CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Is an Open Artery Enough? Assessment and Optimization of Myocardial Perfusion in ST-Elevation MI

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For over two decades, the cornerstone of therapy for acute myocardial infarction (MI) has been the restoration of flow in the infarct-related artery (IRA), based on the "open artery hypothesis." In 1977, Reimer demonstrated that the extent of irreversible ischemic myocardial cell injury is proportional to the duration of epicardial artery occlusion. This "wave front phenomenon of myocyte death" illustrates the importance of epicardial flow in MI. Using coronary angiography, De Wood extended this observation to show the high prevalence of total coronary artery occlusion with thrombus after MI. The Thrombolysis In Myocardial Infarction (TIMI) investigators standardized the assessment of epicardial blood flow using coronary angiography into TIMI flow grades 0 to 3 (Table 1). The angiographic substudy of the Global Utilization of Streptokinase and TPA for Occluded coronary arteries (GUSTO-I) revealed that IRA flow at 90 minutes after thrombolysis correlated with the preservation of left ventricular (LV) function and improved survival. Thus, restoration of TIMI grade 3 flow has become the gold standard for reperfusion success in MI. Nonetheless, approximately 25% of patients with restoration of TIMI grade 3 flow in the epicardial IRA have inadequate reperfusion at the tissue level, using myocardial contrast echocardiography. These patients have poorer global LV systolic function, more malignant ventricular arrhythmias, and an increased incidence of congestive heart failure, progressive LV remodelling, cardiac rupture, and death. This issue of *Cardiology Rounds* examines the pathophysiology behind "no-reflow" in the infarct-related artery, diagnostic modalities to assess myocardial perfusion, and strategies to prevent and treat occluded arteries.

Pathophysiology

After coronary occlusion secondary to plaque rupture and occlusive thrombus formation, ischemia causes ultrastructural damage to both myocytes and the tissue microcirculation. Electron microscopy in canine models shows swollen intraluminal endothelial protrusions and membrane-bound intraluminal bodies that appear to obstruct the capillary lumen.[7] Extravascular swelling from damaged myocytes can also cause mechanical compression of the microcirculation.[7] Once IRA blood flow is restored, there may be sufficient structural damage to the microvasculature to prevent adequate perfusion of cardiac myocytes. These areas of no-reflow are more prominent in the subendocardium.[8] In canine models, no-reflow zones are not visible after 40 minutes of coronary occlusion, but become apparent after 90 minutes, suggesting that a minimum duration of ischemia is necessary for the development of no-reflow.[7] With recanalization of the epicardial artery, these areas of no-reflow become more pronounced with time, as does infarct size when assessed serially at 2, 6, and 48 hours after reperfusion.[9] There is progressive reperfusion injury with platelet and fibrin plugging the microvasculature, endothelial dysfunction from neutrophil infiltration, generation of reactive oxygen species, and activation of the complement system and adhesion molecules.[5] Moreover, distal microembolization of atherosclerotic debris and thrombi after plaque rupture also causes obstruction of the microvasculature. Therefore, microvascular dysfunction after epicardial recanalization is a complex process, likely due to a number of interrelated processes (Figure 1).[5]

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Table 1: TIMI grade flow is a standardized grading system for coronary flow in the epicardial vessel during angiography

TIMI Grade 0	**No perfusion:** No antegrade flow beyond the point of occlusion.
TIMI Grade 1	**Penetration without perfusion:** The contrast material passes beyond the area of obstruction, but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run.
TIMI Grade 2	**Partial reperfusion:** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed are perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the culprit vessel.
TIMI Grade 3	**Complete perfusion:** Antegrade flow into the bed distal to the obstruction occurs as promptly as into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery.

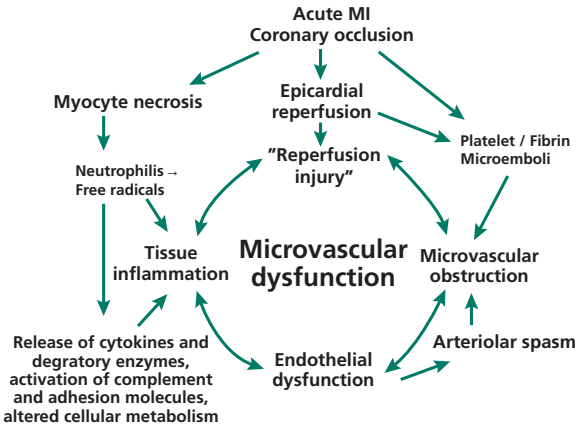
Assessment of myocardial perfusion

As the microcirculation cannot be visualized on coronary angiography, flow at the tissue level must be assessed indirectly. A number of diagnostic modalities are available that can identify impaired perfusion at the myocardial level.

Myocardial contrast echocardiography: Myocardial contrast echocardiography (MCE) was initially performed during angiography by injecting sonicated microbubbles into the IRA to evaluate myocardial contrast enhancement in infarct-zone tissue.[7] Ito demonstrated that in patients with TIMI grade 3 flow in the IRA, recovery of LV function does not occur in those with substantial areas of MCE no-reflow, defined as contrast defects after angioplasty of >25% of the risk-zone determined by MCE prior to recanalization.[10] Intravenous administration of contrast agents have also been studied and found to reliably predict recovery of regional LV function by establishing the presence of viable myocardium with adequate microvascular perfusion in the infarct-related segments.[11]

Coronary Doppler flow wires: Coronary Doppler flow velocity patterns show characteristic profiles in patients with evidence of no-reflow on MCE (Figure 2).[12] In comparison to a normal coronary artery Doppler flow velocity pattern, in which is there is predominantly diastolic antegrade flow down the epicardial artery, no-reflow is characterized by early systolic retrograde flow and high diastolic deceleration rates and

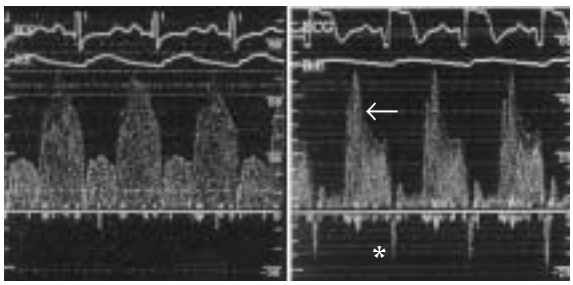
Figure 1: Pathophysiology of microvascular dysfunction after epicardial reperfusion



(Adapted with permission from Roe et al[5])

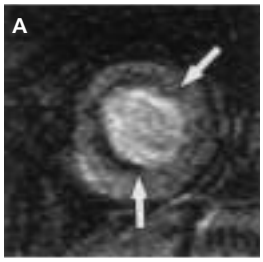
a lower coronary flow reserve.[12] The rapid deceleration of diastolic coronary flow velocity can be explained by capillary obstruction in no-reflow.[6] In normal subjects, the intramyocardial blood capacitance is filled during diastole without an increase in intramural pressure; hence the slope of diastolic deceleration flow velocity is shallow.[6] Capacitance decreases with capillary obstruction. As such, when the coronary inflow exceeds capacitance, there is impedance to inflow in diastole resulting in a rapid decline in coronary flow velocity.[6] Systolic flow reversal can also be explained by capillary obstruction. In normal subjects, as myocardial impedance increases during systole, blood is milked from the intramyocardial venules into the coronary sinus.[6] However, in patients with capillary obstruction, the myocardial blood volume is pushed back into the epicardial coronary artery because it cannot pass the capillary bed to reach the venules resulting in systolic flow reversal within the epicardial artery.[6]

Figure 2: Coronary Doppler flow velocity patterns
A: Normal coronary artery Doppler flow.
B: Doppler flow pattern from an epicardial artery with TIMI 3 flow, but myocardial no-reflow with characteristic rapid deceleration in diastole (arrow) and early systolic retrograde flow (*)



(Adapted with permission from Iwakura et al[12])

Figure 3: Contrast enhanced MRI image from patient with anteroseptal infarct and extensive subendocardial microvascular obstruction seen as regions of hypoenhancement (between arrows)



(Adapted with permission from Wu et al[13])

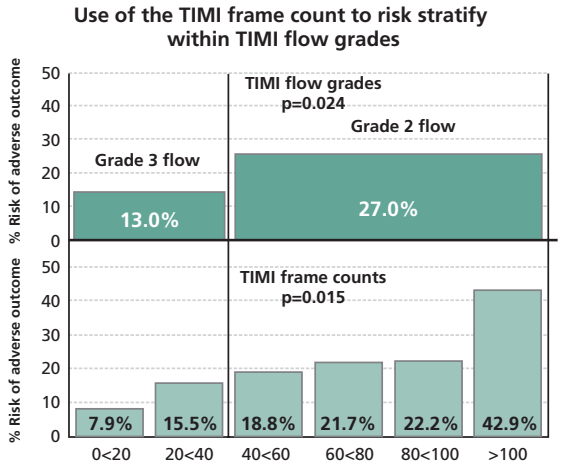
Magnetic resonance imaging (MRI): With contrast enhanced MRI, regions of microvascular obstruction can be visualized as dark, subendothelial zones of hypo-enhancement (Figure 3).[13] Wu and colleagues studied 44 patients post-MI and found that MRI-determined microvascular obstruction is a strong predictor of more frequent cardiovascular complications over 2 years of follow-up, even after correction for infarct size. Thus, cardiac MRI is a promising modality given its potential to assess infarct size, microvascular perfusion, proximal coronary flows, severity, and extent of coronary stenosis, and LV volumes, in addition to regional and global LV function.[5]

TIMI frame count and TIMI myocardial perfusion grade: The corrected TIMI frame count (CTFC) is an angiographic index of epicardial coronary blood flow. It is a count of the number of cine frames required for radiographic contrast to reach standardized distal landmarks on the epicardial artery.[14] Gibson et al examined the CTFC in 1248 patients 90 minutes after fibrinolytic administration.[14] In a multivariate model, the 90-minute CTFC was an independent predictor of in-hospital mortality.[14] Moreover, it identified a subgroup of patients with higher mortality rates despite TIMI grade 3 flow (Figure 4).[14]

In contrast to TIMI flow and CTFC, which assess epicardial artery flow, TIMI myocardial perfusion (TMP) grade flow is a semi-quantitative method that assesses myocardial perfusion angiographically. It assesses the filling and clearance of radiographic contrast from the myocardium, which has a "blush" or ground glass appearance on the coronary angiogram.[15] TMP is graded from "0" (which implies no myocardial perfusion) to TMP grade 3 (which is normal myocardial filling and clearance). The relationship between TMP and mortality was assessed in 762 patients in the TIMI 10B trial.[15] TMP grade flow was a predictor of 30-day mortality post-fibrinolysis that was independent of epicardial artery flow and it also risk-stratified patients with TIMI grade 3 flow into lower and higher risk subgroups (Figure 5).[15]

ST-segment resolution: In canine models of MI, the magnitude of ST-segment elevation correlates well with myocardial necrosis on histological exam. Furthermore, myocardial reperfusion is accompanied by rapid normalization of the ST segments.[16] Multiple studies in patients treated with fibrinolytic therapy have shown a consistent relationship between the degree of ST resolution and subsequent mortality.[16] The absence of ST-segment resolution has a sensitivity and specificity of 77% and 91%, respectively, in predicting microvascular no-reflow based on MCE in patients with TIMI grade 3 flow after primary angioplasty.[17] In patients treated with fibrinolysis, the absence of ST-segment resolution at 90 minutes despite a patent IRA is associated with a significantly worse 30-day mortality.[18] Persistent ST-segment elevation after primary angioplasty despite normal IRA flow has also been correlated with more extensive infarction and worse clinical outcomes, including the rate of cardiac death and recurrent nonfatal MI.[19] Thus, the degree of ST-segment resolution after reperfusion therapy is a reliable non-invasive measure of microvascular perfusion, as well as a predictor of mortality after successful reperfusion.[5]

Figure 4: Risk of death, recurrent MI, shock, congestive heart failure or decreased LV ejection fraction for TIMI flow grades and corrected TIMI frame count (CTFC). Use of CTFC stratifies TIMI grade 3 flow into lower- and higher-risk subgroups: a CTFC 20 carries a risk of adverse outcome of 7.9%, whereas a CTFC >20 to 40 carries a risk of adverse outcome of 15.5% (P=0.17)



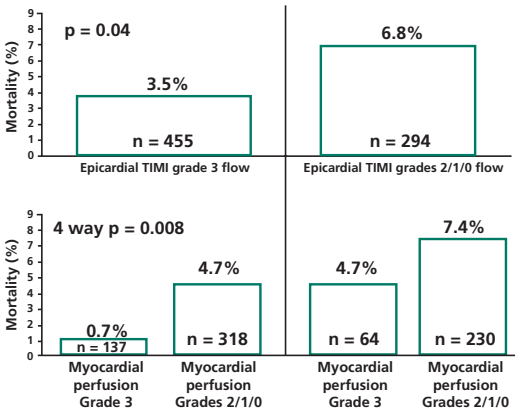
(Adapted with permission from Gibson et al[14])

Prevention and treatment of no-reflow

Given the prognostic implications of microvascular no-reflow, measures to prevent this complication are important. Since no-reflow occurs with more prolonged epicardial artery occlusion, shorter time to reperfusion is critical.

Antiplatelet agents: These agents have potential utility as an adjunctive therapy, given the importance of platelet microemboli and fibrin plugging in the pathogenesis of no-reflow. In patients with TIMI grade 3 flow after primary angioplasty for acute MI, treatment with abciximab improves myocardial

Figure 5: Relationship of both TIMI epicardial flow grade and TMP grade to 30-day mortality. Mortality in patients with epicardial TIMI grade 3 flow (16 [3.5%] of 455 patients) was significantly lower than mortality in patients with TIMI flow 0 to 2 (20 [6.8%] of 294 patients; P=0.04). Among patients with epicardial TIMI grade 3 flow, mortality increased as myocardial perfusion decreased, from 0.73% for TMP grade 3 to 2.9% for TMP grade 2 to 5.0% for TMP grades 0/1 (P=0.03 for TMP grade 3 vs. grades 0 through 2; 3-way P=0.066).



(Adapted with permission from Gibson et al[15])

perfusion as measured by peak flow velocity in the IRA, as well as wall motion index values and global LV function.[20] In patients treated with fibrinolysis in the TIMI 14 trial, combination treatment with abciximab resulted in greater ST-resolution at 90 minutes, reflecting improved myocardial reperfusion.[21] Thus, glycoprotein IIb/IIIa receptor blockers may benefit both pharmacologic and mechanical reperfusion strategies by enhancing myocardial tissue perfusion.

Direct stent implantation: Another strategy to prevent micro-embolization during primary angioplasty is direct stent implantation without balloon predilation. Loubeyre showed the feasibility of this approach in 206 patients with acute MI who were randomized to a direct stent or conventional strategy.[22] There was no significant difference in TIMI grade 3 flow between the groups; however, the direct stent group had a significantly higher rate of ST-segment resolution, indicating improved myocardial tissue perfusion.[22]

Distal protective devices: Mechanical prevention of distal embolization was evaluated in 104 patients during primary angioplasty with the use of the FilterWire, a guidewire that incorporates a nonoccluding polyurethane porous membrane filter.[23] In comparison with a matched control group treated by primary angioplasty alone, patients with this distal protection device had a significant improvement in ST-segment resolution, as well as angiographic myocardial tissue perfusion.[23] Moreover, there was a greater improvement in LV wall motion index and ejection fraction.[23]

The largest trial to date to examine the potential of distal protection devices to enhance microvascular perfusion was the recently completed EMERALD trial.[24] In this trial, 501 patients were randomized within 6 hours of presentation with an acute MI to primary angioplasty alone or to distal protection with the GuardWire Plus system. Although placement of the GuardWire Plus system was feasible and effective in removing atherosclerotic debris and preventing microembolization, it did not translate into any difference in ST-segment resolution, infarct size, or clinical outcomes.

Intracoronary thrombectomy is another mechanical strategy to prevent distal microembolization during primary angioplasty. When 92 patients randomized to thrombectomy or conventional therapy were evaluated, there was greater ST-resolution and improvement in angiographic tissue perfusion in the thrombectomy group.[25]

Pharmacologic agents: Agents that target microvascular dysfunction are potential therapies to improve tissue perfusion when no-reflow occurs. Intracoronary verapamil during primary percutaneous angioplasty enhances tissue perfusion in the infarct region as assessed by MCE before and after verapamil injection.[26] This was associated with a significant improvement in LV wall motion score at 24 days.[26]

Nicorandil – a combination of a nitrate and an adenosine triphosphate-sensitive potassium channel opener – is hypothesized to exert cardioprotective effects after prolonged ischemia.[27] Intravenous administration as an adjunct to primary angioplasty has been shown to result in significant reductions in MCE zones of no-reflow and was associated with improvements in LV function, wall motion score, and regional wall motion.[27] In addition, the incidence of clinical endpoints such as intractable congestive heart failure was lower in the nicorandil group.[27]

Adenosine is an endogenous purine nucleoside that has been shown to reduce post-ischemic ventricular dysfunction and myocyte necrosis and apoptosis in experimental models.[28] Its mechanism of action is potentially through inhibition of free radical formation and neutrophil activation, thereby preventing endothelial damage.[8,29] A number of retrospective studies have shown that intracoronary adenosine reduces the incidence of no-reflow.[8] Marzilli prospectively randomized 54 acute MI patients undergoing primary angioplasty to receive intracoronary adenosine or placebo. Both epicardial blood flow and ventricular function improved and there were significantly fewer clinical events in the adenosine group.[28] The Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial randomized 236 patients

receiving thrombolysis to intravenous adenosine or placebo and showed a 33% reduction in infarct size after 6 days.[29] Despite this, there was no difference in clinical endpoints.[29] These results were confirmed in the larger AMISTAD II trial, in which 2118 patients undergoing fibrinolysis or primary angioplasty were randomized to either low- or high-dose intravenous adenosine or placebo. Although, there was no difference in death or congestive heart failure at 6 months, the high dose adenosine group showed a decrease in infarct size at 5 days.

Complement activation: The role of complement activation in the pathogenesis of microvascular no-reflow was examined by The Complement And ReDuction of INfarct size after Angioplasty or Lytics (CARDINAL) program.[30] This program included 2 phase II trials that tested whether pexelizumab, a monoclonal antibody against C5 complement , reduced infarct size or improved clinical outcomes when used with reperfusion therapy.[30] Pexelizumab was not associated with a smaller infarct size when used as adjuvant therapy with either thrombolysis or primary angioplasty.[30] However, the COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) component of this program showed a significant reduction in 90-day mortality with pexelizumab.[30] These intriguing results suggest an alternative effect of the drug that merits further investigation.

Other cardioprotective manoeuvres that have been studied include hypothermia and glucose-insulin-potassium (GIK) infusions. Although both have protective effects in animal models, neither has been shown to be effective in clinical trials. In the COOLing as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction (COOL-MI) study, 357 patients with acute MI treated with primary angioplasty were randomized to cooling to 33º Celsius using the Reprieve endovascular cooling therapy system. Although feasible and safe, there was no significant effect on infarct size or clinical outcome.[31] The subgroup of patients with anterior MI that were successfully cooled to <35º Celsius did show a statistically significant reduction in infarct size, suggesting that earlier implementation of hypothermia may achieve greater cardio-protection.[31]

GIK infusions prevent reperfusion injury by suppressing free fatty acid levels.[32] In addition, GIK maintains myocardial cell membrane integrity, thereby preventing ischemic cell swelling and subsequent microvascular compression.[32] In the most recent study in acute MI, van de Horst studied 940 patients with an acute MI who were eligible for primary angioplasty, randomly assigned to either a continuous GIK infusion for 8 to 12 h or no infusion. There was no significant improvement in the primary endpoint of 30-day mortality. In the pre-defined subgroup of 856 patients with Killip class 1 symptomatology, there was a statistically significant 28% reduction in mortality.[32] The lack of efficacy in patients with heart failure was hypothesized to be due to the confounding effects of the volume load with the GIK infusion. Nonetheless, the therapeutic application of GIK infusions with reperfusion therapy remains unclear.

Conclusions

Both animal models of coronary artery occlusion and clinical studies have shown evidence of impaired myocardial tissue perfusion despite recanalization of the occluded epicardial artery. Impaired tissue perfusion and no-reflow have adverse prognostic implications. The open artery hypothesis may be an oversimplification as the goals of reperfusion should include not only the rapid and complete restoration of epicardial artery flow, but also of downstream myocardial perfusion. There are a number of promising modalities for detecting impaired tissue perfusion that will be useful complements to angiography in assessing the results of reperfusion therapy. However, effective methods for optimizing myocardial perfusion mechanically or pharmacologically need to be developed and studied in order to further improve outcomes in MI patients.

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This publication is made possible by an educational grant from

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