The never ending quest for an ideal angiographic surrogate of coronary reperfusion

Vijayakumar Subban, Ajit S. Mulasari

Consultant, Department of Cardiology, Institute of Cardiovascular Diseases, Madras Medical Mission, Chennai, India
Director, Department of Cardiology, Institute of Cardiovascular Diseases, Madras Medical Mission, 4A, Dr. JJ Nagar, Mogappair, Chennai 600037, India

Timely restoration of infarct related artery (IRA) patency by either pharmacological or mechanical treatment is the primary goal of reperfusion therapy in acute myocardial infarction (AMI). Early reperfusion improves myocardial salvage which in turn results in superior clinical outcomes. However, it has largely been recognized over the years that substantial number of patients may not achieve tissue level perfusion even after successful recanalization of the epicardial coronaries. This phenomenon is famously known as no-reflow, and has repeatedly been shown to be associated with increased morbidity and mortality following AMI reperfusion.1,2

Since the first demonstration of coronary occlusion as the cause of AMI way back in 1980,3 coronary angiography has played a pivotal role in the evaluation of coronary flow following reperfusion either by thrombolysis or by primary percutaneous coronary intervention (PCI). Several indices have been developed over the past three decades as clinical and experimental studies have provided more insight into the pathophysiology of coronary flow in the setting of acute coronary syndrome (ACS). These indices have been validated in various clinical studies and compared positively with other modalities that assessed reperfusion in ACS. They serve as surrogate end points of reperfusion in various clinical trials and contributed immensely for the evaluation of new treatment modalities that improve coronary perfusion.4–7 This editorial briefly reviews various angiographic metrics used for the assessment of reperfusion including a short discussion on the angiographic predictors of no-reflow, and concludes with their clinical relevance in daily clinical practice.

The angiographic indices are of two types: (1) Indices of epicardial flow, (2) indices of myocardial flow, and they are further divided into qualitative or quantitative (Table 1).

1. Assessment of epicardial blood flow

1.1. TIMI flow grade

TIMI flow grade (TFG) was the first index of epicardial flow developed by Gibson et al,8 in 1985 as a part of Thrombolysis in Myocardial Infarction (TIMI) trial. It classifies coronary flow into four categories (TIMI 0–3) based on the flow rate of the contrast material in the epicardial coronary artery during angiography. The TIMI 2 grade was later subdivided into three subgroups (2a–2c) to further categorize the patients with slow flow.9 TFG is a powerful tool to predict various outcomes (mortality, reinfarction, mechanical complications, arrhythmias and LV functional recovery) following reperfusion therapy. In a meta-analysis of angiographic thrombolytic trials involving 5498 patients, complete perfusion (TFG 3) was associated with significantly lower mortality (3.7%) when compared with either with partial (TFG 2) (6.1%, \( p < 0.0001 \)) or no perfusion (TFG 0–1) (9.3%, \( p < 0.0001 \)).10 Moreover, fibrin specific thrombolytics and primary PCI which could establish TFG 3 more successfully were also associated with lesser mortality compared to streptokinase.9 Clinical events are related not only to establishment of IRA patency, but also to sustained patency. This gave birth to the concept of routine early post lysis PCI.11 The immediate availability and ease of
use has made TFG as the common surrogate end point of reperfusion in clinical trials of both thrombolysis and primary PCI. It also helped in the evaluation of newer thrombolytic agents and mechanical strategies during primary PCI to improve reperfusion in AMI.

Eventhough TFG is a simple parameter which helps to risk stratify AMI patients in the catheterization laboratory, it is limited by its subjectivity and high rate of inter-observer variability even among core laboratories. The qualitative and categorical nature made it difficult to compare among clinical trials.4,5

1.2. Corrected TIMI frame count (CTFC)

TIMI frame count (TFC) was the first quantitative angiographic parameter introduced by the TIMI group in 1991. It objectively measures the time taken by the contrast agent to reach a standardized distal landmark by counting the number of cine-frames. Corrected TFC (CTFC) uses a factor of 1.7 to adjust for length in case of left anterior descending coronary artery. The mean CTFC in normal arteries was 21.0 frames with a standard deviation of only 3.1 frames.12 Analysis of CTFC has given more insight into the pathophysiology of ACS: (1) Flow in the IRA is slower than that in the non-IRAs and further flow in the non-IRA in AMI patients is slower than that in normal patients, (2) the distribution of IRA flow is unimodal, rather than expected two peaks from slow and normal flows, (3) IRA revascularization corrects flow in IRA to that of non-IRA rather that to that in normal arteries, (4) CTFC in STEMI patients is more than that in non STEMI ACS patients, (5) flow in IRA of survivors is faster than that in nonsurvivors, (5) there exists a subgroup of patients within TFG 3 with CTFC of <14 (TFG 4) which was associated with 0% mortality, (6) for every 10-frame rise in CTFC mortality increases by 0.7%.12,13 In contrast to TFG, CTFC is an objective and continuous variable with high reproducibility and excellent agreement among core laboratories. Moreover, it provides additional prognostic information on clinical outcomes following AMI reperfusion both by thrombolysis and primary PCI. Despite these advantages, it still remains an index of epicardial flow and does not provide much information about the microvascular patency.4,5

<table>
<thead>
<tr>
<th>Table 1 – Angiographic indices of coronary reperfusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indices of epicardial flow</td>
</tr>
<tr>
<td>Qualitative</td>
</tr>
<tr>
<td>TIMI flow grade (TFG)</td>
</tr>
<tr>
<td>Quantitative</td>
</tr>
<tr>
<td>Corrected TIMI frame count (CTFC)</td>
</tr>
<tr>
<td>Indices of microvascular flow</td>
</tr>
<tr>
<td>Qualitative</td>
</tr>
<tr>
<td>Myocardial blush grading (MBG)</td>
</tr>
<tr>
<td>TIMI myocardial perfusion grading (TMPG)</td>
</tr>
<tr>
<td>Quantitative</td>
</tr>
<tr>
<td>Quantitative Blush Evaluator Score</td>
</tr>
<tr>
<td>TIMI myocardial frame count</td>
</tr>
<tr>
<td>Coronary clearance frame count</td>
</tr>
<tr>
<td>TIMI myocardial perfusion frame count</td>
</tr>
<tr>
<td>Combined Angiographic perfusion score (APS)</td>
</tr>
</tbody>
</table>

2. Metrics of myocardial perfusion

Pharmacological and mechanical reperfusion strategies evolved over the past two decades have made it possible to achieve optimal epicardial flow in more than 90% of the patients. However, from the non-invasive imaging modalities of myocardial perfusion it became evident that tissue level perfusion remained poor in substantial number of patients with TFG 3 and were associated with poor acute and long-term outcomes. This mandated the development of new angiographic end points of tissue level perfusion.14

2.1. Qualitative

There are two important qualitative indices of myocardial perfusion, namely, myocardial blush grading (MBG) and TIMI myocardial perfusion grading (TMPG). Both are based on the dynamics of the myocardial blush or ground glass appearance during coronary angiography.

MBG was the first grading system for assessment of microvascular perfusion developed by Van’t Hof et al13 in 1998. By comparing the intensity contrast (blush intensity) in the infarct territory with that of unaffected ipsilateral or contralateral territories, they divided microvascular flow into four grades (MBG 0–3). In their study of 777 patients, MBG was well related to the extent of early ST-segment resolution, enzymatic infarct size, left ventricular ejection fraction, and importantly mortality following primary angioplasty.14 This was further confirmed in various clinical studies involving thousands of patients.15,16

The real world application of MBG outside the core laboratories was evaluated in a study of 2118 patients who had primary PCI in various trials, showed that operator- scored MPG was a strong independent predictor of mortality corrected for other predictive variables such as TFG. This study showed that MPG could be applied successfully in daily practice to predict the outcomes following primary PCI.17

TMPG was developed by TIMI group and it measures the time for contrast medium filling and or clearance from the myocardium. Similar to MBG, it is also graded from 0 to 3. In a study of 762 patients in the TIMI-10B trial, the mortality was lowest in patients with TMPG 3 (2.0%), intermediate in TMPG 2 (4.4%) and highest in TMPG 0/1 (6.0%; 3 way p = 0.05). TMPG further stratified patients with normal epicardial flow (TFG 3) such that the 30 day mortality was lowest for TMPG 3 (0.73%), intermediate for TMPG 2 (2.9%) and highest for TMPG 0/1 (5.0%, p = 0.03 for TMPG 3 vs 0/1/2, 3 way, p = 0.066). In addition, TMPG was correlated with mortality after adjusting for TFG, CTFC, anterior wall myocardial infarction, pulse rate on admission, female sex and age.18 Later, TMPG was validated using quantitative assessment by digital subtraction angiography and correlating it with ST-segment resolution in STEMI patients. In addition, contrast dynamics were also assessed in non-ACS patients without obstructive CAD. Comparing to normal patients, patients with AMI had impaired microvascular perfusion as evidenced by reduction in peak myocardial contrast intensity, the rate of rise in contrast intensity, the myocardial blush circumference and the rate of growth of myocardial blush circumference. However, the dynamics in
STEMI patients with TMPG 3 were equal to those in normal patients. This explained the remarkably low mortality in patients with TFG 3/TMPG 3. In addition, ST-segment resolution and TMPG were significantly related.\textsuperscript{19}

Ungi et al.\textsuperscript{20} directly compared the MBG and TMPG methods in a study of 62 patients undergoing primary PCI, and found that TMPG better correlated with enzymatic infarct size, ST-segment resolution and left ventricular ejection fraction (LVEF) than MPG. They concluded that the clearance dynamics of contrast (TMPG) might be a better method for assessing microvascular perfusion than the densitometric method (MBG).

Though both the methods are widely used for assessing microvascular perfusion, as with other qualitative methods, high inter-observer variability is a major limitation of these methods.\textsuperscript{4}

### 2.2. Quantitative

To further improve upon the subjective nature of myocardial perfusion parameters, various quantitative indices have been developed. Digital subtraction angiography (DSA) was the most commonly used modality to assess microvascular perfusion. DSA was used to measure myocardial blush area and blush intensity (MBG quantification) and speed of myocardial blush entry and exit (TMPG quantification). New DSA techniques like ‘moving mask’ were developed to neutralize the cardiac movements.\textsuperscript{4}

#### 2.2.1. Quantitative Blush Evaluator Score

Haecck et al.\textsuperscript{21} proposed a computer-assisted myocardial blush quantification system — “Quantitative Blush Evaluator Score” (QuBE) to measure myocardial perfusion in patients with STEMI. In their study, QuBE score significantly correlated with core lab-adjudicated myocardial blush grade, ST-segment resolution immediately after PCI and with the post infarction CK–MB values. However, complex procedure and the offline nature limited its wide clinical applicability.

#### 2.2.2. TIMI myocardial frame count

Wong et al.\textsuperscript{22} used a counting system based on cTFC to objectively evaluate the microvascular flow dynamics in ACS patients, by assessing the time required for the contrast to enter the myocardium and then to reach the peak intensity. Both the parameters were prolonged in STEMI when compared to NSTEACS.\textsuperscript{22}

#### 2.2.3. Coronary clearance frame count

Coronary clearance frame count was introduced by Perez de Prado et al, as a quantitative measure of myocardial blood flow. It is an opposite index of cTFC and measures the time required for the clearance of contrast agent from the examined coronary artery post primary PCI. The frame in which contrast clears from the ostium is used as frame 0 and that in which it washes into the same coronary artery distal landmark defined by the TIMI group was considered as the last frame. It was positively correlated with both TMPG and MBG (p < 0.001) and a cut-off value of 45 frames predicted TMPG with a sensitivity of 75% and specificity of 70%. However, this method was not further validated in clinical studies.\textsuperscript{23}

#### 2.2.4. TIMI myocardial perfusion frame count

In a further step for quantitative assessment of TMPG, Ding et al.\textsuperscript{24} proposed a new perfusion index by objectively measuring the time interval of myocardial perfusion dynamics. They extended cTFC which is applied for epicardial flow assessment to the myocardial level by measuring the time required for contrast entry into and out of microcirculation. It was a quantitative and continuous index and a value of <90 frames was defined as the cut-off for normal arteries that does not differ for the three major epicardial coronaries and the standard deviation was low. When they analyzed 137 STEMI patients post procedure only 52 (38%) had TMPFC of <90. The mean TMPFC was significantly higher when RCA was the culprit artery. Moreover, in multivariate analysis, TMPFC was an independent predictor of both the 30 day and 6 month MACE. TMPFC compared positively with standard indices of epicardial (TFG and cTFC) and myocardial perfusion (TMPG and MBG). They also assessed the reproducibility of different perfusion parameters which showed moderate agreement for TFG and MBG and good agreement for TMPG, cTFC, and TMPFC.

### 3. Combined assessment epicardial and myocardial blood flow

#### 3.1. Angiographic perfusion score (APS)

It has been shown in clinical studies that the epicardial flow (TFG) both before and after primary/rescue PCI and similarly the myocardial perfusion (TMPG) both before and after primary/rescue PCI are associated with clinical outcomes. With this background, Gibson et al.\textsuperscript{25} devised an additional angiographic scoring system incorporating the above parameters. The APS is a 12 point scoring system which divides patients into 3 groups: failed perfusion (0–3), partial perfusion (4–9), and full perfusion (10–12). The APS was evaluated initially in 877 STEMI patients from two randomized trials in which it predicted death or myocardial infarction (failed, 16.7% [n = 18]; partial, 2.5% [n = 155]; full, 2.4% [n = 82]; p = 0.039 for trend) and SPECT infarct size (failed, median 39%; partial, 12% [n = 79]; and full, 8% [n = 35]; p = 0.002). In addition, no patient with full APS died and the mortality rate was 11.1% in patients with a failed APS (p = 0.03). Similarly, in patients who underwent late angiography and PCI following thrombolysis in Clopidogrel as Adjunctive Reperfusion Thera–Thrombolysis in Myocardial Infarction 28 (CLARITY–TIMI 28) study, APS predicted mortality at 30 days and in addition, full perfusion was associated with a lower incidence of recurrent myocardial infarction (MI), a composite of death and MI, recurrent myocardial ischemia, ventricular tachyarrhythmia, congestive heart failure and shock (p < 0.05 for all trends).\textsuperscript{26} Rakowski et al.\textsuperscript{27} assessed the correlation between APS and CMR parameters and N-terminal pro-brain natriuretic peptide at 6 months. Patients with APS > 10 had significantly lower infarct size, LV volumes, higher EF and lower NT pro-BNP levels.
4. Angiographic markers of no-reflow

In addition to the assessment of epicardial and microvascular flows, angiography can also predict certain adverse features which place the patient at high risk for distal embolization and no-reflow following coronary intervention in ACS setting. Yip et al., in their study of 794 patients who underwent primary PCI, identified the presence of the following six angiographic features associated with increased incidence of no-reflow: (1) IRA occlusion with an abrupt cut-off pattern, (2) accumulated thrombus (>5 mm) proximal to the occlusion, (3) floating thrombus, (4) persistent contrast stasis beyond the level of obstruction, (5) IRA reference lumen diameter ≥ 4 mm, and (6) accumulated thrombus with the greatest linear dimension more than three times the RLD in an incompletely occluded IRA.

5. What are the clinical implications of assessing myocardial perfusion?

The angiographic metrics have been validated in clinical trials and also positively compared with other invasive and non-invasive diagnostic modalities of microvascular dysfunction in the setting of ACS. These indices have now become important stratification tools in the catheterization laboratory as they are simple, readily available at no extra cost, easy to use with practice, and applicable to any patient undergoing intervention for ACS. Moreover, the risk stratification is possible immediately after PCI, well before the results of other prognostic modalities such as ST-segment resolution, peak biomarker values, echocardiogram assessed ejection fraction, or cardiac magnetic resonance obtained infarct size, are available. In addition, they further risk stratify ACS patients over and above the clinical indices routinely used in clinical practice and identify patients who will be at high risk of clinical events following intervention, in the form of left ventricular adverse remodeling resulting in left ventricular dysfunction and left ventricular failure, arrhythmias, reinfarction and mortality. Further, they also could identify subgroups of patients with greatest potential for myocardial salvage which could be a target for anti-no reflow medications and other novel myocardial protective therapies. Moreover, these patients may need close follow up to optimize the treatment strategies in the form of medications and devices.

Angiographic indices of coronary reperfusion play a pivotal role in the assessment of prognosis following reperfusion in the setting of ACS. With the better understanding of the pathology, newer markers evolved over the years. As none of the existing parameters predict outcomes accurately, the quest for the ideal marker will continue. Currently, the use of combination of indices assessing both epicardial and myocardial flows like APS might be an attractive strategy.


