

Coronary Revascularization Versus Myocardial Reperfusion in Acute Myocardial Infarction

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The pathogenesis of the ST-segment elevation myocardial infarction (STEMI) consists of the rupture or disruption of an atherosclerotic plaque, followed by a sudden thrombotic coronary occlusion. To support this physiopathogenic mechanism, some pioneering studies performed more than 40 years ago (1) showed that intracoronary fibrinolysis could restore perfusion to the jeopardized myocardial territory. In the 1980s, mortality reduction with systemic thrombolytic therapy generated a new standard of care for the treatment of these patients. However, thrombolytic therapy is limited by inadequate suboptimal rates of patency, and subsequently it has been shown that mechanical revascularization with angioplasty (PCI) offers even greater clinical benefits to patients with STEMI. (2) In this regard, the goal of reperfusion treatment is to re-establish a patent infarct-related epicardial artery as soon as possible.

The TIMI (Thrombolysis in Myocardial Infarction) group has categorized epicardial coronary flow into four grades (0-3) in order to standardize the angiographic characterization of reperfusion. The restoration of TIMI flow grade 3 (normal epicardial flow) in patients with STEMI is associated with improved survival and enhanced recovery of ventricular function. However, the angiographic picture only gives an acute image of the flow in the epicardial artery and, therefore, a TIMI flow grade 3 does not necessarily mean that microvascular flow and myocardial perfusion have been normalized. (3)

Despite the high rate of success of primary PCI, about 15-30% of the patients have inadequate myocardial perfusion in the absence of angiographic evidence of mechanical obstruction of the vessel. (4) This 'no-reflow' phenomenon may be due to injured microvasculature following myocardial ischemia, with reperfusion injury caused by neutrophil infiltration, free radicals, and activation of the complement system. (3) Especially after primary PCI, microvascular obstruction may be caused by embolization of material and atheromatous and thrombotic debris, both spontaneously and after mechanical dilation of the infarct-related artery. This inadequate myocardial perfusion is clinically relevant, since it is associated

with more extensive infarctions, greater deterioration of the ventricular function, and worse clinical outcomes. (5)

A study by Cura et al. is published in this issue of the *Revista Argentina de Cardiología*; it focuses on identifying associated independent factors, such as the absence of tissue reperfusion after primary angioplasty. (6) The authors analyzed 140 patients prospectively included in the randomized study Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction Trial (PREMIAR). (7) This study evaluated the use of a filter distal protection device during angioplasty in patients with acute ST-segment elevation myocardial infarction at high risk of thrombosis (including only baseline TIMI 0-2 flow). The primary end point of the study was the rate of complete ST-segment resolution at 60 minutes, defined as ST³ 70% reduction with the use of continuous monitoring. A model of logistic regression was developed to identify independent predictors.

As for results, complete resolution of ST-segment derivation 60 minutes after PCI was observed in 63% of the patients, while 37% presented incomplete resolution with higher rates of mortality, reinfarction, and/or heart failure at 30 days (18.9% versus 8.5%; $p = 0.07$). Patients with absence of adequate tissue reperfusion had anterior infarction (79% versus 33%; $p = 0.001$), higher heart rate (81 ± 20 versus 70 ± 15 ; $p < 0.001$), and less proportion of history of current smokers (25% versus 51%; $p = 0.002$) more frequently, compared to those with optimal tissue reperfusion. In addition, there was a trend towards greater prevalence of diabetes (26% versus 16%; $p = 0.13$), longer time interval from the onset of symptoms to angioplasty (217 ± 167 versus 182 ± 134 minutes; $p = 0.19$), and Killip class > 1 (30% versus 17%; $p = 0.07$), respectively. Multivariate analysis demonstrated that anterior infarction (OR 8.22, CI 95% 3.67-18.4; $p < 0.001$) was associated with absence of complete reperfusion, while the use of glycoprotein IIb/IIIa inhibitors (OR 4.21, IC 95% 1.34-13.22; $p = 0.014$) and current smoking (OR 3.84, IC 95% 1.58-9.50; $p = 0.003$) were correlated to complete

reperfusion. Finally, the authors conclude that *“a considerable proportion of patients undergoing primary angioplasty do not achieve adequate tissue reperfusion. This phenomenon is associated with adverse outcomes. Anterior myocardial infarction correlates with less degree of tissue reperfusion. Conversely, current smoking and the use of glycoprotein IIb/IIIa inhibitors are associated with better tissue reperfusion after primary angioplasty”*.

BEYOND EPICARDIAL PATENCY: HOW SHOULD REPERFUSION OF INFARCT-RELATED ARTERY BE EVALUATED IN CLINICAL PRACTICE?

Epicardial revascularization versus myocardial reperfusion

ST-segment elevation on the ECG of the acute phase of AMI is caused by myocytes, deprived of oxygen, and therefore ATP-dependent transmembrane ion gradients are lost. (3) A ST segment elevation recovery quantifies the reversal of this adverse electrophysiologic condition, and has proved to be one of the most predictive measures of cellular response to reperfusion. (3) ST-segment recovery represents both reversal of ischemia and eventual interruption of infarction, defined as a ST-segment elevation recovery > 50% on early ECG (indicative of transmural myocardial lesions), in the absence of posterior elevation of biomarkers at more than twice the normal maximum value. (8)

In this regard, continuous or serial monitoring of ST-segment appears to be fundamental to evaluate not only the epicardial patency but also –and more significantly– tissue reperfusion adaptation after pharmacologic or mechanical revascularization of the infarct-related artery. For some years now, our group has demonstrated that persistent ST-segment elevation > 50% in patients with TIMI 3 flow after successful thrombolysis is an independent predictor of poor outcomes in late follow-up. (9) This finding reflects a complex and non-linear relationship between epicardial coronary flow and myocardial reperfusion after restoring arterial patency in AMI.

From the physiopathologic point of view, this could be reasonably explained by the assumption that there is a good correlation between a clinical marker of ischemic reduction (ST segment elevation resolution) and successful functional restoration of myocardial perfusion. Based on our results, and even accepting that there could be certain limitations to the correlation between reperfusion and ST improvement (temporal relation between anatomic flow restoration, necrosis progression, viability of myocardium at risk, and no-reflow phenomenon), clinical markers like ECG could correlate better to functional reperfusion than the isolated image of angiographic patency. (9)

This fact was researched by Santoro et al., (10) who studied the relation between ST-segment changes and myocardial perfusion evaluated by contrast

echocardiography in patients with acute myocardial infarction treated with primary PCI. The main finding of this study was that, after successful PCI, different myocardial perfusion patterns were associated with different ST-segment changes. In the group of patients with adequate myocardial reperfusion, a rapid reduction of the S-ST was observed, while in the “no-reflow” group there were no significant changes. Rapid reduction of ST-segment elevation could indicate immediate resolution of ischemic injury related to early and complete restoration of myocardial perfusion. (10)

The study by Cura et al. focuses on a key topic to analyze the result of primary PCI in STEMI, regarding the evaluation of obtaining adequate myocardial flow in those patients whose procedure has been successful with TIMI 3 flow in the epicardial artery. On the other hand, it aims at determining predictors associated with the absence of adequate tissue reperfusion to identify a subgroup of patients who should be assessed for alternative therapies. In this regard, persistent ST-segment elevation after successful epicardial revascularization confirms that it is a clinical indicator of worse prognosis even in those patients with TIMI 3 flow after successful PCI.

PREDICTORS OF MYOCARDIAL TISSUE REPERFUSION AFTER PRIMARY PCI

In the analysis by Cura et al. there are three factors that deserve further discussion: anterior infarction as predictive variable of worse reperfusion, the importance of time to reperfusion, and the influence of diabetes.

Anterior myocardial infarction: larger ischemic territory, and the importance of grade 3 ischemia on the ECG

It is interesting to compare the data from the study of Cura et al. to those reported by McGehee et al., (11) who retrospectively analyzed 155 patients who underwent primary PCI to compare ST resolution according to the characteristics of the admission ECG. They defined grade 3 ischemia as the terminal QRS distortion, represented by: 1) absence of S wave in derivations with terminal S wave configuration (V1-V3), or 2) J point elevation > 50% of R wave amplitude in more than two derivations, usually lower (II, III, AVF). On the other hand, patients presenting initial ST segment elevation but none of the above criteria were defined with grade 2 ischemia according to ECG evaluation.

Among the baseline characteristics for both groups, patients with grade 3 ischemia were older, with lower percentage of smokers, higher incidence of anterior infarction and more symptoms-admission time. For these patients, ST-segment resolution was significantly lower than for those with grade 2 ischemia (35% versus 75%), while anterior infarction, grade 3 ischemia, greater pain duration, and greater initial

S-ST on ECG were predictors of a lower rate of ST-segment resolution post PCI.

As a preliminary conclusion, this overlap among predictors identified in both studies probably stresses the significance of the larger ischemic territory in the anterior infarction, evidenced by the grade 3 ischemia on ECG. This finding is not provided by the study of Cura et al.; however, it would be interesting that the authors analyzed the variable of grade 3 ischemia on ECG regarding anterior infarction and its probable association with unsuccessful tissue reperfusion.

Time as variable associated with success of reperfusion

As discussed before, nearly 10% of patients treated with reperfusion do not develop increased enzyme levels and present total reversal of ST-segment elevation, which is consistent with the interruption of infarction. The earlier the reperfusion, the higher the chances of “aborting” the infarction; this means that the treatment administered within the hour of the onset of symptoms may result in up to 25% of infarct abortion, thus improving ventricular function, and survival. (8)

Impact of diabetes mellitus on myocardial perfusion after primary PCI

Prasad et al. investigated the impact of diabetes mellitus on myocardial perfusion after primary PCI utilizing myocardial blushing grade and ST segment elevation resolution. (12) They determined reperfusion success in those with and without diabetes mellitus in two substudies of the CADILLAC. Patients with diabetes mellitus had a higher rate of absent myocardial perfusion (grade 0/1, 56% versus 47.1%; $p = 0.01$) and absent ST resolution (20.3% versus 8.1%; $p = 0.002$). Diabetes mellitus was an independent predictor of absent myocardial perfusion (grades 0/1, HR 1.63, CI 95% 1.17-2.28; $p = 0.004$) and absent ST resolution (HR 2.94, CI 95% 1.64-5.37; $p = 0.005$). Therefore, despite similar high rates of TIMI flow grade 3 after primary PCI, patients with diabetes are more likely to have abnormal myocardial perfusion as assessed by both incomplete ST resolution and reduced angiographic myocardial perfusion. Diminished microvascular perfusion in diabetics after primary PCI may contribute to post AMI adverse outcomes.

CONCLUSIONS AND FUTURE PERSPECTIVES

The study of Cura et al. is a valuable contribution to our understanding of the reperfusion physiopathology after primary PCI for acute myocardial infarction. In general, its outcomes confirm the data provided by

several previous studies that investigated the differences between patency restoration of the infarct-related artery and functionally effective tissue reperfusion.

Considering variables that can predict “no-reflow” phenomenon after successful PCI is an important tool to undertake new randomized studies aiming at research on pharmacological and/or mechanical interventions that contribute to improving tissue perfusion for these patients. Hopefully, this exciting goal of optimizing reperfusion outcomes will allow us to improve our patients’ prognosis in the near future.

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