



Has My Patient Achieved Adequate Myocardial Reperfusion?

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For two decades, the goal of reperfusion has been restoration of normal epicardial blood flow.¹⁻⁴ It has, however, become increasingly apparent that not all TIMI grade 3 flow is created equally, and attention has shifted downstream to the restoration of normal myocardial perfusion to fully optimize clinical outcomes.^{3,4} The goal of this Clinician Update is to provide clinicians with a better understanding of myocardial perfusion in terms of its importance, assessment, and treatment in clinical practice.

Case Presentation

A 59-year-old man presented to the emergency room with 2.5 hours of crushing substernal chest pain. The ECG showed 4 mm of ST-segment elevation in precordial leads V₁ through V₄, which was consistent with the diagnosis of acute anterior myocardial infarction. Primary angioplasty/stenting of a totally occluded left anterior descending artery was performed 90 minutes after presentation to the emergency room, resulting in

restoration of normal Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. The myocardium, however, appeared pale, which is consistent with TIMI myocardial perfusion grade (TMPG) 0 flow³ (Figure, A). Although improved, the patient's ST segments remained elevated. Multiple doses of 100 μ g of intracoronary adenosine were administered through the central lumen of the balloon catheter, resulting in restoration of TMPG 3 flow (Figure, B). After adenosine administration, the corrected TIMI frame count (CTFC)² improved from 50 frames to 35 frames. There was >70% resolution of ST-segment elevation, and the patient was free of chest pain.

Restoration of Normal Epicardial Blood Flow

Although rates of TIMI grade 3 flow approaching 100% after primary percutaneous coronary intervention (PCI) have been reported, these high rates are generally obtained when a "3 cardiac cycles to fill the artery" definition is applied.⁵ When assessed more quan-

titatively and rigorously according to the original TIMI definition, rates of TIMI grade 3 flow may in fact approximate only 80%.⁶ Indeed, at the completion of stenting, the CTFC in the case study patient was 50 frames, which is a rate slower than the cutpoint of <40 frames often observed among patients with TIMI grade 3 flow.² This is consistent with the observation that more than one-third of patients have persistently abnormal CTFCs after stent placement as adjunctive therapy in acute myocardial infarction.⁷ The persistent slowing of epicardial blood flow is not caused by the 13% residual stenosis but rather is more likely related to heightened downstream resistance. Persistent slowing of flow despite relief of stenosis is associated with a rise in mortality rate from 0.8% to 9.7% ($P=0.003$).⁷

Restoration of Normal Myocardial Perfusion

Multiple lines of evidence indicate that impaired tissue perfusion can be present even despite restoration of normal

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Movies showing TIMI myocardial perfusion grades and their associated mortality rates are available in the online-only Data Supplement at <http://www.circulationaha.org>.

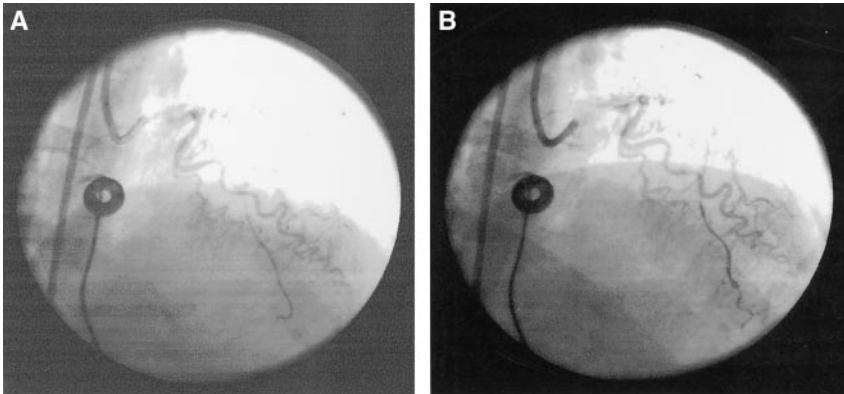
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A, Patent left anterior descending artery after stent placement. Note the pallor of the myocardium (TMPG 0). B, Same patient after administration of intracoronary adenosine. Note that the myocardium fills more darkly with contrast agent (TMPG 3).

epicardial flow. To measure myocardial perfusion angiographically, new measures, such as the TMPG, have been developed.^{3,4} In brief, in TMPG 0, there is 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 is washed out slowly and is strongly persistent at the end of the injection; and in TMPG 3, there is normal entrance and exit of dye through the myocardium, and it is mildly persistent at the end of the injection. Movies showing these TMPGs and their associated mortality rates can be viewed in the online-only Data Supplement.

The importance of normal tissue perfusion in both ST-segment elevation myocardial infarction (STEMI) and unstable angina/non-STEMI (UA/NSTEMI) has gained increasing recognition. In the STEMI setting, the pre-PCI TMPG is a multivariate predictor of 2-year mortality.^{3,4} Indeed, among patients with restoration of normal epicardial TIMI grade 3 flow, there is a 7-fold gradient in mortality (from 0.7% to 5.4%) if normal tissue perfusion has not been restored.³ Likewise, in the setting of UA/NSTEMI, TMPG 0/1 on diagnostic cardiac catheterization is associated with troponin elevations. Persistence after PCI is associated with post-PCI creatine kinase release and a higher risk of death or

myocardial infarction at 6 months and at 1 year.^{8–10} Taken together, these findings suggest a pathophysiological link among impaired tissue level perfusion, the release of cardiac markers, and adverse clinical outcomes in a variety of settings.

Another related method for assessing tissue perfusion is myocardial contrast echocardiography,¹⁰ which has a demonstrated association with TMPG. To characterize the kinetics of dye entering the myocardium more quantitatively, digital subtraction angiography has been used to estimate the rate of rise in brightness (gray per second) and the rate of growth of blush (centimeters per second). Digital subtraction angiography techniques have shown that glycoprotein IIb/IIIa inhibition is associated with more rapid filling of the myocardium in the setting of unstable angina.¹¹

The ECG is another useful clinical marker of tissue perfusion. Greater ST resolution on the static and the continuous ECG correlate with TIMI grade 3 flow, TMPG 3, smaller infarct sizes, and improved survival.^{12–15} Restoration of TMPG 3 is associated with higher rates of complete ST resolution on the static ECG and doubles the rapidity of achieving the time to stable ST-segment resolution.¹⁵ Although the ECG and the blush rate are associated, they provide independent prognostic information about infarct size.¹⁶ This

electrical-mechanical dissociation is apparent to the interventional cardiologist who has restored epicardial blood flow only to observe persistent ST-segment elevation.

Agents requiring an intact endothelium, such as nitroglycerin, may not be helpful in instances in which profound damage has already been sustained by the microvasculature. For example, clinical symptoms, ECG, CTFC, and TMPG all improved in our case presentation patient after intracoronary adenosine administration. It has been my experience that TMPG 0 may improve to TMPG 3 with the aggressive use of vasodilators, but stains of the myocardium (TMPG 1), which may reflect dye extravasation, may be refractory to therapy. Other agents such as verapamil, diltiazem, nicardipine, and nitroprusside are also used clinically to improve epicardial flow and by inference myocardial perfusion (Table).^{17–21} Data from Gregorini and colleagues²¹ suggest that heightened α -adrenergic tone after stent placement may play a role in mediating flow delays and may therefore be a pharmacological target for treatment.²¹

Randomized trial data are sparse with regard to the efficacy of these agents in improving myocardial perfusion. In one relatively small trial, intracoronary adenosine at relatively high doses (100 μ g during each intracoronary injection) was administered via the central lumen of an inflated balloon up to a total dose of 4000 μ g. Administration via the guiding catheter may not achieve adequate dosing because of reflux of drug into the aorta. Because transient bradycardia can occur, consideration should be given to the prophylactic placement of a temporary pacemaker in large inferior myocardial infarctions. Administration of high-dose intracoronary adenosine in this trial was associated with improved echocardiographic and clinical outcomes.¹⁷ In the randomized VAPOR (VAsodilator Prevention Of no-Reflow) trial, intragraft verapamil (200 μ g IC) was associated with a



Agents Used to Treat Impaired Myocardial Perfusion*

	Dose	Side Effects
Adenosine	100 μ g IC to a total dose of 4000 μ g Half-life is 6 seconds. Adenosine can be repeatedly administered when pulse and blood pressure normalize	Bradycardia, hypotension, difficulty breathing
Verapamil	200 μ g IC as a single dose to a total of 1000 μ g (1 mg)	Bradycardia, hypotension
Diltiazem	200 μ g IC as a single dose to a total dose of 1000 μ g (1 mg) IC	Bradycardia, hypotension
Nicardipine	200 μ g IC as a single dose to a total dose of 1000 μ g (1 mg) IC	Lower incidence of bradycardia, hypotension with this vasoselective agent
Nitroprusside†	100 μ g IC as a single dose to a total dose of 1000 μ g (1 mg) IC	Lower incidence of bradycardia, hypotension

*Administration of these agents is not listed as an approved indication in the package insert (ie, off-label use).

†Median dose was 200 μ g IC in the Hillegass study.²⁰

reduction in no-reflow during saphenous vein graft PCI. Verapamil administration, however, may be associated with a decline in contractility and bradycardia.¹⁸ Among patients with minimal coronary artery disease, use of intracoronary nicardipine has been associated with lower rates of hypotension and bradycardia than use of diltiazem or verapamil, but randomized data in the no-reflow setting are lacking.¹⁹ Intracoronary nitroprusside administration at a median dose of 200 μ g produces improved CTFCs among patients with no-reflow and may also be associated with a lower incidence of hypotension and bradycardia.²⁰ When one of the above agents fails to produce satisfactory results, an alternative agent may be effective. Randomized clinical trials of antiinflammatory agents, complement-activation inhibitors, adhesion molecule antibodies, and glucose/insulin/potassium therapy have all yielded insignificant results to date.

Conclusion

This case demonstrates that despite restoration of epicardial flow, myocardial perfusion can remain impaired on both the angiogram and the ECG. Agents directed at the microvasculature are likely to play a critical role in achieving not only epicardial but also myocardial reperfusion. Although several therapeutic agents are available in

this setting, further prospective randomized trials are needed to compare their efficacy.

References

1. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. *N Engl J Med*. 1985;312:932–936.
2. Gibson CM, Cannon CP, Daley WL, et al. The TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*. 1996;93:879–888.
3. Gibson CM, Cannon CP, Murphy SA, et al, for the TIMI 10B Investigators. Relationship of TIMI myocardial perfusion grade to mortality following thrombolytic administration. *Circulation*. 2000;101:125–130.
4. Gibson CM, Cannon CP, Murphy SA, et al, for the TIMI Study Group. Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation*. 2002;105:1909–1913.
5. Gibson CM, Ryan K, Sparano A, et al, for the TIMI Study Group. Methodologic drift in the assessment of TIMI grade 3 flow and its implications with respect to the reporting of angiographic trial results. *Am Heart J*. 1999;137:1179–1184.
6. Gibson CM, Murphy SA, Menown I, et al, for the TIMI Study Group. Determinants of coronary blood flow following thrombolytic administration. *J Am Coll Cardiol*. 1999;34:1403–1412.
7. Wong GC, Kraimer N, Pai R, et al, for the TACTICS-TIMI 18 Study Group. Elevations in troponin T are associated with abnormal tissue level perfusion: a TACTICS-TIMI 18 substudy. *Circulation*. 2002;106:202–207.
8. Gibson CM, Murphy SA, Hynes C, et al, for the ESPRIT study group. Relationship of CK-MB release to TIMI myocardial perfusion grade following intracoronary stent placement: an ESPRIT substudy. *Am Heart J*. 2002;143:106–110.
9. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis: a predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation*. 1992;85:1699–1705.
10. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the no reflow phenomenon: a predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation*. 1996;93:223–228.
11. Gibson CM, Cohen D, Cohen E, et al, for the ESPRIT study Group. Treatment with eptifibatid and coronary flow reserve (CFR) following elective stent placement: an ESPRIT substudy. *Am J Cardiol*. 2001;87:1293–1295.
12. Schroder R, Dissmann R, Bruggemann T, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol*. 1994;24:384–391.
13. van't Hof AWJ, Liem A, de Boer M-J, et al. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. *Lancet*. 1997;350:615–619.
14. Krucoff MW, Croll MA, Pope JE, et al. Continuous 12-lead ST-segment recovery analysis in the TAMI 7 study: performance of a noninvasive method for real-time detection of failed myocardial reperfusion. *Circulation*. 1993;88:437–446.
15. Gibson CM, Giugliano RP, Roe MT, et al. Impaired TIMI epicardial flow and myocardial perfusion grades are associated with increased time to ST segment recovery in ST segment elevation MI: an INTEGRITI substudy. *Circulation*. 2002;106(suppl II):II-598.
16. Angeja BG, Gunda M, Murphy SA, et al. TIMI myocardial perfusion grade and ST segment resolution: association with infarct size as assessed by single photon emission computed tomography imaging. *Circulation*. 2002;105:282–285.



17. Marzilli M, Orsini E, Marraccini P, et al. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation*. 2000; 101:2154–2159.
18. Michaels AM, Appleby M, Dauterman K, et al. Pretreatment with intragraft verapamil prior to percutaneous coronary intervention of saphenous vein graft lesions: results of the randomized, controlled vasodilator prevention of no-reflow (VAPOR) trial. *J Invasive Cardiol*. 2002;14:299–302.
19. Fugit MD, Rubal BJ, Donovan DJ. Effects of intracoronary nicardipine, diltiazem and verapamil on coronary blood flow. *J Invasive Cardiol*. 2000;12:80–85.
20. Hillegass WB, Dean NA, Liao L, et al. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. *J Am Coll Cardiol*. 2001;37:1335–1343.
21. Gregorini L, Marco J, Farah B, et al. Effects of selective alpha1- and alpha2-adrenergic blockade on coronary flow reserve after coronary stenting. *Circulation*. 2002 3;106: 2901–2907.