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Microvascular Obstruction In PCI - A Review

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Introduction

Successful revascularization of the epicardial coronary artery can be achieved in over 90% of percutaneous coronary intervention procedures. However, post procedural microvascular obstruction, despite the presence of normal epicardial flow, remains an important limitation which substantially reduces the beneficial effects of percutaneous coronary intervention. In this review article, a number of different methods available to diagnose microvascular obstruction after percutaneous coronary intervention are outlined. We also discussed the various pharmacological and mechanical strategies to reduce the occurrence of microvascular obstruction. In this regard, pretreatment with antiplatelet therapy remains crucial. In urgent percutaneous coronary intervention for acute myocardial infarction, available data suggest that manual thrombus aspiration device is beneficial in reducing the occurrence of procedure-related microvascular obstruction and possibly improve long-term clinical outcomes.

In the setting of ST-segment elevation myocardial infarction (STEMI), urgent PCI restores coronary perfusion, reduces myocardial damage, and improves survival. Over the last decade, the paradigm has shifted from epicardial artery patency to microvascular perfusion Distal embolization of atherosclerotic and/or thrombotic materials is most likely the predominant pathophysiological mechanism leading to post-PCI microvascular obstruction

Other proposed contributing factors include coronary spasm, dissection, endothelial dysfunction, and inflammation. The relative contribution of these factors may differ in different clinical settings. Microvascular obstruction after PCI is associated with adverse long-term clinical outcomes, including higher risk of death and myocardial infarction. As a result, various pharmacological and nonpharmacological strategies have been evaluated to prevent post-PCI microvascular obstruction. Recently, lesion composition determined by IVUS(necrotic core and thin-cap fibroatheroma) MSCT has been shown to be of predictive value for occurrence of post-PCI microvascular obstruction.

Techniques for diagnosing microvascular obstruction after PCI –invasive and noninvasive

Thrombolysis In Myocardial Infarction Flow Grade-

Measures how rapidly the radiographic dye opacifies the target epicardial coronary artery. Antegrade coronary flow is divided into 4 grades, TIMI grade 0 to grade 3. TIMI grade 3 flow is considered as normal, brisk coronary flow, TIMI grade 0 to grade 2, as no-reflow phenomenon (some consider TIMI grade 2 flow as slow-flow). Caveat of using TIMI flow grade is that mechanical obstructions (such as occlusive thrombus, flow-limiting dissection and significant residual stenosis) at the level of epicardial artery need to be excluded before the diagnosis of no-reflow can be made.

Myocardial Blush Grade. (MBG)

Refers to the relative "blush," or intensity, of the radiopacity of myocardial tissue and the rapidity with which this enhancement clears. The more intense the myocardial blush of the contrast medium and the faster its clearance, the better the microvascular perfusion. The MBG is classified 4 grades, from 0 to 3. The detailed definition is shown in Table 2. In the absence of mechanical obstructions at the level of epicardial artery, microvascular obstruction is defined as MBG 0/1. TIMI myocardial perfusion grade is a similar technique derived by another group.[3]

Corrected TIMI Frame Count

The TIMI frame count determines the number of cineangiographic frames, which are commonly acquired at 25 to 30 frames per second, that is required for contrast dye to fill the epicardial vessels or to reach a standardized distal landmark. A low TIMI frame count represents rapid coronary perfusion; conversely, a high TIMI frame count represents slow coronary perfusion.

The frame count number after adjustment for vessel length is termed the corrected TIMI frame count (CTFC). In the absence of mechanical obstructions at the level of epicardial artery, microvascular obstruction is traditionally defined as CTFC > 28

Coronary Flow Reserve. Coronary flow reserve (CFR)- Analyzed with a 0.014-inch Doppler-tipped guidewire positioned at the target coronary artery.[6] With induction of hyperemia by intracoronary or intravenous adenosine, CFR is computed as the ratio of hyperemic average peak velocity to baseline average peak velocity. A CFR of less than 2.0 is often considered abnormal.

Index of Microcirculatory Resistance. Index of microcirculatory resistance (IMR)- A novel index for measuring microvascular obstruction. Like CFR, IMR requires placement of a pressure sensor/thermistor-tipped guidewire into the target coronary artery. The IMR is derived by dividing distal coronary pressure by the inverse of the hyperemic mean transit time (a correlate to absolute flow) measured simultaneously with the coronary pressure wire. IMR has the advantages of being specific for microvascular circulation and independent of Epicardial obstruction and hemodynamic condition.

Noninvasive Methods

ST-segment Resolution on 12-Lead Electrocardiography. Measurement of STsegment resolution on 12-Lead electrocardiography (ECG) using a hand held caliper is a simple and inexpensive method to assess microvascular perfusion after STEMI. After coronary reperfusion therapy, complete ST-segment resolution implies good microvascular perfusion and favorable prognosis, whereas sustained or additional elevation of the ST segment is associated with unfavorable functional and clinical outcomes.

Single Photon Emission Computed Tomography-

Administration of macroaggregated albumin microspheres in Single photon emission computed tomography (SPECT) scan and subsequent monitoring the distribution is a useful method to study microvascular obstruction, especially after revascularization of epicardial coronary arteries for myocardial infarction. Residual macroaggregated albumin perfusion defect reflects the area of microvascular obstruction in the presence of birsk epicardial blood flow

Myocardial Contrast Echocardiography-

Myocardial contrast echocardiography uses microbubbles during echocardiography. These microbubbles remain exclusively within the intravascular space; hence, their presence within any myocardial territory implies intact microvasculature within that region. Myocardial contrast intensity reflects the concentration of microbubbles within the myocardial capillaries and, therefore, myocardial blood volume. In patients undergoing PCI for acute myocardial infarction, the myocardial contrast echocardiography technique has been applied to determine restoration of microvascular integrity , failure of which causes low-flow or no-reflow phenomenon despite revascularization of epicardial vessels) that ultimately impacts on left ventricular reverse remodeling.

Contrast-Enhanced Cardiac Magnetic Resonance Imaging-

In a first-pass myocardial perfusion study, images are acquired as soon as the gadolinium contrast is injected. Early enhancement images, acquired within 1 to 2 minutes after gadolinium contrast administration, allow the in vivo visualization of regions of no reflow or microvascular obstruction in acute myocardial infarction. These regions manifest as hypointense (dark) areas usually within the subendocardium of the infracted territory. In animal models, the hypointense regions correlate with microvascular obstruction within the infarct core on histopathologic examination. Late enhancement images, obtained 5 to 10 minutes after contrast administration, reveal infarcted myocardium as hyperintense (bright) regions within the myocardium.

Biomarkers-

Myonecrosis, commonly defined as elevation of serum levels of cardiac enzymes (Creatine Kinase, CK and Creatine Kinase-MB fraction, CK-MB) after an otherwise successful nonurgent PCI, occurs in up to 30% of patients. Evidence of microvascular obstruction by MRI has been demonstrated in patients with cardiac enzyme elevation after PCI. Most episodes of post-PCI myonecrosis are clinically silent. Nevertheless, there is a stepwise increase in the risk of long-term adverse events with increasing levels of cardiac enzyme elevation. Although troponin elevation has been incorporated into the diagnosis of acute myocardial infarction, the prognostic implication of troponin elevation after PCI is controversial.

Antiplatelet Agents-

Antiplatelet therapy preserves microvascular integrity by inhibiting formation of platelet thrombi that can occlude the microcirculation. In nonurgent PCI, loading with 600 mg of clopidogrel before PCI resulted in myonecrosis in 14% of patients, compared with myonecrosis in 26% of patients after 300 mg loading dose of clopidogrel. Prasugrel, a novel thienopyridine, was found to be more effective than clopidogrel in reducing PCI-related myocardial injury in patients with acute coronary syndrome. Ticagrelor, a reversible oral P2Y12 receptor antagonist, are currently under phase III clinical investigation.

Adjunctive glycoprotein IIb/IIIa inhibitors reduce microvascular obstruction after PCI. To date, robust data support the use of adjunctive glycoprotein IIb/IIIa inhibitors in patients with high-risk acute coronary syndrome.[12] Intracoronary administration is associated with a several-hundred-fold increase in the local concentration of the agent. There has been suggestion that the benefits of glycoprotein IIb/IIIa inhibitors are greater after intracoronary compared with intravenous administration, although lack of data on area-at-risk at baseline and small sample size remain the major limitations of the study.[13] Bivalirudin was shown to be associated with reduced bleeding complications while preserving ischemic endpoints when compared with glycoprotein IIb/IIIa inhibitors .

Statins-

The antiinflammatory effect of statins may reduce myonecrosis after PCI. In a double-blind, randomized trial, pretreatment with 40 mg of atorvastatin for 7 days before PCI reduced myonecrosis from 35% to 12%.[14] In a meta-analysis including mostly retrospective and observational studies, 196 of 2149 patients (9.1%) in the statin-treated group developed myonecrosis, compared with 455 of 2602 patients (17.5%) in the control group (P < .01). Subject to limitations of this analysis, it was concluded that routine pretreatment with statins may decrease PCI-related myonecrosis. Large randomized controlled trials addressing the dose, duration, and type of statin on PCI-induced myonecrosis are warranted. Nonetheless, as aggressive lipid lowering is indicated for patients with symptomatic coronary artery disease per se, most patients are already being treated with statins at the time of PCI.

Beta-Blockers-

The microcirculatory protective effect of beta-blockers was studied in a double-blind randomized trial. A total of 150 patients undergoing nonurgent PCI were assigned to intracoronary propranolol or placebo groups. Postprocedural myonecrosis as evidenced by elevation of cardiac enzymes occurred less commonly in the propranolol group (17%) than the placebo group (36%, P = .01), suggesting a protective effect of the beta-blocker. At 30 days, the composite endpoint of death, postprocedural myocardial infarction, non-Q wave myocardial infarction after PCI, hospitalization, or urgent target lesion revascularization was lower in the propranolol group (18%) than the placebo group (40%, P = .001).[15]

Adenosine-

Adenosine is a naturally occurring nucleoside with a half-life in blood of less than 10 seconds. Results from an animal study suggested that endogenous release of adenosine could compensate for the distal embolization of small particles. Results from a small study involving 28 patients suggested that adenosine infusion may reduce the occurrence of myonecrosis after nonurgent PCI. In a prospective randomized study, we found that pretreatment with 50µg of adenosine decreases the incidence of myonecrosis from 39% to 13% after PCI to de novo native coronary arteries, compared to standard PCI without pretreatment. In patients undergoing urgent reperfusion therapy for acute myocardial infarction, early studies suggested that adenosine infusions may reduce heart muscle damage. However, some studies did not demonstrate a significant benefit of adenosine pretreatment, possibly due to the overwhelming amount of red thrombi that embolize during acute myocardial infarction and the fact that adenosine was administered only after the onset of acute infarction, by which time significant distal embolization would have already occurred.

Nicorandil. Nicorandil has a hybrid characteristic of nitrate and ATP-sensitive potassium channel opener. In preliminary studies, administration of nicorandil reduced the occurrence of microvascular obstruction after PCI for stable and unstable coronary syndrome. Further studies are warranted to determine the optimal dose and route of administration, as well as potential side effects of adjunctive nicorandil in PCI.

Mechanical Strategies to Prevent Microvascular Obstruction

Thrombectomy devices

Remove intracoronary thrombus by generating an active and strong suction force. The thrombus is fragmented into many small microemboli that are aspirated as the thrombectomy catheter is moved forward and backward across the coronary lesion. The XSizer device (EndiCOR Inc., San Clemente, California, USA) and the rheolytic thrombectomy device (AngioJet, Possis Medical, Minneapolis, Minnesota, USA) are the prototypes. Although based on similar working principles, manual thrombus aspiration devices generate lower vacuum suction force compared with X-Sizer and rheolytic thrombectomy devices.

Technique: Advantages -Disadvantages

Invasive

TIMI flow grade A simple method for routine clinical use. Visual estimation, inter-observer variability. Only captures angiographic no-flow phenomenon.

Myocardial blush grade Can be performed during the PCI procedure without additional cost. Duration of the angiographic run must be adequately long to see the venous phase of the contrast passage. Specific views required.

Corrected TIMI frame count Simple and inexpensive. can be performed during the PCI procedure without additional cost. A small cine magnification is required to capture the path of the entire target artery. Time consuming when it is used real-time.

Coronary flow reserve Relative ease of performance. Quantitative.

Interrogates the flow status of both the epicardial artery and the microcirculation. Affected by hemodynamic condition, left ventricular hypertrophy. Small risk of iatrogenic complication from the pressure wire.

Index of microcirculatory resistance

Non-invasive

Relative ease of performance and interpretation. Quantitative.

Small risk of iatrogenic complication from the pressure wire. Normal value unknown.

Resolution of ST-segment

Elevation on ECG

A simple and inexpensive method to assess microvascular perfusion after ST-segment elevation myocardial infarction, widely available. Only suitable for ST-segment elevation myocardial infarction. Suboptimal resolution may reflect either epicardial artery occlusion or microvascular obstruction.

Single photon emission computed tomography

Widely available. Injection of radioactive substance.

Contrast echocardiography Determination of ventricular volumes, function, and other consequences of myocardial infarction. Limited availability. Depends on image quality. Artifacts.

Cardiac magnetic resonance imaging

High spatial resolution. Determination of ventricular volumes, function, and other consequences ofmyocardial infarction. Unencumbered by windows of access and the risk of radiation exposure. Limited availability and expensive. Artifact in patients who cannot hold their breath or who have arrhythmia or claustrophobia. Risk of nephrogenic systemic fibrosis in patients with renal failure.

Biomarkers Widely available. No special technique required. Interpretation can be difficult in myocardial infarction, due to baseline elevation of cardiac enzymes. Unable to discriminate myonecrosis from myocardial injury due to side branch occlusion

Myocardial Blush Grade Definition

0 No myocardial blush or contrast density. Myocardial blush persisted ("staining").

1 Minimal myocardial blush or contrast density.

2 Moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery.

3 Normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral noninfarct-related coronary artery.

References

1. Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H, Matsui H, Toki Y, Ito T, Hayakawa T. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. *J Am Coll Cardiol.* 2000; 36: 1202–09
2. Stone GW, Webb J, Cox DA, Brodie BR, Qureshi M, Kalynych A, Turco M, Schultheiss HP, Dulas D, Rutherford BD, Antoniucci D, Krucoff MW, Gibbons RJ, Jones D, Lansky AJ, Mehran R. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *JAMA.* 2005; 293: 1063–72.
3. Thibault H, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G, Cung TT, Bonnefoy E, Angoulvant D, Aupetit JF, Finet G, Andre-Fouet X, Macia JC, Raczka F, Rossi R, Itti R, Kirkorian G, Derumeaux G, Ovize M. Long-term benefit of postconditioning. *Circulation.* 2008; 117: 1037–44
4. Beek AM, Nijveldt R, van Rossum AC et al (2009) Intramyocardial hemorrhage and microvascular obstruction after primary percutaneous coronary intervention. Int J Cardiovasc Imaging. doi:10.1007/s10554-009
5. El-Jack SS, Suwatchai P, Stewart JT, Ruygrok PN, Ormiston JA, West T, Webster MW. Distal embolization during native vessel and vein graft coronary intervention with a vascular protection device: predictors of high-risk lesions. *J Interv Cardiol.* 2007; 20: 474–80
6. Napodano M, Ramondo A, Tarantini G, Peluso D, Compagno S, Fraccaro C, Frigo AC, Razzolini R, Iliceto S. Predictors and time-related impact of distal embolization during primary angioplasty. *Eur Heart J.* 2009; 30: 305–13
7. Ronen Jaffe Alexander Dick, Bradley H. Strauss, Prevention and Treatment of Microvascular Obstruction-Related

Myocardial Injury and Coronary No-Reflow Following Percutaneous Coronary Intervention J Am Coll Cardiol Intv, 2010; 3:695-704, doi:10.1016/j.jcin.2010.05.004

8. The pathogenesis and treatment of no-reflow occurring during percutaneous coronary intervention Mohammad-Reza Movahed, Samuel M. Butman Cardiovascular Revascularization Medicine 2008; 9(1): 56-61.

9. Anterograde recanalisation of the radial artery followed by transradial angioplasty , 03 September 2010 Zoltán Ruzsa, László Pintér, Ralf Kolvenbach Cardiovascular Revascularization Medicine October 2010 (Vol. 11, Issue 4, Pages 266.e1-266.e4)

10. Widimsky P, Bilkova D, Penicka M, et al. Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention. Five years' follow-up of the PRAGUE-2 trial. Eur Heart J 2007;28:679–84.

11. Stenestrand U, Lindback J, Wallentin L. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. JAMA 2006;296:1749–56.

12. Morgan KP, Leahy M, Sheedy C, et al. United Kingdom Primary Angioplasty Costeffectiveness Study (UK Paces) 30 day out-come data. Heart 2005;91(Suppl I):A27.

13. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;293:1063–72.

14. Ali A. AngioJet rheolytic thrombectomy in patients undergoing primary angioplasty for acute myocardial infarction (AIMI study). Transcatheter Therapeutics 2004; tctmd.com.

15. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21