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New Universal Definition of Myocardial Infarction

Applicable After Complex Percutaneous Coronary Interventions?

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Objectives This study aimed to characterize myocardial infarction after percutaneous coronary intervention (PCI) based on cardiac marker elevation as recommended by the new universal definition and on the detection of late gadolinium enhancement (LGE) by cardiovascular magnetic resonance (CMR). It is also assessed whether baseline inflammatory biomarkers are higher in patients developing myocardial injury.

Background Cardiovascular magnetic resonance accurately assesses infarct size. Baseline C-reactive protein (CRP) and neopterin predict prognosis after stent implantation.

Methods Consecutive patients with baseline troponin (Tn) I within normal limits and no LGE in the target vessel underwent baseline and post-PCI CMR. The Tn-I was measured until 24 h after PCI. Serum high-sensitivity CRP and neopterin were assessed before coronary angiography.

Results Of 45 patients, 64 (53 to 72) years of age, 33% developed LGE with infarct size of 0.83 g (interquartile range: 0.32 to 1.30 g). A Tn-I elevation >99% upper reference limit (i.e., myocardial necrosis) (median Tn-I: 0.51 μg/l, interquartile range: 0.16 to 1.23) and Tn-I >3× upper reference limit (i.e., type 4a myocardial infarction [MI]) occurred in 58% and 47% patients, respectively. LGE was undetectable in 42% and 43% of patients with periprocedural myocardial necrosis and type 4a MI, respectively. Agreement between LGE and type 4a MI was moderate (kappa = 0.45). The levels of CRP or neopterin did not significantly differ between patients with or without myocardial injury, detected by CMR or according to the new definition (p = NS).

Conclusions This study reports the lack of substantial agreement between the new universal definition and CMR for the diagnosis of small-size periprocedural myocardial damage after complex PCI. Baseline levels of CRP or neopterin were not predictive for the development of periprocedural myocardial damage. (J Am Coll Cardiol Intv 2010;3:950–8) © 2010 by the American College of Cardiology Foundation

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The new "universal" definition of myocardial infarction (MI) after percutaneous coronary interventions (PCI) is based on the elevation of cardiac markers >3 × 99th percentile of the upper reference limit (URL) (1,2). Cardiovascular magnetic resonance (CMR) can directly visualize areas of myocardial damage with late gadolinium enhancement (LGE) in all segments of the left ventricle (LV) and can accurately assess infarct size (3,4). Recently, high dose atorvastatin has been shown to reduce the incidence of periprocedural MI in a randomized placebo trial (5). Statins have been shown to reduce the levels of C-reactive protein (CRP) and exert an anti-inflammatory effect (6,7). Several studies have shown that baseline elevated inflammatory biomarkers, such as CRP and neopterin—a marker of macrophage activity—predict adverse clinical events following PCI (8–12). To date, it is unknown whether the occurrence of periprocedural myocardial damage according to the new universal definition is paralleled by the development of LGE on CMR. We therefore aimed to report the incidence of periprocedural myocardial damage according to the new definition and as LGE detected by CMR, further assessing the extent of infarcts, their effect on LV function, and their predictors. We also investigated whether patients who develop periprocedural myocardial damage have elevated levels of baseline CRP and neopterin.

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Methods

Ethics. This study was performed according to the principles of the Declaration of Helsinki and was approved by the Royal Brompton Hospital National Health Service institutional ethics committee. Each patient gave written informed consent.

Patient population. Between December 2005 and April 2008, 45 consecutive patients undergoing complex PCI, with either stable or unstable angina were prospectively enrolled. Unstable angina was classified according to Braunwald classification (13). Patients with class I to III B were enrolled. Stable angina was classified as chest pain on exertion with a stable pattern for at least the last 6 months preceding the admission. All patients with baseline elevation of troponin I (Tn-I) above the upper limit of normal of 0.04 μg/l or of creatine kinase-myocardial band (CK-MB) levels above the upper limit of normal of 5.9 μg/l were excluded. Additional exclusion criteria were previous documented MI or presence of LGE in the territory of the vessel targeted for intervention, previous revascularization of the culprit lesion by PCI or coronary artery bypass graft and contraindications to CMR. Patient clinical characteristics are shown in Table 1; baseline angiographic and procedural characteristics (CMR vessel analysis) are shown in Table 2.

Treatment and procedures. The PCI was performed with standard techniques via a femoral or radial approach, with 6- or 7-F sheaths. Patients not preloaded with oral aspirin and clopidogrel received, as is standard practice in our institution, a loading dose of intravenous aspirin 300 mg and clopidogrel 300 mg (if given ≥6 h before PCI) or 600 mg (if given <6 h before PCI). Intravenous heparin (70 to 100 UI/kg body weight at the operator's discretion) was administered before PCI with subsequent boluses aiming at achieving an activating clotting time (ACT) between 250 and 300 s. Abciximab was administered electively or as a bail-out for slow flow at the operator's discretion.

CMR protocol. The CMR scans were performed with a 1.5-T scanner (Siemens Avanto, Erlangen, Germany) with the use of an 8-channel phased array cardiac coil. Eligible patients underwent CMR within 48 h of their procedure and 12 to 48 h after PCI. Cine images were obtained with a steady-state free-precession sequence in 2 long-axis and multiple consecutive short-axis views encompassing the LV from base to apex. Typical image parameters were: echo time = 1.6 ms, repetition time = 3.2 ms, time/cine frame 51 ms, alpha = 60 degrees, matrix = 256 × 256, slice thickness = 8 mm, gap = 2 mm (14). The LGE images were acquired 10 to 15 min after intravenous injection of 0.1 mmol/kg body weight gadolinium- diethylene-triamine penta-acetic acid in the identical long- and short-axis planes with a segmented inversion recovery gradient echo sequence (repetition time = 600 ms, echo time = 3.8 ms, alpha = 25 degrees, slice thickness 8 mm, gap 2 mm, typical pixel size = 1.7 × 1.4 mm) (15). The inversion time was progressively optimized and adjusted to adequately null normal myocardium (typical values 320 to 440 ms). The LGE images were phase-swapped to exclude artefact.

CMR analysis. All CMR studies were analyzed offline with a dedicated workstation with semi-automated software (CMRTools, Cardiovascular Solutions, London, United Kingdom). All measurements were performed by 2 experienced readers (A.G. and C.B-D.), blinded to whether the scan was before or after PCI and to the PCI results except

Abbreviations and Acronyms

AUC = area under the (receiver operating characteristics) curve
BC = bias corrected
CI = confidence interval
CK-MB = creatine kinase-myocardial band
CRP = C-reactive protein
hs-CRP = high-sensitivity C-reactive protein
IQR = interquartile range
LGE = late gadolinium enhancement
LV = left ventricle
LVEF = left ventricular ejection fraction
TIMI = Thrombolysis In Myocardial Infarction
TMPG = Thrombolysis In Myocardial Infarction perfusion myocardial grade
Tn-I = Troponin-I
URL = upper reference limit

Table 1. Patient Characteristics

	All (n = 45)	No LGE (n = 30)	Any LGE (n = 15)	p Value
Age, yrs	64 (53–72)	65 (56–73)	56 (44–69)	0.04
Male	33 (73)	21 (30	12 (80)	0.72
Diabetes mellitus	7 (15)	5 (16)	2 (13)	1
Hypertension	30 (66)	21 (70)	9 (21)	0.50
Smoking	9 (20)	4 (13)	5 (33)	0.14
Hypercholesterolemia	37 (82)	25 (83)	12 (80)	1
Family history of IHD	27 (60)	18 (60)	9 (60)	1
Unstable syndrome	7 (15)	4 (13)	3 (20)	0.67
Previous PCI	10 (22)	7 (23)	3 (20)	1
Previous CABG	0 (0)	0 (0)	0 (0)	1
LVEF (%), mean ± SD	70 ± 10	69 ± 11	70 ± 7	0.71
Multiple lesions treated	16 (35)	10 (33)	6 (40)	0.66
Multiple vessels treated	6 (13)	3 (10)	3 (20)	0.38

All values given as n (%) unless otherwise indicated. Continuous values are presented as mean ± SD, or median (interquartile range) as appropriate.

CABG = coronary artery bypass graft; IHD = ischemic heart disease; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

for the knowledge of the treated artery. Baseline and post-procedural quantitative left ventricular ejection fraction (LVEF) and end-diastolic and end-systolic volumes were calculated from the short-axis views excluding the papillary muscles. Evaluation of location of LGE was performed according to the 17 myocardial segment classification relative to the specific coronary artery territory of distribution (16). New myocardial damage was manually traced and calculated from the short-axis images, and it was defined as area of LGE with signal intensity >2 SDs compared with remote myocardium. This area of new myocardial scar is then expressed in grams (assuming 1.05 g/ml as the specific gravity of the myocardium). The occurrence of myocardial damage was defined as the detection of new LGE areas compared with baseline and was classified as "adjacent" when it was in segments located in the same short-axis section where the stent was positioned or "distal" (Fig. 1) when it was at least 10 mm (one short-axis frame away) from the stent section (corresponding to 10 mm) (8).

Angiographic analyses. Angiographic analyses were performed by an experienced reader blinded to CMR results (GF). The Thrombolysis In Myocardial Infarction (TIMI) flow grade (17), corrected TIMI frame count (18), and TIMI perfusion myocardial grade (TMPG) (19) were evaluated. These parameters were assessed before and after PCI and after each phase of the angioplasty (pre-dilation, stenting, post-dilation) when corresponding cine runs were available. Impairment of flow was defined as the reduction of TIMI flow or TMPG during any phase of the angioplasty procedure, including transient reductions of at least 1 grade, or the achievement of a final TIMI <3 or TMPG <3. Quantitative coronary angiography was performed with validated software (Medis Medical Imaging Systems, Leiden, the Netherlands); the following parameters were measured: minimal luminal diameter, reference diameter, lesion length, and stenosis percentage.

Biochemical measurements. The Tn-I and CK-MB were assessed at baseline and every 6 h after the procedure until 24 h time or until a trend to reducing levels was detected and peak value of each biomarker was considered for the analysis. The upper limit of normality, which corresponds to the 99% percentile URL, was 0.04 μg/l for Tn-I and 5.9 μg/l for CK-MB. According to previous definition (1,2), the elevation of Tn-I or CK-MB above the 99% percentile URL after PCI was classified as periprocedural myocardial necrosis, and elevations above 3 times the 99% percentile URL were defined as periprocedural MI (4a type). We also report elevation in Tn-I above 1 μg/l, a cutoff used in a previous study (4). Baseline high-sensitivity (hs) CRP and neopterin measurements were performed 6 to 12 h before PCI. The hs-CRP was measured with COBAS Integra (Roche Diagnostics Limited, Lewes, East Sussex, United Kingdom). The CRP-Latex assay was used in both the high-sensitivity application (analytical range 0.2 to 12 mg/l) and the normal application (analytical range 2 to 160 mg/l). Analytical precision of the hs-CRP-Latex assay was 7.6% at a level of 1.02 mg/l, 3.3% at 1.79 mg/l, and 1.3% at a level of 4.36 mg/l. Samples outside the analytical range of the hs-CRP-Latex assay were analyzed by the CRP-Latex assay in the normal application. The analytical precision of the

Table 2. Post-PCI Biomarkers Elevation and Agreement With LGE

	Any Elevation >99% URL	Type 4a MI	Tn-I >1 μg/l	Elevation >99% and <3× URL
Tn-I, n (%)	26 (58)	21 (47)	8 (18)	5 (11)
CK-MB, n (%)	13 (29)	5 (11)		8 (18)
Tn-I, μg/l, median (range)	0.51 (0.16–1.23)	0.76 (0.30–1.69)	1.73 (1.46–2.22)	0.08 (0.07–0.09)
CK-MB, μg/l, median (range)	12.5 (10.5–20.0)	22.7 (20.0–40.0)		11.3 (9.7–12.55)
LGE, κ Cohen's	Tn-I CK-MB	Tn-I CK-MB	Tn-I	Tn-I CK-MB
	0.55 0.59	0.45 0.16	0.38	0.16 0.49

CK-MB = creatine kinase-myocardial band; LGE = late gadolinium enhancement; MI = myocardial infarction; Tn-I = troponin I; URL = upper reference limit.

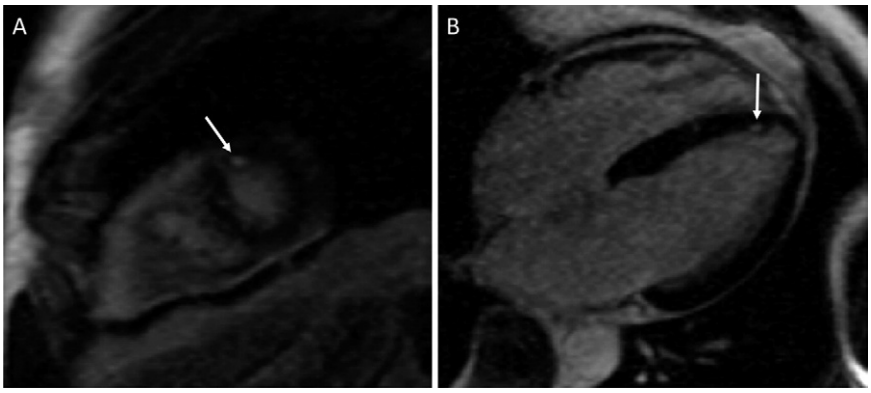

Figure 1. Cardiac Magnetic Resonance Example of Distal Embolization After Percutaneous Coronary Intervention

(A) Short-axis view, **(B)** 4-chamber view. Distal embolization illustrated by late gadolinium enhancement **(white arrows)**.

normal CRP-Latex assay was 2.4% at a level of 29.5 mg/l and 1.3% at a level of 113 mg/l. Neopterin serum concentration was measured with a commercially available immunoassay (enzyme-linked immunosorbent assay kit, IBL, Hamburg, Germany). The limit of detection was 1.5 nmol/l. The analytic precision of the assay was 3% at the level of 7.7 nmol/l and 4% at the level of 20 nmol/l.

Statistical analysis. Distribution of continuous variables was assessed by visual estimation of frequency histograms and with the use of the Shapiro-Wilk test. Continuous variables that followed a normal distribution were described by mean ± SD, and those showing a non-normal distribution were described by median and interquartile range (IQR); comparisons among 3 groups were performed with Kruskal Wallis test, due to the presence of non-normal distribution of variables; Mann Whitney *U* test or unpaired *t* test were used as appropriate for the comparison between 2 groups. Rates were compared by chi-square test or Fisher exact test, as appropriate. The agreement between the presence of LGE and periprocedural damage assessed by biomarkers was assessed using Cohen's kappa (κ), where 0.0 to 0.20 indicates slight agreement, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 1.00 good agreement. The relation between myocardial grams of LGE and Tn-I or CK-MB blood levels after PCI was assessed with the Spearman's rank test, because the linearity assumptions between these variables were not met; the significance of the difference between these 2 correlation coefficients was assessed with a *t* test for the comparison of 2 dependent correlations from the same sample (20). The diagnostic accuracy of post-PCI Tn-I and CK-MB levels to identify new LGE areas was assessed with the use of receiver operating characteristics curves, with the calculation of the area under the curve (AUC) and its 95% confidence interval (CI). Bootstrap estimation of the 95% CI of the AUC was also performed with the bias corrected (BC) method after 5,000 replications. The LVEF data were analyzed with mixed effect linear regression with time (baseline and post-PCI) and group (identifying LGE, periprocedural myocardial necrosis, and type 4a MI) and the interaction between them as fixed effects and patient and group as random effects (random intercept and coefficient, respectively). Previous studies (21,22) reported an incidence of post-PCI LGE damage ranging from 23% of vessels analyzed to 63% of patients enrolled, in study populations of 52 and 40 patients, respectively. To achieve a comparable sample size in our study, we enrolled 45 patients, estimating

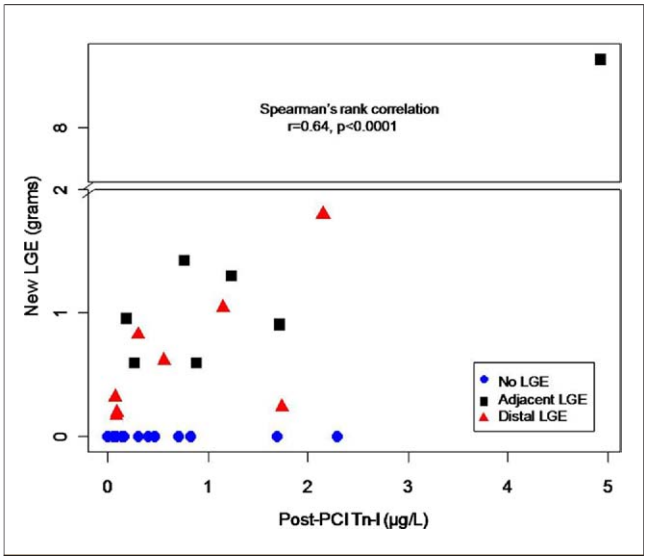

Figure 2. Correlation Between Infarct Grams Assessed as LGE and Tn-I Levels After PCI

Blue circles represent patients without late gadolinium enhancement (LGE); **black squares** represent patients developing adjacent LGE; and **red triangles** represent patients with distal LGE. The Y axis has been modified with a break between 2 and 7.5, due to the presence of an outlier. Tn-I = troponin I; PCI = percutaneous coronary intervention.

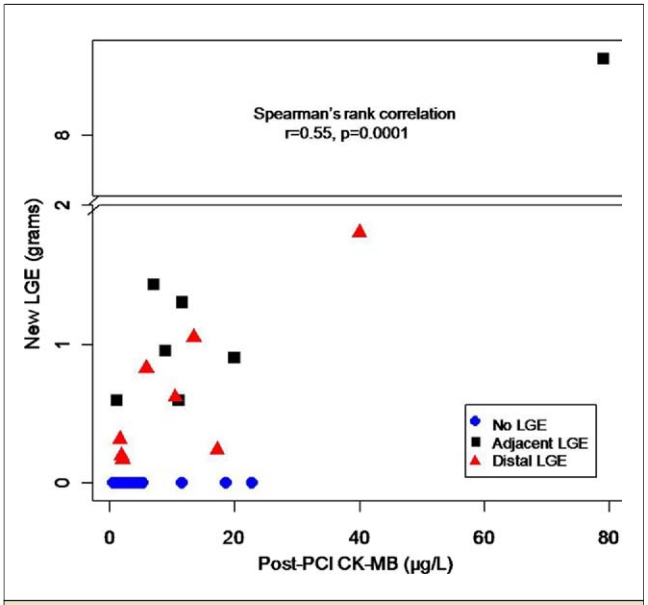

Figure 3. Correlation Between Infarct Grams Assessed as LGE and CK-MB Levels After PCI

Blue circles represent patients without LGE; **black squares** represent patients developing adjacent LGE; and **red triangles** represent patients with distal LGE. The Y axis has been modified with a break between 2 and 7.5, due to the presence of an outlier. CK-MB: creatine kinase-myocardial band isoenzyme; other abbreviations as in Figure 2.

an expected incidence of post-PCI LGE damage of 30%. A 2-tailed p value <0.05 was the level of statistical significance. The STATA version 10.1 (Statacorp, LP, College Station, Texas) statistical software was used.

Results

Incidence and extent of periprocedural myocardial damage. New areas of LGE after PCI developed in 15 of 45 (33.3%) patients, with a median infarct size of 0.83 g (IQR 0.32 to 1.30) corresponding to 0.53% (IQR 0.41% to 1.05%) of total LV mass. Of note, infarct size was <1.5% of total LV mass in 14 of 15 patients, with only 1 patient developing a periprocedural infarct corresponding to 8% of total LV mass. Distal new LGE areas occurred in 8 of 15 patients (53.3%) and adjacent LGE in 7 of 15 (46.7%) with an infarct size of 0.47 g (IQR 0.22 to 0.94 g) versus 0.96 g (IQR 0.60 to 1.43 g, respectively, p = 0.1). Patients who developed new LGE were younger (Table 1) with no other difference in baseline clinical characteristics. Post-PCI Tn-I and CK-MB values are reported in Table 2. Of note, new LGE areas were not detectable in 42% (11 of 26) and in 23% (3 of 13) of patients with periprocedural myocardial necrosis defined as Tn-I or CK-MB elevations, respectively, in 43% (9 of 21) and 40% (2 of 5) of patients with type 4a MI, defined as Tn-I or CK-MB elevations, respectively, and in 25% (2 of 8) of patients with Tn-I rise >1 μg/l.

All patients with LGE elevation had periprocedural myocardial necrosis defined as Tn-I elevation.

The agreement of LGE with Tn-I and CK-MB was never substantial (Table 2). Grams of new LGE correlated with Tn-I levels after PCI, r = 0.64, p < 0.0001, and with CK-MB levels, r = 0.55, p = 0.0001 (p = 0.17 for the comparison between the 2 correlations) (Figs. 2 and 3). The AUC derived from receiver operating characteristics curves analysis for the prediction of new LGE was 0.85 (95% CI: 0.74 to 0.96; BC 95% CI: 0.72 to 0.94) for Tn-I levels and 0.79 (95% CI: 0.65 to 0.94; BC 95% CI: 0.63 to 0.92) for CK-MB (p = 0.22 for the comparison between AUC) (Fig. 4).

Effect of PCI and periprocedural myocardial damage on LVEF. The change in LVEF from baseline after PCI was not statistically significant (−2.14%, 95% CI: −4.7 to 0.43, p = 0.10). The occurrence of periprocedural damage did not significantly affect LEVF change between baseline and after PCI (LGE: −3.27%, 95% CI: −8.59 to 2.02, p = 0.23); periprocedural necrosis Tn-I (−2.32, 95% CI: −7.44 to 2.79, p = 0.37); periprocedural necrosis CK-MB (−2.78%, 95% CI: −8.30 to 2.75, p = 0.32); type 4a MI Tn-I (−4.23%, 95% CI: −9.21 to 0.76, p = 0.09); type 4a MI CK-MB (1.06%, 95% CI: −6.93 to 9.06, p = 0.79); Tn-I 1μg/l (−0.67%, 95% CI: −6.54 to 5.21, p = 0.82).

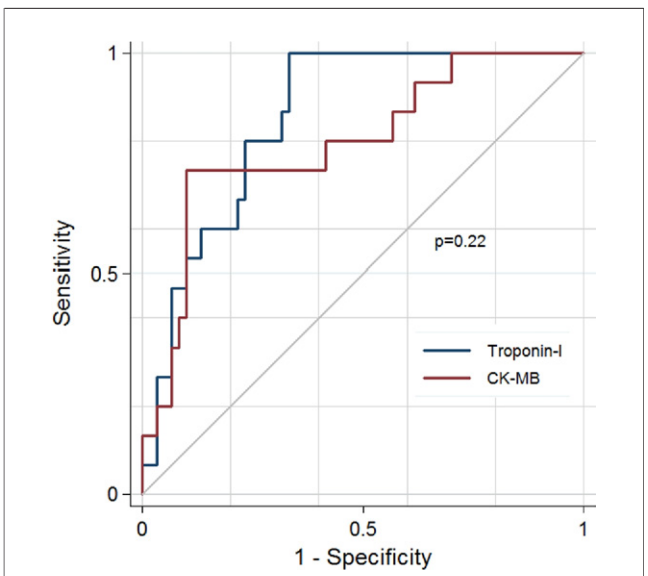

Figure 4. Receiver Operating Characteristic Curve Describing the Ability of Troponin-I and Post-CK-MB to Correctly Classify Patients Developing Late Gadolinium Enhancement

Troponin-I **(blue line)** and after creatine kinase-myocardial band (CK-MB) **(red line)**. The area under the curve was 0.85, (bias corrected 95% confidence interval: 0.72 to 0.94) for troponin I and 0.79 (bias corrected 95% confidence interval: 0.63 to 0.92) for after CK-MB; p = 0.22 for the comparison between the 2 markers.

Predictors of periprocedural myocardial damage. Angiographic analysis was performed on 52 CMR territories, including 2 vessels treated in 6 patients and a very large first diagonal of a bifurcation lesion (Table 3). Because serial lesions were present in 5 vessels, 57 lesions in total were considered. New LGE areas were detected in the territory distribution of 15 of 52 (23%) vessels. Among baseline angiographic and procedural characteristics, post-dilation was more frequent in the group developing new LGE areas compared with the other group (100% vs. 73%, p = 0.046). Final angiographic indexes of myocardial perfusion did not significantly differ between groups (Table 3).

Inflammation and periprocedural damage. The levels of CRP and of neopterin were not significantly different in patients developing LGE as compared with the remaining (CRP: 5.0 mg/l [IQR 1.0 to 8.1] vs. 2.51 mg/l [IQR 1.3 to 7.4], p = 0.72; neopterin: 6.6 nmol/l [IQR 4.9 to 7.7] vs. 6.5 nmol/l [IQR 4.4 to 9.5], p = 0.46). When considering 3 groups—patients with distal LGE, adjacent LGE, and no LGE—there was no significant difference in the levels of CRP (7.4 mg/l [IQR 2.5 to 61.9], 2.2 mg/l [IQR 0.9 to 6.3], 2.5 mg/l [IQR 1.3 to 7.4], respectively, p = 0.15) or neopterin (7.1 nmol/l [IQR 6.1 to 8.3], 4.9 nmol/l [IQR 4.4 to 9.0], 6.5 nmol/l [IQR 4.4 to 9.5], respectively, p = 0.18). Table 4 reports baseline levels of CRP and neopterin according to periprocedural myocardial damage. No significant difference was found between groups.

Discussion

This study reports the lack of substantial agreement between the new universal definition (1,2) and CMR for the

Table 3. Baseline Angiographic and Procedural Characteristics

	Vessels (n = 52)	No LGE (n = 37)	Any LGE (n = 15)	p Value
Bifurcation	18 (35)	12 (32)	6 (40)	0.65
CTO	5 (9)	4 (11)	1 (6)	1
Treated vessel				0.40
LAD	26 (50)	19 (51)	7 (47)	
LCX*	11 (21)	6 (16)	5 (33)	
RCA	15 (29)	12 (32)	3 (20)	
Ambrose B2-C type	30 (57)	21 (57)	9 (60)	0.91
Total stent length, mm	22 (15–32)	20 (14–32)	23 (16–28)	0.86
Number of stents				0.48
0	1 (2)	0 (0)	1 (7)	
1	34 (65)	25 (68)	9 (60)	
2	12 (23)	9 (24)	3 (20)	
3	4 (8)	2 (5)	2 (13)	
4	1 (2)	1 (3)	0 (0)	
DES use	34 (65)	25 (68)	9 (60)	0.60
Pre-dilation	43 (83)	30 (81)	13 (87)	1
Post-dilation	42 (81)	27 (73)	15 (100)	0.046
Max pressure inflation, atm	16.3 ± 3.5	16.1 ± 3.5	17.0 ± 3.4	0.37
Max balloon diameter, mm	3.2 ± 0.48	3.2 ± 0.45	3.2 ± 0.56	0.77
QCA measurement				
MLD pre, mm	0.63 (0.4–0.97)	0.66 (0.4–1.2)	0.62 (0.4–0.7)	0.53
Stenosis severity, %	68.3 ± 17.5	67.5 ± 17.9	70.6 ± 16.3	0.54
Stenosis length, mm	9.6 (8.1–14.1)	9.9 (8.2–14.1)	9.4 (7–14.4)	0.66
Final TIMI flow grade 3	49 (94)	34 (92)	15 (100)	0.55
Final TMPG 3	39 (75)	27 (73)	12 (80)	0.73
Flow impairment	20 (38)	15 (41)	5 (33)	0.76
Final cTFC, median (range)		10 (7–13)	8.5 (6–11)	0.42

Cardiovascular magnetic resonance (CMR) vessel analysis. All values given as n (%) unless otherwise indicated. *A large anatomic first diagonal was the vessel treated corresponding to the CMR left circumflex artery (LCX) territory. Continuous values are presented as mean ± SD, or median (interquartile range) as appropriate.

cTFC = corrected Thrombolysis In Myocardial Infarction frame count; CTO = chronic total occlusions; DES = drug-eluting stent; LAD = left anterior descending artery; LGE = late gadolinium enhancement; MLD = minimal lumen diameter; QCA = quantitative coronary analysis; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction; TMPG = Thrombolysis In Myocardial Infarction myocardial perfusion grade.

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Table 4. Inflammatory Biomarkers and Periprocedural Damage

	CRP, mg/l	p Value	Neopterin, nmol/l	p Value
PP necrosis (Tn-I)		0.61		0.81
Yes	4.3 (1.3–8.1)		7.1 (5.0–8.7)	
No	2.4 (1.5–6.0)		6.0 (4.4–9.7)	
4a MI (Tn-I)	4.5 (0.8–8.1)	0.82	6.6 (4.9–9.0)	0.92
Yes	2.5 (1.5–6.0)		6.5 (4.7–9.0)	
No				
Tn-I 1 μg/l				
Yes	2.9 (1.3–6.3)	0.59	7.1 (3.4–9.0)	0.63
No	4.2 (1.3–8.1)		6.5 (4.9–9.0)	
PP necrosis (CK-MB)		0.94		0.79
Yes	4.0 (1.3–8.1)		7.7(4.9–9.0)	
No	2.5 (1.3–7.4)		6.1 (4.7–9.0)	
4a MI (CK-MB)		0.68		0.74
Yes	2.9 (1.7–5.0)		8.6 (5.7–9.1)	
No	4.2 (0.9–8.1)		6.1 (4.7–9.0)	

CK-MB = creatine kinase-myocardial band; CRP = C-reactive protein; MI = myocardial infarction; PP = periprocedural; Tn-I = troponin I.

diagnosis of periprocedural myocardial damage. Furthermore, it shows that the size of periprocedural damage is small, regardless of the definition used, with no significant impairment in LVEF in the acute phase. Finally, it identifies procedural factors, such as the use of post-dilation, as potential contributors to LGE, but could not demonstrate a significant elevation in baseline CRP or neopterin levels in patients developing periprocedural myocardial damage.

In our study, infarcts were much smaller than previous studies (3,4) and were below the threshold of 1 μg/l of Tn-I in the vast majority of cases. The absence of substantial agreement ($\kappa < 0.61$) between biochemical assays and CMR might depend in part on the higher sensitivity threshold of LGE, due to partial volume effects and the use of a 2-mm gap between the 8-mm-thick inversion-recovery slices that increases the risk for some LGE to be confined to the 2-mm gap, and the use of different assays of Tn-I with an upper limit of normality 25 times smaller than that in the previous study (4). Furthermore, distal micro-embolization usually leads to multiple micro-infarcts with patchy distribution (23). Any such micro-infarct might not be large enough to be detected by LGE, but the cumulative necrosis can be detected by Tn-I and CK-MB, therefore accounting for the imbalance in sensitivity of LGE relative to Tn-I in the present study. However, troponin release has been shown to occur also without irreversible myocardial damage in athletes after a marathon, as a consequence of enhanced myocyte membrane permeability because of increased oxygen radical production (24). Cardiac embolization damage has been shown to be worsened by oxygen radicals in an animal model (25). Therefore, in the setting of a small increase in myocardial enzymes, as in our study, the risk that cardiac markers might falsely detect irreversible damage should be considered.

The impact of troponin elevation after PCI has been investigated by recent meta-analyses (26,27) that have shown that both troponin elevation and type 4a MI are associated with increased risk of major adverse cardiac end points and of mortality, both in-hospital and at 18-month follow-up. We did not address the clinical prognostic value of myocardial damage at follow-up; thus we cannot verify whether elevation in cardiac markers show a differential prognostic impact as compared with LGE.

The presence of small sized infarcts and the absence of significant LVEF impairment from baseline in the acute phase of PCI, due to periprocedural myocardial damage, are encouraging; however, recent studies have documented a negative prognostic value of LGE independently of its size (28,29). Factors that might have played a role in minimizing the extent of periprocedural myocardial damage in our study were the systematic wiring of side branches to avoid occlusion and appropriate stent selection. We found that the prevalence of post-dilation was higher among patients who developed LGE, suggesting that post-dilation might enhance plaque fragmentation with downstream embolization or facilitate side branch occlusion. It is also plausible that post-dilation might cause stent overexpansion in some cases, a factor that has been shown to be associated with no-reflow phenomenon in the setting of acute MI (30).

We could not detect a significant difference in baseline levels of CRP and neopterin between patients with or without myocardial damage. However, the small sample size and the absence of prospective selection of patients on the basis of high versus low levels of inflammatory biomarkers with a cutoff might have played a role for the absence of significant results. The detection of higher, albeit not significant levels of CRP in patients with distal LGE as compared with adjacent LGE and those without LGE might deserve further investigation in larger studies, because a pathophysiological rationale underlying such association might be an enhanced microcirculatory vulnerability or increased coronary plaque susceptibility to embolization upon balloon or stent manipulation in patients with higher levels of CRP (31).

Study limitations. The main limitation is the small sample size. The use of a CMR 3-dimensional pulse sequence with complete coverage of the entire LV or a 2-dimensional pulse sequence with thin slices (6 or 7 mm) and no gap, a more sensitive imaging sequence, and a higher dose of MR contrast (i.e., 0.20 mmol/kg body weight gadolinium-diethylenetriamine penta-acetic acid) might have lead to a higher correlation between CMR LGE and biomarkers of necrosis. We did not assess the size and number of embolizing particles, because we did not perform intracoronary Doppler recording of embolizing events. It is possible that the incidence of distal embolization was lower in this study,

because PCI of vein grafts and patients with unstable angina with positive troponin were excluded.

Conclusions

This study reports the lack of substantial agreement between myocardial infarction biomarker changes and CMR for the diagnosis of small-sized periprocedural myocardial damage after complex PCI. Myocardial damage, independently of the definition used, is of small size and does not significantly affect LVEF in the early phase after PCI. Finally, this study suggests that post-dilation might be a contributing factor to LGE and shows that baseline levels of CRP and neopterin are not significantly higher in patients who develop periprocedural myocardial damage.

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Key Words: C-reactive protein ■ cardiovascular magnetic resonance imaging ■ distal embolization ■ neopterin ■ percutaneous coronary interventions.