

# Measuring reperfusion in the catheter laboratory

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## Abstract

Primary angioplasty has evolved as the reperfusion strategy of choice in acute ST-segment elevation myocardial infarction. Unlike thrombolytic therapy, it allows for direct visualization of the coronary anatomy and a targeted approach to revascularization. This is associated with significant improvements in culprit artery patency, distal myocardial perfusion, and, ultimately, patient prognosis. Assessment of reperfusion in this setting is heavily dependent upon the angiographic profile of the infarct-related artery after intervention. This incorporates both anatomical and physiological aspects of coronary function, with further delineation of epicardial and microvascular components of total coronary flow. More recent advances in contrast echocardiography and Doppler flow analysis have allowed for increasingly sophisticated and diverse measures of reperfusion that complement angiography and can all be used at the time of intervention in the catheter laboratory. Such information can guide immediate adjuvant therapy during angioplasty, in addition to identifying higher-risk groups of patients.

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## Introduction

The main therapeutic strategy in ST-segment elevation myocardial infarction is the prompt restoration of blood flow to the distal myocardial bed of the culprit coronary artery. Primary percutaneous intervention is now widely accepted as the therapeutic treatment of choice. An invasive strategy allows for direct angiographic assessment of the epicardial coronary anatomy before and after targeted intervention is delivered, thereby eliminating the need for surrogate markers of reperfusion. Angiography remains the gold standard for measuring reperfusion. It provides both anatomical and physiological information about coronary flow, reflecting primarily, but not exclusively, the relative contribution of epicardial

and microvascular resistances, respectively. The distinction between epicardial and myocardial reperfusion is of increasing importance as our understanding and our capacity to measure microvascular function improve. Indeed, microvascular integrity beyond the stented lesion is now recognized as an independent outcome marker of revascularization [1–3]. More contemporary measures of the microvasculature, such as myocardial contrast echocardiography and Doppler coronary flow profiling, now complement the angiogram and electrocardiogram (ECG). These can all be measured simply in the catheter laboratory in order to guide delivery of treatment and identify those individuals at risk from incomplete epicardial or myocardial reperfusion.

## Anatomical reperfusion

### ***Epicardial reperfusion: the Thrombolysis In Myocardial Infarction (TIMI) flow grade and corrected TIMI frame count***

Coronary angiography allows for both a two-dimensional quantitative analysis of residual lumen stenosis after percutaneous intervention and an assessment of coronary flow beyond the lesion intervened upon. These two components are not mutually exclusive, and both are important considerations in determining the success of revascularization in acute myocardial infarction. The first angiographic score of reperfusion was devised by the Thrombolysis In Myocardial Infarction (TIMI) study group for use in the early major trials of thrombolytic agents [4]. The TIMI flow grade provides a simple score of epicardial flow, graded 0–3 according to set angiographic criteria:

TIMI 3: Normal antegrade flow and contrast clearance from the epicardial artery beyond the (stented) obstruction (*complete perfusion*).

TIMI 2: Full opacification of the distal artery, but with slower contrast flow or clearance, or both, beyond the (stented) obstruction compared with a non-culprit artery or the culprit artery proximal to the lesion (*partial reperfusion*).

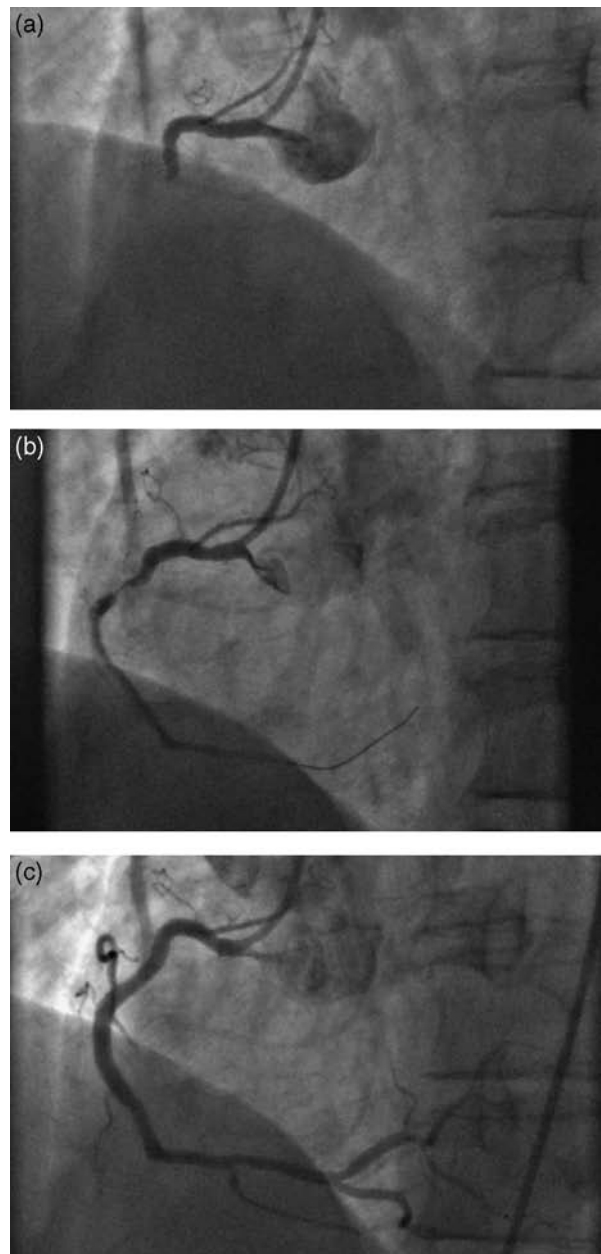
TIMI 1: Contrast flow in part, but not all, of the artery distal to the (stented) obstruction (*penetration without perfusion*).

TIMI 0: No antegrade contrast flow beyond the point of occlusion (*no perfusion*).

TIMI flow grade is now regarded as the benchmark by which coronary flow is assessed before and after intervention (*Figure 1*), and has become established as one of the most important markers of reperfusion in contemporary interventional trials.

Early use of the TIMI flow grade in thrombolysis trials defined a clear and stepwise improvement in patient outcome with each individual TIMI flow grade [5]. This has translated itself into a variety of interventional settings for acute myocardial infarction, including rescue angioplasty [6], revascularization in cardiogenic shock [7], and intra-aortic balloon-pump-supported therapy [8]. Unlike the thrombolysis trials, however, the prognostic merit of TIMI flow usually relates to a binary comparison of “successful” and “unsuccessful” revascularization, defined by a set TIMI flow grade threshold with or without reference to residual lumen stenosis after the intervention.

The major disadvantage of the TIMI flow grade is the subjective nature of reporting into a somewhat artificial and rigid classification of coronary flow. There is at least moderate interobserver variability reported, particularly in culprit arteries with TIMI 2



*Figure 1. Thrombolysis In Myocardial Infarction (TIMI) 0 flow (a) in the right coronary artery of a patient presenting with an acute inferior myocardial infarction. Passage of the guidewire through the obstruction resulted in TIMI 1 flow (b) beyond a tight proximal lesion, which subsequently improved to TIMI 3 flow (c) after successful angioplasty and stenting.*

and 3 flow after reperfusion [9]. Accordingly, the corrected TIMI frame count (cTFC) was devised in order to provide a more objective and less variable assessment of reperfusion. This angiographically derived measure describes the number of cineframes required for dye to reach defined distal landmarks of the three main epicardial arteries:

- (1) Left anterior descending (LAD): the distal bifurcation point of the left anterior descending artery.

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- (2) Right coronary artery (RCA): the first branch of the posterolateral artery of the right coronary artery.
- (3) Left circumflex artery (LCx): the most distal bifurcation of the obtuse marginal branch of the left circumflex system.

The cTFC depends upon a set acquisition frame-rate of 30 frames per second, standardized guide catheters, and sustained maximal epicardial vasodilatation. Otherwise, there is a remarkably low variance in measurements regardless of force of injection, dye contrast used, cardiac output, and heart rate [9,10]. The normal cTFC for the RCA and circumflex vessels is approximately 21 frames; for the LAD it is 36 frames. This disparity is in part a result of the longer course of the LAD in most individuals, but it also reflects a slightly slower flow – another confounding issue in using the TIMI flow grade. Conversely, the cTFC is a continuous measure and a correction factor of 1.7 is therefore used for LAD measurements [10].

Many studies now have identified an association between patient outcome and the cTFC in primary angioplasty trials [11,12]. Although certain prognostic threshold parameters are likely, the particular merit of the cTFC is its sensitivity to detect relative improvements in epicardial flow within TIMI flow grades. This is particularly true within TIMI 3, in which, in the absence of any residual stenosis, subtle hindrances in flow are probably caused by downstream microvascular obstruction or dysfunction.

### Myocardial perfusion: myocardial contrast echo and the myocardial perfusion scores

Restoration of TIMI 3 epicardial flow remains the key target of interventional revascularization in acute myocardial infarction. However, up to 40% of the patients will fail to achieve adequate perfusion of the microvasculature beyond the stented lesion and

this, in itself, is associated with a worse prognostic outcome [13,14]. Myocardial contrast echocardiography (MCE) provided the first measure of this “no reflow” effect in humans and has remained an important modality against which other techniques have subsequently been tested [1]. Inert, echo-dense microbubbles between 2 and 4  $\mu\text{m}$  in size can now be administered peripherally to determine capillary blood volume and regions of hypoperfusion/obstruction. This correlates well with gold-standard histological assessment and more contemporary measures of microvascular obstruction such as cardiac magnetic resonance imaging – both equally unhelpful in the catheter laboratory. MCE also allows for an accurate assessment of left ventricle dimensions and determination of immediate postinfarct contractile function, and is suggested as the most sensitive and accurate of microvascular measures in predicting longer-term left ventricular recovery [15].

Angiography-derived microvascular perfusion can be assessed from the myocardial blush grade and TIMI myocardial perfusion grade [2,10]. These are both simple descriptive scores of myocardial opacification with contrast, distinct from the epicardial vessel, and provide a score of between 0 (no myocardial blush) and 3 (normal blush and clearance of dye from myocardium) (Table 1). Angiographic myocardial reperfusion correlates well with MCE in the setting of primary angioplasty, and accordingly is an important prognostic outcome marker of myocardial salvage and mortality in spite of TIMI 3 epicardial flow [16,17]. More recently, the TIMI study group have proposed a 12-point angiographic perfusion score as a composite of pre- and postintervention TIMI flow grade (0–3) and TIMI myocardial perfusion grade (0–3) scores, in order to combine epicardial and microvascular perfusion. This has provided robust outcome data and a close correlation with infarct size determined by single photon emission computed tomography, but has yet to prove any more useful than existing angiographic indices [18].

Table 1. The myocardial blush grade and Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade.

Myocardial blush	Grade	TIMI myocardial perfusion
No myocardial blush or contrast density	<b>0</b>	Minimal or absent myocardial blush in the territory of the infarct-related artery
Minimal myocardial blush or contrast density	<b>1</b>	Myocardial blush present, but incomplete clearance of dye between injections (at least 30s)
Moderate myocardial blush or contrast density, but less than that of a non infarct-related artery	<b>2</b>	Myocardial blush present, but slow entry and clearance of dye (strongly persistent opacification beyond 3 cardiac cycles after injection)
Normal myocardial blush or contrast density, comparable to that of a non infarct-related artery	<b>3</b>	Myocardial blush present with normal entry and exit of dye (mild/moderate persistence of dye beyond 3 cardiac cycles but notably reduced during washout phase)

Both are angiographically derived scores of microvascular perfusion, describing the ground-glass or “blush” effect of distal myocardial contrast opacification beyond the infarct-related epicardial artery.

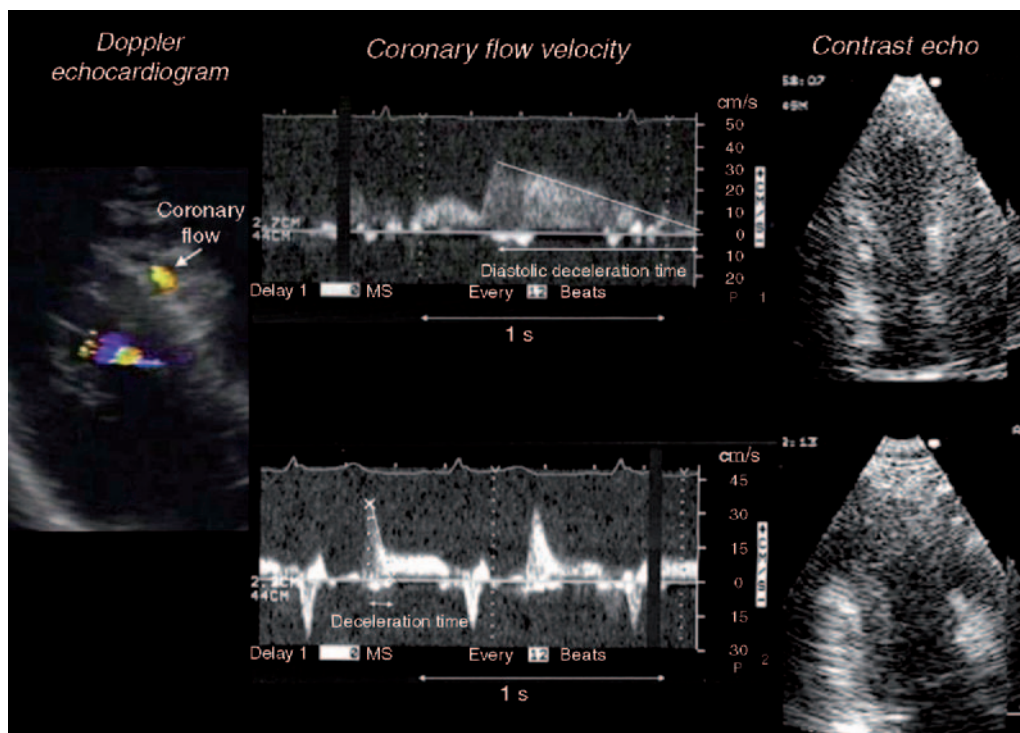


Figure 2. Transthoracic Doppler profile of the left anterior descending (LAD) coronary artery (left and centre) and myocardial contrast echo (right), in two patients who underwent successful revascularization for acute anterior myocardial infarction. The patient with “no reflow” on myocardial contrast echo (bottom images) demonstrated a characteristic coronary flow velocity pattern of increased diastolic peak velocity with rapid deceleration, diminished systolic peak velocity, and systolic flow reversal. (From Ikawura et al [21], with permission.)

## Physiological reperfusion

### Doppler analysis and the electrocardiogram

The advent and expansion in use of fine intracoronary measuring devices has also extended the capacity to define myocardial reperfusion on a “physiological” basis. Intracoronary Doppler interrogation of upstream epicardial flow after primary angioplasty, for example, provides a surrogate measure of downstream microvascular integrity, with both impairment of coronary flow reserve and progressive flow characteristics correlating with deteriorating perfusion defects on MCE, in the following order [19,20]:

- (1) Rapid diastolic deceleration time.
- (2) Systolic flow reversal.
- (3) Diminished antegrade systolic flow.

These findings are reproducible in transthoracic echo Doppler interrogation of LAD flow (Figure 2), and have been suggested as more sensitive of microvascular no-reflow than angiographic or ECG criteria [21].

Finally, although primary angioplasty has rendered the surface ECG redundant as a surrogate marker of epicardial reperfusion, the absence of reperfusion dysrhythmias and persistence of ST-segment elevation in the face of successful intervention and restoration of TIMI 3 epicardial flow correlate

strongly with other measures of microvascular dysfunction. This reflects sustained electrical transmural injury, and less than 50% resolution of ST segments in the infarct-related territory is associated with larger infarct size and significant long-term major adverse cardiac events [22,23]. ■

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