LEADING ARTICLE

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Potential of Microvascular Reperfusion with Adjunctive Pharmacological Intervention

Its Impact on Myocardial Perfusion and Functional Outcomes in Patients with Acute Myocardial Infarction

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Abstract

One of the major limitations of reperfusion therapy in acute myocardial infarction (AMI) is the presentation of no-reflow phenomenon. In 25 to 30% of patients with AMI, myocardial blood flow is occasionally profoundly reduced, even after coronary recanalisation, because of microvascular dysfunction - so-called no-reflow phenomenon. Patients with this phenomenon are regarded as a high risk group among patients with reperfused AMI.

Clinical studies using myocardial contrast echocardiography have demonstrated that intracoronary injection of calcium antagonists or potassium channel agonists in conjunction with coronary reperfusion can augment myocardial blood flow and that this was associated with better functional and clinical outcomes than with percutaneous transluminal coronary angioplasty alone. Thus, it is possible to prevent reperfusion injury and improve cardiac function using a adjunctive pharmacological intervention, either intravenously or by infusion directly into the coronary artery.

1. No-Reflow Phenomenon in the Clinical Setting

Coronary reperfusion using thrombolysis and/or percutaneous coronary angioplasty (PTCA) has been established as an essential therapy of acute myocardial infarction (AMI).[1-3] However, we and other investigators have documented that myocardial blood flow is occasionally profoundly reduced even after coronary recanalisation.[4-10] This severe microvascular dysfunction is called no-reflow phenomenon. Our studies with myocardial contrast echocardiography (MCE) documented that substantial no-reflow phenomenon is observed in 25 to 30% of reperfused patients. The no-reflow phenomenon is associated with profound and broad-spectrum myocardial damage, poor functional outcomes, progressive left ventricular dilation and a high frequency of post-AMI complications.[7,10] Therefore, patients with this phenomenon can be

regarded as high-risk group among reperfused patients.

2. Study Protocol to Define No-Reflow Phenomenon

To define no-flow phenomenon in a patient, we have used the following protocol which we describe to clarify the no-flow phenomenon. Each patient with AMI rested in the supine position. On completion of diagnostic coronary angiography and contrast ventriculography, 2ml of sonicated ioxagrate (Hexabrix-360, Tanabe) containing sonicated microbubbles (mean size 12μm is injected into the left main coronary artery for MCE before and after reperfusion.[7,8] In our studies, we initiated imaging of the apical long-axis and parasternal short-axis views using a commercially available mechanical sector. Images recorded on videotape were analysed using a commercially available off-line computer system. The patients were divided into 2 groups based on the pattern of contrast enhancement in the risk area by MCE performed after reperfusion. The presence or absence of residual contrast defect was the only criterion for patient classification. The measurement used to assess reperfusion was a risk area-length ratio: ratio = (endocardial length of residual contrast defect after reperfusion = no reflow area)/(endocardial length of residual contrast defect before reperfusion = risk area). When this length ratio exceeded 0.25, it was considered indicative of incomplete myocardial reperfusion, the pattern we call no-reflow phenomenon. Recently, Lepper et al.[11] reported that intravenous MCE could be used to define perfusion defects after AMI. Patients in this study underwent MCE with NC100100 with intermittent harmonic imaging.

3. Treatment of No-Reflow Phenomenon

Several studies have attempted to attenuate the ischaemic myocardial damage or microvascular dysfunction with pharmacological intervention. In a canine study, Stahl et al.[12] demonstrated that post-ischaemic myocardial function could be enhanced by augmentation of blood flow with the intravenous administration of vasodilators. Babbit et al.[13] demonstrated that intracoronary administration adenosine attenuated microvascular dysfunction and augmented myocardial blood flow after reperfusion in a canine model. This was associated with an improvement in post-ischaemic myocardial function.

In 236 patients with AMI, Mahaffey et al.[14] demonstrated that the intracoronary administration of adenosine enhances functional improvement compared with a placebo control group. Finally, Marzilli et al.[15] reported that adenosine 4mg in 2ml saline administered directly into the distal coronary vascular bed in 54 patients during primary PTCA ameliorated flow, prevented the no-reflow phenomenon, improved ventricular function, and was associated with a more favourable clinical course versus controls.

These data indicate that augmentation of myocardial blood flow with pharmacological intervention is possible and seems to be associated with favourable functional outcomes.

4. Role of Calcium Antagonists

Theroux et al.[16] reported that intravenous diltiazem reduced mortality, reinfarction or recurrent ischaemia and prevented the need for an urgent intervention, but had no effect on coronary artery patency or left ventricular function and perfusion in 39 patients with AMI. After coronary intervention, a significant number of patients showed angiographical slow flow. Piana et al.[17] reported that intracoronary verapamil can rapidly augment coronary blood flow, possibly as a result of the reversal of microvascular spasm.

The impact of calcium antagonists on myocardial blood flow and its functional outcomes remains unknown in patients with AMI.

In our study,[18] using the protocol described in section 2 we examined the impact of intracoronary verapamil on myocardial perfusion in relation to functional outcomes.[18] We administered intracoronary verapamil 0.5mg shortly after PTCA in 20 patients with AMI. 20 patients with reperfused AMI served as the control group. We performed MCE with intracoronary injection of microbubbles

before and after intracoronary injection of verapamil in order to verify the direct effect of verapamil on post-ischaemic microvascular function. In the verapamil group, even though a no- or low-reflow zone was present within the risk area after PTCA, its size substantially decreased with intracoronary verapamil. The low-reflow ratio decreased significantly from 0.39 ± 0.23 to 0.29 ± 0.17 ($p < 0.05$) after verapamil. And the number of frames required from the initiation of contrast injection to the opacification of the distal landmark significantly decreased from 50 ± 15 to 41 ± 14 ($p < 0.05$) after verapamil. The magnitude of the reduction in wall motion score index, calculated as an average of segmental scores (dysnesia/akinesia = 3 to normal = 0) of 17 segments, from day 1 to day 24 was significantly greater in the verapamil group than in the control group (0.7 ± 0.8 *vs* 0.2 ± 1.3, $p < 0.05$).

These data indicate that intracoronary verapamil after coronary angioplasty can attenuate microvascular dysfunction and thereby augment myocardial blood flow in patients with AMI, leading to a better functional outcome than with PTCA alone.

5. Role of Potassium Channel Agonists

Potassium channel agonists, or adenosine triphosphate (ATP)-sensitive potassium channel (KATP) openers, are another interesting class of drug with potential in the adjunctive treatment of AMI. Nicorandil is a hybrid of a KATP opener and nitrate. In a canine study, Kitakaze et al.[19] documented that nicorandil mimics the effect of ischaemic preconditioning. In patients with AMI, Sakata et al.[20] reported that the single intracoronary administration of nicorandil 2mg after angioplasty improves microvascular function. This was associated with more improvement in post-ischaemic myocardial function compared with the untreated control group.

The mechanism involved in the salutary actions of nicorandil are not known for certain. The contribution of reducing preload and afterload, antifree radical and neutrophil-modulating properties, the opening of KATP channels and the vasodilatation of the small coronary arteries have all been postulated.

Despite the experimental studies suggesting nicorandil mimics the ischaemic preconditioning effect, the salutary effect of intracoronary nicorandil administered just after reperfusion in clinical studies has not been as strong. Therefore, since nicorandil was administrated before reperfusion in the canine model, we thought that it would be better to start administration of nicorandil before coronary reperfusion in our clinical study as well.

Recently, we studied the impact of the intravenous nicorandil in conjunction with coronary angioplasty on myocardial perfusion and clinical and functional outcomes.[21] In the treatment group (n = 41), we administered a bolus injection of nicorandil 4mg just after the diagnosis of AMI followed by a continuous infusion at least for 24 hours at a rate of 6 mg per hour. The results were compared with a placebo control group (n = 40). The magnitude of decrease in wall motion score (6 ± 5 *vs* 3 ± 4, $p < 0.05$) and increase in regional wall motion was significantly greater in nicorandil group (0.7 ± 0.5 *vs* 0.2 ± 0.7, $p < 0.05$). The frequencies of post-AMI complications, including ventricular tachycardia (VT), ventricular fibrillation (Vf), early heart failure (HF; within 3 days after infarction), late HF (beyond the third day after infarction) and in-hospital death were all significantly lower in nicorandil group compared with the control group (VT or Vf 5 *vs* 20%, $p < 0.05$; early HF 15 *vs* 37%, $p < 0.05$; late HF 3 *vs* 12%, $p < 0.05$; in-hospital death 0 *vs* 10%, $p < 0.05$). The frequency of sizable MCE no-reflow phenomenon was significantly lower in the nicorandil group than in the control group (control *vs* nicorandil, 33 *vs* 15%, $p < 0.01$) at the acute stage. These data indicate that the augmentation of blood flow with intravenous nicorandil is associated with significantly better functional and clinical outcomes.

Administration of nicorandil before reperfusion may be an important factor in its effective use. If the no-reflow phenomenon is already established, nicorandil is hardly delivered into no-reflow zone, even though it is delivered by intracoronary injec-

tion. In an experimental study, Villaneuva et al.[22] documented that the size of no reflow varies with time interval after reperfusion. The size of no-reflow is minimal at the moment of coronary reperfusion and it increases until 15 minutes after reperfusion at which point we usually evaluate the presence or absence of this phenomenon in the clinical setting. This indicates that myocardial blood flow may have been present at the moment of reperfusion even in the final no-reflow zone. In such an instance, nicorandil may be effectively delivered to the post-ischaemic microvascular beds in the blood flow at reperfusion, if it is administered prior to reperfusion. In addition, nicorandil may also be delivered to the risk area by collateral flow before coronary reperfusion.

6. Potential of Other Drugs

Other drugs that have a cardioprotective function and have been examined in patients with AMI. Rawischer et al.[23] and Brener et al.[24] reported that abciximab [a glycoprotein (GP)IIa/IIIb inhibitor] improves coronary blood flow after PTCA. Abciximab may inhibit platelet aggregation and possibly thrombus formation in coronary microvasculature, thereby reducing the obstruction to coronary blood flow and the degree of ischaemia. Woods et al.[25,26] reported in the Leicester Intravenous Magnesium Intervention Trial (LIMIT)-2 study, that treatment with intravenous magnesium administered before reperfusion attenuated the progression of myocardial necrosis in patients with AMI. They claimed magnesium would attenuate reperfusion injury and calcium over loading. In contrast, the International Studies of Infarct Survival (ISIS)-4 study did not reach the same result; however, in this study, magnesium was administered after reperfusion.[27] In addition, Herog et al.[28] has claimed that the reason why the two clinical studies had different results with regard to the effect of magnesium, is that the treatment of magnesium needs to be started before reperfusion rather than after reperfusion, and has shown this in the canine model. Forman et al.[29] reported that intracoronary infusion of perfluorochemical emulsion (40 ml/min for 30 minutes) could prevent reperfusion injury in patients with AMI because it may attenuate the activity of neutrophils and prevent the infiltration of neutrophils to the risk area. Finally, Buerke et al.[30] and Rupprecht et al.[31] reported that intravenous Na^+/H^+ exchange inhibition could be of benefit to prevent reperfusion injury in patients with acute anterior MI treated with direct angioplasty because it may attenuate Ca^{2+} influx into cardiomyocytes.

7. Conclusion

Overall, several clinical studies have demonstrated that it is possible to prevent reperfusion injury and improve cardiac function with pharmacological intervention, with infusion of a cardioprotective agent directly into coronary artery or intravenously in patients with AMI. We should not be satisfied with coronary recanalisation. We should attempt to prevent microvascular injury and to preserve microvascular function with the adjunctive pharmacological treatment in patients with AMI.

References

1. Hillis LD, Former S, Braunwald E. Risk stratification before thrombolytic therapy in patients with acute myocardial infarction. J Am Coll Cardiol 1990; 16: 313-5
2. Gruppo Italiano per lo Studio Della Streptkinesi Nell E Infarct (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; I: 397-401
3. Kennedy JW, Ritchie JL, Davis KB, et al. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1983; 309: 1477-82
4. Bates ER, Krell MJ, Dean EN, et al. Demonstration of 'no reflow' phenomenon by digital coronary angiography. Am J Cardiol 1986; 57: 177-8
5. Jeremy RW, Links JM, Becker CC. Progressive failure of coronary flow during reperfusion of myocardial infarction: documentation of the no reflow phenomenon with positron emission tomography. J Am Coll Cardiol 1990; 16: 695-704
6. Feld H, Lichsten E, Schachter J, et al. Early and late angiographic findings of 'no reflow' phenomenon following direct angioplasty as primary treatment for acute myocardial infarction. Am Heart J 1992; 123 (3): 782-4
7. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis: predicator of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992; 85: 1699-705
8. Ito H, Iwakura K, Oh H, et al. Temporal changes in myocardial perfusion patterns in patients with reperfused anterior wall myocardial infarction: their relation to myocardial viability. Circulation 1995; 91: 656-62

9. Ito H, Okamura A, Iwakura K, et al. Myocardial perfusion patterns related to thrombolysis in myocardial infarction grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. Circulation 1996; 93: 1993-9
10. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of 'no reflow' phenomenon: a predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation 1996; 93: 223-8
11. Lepper W, Hoffmann R, Kamp O, et al. Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angiography in patients with acute myocardial infarction. Circulation 2000 May 23; 101 (20): 2368-74
12. Stahl LD, Aversano TR, Becker LC. Selective enhancement of function of stunned myocardium by increased flow. Circulation 1986; 74: 843-51
13. Babbit DG, Virmani R, Forman MB. Intracoronary adenosine administrated after reperfusion limits vascular injury after prolonged ischemia in the canine model. Circulation 1989; 80: 1388-99
14. Mahaffey KW, Puma JA, Barbagelata A, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomised, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1999; 34 (6): 1711-20
15. Marzilli M, Orsini E, Marraccini P, et al. Beneficial effect of intracoronary adenosine as adjunct to primary angioplasty in acute myocardial infarction. Circulation 2000; 101 (18): 2154-9
16. Theroux P, Gregorie J, Chin C, et al. Intravenous diltiazem in acute myocardial infarction: diltiazem as adjunctive therapy to active (DATA) trial. J Am Coll Cardiol 1998; 32 (3): 620-8
17. Piana RN, Paik GY, Mosucci M, et al. Incidence and treatment of 'no reflow' after percutaneous coronary intervention. Circulation 1994; 89: 2514-8
18. Taniyama Y, Ito H, Iwakura K, et al. Beneficial effect of intracoronary verapamil on microvascular salvage in patients with acute myocardial infarction. J Am Coll Cardiol 1997; 30: 1193-9
19. Kitakaze M, Minamino T, Node K, et al. Role of activation of ectopic 5'-nucleotidase in the cardioprotection mediated by opening K+ channel. Am J Physiol 1995; 26: 477-84
20. Sakata Y, Kodama K, Komamura K, et al. Salutary effect of adjunctive intracoronary nicorandil administration on restoration of myocardial blood flow and functional improvement in patients with acute myocardial infarction. Am Heart J 1997; 133: 616-21
21. Ito H, Taniyama Y, Iwakura K, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. J Am Coll Cardiol 1999; 33: 654-60
22. Villaneuva FS, Glasheen WP, Kaul S, et al. Characterization of spatial patterns of flow within the reperfused myocardium by myocardial contrast echocardiography: implication in determining extent of myocardial salvage. Circulation 1993; 88: 2596-606
23. Rawischer D, Levin TN, Cohen I, et al. Rapid reversal of no-reflow using abciximab after coronary device intervention. Cathet Cardiovasc Diagn 1997; 41: 187-90
24. Brener SJ, Barr LA, Burchenal JE, et al. Effect of abciximab on the pattern of reperfusion in patients with acute myocardial infarction treated with primary angioplasty: RAPPORT investigators. ReoPro and primary PTCA organization and randomized trial. J Am Coll Cardiol 1999; 84 (6): 728-30, A8
25. Woods KL, Fletcher S, Roffe C, et al. Intravenous magnesium sulphate in suspected acute myocardial infarction: result of second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 1992; 339: 1553-9
26. Woods KL, Fletcher S. Long-term outcomes after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 1994; 343: 816-9
27. ISIS collaborate groups. ISIS-4: randomized study of intravenous magnesium in over 50,000 patients with suspected acute myocardial infarction. Lancet 1995; 345: 669-85
28. Herog WR, Schoolbag ML, MacMurdy K, et al. Timing of magnesium therapy affects experimental infarct size. Circulation 1995; 92: 2622-6
29. Forman MB, Perry JM, Wilson BH, et al. Demonstration of myocardial reperfusion injury in humans: result of a pilot study utilizing acute coronary angioplasty with perfluorochemical emulsion in the treatment of myocardial reperfusion injury. Am Heart J 1992; 124: 1347-57
30. Buerke M, Rupprecht HJ, vom Dahl J, et al. Sodium-hydrogen exchange inhibition: novel strategy to prevent myocardial injury following ischemia and reperfusion. Am J Cardiol 1999; 83 (10A): 19G-22G
31. Rupprecht HJ, Dahl JV, Terres W, et al. Cardioprotective effects of the Na (+9)/H (+) exchange inhibitor cariporide in patients with acute anterior myocardial infarction undergoing direct PTCA. Circulation 2000; 101 (25): 2902-8

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