

Role of adenosine as an adjunct therapy in the prevention and treatment of no-reflow phenomenon in acute myocardial infarction with ST segment elevation: review of the current data

Marek Grygier, Aleksander Araszkiwicz, Maciej Lesiak, Stefan Grajek

Chair and 1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

INTRODUCTION

Numerous clinical studies have indicated the beneficial effects of timely, optimal (without residual stenosis) and sustained patency of an occluded epicardial artery on infarct size reduction, left ventricular (LV) function and clinical outcomes. While these observations validate the experimental findings of time-dependent myocardial salvage, patients with large regions of ischaemia continue to exhibit significant morbidity and mortality. So it is clear that additional strategies are needed to improve outcomes.

Emerging evidence suggests that maximising myocardial salvage not only involves restoring the full patency of large epicardial coronary arteries, but also maintains blood flow in microcirculation of the reperfused bed [1]. Experimental models convincingly document the concept of progressive microcirculatory failure (the 'no-reflow phenomenon') and no-reflow appears to be an important component of the potential deleterious effect of reperfusion — myocardial reperfusion injury. In animal models, abnormalities of tissue perfusion are associated with an increase of the infarct size, and agents that preserve microvascular flow result in a significant reduction of irreversible myocyte necrosis. Diagnostic techniques to measure tissue perfusion have validated this concept in humans and it is now clear that abnormal tissue perfusion occurs frequently in patients with acute coronary syndromes (ACS) undergoing reperfusion therapy [1–6].

MEASUREMENT AND PREDICTIVE VALUE OF DIFFERENT INDICES OF TISSUE PERFUSION

Although ECG ST-segment resolution is a readily available marker of tissue-level reperfusion, persistence of ST-segment elevation in patients with ST-segment elevation myocardial infarction (MI) may reflect either epicardial artery occlusion or microvascular obstruction [7, 8]. Coronary angiography

allows a semi-quantitative grading of epicardial coronary flow according to widely used Thrombolysis In Myocardial Infarction (TIMI) flow grades [5]. Reduced coronary flow after primary percutaneous intervention (PCI) (TIMI flow 0 to 2) is associated with worse outcome than normal flow (TIMI 3), even when no significant epicardial obstruction remains [5]. TIMI frame count (TFC) assesses the number of angiographic frames required for the contrast medium to reach standard distal landmarks of coronary tree (no-reflow is considered to have occurred when TFC is greater than 40 frames) [9]. Although TIMI flow grade and corrected TFC provide information regarding the patency of epicardial arteries, these methods do not assess local tissue perfusion. Myocardial blush grade (MBG) is a relatively simple (and available in all cath-labs) semiquantitative angiographic method of evaluating tissue perfusion; clinicians use this measurement more and more frequently nowadays. MBG is a quantitative assessment of myocardial density (MBG 0: no myocardial opacification, MBG 3: myocardial opacification with quick clearance indicating good tissue perfusion) [10]. Other diagnostic modalities include myocardial contrast echocardiography, contrast enhanced magnetic resonance imaging (MRI) and computed tomography (CT), and a vasodilatory flow reserve utilising a Doppler flow wire: a close correlation exists between these various methods and MBG. Also a rise in serum cardiac biomarkers after PCI reflects myocardial necrosis secondary to tissue hypoperfusion and ischaemia.

Impaired tissue perfusion occurs in up to 44% of patients with ST segment elevation MI [11, 12]. The highest incidence of impaired tissue perfusion was observed in left anterior descending artery occlusions, and the frequency of this complication was independent of the method of reperfusion. Numerous studies noted a marked discrepancy between epicardial blood flow and tissue perfusion, emphasising that

Address for correspondence:

Marek Grygier, MD, PhD, Chair and 1st Department of Cardiology, Poznan University of Medical Sciences, ul. Długa 1/2, 61–848 Poznań, Poland, fax: +48 618549223, e-mail: mgrygier@wp.pl

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normalisation of epicardial blood flow (TIMI 3) frequently did not result in adequate tissue perfusion (MBC 3) [12]. Studies have also demonstrated that tissue perfusion was an independent predictor of both early and late mortality. Normal tissue perfusion was associated with a significant decrease in infarct size and preservation of ventricular function. Abnormal tissue perfusion correlated with abnormal LV remodelling, congestive heart failure (HF), ventricular arrhythmias and rupture [1, 3, 11–13].

POTENTIAL MECHANISMS OF ABNORMAL TISSUE PERFUSION

Microvascular injury is an important component negating the full beneficial effects of reperfusion therapy [1, 2, 4, 6, 12]. Reperfusion seems to be the key trigger responsible for inducing structural and functional changes (reperfusion injury) in the large and small coronary arteries after ischaemia. The mechanisms responsible for abnormal tissue perfusion are multifactorial and not fully understood [1, 2, 4, 6, 12, 14]. Leukocyte plugging, platelet aggregation, endothelial disruption secondary to activated leukocytes and emboli from thrombus and atheromatous debris may play key roles as mechanical factors. Also some substances from platelets (serotonin, thromboxane A₂, platelet activating factor), leukocytes (leukotrienes), endothelium (endothelin-1), sympathetic nervous system (norepinephrine) and renal (rennin and angiotensin II) may act as vasoconstrictors being responsible for abnormal tissue perfusion. Experimental studies invariably report microvascular obstruction by cellular elements, particularly leukocytes and platelets, in animal models of reperfusion. Activated leukocytes play an important role in impairing tissue perfusion by mechanical obstruction of microvessels and by disrupting the endothelial cell lining of the microvessels by releasing cytotoxic proteolytic enzymes and free radicals. Microvascular spasm induced by the presence of very potent vasoconstrictors in the vascular bed may further compromise tissue perfusion [1, 2, 4, 6, 12, 14].

PREVENTION AND TREATMENT OF NO-REFLOW

Multiple therapies for no-reflow have been tested in animals and to a lesser degree in humans. Niccoli et al. [15] recently summarised the therapies used in the clinics to treat no-reflow. Treatments included mechanical thrombectomy at the time of intervention and various drugs used before, during and after intervention. Prevention of upstream and in situ microvascular thrombosis with IIb/IIIa inhibitors (abciximab) has been shown to improve microvascular perfusion [16]. Mechanical devices for preventing embolisation and removal of plaque and thrombus may have a role in the setting of primary PCI. Svilaas et al. [17] showed that manual thrombus aspiration improved MBC and resolution of ST segment elevation. Improved MBC was associated with better clinical outcome and reduced mortality. However, deployment of a distal ar-

terial protection device during primary PCI did not improve myocardial perfusion and prognosis [18].

Drug treatment aimed at reducing the no-reflow phenomenon may improve myocardial salvage, thus preventing LV remodelling. Various treatment strategies, including the use of vasodilators such as verapamil, calcium channel blockers, nitrates and sodium nitroprusside, have been associated with an improvement in angiographic flow in several studies, but whether these treatment strategies affect clinical outcome is not clear [2, 4, 5].

RATIONALE FOR THE USE OF ADENOSINE IN THE PREVENTION AND TREATMENT OF NO-REFLOW

Adenosine is an endogenous nucleoside produced by the degradation of adenosine triphosphate (ATP). It activates four well-characterised receptors producing various physiological effects that attenuate many of the proposed mechanisms of ischaemia-reperfusion injury. In a normal physiological setting, it is present in a 40-fold greater concentration in endothelial cells, whereas myocytes become the major source of adenosine during ischaemia due to the inability of mitochondria to rephosphorylate adenosine diphosphate and adenosine monophosphate [12].

Although the mechanisms responsible for microvascular injury with subsequent decrease in myocardial blood flow are complex and diverse, adenosine appears to be a crucial counter-regulatory compound in the maintenance of microcirculatory flow due to its numerous pharmacological actions. Firstly, adenosine could decrease mechanical obstruction of capillary channels caused by neutrophil adherence and neutrophil-mediated cellular damage. Secondly, the potent arteriolar vasodilator properties of adenosine would oppose the effects of vasoconstrictor substances present in the vascular bed after reperfusion, such as endothelin, leukotrienes and platelet activating factor. Thirdly, adenosine would reduce the release of vasoconstrictor substances produced by activated platelets and neutrophils [12].

Adenosine is also an important modulator of neutrophil function. It markedly inhibits superoxide anion production by neutrophils and decreases numbers of neutrophils in the reperfused bed. In addition, the ability of adenosine to reduce inflammation by inhibiting multiple cell types involved in cellular immunity may also contribute to tissue protection [12].

Adenosine initiates numerous metabolic events that could be beneficial in the setting of ischaemia and reperfusion. Administration of exogenous adenosine restores ATP levels in viable but energy-deficient cells following myocardial ischaemia. Adenosine may also maintain cell viability by increasing cellular uptake of glucose and reduce oxygen consumption, through its negative inotropic and chronotropic effects and by inhibiting norepinephrine release from sympathetic nerve endings [12].

Adenosine possesses a number of physiological effects that may reduce free radical formation following ischaemia. It also restores calcium homeostasis. Recent studies suggest that

adenosine may play an important role in promoting vascular repair (vasculogenesis) and accelerating the development of new blood vessels (angiogenesis) following vascular injury. Moreover, adenosine is an important endogenous cardioprotective agent that mediates pre- and post-conditioning phenomenon [12].

Adenosine significantly reduces the number of apoptotic cells and is associated with modification of pro- and anti-apoptotic regulatory proteins. The reduction in apoptosis by adenosine may also be secondary to the modification of the release of cytokines, proteolytic enzymes and reactive oxygen species by acute and chronic inflammatory cells in the reperfused bed [12].

EFFECTS OF ADENOSINE ON INFARCT SIZE IN ANIMAL MODELS OF MYOCARDIAL REPERFUSION

The effects of adenosine on myocardial blood flow and infarct size have been investigated in numerous studies. In a closed chest canine model, selective intracoronary administration of adenosine (3.75 mg/min), beginning just before reperfusion and continuing for 60 minutes thereafter, produced a 75% reduction in infarct size expressed as a percentage of the risk region when compared to blood reperfused controls [12, 19]. The reduction in infarct size was associated with an improvement in regional ventricular function in the ischaemic zone. The cardioprotective effects in the canine model have a narrow time window, with the drug losing its effect following three hours of ischaemia [12, 20].

Intravenous adenosine was also efficacious in a canine model when it was administered (140 µg/kg/min) to animals undergoing 90 minutes of regional ischaemia beginning just before reperfusion and continuing for 150 minutes after reperfusion. Treated animals demonstrated a significant decrease in infarct size at 72 hours and improved regional ventricular function. Moreover, adenosine did not significantly affect blood pressure or heart rate [12].

Many animal studies have shown that reperfusion accelerates structural and functional changes in the vasculature of the ischaemic bed, resulting in a progressive decrease in blood flow (no-reflow). Adenosine has been demonstrated to prevent progressive decrease to the inner two-thirds of the myocardial bed at both three and 24 hours after reperfusion following 40–120 minutes of regional ischaemia. Additional studies demonstrate that adenosine preserves endothelial dependent and independent vasodilatory reserve in animals subjected to two hours of ischaemia, and endothelial dependent vasodilation is maintained up to 48 hours after reperfusion [12]. Ultrastructural analysis in animals subjected to 120 minutes or less of ischaemia demonstrate extensive microvascular injury in capillaries in the subendocardium associated with luminal plugging by endothelial projections, neutrophils, platelets and red cells. Adenosine treatment markedly attenuates these changes with relative preservation of endothelial

cells and only occasional obstruction of capillaries by cellular elements. In contrast to these findings, when reperfusion is restored after 120 minutes of ischaemia, infusion of adenosine after 180 minutes of ischaemia followed by reperfusion does not increase blood flow to the inner two-thirds of the myocardium or prevent the no-reflow phenomenon — severe and similar ultrastructural changes are present in both control and treatment groups [12].

CLINICAL TRIALS WITH ADENOSINE AS AN ADJUNCT TO REPERFUSION THERAPY IN ACUTE CORONARY SYNDROMES

Several studies have investigated the benefits of the preventive use of adenosine during and after reperfusion therapy for acute MI. These studies utilised different, sometimes complicated, protocols of adenosine infusion during and after the PCI procedure or thrombolytic therapy (Table 1).

Garratt et al. [21] performed the first clinical study of adenosine in acute MI. In that small pilot study, intravenous adenosine at 70 µg/kg/min was infused over one hour in 35 patients with acute MI (almost 60% anterior) undergoing primary PCI. When compared to historical controls, adenosine-treated patients exhibited significantly greater myocardial salvage.

Clayes et al. [22] in a group of 79 patients with ST segment MI showed that compared to an historical cohort group (200 patients), a 20-minute adenosine 60–90 µg/kg/min intracoronary infusion (respectively to the right and left coronary artery) during primary PCI resulted in better ST segment elevation resolution and less infarct expansion. Although the study was underpowered to evaluate clinical events, major adverse events (i.e. death and re-infarction) occurred more frequently in patients with reperfusion injury compared to those without.

Marzilli et al. [23] in a small but randomised study of 54 patients admitted very early after symptoms onset (within three hours) showed improved angiographic flow and ventricular function one week after reperfusion when a 4 mg bolus of intracoronary adenosine was given distally to the occlusion, just before mechanical reperfusion. Moreover, adverse cardiac events (death, nonfatal MI, recurrent ischaemia and HF) occurred significantly less frequently during in-hospital stay in adenosine than in a placebo group.

In the randomised and placebo controlled AMISTAD-I trial [24], IV adenosine 70 µg/kg/min was given for three hours during and after reperfusion as an adjunct to thrombolysis. In the 236 enrolled patients, there was an overall 33% relative reduction in infarct size when compared to placebo measured by SPECT imaging. The benefit was however limited to patients with anterior infarction, where relative reduction in infarct size was 67%, with little evidence of benefit for infarcts located elsewhere. Myocardial salvage was also significantly greater in anterior infarcts treated with adenosine. In-hospital clinical outcomes occurred with similar frequency between the two study groups, though a trend was present toward

Table 1. Summary of randomised trials comparing adenosine with placebo in patients with acute myocardial infarction with ST segment elevation

Study/Author	Journal (year)	No. of patients	Reperfusion strategy	Route of adenosine	Dose of adenosine	Follow-up time [months]
Marzilli et al. [23]	Circulation (2000)	54	PCI	IC	4 mg (1 min)	In-hospital
AMISTAD-1 [24]	JACC (1999)	236	Thrombolysis	IV	70 µg/kg/min (3 h)	1 and 4
AMISTAD-2 [25, 26]	JACC (2005) Eur Heart J (2006)	2118	Thrombolysis/PCI	IV	50 µg vs. 70 µg/kg/min (3 h)	6
ATTACC study [27]	Eur J Clin Pharmacol (2003)	608	Thrombolysis	IV	10 µg/kg/min (6 h)	6
Stoel et al. [28]	Catheter Cardiovasc Intervent (2008)	51	PCI	IC	60 mg (5–10 min)	12
Fokkema et al. [29]	Circ Cardiovasc Interv (2009)	448	PCI	IC	2 × 120 µg (quickly)	1
Sakuma et al. [30]	Int J Cardiol (2010)	204	PCI	IV	150 µg/kg/min (1 h)	21
Desemet et al. [31]	Eur Heart J (2011)	110	PCI	IC	4 mg (quickly)	12
Grygier et al. [32]	Am J Cardiol (2011)	70	PCI	IC	2–4 mg (quickly)	1
Wang et al. [33]	Clin Exp Pharmacol Physiol (2012)	69	PCI	IV	50 µg/kg/min (3 h)	1

PCI — percutaneous coronary intervention; IV — intravenous; IC — intracoronary

more adverse clinical events in the patients with non-anterior MI assigned to adenosine compared to a placebo. Side effects of adenosine were also slightly more common in adenosine-treated patients with inferior infarcts.

The follow-up AMISTAD-II trial [25] was a double-blind, randomised, multicentre, placebo controlled trial in 2,118 patients only with anterior ST-elevation MI undergoing reperfusion therapy within six hours of symptoms onset, using thrombolysis (60% of patients) or primary angioplasty. Patients were randomised to a three hour infusion of either adenosine 50 µg/kg/min, adenosine 70 µg/kg/min, or a placebo. There was no difference in the primary endpoint (six-month composite rate of death, new onset congestive HF or re-hospitalisation for HF) between the placebo and the pooled adenosine dose groups. A trend was present toward a smaller median infarct size in the pooled adenosine group compared to the placebo. Moreover, adenosine resulted in a marked reduction in infarct size in the high-dose group compared to the placebo.

Post hoc analysis of the AMISTAD-II trial [26] evaluated the effect of time to treatment on the efficacy of adenosine on clinical endpoints. This subanalysis demonstrated that adenosine infusion administered within the first 3.17 hours of onset of anterior ST-elevation MI enhanced one-month and six-month survival and reduced the composite clinical endpoint at six months.

The majority of the patients in AMISTAD-I and AMISTAD-II were treated with thrombolysis, so the state of epicardial reperfusion was mostly unknown. This limitation also applies to the placebo controlled ATTACC study [27], in which 608 patients treated with thrombolysis were randomised to

a small dose of IV adenosine 10 µg/kg/min for six hours or a placebo. The study was prematurely discontinued due to failure to show beneficial effects on the primary endpoint (global and regional ventricular function measured with echocardiography at four days). However, at the six-month follow-up of 292 patients with anterior infarcts, the adenosine group showed a trend for less all-cause mortality and cardiovascular mortality. Furthermore, in a *post hoc* analysis of a subgroup of 181 patients with anterior infarcts and severely depressed LV function, the six-month all-cause mortality and cardiovascular mortality were lower in the treated group.

Stoel et al. [28] investigated the influence of very high-dose intracoronary adenosine (60 mg during 5–10 minutes) in the group of 51 patients with < 70% ST segment resolution after successful primary PCI. All patients were treated with stent and abciximab. Immediately after adenosine, significantly more patients showed optimal ST segment resolution compared to placebo and also mean ST segment resolution was higher after adenosine. In addition, TFC was significantly lower, MBG was higher, and resistance index was lower, in the adenosine group. The authors concluded that intracoronary adenosine accelerated ST segment resolution and recovery of microvascular perfusion assessed by TFC and MBG. However, there was no significant difference between both groups at 12-month follow-up.

Fokkema et al. [29] in a randomised controlled trial of 448 patients with acute ST-elevation MI, randomised patients to two relatively low bolus injections of intracoronary adenosine (2 × 120 µg), the first given after thrombus aspiration and the

second after stenting of the infarct-related artery. The incidence of residual ST-segment deviation < 0.2 mV 30 to 60 minutes after PCI (primary endpoint of the study) did not differ between patients randomised to adenosine or a placebo. In addition, there were no significant differences in secondary outcome measures (ST segment elevation resolution, TIMI flow and MBG, enzymatic infarct size and clinical outcome at 30 days).

Sakuma et al. [30] in a group of 204 patients with first anterior MI, after intravenous administration of a high dose of adenosine (150 $\mu\text{g}/\text{kg}/\text{min}$ started five minutes before the beginning of the primary PCI and continued for up to one hour) observed enhanced ST-segment resolution 90 minutes after recanalisation, reduced the no-reflow ratio, preserved LV systolic function, and prevented LV remodelling at six months after primary PCI compared to placebo. At 21-month follow-up, major cardiac events, defined as cardiac death, re-hospitalisation due to non-fatal MI, congestive HF or malignant arrhythmias, were significantly lowered in the adenosine compared to the placebo group.

Desemet et al. [31] in a single-centre, double-blind, placebo-controlled clinical study randomised a group of 110 patients with ST segment elevation MI (40% anterior), presented within 12 hours from symptoms, to selective intracoronary administration of adenosine (4 mg) distally to the occlusion site or a matching placebo. Adenosine was given immediately before initial balloon inflation. The primary aim of the study was to investigate the effect of high-dose adenosine on microvascular and myocardial salvage by MRI. No significant difference was found in microvascular obstruction and myocardial salvage index assessed by MRI between adenosine- and placebo-treated patients. The authors did not find significant differences in ST-segment elevation resolution, TIMI flow and MBG, enzymatic infarct size or clinical outcome at 30 days and one year after primary PCI between patients randomised to intracoronary adenosine or a placebo.

We recently published the results of a single-centre, prospective, randomised placebo-controlled trial in 70 consecutive patients with acute MI with ST segment elevation undergoing primary PCI which was conducted at our institution [32]. The aim of that study was to examine the role of a new protocol of adenosine administration performed during primary angioplasty on immediate electrocardiographic and angiographic results and clinical outcome. Patients in the study group received two doses of intracoronary adenosine (all together 2 to 4 mg) through the guiding catheter: once immediately after crossing the lesion of the infarct related artery with guidewire, and then after first balloon inflation. We noted that resolution of ST segment elevation was more frequently observed in the adenosine than in the placebo group. Adenosine usage also resulted in better TIMI 3 flow, TFC and MBG. Moreover, adenosine administration was associated with more favourable clinical course.

Wang et al. [33] in 69 patients with acute ST segment elevation undergoing primary PCI (within 12 hours from symp-

toms onset) after intravenous adenosine infusion (50 $\mu\text{g}/\text{kg}/\text{min}$ for three hours), noted improved myocardial perfusion, segmental wall motion and global contractile function.

Recently, Navarese et al. [34] published the first meta-analysis of ten randomised trials investigating angiographic and clinical outcomes in patients with ACS undergoing PCI or thrombolysis and receiving adjunctive adenosine therapy vs. placebo. This meta-analysis showed that adenosine markedly reduced the incidence of no-reflow and ST-segment resolution, but had no influence on mortality, re-infarction or advanced HF (NYHA III–IV).

This meta-analysis requires comment. Measurements of early and late mortality are the most powerful and definite endpoints in clinical trials assessing reperfusion therapy in ACS. However, because timely reperfusion per se reduces infarct size and improves survival, a large number of patients are needed to demonstrate statistically significant reductions in mortality with adjunctive therapies. Therefore most studies presented above have incorporated 'surrogate' endpoints of myocardial salvage and/or infarct size utilising different methods of assessment (ECG, TIMI flow, TFC, MBG, ECHO, SPECT, MRI or CT). Moreover it is known that the area at risk and the final infarct size are larger in anterior than non-anterior MI. Clinical events and mortality are also lower with inferior infarcts, thus requiring more patients to evaluate the efficacy of an adjunctive therapy. Also in some studies included in that meta-analysis (AMISTAD I, AMISTAD II and ATTACC), adenosine was administered after thrombolysis through the intravenous route [24–27]. When excluding these patients from the analysis (almost 77% of the whole group) we end up with seven studies with adenosine as an adjunctive therapy to primary PCI, with one-year follow-up data available in only two of them with less than 200 patients [28, 31]. In our opinion, it is too early to make a definitive conclusion on the lack of potential long-term clinical benefits of adenosine treatment.

CONCLUSIONS

Although some preclinical and clinical studies point towards the beneficial role of adenosine in the prevention and treatment of no-reflow phenomenon in acute MI with ST segment elevation, many unanswered questions remain, including the optimal clinical indication, mode, dosage and timing of application, influence of reperfusion mode, and the exact mechanisms leading to potential benefits. Clarifying these issues will depend on further properly designed, adequately powered and well conducted clinical trials, which will probably provide us with many answers, but also raise new questions.

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