Troponin Elevation After Percutaneous Coronary Intervention Directly Represents the Extent of Irreversible Myocardial Injury
Insights From Cardiovascular Magnetic Resonance Imaging

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Background—Although troponin elevation after percutaneous coronary intervention (PCI) is common, uncertainties remain about the mechanisms of its release and its relationship to the volume of myocardial tissue loss. Delayed-enhancement MRI of the heart has been shown to reliably quantify areas of irreversible myocardial injury. To investigate the quantitative relationship between irreversible injury and cardiac troponin release, we studied the incidence and extent of new irreversible injury in patients undergoing PCI and correlated it to postprocedural changes in cardiac troponin I.

Methods and Results—Fifty patients undergoing PCI were studied with preprocedural and postprocedural (24 hours) delayed-enhancement MRI for assessment of new irreversible myocardial injury. Cardiac troponin I measurements were obtained before PCI and 24 hours after PCI. Of these 50 patients, 24 underwent a further third MRI scan at a median of 8 months after the procedure. Mean patient age was 64±12 years. After the procedure, 14 patients (28%) had evidence of new myocardial hypoenhancement, with a mean mass of 6.0±5.8 g, or 5.0±4.8% of total left ventricular mass. All of these patients had raised troponin I levels (range 1.0 to 9.4 μg/L). Thirty-four patients (68%) had no elevated troponin I and no evidence of new myocardial necrosis on MRI. There was a strong correlation between the rise in troponin I measurements at 24 hours and mean mass of new myocardial hypoenhancement, both early (r=0.84; P<0.001) and late (r=0.71; P<0.001) after PCI, although there was a trend for a reduction in the size of PCI-induced myocardial injury in the late follow-up scan (P=0.07).

Conclusions—In the setting of PCI, patients demonstrating postprocedural elevation in troponin I have evidence of new irreversible myocardial injury on delayed-enhancement MRI. The magnitude of this injury correlates directly with the extent of troponin elevation. (Circulation. 2005;111:1027-1032.)

Key Words: magnetic resonance imaging ▪ myocardial infarction ▪ angioplasty ▪ stents

Considerable debate has taken place about the implications of an elevated troponin level after percutaneous coronary intervention (PCI). Studies have documented that elevation of postprocedural serum cardiac troponin is relatively common and that markedly elevated levels of troponin after PCI are prognostically significant; however, uncertainties remain about the mechanisms and functional significance of small troponin releases after PCI and the direct relationship between procedure-related troponin rise and the volume of myocardial tissue loss. Despite these concerns, current European Society of Cardiology/American College of Cardiology guidelines recognize elevation of cardiac troponin within 24 hours of a PCI procedure in the definition of myocardial infarction.

Cardiovascular magnetic resonance (CMR) imaging allows noninvasive serial assessment of myocardial function and viability with high spatial resolution. Delayed-enhancement MRI (DE-MRI), initially validated in large-animal models, allows assessment of the transmural extent of irreversible injury and is superior to single-photon emission computed tomography for the identification of subendocardial myocardial infarction. Furthermore, it permits quantification of even small areas of myocardial necrosis, both due to native coronary disease and, as we have recently reported, after surgical revascularization. So far, only one study has investigated the role of DE-MRI in identifying myonecrosis in the setting of percutaneous coronary revascularization. Ricciardi et al. in a study of 9 patients who demonstrated postprocedural creatine kinase-MB elevation, found that DE-MRI identified small areas of hyperenhancement, with a median mass of 2 g. Although this initial study was important...
in highlighting the utility of DE-MRI in identifying procedure-related injury, no study has systematically evaluated the incidence and extent of MRI-defined irreversible myocardial injury in the current era of PCI.

In the present study, we prospectively studied the incidence and extent of new DE-MRI–defined irreversible injury in patients undergoing complex PCI and correlated it to post-procedural changes in cardiac troponin I (cTnI). We hypothesized that any level of postprocedural troponin elevation would represent irreversible myocardial injury and that the volume of new myocardial hyperenhancement identified by DE-MRI would show a high correlation with postprocedural elevations in cTnI.

Methods

Ethics

Our institutional ethics committee approved the study, and each patient gave informed written consent. The study was performed according to the principles of the Declaration of Helsinki.

Patient Population

Inclusion criteria were at least one of the following: 2-vessel PCI, planned insertion of >30 mm of stent to a single vessel, or planned treatment of a segment that involved at least 1 side branch >2.0 mm in size. Patients with significantly impaired left ventricular (LV) function on echocardiography were excluded, as were those patients with planned intervention of a saphenous vein graft. From 67 screened patients with these characteristics, 50 patients participated in the present study. We excluded the following patients: those with lack of informed consent (9); those with known contraindication to clopidogrel (300 mg) >24 hours before the procedure. In addition, they received intravenous heparin, either 5000 U or 70 U/kg at initiation. Abciximab was used in all patients and usually administered in the catheterization laboratory immediately before PCI, unless treatment included a chronic total occlusion, in which case it was administered after initial passage of the wire.

Angiographic Analysis

DICOM-recorded angiograms were analyzed offline by an independent experienced operator who was blinded to the results of MRI. Multiple variables were recorded, including the following: bifurcational PCI, 2-vessel PCI, total number of occlusions, lesion number, stent number, total lesion length, total stent length, lesion classification according to American Heart Association classification, intraprocedural side-branch flow impairment and dissection (transient or persisting), and intraprocedural thrombus.

CMR Protocol

Patients were studied in a 1.5-T clinical MR scanner (Siemens Sonata), and steady-state free-progression cine images were acquired in 2 long-axis and 7 to 9 short-axis views, as described previously. A gadolinium-based contrast agent (Gadodiamide, Omniscan, Nycomed Amersham) was then administered intravenously at a dose of 0.1 mmol per kilogram of body weight, and contrast-enhanced images were acquired after a 10-minute delay with the use of an inversion-recovery segmented gradient-echo sequence. Contrast-enhanced images were acquired in long- and short-axis planes identical to the cine images. Typical voxel size was 1.9×1.4×0.7 mm.

CMR Postprocessing and Data Analysis

For analysis of global LV function, the following parameters were determined by planimetry of all the short-axis cine images: LV end-diastolic volume index, LV end-systolic volume index, LV ejection fraction (EF, in %), and LV mass index (in g/m²). Cardiac index (in L·min⁻¹·m⁻²) was then calculated with the heart rate and stroke volume index. Areas of late gadolinium-DTPA hyperenhancement were quantified with computer-assisted planimetry on each of the short-axis images by an observer without knowledge of the cine MR, procedural, or biochemical findings. Hyperenhanced pixels were defined as those with image intensities >2 SDs above the mean of image intensities in a remote myocardial region in the same image. Furthermore, we prospectively identified the site of any new hyperenhancement in relation to the implanted stent. Areas of new hyperenhancement that occurred in the same short-axis image as the stent were classified as adjacent to stent injury, whereas new hyperenhancement that occurred in the myocardium distal to the stent was deemed downstream injury.

Biochemistry

Serum was collected from each patient for measurement of cTnI before PCI and 24 hours after PCI. All cTnI samples were analyzed within 12 hours of specimen collection with an immunosassay analyzer (Immuliite; Diagnostic Products Corporation). The lower limit of quantification was 0.2 μg/L, and the upper limit of the normal in our laboratory was 1.0 μg/L. The assay precision, represented by the percentage coefficient of variation, was 8.4% at 0.8 μg/L, 7.6% at 8.0 μg/L, and 7.6% at 86 μg/L.

Statistical Analysis

Values are expressed as mean (±SD) or median (interquartile range) as appropriate. The paired-sample t test and the unpaired-sample t test were used to compare means within the study group or between subgroups. χ² statistics with Fisher’s exact test was used 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. Binary logistic regression was performed to determine

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**Figure 1.** Flow diagram of all study patients included at the different imaging time points. HE indicates hyperenhancement; *, median values.
which clinical and angiographic parameters predicted the likelihood of myocardial hyperenhancement. Multivariate logistical regression was used to assess the relative contribution of various clinical and angiographic variables to the presence of new hyperenhancement after PCI. A probability value of <0.05 was considered statistically significant.

Results

Patient Characteristics and Follow-Up

The mean age of the study patients was 64±11 years; 43 (86%) were male. Seventeen patients (34%) were diabetic, and 14 (28%) were enrolled into the study within 4 weeks after an acute coronary syndrome.

The median interval between the first CMR scan and PCI was 1 (0–2) day, and the median interval between the procedure and follow up CMR scan was 1 (1–3) day. One patient declined the follow-up CMR scan, and in another patient, the post-PCI troponin measurement was not performed. Therefore, both CMR and troponin results (before and after PCI) were available for 48 (96%) of 50 patients (Figure 1).

Procedural and lesion characteristics are summarized in the Table. Average stent length and lesion length were 24±13 and 15±6 mm, respectively. Twenty-two patients (44%) had double-vessel PCI, and 10 (20%) had attempted reopening of a chronic total occlusion. Overall, of 79 lesions treated, when classified according to the American Heart Association/American College of Cardiology lesion criteria, 29 (37%), 24 (30%), 18 (23%), and 8 (10%) were classed as type C, B2, B1, and A, respectively. Thus, at least two thirds of lesions attempted in the present study were grade B2 or higher, which underlines the high procedural risk of the study cohort.

Delayed-Enhancement MRI

Twenty patients (40%) had some degree of hyperenhancement in their preprocedural MRI scan, with a mean mass of hyperenhanced tissue of 13.3±9.3 g. After the procedure, 14 patients (29%) had evidence of new hyperenhancement, with a mean mass of 6.0±5.8 g, or 5.0±4.8% of total LV mass. All 14 of these patients showed a raised troponin (see below). When all patients were included in the analysis, PCI in this complex lesion cohort resulted in a mean loss of 1.7±4.0 g of myocardial tissue, which corresponds to 1.4±3.3% of absolute LV mass. In patients with new MRI-defined myocardial injury, the site of injury fell into 2 characteristic locations. In 6 (43%) of 14 patients, the new hyperenhancement was located adjacent to the stent (Figures 2 and 3), and in the remainder of the patients (8/14, 57%; Figure 4), hyperenhancement was located in the apical myocardium, distal to the stent.

Figure 2. Two basal short-axis images (left) in a patient before left anterior descending coronary artery (LAD) PCI showing no delayed hyperenhancement. Contrast-enhanced images in the same image plane after PCI (right) reveal new anterolateral wall hyperenhancement (long arrows) adjacent to LAD stent (block arrow). Middle panel shows post-PCI angiogram with position of 3 stents highlighted and good flow in LAD and second diagonal branch (likely affected territory; black arrowhead).

Figure 3. Midventricular short-axis image (A) in a patient before PCI of left anterior descending coronary artery and left circumflex artery, showing no delayed hyperenhancement. Contrast-enhanced image in the same slice position after PCI (C) reveals transmural lateral wall hyperenhancement (arrows). B, Pre-PCI angiogram with the flow in left circumflex, which has occluded after procedure (D).
Time Course of DE-MRI Changes
To assess the temporal changes in myocardial infarction mass, we recalled all 14 patients with documented new hyperenhancement after PCI (new hyperenhancement group), and a randomly selected cohort of 14 of 34 patients without new hyperenhancement after PCI (control group).

Two patients in each group declined a third MRI scan. For the remaining 24 patients, the third scan was performed at a median of 240 days (IQR 110 days) in the new hyperenhancement group and 225 days (IQR 90 days) in the control group. One patient in the new hyperenhancement group had experienced a further (troponin-positive) ischemic event secondary to angiographically documented stent restenosis/subacute thrombosis in the time period between the second and third MRI scans and is hence excluded from the follow-up analysis. In the remaining 11 patients with PCI-induced new myocardial injury, there was a strong trend for the size of this injury to reduce from 5.4±4.8 g in the acute post-PCI scan to 3.8±5.0 g in the late follow-up scan (P=0.07). In contrast, in the control group, the magnitude of preexisting hyperenhancement was similar at the 2 time points: 5.0±8.0 g in the acute post-PCI scan and 4.8±7.0 g in the late follow-up scan (P=0.4).

Relationship of Clinical Outcome and Procedural Characteristics to DE-MRI Findings
Three patients (6%) experienced prolonged chest pain after the procedure or new ECG changes that were clinically indicative of myocardial infarction. All 3 patients had evidence of new myocardial hyperenhancement (range 4.0 to 17.5 g).

Stent length was significantly associated with the likelihood of procedure-related irreversible injury (P=0.04), but neither lesion length, PCI of bifurcation lesions, or chronic total occlusion nor the number of vessels with attempted PCI was associated with new hyperenhancement. No combination of procedural and lesion variables studied was associated with new hyperenhancement by multivariate analysis.

Angiographically evident coronary dissection occurred during the procedure in 10 patients (20%; transient in 7 patients, permanent in 3). In all patients, this was treated with implantation of further stents, with resumption of normal antegrade flow by completion of the procedure. However, new downstream injury was found in only 2 (20%) of these patients with angiographic evidence of dissection. Conversely, in 6 (75%) of 8 patients with new downstream injury, there was no angiographic evidence of dissection. Side-branch flow impairment/occlusion, either transient or permanent, was graded in 12 (24%) of 50 of patients; however, only 3 of these patients (2 with permanent flow impairment and 1 with transient flow impairment) demonstrated evidence of new hyperenhancement.

Cine MRI
The mean preprocedural EF was 67±11%, with 86% of patients having normal LV function (ie, EF >55%) and no patients having an EF <40%. After the procedure, across the whole group, the mean EF was similar at 68±11% (P=0.8). The presence of new hyperenhancement did not have an adverse effect on global LV function. In patients with new hyperenhancement, the preprocedural and postprocedural EFs were 65±8% and 64±11%, respectively (P=0.9), whereas in patients with no new hyperenhancement, the preprocedural and postprocedural EFs were 69±12% and 71±11% (P=0.8), respectively. LV mass index was 62±12 g/m² before PCI and was unchanged at 65±11 g/m² after PCI (P=0.8).

Discussion
Our findings show that all patients with post-PCI troponin I elevation at 24 hours have evidence of new irreversible
myocardial injury on CMR imaging. In these patients, the magnitude of irreversible injury represented, on average, 5% of total LV mass. Furthermore, we found a strong linear correlation between the size of MRI-defined irreversible injury and the 24-hour post-PCI troponin value. Thus, our findings have important implications for the definition of PCI-related myocardial infarction and for understanding the relationship between troponin elevation and irreversible myocardial injury in the setting of PCI.

The present study cohort consisted of patients who displayed high-risk lesion and procedural characteristics, representative of an increasing number of patients presenting for PCI in the current era of stent/device technology and potent antiplatelet therapy. We found that irreversible myocardial injury occurred in ≈30% of patients, despite the use of (preloaded) clopidogrel and abciximab in all patients. The striking correlation between the troponin I rise after the procedure and the magnitude of MRI-defined irreversible injury implies that troponin elevation in the setting of PCI does represent true myocardial cell death, rather than troponin “leak” without cellular necrosis, as has been postulated after coronary artery bypass surgery.15,16

The present study has important implications for the diagnosis of post-PCI myocardial infarction, particularly in light of the recent European Society of Cardiology/American College of Cardiology guidelines on what constitutes a myocardial infarction in these settings. The guidelines state that in relation to PCI, “small infarcts may, and should, be detected by serial blood sampling and analysis before and after the procedure (6 to 8 h and 24 h, respectively).”10 The present results indicate that small infarcts are detected by 24-hour troponin I measurements, and furthermore, that the magnitude of troponin elevation gives an accurate estimate of the size of procedural myocardial infarction. Hence, there is likely to be a continuum of risk between post-PCI troponin elevation and subsequent adverse long-term clinical outcome, modified by factors such as LV function and the amount of myocardium at risk salvaged by the procedure.17

The only previous study to use DE-MRI in identifying myocardinjury after percutaneous coronary revascularization was performed by Ricciardi et al.13 They reported that on 9 patients who demonstrated postprocedural creatine kinase-MB elevation, DE-MRI identified small areas of hyperenhancement with a median mass of 2 g. Most patients in that study, however, did not undergo a pre-PCI MRI scan, so the possibility of preexisting necrosis cannot be excluded. In the present study, despite the inclusion of only those patients with relatively well-preserved LV function, a significant number (40%) of patients had small areas of preexisting hyperenhancement. Hence, serial imaging is necessary in quantifying procedure-related infarct size. Notwithstanding this, the magnitude of myocardial tissue volume loss identified by DE-MRI in the present study is somewhat higher than that reported by Ricciardi et al.13 which most likely reflects the complexity of the patient cohort in the present study. Our follow-up scans demonstrate that there is some reduction in the size of the acutely determined hyperenhancement area with time, which is supported by recent studies after both myocardial infarction and coronary artery bypass surgery.18,19

We believe involution of the scar into a smaller volume is the most likely explanation,20 possibly compounded by partial volume effects of the magnetic resonance technique. A recent study using high-resolution x-ray spectroscopic analysis indicates that gadolinium closely correlates with sodium/potassium concentrations and histologically defined myocardial irreversible injury, which argues against the concept that peri-infarct edema is a possible cause of overestimation of acute infarct size by DE-MRI.21

Our MRI findings indicate that there are 2 distinct sites of new hyperenhancement; the majority of patients demonstrated new irreversible injury in a previously normal area in the apical myocardium. It is likely that this represents new myocardial necrosis resulting from distal embolization of particulate matter during balloon inflation and stenting. In the remaining patients with new hyperenhancement, it was located in the basal or midventricular myocardium, adjacent to the inserted stent. Although it is intuitive to suggest that this might be due to side-branch flow impairment/occlusion, we could not correlate the angiographic grading of side-branch flow with the likelihood of new irreversible injury, and it is possible that this pattern of injury may be caused by disruption of the adventitial blood supply of the vessels to the adjacent territories. In general, angiographic appearance of flow, dissection, and mechanical side-branch occlusion were all poorly predictive of new MRI-defined injury, which possibly implies the important role of collateral vessels and of plaque lesion composition in the occurrence of irreversible injury.22

**Study Limitations**

We measured cardiac troponin, even though postprocedural rises in creatine kinase-MB have the largest body of prognostic evidence for both cardiac mortality and overall major adverse cardiac events.3,23 We chose, however, to compare MRI findings to cardiac troponin changes, because troponin is a more sensitive and specific marker of myocardial necrosis.24,25 and troponin measurements are now recommended in current guidelines for the diagnosis of myocardial infarction.

A small number of patients in the present study had detectable troponin I after PCI, measured between 0.2 µg/L (the lower limit of quantification in our laboratory) and 1.0 µg/L, but no new hyperenhancement on MRI. Although this level of troponin detected is still below the upper limit of normal in our laboratory, we cannot be sure of the exact mechanisms of troponin release in these patients. Finally, the prognostic and late functional significance of new postprocedural myocardial hyperenhancement remains to be determined in larger follow-up studies.

In conclusion, we have shown that there is a moderate incidence of irreversible myocardial injury after complex PCI. Patients demonstrating postprocedural elevation in troponin I have evidence of new irreversible myocardial injury on DE-MRI, and the magnitude of that injury correlates closely with the magnitude of troponin elevation.

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