

Coronary and Myocardial Angiography

Angiographic Assessment of Both Epicardial and Myocardial Perfusion

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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 2 decades.^{1–8} It has become increasingly apparent, however, that clinical outcomes are not only associated with angiographic flow in the epicardial artery, but also with angiographic flow in the myocardium.^{9–13} To this end, the goal of reperfusion therapies has shifted to include reperfusion downstream at the level of capillary bed, and it might be more appropriate that the hypothesis now be termed “the time dependent open artery and open microvascular hypothesis.” The goal of this article is to review angiographic methods used to evaluate myocardial ischemia and infarction and to discuss the insights into the pathophysiology of acute coronary syndromes provided by these angiographic indexes of coronary artery blood flow and myocardial perfusion.

TIMI Flow Grades (TFGs)

For nearly 2 decades now, the Thrombolysis In Myocardial Infarction (TIMI) flow grade classification scheme has been successfully used to assess coronary blood flow in acute coronary syndromes¹ (Table). It has been a valuable tool to compare angiographic outcomes following reperfusion, and the association of the TFGs with clinical outcomes (including mortality) has been well documented.^{2–8} The relationship between TFG and mortality does satisfy what some consider to be 3 criteria required to validate a surrogate end point for mortality, as follows: (1) There is an association between TIMI grade 3 flow and mortality, (2) an agent such as recombinant tissue plasminogen activator improves TIMI grade 3 flow by 22% over another agent such as streptokinase, and (3) the agent tissue plasminogen activator improves mortality 1.1% over streptokinase.

On the basis of this relationship between TIMI flow and mortality observed in the GUSTO I [Global Utilization of Streptokinase and Tissue plasminogen activator (alteplase) for Occluded coronary arteries] angiographic trial, it was anticipated that an additional 20% improvement in TIMI 3 flow would be required to further improve mortality by another 1%. The disparity between the early results of trials evaluating combination therapy [low-dose fibrinolysis combined with full-dose glycoprotein IIb IIIa (GP IIb/IIIa) inhi-

bition] and the lack of mortality benefit in subsequent large-scale clinical trials has raised questions regarding the relationship between improvements in TIMI grade 3 flow and clinical outcomes. Despite the initial optimism of early dose-escalation trials involving low-dose fibrinolytic combined with full-dose GP IIb/IIIa inhibition, later results in blinded parallel dose-confirmation phases yielded a modest 8% average improvement in TIMI grade 3 flow at 60 minutes and an even more modest 4% improvement at 90 minutes among 948 patients studied (Figure 1). On the basis of approximately a 6% improvement in early TIMI grade 3 flow, a 0.3% improvement in mortality in a large-scale mortality trial might be expected (6% observed TFG 3 improvement/20% required TFG 3 improvement for 1% mortality reduction = 0.3%). The results of GUSTO V are in keeping with this modest estimated reduction with mortality rates of 5.9% and 5.6% ($n=16\,588$, $P=NS$).¹⁴

Care must be taken when extrapolating the results of angiographic patency studies to estimate potential clinical benefits. For example, the association of TIMI grade 3 flow with mortality is confounded by the fact that the majority of TIMI grade 2 flow is observed in the left anterior descending artery (LAD) territory, whereas the majority of TIMI grade 3 flow is observed in the right coronary artery (RCA).⁷ Thus, improved outcomes among patients with TIMI grade 3 flow are explained at least in part by the fact that inferior myocardial infarction (MI) location is associated with a lower mortality rate.⁷ Use of a more precise angiographic measure such as the TIMI frame count does support the notion that improved epicardial flow is associated with improved clinical outcomes; however, the magnitude of the clinical improvement associated with TIMI grade 3 flow may have been overestimated and may be nonlinear. Greater clinical benefits may be observed if a closed artery (TIMI grade 0/1 flow) is opened (TIMI grade 2 flow) compared with the magnitude of improvement that might occur if an artery with TIMI grade 2 flow is converted to TIMI grade 3 flow. As more arteries with TIMI grade 2 flow are treated with adjunctive percutaneous coronary intervention (PCI), the prognosis associated with this flow grade may improve. Indeed, 2-year mortality in more recent analyses indicates that the survival advantage of TIMI grade 3 flow over TIMI grade 2 flow at 2 years may not be as great as it once was in the era before aggressive utilization of rescue and adjunctive (PCI).¹⁰

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Definitions of the TFG and the TMPG Systems

Grade	Characteristics
TFG, a grading system for epicardial coronary flow	
0	No perfusion; no antegrade flow beyond the point of occlusion
1	Penetration without perfusion; the contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run
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 is perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the culprit vessel (eg, the opposite coronary artery or coronary bed proximal to the obstruction)
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
TMPG, a grading system for myocardial perfusion	
0	Dye fails to enter the microvasculature; there is either minimal or no ground glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit artery indicating lack of tissue level perfusion
1	Dye slowly enters but fails to exit the microvasculature; there is the ground glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately 30 seconds between injections)
2	Delayed entry and exit of dye from the microvasculature; there is the ground glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (ie, dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not diminish or only minimally diminishes in intensity during washout)
3	Normal entry and exit of dye from the microvasculature; there is the ground glass appearance (“blush”) or opacification of the myocardium in the distribution of the culprit lesion that clears normally, and it is either gone or only mildly/moderately persistent at the end of the washout phase (ie, dye is gone or is mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery; blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3

Indeed, one of the benefits of rescue and adjunctive PCI following fibrinolytic administration may be to reduce reocclusion. The benefit of achieving early patency is greatly reduced if it is not sustained as a result of reocclusion. Reinfarction is associated with a doubling in mortality, which is due to an early divergence in mortality by 30 days.^{15,16} Although early randomized trials failed to demonstrate a benefit in the performance of conventional angioplasty soon after fibrinolytic administration, these trials preceded the use

of stents, thienopyridines, platelet GP IIb/IIIa inhibitors, and the monitoring of activated clotting times. Among 20 101 patients enrolled in recent TIMI trials, performance of PCI during the index hospitalization was associated with a lower rate of in-hospital recurrent MI (1.6% versus 4.5%, $P < 0.001$) and lower 2-year mortality (5.6% versus 11.6%, $P < 0.001$).¹⁶ The rates of PCI were low ($\approx 10\%$) in GUSTO V, and this may account for the modest benefits observed among patients treated with combination therapy. Somewhat paradoxically,

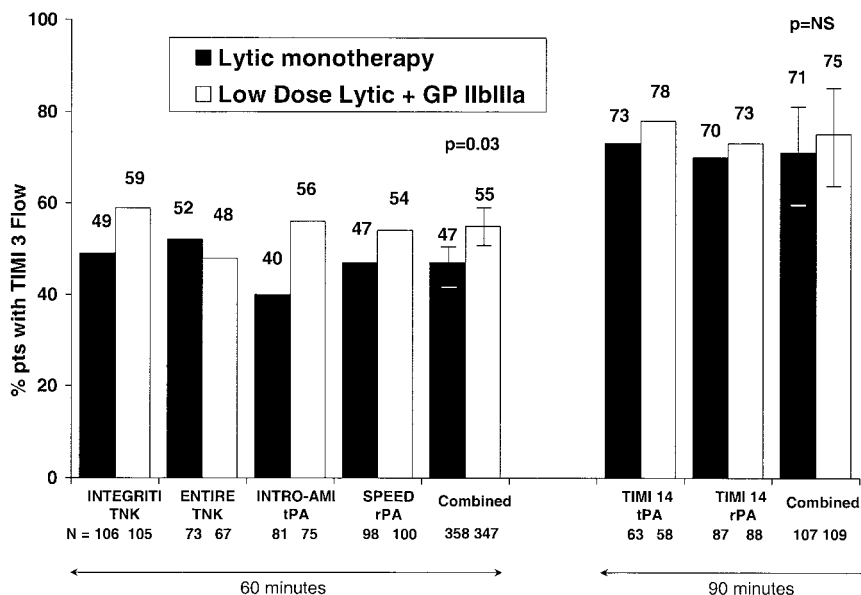


Figure 1. Despite initial optimism after early reports of dose-escalation trials involving low-dose fibrinolytic combined with full-dose GP IIb/IIIa inhibition, later results in blinded parallel dose-confirmation phases yielded a modest 8% average improvement in TIMI grade 3 flow at 60 minutes and an even more modest 4% improvement at 90 minutes among 948 patients studied. TNK indicates tenecteplase.

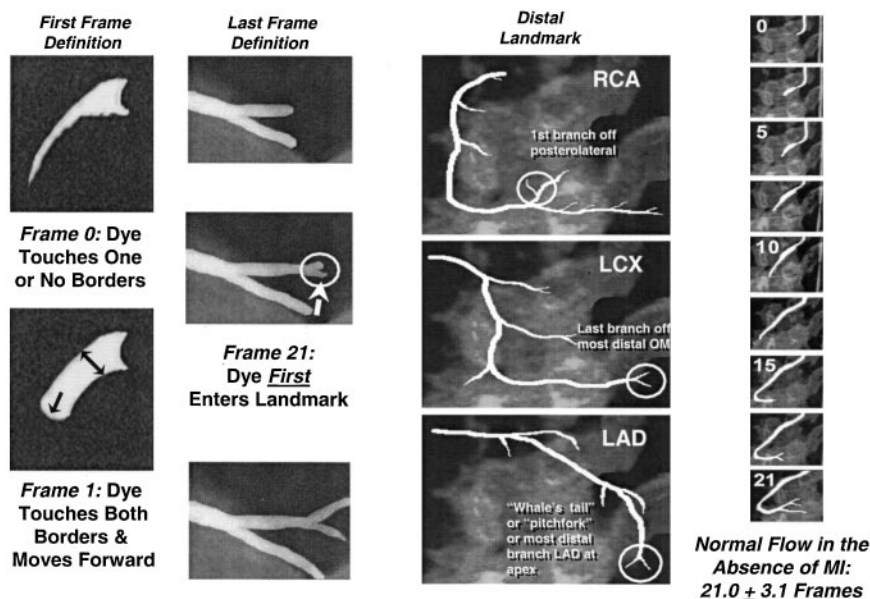


Figure 2. TIMI frame-counting method. In the first frame (lower left panel), a column of near or fully concentrated dye touches both borders of the coronary artery and moves forward. In the last frame (second column), dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery. These standard distal landmarks are as follows: the first branch of the posterolateral artery in the RCA (third column, top panel); in the circumflex system, the most distal branch of the obtuse marginal branch that includes the culprit lesion in the dye path (third column, middle panel); and in the LAD the distal bifurcation, which is also known as the moustache, pitchfork, or whale's tail (third column, bottom panel). Adapted from Gibson et al.⁷

although one of the benefits of combination therapy was touted to be a reduction in “urgent revascularization,” if such revascularization is actually beneficial by virtue of stabilizing the lesion and reducing the risk of reocclusion, then clinical outcomes may in fact be worse if a more successful pharmacological strategy lowers the rate of urgent revascularization.¹⁷ It should also be noted that while these angiographic measures are indexes of flow, and although they are associated with the risk of reocclusion,¹⁸ other nonangiographic processes may also underlie the pathophysiology of reocclusion as well as other clinical outcomes.

Although poorer TFGs and poorer clinical outcomes are clearly associated, the directionality of any causal relationship between the two has not been unequivocally demonstrated. For instance, it is not clear whether slower blood flow causes larger MIs or alternatively whether larger MIs cause slower blood flow as a result of greater edema or microvascular disruption in the myocardium. Furthermore, cessation of coronary blood flow in acute MI does not explain all deaths, as there are other pathophysiological mechanisms by which patients may die in acute MI, such as intracranial hemorrhage. Finally, as discussed below, successful restoration of epicardial patency in the absence of successful myocardial perfusion may not confer large clinical benefits.

The Corrected TIMI Frame Count: A Measure of the Time for Dye to Go Down the Artery

Although the TFG classification scheme has been a valuable tool for comparing the efficacy of reperfusion strategies and in the identification of patients at higher risk for adverse outcomes in acute coronary syndromes, there are limitations to this classification scheme.⁷ To overcome these limitations, one of us (C.M.G.) developed a new, more objective and precise index of coronary blood flow called the corrected TIMI frame count (CTFC), in which the number of cine-

frames required for dye to reach standardized distal landmarks are counted; this is essentially a measure of the time for dye to go down the artery.^{7,8,10}

In the first frame used for TIMI frame counting, a column of dye touches both borders of the coronary artery and moves forward (Figure 2).⁷ In the last frame, dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery (Figure 2). These standard distal landmarks are as follows: in the RCA, the first branch of the posterolateral artery; in the circumflex system, the most distal branch of the obtuse marginal branch, which includes the culprit lesion in the dye path; and in the LAD, the distal bifurcation, which is also known as the “moustache,” “pitchfork” or “whale’s tail” (Figure 2). These frame counts are corrected for the longer length of the LAD by dividing by 1.7 to arrive at the CTFC.⁷ Knowing the time for dye to go down the artery from the CTFC ($CTFC/30$ =seconds), and length of the artery (either from an angioplasty guide wire or by planimetry), dye velocity (cm/s) can also be calculated in a more refined fashion.¹⁹ This refined measure allows calculation of the velocity proximal and distal to the lesion.¹⁹

In contrast to the conventional TFG classification scheme, the CTFC is quantitative rather than qualitative, it is objective rather than subjective, it is a continuous rather than a categorical variable, and it is reproducible.⁷ Using the CTFC, coronary blood flow is unimodally distributed as a continuous variable.⁷ Thus, any division of flow into normal and abnormal categories is somewhat arbitrary. It should be noted that if an epicardial artery is occluded, then a frame count of 100 is imputed. This value of 100 lies near the 99th percentile for frame counts among open arteries in the ST-elevation MI (STEMI) setting. If values are imputed for closed arteries, then nonparametric analyses (eg, Wilcoxon rank sum tests) should be utilized because the dataset often follows a nonparametric distribution.

In multiple studies, the CTFC has been shown to be quite reproducible with a 1- to 2-frame difference between observ-

ers.^{20–32} Similarly, 2 experienced angiographic core laboratories (GUSTO and TIMI) have analyzed the same films from a fibrinolytic trial with discrepancies in 21% of TFG readings (41/194, Kappa=0.76); however, excellent concordance in trial results were seen using the CTFC (overall median difference=0 frames).³² The CTFC is also accurate in that it is highly correlated with Doppler velocity wire measure of coronary flow reserve, distal velocity, average peak velocity, and volumetric flow,^{21–23} as well as fractional flow reserve ($r=0.85$).²⁴

Technical Factors Influencing the CTFC

Normally 21 frames are required for dye to traverse the human coronary artery.⁷ Despite differences in the length of the coronary arteries, the force of injections, the diameter of the arteries, heart rates, cardiac output, and catheter engagement, there is only a 3.1-frame standard deviation among patients with normal flow, and the 95% confidence interval for normal flow extends from >14 frames to <28 frames.⁷ Faster than normal or hyperemic flow is therefore defined as a CTFC <14 frames and constitutes what we now term “TIMI grade 4 flow.”⁷ Although the CTFC is not used to determine the TFGs, in a retrospective analysis, the TIMI Angiographic Core Laboratory tended to classify flow as TIMI grade 2 flow if the CTFC was >40 (≈ 1.3 seconds).⁷

A variety of technical and physiological variables impact the CTFC.^{20,33–36} Use of a power injector to change the force of injection (cc/sec) from the 10th to the 90th percentile of human injection rates lowers the CTFC by only 2 frames,³³ nitrate administration significantly increases the CTFC by ≈ 6 frames ($P<0.001$),²⁰ dye injection at the beginning of diastole significantly decreases the CTFC by 3 to 6 frames,²⁰ and increasing the heart rate by 20 bpm significantly decreases the CTFC by ≈ 5 frames ($P<0.001$).²⁰ It is for this reason that administration of nitrates is often standardized in trials assessing the CTFC as an end point. The mechanical force of injection alone in a closed artery following fibrinolytic therapy will open $\approx 10\%$ of closed arteries,³⁴ but the dye type used for injection is not associated with changes in the CTFC.³⁵

Relation of the CTFC to Clinical Outcomes

The CTFC following fibrinolytic administration is related to a variety of clinical outcomes.^{7,8,10,25–30} Flow in the infarct-related artery in survivors is significantly faster than in patients who die (49.5 versus 69.6 frames; $P=0.0003$).⁸ Mortality increases by 0.7% for every 10-frame rise in CTFC ($P<0.001$).⁸ None of the patients in the TIMI studies who have had a CTFC <14 (hyperemic or TIMI grade 4 flow) died by 30 days.⁸ Likewise, in patients with unstable angina (UA) or non-ST-elevation MI (NSTEMI), the post-PCI culprit flow among survivors is significantly faster than among those patients who died (CTFCs 20.4 versus 33.4 frames, $P=0.017$).³⁷ Again, none of the 376 patients with a CTFC <14 following PCI died, underscoring the fact that, even within the subgroup of patients with “normal flow,” there may be further subgroups with even better flow and even better mortality.³⁷ Multiple studies have now documented an association between the CTFC and clinical out-

comes among patients treated with primary PCI also, and the CTFC has demonstrated greater sensitivity in detecting improvements in epicardial flow compared with the use of TIMI grade 3 flow among patients treated with new device interventions.^{38–42}

With respect to other end points, the CTFC has also been related to a lower rate of restenosis, even when postprocedure diameters were corrected for.³⁷ Thus, not only is “bigger better,” but “faster is better” also.³⁷ Stankovic et al²² have built on these observations further by dividing the CTFC by the minimum lumen diameter to demonstrate that this measure, which integrates both anatomic and functional flow data, is the strongest predictor of restenosis in their study, and we have demonstrated that the ratio is associated with post-PCI death or MI.³⁷ Slower CTFCs on surveillance angiography are also associated with higher rates of transplant rejection.⁴³

Insights Into the Pathophysiology of STEMI and UA/NSTEMI Based on the CTFC

Until recently, it was assumed that flow in nonculprit arteries in the setting of acute coronary syndromes was “normal.” However, the CTFC in uninvolved arteries in acute STEMI (30.5 frames) is in fact 40% slower than normal (21 frames, $P<0.001$).^{7,44–46} In the setting of STEMI, adjunctive and rescue PCI restores flow in culprit vessels that is nearly identical to that of nonculprit arteries in the setting of acute MI (30.5 versus 30.5 frames, $p=NS$),⁴⁴ but this flow remains slower than normal. PCI of the culprit lesion is also associated with improvements in the nonculprit artery after the intervention in both the STEMI and UA/NSTEMI settings.^{44,45} If abnormal flow was present in the nonculprit artery at baseline (ie, CTFC >28), then the improvements in nonculprit flow were more dramatic (10 frames).⁴⁴ It is notable that slower flow throughout all 3 arteries in STEMI is associated with a higher risk of adverse outcomes,⁴⁴ poorer wall motion in remote territories,⁴⁴ poorer tissue perfusion on digital subtraction angiography (DSA),⁴⁵ and a greater magnitude of ST depression in remote territories such as the anterior precordium in inferior MI.⁴⁷ It could be speculated that the poorer flow in nonculprit arteries may be the result of more extensive necrosis in shared microvasculature, or a result of vasoconstriction mediated through either a local neurohumoral or paracrine mechanism. Indeed, Gregorini et al⁴⁸ have demonstrated that the CTFC and fractional wall shortening is improved in both the culprit and nonculprit arteries after administration of α -blockers, indicating that “ α -adrenergic storm” may play a role. Finally, Willerson and others^{49–55} have demonstrated over the past 2 decades that a wide range of vasoconstrictors including thromboxane A₂, serotonin, endothelin, oxygen-derived free radicals, and thrombin are all released in the setting of vessel injury and thrombosis.

It has long been assumed that the residual stenosis in the setting of STEMI is largely responsible for the delay in flow. However, despite a 13% residual diameter stenosis and the relief of intraluminal obstruction that would be anticipated after stent placement, flow remains persistently delayed to 26 frames poststent, and likewise 34% of stented vessels remain

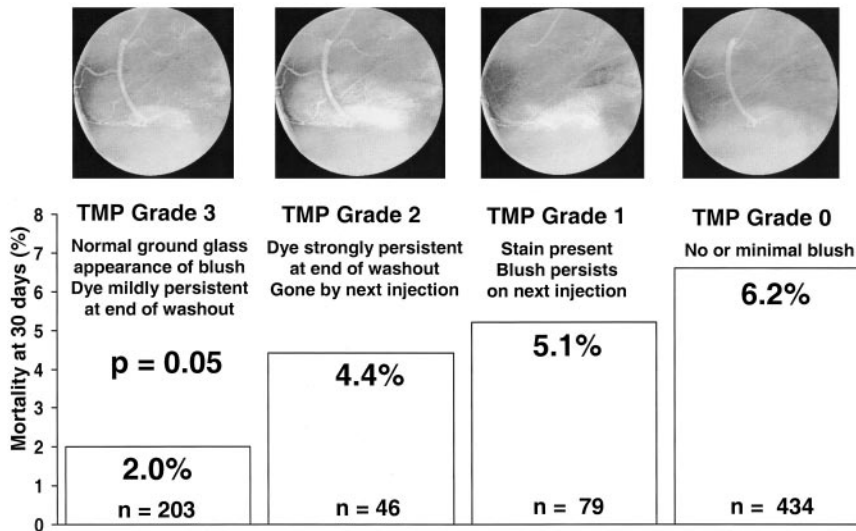


Figure 4. The TMPG assesses tissue-level perfusion using the angiogram and is a multivariate predictor of mortality in acute MI. The TMPG permits risk stratification even within epicardial TIMI grade 3 flow. Despite achieving epicardial patency with normal TIMI grade 3 flow, those patients whose microvasculature fails to open (TMPG 0/1) have a persistently elevated mortality of 5.4% at 30 days. In contrast, those patients with both TIMI grade 3 flow in the epicardial artery and TMPG 3 have a mortality under 1% [0.7% [1/137] vs 4.7% [15/318]; $P=0.05$ using Fisher's exact test for TMPG 3 vs grades 0, 1, and 2). Adapted from Gibson et al.⁹

demonstrated, restoration of TMPG 2/3 is associated with a higher salvage index (0.49 ± 0.42 versus 0.34 ± 0.49 , $P=0.01$) and a smaller final infarct size ($15.4 \pm 15.5\%$ versus $22.1 \pm 16.2\%$ of the left ventricle, $P=0.001$). Indeed, second only to stent placement, restoration of TMPG 2/3 was the next most powerful independent determinant of the myocardial salvage index, and was more closely associated with higher salvage indexes than the TFGs.⁶⁰

The association between a prolonged duration of symptoms before treatment in ST-elevation MI with poorer clinical and angiographic outcomes has led to the phrase "time is myocardium." Indeed, the angiographic data do now provide mechanistic data to support this common notion. The association between increased time from symptom onset to treatment, worsened myocardial perfusion, and increased mortality rate has been demonstrated both in patients treated with fibrinolytic therapy⁶¹ and in those treated with primary angioplasty.^{62,63} Impaired myocardial perfusion on the angiogram has in turn been associated with greater left ventricular end-diastolic pressure⁶⁴ and the presence of overt congestive heart failure on presentation.⁶⁵ Among patients presenting with cardiogenic shock, a restoration of normal myocardial perfusion is associated with improved survival.⁶⁶

There are data associating abnormal myocardial perfusion on the angiogram with slower Doppler velocity measurements in the epicardial artery.⁶⁷ Does abnormal myocardial perfusion slow epicardial flow, or, alternatively, does abnormal epicardial flow impair myocardial perfusion? Although there is likely a bidirectional nature to any causal relationship between the two, after restoration of full epicardial patency (eg, after the scaffolding of the lesion by intracoronary stent placement), it is likely that impaired myocardial perfusion may play a major role in reducing antegrade flow in the epicardial artery. A variety of drugs are available to treat abnormal myocardial perfusion, but aside from adenosine, their association with improved clinical outcomes remains largely untested.⁶⁸

Association of Electrocardiographic Findings With Angiographic Findings in STEMI

The ECG (ST resolution) and the angiogram provide insight into myocardial perfusion. It is notable that both the ST segment resolution and the TMPG provide independent prognostic information with respect to SPECT infarct size.¹¹ Likewise, with respect to clinical outcomes, 2 additional studies have now documented the complementary prognostic information provided by the ECG (degree of ST resolution) and the angiographic blush, with failure to achieve ST resolution and a closed myocardium on angiography following primary PCI carrying a particularly poor prognosis.^{59,69} 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 electrocardiogram may reflect the functional status of the supplied myocardium.¹¹ Measures of both processes appear to be independent and complementary in their prognostic significance. Finally, restoration of normal (TMPG 3) myocardial perfusion is not only associated with complete ST resolution, but it is also associated with earlier ST resolution on continuous ST-segment monitoring.⁷⁰

Similar to what has been observed in the STEMI setting, in the setting of UA/NSTEMI, independent of epicardial blood flow, pre-PCI TMPG 0/1 flow is associated with troponin T and I elevations, and if TMPG 0/1 persists after PCI, the risk of death or MI at 6 months is increased.⁷¹ With respect to the other marker of myonecrosis, creatine kinase (CK)-MB, TMPG 0/1/2 perfusion following PCI in the setting of UA/NSTEMI is associated with a nearly 10-fold rise in the risk of CK-MB elevations (41% versus 4%, $P=0.002$), as well as a higher risk of adverse clinical outcomes at 1 year (32% versus 4%, $P=0.01$).⁷² Taken together, these findings suggest a pathophysiological link between impaired tissue level perfusion, the release of cardiac markers (both before and after PCI), and adverse clinical outcomes in a variety of settings.

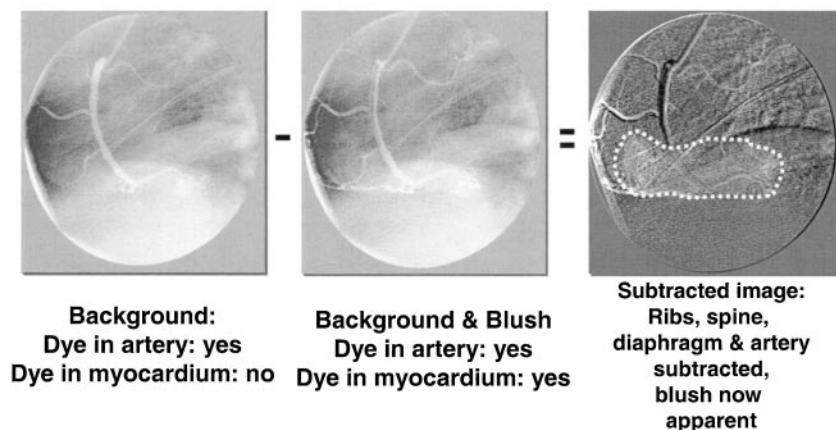


Figure 5. DSA was developed to quantitatively characterize the kinetics of dye entering the myocardium using the angiogram. DSA is performed at end diastole by aligning cineframe images before dye fills the myocardium with those at the peak of myocardial filling to subtract spine, ribs, diaphragm, and epicardial artery. A representative region of the myocardium is sampled that is free of overlap by epicardial arterial branches to determine the increase in the Gray-scale brightness of the myocardium when it first reached its peak intensity. The circumference of the myocardial blush is measured using a handheld planimeter. The number of frames required for the myocardium to first reach its peak brightness is converted into time (seconds) by

dividing the frame count by 30. In this way, the rate of rise in brightness (Gy/sec) and the rate of growth of blush (cm/sec) can be calculated.

To quantitatively characterize the kinetics of dye entering the myocardium using the angiogram, DSA has been utilized. DSA is performed at end diastole by aligning cineframe images before dye fills the myocardium with those at the peak of myocardial filling to subtract spine, ribs, diaphragm, and epicardial artery (Figure 5). A representative region of the myocardium is sampled that is free of overlap by epicardial arterial branches to determine the increase in the Gray-scale brightness of the myocardium when it first reached its peak intensity. The circumference of the myocardial blush is measured using a handheld planimeter. The number of frames required for the myocardium to first reach its peak brightness is converted into time (seconds) by dividing the frame count by 30. In this way, the rate of rise in brightness (Gy/sec) and the rate of growth of blush (cm/sec) can be calculated.⁷³ DSA has demonstrated that despite the placement of a stent and the achievement of TIMI grade 3 epicardial flow among patients in the setting of UA/NSTEMI, addition of the GP IIb/IIIa inhibitor eptifibatid increases the Gy/sec and the cm/sec at which dye enters the muscle.⁷⁴ DSA has also been utilized to document the decrease in the size and brightness of both culprit and nonculprit myocardial perfusion in the STEMI setting compared with normal.⁷⁵

Although the time to fill the epicardial artery has been well characterized in both STEMI and UA/NSTEMI using the CTFC, differences between the syndromes in the time for contrast material to fill the myocardium have now been investigated. A new angiographic measure, the TIMI myocardial frame count (the number of frames from when dye first enters the muscle until it first reaches peak intensity) allows quantitative comparisons of angiographic tissue perfusion. The time for contrast material to fill the myocardium is slower in the setting of STEMI compared with UA/NSTEMI, even after adjusting for other variables known to delay contrast material inflow in the epicardial artery.⁷⁶ It could be speculated that this phenomenon could be due to a greater degree of edema, spasm, or microembolization in the STEMI setting.

Integrating the Assessment of Epicardial and Myocardial Perfusion

There is the need for a simple, broadly applicable angiographic metric that takes into account indices of epicardial and myocardial perfusion both before and after PCI to arrive at a single perfusion grade. The Angiographic Perfusion Score (APS) is the sum of the TFG (0 to 3) added to the TMPG (0 to 3) before and after PCI (total possible grade of 0 to 12).⁷⁷ Failed perfusion can be defined as an APS of 0 to 3; partial perfusion, 4 to 9; and full perfusion, 10 to 12.⁷⁷ Among STEMI patients, the APS is associated with larger SPECT infarct sizes and with the incidence of death or MI, as follows: failed, 16.7%; partial, 2.5%; and full, 2.4% ($P=0.039$). No patient with an APS score of "full" died, whereas mortality was 11.1% among patients with an APS score of "failed" ($P=0.03$). Such an APS, which combines grades of epicardial and tissue level perfusion before and after PCI or at the end of diagnostic cardiac catheterization to arrive at a single angiographic variable that is associated with infarct size and 30 day death or MI, may prove valuable in clinical risk stratification.

Other Angiographic Findings That Are Associated With Adverse Outcome

Lesion Location

Although epicardial and myocardial flow likely play a predominant role in mediating adverse clinical outcomes, other angiographic variables may provide valuable prognostic information. For instance, a greater proportion of the culprit artery distal to the stenosis is associated with higher mortality, poorer ST-segment resolution, and larger infarct sizes, particularly in the LAD distribution.⁷⁸ The planimeted distance from the ostium to the LAD culprit lesion is associated with 30-day death or recurrent MI (odds ratio, 0.79 per centimeter increase in distance down the artery, $P=0.01$).⁷⁸

Pulsatile Flow

Reversal of systolic flow on Doppler velocity wire recordings has been associated with impaired tissue perfusion on myo-

cardial contrast echocardiography in the STEMI setting. On the coronary angiogram, pulsatile flow (systolic flow reversal with cessation of antegrade contrast-dye motion or frank reversal of contrast-dye motion during systole) is likewise associated with higher CTFCs (slower epicardial flow), impaired TMPGs, less complete ($\geq 70\%$) ST-segment resolution (23.5% versus 58.9%, $P=0.008$), and a higher risk of death or reinfarction at 30 days (10.3% versus 5.0%, $P=0.019$) independent of the velocity of antegrade flow in the epicardial artery.⁷⁹ This simple and easily identifiable angiographic flow pattern may also be useful in clinical risk stratification.

Lesion Complexity

Worse angiographic lesion complexity has long been associated with reduced PCI success rates.^{80–84} In the setting of STEMI, greater lesion complexity is also associated with poorer epicardial and myocardial perfusion, both before and after PCI. In a multivariate model, Type C lesion complexity remains associated with increased 30-day mortality (odds ratio, 2.83; 95% CI, 1.44 to 5.57, $P=0.003$) even after controlling for 60-minute TFGs, LAD infarct location, age, performance of PCI, and pulse and systolic blood pressure on admission location.⁸⁵

Future Directions

The integration of newer angiographic parameters such as the TMPG into clinical practice has now begun. Other angiographic parameters, which at this time are predominantly research tools, will require software integration into the imaging chain to facilitate their real-time analysis. For example, just as DSA is performed in peripheral arterial interventions, it is now time that DSA be performed during coronary intervention to facilitate the assessment of myocardial perfusion. DSA can be performed offline if the cinerun is performed with a breath hold and without panning. In a “moving mask technique,” the initial nonopacified frames are subtracted from later frames. Optimal views for the left system include the left lateral projection, and for the RCA include the left anterior oblique cranial projection. Automated frame counting is available in many cardiac catheterization laboratories, and if software modifications were made to measure arterial length, the time to traverse the arterial length could be divided by the frame count (a measure of time) to estimate absolute velocity (cm/sec) in real time.

For decades, the technique we perform has traditionally been referred to as “coronary angiography.” It is now time to shift our eyes away from the obvious epicardial stenosis to assess perfusion of the microvasculature and perform the emerging technique of “myocardial angiography.” An emerging reality is in plain sight for all those who learn to see.

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. Simes RJ, Topol EJ, Holmes DR, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. *Circulation.* 1995;91:1923–1928.
3. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary artery patency, ven-

4. tricular function, and survival after acute myocardial infarction. *N Engl J Med.* 1993;329:1615–1622.
5. Vogt A, Von Essen R, Tebbe U, et al. Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. *J Am Coll Cardiol.* 1993;21:1391–1395.
6. Karagounis L, Sorensen SG, Menlove RI, et al. Does thrombolysis in myocardial infarction TIMI perfusion grade 2 represent a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the TEAM-2 study. *J Am Coll Cardiol.* 1992;17:1–10.
7. Anderson JL, Karagounis LA, Becker LC, et al. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction: ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 study. *Circulation.* 1993;87:1829–1839.
8. 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.
9. Gibson CM, Murphy SA, Rizzo MJ, et al. The relationship between the TIMI frame count and clinical outcomes after thrombolytic administration. *Circulation.* 1999;99:1945–1950.
10. Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality following thrombolytic administration. *Circulation.* 2000;101:125–130.
11. Gibson CM, Cannon CP, Murphy SA, et al. 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.
12. 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.
13. 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.
14. 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.
15. The GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomized trial. *Lancet.* 2001;357:1905–1914.
16. Hudson MP, Granger CB, Topol EJ, et al. Early reinfarction after fibrinolysis: experience from the global utilization of streptokinase and tissue plasminogen activator (alteplase) for occluded coronary arteries (GUSTO I) and global use of strategies to open occluded coronary arteries (GUSTO III) trials. *Circulation.* 2001;104:1229–1235.
17. Gibson CM, Karha J, Murphy SA, et al. Early and long term clinical outcomes associated with reinfarction following fibrinolytic administration. *J Am Coll Cardiol.* 2003;42:7–16.
18. Gibson CM. A union in reperfusion: the concept of facilitated PCI. *J Am Coll Cardiol.* 2000;36:1497–1499.
19. Gibson CM, Cannon CP, Piana RN, et al. Angiographic predictors of early reocclusion in the TIMI 4 trial. *J Am Coll Cardiol.* 1995;25:582–589.
20. Gibson CM, Dodge JT, Goel M, et al. The PTCA guidewire velocity. A new simple method to measure absolute coronary velocity and blood flow. *Am J Cardiol.* 1997;80:1536–1539.
21. Abaci A, Ogunzhan A, Eryol NK, et al. Effects of potential confounding factors on the Thrombolysis In Myocardial Infarction (TIMI) trial frame count and its reproducibility. *Circulation.* 1999;100:2219–2223.
22. Manginas A, Gatzov P, Chasikidis C, et al. Estimation of coronary flow reserve using the Thrombolysis In Myocardial Infarction (TIMI) frame count method. *Am J Cardiol.* 1999;83:1562–1565.
23. Stankovic G, Manginas A, Voudris V, et al. Prediction of restenosis after coronary angioplasty by use of a new index: TIMI frame count/minimal luminal diameter ratio. *Circulation.* 2000;101:962–968.
24. Barcin C, Denktas AE, Garratt KN, et al. Relation of Thrombolysis In Myocardial Infarction (TIMI) frame count to coronary flow parameters. *Am J Cardiol.* 2003;91:466–469.
25. Umman B, Nisanci Y, Sezer M, et al. The relationship between corrected TIMI frame count and myocardial fractional flow reserve. *J Invasive Cardiol.* 2002;14:125–128.

25. French JK, Hyde TA, Amos DJ, et al. Corrected TIMI frame count at 3 weeks influences survival at 5 years but not 10 years after myocardial infarction. *Eur Heart J*. 1998;19:630.
26. Straznicky IT, French JK, Webber BJ, et al. Corrected TIMI frame count at 90 minutes predicts left ventricular function at 48 hours following myocardial infarction treated with streptokinase and heparin or hirulog. *Eur Heart J*. 1998;19:285.
27. French JK, Ellis CJ, Webber BJ, et al. Abnormal coronary flow in infarct arteries 1 year after myocardial infarction is predicted at 4 weeks by corrected Thrombolysis In Myocardial Infarction (TIMI) frame count and stenosis severity. *Am J Cardiol*. 1998;81:665–671.
28. French JK, Straznicky IT, Webber BJ, et al. Angiographic frame counts 90 minutes after streptokinase predict left ventricular function at 48 hours following myocardial infarction. *Heart*. 1999;81:128–133.
29. French JK, Hyde TA, Straznicky IT, et al. Relationship between corrected TIMI frame counts at three weeks and late survival after myocardial infarction. *J Am Coll Cardiol*. 2000;35:1516–1524.
30. Amos DJ, French JK, Andrews J, et al. Corrected TIMI frame counts correlate with stenosis severity and infarct zone wall motion after thrombolytic therapy. *Am Heart J*. 2001;141:586–591.
31. Bahin M, Basoglu T, Canbaz F, et al. The value of the TIMI frame count method in the diagnosis of coronary no-reflow: a comparison with myocardial perfusion SPECT in patients with acute myocardial infarction. *Nucl Med Commun*. 2002;23:1205–1210.
32. Moliterno D, Antman EM, Ohman M, et al. Concordance between core labs in trial results using TIMI flow grades and frame counts. *Circulation*. 2000;102(suppl II):II-590.
33. Dodge JT, Rizzo M, Nykiel M, et al. Impact of injection rate on the TIMI frame count. *Am J Cardiol*. 1998;81:1268–1270.
34. Gibson CM, Anshelevich M, Murphy S, et al. Impact of injections during diagnostic coronary angiography on coronary patency in the setting of acute myocardial infarction from the TIMI trials. *Am J Cardiol*. 2000;86:1378–1379.
35. Gibson CM, Kirtane AJ, Murphy SA, et al. Impact of contrast agent type (ionic versus non-ionic) used for coronary angiography on angiographic, electrocardiographic and clinical outcomes following thrombolytic administration in acute MI. *Catheter Cardiovasc Interv*. 2001;53:6–11.
36. Faile BA, Guzzo JA, Tate DA, et al. Effect of sex, hemodynamics, body size, and other clinical variables on the corrected thrombolysis in myocardial infarction frame count used as an assessment of coronary blood flow. *Am Heart J*. 2000;140:308–314.
37. Gibson CM, Dotani MI, Murphy SA, et al. Correlates of coronary blood flow before and after percutaneous coronary intervention and their relationship to angiographic and clinical outcomes in the RESTORE trial. *Am Heart J*. 2002;144:130–135.
38. Edep ME, Guarneri EM, Teirstein PS, et al. Differences in TIMI frame count following successful reperfusion with stenting or percutaneous transluminal coronary angioplasty for acute myocardial infarction. *Am J Cardiol*. 1999;83:1326–1329.
39. Vrachatis AD, Alpert MA, Georgulas VP, et al. Comparative efficacy of primary angioplasty with stent implantation and thrombolysis in restoring basal coronary artery flow in acute ST segment elevation myocardial infarction: quantitative assessment using the corrected TIMI frame count. *Angiology*. 2001;52:161–166.
40. Hamada S, Nishiue T, Nakamura S, et al. TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction. *J Am Coll Cardiol*. 2001;38:666–671.
41. Capozzolo C, Piscione F, De Luca G, et al. Direct coronary stenting: effect on coronary blood flow, immediate and late clinical results. *Catheter Cardiovasc Interv*. 2001;53:464–473.
42. Bickel C, Rupprecht HJ, Maimaitiming A, et al. The superiority of TIMI frame count in detecting coronary flow changes after coronary stenting compared to TIMI flow classification. *J Invasive Cardiol*. 2002;14:590–596.
43. Fang JC, Kinlay S, Wexberg P, et al. Use of the TIMI frame count for the quantitative assessment of transplant associated arteriosclerosis. *Am J Cardiol*. 2000;86:890–892.
44. Gibson CM, Ryan KA, Murphy SA, et al. Impaired coronary blood flow in non-culprit arteries in the setting of acute myocardial infarction. *J Am Coll Cardiol*. 1999;34:974–982.
45. Gibson CM, Goel M, Murphy SA, et al. Global impairment of coronary blood flow in the setting of acute coronary syndromes: a RESTORE substudy. *Am J Cardiol*. 2000;86:1375–1377.
46. Goldstein JA, Demetriou D, Grines CL, et al. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med*. 2000;343:915–922.
47. Gibson CM, Chen M, Goel M, et al. Precordial ST-segment depression in inferior myocardial infarction is associated with slow flow in the non-culprit left anterior descending artery. *J Thromb Thrombolysis*. 2002;13:9–12.
48. Gregorini L, Marco J, Kozakova M, et al. α -Adrenergic blockade improves recovery of myocardial perfusion and function after coronary stenting in patients with acute myocardial infarction. *Circulation*. 1999;99:482–490.
49. Hirsh PD, Hillis LD, Campbell WB, et al. Release of prostaglandins and thromboxane into the coronary circulation in patients with ischemic heart disease. *N Engl J Med*. 1981;304:685–691.
50. Bush LR, Campbell WB, Kern K, et al. The effects of α 2-adrenergic and serotonergic receptor antagonists on cyclic blood flow alterations in stenosed canine coronary arteries. *Circ Res*. 1984;55:642–652.
51. Willerson JT, Campbell WB, Winniford MD, et al. Conversion from chronic to acute coronary artery disease: speculation regarding mechanisms. *Am J Cardiol*. 1984;54:1349–1354.
52. Apprill P, Schmitz JM, Campbell WB, et al. Cyclic blood flow variations induced by platelet-activating factor in stenosed canine coronary arteries despite inhibition of thromboxane synthetase, serotonin receptors, and α -adrenergic receptors. *Circulation*. 1985;72:397–405.
53. Ashton JH, Golino P, McNatt JM, et al. Serotonin S2 and thromboxane A2-prostaglandin H2 receptor blockade provide protection against epinephrine-induced cyclic flow variations in severely narrowed canine coronary arteries. *J Am Coll Cardiol*. 1989;13:755–763.
54. Eidt JF, Allison P, Noble S, et al. Thrombin is an important mediator of platelet aggregation in stenosed canine coronary arteries with endothelial injury. *J Clin Invest*. 1989;84:18–27.
55. Willerson JT, Golino P, Eidt J, et al. Specific platelet mediators and unstable coronary artery lesions: experimental evidence and potential clinical implications. *Circulation*. 1989;80:198–205.
56. Gibson CM, Murphy SA, Menown I, et al. Determinants of coronary blood flow following thrombolytic administration. *J Am Coll Cardiol*. 1999;34:1403–1412.
57. van't Hof AW, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction. *Circulation*. 1998;97:2302–2306.
58. Lepper W, Sieswerda GT, Vanoverschelde JL, et al. Predictive value of markers of myocardial reperfusion in acute myocardial infarction for follow-up left ventricular function. *Am J Cardiol*. 2001;88:1358–1363.
59. Haager PK, Christott P, Heussen N, et al. Prediction of clinical outcome after mechanical revascularization in acute myocardial infarction by markers of myocardial reperfusion. *J Am Coll Cardiol*. 2003;41:532–538.
60. Dibra A, Mehili J, Dirschinger J, et al. Thrombolysis In Myocardial Infarction myocardial perfusion grade in angiography correlates with myocardial salvage in patients with acute myocardial infarction treated with stenting or thrombolysis. *J Am Coll Cardiol*. 2003;41:925–929.
61. Gibson CM, Murphy SA, Kirtane AJ, et al. Association of duration of symptoms at presentation with angiographic and clinical outcomes following fibrinolytic therapy in patients with ST elevation myocardial infarction. *J Am Coll Cardiol*. In press.
62. De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol*. 2003;42:991–997.
63. De Luca G, van't Hof AW, de Boer MJ, et al. Time-to-treatment significantly affects the extent of ST segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *Eur Heart J*. In press.
64. Kirtane AJ, Bui A, Murphy SA, et al. Association of epicardial and tissue-level reperfusion with left ventricular end-diastolic pressures in ST-elevation myocardial infarction. *J Thromb Thrombolysis*. In press.
65. De Luca G, van't Hof AW, de Boer MJ, et al. Impaired myocardial perfusion is a major explanation of the poor outcome observed in patients undergoing primary angioplasty for ST-segment-elevation myocardial infarction and signs of heart failure. *Circulation*. 2004;109:958–961.
66. Tarantini G, Ramondo A, Napodano M, et al. Myocardial perfusion grade and survival after percutaneous transluminal coronary angioplasty in patients with cardiogenic shock. *Am J Cardiol*. 2004;93:1081–1085.
67. Hoffmann R, Haager P, Lepper W, et al. Relation of coronary flow pattern to myocardial blush grade in patients with first acute myocardial infarction. *Heart*. 2003;89:1147–1151.

68. Gibson CM. Has my patient achieved adequate myocardial reperfusion? *Circulation*. 2003;108:504–507.
69. Poli A, Fetiiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. *Circulation*. 2002;106:313–318.
70. Gibson CM, Karha J, Giugliano RP, et al. Association of the timing of ST-segment resolution with TIMI Myocardial Perfusion Grade in acute myocardial infarction. *Am Heart J*. 2004;147:847–852.
71. Wong GC, Morrow DA, Murphy SA, et al. Elevations in troponin T and I are associated with abnormal tissue level perfusion: a TACTICS-TIMI 18 substudy. *Circulation*. 2002;106:202–207.
72. Gibson CM, Murphy SA, Hynes C, et al. Relationship of CK-MB release to TIMI myocardial perfusion grade following intracoronary stent placement: an ESPRIT substudy. *Am Heart J*. 2002;143:106–110.
73. Gibson CM, de Lemos JA, Murphy SA, et al. Methodologic and clinical validation of the TIMI myocardial perfusion grade in acute MI. *J Thromb Thrombolysis*. 2002;14:233–237.
74. Gibson CM, Cohen D, Cohen E, et al. Treatment with eptifibatide and coronary flow reserve (CFR) following elective stent placement: an ESPRIT substudy. *Am J Cardiol*. 2001;87:1293–1295.
75. Murphy SA, Chen C, Gourlay S, et al. Impaired tissue level perfusion in the non-culprit artery territory in the setting of acute MI. *Am J Cardiol*. 2003;91:325–328.
76. Wong GC, Frisch D, Murphy SA, et al. Time for dye to traverse the epicardial artery and the myocardium in acute ST segment elevation myocardial infarction versus unstable angina/non ST elevation MI. *Am J Cardiol*. 2003;91:1163–1167.
77. Gibson CM, Murphy SA, Morrow DA, et al. Angiographic perfusion score: an angiographic variable that integrates both epicardial and tissue level perfusion before and after facilitated percutaneous coronary intervention in acute myocardial infarction. *Am Heart J*. 2004. In press.
78. Karha J, Murphy SA, Kirtane AJ, et al. Association of proximal culprit artery lesion location with clinical outcomes in acute myocardial infarction. *Am J Cardiol*. 2003;92:913–918.
79. Gibson CM, Karha J, Murphy SA, et al. Association of pulsatile blood flow pattern on coronary arteriography and short-term clinical outcomes in acute myocardial infarction. *J Am Coll Cardiol*. 2004;43:1170–1176.
80. Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *J Am Coll Cardiol*. 1988;12:529–545.
81. Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants or procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. *Circulation*. 1990;82:1193–1202.
82. Myler RK, Shaw C, Stertz SH, et al. Lesion morphology and coronary angioplasty: current experience and analysis. *J Am Coll Cardiol*. 1992;19:1641–1652.
83. Krone RJ, Laskey WK, Johnson C, et al. A simplified lesion classification system for predicting success and complications of coronary angioplasty. *Am J Cardiol*. 2000;85:1179–1184.
84. Wilensky RL, Selzer F, Johnston J, et al. Relation of percutaneous coronary intervention of complex lesions to clinical outcomes (from the NHLBI Dynamic Registry). *Am J Cardiol*. 2002;90:216–221.
85. Gibson CM, Bigelow B, James D, et al. Association of American College of Cardiology/American Heart Association Task Force Classification of Lesion Complexity Following Fibrinolytic Administration with Mortality in ST Elevation Myocardial Infarction. *Am J Cardiol*. 2004. In press.

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