

# Angiographic Evaluation of Epicardial and Microvascular Coronary Flow

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**P**harmacological or mechanical relief of coronary obstruction with restoration of normal flow in the culprit coronary artery has been the goal of therapy in patients with acute myocardial infarction. Although primary percutaneous catheter intervention is highly successful in the restoration of epicardial blood flow, achieving full angiographic patency (TIMI grade 3 flow) in the infarct-related epicardial coronary artery of > 90% of the patients [1,2], tissue perfusion in the area at risk frequently continues to be compromised. Persistent microcirculatory impairment is associated with poor recovery of contractile function [3-9] and adverse clinical outcome [3,10-13]. The major causes of insufficient tissue reperfusion despite a fully patent infarct-related epicardial artery are ischemic microvascular damage, reperfusion-induced regional inflammatory responses, and distal embolization of plaque and thrombus material.

The current concept of optimal reperfusion in acute MI includes not only the rapid and sustained restoration of blood flow in the epicardial infarct-related coronary artery, but also the restoration of perfusion at the tissue level within the jeopardized myocardium [13-16]. Failure to achieve an adequate blood supply at this level has been associated with a greater

infarct size, poor left ventricular function and remodeling, congestive heart failure and higher mortality rates, despite the presence of a patent infarct-related coronary artery [4,17].

Several diagnostic techniques have been employed to evaluate tissue-level microvascular perfusion. Studies using myocardial contrast echocardiography, magnetic resonance, Doppler flow wire, nuclear imaging, ST-segment resolution, myocardial blush, corrected TIMI frame count, and TIMI myocardial perfusion grade, have provided investigators with information on the incidence of no-reflow and its clinical consequences in patients with abnormal myocardial perfusion at the tissue level. These methods are also used in attempts to predict mortality in patients with acute MI. In this article we review the different angiographic methods that are being used in practice or in research to evaluate the efficacy of reperfusion therapies.

## TIMI FLOW GRADE

This method was first introduced in 1985 as part of the Thrombolysis In Myocardial Infarction (TIMI) Trial. The method estimates epicardial flow by evaluating the flow rate of the contrast material in the epicardial coronary artery during angiography. Four grades (0-3) have been defined to evaluate and characterize coronary blood flow in the infarct-related coronary artery [Figure 1] [18].

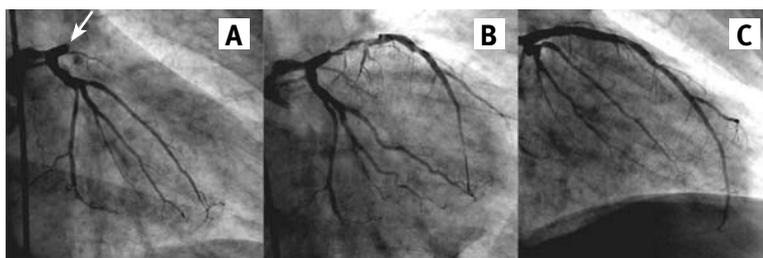
- **Grade 0 (no perfusion):** There is no antegrade flow beyond the point of occlusion.

- **Grade 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 filming sequence.

- **Grade 2 (partial perfusion):** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of the contrast material or its clearance from the vessel distal to the obstruction (or both) is perceptibly slower than those in the opposite coronary artery or the coronary bed proximal to the obstruction.

- **Grade 3 (complete perfusion):** Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as clearance from an uninvolved bed in the same vessel or the opposite artery.

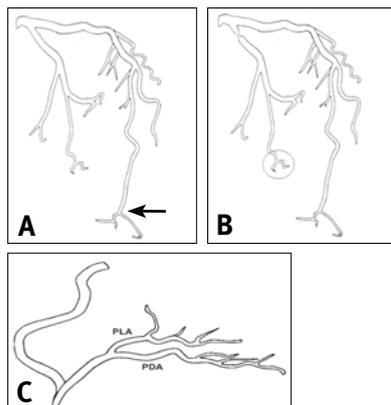
MI = myocardial infarction



**Figure 1.** TIMI flow grade 0. **[A]** The LAD artery is occluded with no antegrade flow beyond the point of occlusion. Passage of the guidewire through the obstruction results in TIMI flow grade 1. **[B]** TIMI flow grade 3. **[C]** After a successful angioplasty and stenting of the LAD.



**Figure 2.** The first frame used for TIMI frame counting of the LAD artery is the first frame in which the contrast dye fully enters the artery. The arrow points to the fully dyed ostium of the LAD.



**Figure 3.** [A] The distal bifurcation of the LAD (i.e., the "mustache," "pitchfork," or "whale's tail"). [B] The distal bifurcation of the segment with the longest total distance that includes the culprit lesion. [C] The first branch of the posterolateral artery.

- **TIMI flow grade 2** is considered as an intermediate stage in the progression from complete obstruction to normal flow. It was found that the outcome of patients with Grade 2 after reperfusion therapy was worse than those with Grade 3, and even sometimes similar to those with Grade 0 and 1 [19-23].

The assessment of TIMI flow grade is based on a subjective comparison of perfusion [24]. This is problematic when comparing data between different observers, centers and trials. Moreover, the conventional flow-grading system is categorical, rather than continuous [25]. These were the main reasons that motivated researchers to develop other, more objective techniques to assess the coronary blood flow.

**Angiographic assessment of the epicardial and myocardial perfusion offers a tool to evaluate the effectiveness of reperfusion therapies and risk-stratify patients with MI**

**TIMI FRAME COUNT**

TIMI frame count is an objective evaluation of coronary flow as a continuous quantitative variable. The angiography is performed in 30 frames per second. The number of frames required for contrast material to reach a distal coronary landmark from the second it first appears in the ostium of the infarct-related artery is counted and recorded. The first frame used for TIMI frame counting is the first frame in which the contrast dye fully enters the artery [Figure 2]. That requires three criteria: a) a column of fully concentrated dye must extend across the entire width of the origin of the artery, b) dye must touch both borders of the origin of the artery, and c) there must be antegrade motion to the dye [25]. Dye may initially track down a single wall of the artery as it leaks from the catheter before the injection, and these frames are not included in the TIMI frame count [25].

The last frame is defined as the frame in which dye first enters a distal, pre-specified landmark branch. Full opacification of the branch is not required. Often, the last frame is best determined by running the cinefilm past the initial opacification of the end-point branch and then moving frame-by-frame in reverse until the end-point branch disappears [25].

The following distal landmark branches are used for analysis:

- The distal bifurcation of the left anterior descending artery (i.e., the "mustache," "pitchfork," or "whale's tail") [Figure 3A] [25].
- In the circumflex system, the distal bifurcation of the segment with the longest total distance that includes the culprit lesion [Figure 3B] [25].
- In the right coronary artery, the first branch of the posterolateral artery [Figure 3C] [25].

Proper panning is essential for evaluating the TIMI frame count.

The LAD and circumflex arteries are often assessed best in either the right or left anterior oblique views with caudal angulation, and the RCA is often assessed best in the left anterior oblique projection with steep cranial angulation [25]. The LAD frame count is 1.7 times longer than the mean of the RCA and circumflex counts. Therefore, the longer LAD

frame counts are corrected by dividing by 1.7 to derive the corrected TIMI frame count [25]. It should be noted that if an epicardial artery is occluded, then a frame count

of 100 is imputed [26].

TIMI flow grade and CTFC evaluate the restoration of blood flow in the epicardial coronary artery after reperfusion therapies. Of the two, the CTFC seems to be a more reproducible assessment of flow in patent infarct arteries than the TIMI flow grade [10,24]. Moreover, the CTFC adds additional prognostic information regarding mortality, adverse outcomes [11] and functional recovery [27].

**MYOCARDIAL BLUSH GRADE**

The MBG is a simple visual assessment of contrast opacification in the affected myocardial territory supplied by the infarct-related coronary artery, relative to non-affected myocardial territories [28]. The filling appears as a myocardial blush, a ground-glass appearance of the myocardium, on the coronary arteriogram [12]. The myocardial blush grades are defined as follows:

- LAD = left anterior descending artery
- RCA = right coronary artery
- CTFC = corrected TIMI frame count
- MBG = myocardial blush grade

- MBG 0: no myocardial blush or contrast density
- MBG 1: minimal myocardial blush or contrast density
- MBG 2: moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery
- MBG 3: normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery.

When myocardial blush persists ("staining"), this phenomenon suggests leakage of the contrast medium into the extravascular space and is therefore graded MBG 0 [13].

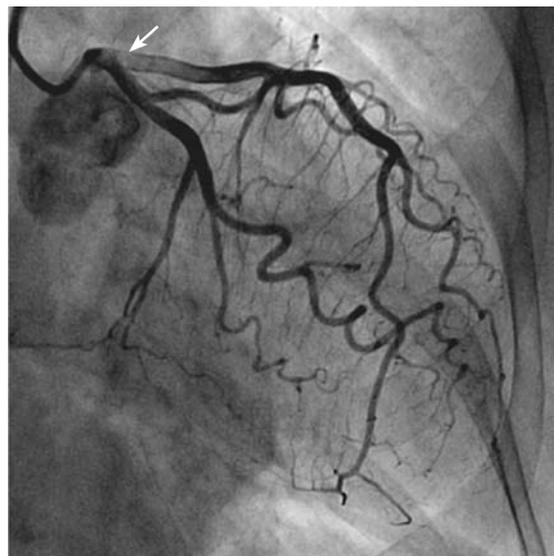
The visually densitometric evaluation of MBG is subjective [29]. There is a computerized video-densitometric technique using background subtraction for blush determination, however it is extremely sophisticated and is not widely applicable [30,31].

### TIMI MYOCARDIAL PERFUSION GRADE

TMPG is a simple, semi-quantitative, angiographic classification scheme that is used to characterize the filling and clearance of myocardial perfusion. The filling appears as a myocardial blush, a ground-glass appearance of the myocardium, on the coronary arteriogram [12]. In contrast to MBG, this index not only defines the intensity of blushing but also focuses on the rate of clearance of contrast opacity from the tissue [16]. 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 (~30 seconds between injections); in TMPG 2, dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after three cardiac cycles of the washout phase and either does not or only minimally diminishes in intensity during washout); and in TMPG 3, there is normal entrance and exit of dye in the myocardium so that dye is mildly persistent at the end of the injection (i.e., three cardiac cycles) [12,14].

The use of the myocardial perfusion as assessed by blush, both in MBG and TMPG, permits risk stratification, even among patients with TIMI grade 3 flow [12,28]. Moreover, in patients achieving normal epicardial perfusion, the degree of myocardial perfusion is strongly associated with infarct size

**Figure 4.** The first frame used for coronary clearance frame count of the LAD. It is the frame in which the contrast medium is seen to be cleared from the ostium of the LAD artery (at least 70% of the width of the artery has been washed free of contrast medium).



and subsequent early and late survival, that is independent of flow in the epicardial artery [12,14,28,29,32,33].

**The most popular method to evaluate epicardial coronary blood flow is the TIMI flow grade. Only by evaluating the myocardial perfusion, in addition to the epicardial perfusion, by using methods like myocardial blush grade (MBG), TIMI myocardial perfusion grade (TMPG), and coronary clearance frame count (CCFC), can we fully estimate the effectiveness of the reperfusion therapy.**

### CORONARY CLEARANCE FRAME COUNT

This method is considered as the opposite index of TIMI frame count. It is a quantitative index that assesses the degree of myocardial reperfusion achieved following primary angioplasty. Here also, the angiography is performed in 30 frames per second. The

CCFC measures the number of cineframes required for the clearance of the contrast medium from the examined artery. The number "0" is the first frame in which the contrast medium is seen to be cleared from the ostium of the artery (at least 70% of the width of the artery has been washed free of contrast medium) [Figure 4] and the "final frame" is that in which the contrast begins to be cleared from the same distal artery landmark proposed by the TIMI Group. As in TIMI frame count, an imputed value of 100 is used in those cases in which contrast is still present at the end of the recording (at least five beats of contrast washout) [16].

According to Perez de Prado et al. [16], who first described the CCFC, this method has a good correlation with known indices of angiographic reperfusion (as CTFC, MBG and TMPG) and has the advantage of being an objective, quan-

TMPG = TIMI myocardial perfusion grade

CCFC = coronary clearance frame count

titative index that is reliable even in the hands of relatively inexperienced practitioners. On the other hand, there were no further studies that validated these results, and at present this method is not used.

## CONCLUSIONS

In this review we describe different coronary angiography methods used to evaluate the efficacy of reperfusion therapies in patients with acute myocardial infarction.

*TIMI flow grade* was the first technique that looked at the coronary flow as a marker of an effective reperfusion therapy. It is a simple and easy-to-use method to assess flow in an epicardial coronary artery [16]. However, it is based on a subjective comparison of perfusion, and it is a categorical rather than continuous method [25].

*Corrected TIMI frame count* also evaluates epicardial flow, but with smaller inter- and intra-observer differences [25]. Many studies have shown that CTFC allows a better reproducible assessment of flow in the infarct-related artery than the TIMI flow grade [10,24], as well as better prognostic information regarding mortality, adverse outcomes [11] and functional recovery [27].

*Myocardial blush grade* is the first angiographic technique for evaluating the myocardial microvascular flow. Instead of looking at the epicardial coronary arteries, in this method the observer is looking at the opacification of the myocardium by the contrast media [13].

*TIMI myocardial perfusion grade* is another method for assessing myocardial perfusion. In contrast to myocardial blush grade, this index not only defines the intensity of myocardial blushing but also focuses on the rate of clearance of contrast opacity away from the myocardium [16]. Both techniques permit risk stratification, even among patients with TIMI grade 3 flow [12,28], and are correlated with infarct size and subsequent early and late survival, that is independent of flow in the epicardial artery [12,14,28,29,32,33].

*Coronary Clearance Frame Count*, the last method described in this review, evaluates the clearance rate of the dye from the artery as a marker of the microvascular function [16]. Although not very popular, it is a very simple and easy-to-use technique that takes into account both the epicardial blood flow and the tissue-level microvascular flow.

In conclusion, coronary angiography offers a tool with which we can evaluate the effectiveness of reperfusion therapies. By assessing the epicardial and myocardial perfusion we will have a better insight to the risk of restenosis, survival rates and even the recovery of myocardial function. This tool can help the physician to risk-stratify the patient and estimate which patient is at a higher risk for adverse outcome, thereby facilitating the best treatment for the specific patient.

Today the most popular method is the TIMI flow grade. Though it is a simple and easy way to evaluate coronary blood flow, it has many limitations. Moreover, there are situations in which flow to the infarcted myocardium is markedly reduced despite the angiographic documentation of "normal" flow in the infarct-related artery [3]. Only by evaluating the myocardial perfusion, in addition to the epicardial perfusion, can we fully estimate the effectiveness of the reperfusion therapy. Because of the great significance of those methods and their relative simplicity, it seems that in the future they will be an independent part of the evaluation of patients after reperfusion therapies.

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