Treatment of No-Reflow Phenomenon with Verapamil after Primary Stent Deployment during Myocardial Infarction

Ibrahim DEMIR,¹ MD, Huseyin YILMAZ,¹ MD, Cengiz ERMIS,¹ MD,
and Oktay SANCAKTAR,¹ MD

SUMMARY

No-reflow phenomenon is the absence of myocardial perfusion despite adequate dilatation of the infarct related coronary artery during percutaneous coronary intervention. It predicts severe left ventricular dysfunction and poor prognosis in acute myocardial infarction (AMI). The present case is a 54 year old Turkish female who presented with chest pain that had started 2.5 hours earlier. The clinical and laboratory findings were consistent with AMI and the coronary angiogram performed for primary angioplasty revealed a 95% thrombotic occlusion with a TIMI grade I flow in the left anterior descending (LAD) coronary artery. A TIMI grade III flow was achieved with direct stent deployment. However, after the placement of a second stent for severe ostial stenosis more proximally and adjacent to the first one, the antegrade flow became TIMI grade O. As the intracoronary medications did not improve the flow, a mechanical occlusion was considered and a third stent was deployed covering the first two stents. A control angiogram revealed the persistence of TIMI grade O flow. A severe and persistent vasospasm was considered at this point and accordingly, intracoronary verapamil was administered in high concentrations by an infusion catheter to the distal LAD which was followed by the immediate achievement of TIMI grade III flow. Intracoronary administration of high dose verapamil can be performed to prevent vasospasm in resistant no-reflow cases with no evidence of mechanic occlusion. (Jpn Heart J 2002; 43: 573-580)

Key words: Myocardial infarction, No-reflow, Verapamil

PROVIDING antegrade coronary flow during AMI limits myocardial necrosis¹⁾ and is known to prevent ischaemic myocardial dysfunction.²⁾ However, some studies have showed the absence of expected functional recovery in the left ventricle, despite normal flow in the epicardial coronary artery.³⁾ The ‘no-reflow’ phenomenon is the absence of myocardial perfusion, despite adequate dilatation of the responsible artery, without a dissection, mechanic obstruction, or distal emboli.^{4,5)} The ‘no-reflow’ phenomenon can be detected by angiography,³⁾ scin-

From ¹ Department of Cardiology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.

Address for correspondence: Ibrahim Demir, MD, Ali Cetinkaya cad. Kinay Ap. No: 35-12, Department of Cardiology, Faculty of Medicine, Akdeniz University, Antalya, Turkey.

Received for publication October 29, 2001.

Revised and accepted May 10, 2002.

tigraphy,^{6,7)} contrast echocardiography,⁸⁻¹⁰⁾ and Doppler flow wire measurements.¹¹⁾ Angiographic definition of no-reflow is an antegrade flow with a TIMI grade $\leq$ II without any mechanical obstruction.⁴⁾ There is a high correlation between no-reflow occurring after AMI and cardiac morbidity and mortality.^{3,12)} In this case report we present the beneficial effects of administration of verapamil via a perfusion catheter to the distal portion of the artery instead of the coronary ostium in a no-reflow phenomenon in the setting of an AMI.

CASE REPORT

A 54 year old Turkish female visited an emergency room complaining of severe chest pain that had started 2.5 hours earlier. Her past medical history was significant for premature menopause and she had a strong family history of coronary artery disease. The physical examination revealed an obese patient with a regular heart rate and rhythm, third heart sound, and bilateral basillary rales in cardiac and respiratory system auscultation. A 12-lead ECG revealed ST segment elevation on the D₁- aVL and precordial leads. The ECG findings in combination with the clinical presentation resulted in a diagnosis of AMI. The patient was immediately taken to the cardiac catheterization laboratory after pre-medications including aspirin, ticlodipine, heparin, and analgesics were given. Right coronary angiography was normal. Next, a 7F XB 3.5 guiding catheter was advanced to the left main coronary ostium and the angiogram of the LAD revealed a 95% thrombotic mid segment stenosis with a distal TIMI grade I flow (Figure 1). The lesion

Figure 1. LAD lesion responsible for the infarct before intervention.

was crossed with a wisdom 0.014 guidewire and a 3.0×18 mm R stent (Orbus Medical Technologies, Inc., Hoewelaken, The Netherlands) was deployed at 13 atm pressure for 25 seconds. TIMI grade III flow was maintained (Figure 2). A lesion in proximal LAD was then noticed to be critical and a 3.5×16 mm NIR stent (Boston Scientific, Boston, USA) was deployed at 14 atm pressure for 20 seconds (Figure 3). The antegrade flow became TIMI grade O after the deployment of this second stent (Figure 3). Neither intracoronary verapamil and nitrate injections nor high pressure levels with a longer angioplasty balloon improved the flow. A third stent (R stent 3.0×38 mm) was deployed covering the first two stents for a probable prolapse of the dissected tissue. The control angiogram showed no change in the distal flow (Figure 3). The angioplasty balloon was advanced forward and pulled back through the stents but this maneuver did not alter the outcome. These findings have increased the probability of a severe distal vasospasm where verapamil and nitroglycerin were unable to penetrate because of the diminished microcirculation. An intracoronary infusion catheter (Cordis) was advanced to the distal artery and 400 μg of verapamil was administered through the aforementioned catheter resulting in an antegrade flow. After injection of another 400 μg of verapamil, the infusion catheter was pulled back and a subsequent angiogram revealed TIMI grade III antegrade flow (Figure 4). The

Figure 2. TIMI 3 flow and LAD ostial lesion after deployment of the first stent.

Figure 3. TIMI 0 flow after the second and third long stent were deployed into LAD.

Figure 4. TIMI 3 flow after verapamil was injected through the infusion catheter.

patient tolerated the procedure well and was subsequently brought to the coronary intensive care unit. She was prescribed ticlodipine, isosorbide-5 mononitrate, low molecular weight heparin, aspirin, and metoprolol. The CK and CK-MB levels at the 6th, 12th, 36th, 48th hours were 740, 3895, 4186, 3995, 2390, 705, and 269 IU/L and 190, 943, 1038, 922, 399, and 92 IU/L, respectively. Echocardiography revealed an ejection fraction of 45%. The patient had an uneventful hospital course and was sent home early the next week on the following medications; ticlodipine, aspirin, nitrate, metoprolol, and statin. The patient is being followed up in the outpatient clinic, is doing well, and had a functional capacity of 9 METS on the treadmill test in the third month of the procedure.

DISCUSSION

The reported frequency of angiographic no-reflow is 2% in elective percutaneous interventions.⁴⁾ It may increase to 11-44% in primary interventions during AMI.¹³⁻¹⁵⁾ It is well known that the no-reflow phenomenon that occurs as a frequent complication of direct revascularization in AMI should be treated. It is reported that an angiographic no-reflow phenomenon during AMI was strongly associated with increased cardiac morbidity and mortality.^{12,16)} The rate of arrhythmia, congestive heart failure, and cardiac death is higher in patients with no-reflow during AMI compared to those without.^{3,12,13)} In addition, other well known risk factors such as increased age, Killip class at admission, low ejection fraction,¹²⁾ and angiographic no-reflow phenomenon are other predictors of morbidity and mortality.¹²⁾

Pathophysiologic no-reflow is defined as decreased tissue blood flow despite an open infarct related artery.⁵⁾ The factors causing no-reflow are reported to be endothelial damage, inflammation, tissue edema,^{5,11)} preinfarct angina,¹⁶⁾ and neutrophil depositions in the microvascular segment.¹⁷⁾ Although myocardial contrast echocardiography, which can demonstrate tissue perfusion, may be beneficial in detecting the frequency of no-reflow,⁸⁻¹⁰⁾ its impractical application limits its efficacy. However, TIMI flow grade is accepted as a simple alternative with which to detect no-reflow without an additional method or extra time.³⁾ Angiographic no-reflow is defined as a blood flow of TIMI grade flow $\leq$ II in an infarct related artery after revascularization during AMI.^{3,4,12)} An increase in microvascular resistance in a lesion area could decrease epicardial coronary blood flow. A correlation between increased microvascular resistance and angiographic no-reflow has been demonstrated in a Doppler guide wire study.¹⁸⁾

There is a high correlation between left ventricular 'remodeling' and 'no-reflow' after AMI. Some of the factors that affect remodeling are infarct area width, flow in the infarct artery, asynergy, and increased wall stress.¹²⁾ No-

reflow seems to have a critical role in all of these parameters. Ejection fraction is generally low in cases with angiographic no-reflow.

The treatment approaches may vary according to the pathophysiology of the phenomenon. In a recent study, the no-reflow rate was found to be 5.9% in patients who had received intracoronary adenosine (24-48 μg) and it was 28.6% in patients who did not.¹⁴⁾ The in-hospital major cardiac event rate was also low in the former group. Another study showed that intracoronary administration of adenosine corrected no-reflow in 10 cases out of 11 during percutaneous intervention in safen vessel grafts.¹⁹⁾ Although adenosine has a beneficial effect on no-reflow, the mechanism of this effect is not known. A study, designed to test glycoprotein IIb/ IIIa receptor inhibitors, showed that intracoronary injection of this agent resulted in TIMI III flow in 2 of 3 patients with no-reflow phenomenon during AMI²⁰⁾ and that no-reflow phenomenon can be prevented by performing predilatation before stent deployment.

Nitroglycerin and verapamil are other agents used frequently for providing microcirculation in percutaneous coronary revascularization interventions. Nitroglycerin is more effective for providing circulation in epicardial coronary arteries, while calcium channel blockers, especially nicardipine and verapamil, are more effective for resolving microvascular coronary spasm.^{15,21)} Verapamil and nicardipine, at doses between 100 and 1000 μg , could be injected safely to the coronary arteries.⁴⁾ Calcium channel blockers are known to decrease myocardial ischemia by increasing coronary collateral flow, resulting in a direct cardioprotective effect in percutaneous revascularisation.²²⁾ Reperfusion injury occurs during early reperfusion in AMI. Injection of calcium channel blockers can prevent 'reperfusion injury' by suppressing the release of calcium ions from sarcoplasmic reticulum.^{22,23)} The reasons for a high no-reflow rate during AMI can be endothelial damage, inflammation, neutrophil accumulation, and distal microembolisation. One other major reason is severe microvascular spasm caused by free oxygen radicals, which are abundant in infarct areas after reperfusion.²³⁾ Calcium channel blockers are effective for minimizing the damage caused by free oxygen radicals. Interventional cardiologists may sometimes confront images like the ones we have just presented, however, a review of the literature reveals no other case with TIMI grade III flow deteriorating to TIMI grade 0 flow because of severe distal vasospasm, which is subsequently treated by verapamil administration through the infusion catheter.

REFERENCES

1. Grines CL, Browne KF, Marco J, *et al.* A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993; 328: 673-9.

2. The GUSTO angiographic investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993; 329: 1615-22.
3. Morishima I, Sone T, Mokuno S, *et al.* Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. *Am Heart J* 1995; 130: 239-43.
4. Piana RN, Paik GY, Moscucci M, *et al.* Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; 89: 2514-8.
5. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974; 54: 1496-508.
6. Hamada S, Nakamura S, Sugiura T, *et al.* Early detection of the no-reflow phenomenon in reperfused acute myocardial infarction using technetium-99m tetrofosmin imaging. *Eur J Nucl Med* 1999; 26: 208-14.
7. Kondo M, Nakano A, Saito D, Shimono Y. Assessment of microvascular no-reflow phenomenon using technetium-99m macroaggregated albumin scintigraphy in patients with acute myocardial infarction. *J Am Coll Cardiol* 1998; 32: 898-903.
8. Ragosta M, Camarano G, Kaul S, *et al.* Microvascular integrity indicates myocellular viability in patients with recent myocardial infarction. New insights using myocardial contrast echocardiography. *Circulation* 1994; 89: 2562-9.
9. Porter TR, Li S, Oster R, Deligonul U. The clinical implications of no reflow demonstrated with intravenous perfluorocarbon containing microbubbles following restoration of Thrombolysis In Myocardial Infarction (TIMI) 3 flow in patients with acute myocardial infarction. *Am J Cardiol* 1998; 82: 1173-7.
10. Leclercq F, Messner PP, Descours Q, *et al.* Combined assessment of reflow and collateral blood flow by myocardial contrast echocardiography after acute reperfused myocardial infarction. *Heart* 1999; 82: 62-7.
11. Michaels AD, Gibson CM, Barron HV. Microvascular dysfunction in acute myocardial infarction: focus on the roles of platelet and inflammatory mediators in the no-reflow phenomenon. *Am J Cardiol* 2000; 85: 50B-60B.
12. Morishima I, Sone T, Okumura K, *et al.* 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: 1202-9.
13. Marzilli M, Gliozheni E, Marraccini P, Fedele S. Primary coronary angioplasty in acute myocardial infarction: clinical correlates of the 'no reflow' phenomenon. *Int J Cardiol* 1998; 65 Suppl 1: S23-8.
14. Assali AR, Sdringola S, Ghani M, *et al.* Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of "no reflow" phenomenon. *Catheter Cardiovasc Interv* 2000; 51: 27-31.
15. Vallejo E, Pena-Duque MA, Norono O, *et al.* The no-reflow phenomenon: its incidence and clinical characteristics in a series of cases. *Arch Inst Cardiol Mex* 1998; 68: 247-52.
16. Takahashi T, Anzai T, Yoshikawa T, *et al.* Absence of preinfarction angina is associated with a risk of no-reflow phenomenon after primary coronary angioplasty for a first anterior wall acute myocardial infarction. *Int J Cardiol* 2000; 75: 253-60.
17. Meisel SR, Shapiro H, Radnay J, *et al.* Increased statement of neutrophil and monocyte adhesion molecules LFA-1 and Mac-1 and their ligand ICAM-1 and VLA-4 throughout the acute phase of myocardial infarction. Possible implications for leukocyte aggregation and microvascular plugging. *J Am Coll Cardiol* 1998; 31: 120-5.
18. Iwakura K, Ito H, Nishikawa N, *et al.* Early temporal changes in coronary flow velocity patterns in patients with acute myocardial infarction demonstrating the "no-reflow" phenomenon. *Am J Cardiol* 1999; 84: 415-9.
19. Fischell TA, Carter AJ, Foster MT, *et al.* Reversal of "no reflow" during vein graft stenting using high velocity boluses of intracoronary adenosine. *Cathet Cardiovasc Diagn* 1998; 45: 360-5.
20. Hamon M, Richardeau Y, Lecluse E, *et al.* Direct coronary stenting without balloon predilation in acute coronary syndromes. *Am Heart J* 1999; 138: 55-9.
21. Fugit MD, Rubal BJ, Donovan DJ. Effects of intracoronary nicardipine, diltiazem and verapamil on coronary blood flow. *J Invasive Cardiol* 2000; 12: 80-5.
22. Chouairi S, Carrie D, Puel J. Myocardial protection with calcium-channel blockers during ischaemia and reperfusion by PTCA. *Eur Heart J* 1995; 16 Suppl H: 3-8.

23. Villari B, Ambrosio G, Golino P, *et al*. The effects of calcium channel antagonist treatment and oxygen radical scavenging on infarct size and the no-reflow phenomenon in reperfused hearts. *Am Heart J* 1993; 125: 11-23.