Plaque Volume and Occurrence and Location of Periprocedural Myocardial Necrosis After Percutaneous Coronary Intervention

Insights From Delayed-Enhancement Magnetic Resonance Imaging, Thrombolysis in Myocardial Infarction Myocardial Perfusion Grade Analysis, and Intravascular Ultrasound

Italo Porto, MD, PhD; Joseph B. Selvanayagam, FRACP, DPhil; William J. Van Gaal, MBBS, FRACP; Francesco Prati, MD, PhD; Adrian Cheng, MB, BS; Keith Channon, MD, FRCP; Stefan Neubauer, MD, FRCP; Adrian P. Banning, MD, FRCP, FESC

Background—Myocardial necrosis can occur during percutaneous coronary intervention (PCI) despite optimal adjunctive pharmacology and careful technique. We investigated the mechanisms of procedural infarction using angiographic analysis, intravascular ultrasound, and delayed-enhancement magnetic resonance imaging.

Methods and Results—Fifty-two patients (64 vessels) who underwent complex PCI were studied. All patients were preloaded with clopidogrel and received glycoprotein IIb/IIIa inhibitors. “Adjacent” myonecrosis was defined as the presence of an area of new gadolinium hyperenhancement close to the stent. “Distal” myonecrosis was defined as situated at least 10 mm downstream from the stent. Fifteen vessels (23%) had evidence of new hyperenhancement after PCI. Of these, 8 (12%) had the distal type, and 7 (11%) had the adjacent type. Intravascular ultrasound showed a significantly greater reduction in plaque volume ($91.6^{11006}51.5$ versus $8^{11006}14^{11006}35$ mm$^3$; $P<0.001$) in the group with distal hyperenhancement compared with patients without new hyperenhancement or adjacent hyperenhancement. In the entire sample, a significant correlation was seen between changes in plaque volume ($r=0.58$, $P<0.001$) after PCI and the mass of new necrosis measured by magnetic resonance imaging. Thrombolysis in Myocardial Infarction perfusion grade assessment of a closed microvasculature after PCI carried an odds ratio of 8.0 (95% confidence interval, 1.4 to 46.1; $P=0.02$) for the occurrence of hyperenhancement, whereas side-branch occlusion was associated with an odds ratio of 16.2 (95% confidence interval, 2.6 to 102.5; $P=0.03$). However, a closed microvasculature was associated with distal hyperenhancement ($P=0.02$), and side-branch occlusion was associated with adjacent hyperenhancement ($P<0.001$).

Conclusions—These data suggest that distal embolization of plaque material occurs in contemporary PCI of native coronary arteries. Efforts to minimize procedural necrosis may require careful review of side branch anatomy and/or use of distal protection during extensive coronary stenting. (Circulation. 2006;114:662-669.)

Key Words: angioplasty ■ embolism ■ magnetic resonance imaging ■ stents ■ ultrasonics

Although the implications of procedural release of cardiac enzymes after percutaneous coronary intervention (PCI) have been controversial previously, recent studies using cardiovascular magnetic resonance (CMR) have demonstrated that postprocedural elevation of creatine kinase–MB1 (CK-MB) and troponin I reflects myocardial necrosis. Using gadolinium delayed-enhancement magnetic resonance imaging (DE-MRI), we demonstrated that the extent of elevation of troponin I measured 24 hours after the procedure is directly related to the absolute mass of new myocardial necrosis.2 During this study we observed 2 distinct patterns of new myocardial necrosis, and we speculated that their etiology could be distal embolization or ischemia caused by side-branch occlusion.2,3

Despite a variety of techniques to minimize compromise of side branches during stenting,4 smaller vessels cannot always be protected, and some compromise of flow down branch vessels may be inevitable when long coronary stents are placed over areas of extensive atheroma.5 Downstream embolization of material from the atheromatous plaque during stent implantation

Received October 6, 2005; revision received April 15, 2006; accepted June 8, 2006.

From the Department of Cardiology, John Radcliffe Hospital (I.P., W.J.V.G., A.P.B.), University of Oxford Centre for Clinical Magnetic Resonance Research (J.B.S., A.C., S.N.), Department of Cardiovascular Medicine, University of Oxford (J.B.S., K.C., S.N.), Oxford, UK; and European Imaging Laboratory Core Lab (F.P.), Department of Cardiovascular Medicine, Catholic University of the Sacred Heart (I.P.), Rome, Italy.

Correspondence to Adrian P. Banning, MD, Department of Cardiology, John Radcliffe Hospital, Oxford, OX3 9DU, UK. E-mail adrian.banning@orh.nhs.uk

© 2006 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.105.593210
may be ubiquitous, but the clinical relevance of embolization in native coronary arteries has been debated, particularly since the disappointing results from studies using distal protection devices in the setting of acute myocardial infarction.

In the present study, we attempted to study systematically the mechanism of myocardial necrosis during PCI of native coronary arteries. We hypothesized that myocardial ischemia caused by impairment of side branch flow could be differentiated from necrosis caused by distal embolization of plaque contents. Therefore, we undertook volumetric and spatial assessment of new myocardial necrosis using DE-MRI and combined these data with procedural angiographic data, angiographic parameters of microvascular integrity, and measurement of changes in atheromatous plaque volume using intravascular ultrasound (IVUS).

Methods

Ethics

The study was approved by our institutional ethics committee, and informed written consent was obtained from each patient.

Patient Sample

Myocardial necrosis is unlikely to occur during PCI of focal atheroma in low-risk patients. Therefore, we enrolled patients undergoing insertion of >30 mm of stent to a single vessel or treatment of a segment that involved at least 1 major side branch >2.0 mm in size and patients undergoing planned 2-vessel PCI. Patients were excluded if they had had previous stent insertion or recent severe unstable angina (Braunwald class III). Patients were also excluded if they were undergoing graft PCI and/or if there was evidence of significantly impaired left ventricular function on echocardiography.

The first 50 patients were reported as part of a protocol aimed at defining the relationship between troponin I release after PCI and new areas of necrosis. An additional 33 patients were enrolled subsequently, resulting in a total of 83 patients. In this study we analyzed 58 consecutive patients who underwent complete IVUS examination during PCI, except 1 patient with intraoperative thrombus formation and a patient with persistent extensive coronary dissection (class C-D). Four additional patients were excluded because of inadequate quality of IVUS images (mainly extensive calcification), leaving a total study sample of 52 patients. Analysis was performed for each treated vessel (n=64), as 12 patients had 2-vessel PCI. The clinical characteristics of the studied sample are listed in Table 1.

Treatment and Procedures

PCI was performed by 1 of 2 experienced interventional cardiologists (A.P.B., K.C.). All patients were preloaded with aspirin and clopidogrel (300 mg) >24 hours before the procedure. In addition, they received intravenous heparin, either 5000 U or 70 U/kg at initiation. Nitroglycerin (250 μg) was administered consistently before any IVUS recording. Abciximab was used in all patients.

IVUS examination was performed with the use of the Galaxy II console and Atlantis SR Pro (Boston Scientific, Natick, Mass) catheters. First, IVUS examination was performed either before the intervention or after predilation with a 1.5-mm balloon (chronic total occlusions, very severe lesions) and repeated after stent implantation and final postdilation. Images were digitally acquired at 30 frames per second. The imaging probe was positioned distal to the target lesion and withdrawn at 0.5 mm/s with the use of a motorized pullback device. Images were stored on Digital Imaging and Communications in Medicine DVDs for offline analysis.

CMR Imaging Time Points, CMR Protocol, and CMR Postprocessing and Data Analysis

CMR was performed >2 hours before the procedure and 24 hours subsequently. Patients were studied with the use of a predefined protocol in a 1.5-T clinical MR scanner (Siemens Sonata, Erlangen, Germany). A gadolinium-based contrast agent (Gadodiamide, Omniscan, Nycomed Amersham, Uppsala, Sweden) was then administered intravenously, and contrast-enhanced images were acquired after a 10-minute delay with the use of an inversion-recovery segmented gradient-echo sequence. Areas of late gadolinium–diethylenetriamine pentaacetic acid hyperenhancement were quantified with computer-assisted planimetry on each of the short-axis images by an experienced observer (J.B.S.) without knowledge of the cine MRI, procedural, or biochemical findings. Hyperenhanced pixels were defined as those with image intensities >2 standard deviations above the mean of image intensities in a remote myocardial region in the same image.

In each scan, the implanted stents were identified, and the relationship of new areas of hyperenhancement was calculated in relation to the stent. Areas of new hyperenhancement that occurred in the same short-axis image as the stent were classified as “adjacent” injury. Hyperenhancement in the myocardium downstream from the stent (at least 10 mm) was deemed “distal” injury if there was at least 1 short-axis segment of “normal” myocardium with no hyperenhancement between the stent and the identified necrosis. The diagnostic coronary angiogram was used as the gold standard in defining the contribution to a specific vessel of the affected myocardial segments. Each of the 3 (basal, midventricular, and apical) short-axis slices was ascribed a coronary artery territory according to standard criteria. All data were analyzed in a blinded fashion.

Therefore, for further analysis, 3 groups were defined as an adjacent new hyperenhancement pattern, a distal new hyperenhancement pattern, and a normal group with no evidence of new hyperenhancement.

Angiographic Analysis

Angiographic analysis was performed offline. Coronary angiograms were evaluated by 2 experienced readers (W.J.V.G., I.P.) without knowledge of the MRI data. Flow in the epicardial arteries was assessed for Thrombolysis in Myocardial Infarction (TIMI) flow grade and corrected TIMI frame count with the use of a standard technique. TIMI myocardial perfusion grade (TMPG) was used to assess myocardial tissue-level perfusion in the area supplied by the treated vessel. A “closed” microvasculature was either TIMP G0 or TIMP 1, with TIMP 2 or TIMP 3 representative of an “open” microvasculature, as previously described.

Side branch impairment was reviewed thoroughly by side-by-side analysis of cine loops before PCI and the final result. Any angiographically visible side branch likely to be directed toward the left ventricular myocardium was considered; only atrial and right ventricular arteries were excluded. Side branch impairment was defined as any nontransient impairment in flow, either TIMI 1 or TIMI 0 (occlusion).

IVUS Analysis

Quantitative analyses were performed on all IVUS procedures. All the measurements were performed blindly within the European Imaging Laboratory Core Laboratory, Rome, Italy (L.P.). Cross sections were analyzed for every millimeter of vessel (60 frames) with the use of commercially available software (Tape Measure, INDEC Co, Sunnyvale, Calif) on the basis of reproducible arterial landmarks (side branches, calcium deposits, aortic/coronary junction), the same arterial segments were identified at the preintervention and postintervention assessments. The analyzed arterial segment encompassed the stented segments and 3 mm of the proximal and distal reference segments to take into account axial plaque redistribution.

| TABLE 1. Procedural and Lesion Characteristics of the Study Patients (n=52) | 2.3±1.4 (1–4) |
| Stent length, mm (range) | 31±18 (8–86) |
| Two-vessel PCI, % | 22 |
| Bilirubin, % | 28 |
| Chronic total occlusion, % | 23 |
The data are presented as mean values and include lumen area, the total vessel area delimited by the external elastic membrane (EEM) area, and the plaque area, measured as plaque plus media area in both the stented and the reference segments. The difference between pre- and post-PCI plaque area was defined as the index of the decrease in plaque volume (\(\Delta\)plaque area). The differences in mean lumen area, plaque area, and EEM area between the procedural steps were calculated. A volumetric analysis was performed to enable a more accurate assessment of changes in plaque dimensions. EEM, lumen, and plaque volumes were calculated with the use of Simpson's formula.16–19

All of the IVUS analyses were performed in agreement with the American College of Cardiology consensus document.20

**Statistical Analysis**

Values are expressed as mean (± standard deviation) or median (interquartile range) as appropriate. All analyses were performed by vessel. Paired sample \(t\) test and unpaired sample \(t\) test were used to compare normally distributed variables. We used \(\chi^2\) statistics for comparison of discrete variables. Continuous variables that were not distributed normally were compared with the Mann-Whitney \(U\) test, and correlation between such variables was made with the Spearman rank test.

Reproducibility work done before in our CMR unit in >100 patients with chronic myocardial infarction showed that the coefficient of variation of the DE-MRI technique is 3%. On the basis of this information, we set a 5% increase in hyperenhancement volume as a significant increase when there were cases of preexisting hyperenhancement, or, if the new hyperenhancement was in a previously unaffected area, no limit was placed.

To test IVUS intraobserver variability, a random subset of 15 patients was measured twice, and agreement was tested by use of a linear regression analysis expressed as the correlation coefficient. ANOVA with post hoc test, with unequal variance in subgroups taken into account, was used to compare various parameters among the 3 different groups as defined by DE-MRI.

Binary logistic regression was performed to determine the likelihood of different angiographic variables to predict the presence of new DE. Probability values <0.5 were considered statistically significant. Statistical analysis was performed with the use of SPSS 13.0 (SPSS Inc, Chicago, Ill).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Results**

**Patient Characteristics**

The mean age of the study patients was 63±10 years, and 46 (88%) were male. Eighteen patients (28%) were enrolled into the study within 4 weeks of an acute coronary syndrome. Procedural and lesion characteristics are summarized in Table 1.

**Angiographic Analysis**

Average TIMI class before PCI was 2.1±1.2, with an average corrected TIMI frame count (c-TFC) of 37±34 frames. Open microvasculature before PCI was present in 46 vessels (72%). Coronary artery dissection (class C-D) occurred in 6 vessels (9%) and was corrected by stenting.

After PCI, mean TIMI class was 3.0±0.2, and mean TIMI frame count was 13±9 frames. Open microvasculature after PCI was present in 56 vessels (87%). Thus, 8 vessels (13%) showed impaired microvascular integrity. Eight vessels (13%) also showed evidence of side branch impairment after PCI, as defined above.

Stent length was not significantly different in the 3 groups defined by CMR (29±18.7 mm in the no hyperenhancement group, 35.5±15.9 mm in the distal hyperenhancement group, and 41.4±18.4 mm in the adjacent hyperenhancement group; \(P=0.2\) by ANOVA).

Thirty-four vessels received at least 1 drug-eluting stent. A paclitaxel-eluting stent (TAXUS Express, Boston Scientific) was used in 32 cases, and a sirolimus-eluting stent (Cypher, Cordis/J&J, Miami, Fla) was used in the remaining 2 cases. No vessel received different types of drug-eluting stents. The presence of at least 1 drug-eluting stent was not associated with new hyperenhancement on the second MRI scan (\(\chi^2=1.35, df=1, P=0.25\)). At least 1 region of stent overlap was present in 29 vessels and showed a tendency to be associated with new hyperenhancement (\(\chi^2=3.60, df=1, P=0.058\)) and with the adjacent type of new hyperenhancement (\(\chi^2=5.527, df=2, P=0.063\)).

**IVUS: Variations in Vessel and Plaque Dimensions**

Predictably, IVUS demonstrated that stenting led to a significant increase in absolute lumen and vessel dimensions as well as a significant reduction in plaque area (Table 2). Approximately 20% of the poststenting lumen enlargement was attributable to plaque reduction and 80% to vessel wall expansion. Intraobserver variability was low, with good agreement between the 2 measurements for both lumen area (Pearson \(r=0.91, P<0.001\)) and EEM area (Pearson \(r=0.89, P<0.001\)).

**Post-PCI DE-MRI Findings**

Overall, 15 vessels (23%) had evidence of new myocardial hyperenhancement on their post-PCI MRI scan. Of these, 8 (53%) had the distal type of new hyperenhancement, and 7 (47%) had the adjacent type of new hyperenhancement. In 2 patients with adjacent injury, new hyperenhancement was visible in the segment with stent artifact and in the next short-axis slice (but not subsequent slices). No patient had combined distal and adjacent hyperenhancement. Mean mass of hyperenhancement in the 15 affected vessels was 7.6±6.2 g and was not significantly different between the 2 distributions of necrosis (\(U=15.5, P=0.6\) by Mann-Whitney test).

**Angiographic Predictors of Size and Location of New Areas of Delayed Enhancement**

We used a logistic regression model to test whether angiographic impairment of a side branch or the presence of a closed microvascular after PCI predicted the occurrence of new hyperenhancement. The entire model was significant, and the contribution of each predictor was independent. A closed microvasculature after PCI carried an odds ratio of 8.0 (95% confi-
When the type of new hyperenhancement was taken into consideration, it was evident that a closed microvasculature was associated with the distal pattern of new hyperenhancement ($\chi^2=12.13$, $df=2$, $P=0.02$), whereas side-branch occlusion was associated with the adjacent pattern of new hyperenhancement ($\chi^2=25.40$, $df=2$, $P<0.001$) (Figure 1).

cTFC after PCI showed a significant correlation with variation in plaque area (Spearman $\rho=0.3$, $P<0.02$) and a trend toward a correlation with plaque volume changes ($\rho=0.22$, $P=0.08$) during PCI.

**Two-Dimensional and Volumetric IVUS: Evidence of Distal Embolization**

Preprocedural and postprocedural 2-dimensional and volumetric IVUS variables were compared among the 3 MRI-defined groups. Preprocedural plaque area and volume were higher in vessels with a distal type of hyperenhancement after stenting compared with the other 2 groups (Table 3).

Changes in plaque area and volume before and after the procedure were assessed, and a significantly greater reduction in plaque area ($P<0.001$ against both other groups by ANOVA) was seen in the distal hyperenhancement group (2.6±0.8 mm$^2$) compared with patients without new hyperenhancement (0.3±0.6 mm$^2$) or with the adjacent pattern of new hyperenhancement (0.4±0.2 mm$^2$). Furthermore, the distal hyperenhancement group showed a significantly greater decrease in plaque volume compared with the other 2 groups (91.6±51.5 versus $8\pm14$ versus $20\pm35$ mm$^3$; $P<0.001$ versus both other groups by ANOVA) (Figure 2).

### Table 3. IVUS Volumetric Measurements in 64 Stented and Reference Segments

<table>
<thead>
<tr>
<th></th>
<th>No New Hyperenhancement</th>
<th>Distal Hyperenhancement</th>
<th>Adjacent Hyperenhancement</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEM, mm$^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>11.6±3.4</td>
<td>12.6±2.2</td>
<td>10.6±3.4</td>
<td>0.3</td>
</tr>
<tr>
<td>After</td>
<td>14±3.7</td>
<td>15.1±1.9</td>
<td>12.7±4.1</td>
<td>0.4</td>
</tr>
<tr>
<td>EEM volume, mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>314.8±209.9</td>
<td>463.4±243.9</td>
<td>437.6±202</td>
<td>0.1</td>
</tr>
<tr>
<td>After</td>
<td>382.2±252.2</td>
<td>548±279.5</td>
<td>522.5±257.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Lumen area, mm$^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>4.8±2.1</td>
<td>3.9±2</td>
<td>4.8±1.7</td>
<td>0.4</td>
</tr>
<tr>
<td>After</td>
<td>7.6±2.3</td>
<td>9±2</td>
<td>7.3±2.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Lumen volume, mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>127.2±89.4</td>
<td>140.9±96.8</td>
<td>204.1±109.1</td>
<td>0.1</td>
</tr>
<tr>
<td>After</td>
<td>202.1±128.4</td>
<td>317.2±170.3</td>
<td>308.5±165.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plaque area, mm$^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>6.7±2.4</td>
<td>8.6±1.3</td>
<td>5.8±2.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>After</td>
<td>6.4±2.4</td>
<td>6.1±1.7</td>
<td>5.3±2.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Plaque area, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>58.4±12.5</td>
<td>69.8±11.9</td>
<td>54.3±10.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>After</td>
<td>45.6±10.6</td>
<td>40.4±10.4</td>
<td>41.6±10.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Plaque volume, mm$^3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>187.5±139.6</td>
<td>322.5±174.2</td>
<td>233.4±109.6</td>
<td>0.1</td>
</tr>
<tr>
<td>After</td>
<td>180.1±140</td>
<td>230.7±137.9</td>
<td>214±101.2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*ANOVA.
An example of angiogram-IVUS-MRI correlation that identifies distal embolism as a cause of new myocardial necrosis is shown in Figures 3 and 4.

Correlation of Plaque Changes With Extent of New Hyperenhancement

In the entire sample, a significant correlation was found between the change in plaque area after PCI and the mass of new necrosis in grams ($\rho=0.45, P<0.001$). This correlation, as expected, became stronger when plaque volume changes were considered ($\rho=0.58, P<0.001$). Identification of the 3 MRI subgroups (Figure 5) showed that plaque volume changes were significantly correlated with the mass of new hyperenhancement only in the distal hyperenhancement group ($\rho=0.84, P=0.009$) but not in the adjacent hyperenhancement group ($\rho=0.68, P=0.094$).

Discussion

The present study demonstrates that both impairment of flow in coronary side branches and distal embolization of atheromatous material contribute to myocardial necrosis during PCI. Occlusion of small side branches is associated with necrosis adjacent to the implanted stent. Distal necrosis in the dependent vascular territory occurs when atheromatous plaque is embolized. The volume of embolized material measured by IVUS is directly proportional to the amount of myocardial necrosis. Both patterns of necrosis appear to be quantitatively similar and occur despite aggressive antithrombotic therapy with aspirin, heparin, preloaded clopidogrel, and abciximab.

Previous investigators have used MRI to study procedural injury caused by PCI. Ricciardi et al\textsuperscript{1} studied 14 patients and demonstrated new areas of hyperenhancement after PCI. Because no pre-PCI MRI scan was performed, the presence of preexisting hyperenhancement could not be excluded. In the present study we used simultaneous and comprehensive assessment of microcirculatory function (with myocardial blush), side branch impairment (with angiography), and plaque volume (with IVUS), combined with spatial analysis by MRI.

Microvascular obstruction, as measured by impaired TMPG, has been associated with enzyme-defined microinfarction in both high-risk\textsuperscript{14} and elective\textsuperscript{21} PCI patients. Herrmann et al\textsuperscript{22} found that a reduction of relative coronary flow velocity reserve correlates with CK-MB elevation, suggesting that abnormalities in tissue-level perfusion may play a considerable role in the mechanism of cardiac enzyme elevation. Recently, MRI visualization of microinfarction has been linked with impaired TMPG in 14 patients.\textsuperscript{3} Our evaluation of the TMPG confirms these previous results but is further validated by consistency with 2 other techniques (CMR and IVUS) and extends these results to a larger sample undergoing elective PCI.

Atheromatous plaque burden measured with IVUS before PCI has been shown to be proportional to procedural enzyme release,\textsuperscript{23} and Ahmed et al\textsuperscript{17} concluded that lumen enlargement with stenting involved vessel expansion with significant axial localized atheroma.

Figure 3. Pre-PCI angiographic-IVUS–DE-MRI correlation in a single patient. Preprocedural angiogram of the right coronary artery (left) showed a 60% to 70% stenosis midvessel. IVUS examination (middle; 4 slices taken at 1-mm distance in the middle of the plaque; red line borders lumen area, and blue line depicts EEM area, with the difference being plaque area) showed a large plaque burden with hypoechoic features, suspicious for large necrotic core. DE-MRI before PCI (right) showed no evidence of preexisting myocardial necrosis.
redistribution of plaque into the adjacent reference segments. The net loss of plaque volume was thought to represent a combination of plaque redistribution, compression, and/or embolization. In patients with severe unstable angina (with no glycoprotein IIb/IIIa inhibition or clopidogrel), Prati et al were able to show a PCI-related pronounced reduction in plaque volume, and reduction in plaque area was directly proportional to the rise in CK-MB. In patients undergoing primary PCI, Sato et al demonstrated a decrease in plaque volume that was significantly larger in patients with inadequate reflow than in those with normal reflow and showed that changes in plaque volume were significantly correlated with c-TFC after PCI. These previous studies used enzyme elevation as a surrogate of myocardial necrosis, but the results of the present study demonstrate for the first time a direct relationship between change in atheromatous plaque volume and the actual volume of myocardial necrosis. Previous investigators were unable to exclude mechanical compromise of side branches as a cause of the myocardial necrosis, but by using MRI to spatially differentiate between a distal type and an adjacent pattern of necrosis, we were able to exclude those areas of injury caused by mechanical vessel occlusion.

Incidental minor side-branch occlusion is a well-established mechanism of periprocedural myonecrosis, and in the present study we attempted to differentiate it from injury related to distal embolization. We have shown that both mechanisms resulted in areas of necrosis of similar size. Interestingly, some of our patients showed the adjacent type of post-PCI necrosis in the absence of any detectable side branch event. Although one cannot exclude that unseen side-branch occlusion may be responsible, it is also possible that stretch damage resulting in periadventitial necrosis may occur, as observed in experimental models of angioplasty.

In this small sample, no patients had both adjacent and distal patterns of delayed hyperenhancement. All of our patients either had new areas of hyperenhancement in the same short-axis slice as the stent or showed at least 1 short axis between the stent and the new, distal area of necrosis. Two (2 of 7) patients with adjacent injury had new hyperenhancement in the segment with the stent artifact and in the next short-axis slice (but not subsequent slices). These patients and segments were classified as adjacent because our definition of the distal pattern required a segment of completely uninjured myocardium to be present. This may contribute to a reduced recognition of distal injury. It is also possible that injury may have been missed by CMR if it was below the detectable limit of the technique. However, with the sequences used in the present study, a group of 10 hyperenhanced pixels (voxel, 1.9×1.4×7 mm) in a typical image would represent an infarction of 0.19 g or a region one thousandth of the left ventricular myocardial mass.

Figure 4. Post-PCI angiographic-IVUS–DE-MRI correlation in the same patient as in Figure 3. Postprocedural angiogram (left) showed good angiographic result from stenting, IVUS examination (middle; parameters as in Figure 3) showed a significantly reduced plaque burden due to plaque compression and extrusion/embolism. DE-MRI before PCI (right) showed a focal area of endocardial hyperenhancement in the inferolateral segment (arrow). Calculated mass of new necrotic tissue was 2 g. Location of the hyperenhanced area and IVUS examination strongly suggest distal embolization of plaque material as the underlying cause. In the same patient, TMPG was reduced from 3 (before PCI) to 1 (after PCI).

Figure 5. Scatterplot of the plaque volume (mm³) after coronary stenting vs mass (g) of new myocardial hyperenhancement (HE). Symbols represent no new HE (●), distal hyperenhancement (♦), and adjacent hyperenhancement (★).

Clinical Impact
We studied a contemporary sample, including many patients who had 2-vessel PCI, total occlusions, and bifurcations. Our
sample was procedurally complicated (average stent length was 31 ± 18 versus 12 ± 3 mm in Reference 18), and glycoprotein IIb/IIIa inhibition was administered in all patients. We elected not to perform a qualitative IVUS analysis and not to assess the plaque remodeling because the vast majority of patients had long, complicated plaques. We also chose not to attempt to define the proportion of thrombus in any lesion, a well-known limitation of IVUS imaging. The relative correlation of final c-TFC after PCI with the Δplaque area and volume has been demonstrated by Sato et al.19 in primary angioplasty. In the same setting, other researchers have also shown that abciximab does not affect the total number and the mean total volume of embolized material or its qualitative composition.30 This perhaps suggests that a similar mechanism of distal embolization, possibly consisting of plaque debris rather than thrombotic material, may occur in both elective and primary PCI for acute myocardial infarction.

In patients with stable angina, dislodged embolic material has been identified,31 but this process has been best characterized in vein graft disease, in which displacement of plaque debris into the distal vascular bed clearly contributes to the “no-reflow” phenomenon.32 Limiting downstream embolization with distal protection devices to capture and remove the material improves clinical outcomes and is increasingly considered to be routine practice when vein graft disease is treated. We can speculate that this downstream injury may be preventable with distal capture techniques in native vessels, but it is unlikely that the current bulky devices would be deployable in diffusely diseased tortuous native vessels. Whether the areas of injury would be larger in the absence of such potent antiplatelet therapy cannot be answered by the present investigation.

In the present study we provide direct evidence that plaque volume reduction (as a consequence of distal embolization of plaque material) occurs in contemporary PCI, even when patients are treated with a full antithrombotic regimen, and the consequence is a new myocardial infarction. The extent of the infarct can be measured quantitatively with the use of DE-MRI. Occlusion of small side branches may also provoke postprocedural myocardial infarction. The clinical consequences of these events will depend on infarct size and location and preexisting left ventricular function. Further efforts to minimize procedural events may require aggressive attempts to “save” small side branches and/or the use of distal embolization protection during implantation of extensive coronary stents.

Recent advances in stent technology have resulted in continual increases in the patient population that can be treated with PCI. These data illustrate that taking PCI into the patient groups that may have been considered surgical in the past presents continued challenges that have not yet been addressed by current technology and technique.

**Study Limitations**

We acknowledge that because of our relatively small sample size, the present study suffers from imprecise estimation of response features and risk factors for new hyperenhancement. The large range of stent length (8 to 86 mm) may lead to concerns about the value of volumetric IVUS measurements in patients. It should be noted, however, that change in plaque volume depends on stent length and change in plaque area. The variation in plaque area itself was already significantly greater in the distal hyperenhancement group than in the other 2 groups, and the volumetric measurement only increases the predictive value, thus excluding a significant effect of stent length.

This series was composed of selected patients who do not represent a “typical” PCI population. Although no single patient- or lesion-related parameter has been clearly linked to an increased risk of periprocedural necrosis, there is broad agreement that long stents, involvement of a major side branch in the treated lesion, or multivessel intervention is associated with an increased risk. Thus, we deliberately selected a high-risk sample and did not randomize patients. Comparisons were made among 3 groups defined by the pattern of MRI-detected cardiac damage. Our definition of distal and adjacent post-PCI myocardial necrosis is an arbitrary one, but even if this distinction is disregarded, a significant correlation between the reduction in plaque volume and the amount of new necrosis in grams remains.

**Sources of Funding**

This work was supported in part by the British Heart Foundation, by the Medical Research Council, and by an unrestricted research donation from Boston Scientific, United Kingdom. Dr Porto is funded in part by the postgraduate program in Molecular and Cellular Cardiology, Catholic University of the Sacred Heart, Rome, Italy. Dr Selvanayagam is funded by the British Heart Foundation.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Elevation of cardiac enzymes can occur during percutaneous coronary intervention (PCI) despite optimal adjunctive pharmacology and careful technique. There has been extensive debate about the significance of this necrosis, but recent studies have confirmed that elevation of troponin after PCI reflects myocardial necrosis quantifiable by magnetic resonance imaging (MRI). In this study, we used delayed-enhancement MRI together with careful angiographic analysis and assessment of Thrombolysis in Myocardial Infarction myocardial perfusion grade and intravascular ultrasound to investigate the mechanisms of procedural myocardial infarction. We defined 2 distinct patterns of necrosis: "adjacent" myonecrosis, defined as the presence of an area of new gadolinium hyperenhancement close to the stent, presumptively due to side branch impairment, and "distal" myonecrosis, defined as situated at least 10 mm downstream from the stent, due to distal embolism. In patients with the distal pattern of hyperenhancement, change in plaque volume after PCI was directly related to the volume of new myocardial necrosis. These data suggest that distal embolization of plaque material occurs in contemporary PCI of native coronary arteries, causing areas of new myocardial infarction. The volume of embolized material relates directly to the volume of new necrosis detected by MRI. Myocardial necrosis also occurs in areas adjacent to the stent, but this is related to occlusion of small side branches. These data give new insights into mechanisms of injury after PCI and suggest that efforts to minimize procedural necrosis may require careful review of side branch anatomy and/or use of distal protection during extensive coronary stenting.
Plaque Volume and Occurrence and Location of Periprocedural Myocardial Necrosis After Percutaneous Coronary Intervention: Insights From Delayed-Enhancement Magnetic Resonance Imaging, Thrombolysis in Myocardial Infarction Myocardial Perfusion Grade Analysis, and Intravascular Ultrasound
Italo Porto, Joseph B. Selvanayagam, William J. Van Gaal, Francesco Prati, Adrian Cheng, Keith Channon, Stefan Neubauer and Adrian P. Banning

_Circulation_. 2006;114:662-669; originally published online August 7, 2006; doi: 10.1161/CIRCULATIONAHA.105.593210

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 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/114/7/662

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/