

# Improving perfusion at reperfusion

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## Abstract

Early reperfusion of the ischemic myocardium has been shown to reduce mortality in acute myocardial infarction. Unfortunately, reperfusion, although necessary to relieve ischemia, may be followed by morphological, functional, and electrical changes that result in additional myocardial damage, known as reperfusion injury. In animal models, several pharmacologic agents and reperfusion strategies have been shown to be effective in preventing reperfusion injury, but most of these measures have failed when transferred to humans. Adenosine is one exception, because it has been shown to limit ischemia-reperfusion damage in several animal models, and has been successfully tested in man. The administration of adenosine as an adjunct to primary percutaneous transluminal coronary angioplasty early in acute myocardial infarction improved myocardial blood flow, prevented the no-reflow phenomenon, reduced the incidence of adverse cardiac events, and improved recovery of ventricular function. More recently, favorable results have been reported with myocardial postconditioning. However, neither of these two therapeutic strategies has been definitively confirmed in man, and their use remains limited to research-oriented laboratories, so that the problem of preventing reperfusion injury and limiting infarct size in the setting of acute myocardial infarction remains largely unsolved.

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**Keywords:** Reperfusion injury, no-reflow phenomenon, adenosine, postconditioning, infarct size, acute myocardial infarction

## Introduction

Evidence-based data for the management of acute myocardial infarction (AMI) have 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, which include unstable angina, non Q-wave myocardial infarction, and Q-wave myocardial infarction [1].

The majority of patients presenting with ST-segment elevation will eventually develop a transmural myocardial infarction. The primary goals of treatment for patients presenting with ST-segment elevation are the reduction of mortality and the prevention of late morbidities. The potential for prevention of cardiac death and reduction of myocardial damage is greatest very early in AMI. Fifty percent of the patients who die of AMI do so before reaching a hospital, the major risk of

ventricular tachycardia or ventricular fibrillation occurring during the first 4 h after the onset of symptoms.

Perhaps the most significant advance in treatment of cardiovascular disease in the past decade has been reperfusion therapy for AMI. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-1 trial, the first mega-trial to show reduction in mortality associated with fibrinolytic therapy, demonstrated that patients derived the greatest benefit of treatment during the first 3 h, with a maximum reduction in mortality of 47% for patients treated in the first 1 h.

At present, salvage of jeopardized myocardium in acute myocardial infarction appears to be determined mostly by:

- the duration of ischemia
- the stable patency of the infarct-related artery
- a preserved microvascular function.

### Time to reperfusion

In animal models, infarct size and left ventricular function are adversely affected, in a non linear fashion, by the duration of coronary occlusion [2]. In dogs, reperfusion after 5–15 min of coronary occlusion leads to virtually complete salvage of myocardium. Significant salvage is still possible even after 3 h of occlusion; however, no improvement of regional function results when perfusion is restored after 3 h of ischemia [3].

Attempts to confirm this association in clinical studies have yielded conflicting results [4–6]. A recent study examining the impact of time on several outcome variables concluded that the beneficial effect of thrombolysis on infarct size and ejection fraction was restricted to treatments given within 2 h of the onset of symptoms [7]. The greatest benefit for mortality was also achieved when thrombolysis was given within 2 h. These observations support the concept that time-dependent myocardial salvage is the explanation for the early survival benefit. Beyond that time, reduction in infarct size was markedly attenuated, and the mortality benefit thus clearly exceeds the impact of therapy on ventricular function and myocardial salvage [8,9].

Restoration of blood flow before the ischemic myocardium becomes fully necrotic is therefore mandatory if infarct size is to be limited in AMI.

### Patency of the infarct-related artery

Recanalization of the infarct-related artery is of paramount importance, and intense research continues in order to identify the thrombolytic strategy that achieves the greatest rate of patency [10]. However, even with the “gold standard” of accelerated alteplase, aspirin, and heparin, Thrombolysis In Myocardial Infarction (TIMI) 3 patency is obtained only in 50% of patients, with effective reperfusion being obtained in two-thirds of these, and re-occlusion being observed in up to one-third by 3 months [11]. The addition of glycoprotein IIb/IIIa blockers to thrombolytic agents does not seem to improve TIMI 3 patency, or to reduce the frequency of re-occlusion.

Direct coronary angioplasty is superior to fibrinolytic therapy in the restoration of patency of the infarct-related artery. Primary percutaneous coronary intervention assures a greater rate of TIMI 3 flow, and is associated with lower rates of re-occlusion and postinfarction ischemia. However, mortality rates have not declined as expected, and in the vast majority of patients, left ventricular function does not recover, despite a “successful” procedure [12].

A convincing explanation for this frustrating observation refers to the time delay between occlusion of

the infarct-related artery and its recanalization. In practice, this time interval often exceeds myocardial tolerance to ischemia – that is, the infarct-related artery is re-opened when necrosis of the jeopardized myocardium is already complete.

Unfortunately, early recanalization of the infarct-related artery, which is mandatory to salvage jeopardized myocardium and limit infarct size, may be the cause of further myocardial damage, unless measures are taken to prevent the adverse effects of oxygenated blood returning to tissues previously exposed to ischemia – the so-called “no-reflow” phenomenon.

### Improving perfusion at reperfusion

Several reports indicate that dysfunctional coronary microcirculation is an important determinant of prognosis for patients with AMI. 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 [13]. In 31 patients with their first myocardial infarction, the coronary flow velocity pattern measured after successful primary stenting was predictive of recovery of regional and global left ventricular function [14].

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 [15]. Long-term follow-up of patients with AMI treated with aspirin and heparin followed by primary percutaneous transluminal coronary angioplasty (PTCA) has shown that, in patients with evidence of reperfusion before PTCA, outcomes were strikingly better, with less cardiogenic shock, improved procedural results, smaller infarct size, and reduced mortality [16].

Adenosine, an endogenous purine nucleoside, antagonizes many of the biochemical and physiological mechanisms implicated in ischemia-reperfusion injury, and has been shown to limit microvascular damage, and to reduce postischemic ventricular dysfunction. The administration of adenosine in the ischemic territory before vessel re-opening is feasible and safe in the setting of primary percutaneous coronary intervention, and can maximize salvage of jeopardized myocardium by limiting or preventing reperfusion damage [17]. Patients receiving intracoronary adenosine had a more favorable clinical course and a better recovery of left ventricular function at discharge when compared with patients treated with PTCA alone [17,18]. Less impressive results have been obtained when the same agent was given intravenously [19,20].

In animal models, an alternative effective strategy to limit infarct size is “myocardial preconditioning”:

myocardium previously exposed to a short period of ischemia develops a marked resistance to subsequent coronary occlusion [21]. Preconditioning poses obvious problems to be transferred to clinical practice, given the unpredictability of the acute coronary events, but it could be substituted by a strategy of intermittent reperfusion at the time of primary percutaneous coronary intervention. It has been reported that, in animal models, brief sequences of ischemia-reperfusion applied after the end of the ischemic period ("post-conditioning") give a myocardial protection comparable to that of classic preconditioning [22–24]. This strategy has recently been tested in man, with encouraging results [25].

## Conclusions

Early reperfusion associated with protection from reperfusion injury appears to be the most effective strategy to reduce acute mortality and prevent late morbidity in AMI. To date, intracoronary administration of adenosine and postconditioning appear to be the only two strategies available in man to protect the ischemic myocardium and limit infarct size. Both have been proved to be feasible and safe in the setting of primary percutaneous coronary intervention. However, their clinical application is currently limited to research-oriented laboratories, and their efficacy is in need of conclusive supportive evidence. ■

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