Commentary

Importance of the TIMI frame count: implications for future trials

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Abstract

Although the TIMI (Thrombolysis In Myocardial Infarction) flow grade classification scheme is widely used to assess angiographic outcomes, it is limited by poor reproducibility and its categoric nature. The corrected TIMI frame count (CTFC) is a simple, more objective continuous variable index of coronary blood flow that can be broadly and inexpensively applied. This measure of the time for dye to traverse a coronary artery is both accurate (highly correlated with Doppler velocity measurements) and precise (reproducible). The method has been prospectively validated as providing independent risk stratification above and beyond the conventional TIMI flow grades. It has been shown to be a predictor of restenosis, and has been of value in elucidating the underlying pathophysiology of acute myocardial infarction. In view of the above and its ease of use, we anticipate that CTFC will become a widely used method to evaluate coronary blood flow.

Keywords: coronary blood flow, corrected TIMI frame count, myocardial blood flow, myocardial infarction, thrombolysis

Introduction

The TIMI (Thrombolysis in Myocardial Infarction) flow grade is a widely used method for the assessment of coronary artery flow in acute coronary syndromes. Flow in coronary arteries is classified as grade 0 (no flow), grade 1 (penetration without perfusion), grade 2 (partial perfusion) or grade 3 (complete perfusion). TIMI grade 3 flow requires that antegrade flow distally be as rapid as antegrade flow proximally. The PAMI (Primary Angioplasty in Myocardial Infarction) investigators have redefined TIMI grade 3 flow as opacification of the vessel within three cardiac cycles (ie 'PAMI' grade 3 flow) [1]. This new definition increases the number of arteries that are considered to have normal flow by about 10% over the original definition of TIMI grade 3 flow, requiring adjustment of analyses comparing original and redefined TIMI grade 3 flows [2].

Limitations of the TIMI flow method

The TIMI flow method for defining coronary artery flow has proven useful in assessing reperfusion strategies over the past 15 years. However, a number of limitations have become apparent. TIMI flow grade assessment is limited by interobserver variability (core laboratories agree 71% of the time) [3] and by the need for a more objective quantification of the different degrees of complete perfusion in a coronary artery. In order to overcome these problems, the TIMI frame count was developed as a more quantitative index of coronary artery flow [4].

CTFC = corrected TIMI frame count; LAD = left anterior descending artery.

Corrected TIMI frame count

Technique

In the CTFC method, the number of frames required for dye to reach a standardized distal landmark is counted. A correction factor is required to compensate for the longer length of the left anterior descending artery (LAD) compared with the circumflex and right coronary arteries (the number of frames required for dye to traverse the LAD is divided by 1.7). The frame count number after adjustment for vessel length is given the term 'corrected TIMI frame count' [4].

The first frame taken for measurements is the frame in which dye touches both borders of the coronary artery and moves forward with at least 70% opacification of the vessel lumen. The standardized distal landmarks are taken as the first branch of the posterolateral artery for the right coronary artery, most distal branch of the obtuse marginal branch for the circumflex, and the distal bifurcation for the LAD (also known as the 'whale's tail' branch of the LAD). The number of frames from the first frame to the last frame when dye enters the standardized distal landmark is counted. Centers that use image acquisition at speeds other than the most widely used frame rate in the US of 30 frames/s need to adjust CTFC assessments accordingly. For example, in the use of images acquired at 15 frames/s, frame counts are multiplied by a factor of 2 to derive the CTFC.

Highly reproducible results are obtained with very low interobserver and intraobserver variability [4]. Differences between observers are less than 0.75 frames [5] and the correlation between observers is 0.97–0.99 [6]. Varying the force of dye injection may change the frame count by up to 2 frames, which is a relatively small and insignificant difference from a clinical trial perspective [7]. Alterations in catheter size do not affect CTFC measurements [8]. Administration of nitrates, which cause enlargement of the artery and the volume to be filled with dye significantly, increases the CTFC by approximately 6 frames [8]. It is therefore important to standardize use of nitrates in studies that involve CTFC measurement, or to at least confirm that nitrate use is well balanced across arms of the trial. Injections during diastole reduce the CTFC by 6 frames [8]. Pacing at a faster heart rate (20 beats/min) reduced the CTFC by 5 frames [8].

Applications

The CTFC technique is a simple and inexpensive technique for calculation of coronary flow reserve, and is highly correlated ($r=0.88$, $P=0.0001$) with coronary flow reserve measurements obtained using the Doppler guidewire [9]. It is also correlated with volumetric flow and resting distal average peak velocity [6]. Distance along coronary arteries measured using angioplasty guidewires may be combined with TIMI frame count measurements to give absolute velocity and flow assessments that are sensitive to small changes in perfusion [10]. Indeed, although patients often have TIMI grade 3 flow both before and after the intervention, the velocity may in fact double in these patients [10]. Flow in coronary arteries after myocardial infarction or percutaneous coronary intervention is unimodally distributed across a broad range. By using the continuous variable of CTFC, it is apparent that not all TIMI grade 3 flows are created equally, and TIMI grade 3 flow can be subdivided into a wide range of velocities, providing greater risk stratification within TIMI grade 3 flow [11].

Use of the more precise CTFC has resulted in a number of interesting observations. A normal frame count is 21 ± 3 [4]. TIMI grade 3 flow in coronary arteries after thrombolysis is actually slower than normal (35.6 ± 20.8). Furthermore, previous thrombolysis studies using TIMI flow assessments have assumed basal flow in the nonculprit artery to be normal. However, assessment of CTFC has demonstrated a 45% higher frame count (21 versus 31 frames) for basal flow in the uninvolved artery [12]. This global impairment of flow in all three arteries is related to a higher risk of mortality [12]. As flow improves in the culprit artery in the setting of an acute myocardial infarction, flow also increases in the nonculprit artery. Variables other than lumen geometry slow flow in acute myocardial infarction; longer lengths of artery distal to the stenosis (more myocardium jeopardized), delayed achievement of patency, LAD location, and the presence of thrombus are all related to slower culprit artery flow [13].

By comparing the CTFC associated with different thrombolytic regimens, pharmacologic efficacy can be determined with greater statistical sensitivity compared with the previously used TIMI flow grades [14]. It is entirely possible that two drugs might have the same rate of TIMI grade 3 flow, but the velocity of TIMI grade 3 flow may be faster for one drug compared with another. As pharmacologic efficacy improves, the need to be able to discern subtle differences in flow also increases. Indeed, the CTFC was a sensitive measure of efficacy in the TIMI-14 trial of combination therapy [15].

CTFC measurements are very useful in predicting clinical outcomes. Low CTFCs after reperfusion in myocardial infarction are associated with low mortality rates. Indeed, we have again shown that not all TIMI grade 3 flows are created equally, and that even faster TIMI grade 3 flow is associated with even better outcomes. For example, those patients with a CTFC of less than 14 after thrombolysis sustained 0.0% mortality in acute myocardial infarction [16]. This hyperemic flow is what we have now come to term 'TIMI grade 4 flow'. The CTFC 90 min after myocardial infarction has been shown to predict left ventricular function at 48 h after myocardial infarction [17]. The CTFC measured 90 min after thrombolysis has also been related to improved in-hospital and 1-month clinical outcomes

[16]. Furthermore, CTFC at 1 month after myocardial infarction is highly correlated with infarct-related flow at 1 year [5]. Finally, repeat angiography after myocardial infarction or unstable angina demonstrates continued impairment in coronary artery flow 10 weeks after presentation [18], and CTFC measurements are also a predictor of reocclusion in patent infarct-related arteries [19].

The CTFC has been shown to be of value in the evaluation of percutaneous interventions. The CTFC divided by the minimum lumen diameter at the end of the intervention was the most powerful predictor of restenosis in a recent report [6]. Thus, both 'bigger and faster' is better [6]. Indeed, we have shown that the CTFC is of independent predictive value with respect to restenosis above and beyond the minimum lumen diameter and the reference diameter. We have also shown that it is related to mortality after coronary intervention in the setting of unstable angina and non-Q-wave myocardial infarction [20]. Stenting in acute myocardial infarction has been associated with a greater improvement in coronary artery flow as measured using the CTFC method [21].

Although establishing flow in acute myocardial infarction is important, this does not necessarily result in microvascular perfusion at the tissue level [22]. We have recently demonstrated [22] that inadequate perfusion of the myocardium using the TIMI myocardial perfusion grade is related to higher mortality. Despite achieving normal epicardial TIMI grade 3 flow or a CTFC of below 40, those patients with a closed microvasculature (TIMI myocardial perfusion grade 0, a pale myocardium) had a mortality of over 5%, whereas those patients with normal perfusion at the level of the myocardium (TIMI myocardial perfusion grade 3 flow) had a mortality of under 1%. Thus, restoration of epicardial blood flow is adequate, but not sufficient to ensure an optimal outcome. It is the restoration of flow at both the epicardial and tissue level that yields the best clinical outcomes. We have shown that those patients with a residual impairment of flow (a CTFC >28) despite a minimal 16% residual stenosis have a mortality rate 12 times higher than that in patients with normal flow. This again points to the critical nature of the microvasculature in determining outcomes, despite the relief of the stenosis [13].

Conclusion

The TIMI Frame Count is accurate and precise. Its simplicity and ease of use should allow it to be broadly applied to provide further insight into pathophysiology and the efficacy of reperfusion strategies

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