

# Ischemia-reperfusion and microvascular dysfunction: implications for salvage of jeopardized myocardium and reduction of infarct size

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(Ital Heart J 2001; 2 (Suppl 3): 40S-42S)

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## Introduction

Understanding of the pathogenetic mechanisms and strategies for the management of acute myocardial infarction (AMI) has evolved dramatically in the past decade. AMI and unstable angina are now recognized as part of a spectrum of clinical disease collectively identified as acute coronary syndromes that include unstable angina, non-Q-wave myocardial infarction, and Q-wave myocardial infarction<sup>1</sup>. The majority of patients presenting with ST-segment elevation will eventually develop transmural myocardial infarction.

The primary goals of therapy for patients presenting with ST-segment elevation are reduction of myocardial necrosis and prevention of major adverse cardiac events. The potential for prevention of cardiac death and reduction of myocardial damage is greatest very early in AMI. Half of the patients who die of AMI do so before reaching a hospital, the greatest risk of ventricular tachycardia/ventricular fibrillation occurring during the first 4 hours after the onset of symptoms.

Perhaps the most significant advance in the treatment of cardiovascular diseases in the last decade is the demonstration of the safety and efficacy of reperfusion therapy. The GISSI-1 trial was the first megatrial to demonstrate a statistically significant reduction in mortality associated with fibrinolytic therapy. In that study, the greatest benefit was found when patients were treated during the first 3 hours, with a maximum reduction in mortality of 47% for patients treated in the first hour<sup>2</sup>.

Subsequent studies, testing different thrombolytic agents and treatment strategies, have consistently confirmed these observations. Salvage of jeopardized myocardium appears primarily determined by: 1) time to reperfusion, 2) patency of the infarct-related artery, and 3) microvascular function after the ischemia-reperfusion sequence.

## Time to reperfusion

In experimental models, infarct size and left ventricular function are determined, in a non-linear fashion, by the duration of coronary occlusion, severity of ischemic damage varying with the animal species<sup>3</sup>.

In dogs, reperfusion after 5 to 15 min of coronary occlusion leads to virtual complete salvage of the myocardium. Significant salvage is still possible after occlusions lasting up to 3 hours. No improvement of regional function results when coronary flow is restored after an occlusion lasting > 3 hours<sup>4</sup>.

Attempts to confirm this association in clinical studies have yielded conflicting results<sup>5-7</sup>. A recent study examining the impact of time on multiple outcome variables concluded that the beneficial effect of thrombolysis on infarct size and ejection fraction is restricted to treatments given within 2 hours of symptom onset<sup>8</sup>. The greatest mortality benefit was also achieved when thrombolysis was given within 2 hours. These observations support the concept that time-dependent myocardial salvage is the explanation for the benefit ob-

tained with early administration of thrombolytic agents.

Beyond that time, infarct size reduction was markedly attenuated, and clinical benefits achieved with thrombolytics clearly exceed the impact of this therapy on ventricular function and myocardial salvage<sup>9,10</sup>.

### Patency of the infarct-related artery

Importance of patency of the infarct-related artery has been conclusively demonstrated and intense research continues in order to identify the thrombolytic strategy that achieves the highest patency rate<sup>11</sup>. However, even with the “gold standard” of thrombolytic cocktail of accelerated alteplase, aspirin, and heparin, TIMI 3 patency is obtained only in 50% of patients, with effective reperfusion being obtained in two thirds of these, and reocclusion being observed in up to one third by 3 months<sup>12</sup>.

Addition of glycoprotein IIb/IIIa blockers to thrombolytics neither seems to improve TIMI 3 patency nor to reduce frequency of reocclusion.

Direct coronary angioplasty is superior to fibrinolytic therapy in the restoration of patency of the infarct-related artery. Coronary angioplasty provides a higher rate of TIMI 3 flow, is successful in > 90% of patients, and is associated with lower rates of reocclusion and postinfarction ischemia. Primary stenting for myocardial infarction is currently being evaluated in ongoing studies. However, mortality rates have not declined as expected, and patients are often encountered who do not recover left ventricular function despite successful angioplasty and stenting<sup>13</sup>.

### Microvascular function

Assessment of microvascular function early in AMI is gaining increasing attention since the demonstration that dysfunctional coronary microcirculation is an important determinant of prognosis for AMI patients. Lack of myocardial perfusion immediately after successful thrombolysis, as assessed by contrast echocardiography, is a predictor of poor recovery of left ventricular function and is associated with a worse prognosis<sup>14</sup>. In 31 patients with their first myocardial infarction, coronary flow velocity pattern measured after successful primary stenting was predictive of recovery of regional and global left ventricular function<sup>15</sup>.

More recently it has been reported that the presence of residual flow within the infarct area before reperfusion results in good myocardial salvage and rapid functional recovery from myocardial stunning<sup>16</sup>. Long-term follow-up of patients with AMI treated with aspirin and heparin followed by primary angioplasty has shown that in patients with evidence of reperfusion before

coronary angioplasty, outcomes were strikingly better with less cardiogenic shock, improved procedural results, smaller infarct size, and reduced mortality<sup>17</sup>. However, if this benefit comes from the blockage of the IIb/IIIa receptor or from interference with other platelet receptors or with different cell populations (endothelial cells? white blood cells?) is unknown<sup>18</sup>.

The relevance of microvascular damage in the natural history of myocardial infarction is consistent with the benefits achieved by treatment strategies directly aimed at protecting coronary microcirculation from reperfusion damage. In animal models, pretreatment with adenosine limits ischemia-reperfusion damage in coronary and intestinal microcirculation. In man, distal intracoronary administration of adenosine as an adjunct to primary angioplasty in patients admitted within 3 hours of symptom onset of an AMI prevented the no-reflow phenomenon, reduced the incidence of adverse cardiac events and improved recovery of ventricular function<sup>19</sup>.

### References

1. Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 7: The era of reperfusion. Section 1: Acute coronary syndromes. *Circulation* 2000; 102 (Suppl I): I172-I203.
2. GISSI-1 Investigators. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; i: 397-402.
3. Reimer KA, Jennings RB. The “wavefront phenomenon” of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Lab Invest* 1979; 40: 633-44.
4. Lavalley M, Cox D, Patrick TA, Vatner SF. Salvage of myocardial function by coronary artery reperfusion 1, 2, and 3 hours after occlusion in conscious dogs. *Circ Res* 1983; 53: 235-47.
5. Raitt MH, Maynard C, Wagner G, et al. Relation between symptom duration before thrombolytic therapy and final infarct size. *Circulation* 1996; 93: 48-53.
6. Newby LK, Rutsch WR, Califf RM, et al, for the GUSTO-I Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. *J Am Coll Cardiol* 1996; 27: 1646-55.
7. Boersma E, Maas AC, Derckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996; 348: 771-5.
8. Chareonthaitawee P, Gibbons RJ, Roberts RS, et al, for the CORE Investigators. The impact of time to thrombolytic treatment on outcome in patients with acute myocardial infarction. *Heart* 2000; 84: 142-8.
9. Milavetz JJ, Giebel DW, Christian TF, et al. Time to therapy and salvage in myocardial infarction. *J Am Coll Cardiol* 1998; 31: 1246-51.
10. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1998; 32: 1312-9.
11. Brodie BR, Stuckey TD, Kissling G, et al. Importance of infarct-related artery patency for recovery of left ventricular

- function and late survival after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1996; 28: 319-25.
12. Wilcox R. Patency, perfusion, performance - the desirable triplets of combination thrombolytic therapy. *Eur Heart J* 2000; 21: 1495-7.
  13. Natarajan MK, Mehta S, Yusuf S. Management of myocardial infarction: looking beyond efficacy. *J Am Coll Cardiol* 2000; 2: 380-1.
  14. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis: a predictor of poor recovery of left ventricular function in acute myocardial infarction. *Circulation* 1992; 85: 1699-705.
  15. Wakatsuki T, Nakamura M, Tsunoda T, et al. Coronary flow velocity immediately after primary coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction. *J Am Coll Cardiol* 2000; 35: 1835-41.
  16. Lim YJ, Masuyama T, Mishima M, et al. Effect of pre-reperfusion residual flow on recovery from myocardial stunning: a myocardial contrast echocardiography study. *J Am Soc Echocardiogr* 2000; 13: 18-25.
  17. Brodie BR, Stuckey TD, Hansen C, Muncy D. Benefit of coronary reperfusion before intervention on outcomes after primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2000; 85: 13-8.
  18. Scarborough RM, Kleiman NS, Phillips DR. Platelet glycoprotein IIb/IIIa antagonists. *Circulation* 1999; 100: 437-44.
  19. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000; 101: 2154-9.