Detection of Intracoronary Thrombus by Magnetic Resonance Imaging in Patients With Acute Myocardial Infarction

C.H.P. Jansen, MD; D. Perera, MRCP, MD; M.R. Makowski, MD, PhD; A.J. Wiethoff, PhD; A. Phinikaridou, PhD; R.M. Razavi, MD; M.S. Marber, MD, PhD; G.F. Greil, MD; E. Nagel, MD, PhD; D. Maintz, MD; S. Redwood, MD; R.M. Botnar, PhD

Background—Persistent intracoronary thrombus after plaque rupture is associated with an increased risk of subsequent myocardial infarction and mortality. Coronary thrombus is usually visualized invasively by x-ray coronary angiography. Non–contrast-enhanced T1-weighted magnetic resonance (MR) imaging has been useful for direct imaging of carotid thrombus and intraplaque hemorrhage by taking advantage of the short T1 of methemoglobin present in acute thrombus and intraplaque hemorrhage. The aim of this study was to investigate the use of non–contrast–enhanced MR for direct thrombus imaging (MRDTI) in patients with acute myocardial infarction.

Methods and Results—Eighteen patients (14 men; age, 61±9 years) underwent MRDTI within 24 to 72 hours of presenting with an acute coronary syndrome before invasive x-ray coronary angiography; MRDTI was performed with a T1-weighted, 3-dimensional, inversion-recovery black-blood gradient-echo sequence without contrast administration. Ten patients were found to have intracoronary thrombus on x-ray coronary angiography (left anterior descending, 4; left circumflex, 2; right coronary artery, 4; and right coronary artery–posterior descending artery, 1), and 8 had no visible thrombus. We found that MRDTI correctly identified thrombus in 9 of 10 patients (sensitivity, 91%; posterior descending artery thrombus not detected) and correctly classified the control group in 7 of 8 patients without thrombus formation (specificity, 88%). The contrast-to-noise ratio was significantly greater in coronary segments containing thrombus (n=10) compared with those without visible thrombus (n=131; mean contrast-to-noise ratio, 15.9 versus 2.6; P<0.001).

Conclusion—Use of MRDTI allows selective visualization of coronary thrombus in a patient population with a high probability of intracoronary thrombosis. (Circulation. 2011;124:416-424.)

Key Words: atherosclerosis ■ coronary artery disease ■ magnetic resonance imaging ■ myocardial infarction ■ thrombosis

Patients with symptoms suggestive of acute coronary syndrome (ACS) should be evaluated rapidly. The most urgent priority is to identify those with ST-segment–elevation myocardial infarction (STEMI) who should be considered for immediate reperfusion therapy. Whereas serial ECG is the only test required to identify STEMI, only one third of patients with unstable angina or non-STEMI display acute ST-segment changes at presentation.1–4 Given the heterogeneity of potential outcomes in these patients,5 intensive medical therapy and invasive management should be tailored to the patient’s risk of an ischemic cardiac event or a treatment-related complication.6,7 Therefore, early risk stratification has lifesaving implications8 and requires a careful assessment of the patient’s history findings on physical examination, ECG, and cardiac biomarker assay. Other tests that are also commonly performed include computed tomography coronary angiography,9 nuclear perfusion imaging,9 and rest10 and stress11 echocardiography, which have high negative predictive values but relatively low positive predictive values.

Clinical Perspective on p 424

Because the majority of ACSs are believed to be caused by rupture or erosion of an atherosclerotic plaque with subsequent intraluminal thrombosis resulting in partial or complete occlusion of a coronary artery,12,13 a rapid applicable throm-
bus imaging test may be useful to aid optimal medical therapy and to guide early invasive management. Recently, non-contrast-enhanced T1-weighted magnetic resonance (MR) imaging (MRI) of methemoglobin within evolving thrombus or intraplaque hemorrhage has been exploited by taking advantage of its short T1 relaxation time. Several studies have demonstrated its usefulness to detect fresh thrombus in the settings of deep vein thrombosis, pulmonary embolus, acute arterial occlusion, hemorrhage in complex carotid,14,15 and, more recently, coronary plaque.16,17 The aim of this proof-of-concept study was to investigate the feasibility of non-contrast-enhanced MRI to detect intracoronary thrombus formation in patients after myocardial infarction.

Methods

Study Population
Between August 2008 and September 2009, 18 patients (14 men; age, 61±9 years) with acute myocardial infarction who were not eligible for primary percutaneous coronary intervention, including patients with non–ST-elevation ACS (non-STEMI and unstable angina) and those who had received thrombolysis for STEMI (on clinical and ECG criteria), were prospectively enrolled within 72 hours (45±24 hours) after the initial onset of symptoms. Diagnosis of acute myocardial infarction was based on elevation of cardiac biomarkers with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia, or development of pathological Q waves. Patients eligible for primary percutaneous coronary intervention and those with clinical or ECG evidence of ongoing ischemia, heart failure (New York Heart Association grade IV), or significant cardiac arrhythmia were excluded from the study. Furthermore, patients <18 years of age, patients with mental disorders, those unable to give consent, those with claustrophobia, patients with known allergies or contraindications to gadolinium or iodine, women who were pregnant or breastfeeding, and those with impaired renal function (glomerular filtration rate <30 mL/min) were excluded from the study. All patients were scanned successfully within 24 hours (median, 5.2 hours; range, 1.4 to 23.7 hours) before invasive x-ray coronary angiography (XCA). During XCA, patients underwent thrombus aspiration and coronary stenting and received glycoprotein IIb/IIIa inhibitors at the discretion of the operator. The study was approved by the local research ethics committee (study 08/H0802/101). Written informed consent was obtained from all patients before inclusion in the trial.

Magnetic Resonance Imaging
All subjects were scanned in the supine position in a 3-T MRI scanner (Achieva, Philips Healthcare, Best, the Netherlands) equipped with a 32-channel cardiac coil and an advanced cardiovascular software package (release 2.6.3). Vital signs were monitored continuously throughout the entire MR examination with a 4-lead ECG, a respiratory belt, and a blood oxygenation sensor. After localization of the coronary arteries with a rapid 3-dimensional T2-prepared fast-gradient-echo scan,18 double-oblique imaging planes parallel to the native left and right coronary artery system were defined subsequently using a 3-point-plan-scan tool.19

For visualization of intracoronary thrombus, a navigator-gated, cardiac-triggered, fat-suppressed T1-weighted 3-dimensional gradient-echo inversion-recovery sequence was used.15,16,19 Imaging parameters included the following: field of view, 320×320 mm; matrix, 256×256; acquired in-plane resolution, 1.25×1.25 mm; reconstructed slice thickness, 1.5 mm (acquired, 3 mm); acquisition window, 80 to 100 milliseconds; repetition time/echo time, 5.8 milliseconds/1.9 milliseconds; flip angle, 20°; startup cycles, 5; and number of slices, 20. The patient-specific inversion time (441±56 milliseconds) was adjusted to null blood signal with a Look-Locker sequence. Magnetic resonance for direct thrombus imaging (MRDTI) was immediately followed by coronary lumen scans as described earlier.20 Imaging parameters, including imaging plane and voxel size, were identical to those for MRDTI except the following: repetition time/echo time, 5.5 milliseconds/1.6 milliseconds; flip angle, 20°; and T2 preparation instead of a nonselective inversion prepulse.

X-Ray Coronary Angiography and Thrombus Definition
X-ray coronary angiography was performed using standard techniques with multiple projections. Angiographically evident thrombus was defined as a Thrombolysis in Myocardial Infarction (TIMI) thrombus grade between 2 and 5 or when visible embolization of intraluminal material downstream was present.21 In view of the acuity of presentation, all total occlusions were considered to contain thrombus. (In TIMI thrombus grade 0, no cineangiographic characteristics of thrombus are present. In TIMI thrombus grade 1, possible thrombus is present with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex “meniscus” at the site of total occlusion suggestive but not diagnostic of thrombus. In TIMI thrombus grade 2, there is definite thrombus with greatest dimensions up to half the vessel diameter. In TIMI thrombus grade 3, there is definite thrombus but with the greatest linear dimension at least half but smaller than 2 times the vessel diameter. In TIMI thrombus grade 4, there is definite thrombus with the largest dimension 2 vessel diameters. And in TIMI thrombus grade 5, there is total occlusion).

Thrombus Extraction and Histology
Thrombus aspiration was carried out as per usual clinical care.22 Immediately after thrombus extraction, the device filter that contained thrombus was frozen and stored in liquid nitrogen. Thrombus specimens were processed routinely for paraffin embedding. The formalin-fixed, paraffin-embedded tissue blocks were serially sectioned to 10 μm and stained with hematoxylin and eosin and Mason trichrome at 5 levels. Thrombi were classified into groups according to previous described definitions of thrombus age.23 Fresh thrombus, lytic thrombus, and organized thrombus. Thrombus material with a heterogeneous composition was graded according to the age of the oldest part. Histopathological characteristics included layered patterns of platelets, fibrin, erythrocytes, and intact granulocytes for fresh thrombus; areas of colliquation necrosis and karyorrhexis of granulocytes in lytic thrombus; and in-growth of smooth muscle cells with or without depositions of connective tissue and capillary vessel in-growth in organized thrombi.

Analysis
For 3-dimensional multiplanar reformating and objective image analysis of MR coronary angiography and MRDTI data sets, a previously described postprocessing tool was used.25 An 8-segment model26 (Figure 1) was used for comparison with XCA findings, which were evaluated by 2 senior interventional cardiologists (D.P., S.R.). Coronary artery length of each segment was measured as described previously.27 Segments including a stent and segments distal to a stent were excluded from analysis because of susceptibility artifacts and Faraday shielding effects, which often result in inadequate blood nulling distal to stents. To highlight the anatomic relationship between contrast enhancement and morphology, images were automatically fused (OtsirX28) in a manner similar to positron emission tomography/computed tomography (Figure 2).

Findings were classified into 3 categories: “normal” coronary segments without visually apparent thrombus, affected coronary segments with visually apparent thrombus and nonthrombosed blood, and segmented intracoronary thrombus formation. The signal-to-noise ratio of normal coronary segments was determined by manual segmentation of coronary lumen area and by calculating the mean signal of nonthrombosed blood as described previously (Figure 2 D).19 In case of visually apparent thrombus, affected coronary segment signal-to-noise ratio was calculated as the mean signal of nonthrombosed blood and intracoronary thrombus. The thrombus signal-to-noise ratio was determined by manual segmentation of visually apparent thrombus area (Figure 2 E, red).
Noise was determined in a region of interest placed in the lung with the exclusion of areas with visible vascularization. The contrast-to-noise ratio (CNR) was measured between category (SI\text{category}) and aortic blood signal (SI\text{blood}): \text{CNR} = (\text{SI}\text{category} - \text{SI}\text{blood})/N, where N is noise. Data are expressed as mean ± SD. To account for variation in signal intensity across the field of view resulting from spatial variation of the coil sensitivity, an automatic correction for coil sensitivity (CLEAR) was applied. Relative CNR values were calculated as the ratio between the visually apparent thrombus area, area of the entire affected coronary segment (including thrombus formation and nonthrombosed blood), or area of normal segments without thrombus and the averaged CNR of the corresponding entire left or right coronary system.

Statistical Analysis

Statistical analysis was performed with PASW Statistics software (release version 18.0.0, SPSS Inc, Chicago, IL) and SAS 9.2 (SAS Institute Inc, Cary, NC). Values are reported as mean ± SD or mean with 95% confidence interval (CI) or as median (range) for nonnormally distributed data. A paired Student t test was applied for the comparison of continuous variables, and the Wilcoxon signed-rank test was used for categorical variables. A value of P < 0.05 was considered to indicate statistical significance. To account for the lack of independence in per-segment comparisons, segments without thrombus, segments including thrombus, adjacent segments of the same vessel or coronary system, and thrombus formation were evaluated with repeated measures mixed linear models with compound symmetry as the working correlation matrix to account for multiple measurements per patient. Differences in the CNRs of the groups (segments with thrombus versus segments without thrombus versus thrombus) were tested within the mixed model with t tests. Receiver-operating characteristics were used to select absolute and relative cutoff values for CNR to provide an optimal tradeoff between sensitivity and specificity for discrimination between segments with and without thrombus. Because of the small sample size, this exploratory receiver-operating characteristics analysis was not corrected for correlations between segments within a patient. Odds ratios were calculated for CNRs along with 95% CIs (Wald approach). Receiver-operating characteristics analysis was used to select an optimal cut point for prediction and to assess the predictive value in terms of sensitivity, specificity, and accuracy of the final model. The selection of the optimal cut point was based on the Youden index, ie, the maximum sum of sensitivity and specificity. In addition, sensitivity, specificity, and accuracy of MRI compared with the standard of reference (XCA) were calculated, along with exact 95% CIs (Clopper-Pearson).

Results

Patient and Baseline Characteristics

Patient and baseline characteristics of the study population are summarized in Table 1. A total of 18 patients (14 men; age, 61 ± 9 years) with STEMI and late presentation (n = 3), thrombolysis for STEMI with ST resolution < 90 minutes (n = 1, non-thrombus group), thrombolysis for STEMI with ST resolution > 90 minutes (n = 12), and non-STEMI (n = 2) were included in...
Table 1. Baseline Characteristics of Patients With Acute Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Patients With Intracoronary Thrombus Formation (n=10)</th>
<th>Patients Without Intracoronary Thrombus Formation (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.9±8.6</td>
<td>63.6±9.5</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (100)</td>
<td>4 (50)*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.4±13.1</td>
<td>71.9±12.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5±3.1</td>
<td>24.8±2.3</td>
</tr>
<tr>
<td>Median risk factors, n</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>8 (80)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>6 (60)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (20)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>5 (50)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Family history of CAD, n (%)</td>
<td>5 (50)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>ST-segment elevation, n (%)</td>
<td>8 (80)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Anterior STEMI, n (%)</td>
<td>4 (40)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>6 (60)</td>
<td>7 (88)</td>
</tr>
<tr>
<td>Median blood pressure, mm Hg</td>
<td>125/78</td>
<td>120/68</td>
</tr>
<tr>
<td>Median heart rate, bpm</td>
<td>64</td>
<td>75</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin T, ng/mL</td>
<td>1.5 (0.5–8.0)</td>
<td>2.0 (0.2–4.3)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.6±4.5</td>
<td>13.5±1.9</td>
</tr>
<tr>
<td>Leukocytes, ×10⁹</td>
<td>11.6 (5.8–14.4)</td>
<td>10.7 (6.1–35.0)</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>3.8 (&lt;5–9)</td>
<td>10.7 (&lt;5–88)</td>
</tr>
<tr>
<td>Platelets, ×10⁹</td>
<td>227 (189–328)</td>
<td>203 (81.3–309)</td>
</tr>
<tr>
<td>Predicted mortality at TIMI risk score at 30 d, †</td>
<td>5.9 (1.6–7.3)</td>
<td>9.9 (2.2–23.4)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; STEMI, ST-segment–elevation MI; and TIMI, Thrombolysis in Myocardial Infarction Study Group.

*P<0.01 for the comparison of acute myocardial infarction with versus without intracoronary thrombus formation.

†Exclusion of non-STEMI (2 patients in the thrombus group with a predicted mortality at 14 days of 1.0% and 1.2%).

this study. At the time of inclusion, all sis for STEMI with patients (14 men; At the time of inclusion, all patients had no clinical or ECG evidence of ongoing ischemia. Cardiac MR scans were performed within 72 hours (median, 45.2 hours; 8.3 to 70.8 hours) after the onset of symptoms. After MRI (median, 5.2 hours; 1.4 to 23.7 hours), XCA showed intracoronary thrombus formation in 10 patients (STEMI, n=8). Patients with intracoronary thrombus had a higher number of cardiovascular risk factors (median risk factors, 3 versus 2; P=NS), were more obese (body mass index, 26.5±3.1 versus 24.8±2.3 kg/m²; P=NS), and were younger (age, 58.9±8.6 versus 63.6±9.5 years; P=NS) compared with patients without intracoronary thrombus burden. The incidence of ST-segment elevation (n=8) and anterior myocardial infarction (n=4) was identical in both groups.

Angiographic Findings

Angiographic findings are summarized in Tables 2 and 3. In patients with intracoronary thrombosis, thrombus was found in the left anterior descending artery (LAD; n=5), left circumflex artery (n=2), and right coronary artery (RCA; n=4). One patient

Table 2. Angiographic Findings in Patients With Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Vessel with disease, n (%)</th>
<th>Patients With Intracoronary Thrombus Formation (n=10)</th>
<th>Patients Without Intracoronary Thrombus Formation (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel with disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unobstructed</td>
<td>0 (0)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>1-Vessel disease</td>
<td>5 (50)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>2-Vessel disease</td>
<td>4 (40)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>3-Vessel disease</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Maximum degree of stenosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (0)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>1%–49%</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>50%–74%</td>
<td>1 (10)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>75%–94%</td>
<td>3 (30)</td>
<td>3% (37.5)</td>
</tr>
<tr>
<td>95%–99%</td>
<td>0 (0)</td>
<td>2% (25)</td>
</tr>
<tr>
<td>Complete occlusion</td>
<td>6 (60)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Thrombus location, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>4 (40)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>2 (20)</td>
<td></td>
</tr>
<tr>
<td>Thrombus classification, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI thrombus grade 1</td>
<td>0 (0)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>TIMI thrombus grade 2</td>
<td>1 (10)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIMI thrombus grade 3</td>
<td>1 (10)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIMI thrombus grade 4</td>
<td>1 (10)*</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIMI thrombus grade 5</td>
<td>7 (70)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

RCA indicates right coronary artery; LAD, left anterior descending; LCx, left circumflex; and TIMI, Thrombolysis in Myocardial Infarction Study Group.

*Patient with marked proximal ectasia of all major coronary vessels with heavy thrombus load in the posterior left ventricular branch and posterior descending artery ostium of the dominant RCA.

†Thrombus confirmed by thrombectomy.

with anterior STEMI and delayed ST resolution was diagnosed with thrombus formation at 2 separate locations within the left coronary system. X-ray coronary angiography showed a complete occlusion of the proximal left circumflex artery with heavy thrombus burden and a complex lesion in the proximal LAD involving the first diagonal branch with partial thrombosis. In nonocclusive infarct-related coronary arteries, angiographically evident thrombus (TIMI grade 2 to 4, n=4) was confirmed by thrombus aspiration, whereas thrombus detection in patients with complete occlusion (TIMI grade 5, n=7) was based on angiographic findings and acuity of presentation. X-ray coronary angiography revealed a normal coronary angiogram in 2 patients of the nonthrombus group.

Magnetic Resonance for Direct Thrombus Imaging Findings

Cardiac MR scans were successfully performed in all 18 subjects; 98% of segments (n=141 of 144) could be analyzed on MRDTI. Nondiagnostic image quality was observed in the mid LAD (segment 7) of 1 patient without thrombus and in the mid and distal RCA (segments 2 and 3) of 1 patient with
LAD thrombus. Magnetic resonance coronary angiography fused with MRDTI (Figure 2C) suggested intracoronary thrombus formation in 10 of 18 patients. Compared with the gold standard XCA, visual assessment allowed correct classification of 9 patients (sensitivity, 91%; 95% CI, 0.6 to 1.0) with and 7 patients (specificity, 88%; 95% CI, 0.5 to 1.0) without intracoronary thrombus formation. The false-negative case was observed in a patient with marked proximal ectasia of all major coronary vessels with heavy thrombus load in the posterior left ventricular branch and posterior descending artery ostium of the dominant RCA. These distal branches, which are not included in the 8-segment model, were not covered by the MRDTI scan. The false-positive case was observed in a patient with anterior STEMI and failed thrombolysis. The corresponding intravascular ultrasound showed a tight proximal LAD stenosis with diffuse atheroma, positive remodeling, and signal attenuation. The XCA was performed within 2 hours after the MRDTI scan and did not confirm MRDTI findings.

### Magnetic Resonance for Direct Thrombus Imaging: Quantitative Assessment

Absolute CNR values of coronary segments without thrombus (n=141; mean, 2.6; 95% CI, 1.8 to 3.3), coronary segments with thrombus (n=10; mean, 5.6; 95% CI, 4.2 to 7.0), and thrombus alone (n=10; mean, 15.9; 95% CI, 14.4 to 17.1) were found to differ significantly (P<0.001; Figure 3).

A CNR threshold of 8 (determined by receiver-operating characteristics analysis) allowed correct classification of 9 patients (sensitivity, 91%; 95% CI, 0.6 to 1.0) with 7 patients (specificity, 88%; 95% CI, 0.5 to 1.0) without intracoronary thrombus formation. This corresponds to an accuracy of 89% (95% CI, 0.65 to 0.99) in this selected patient population with a high probability of intracoronary thrombosis. Misclassified patients were identical to the visual assessment finding.

Relative CNR values of coronary thrombus (range, 222% to 585%) were significantly increased (P<0.0001) compared with entire segments with visually apparent thrombus (range, 86% to 156%) and without visually apparent thrombus (range, 2% to 256%; Figure 4). A relative CNR threshold of 280 (Figure 4, red line) resulted in a true-positive detection in 8 of 10 patients and true exclusion of intracoronary thrombus formation in 7 patients. Compared with visual assessment and absolute CNR values, the application of a relative CNR cutoff value resulted in an additional false-negative classification. The corresponding XCA in this patient with non-STEMI showed total occlusion of the proximal LAD with retrograde flow from the RCA. Coronary thrombus was aspirated before intervention.

### Histology

Thrombus aspiration was performed in 3 male patients as per usual clinical care. Thrombus was found in the proximal LAD.
Histological analysis (Figure 5) showed fresh thrombus composed of layered patterns of thrombocytes, nonfragmented erythrocytes, and intact granulocytes in all 3 patients.

Discussion

Black-blood non–contrast-enhanced MRDTI facilitated visualisation of intracoronary thrombosis in 10 patients shortly after myocardial infarction. Image fusion with corresponding MR angiography allowed direct and successful thrombus visualization in the LAD (n=10), left circumflex artery (n=2), and RCA (n=3) with high contrast between thrombus, blood pool, and surrounding tissues such as myocardium and epicardial fat. In 18 patients with acute myocardial infarction, visual analysis of MRDTI resulted in a sensitivity of 89% and a specificity of 88% for the detection of intracoronary thrombus compared with subsequent invasive assessment by XCA. Mean intracoronary thrombus CNR (15.9; 95% CI, 14.4 to 17.1), affected coronary segments with thrombus (mean, 5.6; 95% CI, 4.2 to 7.0), and normal segments without thrombus (mean, 2.6; 95% CI, 1.8 to 3.3) were found to differ significantly (P<0.001).

During the last decade, there has been increasing interest in exploiting the T1-shortening effect of methemoglobin for the detection of acute and chronic thrombus in the setting of deep vein thrombosis, pulmonary embolus, and acute arterial occlusion or for the detection of complex atheromatous carotid plaque.14,29–31 Methemoglobin formation occurs as a result of the maturation of thrombus as hemoglobin passes through the stages of oxyhemoglobin to deoxyhemoglobin and methemoglobin. The paramagnetic effect of methemoglobin (containing 5 unpaired electrons) was first exploited by Wielopolski et al29 using black-blood non–contrast-enhanced inversion-recovery MRI to accentuate intravascular clot by altering the effective inversion time to null flowing blood. Because inversion-recovery MRI images typically do not yield detailed anatomic information, it is often necessary to colocalize areas of positive contrast with anatomic information. In 1997, Moody et al30 combined direct visualization of intraluminal emboli with the depiction of the pulmonary vasculature using a MR angiographic method in patients with pulmonary embolism. Applied to patients with deep venous thrombosis, this technique allowed reliable detection of venous thrombosis in 17 of 18 patients.32 Compared with MRI of thrombosis in the pulmonary vascular tree, carotid arteries, or venous system, MRI of the coronary arteries remains technically demanding owing to cardiac and respiratory motion, their small size, and their tortuous 3-dimensional course. With the development of advanced motion compensation techniques33 in concert with T2 preparation, local inversion, or inversion recovery–prepared 3-dimensional sequences, coronary lumen, plaque, and thrombus imaging has become feasible.16,17,26,34,35

Targeted Imaging of Thrombus

The feasibility of imaging intracoronary thrombosis was first demonstrated in a swine model of in-stent thrombosis.19 Compared with the present study, visualization of intracoronary thrombus formation was based on the administration of a fibrin-binding contrast agent, EP-2104R (EPIX Pharmaceuticals Inc). This contrast agent was recently investigated in patients with suspected pulmonary embolism (n=6), deep
venous thrombosis (n=8), carotid artery thrombus (13), left and right atrial thrombus (n=8), and left ventricular (n=9) and aortic arch (n=8) thrombi in an initial phase II trial.36,37 Findings were compared with non–contrast-enhanced MRI similar to the technique used in the present study. The fibrin-binding contrast agent, EP-2104R, allowed good visualization of carotid (12 of 13), left ventricular (9 of 9), and aortic arch (6/8) thrombi. Although MRDTI (not available in all subjects) showed similar results for left ventricular (9 of 9) and aortic arch (4 of 6) thrombi, the diagnostic accuracy for carotid artery thrombi (4 of 13) was reduced. Although CNR values of non–contrast-enhanced thrombus in the present study were comparatively lower (15.9±5.1 versus 29±14),36 MRDTI and EP-2104R showed a similar sensitivity for visualization of arterial thrombus (89% versus 90%). Compared with non–contrast-enhanced thrombus, the fibrin-targeted approach allows imaging of acute and chronic thrombus38,39 but is currently restricted to preclinical use only.

Clinical Implications
Non–ST-elevation ACS represents a growing clinical challenge because most ACSs and acute myocardial infarctions are not associated with STEMI.1–3 Although patients with ECG changes indicative of ischemia and/or positive biomarkers of myocardial necrosis should be considered for early coronary angiography, differential diagnosis and treatment in the remaining spectrum of patients remains challenging. This heterogeneous group includes a subgroup who would benefit from very early intervention (<24 hours),40 whereas others may have an improved outcome with initial medical optimization, including antiplatelet and antithrombotic treatment.5 Conventional clinical risk-scoring methods have not been able to clearly distinguish these groups.7–40 Because the majority of ACSs are believed to be caused by rupture or erosion of an atherosclerotic plaque with subsequent intracoronary thrombosis resulting in partial or complete occlusion of a coronary artery,12,13 a technique that allows noninvasive detection of thrombus may further enhance risk stratification and allow treatment to be tailored in this high-risk population.

Limitations
This study was performed as exploratory pilot study to obtain feasibility data on black-blood non–contrast-enhanced MRDTI and to generate first hypotheses to adequately plan and power future clinical studies on this topic. Generalizability of our results is limited by selection bias because the feasibility of black-blood non–contrast-enhanced MRDTI was tested in a selected patient population with a high probability of intracoronary thrombosis. Although several studies have shown high sensitivity of MRI for the detection of venous and arterial thrombi,14,15 differentiation between complex atherosclerotic plaques and mural thrombosis remains difficult because of the complex composition (eg, platelets, fibrin, and red blood cells) of thrombus and resultant complex MR signal characteristics on T1-, T2-, and proton density–weighted images of arterial thrombi. This might explain the false-positive classification of coronary thrombus in 1 patient with acute myocardial infarction. The contribution of intraplaque hemorrhage to the increased MR signal intensity cannot be excluded in this patient and might explain the false-positive classification of thrombus. The subsequent intravascular ultrasound examination revealed a plaque positive remodeling and signal attenuation at the

Figure 5. Magnetic resonance for direct thrombus imaging (MRDTI) and thrombus histology findings. Thrombus extraction data are shown from a 53-year-old man with inferior myocardial infarction after failed thrombolysis (tenecteplase). Magnetic resonance angiography (A) of the 53-year-old man with inferior myocardial infarction after failed thrombolysis (tenecteplase) showed irregular vessel wall delineation of the mid right coronary artery (RCA). The MRDTI (B) displays high signal intensity within the mid RCA, suggesting intracoronary thrombus formation. Corresponding x-ray coronary angiography (C) revealed complete RCA occlusion with heavy thrombus load. Thrombosuction was performed with an Export aspiration catheter, and a significant amount of thrombus could be removed (D). Histological thrombus analysis (hematoxylin and eosin; E and F) and Mason trichrome stain (G through I) showed fresh thrombus composed of layered patterns of thrombocytes (§), erythrocytes (*), and intact granulocytes (#).
corresponding location. These findings were in concordance with the potential presence of intraplaque hemorrhage as described by Moody et al., Kawasaki et al., and Sirol et al.

Because of the small numbers of patients investigated in this pilot study, the CIs for the diagnostic parameters are very wide. Moreover, small numbers of patients limit the statistical power of analysis on a per-patient basis, precluding assessment of significant differences. Therefore, all comparisons and P values presented here are descriptive.

Conclusions
Black-blood non–contrast-enhanced MRDTI facilitates non-invasive diagnosis of intracoronary thrombus without the need for molecular MR contrast agents currently restricted to preclinical use. In a selected group of patients with high probability of intracoronary thrombosis, non–contrast-enhanced MRDTI allowed the detection or exclusion of coronary thrombus with high accuracy. Further studies are now warranted to investigate the clinical utility in more heterogeneous groups of patients with non-STEMI.

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Disclosures
Dr Wiethoff is employed by Philips Healthcare. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Non–ST-segment–elevation acute coronary syndromes represent a growing clinical challenge in that most acute coronary syndromes or acute myocardial infarctions are not associated with ST-elevation myocardial infarction. Although patients with ECG changes indicative of ischemia and/or positive biomarkers of myocardial necrosis should be considered for early coronary angiography, differential diagnosis and treatment in the remaining spectrum of patients are challenging. This heterogeneous group includes a subgroup that would benefit from very early intervention (<24 hours), whereas others may have an improved outcome with initial medical optimization, including antiplatelet and antithrombotic treatment. Conventional clinical risk-scoring methods have not been able to clearly distinguish these groups. Because the majority of acute coronary syndromes are believed to be caused by rupture or erosion of an atherosclerotic plaque with subsequent intraluminal thrombosis resulting in partial or complete occlusion of a coronary artery, a technique that allows noninvasive detection of thrombus may further enhance risk stratification and allow treatment to be tailored in this high-risk population.
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