NO REFLOW PHENOMENON

Omid Hashemifard[(1)]

***ARYA Atherosclerosis Journal* 2009, 5(3):**

Date of submission: 15 Apr 2009, ***Date of acceptance:*** 12 Jun 2009

Definition

No reflow is a phenomenon in which myocardial ischemia and reduced antegrade flow occur despite the absence of proximal stenosis, spasm, dissection, or embolic cut off of major distal branches.[1] In another word no reflow phenomenon means failure of restoration of myocardial flow despite removal of epicardial coronary obstruction.[2] The incidence is 2% with plain balloon angioplasty (PTCA), 7% in patients undergoing rotational atherectomy, 12% for primary percutaneous coronary intervention (PCI), and much higher at 42% for PCI of degenerated Saphenous Vein Graft (SVG).[3] No reflow is a strong predictor of mortality after PCI. The mortality of patients who developed no reflow has been estimated to be 8% Predictors of no reflow include a higher plaque burden, thrombus, lipid pools by intra vascular ultra sonography (IVUS), higher lesion elastic membrane cross sectional area, preinfarction angina and thrombolysis in myocardial infarction (TIMI) flow grade 0 on the initial coronary angiogram.

Mechanism

The cause is mainly embolization of atheromatous material (gruel). Particles are composed of cholesterol clefts, lipid rich macrophages, fragments of fibrous cap, necrotic lesion core and fibrin. This is aggravated by microembolization of platelet-rich thrombi that release vasoactive agents (e.g., serotonin and thromboxane A2), leading to intense arteriolar vasopasm in the distal vasculature. In the animal laboratory, experimental no reflow has been shown to be due to the plugging of capillaries by red blood cells and neutrophils, myocyte contracture and local intracellular and interstitial edema.[4,5]

A loss of capillary autoregulation and severe microvascular dysfunction are the ultimate physiologic consequences of these microscopic anatomic alterations. Debris of varying sizes of particulate has variable effects on microcirculatory plugging. The effect of particle size on microvascular dysfunction has been mostly investigated during rotablation. Rotational atherectomy mostly creates particle size less than 6 micron. These smaller particles pass through the capillary circulation in the same manner as red blood cells. Larger particles, which comprises about 20% of the rotational atherectomy debris or particle load, are trapped in the microcirculation and contribute to slow flow and Creatine kinase (CK) elevations from this procedure[5]. Some of the more common mechanisms of no reflow is shown in Table 1.

Table 1. Proposed Mechanisms of No Reflow

Microvascular constriction and vasospasm
Distal embolization of thrombus or atherosclerotic debris or both
Oxygen free-radical-mediated endothelial injury
Capillary plugging by red blood cells and activated Neutrophils
Neutrophil-mediated endothelial cell dysfunction or Vasoconstriction
Intramural hematoma
Loss of capillary integrity due to completed myocardial Infarction

Differential Diagnosis

The differential diagnosis of an apparent no reflow phenomenon is dissection or acute thrombotic formation in the proximal or distal segment (which is not well appreciated by conventional angiography) and catheter damping. It is occasionally difficult to precisely differentiate these causes and it is sometimes necessary to treat all of them (for example additional stenting in the inlet and outlet of stented lesion). A transport or infusion catheter can be inserted through the wire and advanced to the distal segment of the no reflow area. Then the wire is removed. Pressure gradient between the tip of the microcatheter and guide is measured, and contrast injection through the end hole will help to make distinction between no reflow and proximal obstructive lesion. Then injection of 3-5 cc of contrast agent with slow withdrawal of the catheter into the guide is useful to reveal any proximal disease.[1] The results and management are summarized in tables2 and 3.

1- Interventional Cardiologist, Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: hashemi365@yahoo.com

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Table 2. Differential diagnosis of No Reflow phenomenon

a. If there is a pressure gradient, the cause could be due to proximal vessel obstruction or extensive intragraft pathology .The injection of contrast in the distal vasculature will show a patent distal artery . The treatment is correction of the proximal obstructive lesion.
b. If there is no pressure gradient and no single large embolus to explain the reduction of the flow, and the contrast wash out remains poor in distal bed , then the patient has no reflow .This diagnosis of distal microvascular spasm and obstruction is a diagnosis of exclusion.
c. If there is no gradient, however, the pullback angiography could show a distal severe lesion that was not seen by conventional antegrade angiography through the guide because the contrast could not reach the distal segment .Correction of the lesion should resolve the apparent no reflow phenomenon and the symptoms of the patient

Table 3. The characteristics of No Reflow phenomenon and its differential diagnoses

Diagnosis	Proximal Lesion	No -reflow	Distal lesion
Pressure gradient	(+)	(-)	(-)
Distal flow	Patent	No flow	Slow flow due to distal Lesion

Management

Supportive measures

Treatment of the no reflow phenomenon involves basic supportive measures for the patient, including fluid resuscitation, attention to oxygenation airway management, and blood pressure maintenance with pressors or inotropes (Table 4). Maintenance of blood pressure is especially important, because distal perfusion pressure is necessary for recovery from no reflow and also for delivery of pharmacologic therapy to the distal vascular bed. When no reflow occurs in the right coronary artery or inferior distribution, atropine therapy may be necessary to treat the reflex hypotension and bradycardia that may occur. Intra aortic balloon pump therapy for blood pressure support is another mainstay of treatment in refractory cases.[7,8]

Table 4. Initial evaluation and treatment of No Reflow phenomenon

Excludedissection, thrombus, spasm at lesion site (IVUS, distalcontrast injection, or translesion pressure gradient may be useful)
Achieve adequate ACT (250-300 s with unfractionated heparin if a llb/llla inhibitor has been given, >300 s if one has not been given, and 325-375 s with direct thrombin inhibitors)
Ensure sufficient oxygenation and airway management
Treat vagal reactions (IV atropine and fluids)
Maintain adequate perfusion pressure with IV fluids, Vasopressors, inotropes, and IABP if necessary
Administer intracoronary nitroglycerin (100-200 µg up to 4 doses) to exclude epicardial spasm
Consider administering a glycoprotein llb/llla receptor Inhibitor
Administer pharmacologic agents through an infusion catheter or the central lumen of the balloon catheter to assure drug delivery to the distal bed

Pharmacologic therapy

The basis of most therapies for no reflow is intra coronary pharmacotherapy, which often rapidly restores flow and reestablishes a more stable condition. A wide array of pharmacologic agents has been used for this therapy. None of them have clear proven therapeutic value in a trial setting. Most of the practice involved with pharmacotherapy for no reflow is based on operator experience and thus anecdote.

Pharmacologic agents are administered into the affected vascular bed through a distal catheter. When drugs are given through a guiding catheter, they will preferentially flow to areas that have preserved run off. For example, when there is slow flow in the distal circumflex artery injection into a left system guide catheter will result in the injected agent going to the contralateral vessel and never reaching the target vascular bed. Thus an infusion catheter or an over the wire balloon catheter must be delivered distal to the target lesion in the distal vasculature and injections given through this catheter.[1]

Intracoronary nitroglycerin has been the traditional first line agent for this therapy. However the response of the no reflow phenomenon to nitroglycerin has been poor and it is not realistic to recommend this as a first line therapy. Several other agents have shown more effect (Table 5).

Agents that have shown positive results in at least small reported series include adenosine, verapamil, and nitroprusside.[11,12]

Intracoronary verapamil has a success rate of two thirds in cases of no reflow especially those due to rotational ablation and it also improves all patients who had no reflow during SVG intervention. Nitroglycerin had no effect in this study.

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Table 5. Intracoronary drug therapy for No Reflow phenomenon

First-Line Management
Adenosine (10-20 µg bolus)
Verapamil (100-200 µg boluses or 100 µg/min up to 1000 µg total dose with temporary pacer on standby)
Nitroprusside (50 -00 µg bolus, up to 1000 µg total Dose)
Evidence less Strong
Rapid, moderately forceful injection of saline or blood (to "unplug" microvasculature)
Diltiazem (0.5-2.5 mg over 1 min up to 5 mg)
Papavarine (10-20 µg)
Nicardipine (200 µg)
Nicorandil (2 µg)
Epinephrine (50-200 µg)
Never Shown to Be Effective
Intracoronary nitroglycerin
Coronary artery bypass grafting
Stent placement at site of original stenosis. If widely patent
Thrombolytics (eg, urokinase, tissue plasminogen Activator)

Adenosine has similarly been evaluated in a small number of patients with positive results. In one series of vein graft intervention, adenosine was successful in the majority of cases. Multiple doses and higher doses of adenosine have been found to be more effective than low doses.

One small experience exists which demonstrates the efficacy of nitroprusside even in cases refractory to intracoronary calcium blockers.[5]

Forceful injection of saline or blood has been described as a method for hydraulically dislodging platelet aggregates or microthrombi from the distal vasculature.[1]

Intravenous and intracoronary platelet glycoprotein 2b/3a inhibitors have been described as successful in some cases, but the results seem to be variable. A review of the effects of 2b/3a inhibitor agents in more than 4000 patients in the EPIC Evaluation of 2b/3a Platelet receptor antagonist 7E3 in Preventing Ischemic Complications (and EPILOG) Evaluation in PTCA to improve Long Term Outcome with Abcximab GP 2b/3a Blockade trials failed to show any benefit from the use these agents in SVG interventions. Placebo treated patients had a 16.3% incidence of complications versus 18.6% in those received abciximab.[12,13]

Various other agents have been described including several other calcium channel blockers. Intracoronary has been described as effective in this setting, as well, and has an advantage because it will not cause blood pressure decline in patients in whom that is already a problem. Skelding et al identified 29 patients in whom intracoronary epinephrine was administered for coronary no reflow. Administration of a mean dose of 139 ± 189 µ resulted in establishment of TIMI grade-3 flow in 69% of patients. Mean TIMI flow increased from 1 to 2.7 (P = 0.0001). Heart rate increased on average from 72 to 86 beats per minute, but no cases of rhythm disturbances were noted. Nicardipine has been studied in animal models and was successful in patient experiences. Nicorandil and papaverine has been used with some success intravenously.

Intracoronary thrombolytic agents are ineffective, even when thrombotic embolization is grossly visible. Mechanical disruption of these thromboemboli is probably more effective than use of thrombolytic agents.[8-11]

Prevention

No reflow has been a fearful complication of PCI since the inception of balloon angioplasty. It is clear that preventive measures including embolization protection devices should be used in high risk settings for the no reflow phenomenon. SVG intervention has been proven to be safer with embolization protection, and these devices should be used in conjunction virtually all SVG interventions. Mechanical thrombectomy with extraction devices has proven efficacy in preventing no reflow in setting of primary PCI of acutemyocardial infarction AMI.[14,15]

References

1. Nguyen TN, Colombo A, Hu D, Grines CL, Saito S. Practical handbook of advanced interventional cardiology: tips and tricks. 3rd ed. Philadelphia: Wiley-Blackwell; 2007.
2. Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. J Am Coll Cardiol 2009; 54(4): 281-92.
3. Monassier JP. Reperfusion injury in acute myocardial infarction :from bench to cath lab. part II: clinical issues and therapeutic options. Arch Cardiovasc Dis 2008; 101(9): 565-75.
4. van Gaal WJ, Banning AP. Percutaneous coronary intervention and the no-reflow phenomenon. Expert Rev Cardiovasc Ther 2007; 5(4): 715-31.
5. Vrints CJ. Pathophysiology of the no-reflow phenomenon. Acute Card Care 2009; 11(2): 69-76.
6. Alfayoumi F, Srinivasan V, Geller M, Gradman A. The no-reflow phenomenon: epidemiology, pathophysiology, and therapeutic approach. Rev Cardiovasc Med 2005; 6(2): 72-83.

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7. Boztosun B, Gunes Y, Kirma C. Current management of no-reflow. Anadolu Kardiyol Derg 2006; 6(3): 255-60.
8. Gersh BJ. Optimal management of acute myocardial infarction at the dawn of the next millennium. Am Heart J 1999; 138(2 Pt 2): S188-S202.
9. Galiuto L, Crea F. No-reflow: a heterogeneous clinical phenomenon with multiple therapeutic strategies. Curr Pharm Des 2006; 12(29): 3807-15.
10. Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. J Am Coll Cardiol 2001; 37(5): 1335-43.
11. Rawitscher D, Levin TN, Cohen I, Feldman T. Rapid reversal of no-reflow using abciximab after coronary device intervention. Cathet Cardiovasc Diagn 1997; 42(2): 187-90.
12. Ellis SG, Lincoff AM, Miller D, Tcheng JE, Kleiman NS, Kereiakes D, et al. Reduction in complications of angioplasty with abciximab occurs largely independently of baseline lesion morphology .EPIC and EPILOG investigators; evaluation of 7E3 for the prevention of ischemic complications; evaluation of PTCA to improve long-term outcome with abciximab GPIIb/IIIa receptor blockade. J Am Coll Cardiol 1998; 32(6): 1619-23.
13. Tsao TP, Cheng SM, Cheng CC, Yang SP. Comparison of intracoronary adenosine and isosorbide dinitrate on no-reflow/slow flow during rotational atherectomy. Acta Cardiol 2009; 64(2): 225-30.
14. Brodie BR. Adjunctive thrombectomy with primary percutaneous coronary intervention for ST-elevation myocardial infarction: summary of randomized trials . J Invasive Cardiol 2006; 18 (Suppl C): C24-C27.
15. Moris C, Lozano I, Martin M, Rondan J, Avanzas P. Embolic protection devices in saphenous percutaneous intervention. EuroIntervention 2009; 5 (Suppl D): D45-D50.

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