Epicardial and microvascular reperfusion with primary percutaneous coronary intervention

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Restoration of normal flow and tissue-level perfusion are key factors in the reduction of mortality in acute myocardial infarction. The goal of reperfusion during primary percutaneous coronary intervention (PCI) should be to restore not only epicardial patency and flow, but also downstream myocardial tissue perfusion. This review will focus on the techniques able to evaluate and quantify epicardial and microvascular perfusion and on the available therapeutic tools that may be useful in primary PCI. After primary PCI, rates of TIMI flow grade 3 of 80 to 100% have been reported. Furthermore, after stenting during primary PCI more than one third of patients have persistently abnormal corrected TIMI frame counts related to increased downstream resistance. Achievement of TIMI flow grade 3 is no longer sufficient to define an optimal result of primary PCI and restoration of normal tissue-level perfusion is also required. Coronary no/slow reflow and myocardial hypoperfusion after otherwise successful recanalization of infarct-related arteries may involve more than just classical non-reperfusion of the myocardium that is already dead: distal embolization of debris or microparticulate atheromatous material, capillary edema, inflammation, and neurohormonal reflexes and vasoconstriction may play a crucial role. Evolving treatments of the no-reflow phenomenon are directed toward the restoration of microvascular flow abnormalities because these either directly or indirectly contribute to cell death. Promising adjunctive therapies that may reduce microemboli include intensive antiplatelet therapy with aspirin and ticlopidine, platelet glycoprotein IIb/IIIa inhibitors, coronary vasodilators, and embolization protection devices. Therapy targeting microvascular vasospasm also appears promising. Finally a variety of interventional new approaches have been focused on the setting of primary PCI, like atherectomy and thrombectomy devices, distal protection devices, hypothermia and hyperoxemic therapy, that are under investigation in numerous trials before they can be used routinarily.

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Timely restoration of normal antegrade flow and tissue-level perfusion are key factors in the reduction of mortality in acute myocardial infarction (AMI)[1]. Thus, the restoration of full patency is the prerequisite to avoid or limit myocardial infarction and mediates patient's ventricular volume and survival after AMI[2,3]. Correlations between sustained patency of the infarct-related artery and improved clinical outcomes culminated in the "open-artery hypothesis" which has been the cornerstone of therapeutic strategies for AMI for over a decade. Initially introduced as an alternative to fibrinolytic therapy (to circumvent contraindications to its use and the risk of intracranial hemorrhage), primary percutaneous coronary intervention (PCI) is now increasingly recognized as the reperfusion therapy of choice[4]. The ability to restore robust coronary flow promptly in more than 90% of patients and the nearly linear relation between patency of the infarct-related artery at 90 min after the initiation of reperfusion therapy and in-hospital mortality rates lend credibility to the momentum behind primary PCI for patients with AMI. However, by long time it is clear that most patients do not achieve TIMI flow grade 3 after emergency PCI and successful reopening of an occluded coronary artery does not necessarily lead to recovery of left ventricular function. Thus, the open-artery hypothesis may be an oversimplification, because the goal of reperfusion should be to restore not only upstream epicardial patency and flow, but also downstream myocardial tissue perfusion. Microvascular dysfunction after reperfusion therapy may, in fact, profoundly affect function of cardiac myocytes and interstitium, with important pathophysiological and prognostic implications[5,6]. The downstream of the open-artery hypothesis is expected to redefine the goals of reperfusion strategies to include not only rapid and sustained epicardial patency, but also restored microvascular flow and myocardial tissue perfusion[7].

This review will focus on the more promising techniques able to measure and quantify both epicardial and microvascular perfusion and on the available therapeutic tools targeted to restore optimal tissue perfusion that may be implemented during and shortly after primary PCI.

Restoration of normal epicardial blood flow

Angiographic assessment of epicardial coronary artery blood flow has played a pivotal role in our understanding of the "time-dependent open-artery hypothesis" and in the evaluation of reperfusion strategies over the past two decades[8], and the TIMI flow grade classification scheme has been successfully used to assess coronary blood flow in acute coronary syndromes[9]. However, although poorer TIMI flow grades and poorer clinical outcomes are clearly associated, the directionality of any causal relationship between the two has not been unequivocally demonstrated.

After primary PCI, rates of TIMI flow grade 3 approaching 100% have been reported. These high rates are generally obtained when a "three cardiac cycles to fill the artery" definition is applied[10]. When assessed more quantitatively and rigorously according to the original TIMI definition, rates of TIMI flow grade 3 may in fact approximate only 80%[11]. Furthermore, after stenting during primary PCI more than one third of patients have persistently abnormal corrected TIMI frame counts[12]. The persistent slowing of epicardial blood flow in the presence of minimal or absent residual stenosis is more likely related to heightened downstream resistance. Thus, achievement of TIMI flow grade 3, though still a necessary component, is no longer sufficient to define an optimal result of primary PCI; restoration of normal tissue-level perfusion is also required.

Pathophysiology of tissue-level perfusion during and after primary percutaneous coronary intervention

The pathophysiological mechanisms of impaired myocardial perfusion after PCI in the setting of AMI remain unclear. Unlike animal models of coronary occlusion, the clinical setting of AMI involves an atherothrombotic occlusion with its innate risk of distal embolization when crushed or fragmented mechanically. Thus, coronary no/slow reflow and myocardial hypoperfusion after otherwise successful recanalization of infarct-related arteries may involve more than just classical non-reperfusion confined to the myocardium that is already dead.

Mechanical manipulation during PCI or stent implantation can lead to embolization of debris or calcified plaque material or exposure of thrombogenic material at intravascular sites[13]. The embolization also includes microparticulate atheromatous material, as it has been routinely demonstrated through the use of embolus capture devices[13]. Because microemboli necessarily stream preferentially to well perfused and viable myocardium, microembolization kills potentially salvageable myocardium. Thus, the vital question is, of course: how much of the coronary no/slow reflow and myocardial hypoperfusion seen after primary PCI reflects the classical no-reflow phenomenon caused by necrosis, and how much reflects PCI-induced distal microembolization causing more necrosis? The atherothrombotic burden may prove to be critical. A recent study has shown that the angiographic no-reflow phenomenon after primary PCI correlates with intravascular ultrasound lesion morphology[14]. In particular, the analysis showed that lipid pool-like image and lesion elastic membrane cross-sectional area are independent predictive factors of the no-reflow phenomenon after primary PCI for AMI[14]. Finally, mechanisms other than mechanical embolization, such as capillary edema, inflammation, and neurohormonal reflexes and vasoconstriction that results in hypoperfusion, may play at least some role[15].

Assessment of microvascular dysfunction during primary percutaneous coronary intervention

Until recently, we have had limited access to diagnose microvascular obstruction in living patients and therefore to assess the effects of different therapeutic tools on microcirculation. With the availability of imaging technology, microvascular dysfunction has been documented in a far greater proportion of patients undergoing primary PCI than ever conceived. There are a number of methods for assessing tissue-level myocardial reperfusion including angiographic, echocardiographic and nuclear techniques as well as simple markers such as ST-segment resolution.

Myocardial contrast echocardiography. Myocardial contrast echocardiography (MCE) is ideal for measuring microcirculatory flow because of its good spatial and temporal resolutions and because it utilizes tracers that have an intravascular rheology similar to that of red blood cells[16]. MCE uses microbubbles that remain in the intravascular space and are very effective ultrasound scatterers and therefore can be used to track the passage of red cells through the tissue. Because 90% of the microvasculature consists of capillaries[16], the spatial distribution of these bubbles in the myocardium provides an assessment of regional capillary integrity.

Normal microvascular perfusion is present in regions of viable myocardium, whereas regions of necrosis do not demonstrate microvascular perfusion or show poor perfusion[17]. Thus, after successful reperfusion, MCE can detect the extent of myocardium within the

risk area in which the microvasculature has not been destroyed by prolonged ischemia and which consequently may show late functional improvement. Three different perfusion patterns in the infarct bed have been described after reperfusion: no opacification, patchy or intermediate opacification, and homogeneous opacification[18]. Dysfunctional regions with extensive myocardial opacification show near-normal function at follow-up, while those with no opacification show the most dysfunction. Areas where the spatial extent of microvascular perfusion was intermediate or patchy show intermediate function at follow-up[18]. Thus, MCE has the potential to provide an optimal assessment of microvascular integrity and viability in patients with AMI undergoing reperfusion therapy. The assessment of microvascular integrity by using intracoronary MCE has been investigated extensively[18-26].

More recently, it has been possible to quantify the degree of microvascular inflammation after reperfusion using microbubbles that are specially designed for site-specific imaging. Either the microbubble shell surface is modified (to make them more "sticky" to leukocytes) or ligands are incorporated on the shell surface that adhere to specific adhesion molecules expressed either on the leukocytes or the endothelial surface[27,28]. There, bubbles are injected as a bolus after reperfusion and time is allowed for them to clear from the systemic circulation before imaging is initiated. At that time, microbubbles are seen to be retained at activated sites within the myocardium.

Angiographic markers. To measure myocardial perfusion angiographically, new measures, such as the TIMI myocardial perfusion grade (TMPG), have been developed[12]. In the TMPG system, TMPG 0 represents minimal or no myocardial blush; in TMPG 1, dye stains the myocardium, and this stain persists on the next injection; in TMPG 2, dye enters the myocardium but washes out slowly so that it is strongly persistent at the end of the injection; and in TMPG 3, there is normal entrance and exit of dye in the myocardium. Another method of assessing myocardial perfusion on the angiogram is the myocardial blush grade (MBG) developed by van't Hof et al.[29]. A grade of 0 (no blush) and a grade of 3 (normal blush) are the same in the TMPG and MBG systems. Thus, normal perfusion in the myocardium carries a score of 3 in both the TMPG and MBG systems, and a closed muscle carries a score of 0 in both systems. Both parameters represent angiographic surrogate of myocardial perfusion and have been studied in several single-center retrospective series of patients undergoing primary PCI[12]. So far, the largest analysis examining the implications of myocardial perfusion status by myocardial perfusion gradient after primary PCI for AMI is that from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial[30]. The major finding of this analysis was that, despite achievement of TIMI flow grade 3 in > 96% of patients after primary PCI, normalized myocardial perfusion, as assessed by the MBG, was present in < 20% of patients. Furthermore, abnormal myocardial perfusion post-PCI was a powerful correlate of early and late mortality, even in patients with TIMI flow grade 3 supporting the evidence that the MBG is capable of stratifying patients with TIMI flow grade 3 into different long-term risk categories[30].

Other in-cath-lab techniques to assess microvascular integrity during primary percutaneous coronary intervention. The coronary flow velocity spectrum after a successful primary PCI with an optimal tissue-level perfusion usually shows a diastolic predominant pattern[31]. In contrast, Doppler flow wire studies in TIMI flow grade 2 or MCE no-reflow patients, show systolic flow reversal, reduced antegrade systolic flow, and antegrade diastolic flow with a rapid deceleration slope[31]. Because of the reduced diastolic antegrade flow and presence of systolic flow reversal, coronary inflow to the myocardium is reduced. Microvascular dysfunction results in a decrease in the intramyocardial blood pool and an increase in microvascular impedance. Thus, in patients with no reflow, the blood pool would be rapidly filled in the early phase of diastole, resulting in the rapid deceleration of diastolic antegrade flow and thus in a decrease in the duration of diastolic antegrade flow. On the other hand, during systole the pooled blood could not be smoothly squeezed into the venous circulation and thus would be pushed back to the epicardial coronary artery to produce early systolic retrograde flow.

The use of coronary flow reserve to assess the microcirculation independently is limited in that coronary flow reserve interrogates the flow status of both the epicardial artery and the microcirculation. Recently a novel index of microcirculatory resistance, independent of the epicardial flow, defined as distal coronary pressure divided by the inverse of the hyperemic mean transit time (a correlate to absolute flow), measured simultaneously with the coronary pressure wire, has been proposed as a valuable tool for distinguishing between normal and abnormal microcirculatory function[32]. This index could be applied in the cardiac catheterization laboratory as a means for interrogating and quantifying microcirculatory resistance. Because the method employs a standard coronary pressure wire, fractional flow reserve can be determined simultaneously and further help to distinguish epicardial disease from microcirculatory dysfunction[32].

Association of electrocardiographic findings with angiographic findings in ST-elevation myocardial infarction. The dissociation between electrical and traditional angiographic findings is frequent and apparent to the interventional cardiologist who has restored epicardial blood flow but observes persistent ST-segment

elevation. The ECG (ST-segment resolution) and the new angiographic markers provide complementary insights into myocardial perfusion. A greater ST-segment resolution on the static and continuous ECG correlate with TIMI flow grade 3, TMPG 3, smaller infarct sizes, and improved survival[33]. Restoration of TMPG 3 is associated with higher rates of complete ST-segment resolution on the static ECG and doubles the rapidity of achieving the time to stable ST-segment resolution[34]. Although the ECG and the blush rate are associated, they provide independent prognostic information about infarct size[34]. Two recent studies have documented the complementary prognostic information provided by the ECG and the angiographic blush, with failure to achieve ST-segment resolution and a closed myocardium on angiography following primary PCI carrying a particularly poor prognosis[35,36]. These data suggest a potential electromechanical dissociation between microvascular blood flow and myocyte function. Whereas the angiogram may reflect mechanical patency of the microvasculature and the integrity of the endothelium, the ECG may reflect the functional status of the supplied myocardium[37].

Treatment of microvascular dysfunction in the setting of primary percutaneous coronary intervention

Evolving treatments of the no-reflow phenomenon are directed toward reversal of microvascular flow abnormalities because these either directly or indirectly contribute to cell death. Promising adjunctive therapies that may reduce microemboli include intensive antiplatelet therapy with aspirin and ticlopidine or clopidogrel, platelet glycoprotein IIb/IIIa inhibitors, coronary vasodilators, and embolization protection devices.

Treating platelet microthromboembolism with aggressive antiplatelet therapy has yielded encouraging results. The collective experience from randomized clinical trials of glycoprotein IIb/IIIa inhibition in primary PCI reinforces the efficacy of platelet inhibition in myocardial infarction[38].

Therapy targeting microvascular vasospasm also appears promising. Improved TIMI flow has been reported with intracoronary papaverine or nitroprusside administered directly into the infarct-related artery[39]. A modest improvement in both angiographic flow and MCE perfusion, better functional recovery, and less left ventricular remodeling was reported with intracoronary verapamil compared with placebo in AMI patients undergoing PCI[40].

Adenosine can induce coronary artery vasodilation, reverse coronary spasm, and replenish high-energy phosphates. It can reduce afterload and heart rate, thus decreasing myocardial oxygen demand. In addition, it has antiplatelet and antineutrophil effects that may help prevent no reflow in the clinical setting[41]. Intracoronary adenosine after reperfusion attenuates progression of microvascular dysfunction and augments recovery of myocardial contractile function independent of its vasodilator effects[42]. The Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial reported that adenosine reduces infarct size in patients with anterior AMI[43]. These studies paved the way for a more definitive study, the AMISTAD II[44]. In this study, 2084 patients with AMI were randomized to a 3-hour infusion of adenosine or placebo within 15 min of reperfusion. Adenosine therapy was associated with smaller infarct sizes and a non-significant trend toward less incidence of congestive heart failure or death. In the contemporary interventional practice, intracoronary adenosine use is limited to treatment of no reflow – and at a much smaller dose than the one utilized in the published studies[41].

Recent interest has focused on nicorandil, a hybrid of mitochondrial K_{ATP} channel opener and a nitrate. It reduces preload and afterload, dilates coronary resistance vessels, reduces myocyte Ca^{2+} overload, and attenuates neutrophil activation[45]. Nicorandil has been shown to reduce infarct size and improve microvascular perfusion[46], cardiac function and clinical outcomes when administered in conjunction with primary PCI[47].

Finally, a long list of drugs used in this setting yielded negative or controversial results[41].

High-tech primary percutaneous coronary intervention. There is considerable interest in extrapolating recent advances in new devices from other settings in interventional cardiology to AMI. A variety of interventional approaches has been targeted to AMI interventions, but useful clinical investigation in this area has been hampered by: 1) the delayed recognition of adequate devices to treat the target lesion most optimally; 2) the difficulty to properly assess important differences among different strategies without "major" mortality trials, and 3) consequently, the low performance of surrogate endpoints.

The X-Sizer is an atherectomy and thrombectomy device designed to aspirate excised atheroma, thrombus, and debris. Recently presented results (Lefevre T., TCT 2003, unpublished data) from the randomized X-AMINE ST trial suggest that the use of the X-Sizer in thrombotic lesions improves flow and possibly also outcomes.

The AngioJet Rheolytic Thrombectomy system is a catheter-based device that uses a high-speed saline jet to create a vacuum to break up and then suck out the blood clot. It has been evaluated in the AiMI trial, which aimed to compare final infarct size and clinical and angiographic outcomes in AMI patients treated with rheolytic thrombectomy followed by immediate PCI vs primary PCI alone (without thrombectomy). Unfortunately, the trial showed a trend toward a larger infarct size (the primary endpoint) and a higher mortality in the AngioJet group (Ali A., TCT 2004, unpublished data).

Distal protection devices have been developed to prevent distal embolization of microparticles. New catheter systems, such as the PercuSurge, Angioguard, and Filterwire devices, have been developed to contain and retrieve microparticles, thus protecting against distal embolization. Again, the multicenter, prospective, randomized Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial aiming to assess PercuSurge specifically in AMI patients failed to show favorable results[48].

Hypothermia to 32-34°C can be performed safely as an adjunct to primary PCI for AMI and has been tested in the COOL-MI trial (O'Neill W., TCT 2003, unpublished data). Hyperbaric oxygen therapy is another attractive option, and is known to attenuate microvascular dysfunction and reperfusion microvascular ischemia, as demonstrated in both experimental models and patients with AMI. However, treating patients in a hyperbaric oxygen therapy chamber or with a conventional oxygenator is impractical and difficult. Aqueous oxygen is a newly developed solution containing extremely high oxygen concentrations (1-3 ml O_2/ml saline). The aqueous oxygen system mixes aqueous oxygen solution with a patient's blood from an arterial puncture and delivers the hyperoxemic blood to targeted ischemic myocardium via an infusion catheter for regional correction of hypoxemia and production of hyperoxemia[49]. This technique has been tested in the AMIHOT trial. However, both hypothermia and hyperbaric oxygen therapy failed to achieve the predefined endpoints in their respective randomized trials (O'Neill W., ACC 2004, unpublished data). These negative results may be explained by the multifactorial pathophysiology of microvascular dysfunction during AMI which does not allow an optimal performance of specific devices when used alone. Other potential explanations stem from the intrinsic nature of the surrogate endpoint that 1) should correlate with the clinical endpoint of interest (does MIBI infarct size correlate with late mortality better than left ventricular function?); 2) should capture the total effect of all the treatment mechanisms of action on the clinical endpoint of interest (which has a multifactorial composition); and finally 3) should be easier to measure than the clinical endpoint of interest. We will need data from rigorously performed randomized trials before it is possible to suggest that such devices will ultimately be considered standard of care and be used in virtually all patients undergoing AMI intervention.

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