

# Successful Reperfusion Therapy: From Epicardial to Myocardial Salvage

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The treatment of acute myocardial infarction was long focussed on restoration of epicardial patency. Rapid and sustained patency of the infarct related vessel was the main goal.<sup>1,2</sup> The Thrombolysis and Myocardial Infarction (TIMI) phase 1 trial introduced a standard for flow assessment in the infarct-related vessel after thrombolytic therapy.<sup>3</sup> In that thrombolytic era, the angiographic definition of perfusion of the epicardial coronary vessels was based on the assumption that grades 0 and 1 were effectively occluded and grades 2 and 3 provided adequate reperfusion. This scoring system has been commonly used to assess the immediate effectiveness of reperfusion therapy.

Somewhat later, a landmark study showed that only TIMI 3 flow was associated with improved mortality. Clinical outcome with TIMI 2 flow was comparable to TIMI 0 or 1 flow.<sup>4,5</sup> Hereafter, only patients with TIMI 3 flow were defined as having successful reperfusion. From the trials which compared different lytic agents, it became evident that the best thrombolytic regime, the accelerated administration of recombinant tissue Plasminogen Activator (rtPA), resulted in successful reperfusion (TIMI 2 or 3 flow) in 80% of patients and TIMI 3 flow in only 60% of patients.<sup>6</sup> In the early nineties it was shown that primary angioplasty was able to induce TIMI 3 flow in 90%-95% of patients, resulting in improved outcome as compared to lytic therapy. However, it was the great achievement of myocardial contrast echocardiography which showed for the first time that not only epicardial reperfusion was more often impaired in lytic treated patients, but myocardial reperfusion as well. Myocardial contrast echocardiography performed during and shortly after the primary coronary angioplasty procedure also confirmed that in some patients, with TIMI 3 flow of the infarct-related vessel, the myocardium is not

perfused after intracoronary injection of sonicated microbubbles<sup>7</sup> and this was associated with increased left ventricular dilatation and a worse outcome.<sup>8</sup> This led to the opinion that not only epicardial flow is important (represented by TIMI flow grading) but that the extent of myocardial reperfusion also plays a role and that optimal reperfusion therapy should be aimed at both restoring epicardial and myocardial flow. A new definition of success of reperfusion was introduced requiring evidence both of epicardial as well as myocardial reperfusion. This again led to the so called (myocardial) 'no-reflow' phenomenon, reflecting a state of impaired myocardial flow despite normal flow of the epicardial infarct-related vessel. This is known to be associated with a poor clinical outcome.<sup>9</sup> The pathophysiologic mechanism of no-reflow has been studied in humans as well as in the animal laboratory and is based on extensive damage to the microcirculation of the myocardium. Prolonged ischemia leads to cell death, the release of several vasoactive substances and neutrophils resulting in vasospasm and plugging of the small arterioles. This is not only caused by ischemia but may also be related to the relief of ischemia, the reperfusion itself, so-called reperfusion injury, although this has mainly been studied in animal models.

Monitoring myocardial (no re-)flow however, is difficult and many of the current methods, like myocardial contrast echocardiography, dobutamine stress echocardiography, TIMI frame count, post angioplasty intracoronary flow measurements, positron emission tomography scanning, or magnetic resonance imaging are not applicable in routine clinical practice. Therefore one sought to find simple parameters which might be able to reflect the extent of myocardial reperfusion.

In this issue of *Revista Española de Cardiología*, Ndrepepa et al describe the relationship of the myocardial perfusion grade (MPG) and indexes of myocardial salvage, as assessed by single photon emission computed tomography (SPECT) scanning before and after reperfusion.<sup>10</sup> The MPG, like the myocardial blush grade (MBG) are both parameters reflecting the extent of myocardial reperfusion. The only difference is that the TIMI MPG also weighs

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the speed of disappearance of contrast from the microvasculature. Both parameters have shown to be independent predictors of short and long term mortality.<sup>11,12</sup> The blush or perfusion of myocardial tissue is the reflection of filling of the small arterioles of the myocardium with contrast. This blush is present on every diagnostic coronary angiogram and has been used in studies to calculate myocardial flow reserve.<sup>13</sup> Decreased blushing of myocardial tissue suggests that some epicardial flow bypasses the microcirculation and shunts directly into one of the greater cardiac veins. It is therefore questionable whether "normal" TIMI flow and absent myocardial blush may coexist. The Munchen group previously showed that no patient with TIMI less than 3 flow had optimal myocardial reperfusion (MPG grade 3).<sup>14</sup>

This group now showed that in patients with successful epicardial reperfusion (TIMI 3 flow) after primary percutaneous coronary intervention, reduced myocardial perfusion was associated with reduced myocardial salvage and larger infarct size. All angiograms were scored off-line at a core lab by independent operators. A very interesting finding was that the myocardial salvage index and long term mortality did not differ between patients with MPG 2 or MPG 0-1. This suggests that any reduction of myocardial reperfusion is bad, similar to the finding that any reduction in epicardial flow is associated with poor outcome. Therefore successful reperfusion should be defined as TIMI 3 flow in combination with MPG 3. In the study of Ndrepepa, this optimal reperfusion was found in the large majority of patients (66%). Severely impaired myocardial reperfusion (MPG 0-1) was present in 18% of patients. The very first publication on MBG showed that MBG 0-1 was present in 30% of patients, however, this trial also included patients with TIMI flow less than 3.<sup>11</sup> A later publication showed that 11% of patients had severely impaired MBG, despite TIMI 3 flow.<sup>15</sup> One might conclude that between 10% and 30% of patients have impaired myocardial reperfusion despite successful epicardial reperfusion. This difference in the rate of poor myocardial reperfusion after successful percutaneous coronary intervention is probably related to the fact that the TIMI MPG also evaluates the disappearance of contrast from the capillaries and blush only the initial staining of the microcirculation. Another limitation of the 2 scoring parameters is the reproducibility of measurements. Intra- and interobserver variability vary between 85% and 95%. Recently, a more objective way of scoring myocardial blush or perfusion was developed and is based on computer-assisted myocardial blush quantification, called Qube.<sup>16</sup> Both the entrance as well as the disappearance of contrast is evaluated using Qube. It showed that in patients with TIMI 3 flow and good myocardial blush (MBG 2 or 3), Qube was able to

further differentiate myocardial reperfusion and predict clinical outcome within this population.

A very interesting finding of the work by Ndrepepa et al is that patients with reduced MPG after percutaneous coronary intervention had a larger necrotic portion of the initial perfusion defect at the baseline SPECT image and these patients also presented later. This finding of a larger necrotic core before reperfusion therapy is consistent with the finding that 40% of patients with acute myocardial infarction have much older obliterating clots, and suggests that the impaired myocardial reperfusion in these patients might be due to longstanding repetitive obstruction before definite vessel occlusion.<sup>17</sup>

The German investigators also showed that reduced myocardial reperfusion was associated with a larger area at risk (jeopardized myocardium). This is probably the reason that patients with anterior infarct location and patients with signs of heart failure had less optimal myocardial reperfusion. These data are consistent with a previous study showing that the poor outcome of patients who present with heart failure is related to poor myocardial blush or perfusion.<sup>18</sup>

Unfortunately, the German investigators did not report whether mechanical aspiration was used in this cohort of patients. The Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS) trial (MBG as the primary end point) showed a significant improvement of myocardial blush with the use of thrombus aspiration with the Export catheter (Medtronic). The incidence of MBG 0-1 was reduced from 26.3 to 17.1%. This routine use of mechanical thrombus aspiration was associated with a significantly lower one year cardiac mortality. This finding might be extrapolated to the work of Ndrepepa et al, who nicely showed the relationship between MBG or MPG and myocardial salvage. The investigators should be congratulated with these findings and emphasize that only viable tissue can be salvaged. Therefore all efforts should be aimed at diagnosing acute myocardial infarction at the earliest possible time point, preferably in the ambulance, where effective antithrombotic and anti-platelet agents can be given in order to improve reperfusion before arrival of the patient in the cath-lab. Time is muscle and myocardial salvage.

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