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The time-dependent open vasculature hypothesis

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In both experimental animal models and in clinical trials of acute myocardial infarction, it has been observed that more rapid restoration of flow in the infarct artery results in improved clinical outcomes, leading to a paradigm known as the "time-dependent open artery hypothesis." While improved epicardial flow following reperfusion strategies in the acute myocardial infarction (MI) setting has been associated with improved clinical outcomes, emerging data support the notion that improved perfusion at the tissue level or at the level of the myocardium is also critical for improved clinical outcomes. Perhaps this paradigm should now be called the "open vasculature hypothesis," rather than simply the "open artery hypothesis,"[1] because it has been shown that improved tissue level perfusion (either on the angiogram,[2] the echocardiogram,[3] or the electrocardiogram[4]) is related to improved clinical outcomes independent of flow in the epicardial artery.

There are 4 components to the new "time-dependent open vasculature hypothesis," namely the achievement of :

- **early flow**
- **full microvascular flow**
- **full epicardial flow; and finally**
- **preserved or sustained flow.[1]**

In the acute MI setting, pharmacologic strategies may more fully satisfy the first two criteria (they rapidly open epicardial vessels and the microvasculature), but mechanical interventions may better satisfy the latter two criteria (full and sustained reperfusion). Insofar as clinical outcomes in acute MI are related to the attainment of not just one, but rather to the fulfillment of all 4 prerequisites of the "time-dependent open vasculature hypothesis," it may be optimal to offer the best of two complementary strategies by combining the speed of patency and improved microvascular function provided by a pharmacologic strategy with the speed of flow following more definitive (albeit later) mechanical intervention.[1,5,6] This grand rounds reviews angiographic data supporting the role of the microvasculature in the setting of acute coronary syndromes, and discusses the angiographic evaluation of strategies to improve myocardial perfusion.

20 years of acute MI data: The time-dependent open artery hypothesis

Over the past two decades, faster flow has been associated with improved clinical outcomes both in the acute MI setting[7-9] and in the setting of unstable angina following percutaneous coronary intervention (PCI).[10] TIMI grade 3 flow or "normal flow" has been shown to be associated with superior outcomes when compared to TIMI grades 0-2[7-9] (Figure 1). While useful, one of the problems with this convenient scheme of assessing blood flow is the lack of reproducibility between angiographers who agree in their assessment of TIMI grade 3 flow in only 71% of cases.[11] This led us at the TIMI group to develop a quantitative assessment – the TIMI frame count – which is based on the number of angio-

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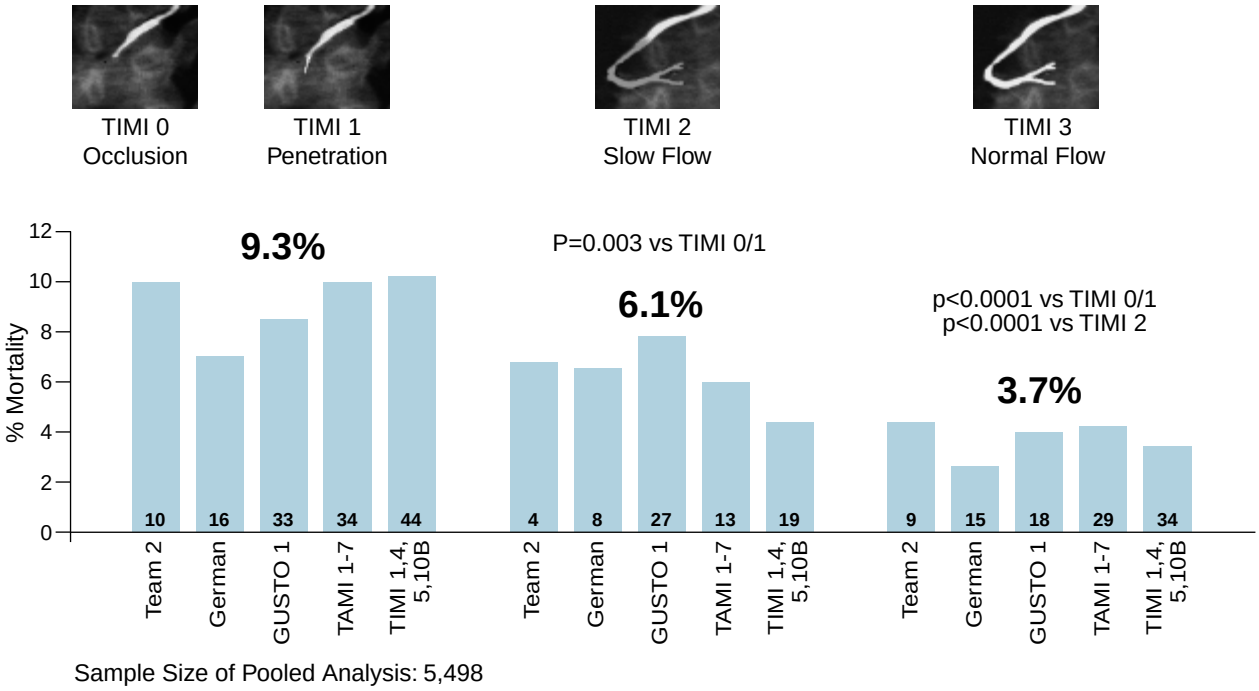
Figure 1: Restoration of "Normal" Epicardial Flow Yields Better Outcomes

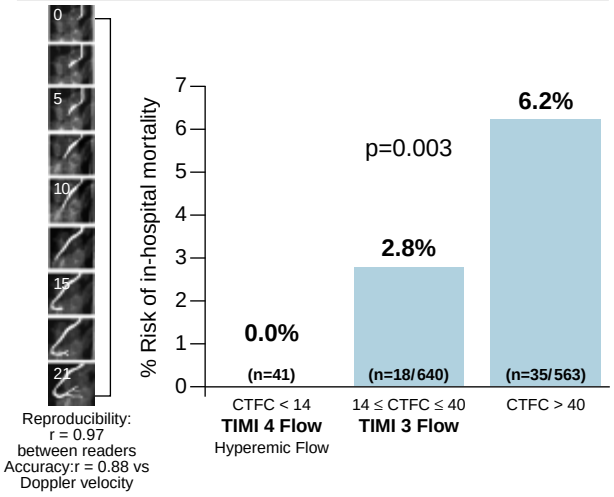


graphic frames needed for dye to traverse the artery.[12] Each frame is 1/30th of a second, so in essence we are using the cinefilm as a stopwatch.

Beyond TIMI Grade 3 flow: TIMI Grade 4 flow

Using the TIMI frame count or the stopwatch, it has recently become increasingly apparent that "not all TIMI grade 3 flow is created equally."[9,12] We have recently demonstrated that within TIMI grade 3 flow, there is a group of patients with even faster (a TIMI frame count < 14) than normal flow or hyperemic flow. We term this "TIMI grade 4 flow." Patients with this very fast flow have even better outcomes than those patients with slower TIMI grade 3 flow (Figure 2).[9] Thus, even among patients with TIMI grade 3 flow, even faster flow is related to even better outcomes in the setting of acute MI. In order to have hyperemic flow, the integrity of the microvasculature must be preserved.

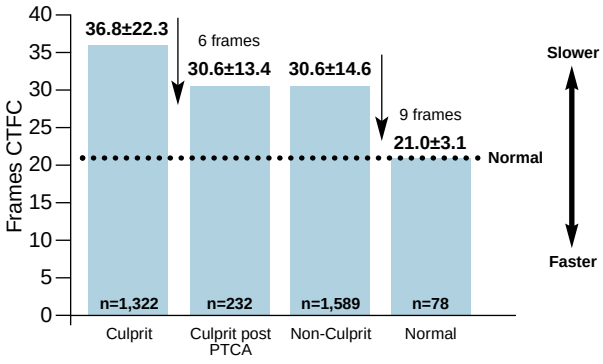
Figure 2: Even faster epicardial coronary blood flow is related to better outcomes



Acute MI impairs flow globally throughout the entire heart in all three arteries: A global microcirculatory abnormality

Recently, we reported that epicardial flow is not only abnormal in the culprit artery, but also in non-culprit arteries, both in acute MI and in the setting of unstable angina [13,14] (Figure 3). While it normally requires 21 frames for dye to traverse an epicardial artery in the absence of acute MI, flow in uninvolved arteries is slowed to over 30 frames, or reduced by 40%, in the acute MI setting.[13] As a matter of fact, in 25% of cases, flow in the uninvolved artery is actually slower than the culprit artery. Thus, acute MI impairs coronary blood flow globally rather than in just the culprit artery. It is also notable that percutaneous coronary intevention (PCI) of the culprit artery does not restore normal flow or a frame count of 21. Indeed, the flow following PCI is often the same as that in non-culprit arteries: over 30 frames[13] (Figure 3). While PCI improves the culprit TIMI frame count by approximately 6 frames in the acute MI setting (from 36.8 to 30.6 frames), there are still 9 frames of improvement that are needed to restore flow to normal (21 frames). This persistent delay in

Figure 3: Acute MI slows blood flow globally throughout the heart in acute MI[13]



flow is most likely a consequence of abnormalities in the downstream microvasculature.

This global reduction in flow has important clinical implications as slower global flow in all three arteries is associated with a higher risk of adverse outcomes including mortality.[13] Recently, we have shown that there is also delayed flow in the non-culprit artery in the setting of unstable angina.[14] Of note, flow in the uninvolved artery improves following PCI of the culprit artery. Non-culprit flow improves by nearly 10 frames if it was abnormal to begin with. Likewise, Gregorini et al have shown that flow in the uninvolved artery also improves following PCI in the setting of acute MI. After 15 minutes of observation, however, flow in both the culprit and non-culprit arteries again slowed back down to pre-intervention values. Flow was then restored to normal after the administration of alpha blockers.[15] These findings indicate that flow may be impaired as a result of heightened downstream microvascular obstruction, as a result of alpha adrenergic neural reflexes, spasm, or thrombotic occlusion of microvessels.

Despite elimination of the stenosis following stent placement, one-third of patients have persistently abnormal flow due to microcirculatory dysfunction in the acute MI setting

One procedure that is commonly used to improve coronary blood flow is intracoronary stenting. Even though the residual stenosis was only 16% following adjunctive stent placement in the TIMI trials, normal flow was still not restored in up to one-third of patients.[16] Despite this minimal residual stenosis after stent placement, if flow remains abnormal (a TIMI frame count > 28 or greater than the 95th percentile for normal flow),[6] then mortality is significantly higher (the odds of death are 12.6 times higher, 9.7% vs 0.8%, p=0.007).[16] Larger stent sizes were associated with a higher risk of slower flow, and "bigger may not always be better." Again, these findings suggest that there are critical untreated determinants of epicardial blood flow other than the stenosis that are related to adverse outcomes.

Stenting in AMI: The promise and the embolus

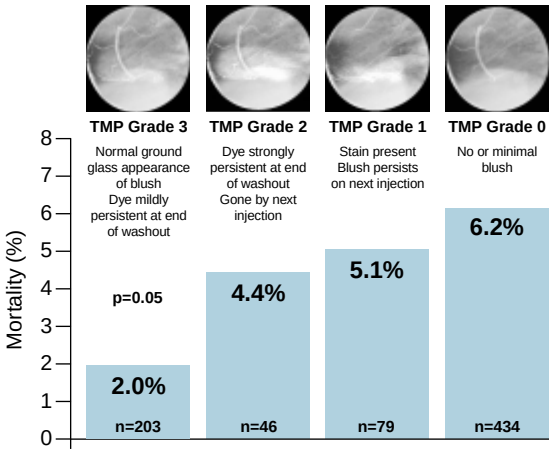
While stenting fulfilled the promise of reducing restenosis compared with conventional primary angioplasty in the PAMI stent trial, there was a troubling observation that one month- and six-month mortality were higher among stented patients, particularly among those with a closed vessel prior to intervention.[17,18] This has raised concern that stenting may increase the risk of downstream embolization of both large and small atheroembolic particles.

There are two broad categories of devices that may reduce the potential for mechanical embolization. One is a balloon device that is inflated distal to the stenosis (the PERCUSURGE ™ device) whereby trapped material is aspirated from the lumen following PCI. Other devices are filters that trap embolic debris. However, mechanical embolization may not be the sole problem following PCI. There may also be downstream vasoconstrictor release following device deployment. When you cut yourself, your body minimizes bleeding by forming a blood clot. The other way that your body minimizes bleeding is through vasoconstriction. Activated platelets release potent vasoconstrictors such as serotonin. While it is a good thing to vasoconstrict when you have a wound, if that vasoconstriction occurs downstream to damage the vessel wall in the myocardium, this is bad. At baseline, patients have low levels of serotonin in the coronary sinus. Leosco et al have shown that following dilation of the lesion with conventional balloon angioplasty, serotonin levels rise dramatically, nearly 30-fold.[19] Furthermore, following intracoronary stent placement, serotonin levels rise approximately 120-fold, much more than following conventional balloon angioplasty.[19] This may be because stenting causes greater arterial damage with greater platelet deposition and greater platelet activation, which in turn, leads to more serotonin release. While mechanical strategies may be developed to prevent distal embolization, platelet activation and the release of potent vasoconstrictors that occurs after device deployment may be another problem that requires treatment. Glycoprotein IIb/IIIa inhibitors may be a natural choice to treat this problem insofar as they prevent platelet activation. Other agents such as calcium channel blockers, alpha blockers, nitroprusside, and adenosine may also be useful in reducing microvascular spasm.

Assessing the microvasculature: Use of myocardial contrast echocardiography and angiography

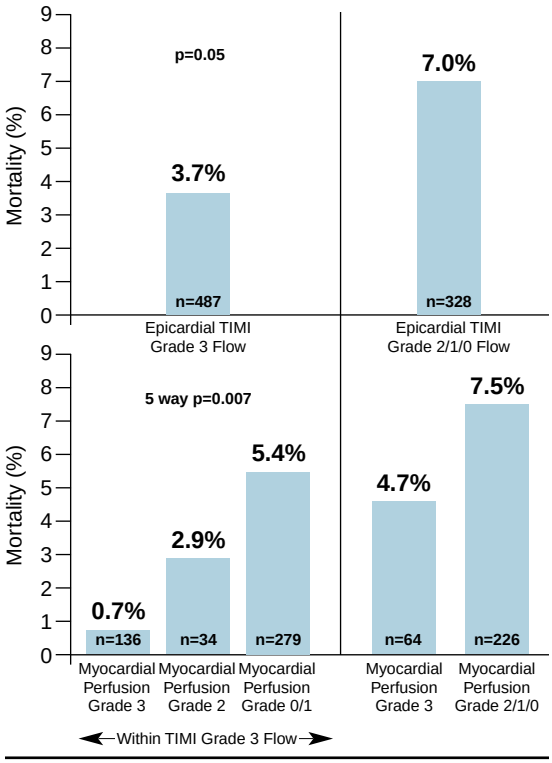
Myocardial contrast echocardiography has shed light on the role of tissue level perfusion in determining clinical outcomes in the acute MI setting. If there is no reflow, where no

Figure 4: TIMI Myocardial Perfusion (TMP) Grades



microbubbles enter the myocardium, then there is a higher risk of arrhythmia, congestive heart failure, or death.[3] Myocardial contrast echocardiography requires additional expertise, time, microbubbles, and expense which may limit its widespread applicability. Recently, our goal at the TIMI group has been to develop and validate a simple semi-quantitative technique that does not require sophisticated ancillary equipment that could be conveniently and broadly applied by catheterization laboratory-based clinicians to assess tissue level perfusion from the angiogram alone.[2] This simple angiographic technique is called the TIMI Myocardial Perfusion Grade and is illustrated in Figure 4.[2] Actual video clips of the TIMI blush system can be viewed at www.perfuse.org or www.timi.org.

Figure 5: Relationship of TIMI flow grade and myocardial perfusion grade to mortality[2]



While the TIMI flow grades and the TIMI frame count assess flow in the epicardial arteries, the TIMI myocardial perfusion grades (TMPG) assess flow at the tissue level. The four panels at the top of Figure 4 demonstrate the four TIMI myocardial perfusion grades.

• In TIMI myocardial perfusion grade 3, there is the normal ground glass appearance of myocardial blush diffusely, and at the end of the washout phase, dye is only mildly persistent or is gone.

• In TIMI myocardial perfusion grade 2, dye enters the myocardium, but accumulates and exits more slowly so that at the end of the washout phase, dye in the myocardium is strongly persistent.

• In TIMI myocardial perfusion grade 1, the dye does not leave the myocardium and there is a stain on the next injection.

• In TIMI myocardial perfusion grade 0, dye does not enter the myocardium and there is minimal or no blush apparent during the injection and washout phases.

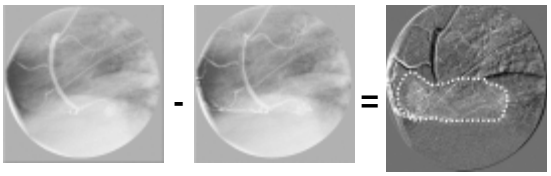
As shown in Figure 4, normal TIMI myocardial perfusion grade 3 flow was associated with improved mortality.[2]

Not all TIMI Grade 3 flow is created equally

For years, the goal of revascularization strategies has been to restore normal TIMI grade 3 flow to the epicardial artery. As the data in Figure 5 show, restoration of epicardial TIMI grade 3 flow is necessary, but not sufficient.[2] Normal flow must also be restored to the myocardium. The new TIMI myocardial perfusion technique permits independent risk stratification within TIMI grade 3 flow. Those patients with TIMI grade 3 flow in the epicardial artery (shown on the left of the figure) who had a closed microvasculature (TMPG 0/1 flow) had a higher mortality (5.4%) than those with TMPG 2 (2.9%) or TMPG 3 flow (0.7%)(p=0.007)(Figure 5).[2] Thus, even among patients with TIMI grade 3 flow in the epicardial artery, there was a 7-fold gradient in mortality depending upon the extent of microvascular perfusion. Indeed, the TIMI myocardial perfusion grade was a multivariate predictor of 30-day mortality, independent of age, gender, admission pulse, anterior MI location, the TIMI frame count, and the TIMI flow grade,[2] and we have now documented that even at 2 years following thrombolytic therapy, the TMPG is a multivariate predictor of mortality, independent of flow in the epicardial artery.[20.]

While the above data apply to patients treated with thrombolysis, recently Stone et al have shown that

Figure 6: Computerized measurements of blood flow in the heart muscle



Background: Dye in artery, no dye yet in the myocardium

Dye in artery and dye now in myocardium

Subtracted image: Ribs, spine, diaphragm & artery subtracted, blush now apparent

among patients with TIMI Grade 3 flow following PCI in AMI, patients with myocardial Grade 3 blush have markedly improved outcomes compared with those patients with a closed microvasculature.[21] It is notable that only one-third of patients undergoing PCI in acute MI have normal Grade 3 blush. Thus, the majority of PCI patients may require further work downstream to open up the microvasculature. We have recently reported that an elevated white blood cell count at the time of presentation with AMI is related to poorer tissue level perfusion as measured by the TMPG, and thus ongoing inflammation may be a critical determinant in attenuating myocardial reperfusion, and may also be a target of future pharmaceutical interventions.[22]

Relationship between blush grade and other tools to assess the microvasculature

Recently, Lepper et al demonstrated that the different blush grades are related to other tools used to assess the microvasculature.[23] Patients with normal myocardial blush have improved myocardial contrast echo findings, improved coronary flow reserve, and improved wall motion on echocardiography. Among patients with epicardial TIMI grade 3 flow, improved flow in the microvasculature by the TMPG method is also associated with improved EKG resolution by the Schroeder criteria.[24] Thus, use of the epicardial TIMI flow grade and the microvascular TIMI myocardial perfusion grade allows assessment of two important and complementary outcomes of thrombolytic therapy from a coronary angiogram alone and can be conveniently, inexpensively and broadly applied by clinicians.

Quantitating the myocardial blush using digital subtraction angiography (DSA)

Recently, we have moved beyond simply assessing myocardial blush visually. We are now using digital subtraction angiography, or DSA, to quantitate the kinetics of dye entry into the myocardium. How DSA works is shown in Figure 6. An image is saved before dye fills the myocardium. This is used as the "background image" and it contains an image of the ribs, spine, lung and the artery itself. Next, an image is stored from several heart beats later, at a time when dye has filled the myocardium. We call this the "blush image." The "background image" without blush is then subtracted from the "blush image" to remove the ribs, spine and artery. This isolates a picture of the dye in the heart muscle. We then measure the size of the blush, the brightness of the blush, and how long it took for the blush to become that big and that bright.

Improving tissue level perfusion with glycoprotein IIb/IIIa inhibition

The ESPRIT trial was a double-blind trial of planned, non-urgent stenting of native coronary arteries in 2,064 patients who were randomized in a 1:1 ratio between eptifibatide and placebo immediately before planned percutaneous coronary stent implantation.[25] In an angiographic substudy of 65 patients, we used the above DSA technique and recently reported at the AHA that therapy with eptifibatide made the myocardial blush bigger, brighter and it filled faster following adenosine administration.[25] We also found that abnormal tissue level perfusion (TMPG grades 0/1/2) was associated with increased creatine kinase release and higher clinical event rates (despite all patients having normal TIMI grade 3 flow at the completion of stenting).[25]

Recently, two groups have shown that the TIMI frame count before and after adenosine is highly correlated with coronary flow reserve (CFR) as assessed using a Doppler velocity wire (r=0.88).[26,27] In essence, if the time for dye to travel down the artery is cut in half, that must mean that the velocity was doubled. Following stent placement, we recently demonstrated at this year's AHA that coronary flow reserve is improved among patients taking eptifibatide, compared with patients taking placebo.[25]

These data suggest that impaired tissue level perfusion is associated with the release of CK-MB following PCI and may explain, in part, the growing body of literature relating the release of CK-MB to poorer clinical outcomes and the impact of glycoprotein IIb/IIIa inhibition in improving these outcomes.

The time-dependent open vasculature hypothesis: The five laws

The five laws of the time-dependent open vasculature hypothesis are as follows:

- Not all TIMI grade 3 flow is created equally
- TIMI grade 3 flow is necessary but not sufficient

• It is the restoration of normal tissue level reperfusion that optimizes outcomes

• Time is myocardium: faster restoration of flow is related to improved clinical outcomes[28]

• Sustained flow and the absence of reocclusion is related to improved outcomes[29]

While the choice of a revascularization strategy may vary depending upon the time of day, the hospital setting, etc., these 5 pathophysiologic imperatives serve as useful guideposts in implementing the most effective reperfusion strategy.

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