Magnetic Resonance Imaging and Troponin Elevation Following Percutaneous Coronary Intervention

New Insights Into Myocyte Necrosis and Scar Formation*

Paul Schoenhagen, MD,† Harvey D. White, DSc‡
Cleveland, Ohio; and Auckland, New Zealand

Serum biomarker evidence of myocyte necrosis is frequently found after percutaneous coronary intervention (PCI). About 20% of patients develop elevated levels of creatine kinase-myocardial band (CK-MB) (1,2) and up to 48% of patients develop elevated troponin levels following PCI (2–9). Several mechanisms related to procedural complications such as side branch occlusion, dissection, and disruption of collateral flow have been proposed for these elevations. The concept of plaque embolization at the time of balloon inflation or stent deployment leading to myocardial necrosis and scar formation has been supported by observations with magnetic resonance imaging (MRI) and late gadolinium enhancement (LGE) “scar” imaging after PCI (10). These data show an association between post-PCI elevations of troponin I with MRI-detectable scar formation.

Following stenting, LGE may occur at the site of stent deployment and distally in the treated coronary artery (11). Intravascular ultrasound has shown a correlation between changes in plaque volume before and after PCI and the mass of distal hyperenhancement, but not with hyperenhancement at the site of stenting. Thus providing indirect evidence that plaque embolization has occurred.

Furthermore, post-PCI elevation of troponin I levels have been shown to be related to abnormal tissue perfusion (12) independent of the presence of thrombus, epicardial flow, or characteristics of the coronary artery stenosis undergoing PCI. Elevated biomarker levels are also associated with higher atheromatous plaque burden (13).

The universal definition of myocardial infarction (MI) designates biomarker increase (with troponin preferred) from a normal baseline to a level 3 times the 99th percentile as PCI-related MI (Type 4a) (14). The importance of the association between elevated biomarker levels after PCI and prognosis continues to be debated. Several studies have shown that the elevation of troponin levels after PCI is strongly associated with the composite of death and MI (2,5). However, the associations have usually been with early outcomes (hospital or 90 days) and not with later follow-up (4). A further important consideration is the level of the elevation with 1 study (6) showing that only troponin levels >5 times the upper limit of normal were prognostically important. In some studies (7), prognosis did not seem to be influenced if baseline pre-PCI levels were not elevated (15).

A recent meta-analysis (9) of 15 studies showed that patients with normal baseline and any elevation of post-PCI troponin levels had increased risk of major adverse cardiac events (death, MI, repeat PCI, and coronary artery bypass graft [CABG]) when compared with those patients without troponin elevation at an average follow-up of 17.7 months. For patients fulfilling the universal definition of type 4a MI (14), there was a further increased risk: odds ratio: 2.5 (95% confidence interval 1.26 to 4.00). Patients with elevation of troponin <3 times the upper limit of normal did not have a worse prognosis during follow-up. In general, serum biomarkers do not allow the characterization of localization and distribution of the underlying pathological process.

This limitation can be overcome by correlation with imaging modalities, as exemplified by the study of Locca et al. (16) in the current issue of JACC: Cardiovascular Interventions, which compared elevation of troponin I levels measured by (Beckman Access 2 [Beckman Coulter, Brea, California]) analyzer, which is clinically useful but not guideline compliant (17) to MRI and LGE after PCI in 45 patients. New LGE occurred in 33.3% of patients. The scars were mostly small including <1.5% of left ventricular mass in 14 of 15 patients and had no effect on ejection fraction. The site of the infarction was distal in 53% and proximal in 47% of patients. Interestingly, post–stent dilation, probably by causing more plaque embolization, was the only factor associated with LGE. Elevation of biomarkers beyond 3 times the upper limit of normal occurred with CK-MB in 11% of patients and with troponin I in 47% of patients. Correlation of LGE with elevation of biomarkers was moderate, occurring in 40% of patients with elevation of creatine kinase-myocardial band and 43% of patients with elevation of troponin I.

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From the † Imaging Institute and Heart and Vascular Institute, Cardiovascular Imaging, Cleveland Clinic, Cleveland, Ohio; and the ‡Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand. Dr. Schoenhagen reports that he has no relationships to disclose. Dr. White has received research grants from Sanofi-Aventis, Eli Lilly, The Medicines Company, National Institutes of Health, Pfizer, Roche, Johnson and Johnson, Schering-Plough, Merck Sharpe and Dohme, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo Pharma Development, and Bristol-Myers Squibb. He has also received a consultancy fee from Regado Biosciences.
The underlying mechanism of MRI myocardial tissue enhancement with nonspecific extracellular contrast agents such as gadolinium is the increased distribution volume for these molecules within the infarct region with delayed washout in comparison to the normal myocardium (18). Delayed contrast-enhanced MRI is well validated in the identification of chronic myocardial scar (19,20). It has sufficient spatial resolution to differentiate patterns of transmural or subendocardial necrosis in the distribution of obstructed vessels (20,21), and more diffuse, patchy patterns of necrosis related to distal embolization (22). In several single-center trials, the prognostic impact of MRI-detected scar has been demonstrated in different patient populations (23–25).

It is important to consider issues related to scar size with LGE imaging. The minimal detectable scar volume depends on the spatial resolution of the MRI sequence. In the current study (16), similar to most other studies, spatial resolution was 1.4 × 1.7 mm in plane with slice thickness of 8 mm and a 2-mm gap. Therefore, the minimal resolvable volume from a theoretical standpoint would be about 0.02 ml. However, practically, a bigger volume (a few times the minimal resolvable volume) is necessary to differentiate scar from noise. In the current study (16), the mean scar size was 0.83 g (about 40 times the minimal resolvable volume), equivalent to 0.53% of the size of the normal left ventricular myocardium. This is relatively small in comparison to other studies after intervention (2 g) (22), PCI and CABG (5 g) (26), CABG (4.4 g) (27), and reperfused acute MI (20.6 g) (28). The timing between myocardial injury and LGE imaging is important, because serial MRI studies performed during the acute phase of MI have shown that the size of delayed gadolinium enhancement may significantly change immediately after reperfusion, secondary to resolution of interstitial edema in reversibly injured myocardium within the peri-infarction zone (28–31).

Previous studies describe LGE imaging for the identification, characterization and quantification of periprocedural myocardial necrosis after PCI (22,26,30) and coronary bypass surgery (CABG) (27). In these studies, the mass of infarcted tissue correlated with elevation of biochemical markers of myocardial damage (32). In contrast, the current data by Locca et al. (16) demonstrate that in many patients with elevated troponin I, LGE imaging could not identify evidence of scar. The investigators raise the question as to whether current cutoff levels of biomarkers are too sensitive, leading to overdiagnosis of post-PCI MI. An alternative explanation in the context of uncomplicated PCI would be small and patchy myocardial necrosis related to distal embolization of plaque (11,22,33). False negative results with LGE imaging would be expected in patients with multiple small areas of necrosis, if individual scar area were smaller than the spatial limitation of the MRI sequence.

Animal and post-mortem studies may provide further insights. However, more important will be clinical trials comparing quantitative extent of biomarker elevation and LGE scar with clinically meaningful outcome. Small studies show an independent predictive value of delayed LGE imaging in patients undergoing coronary revascularization, either PCI or CABG, during a median follow-up of 2.9 years (26). However, long-term outcome data from well-designed, prospective, multicenter trials are lacking. In the design of such trials, it will be critical to consider the inability of differentiating procedure-related versus pre-existing infarction, therefore requiring pre- and post-operative MRI acquisitions. Strict standardization of image acquisition and analysis, including contrast dose and threshold definition for identification of scar is vital (34–36). A limitation of MRI is the contraindication in patients with reduced kidney function (glomerular filtration rate <30 ml/min) because of concerns about nephrogenic systemic fibrosis (37). Table 1 compares troponins, including the newer higher sensitivity troponins (38), with MRI for detecting myocyte necrosis. Much of the data are evolving.

Future clinical trials, correlating clinical outcome with both biomarkers and comprehensive MRI imaging (LGE and T2-weighted), characterizing scar and the at-risk area early after infarction, respectively (31,39,40), will provide important further insight into periprocedural necrosis. However, even if such data will eventually be available, it is unrealistic to propose pre- and post-procedural LGE for routine PCI. In the context of the current debate about health care costs, it appears more realistic that such data will calibrate levels of biomarker elevation to corresponding scar.

### Table 1. Comparison of Troponins With MRI for Detecting Myocyte Necrosis

<table>
<thead>
<tr>
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<th>Contemporary Troponin Assays</th>
<th>Higher Sensitivity Troponin Assays</th>
<th>MRI</th>
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</thead>
<tbody>
<tr>
<td>Cutoff: normal vs. pathologic</td>
<td>Well-defined</td>
<td>Evolving (38)</td>
<td>Evolving</td>
</tr>
<tr>
<td>Sensitivity/spatial resolution</td>
<td>Very sensitive, no localization</td>
<td>Extremely sensitive, no localization</td>
<td>Localization, but limited spatial resolution</td>
</tr>
<tr>
<td>Time pattern of rise and fall</td>
<td>Well known but limitations, e.g., delayed response from nonreperfused myocardium</td>
<td>Evolving</td>
<td>Decrease of scar area during the first week (28)</td>
</tr>
<tr>
<td>Method standardization</td>
<td>High</td>
<td>High</td>
<td>Evolving</td>
</tr>
<tr>
<td>Relation with prognosis</td>
<td>Controversial (2,4,5–8,15)</td>
<td>Evolving</td>
<td>Evolving</td>
</tr>
<tr>
<td>Fulfills universal definition of MI</td>
<td>Few</td>
<td>Yes</td>
<td>No</td>
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MI = myocardial infarction; MRI = magnetic resonance imaging.
mass and distribution and help define clinical biomarker criteria for defining post-PCI MI.

References

34. Amado LC, Gerber BL, Gupta SN, et al. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a


Key Words: coronary artery bypass graft ■ late gadolinium enhancement ■ magnetic resonance imaging ■ myocardial infarction ■ myocyte necrosis ■ percutaneous coronary intervention ■ scar ■ serum biomarker ■ troponin.