

REVIEW

Coronary flow evaluation in patients undergoing percutaneous coronary interventions

Pavel Platon¹

Abstract: Percutaneous coronary intervention in coronary artery disease has increased considerably over the past years, currently outnumbering the total amount of coronary artery bypass procedures. With the ever-increasing life expectancy and the improvements in cath-lab equipment and training, the number of percutaneous coronary intervention procedures is expected to rise in the near future. Thus, further research is needed to define and strengthen current indications and analyze available data.

Keywords: Cardiovascular disease, coronary artery disease, percutaneous coronary intervention, STEMI, TIMI flow grades.

Rezumat: Numărul intervențiilor de angioplastie coronariană a crescut considerabil în ultimii ani, depășind în prezent numărul pacienților la care se efectuează by-pass aorto-coronarian. Odată cu creșterea speranței de viață și a tehnicității, în laboratoarele de proceduri invazive, se așteaptă o creștere în viitorul apropiat al intervențiilor coronariene percutane. Prin urmare, pe mai departe este necesar ca cercetările să definească și să întărească indicațiile curente de revascularizare miocardică intervențională prin analiza datelor.

Cuvinte cheie: boala cardiovasculară, boala coronariană, intervențiile percutane, sindromul coronarian acut cu supradenivelare de segment ST, gradul fluxului coronarian- TIMI.

INTRODUCTION

LIFE expectancy is constantly increasing and with it coronary artery disease has become the predominant cause of substantial morbidity and mortality amongst population in the developed countries¹⁻². Interventions aimed at risk factor modification, optimization of medical therapy and patient education are effective methods of preventing and managing coronary artery disease³⁻⁴. When all these approaches fail, invasive therapy is often necessary.

Coronary balloon angioplasty was introduced for the first time in 1977 by Gruentzig and since then, aided by the evolution of equipment (mainly by the development of coronary stents) and vast improvements in operator experience, has come to address a large spectrum of coronary artery disease patients including those with multivessel lesions⁵, total artery occlusions and occluded bypass grafts⁶. Furthermore, the addition of drug eluting stents (DES), aspiration, thrombectomy and rotational atherectomy techniques increased the array of resources available for PCI.

Thus, safe and efficient revascularization can be achieved in almost any type of coronary lesion with technological progress that has taken less than half a century.

REPERFUSION THERAPY

Spontaneous rupture of a thin-capped atherosclerotic plaque with a lipid-rich core is the first event that takes place in acute coronary syndromes⁷. Platelet activation and aggregation with thrombus formation is followed by progression towards complete obstruction of the vessel lumen with distal ischemia and myocardial infarction⁸. It is currently accepted that most of the thrombotic occlusion persists in patients presenting with acute ST-segment elevation myocardial infarction and pharmacological or interventional therapy is necessary for rapid restoration of blood flow to the injured myocardium⁹.

The appropriate time interval for efficient intervention is well established - 12 hours according to the guidelines and each 30-minute delay from symptom onset increases 1-year mortality rates¹⁰. This therapeutic

¹ „Prof. Dr. C.C. Iliescu” Emergency Institute of Cardiovascular Diseases, Bucharest, Romania

▼ Contact address:

Pavel Platon, MD
 „Prof. Dr. C.C. Iliescu” Emergency Institute of Cardiovascular Diseases,
 258 Fundeni Avenue, 022328, Bucharest, Romania.
 E-mail: pavelplaton@yahoo.com

window may be hard to define in some patients with equivalents of ischemic symptoms or atypical presentations¹¹. Although thrombolysis significantly reduces mortality compared to placebo, primary percutaneous coronary intervention is the standard preferred treatment for this category of patients on the condition that experienced operators in an adequate catheterization laboratory¹² perform it. This recommendation is supported by evidence, which shows lower mortality and additional long-term benefits in patients treated in high-volume centers, per procedural complications being more common than in the case of elective PCI due to patients, which are often hemodynamically, or electrically unstable¹³.

However, a majority of patients comes into first contact with a non-PCI capable center and often a pharmaco invasive strategy is employed with similar results as primary PCI strategy regarding mortality, although with higher rates of bleeding complications¹⁴⁻¹⁶.

The complexity involved in the variation of blood flow through an infarct related artery cannot fully be represented by a brief image in time with a simple angiographic view¹⁷⁻¹⁸.

A standardized method for clinical practice and comparing different research data was necessary, hence a grading system termed TIMI flow grade, or TFG (Thrombolysis in Myocardial Infarction) was defined in the early 1980s. Several angiographic studies have shown correlation between the TIMI flow grades short-term, long-term outcomes and mortality in STEMI patients undergoing PCI¹⁹⁻²¹.

Grade TIMI 0 indicates no flow at all distal to the obstruction, while grade TIMI 1 indicates a tendency for penetration with contrast material beyond the obstruction point without pacifying the entire artery. These patients have the highest rates of mortality, worse NYHA functional class at follow-up and required more reinterventions²²⁻²³. Grade TIMI 2 represents adequate perfusion of the affected vessel down to the distal bed, but with delayed flow while grade TIMI 3 suggests restoration of perfusion with normal vessel flow. These patients have the lowest rates of mortality registered by research (6.4% versus 32.9% in the TIMI 0-1 group) and thus the objective of all coronary interventions is to restore normal TIMI 3 flow within the affected coronary vessel²⁴⁻²⁵.

One of the first studies that researched TIMI flow in primary PCI for STEMI patients found that strong predictors for post-interventional flow are age, infarct

localization, multivessel disease, diabetes mellitus, and inefficient thrombolytic therapy²⁶.

Although TIMI flow grade is generally the most used tool in clinical practice, it is sometimes restricted by its several limitations such as the subjective description and being an operator dependent parameter²⁷. Other angiographic criteria developed by Gibson, the TIMI Frame Count, also known as corrected TIMI frame count (CTFC), is a semi-quantitative method for assessing blood flow defined as the number of angiographic cine frames necessary for contrast substance to arrive in the distal circulation after the point of interest²⁸. This index is considered simpler, more objective and reproducible and thus can be used to differentiate between low-risk and high-risk groups of TIMI 3 patients²⁹.

The microvascular flow, assessed by myocardial blush grades (MBG) is described as follows: grade 0 refers to no myocardial blush or "persistent stain" suggesting the exit of contrast substance into the extravascular space, grade 1 indicates minimum myocardial blush, grade 2 - moderate myocardial blush and grade 3 refers to normal myocardial blush, similar to unaffected areas. For proper grading, it is necessary to run long enough fluoroscopy acquisitions to capture the venous phase of contrast clearance³⁰. In HORIZONS-AMI trial, myocardial blush grades of 2-3 were achieved in 77% of patients and MBG was found to be an independent predictor of mortality and long-term benefits, but no correlation between MBG and ST segment resolution were found³¹. Another study, which evaluated the MBG in 2118 consecutive STEMI patients found this marker to be prognostic for 1 year all-cause mortality and noted that it should be used in addition to TIMI flow grade evaluation³².

Although the main focus of the reperfusion therapy is to alleviate and obtain an angiographically satisfying image of blood flow in the epicardial artery, the ultimate goal still remains to improve perfusion at the microcirculation level. This concept is emphasized most notably while experiencing the "no reflow" phenomenon with persistence of poor myocardial perfusion after resolution of the infarct related artery occlusion. First described in 1974 by Kloner, "no reflow" is a multi-factorial and complex complication that is not yet fully understood. It is generally agreed that there is a combination of underlying key mechanisms, which add to distal perfusion disruption. No reflow is associated with left ventricular remodeling, poor clinical outcome and heart failure with reduced left ventricular ejection fraction³³.

Longer periods of ischemia (more than 90 minutes), distal thrombus embolization (promoted by fibrinolytic therapy), mechanical fragmentation of the atherosclerotic lesion during PCI and endothelial dysfunction followed by platelet-mediated aggregation are decisive components that contribute to it. Reperfusion injury can also cause myocardial cell edema, oxygen free radical formation, local inflammatory response with cytokine activation and coronary vasospasm³⁴. A similar perfusion anomaly, called the slow flow phenomenon (CSFP) is an entity defined by late contrast artery opacification that is observed in up to 5% of patients undergoing diagnostic coronarography and has poor prognostic implications³⁵. Impaired myocardial flow is associated with cardiac arrhythmias, contractile dysfunction and heart failure.

Amidst the techniques used for diagnosis and assessment of the no-reflow status, myocardial contrast echocardiography (MCE) is considered the gold standard, while coronary angiography and magnetic resonance imaging are reasonable alternatives. Qualitative evaluation involving coronary angiography relies on TIMI flow grades, corrected TIMI frame count and myocardial blush grade. Comparative data of TIMI grade 2 flow or lower and MCE evaluation show the presence of substantial no-reflow zone in this subgroup. Also, ECG pattern that is not consistent with reperfusion evolutivity (>50% resolution of ST elevation in less than 90 minutes) is also suggestive of no-reflow phenomenon. Literature data suggests that this group of patients has negative long-term prognostic with a higher risk of mortality and developing heart failure. Meanwhile, in patients where ST-segment resolution is achieved and early T wave inversion, comparative data with MCE show a high correlation with successful myocardial reperfusion and better long-term outcomes³⁶.

As for treatment of “no-reflow”, up to date, there are several studies that investigated the use of vasodilators such as verapamil or adenosine showing moderate or no benefit³⁷. Another proposed solution to this problem was the deferred stenting strategy as an addition to reduce microvascular load and to protect the distal microcirculation³⁸. Recent studies showed controversial results in that perspective which prompted current guidelines advising against this procedure.

Thrombus aspiration may be used during primary PCI to avoid distal embolization and to protect tissue perfusion. There is conflicting evidence regarding this procedure. The TAPAS trial, which included 1071 pa-

tients undergoing PCI vs thrombus aspiration + PCI, investigated the post procedural frequency of myocardial blush grade 0 or I and post procedural frequency of TIMI 3 flow grade. This study showed a significant 1-year clinical improvement and lower mortality rates in the thrombus aspiration group³⁹.

The TASTE Swedish trial, which included 7244 patients divided into the same groups, failed to show any significant differences between the PCI group and the group that received additional thrombus aspiration therapy⁴⁰. Moreover, the recent TOTAL trial, with 10.063 patients showed that, while routine thrombectomy had no impact on total cardiovascular death and recurrent myocardial infarction, it increased the rate of stroke. Thus, current guidelines do not recommend the use of routine thrombus aspiration during primary PCI¹⁰.

There is scarce data in the literature with focus on intracoronary fibrinolysis or antithrombotic agents in patients with STEMI and large intraluminal thrombus, a situation associated with adverse results such as failure of thrombus aspiration and difficulty in obtaining proper reperfusion.

Massive thrombi are often hard to aspirate through a narrow catheter increasing the risk of rupture and embolization downstream. Few case studies, which included less than 100 patients, showed TIMI flow and myocardial blush improvement by at least 1-grade and mortality benefits in such cases. One particular research displayed marked improvements from TIMI flow 0-1 in 84% patients before thrombolysis to TIMI flow 3 in 75% patients post intracoronary thrombolysis⁴¹.

The INFUSE-AMI randomized trial evaluated intracoronary administration of abciximab and aspiration thrombectomy in patients with anterior myocardial infarction and showed smaller infarct size by bolus abciximab and no benefit of thrombaspiration⁴². A meta-analysis overseeing eight randomized trials enrolling a total of 3259 patients compared mortality, recurrent myocardial infarction, post procedural TIMI 3 and MBG perfusion grades and showed that intracoronary administration of abciximab was associated with significant benefits with regarding to myocardial perfusion.

CONCLUSION

The wide spectrum of coronary artery disease varies from stable angina to acute coronary syndromes. Atherosclerotic plaque rupture with subsequent thrombus formation is the main cause of coronary artery occlusion and ST elevation myocardial infar-

tion. Brisk opening of the affected artery is crucial for restoring blood flow to the injured myocardium. Percutaneous coronary intervention is currently recommended by the guidelines as the standard treatment of choice, with large randomized studies that shown significant improvements in long-term mortality and morbidity. Nevertheless, normal myocardial perfusion is not currently achieved in all treated patients. Several problems arise, from logistical issues that prevent timely intervention to peri-procedural complications such as no reflow phenomenon and conflicting literature data regarding the proper therapeutic attitude in particular scenarios. Different coronary flow evaluation tools have been developed and standardized for aiding both clinical practice and research. TIMI flow grade, TIMI frame count and myocardial blush grade are well-established instruments with strong data supporting correlation between these and long term outcomes. Further research is needed to identify other indicators for evaluating coronary blood flow as well as myocardial perfusion.

Conflict of interest: none declared.

References

- Zhu KF, Wang Ym, Prevalence of coronary heart disease and its relationship with human development index: A systematic review. *Eur J Prev Cardiol* 2016; 23: 530-43.
- Gaziano TA, Bitton A, Growing epidemic of coronary heart disease in low- and middle-income countries. *Curr Probl Cardiol*. 2010 35(2): 73-115.
- NICE Public Health Guidance 25. Prevention of Cardiovascular disease. (<http://www.nice.org.uk/guidance>).
- Cooney MT, Dudina A, Whincup P, Capewell S, Menotti I. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. *Eur J Cardiovasc Prev Rehabil* 2009;16:541-549.
- Bravata DM, Gienger AL, McDonald KM, Sundaram V, Perez MV, Varghese R, et al. Systematic Review: The Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Graft Surgery. *Ann Intern Med*. 2007;147:703-716.
- Serruys PV, Morice MC. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009; 360:961
- Davies, M. (2000). The pathophysiology of acute coronary syndromes. *Heart*, 83(3), 361-366.
- Ambrose, J. A., & Singh, M. (2015). Pathophysiology of coronary artery disease leading to acute coronary syndromes. *FI000 Prime Reports*, 7, 08.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomized trials. *Lancet* 2003;361(9351):13-20
- 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European Heart Journal* (2017) 00, 1-66.
- Ahmed AH, Shankar K, Eftekhari H, et al. Silent myocardial ischemia: Current perspectives and future directions. *Experimental & Clinical Cardiology*. 2007;12(4):189-196.
- Ao Badheka, NJ Patel, et al. Impact of annual operator and institutional volume on percutaneous coronary intervention outcomes: a 5-year United States experience. *Circulation*. 130(16): 1392. 2014.
- West RM, Cattle BA, Bouyssié M, Squire I, et al. Impact of hospital proportion and volume on primary percutaneous coronary intervention performance in England and Wales. *Eur Heart J* 2011; 32(6):706-711.
- Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, 'PRAGUE' Study Group Investigators. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicenter trial—PRAGUE-2. *Eur Heart J* 2003;24(1):94-104.
- Jeronimo S, Campante T. Primary PCI in ST-elevation myocardial infarction: mode of referral and time to PCI. *Rev. Port Cardiol* 2012. 31(10):641-6
- Gehani A, Arafa S. Primary coronary angioplasty for ST-Elevation Myocardial Infarction in Qatar: First nationwide program. *Glob Cardiol Sci Pract*. 2013 Nov 1;2012(2):43-55.
- Duncker DJ, Merkus D. Regulation of coronary blood flow. Effect of coronary artery stenosis. *Arch Mal Coeur Vaiss*. 2004 Dec; 97(12):1244-50.
- Duncker DJ, Koller A. Regulation of coronary blood flow in health and ischemic heart disease. *Prog Cardiovasc Dis*. 2015 Mar-Apr; 57(5):409-22.
- De Luca G, Ernst N. Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol*. 2004 Apr 21;43(8):1363-7.
- Kalińczuk L, Karcz M, Petryka J, Kaczmarska E, Comparison of prognostic value of epicardial blood flow and early ST-segment resolution after primary coronary angioplasty. ANIN - Myocardial Infarction Registry. *Kardiol Pol*. 2007 Jan;65(1):1-10;
- Stringer KA. TIMI grade flow, mortality, and the GUSTO-III trial. *Pharmacotherapy*. 1998 Jul-Aug; 18(4):699-705.
- Uyarel H, Ayhan E, Cicek G. Suboptimal coronary blood flow after primary percutaneous coronary intervention for acute myocardial infarction: incidence, a simple risk score, and prognosis. *Coron Artery Dis*. 2012 Mar; 23(2):98-104.
- C. Michael Gibson, MS, MD; Christopher P. Cannon, MD; Sabina A. Murphy Relationship of the TIMI Myocardial Perfusion Grades, Flow Grades, Frame Count, and Percutaneous Coronary Intervention to Long-Term Outcomes After Thrombolytic Administration in Acute Myocardial Infarction. *Circulation*. 2002; 105:1909-1913.
- Kammler J et al. TIMI 3 flow after primary angioplasty is an important predictor for outcome in patients with acute myocardial infarction. *Clin Res Cardiol* 2009; 98(3):165-70.
- Mehta RH, Ou FS, Peterson ED, Clinical significance of post-procedural TIMI flow in patients with cardiogenic shock undergoing primary percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2009 Jan; 2(1):56-64.
- The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial. *N Engl J Med* 1985, 932-6.
- C. Michael Gibson, Christopher P. Cannon, William L. Daley. TIMI Frame Count. *Circulation*. 1996; 93:879-888.
- Appleby MA, Michaels AD, Chen M, Michael CG. Importance of the TIMI frame count: implications for future trials. *Current Controlled Trials in Cardiovascular Medicine*. 2000; 1(1):31-34.
- Hamada S, Nishiue T, Nakamura S; et al. (2001). «TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction». *J. Am. Coll. Cardiol*. 38 (3): 666-71. PMID
- Hoffmann R, Haager P, Arning J, Usefulness of myocardial blush grade early and late after primary coronary angioplasty for acute myocardial infarction in predicting left ventricular function. *Am J Cardiol*. 2003 Nov 1; 92(9):1015-9.
- Brener SJ, Dizon JM, Mehran R, Complementary prognostic utility of myocardial blush grade and ST-segment resolution after primary percutaneous coronary intervention: analysis from the HORIZONS-AMI trial. *Am Heart J*. 2013 Oct;166(4):676-83
- Kampinga MAI, Nijsten MW, Gu YL, Is the myocardial blush grade scored by the operator during primary percutaneous coronary intervention of prognostic value in patients with ST-elevation myocardial infarction in routine clinical practice? *Circ Cardiovasc Interv*. 2010 Jun 1; 3(3):216-23.

33. Ito H et al. (1996) Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 93: 223–228.
34. Kloner RA. No-reflow phenomenon: maintaining vascular integrity. *J Cardiovasc Pharmacol Ther.* 2011 Sep-Dec; 16(3-4):244-50.
35. Wang X, Nie S-P. The coronary slow flow phenomenon: characteristics, mechanisms and implications. *Cardiovascular Diagnosis and Therapy.* 2011; 1(1):37-43.
36. SanjivKaul, The "no reflow" phenomenon following acute myocardial infarction: Mechanisms and treatment options, *Journal of Cardiology* Volume 64, Issue 2, August 2014, Pages 77-85
37. Harding SA. The role of vasodilators in the prevention and treatment of no-reflow following percutaneous coronary intervention. *Heart.* 2006; 92(9):1191-1193.
38. Carrick D, Oldroyd KG, McEntegart M, et al. A Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or Slow-Reflow in Acute ST-Segment Elevation Myocardial Infarction (DEFER-STEMI). *Journal of the American College of Cardiology.* 2014; 63(20):2088-2098.
39. Sanjit S. Jolly, M.D., John A. Cairns, M.D., Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy. *N Engl J Med* 2015; 372:1389-1398.
40. Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction. *N Engl J Med* 2013; 369:1587-1597
41. Boscarelli D, Vaquerizo B, Miranda-Guardiola F. Intracoronary thrombolysis in patients with ST-segment elevation myocardial infarction presenting with massive intraluminal thrombus and failed aspiration. *Eur Heart J Acute Cardiovasc Care.* 2014 Sep; 3(3):229-36.
42. Stone GW1, Maehara A, Witzenbichler B, Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA.* 2012 May 2; 307(17):1817-26.
43. De Luca GI, Verdoia M, Suryapranata H. Benefits from intracoronary as compared to intravenous abciximab administration for STEMI patients undergoing primary angioplasty: a meta-analysis of 8 randomized trials. *Atherosclerosis.* 2012 Jun; 222(2):426-33.
44. Simina Crisan, Cristina Vacarescu, Alina-Ramona Nicola, Microcirculation as a target of myocardial reperfusion in acute coronary syndromes. *Romanian Journal of Cardiology* 2016 (26), 435-437.