Functional and structural correlates of persistent ST elevation after acute myocardial infarction successfully treated by percutaneous coronary intervention

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Background: In the thrombolytic era, persistence of ST-segment elevation was considered a marker of left ventricular (LV) aneurysm. ST-segment elevation may still be found persistently raised after successful primary percutaneous coronary intervention (PCI). Echocardiographic correlates of this finding, however, are still poorly known.

Methods and results: 82 consecutive patients with first ST-segment elevation myocardial infarction and successful PCI were divided into patients with persistent ST-segment elevation at discharge (sum of ST >4 mm) (n=33) and those without persistent ST-segment elevation (n=49). Conventional and myocardial contrast echocardiography were performed at discharge and at 6 months. At discharge, LV aneurysm was more common in patients with persistent ST elevation (27% vs 8%, $p<0.005$). Similarly, the wall motion score index was higher (2.5 vs 2.0, $p<0.005$) and microvascular damage larger (2.3 vs 1.8, $p<0.005$) in patients with persistent ST-segment elevation. At 6 months' follow-up, LV volumes were similar in the two groups.

Conclusions: After primary PCI, persistent ST-segment elevation is associated with LV aneurysm formation in 30% of cases, it is not associated with significantly larger LV dilatation but with larger microvascular damage and dysfunctioning risk area.

In the pre-thrombolytic and thrombolytic eras, persistent ST-segment elevation on 12-lead ECG was found to be associated with the development of postinfarct left ventricular (LV) aneurysm, often as result of failure of reperfusion treatment.¹ Currently, in the era of primary or rescue percutaneous coronary intervention (PCI), ST segment may still be found persistently raised at discharge.² The incidence of this phenomenon, together with its relation with microvascular and myocardial damage as well as with LV aneurysm and remodelling is still unknown. Therefore, we designed a prospective observational study to assess the incidence of persistent ST-segment elevation after acute myocardial infarction (STEMI) in consecutive patients treated by either primary or rescue PCI and in whom myocardial damage, LV aneurysm and LV remodelling were assessed by conventional two-dimensional echocardiography, and microvascular damage was assessed by myocardial contrast echocardiography (MCE).

SUBJECTS AND METHODS

Study group

Consecutive patients referred to our catheterisation laboratory between January and December 2005 for primary or rescue PCI within 12 hours of onset of STEMI entered the study. Diagnosis of STEMI was based on the following: typical chest pain lasting for more than 30 minutes and unresolved by nitroglycerine; ST-segment elevation >0.1 mV in at least two contiguous leads in the initial ECG. Exclusion criteria were: cardiogenic shock or clinical instability; left bundle branch block or pacemaker; inadequate echocardiographic image quality; inability to obtain informed consensus.

The ethics committee of the Catholic University of the Sacred Heart approved the study and all patients gave informed consent to participate in the study.

PCI and drugs

In all patients, catheterisation was performed by the percutaneous femoral approach. After diagnostic coronary angiography, intracoronary nitroglycerine 0.1 mg was given to reverse any possible epicardial spasm. Then, in all patients, primary PCI with stenting of the infarct-related artery was performed according to the clinical protocol applied at our institution. All patients were treated with heparin (initial weight-adjusted intravenous bolus, then further boluses administered to obtain an activated clotting time of 250–300 seconds in patients treated with abciximab and >300 seconds in the remaining subjects) and with double antiplatelet treatment with aspirin and clopidogrel (loading dose of 300 mg followed by 75 mg/day) for at least 4 weeks. Unless contraindicated, abciximab (0.25 mg/kg bolus plus infusion of 0.125 µg/kg/min for 12 hours) was intravenously administered in all patients undergoing primary PCI, whereas in those for whom thrombolysis had failed, abciximab use was left to the operator's discretion.

Coronary angiograms were stored on compact disks for offline analysis. Flow in the infarct vessel was graded by the Thrombolysis In Myocardial Infarction (TIMI) flow classification. Successful PCI was defined as the restoration of TIMI 3 flow. Residual stenosis of the culprit artery after PCI was <20% in all patients.

In all patients, TIMI grade and myocardial blush grade were semiquantitatively scored by digital coronary angiography.

Abbreviations: AMI, acute myocardial infarction; CDL, contrast defect length; CK, creatine kinase; CSI, contrast score index; LV, left ventricular; MCE, myocardial contrast echocardiography; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction

Electrocardiography

A 12-lead ECG was recorded in all patients on admission to the hospital, in the coronary care unit 90 minutes after PCI and at hospital discharge (5 (SD 2) days after admission). ST-segment analysis was performed by an investigator who was unaware of the clinical, angiographic and outcome data. The sum of ST-segment elevation was measured 20 ms after the end of the QRS complex in leads I, aVL and V1–V6 for anterior, and leads II, III, aVF, and V5–V6 for non-anterior myocardial infarction.³ The ST-segment was considered persistently raised when the sum of ST elevation was ≥ 0.4 mV in the leads relative to the acute myocardial infarction (AMI) location.⁴ Because a cut-off point of persistent ST elevation has not been clearly shown in the literature, we considered the median value of the population of the largest study that had analysed the correlation between persistent ST-segment elevation and LV remodelling.⁴ This median value of 0.4 mV was comparable with that of our study group. The reproducibility of the classification of ECG was obtained by reanalysis of 50 ECGs by a second independent reader; agreement between the two readers was reached in 90% of cases, with a correlation coefficient of 0.90 (95% CI 0.83 to 0.94).

Myocardial contrast echocardiography

In all patients, baseline transthoracic two-dimensional echocardiography and MCE were performed at discharge, at the same time as ECG evaluation, and transthoracic two-dimensional echocardiography was repeated at 6-months' follow-up.

MCE studies were performed using real-time contrast pulse sequencing operating on a Sequoia ultrasound system (Siemens Medical Solutions, Munich and Berlin, Germany) as previously reported.⁵ Contrast pulse sequencing is a new real-time MCE method that, thanks to the analysis of non-linear response of contrast bubbles in fundamental and higher harmonics, can provide an image with an excellent signal-to-noise ratio and with particularly high sensitivity and penetration using a very low mechanical index.

Acoustic power and compression were maximised and gain settings were optimised at the onset of each study and held constant throughout. The focus was initially set at two-thirds of the depth of the image, and then moved to the level of the myocardial segment to examine it. The definitive setting of the

ultrasound images was optimised after initial contrast infusion, kept constant throughout the study and matched at the follow-up MCE study.

The intravenous contrast used in this study was Sonovue (Bracco Imaging SpA, Milan, Italy), a second-generation ultrasound contrast agent that consists of microbubbles containing sulphur hexafluoride surrounded by a phospholipid shell. The mean size and concentration of microbubbles are 2.5 μm and $1\text{--}5 \times 10^8/\text{ml}$, respectively. It is reconstituted by the addition of normal saline to the final solution of 5 ml. Sonovue was given intravenously at the rate of 1 ml/min.

Contrast images were acquired in apical four-chamber, two-chamber and long-axis view; as soon as myocardial video-intensity had reached a plateau, a flash of ultrasound with very high mechanical index was given to destroy microbubbles in the sector and then the replenishment of bubbles was observed and digitally acquired and stored onto a magneto optical disk.

Data analysis

Two experienced observers who had no knowledge of the patient identity carried out visual analysis of echocardiograms; disagreement was resolved by consensus. Images were randomised across time points and patients. Regional wall motion was semiquantitatively scored (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) and a regional wall motion score index was calculated by the sum of the score of all segments divided by the total number of dysfunctioning segments. An LV aneurysm was considered to be a well-localised bulging of the LV border both in diastole and in systole. The intra- and interobserver reproducibility for the identification of an LV aneurysm was 100%.

End-diastolic and end-systolic LV volumes were calculated from four-chamber and two-chamber views using the modified Simpson biplane method.

Cardiac enzymes were sampled at admission and then every 6 hours; enzymatic infarct size was calculated by peak creatine kinase (CK).

Myocardial opacification at MCE, the echocardiographic measure of microvascular obstruction, was visually assessed in each myocardial segment and semiquantitatively scored. A single perfusion score was assigned as 1 = normal; 2 = reduced; 3 = absent opacification⁵ (fig 1). A regional contrast score index (CSI) was calculated as the sum of the MCE score in each segment divided by the total number of segments with reduced or absent opacification. The endocardial length of transmural contrast defect (CD score = 3) (CDL) was calculated in each apical view, averaged and expressed as a percentage of LV length. Patients were considered as "no-reflow" if CDL was $\geq 25\%$ of the LV endocardial length.

Statistical analysis

Continuous variables (presented as mean (SD)) were compared by the Student *t* test for normally distributed variables and by the Wilcoxon sum rank test for non-normally distributed variables. Categorical variables were expressed as the number of subjects and percentages and were analysed by χ^2 or the Fisher exact test, as appropriate.

To analyse the association between clinical and echocardiographic variables and persistent ST-segment elevation, a stepwise backward multivariable regression analysis was conducted including all variables presenting a *p* value < 0.1 at univariate analysis. Statistical analysis was performed with the SPSS software package for Windows 11.0 (SPSS Inc., Chicago Illinois, USA). Differences were considered significant at $p \leq 0.05$.

Figure 1 Example of myocardial contrast echocardiography images in four-chamber (A) and long-axis (B) views. The microvascular network reached by microbubbles is coloured orange, while the area of microvascular obstruction is shown as a black area (within red arrows). The microvascular obstruction is small and patchy (score 2) in (A) and large and transmural (score 3) in (B).

Table 1 Clinical and angiographic characteristics of the study group

Characteristics	Persistent ST elevation (n = 33)	Resolved ST elevation (n = 49)	p Value
Age (years), mean (SD)	60 (3)	57 (2)	NS
Gender: male	26 (78)	41 (83)	NS
Smokers	26 (79)	34 (69)	NS
Hypercholesterolaemia	19 (58)	22 (45)	NS
Hypertension	21 (64)	28 (57)	NS
Diabetes mellitus	7 (21)	5 (10)	NS
Anterior AMI	33 (100)	25 (51)	<0.001
Symptoms-to-angiography time (h), mean (SD)	4.6 (3.2)	4.3 (3.8)	NS
Rescue PCI	13 (39)	11 (22)	NS
Multivessel disease	19 (57)	10 (20)	NS
Peak CK, mean (SD)	3810.28 (1614.5)	2217.7 (16207)	<0.001
TIMI 3 grade	27 (82)	42 (86)	NS
Blush 3 grade	20 (61)	31 (63)	NS

Results are shown as No (%) unless otherwise stated.

AMI, acute myocardial infarction; CK, creatine kinase; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

RESULTS

Ninety-four consecutive patients with first STEMI, treated by primary or rescue PCI within 12 hours of symptom onset were considered for possible enrolment. After an initial clinical evaluation, 12 patients were excluded from the study, five owing to inadequate echocardiographic image quality, three because of pacemaker-guided rhythm, four because of left bundle branch block.

The final study group comprised 82 patients (71 male, mean (SD) age 59 (26) years), 12 were diabetic, 49 hypertensive, 60 smokers, 41 hypercholesterolaemic. AMI was anterior in 58 patients, inferior in 15 patients, and lateral in 10 patients. The culprit artery was the left anterior descending in 57 patients,

the right coronary in 15 patients, and the circumflex in 10. Thirty patients had one-vessel disease, 23 had two-vessel disease and 29 had three-vessel disease. All patients underwent successful PCI, primary in 58 cases and rescue in 24. Residual stenosis was <20% in all patients and TIMI flow was 3 in 69 patients and 2 in 22 patients.

Incidence of persistent ST-segment elevation

Based on 12-lead ECG analysis recorded at hospital discharge, 33 patients (40%) had persistent ST-segment elevation and 49 (60%) showed resolved ST-segment elevation. Table 1 shows the clinical characteristics of the two groups of patients. Of all

Figure 2 (A) Wall motion score index (WMSI) is higher in patients with persistent than in those with resolved ST-segment elevation, both at discharge and at follow-up. * $p < 0.005$ vs persistent ST-segment elevation. (B) The percentage of patients developing a left ventricular (LV) aneurysm is much higher in patients with persistent than in those with resolved ST-segment elevation, both at discharge and at follow-up. * $p < 0.005$, † $p < 0.05$ vs persistent ST-segment elevation.

Figure 3 (A) Contrast score index (CSI) is higher in patients with persistent than in those with resolved ST-segment elevation, both at discharge and at follow-up. * $p < 0.001$, † $p < 0.005$ vs persistent ST-segment elevation. (B) The length of contrast defect (CDL) is much higher in patients with persistent than in those with resolved ST-segment elevation, both at discharge and at follow-up. * $p < 0.001$ vs persistent ST-segment elevation.

Figure 4 (A) End-systolic volumes (ESV) are slightly and not significantly higher in patients with persistent than in those with resolved ST-segment elevation, both at discharge and at follow-up. (B) End-diastolic volumes (EDV) are larger in patients with persistent than in those with resolved ST-segment elevation only at discharge, while they are similar at follow-up. * $p<0.05$ vs persistent ST-segment elevation.

the analysed clinical variables, infarct site and enzymatic infarct size were different between the two groups, with the AMI being anterior in 100% of patients with persistent ST-segment elevation and 47% in patients with resolved ST-segment elevation ($p<0.001$) and larger in persistent ST-segment elevation ($p<0.001$). Time to and modality of (primary vs rescue) PCI were not different between the groups.

Myocardial dysfunction

Regional contractile function, as expressed by the wall motion score index, was significantly more impaired in patients with persistent ST-segment elevation, both at discharge and follow-up ($p<0.005$) (fig 2A). LV aneurysm was present in 13 patients (16%) at discharge and confirmed in 12 patients at follow-up (15%). Aneurysm was more common in patients with persistent than in patients with resolved ST-segment elevation, both at discharge ($p<0.05$) and at follow-up ($p<0.005$) (fig 2B).

Microvascular damage

Regional microvascular obstruction, as semiquantitatively scored by the CSI (fig 3A) and measured in its longitudinal extent as CDL (fig 3B), was larger in patients with persistent ST-segment elevation, both at baseline ($p<0.001$) and at follow-up ($p<0.005$ for CSI and $p<0.001$ for CDL). No-reflow was present in a larger percentage of patients with persistent ST-segment elevation (62% vs 11%, $p<0.005$).

LV remodelling

Although, end-systolic LV volumes did not show significant differences between groups ($p=NS$) (fig 4A), end-diastolic

volumes were larger in persistent ST-segment elevation ($p<0.05$) at baseline, and they were similar between the two groups at follow-up (fig 4B).

Functional and structural correlates of persistent ST-segment elevation

Among all the clinical, functional and structural measures analysed, peak CK, anterior AMI, LV aneurysm and microvascular damage were significantly associated with persistent ST-segment elevation at univariate analysis ($p<0.05$, $p<0.001$, $p<0.05$ and $p<0.005$, respectively). However, when modelled in a multivariate analysis, none of these factors was independently associated with persistent ST-segment elevation.

DISCUSSION

For the first time, we report myocardial and microvascular structural and functional correlates of persistent ST elevation after primary PCI. In this study, persistent ST-segment elevation was associated with LV aneurysm formation in 30% of cases; furthermore it was associated with larger coronary microvascular damage and dysfunctioning myocardial risk area in the absence of significantly more severe LV remodelling.

Persistent ST-segment elevation and LV aneurysm

Early studies showed that persistent ST-segment elevation after STEMI might be a marker of LV aneurysm.¹⁻⁶ However, several investigators have subsequently reported controversial findings.⁷⁻⁸ More recently, in the thrombolytic era, persistent ST-segment elevation has not been considered strictly associated with LV aneurysm formation, but more likely to occur with regional contractile dysfunction.⁹ In this study, persistent ST-segment elevation was found in 40% of cases after primary or rescue PCI and was associated with LV aneurysm in a minority (30%) of patients. Although it was not the purpose of this study, we also looked at the persistence of ST elevation at 6 months' follow-up and we did not observe significant changes from discharge.

Persistent ST-segment elevation and myocardial and microvascular damage

In the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial comparing mortality in 6010 patients randomised to receive either reteplase or streptokinase as thrombolytic treatment for STEMI, ST-segment resolution was the most powerful independent predictor of 35-day mortality.¹⁰ In this trial, the authors report a close correlation between ST-segment resolution and the extent of infarct area as measured by peak CK level. More recently, persistent ST-segment elevation after successful PCI was found to be associated with worse LV ejection fraction and with a higher incidence of in-hospital and long-term mortality and congestive heart failure.² However, in this study the anatomical correlates of persistent ST-segment elevation were not explored and the presence of microvascular damage as a possible pathophysiological link between such post-PCI persistent ST-segment elevation and worse patient outcome was only postulated.²⁻¹¹ In our study we analyse, for the first time, structural and functional correlates of persistent ST-segment elevation and report that regional contractile dysfunction and microvascular damage are greater in patients with persistent than in patients with resolved ST-segment elevation. At univariable and multivariable analysis, peak CK, anterior AMI, LV aneurysm and microvascular damage were significantly, but not independently, associated with persistent ST-segment elevation. Taken together, these data indicate that the closest anatomical correlate of persistent ST-segment elevation is the extent of

necrotic myocardial damage as indirectly measured by peak CK, LV aneurysm formation and microvascular damage, and that it is usually larger in anterior AMI.

Persistent ST-segment elevation and LV remodelling

Recent clinical data demonstrate that the extent of microvascular damage is associated with adverse LV remodelling after AMI.⁴⁻¹² Manes *et al* showed that predischARGE ST-segment elevation may be a useful tool for early identification of patients at risk of ventricular enlargement and persistent dysfunction after myocardial infarction.⁴ However, in our study LV remodelling was no different between patients with and without persistent ST-segment elevation. The discrepancy between our study and that of Manes *et al*⁴ may be explained by the difference between the reperfusion strategy used in the two study groups—primary or rescue PCI in all our patients, either thrombolysis or PCI in 87% of the patients of Manes *et al*. Thus, the incidence and genesis of persistent ST-segment elevation and of LV remodelling in the two study groups may be different. The lack of association between persistent ST-segment elevation and LV remodelling found in our study is not entirely surprising, because persistent ST-segment elevation may be interpreted as an ECG marker of the extent of myocardial necrosis, whereas LV remodelling is a complex phenomenon in which the extent of necrosis plays a part, but it is not the only determinant.¹³ On the other hand, the extent of microvascular damage, associated, although not independently, with persistent ST-segment elevation, is the best determinant of LV remodelling,⁵⁻¹² probably because it is not only an expression of infarct size but also of global microvascular dysfunction.

CONCLUSIONS

As far as we know, this is the first study reporting the clinical correlates of persistent ST-segment elevation after MI treated with primary or rescue PCI. Such an ECG sign at hospital discharge may be considered associated with a large infarct size, and, in 30% of cases, with LV aneurysm formation and with continuing LV remodelling.

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