast delay of 0.3±0.1 seconds acutely versus 0.4±0.2 seconds at follow-up, \( P=\text{NS} \)).

**Relationship of Abnormal Reperfusion Patterns, Extent of Infarction, and Lesion Characteristics to Recovery of LV Function**

Follow-up CMR also revealed reduced LV systolic thickening at 3 months in AMI segments with >75% transmural infarction identified by delayed hyperenhancement (38±6% versus 55±4%, \( P=0.02 \)). On a segmental basis, both the presence of a severe perfusion delay within 24 hours of reperfusion and also >75% transmural infarction were independent predictors of impaired LV systolic thickening at 3 months (coefficient of regression \(-23.6, P=0.002 \) for severe perfusion delay; coefficient of regression \(-14.1, P=0.048 \) for >75% for transmural infarction). On an individual patient basis, there was a negative correlation between the mean contrast delay within the perfusion region of the IRA acutely and improvement of overall ejection fraction at 3 months (\( R=-0.54, P<0.05 \); Figure 4A). Conversely, there was no correlation between the mean contrast delay at 3 months and recovery of ejection fraction (\( R=-0.26, P=\text{NS} \); Figure 4B).

Because our AMI group had a variety of lesion grades that could also affect later vessel patency and hence recovery of function, we assessed the contribution of lesion grade, vessel diameter, and time to reperfusion in addition to the mean acute wash-in delay of the infarct region in predicting recovery of LV function. On multiple linear regression, only the mean acute wash-in delay remained an independent predictor of recovery of function at 3 months (coefficient of regression \(-8.8, P<0.02 \)).

**Clinical Outcomes: In-Hospital and 3-Month Follow-Up**

All AMI patients experienced an uncomplicated clinical course after AMI, with no recurrent angina during the acute hospital admission. One patient underwent PCI for a coronary stenosis not in the IRA. During the 3-month follow-up period, 2 patients (10%) experienced postinfarction angina that was successfully treated with PCI (1 for restenosis of the IRA and 1 for de novo stenosis in another coronary artery). Coronary artery bypass grafting was performed in 2 more patients with triple-vessel coronary artery disease who had no ongoing angina before operation. No deaths and no cardiac failures were recorded in the 3-month study period.

**Discussion**

By use of CMR, we identified microvascular perfusion defects in the vast majority of AMI patients despite excellent...
angiographic results after PCI. Furthermore, there was minimal recovery of systolic function in LV segments with marked impairment of microvascular perfusion acutely and a negative correlation between the acute perfusion delay and improvement of overall LV ejection fraction. Importantly, the presence of severely delayed microvascular reperfusion was predictive of impaired LV systolic function independently of the transmurality of infarction.

Although the transmural extent of myocardial scarring in AMI identified by CMR is a strong predictor of reduced recovery of wall motion, our data suggest that acutely (within 24 hours of reperfusion), the dynamics of microvascular reperfusion characterized by CMR perfusion identify an area of myocardium surrounding the scarred tissue, which, although viable, may have severely impaired microvascular flow. Such an ischemic “penumbra” may be at risk in the ensuing days of further cell death or triggering conversion to hibernation over a longer period. Previously, the lack of recovery in the region of infarction despite restoration of patency to the IRA has been attributed largely to “reperfusion injury” mediated through myocardial apoptosis, the generation of free radicals, and associated inflammatory response. Our findings extend previous work highlighting impaired microvascular perfusion in AMI despite conventionally successful reperfusion therapy, with a low likelihood of recovery of function in these affected regions. Many of the proposed mediators, such as microvascular spasm, platelet plugging, and distal embolization, are treatable in the acute period. Preliminary CMR perfusion data from our group suggest that adjunctive glycoprotein IIb/IIIa blockade with PCI for AMI reduces the extent of irreversible microvascular injury within the hypoperfused area.

An important caveat to our findings is the lack of angiographic follow-up at 3 months, because late occlusion of the IRA may also contribute to impaired recovery of function, with different arterial lesion types leading to different degrees of late IRA patency. However, the acute microvascular reperfusion remained the only independent predictor of later recovery when lesion grade, vessel diameter, and time to reperfusion were analyzed with multiple regression. Furthermore, 3-month follow-up demonstrated improved perfusion in LV segments with an initially severe perfusion delay and no correlation between the 3-month perfusion score and recovery of function. Finally, although CMR scanning at day 3 after stent placement for AMI is safe, there are few data on the effects on patients within 24 hours of stent placement. We identified no adverse effects of our CMR protocol at 3-month clinical follow-up and have previously demonstrated no significant heating effects of MRI on a range of stents in an ex vivo model. We therefore believe that CMR is safe even within the very early poststent period.

The cornerstone of reperfusion therapy for AMI is the restoration of adequate microvascular reperfusion in the infarct territory. Although restoration of the IRA is a critical first step, our data suggest that in many instances this is only the first step, because microvascular perfusion is impaired in the majority of instances. Further investigation of this important phenomenon by use of the techniques and findings from our research are vital to the future development of strategies for AMI aimed at restoring complete microvascular reperfusion.

Acknowledgments

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