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Adenosine as cardioprotective in off-pump coronary artery bypass grafting



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Abstract

Objective: To assess the effect of adenosine as a cardioprotective drug and its role in attenuating ischemia-reperfusion injury during off-pump coronary artery bypass surgery.

Background: Cardioprotective drugs have long been investigated for use during off-pump coronary artery bypass surgery to attenuate ischemia-reperfusion injury and limit hemodynamic instability. Adenosine has been investigated due to its cardioprotective effect that is mediated through A1 and A3 adenosine receptors. Stimulation of these receptors reproduces the infarct-limiting effect of ischemic preconditioning.

Methods: After approval of the local ethics committee and informed written consent, fifty patients undergoing elective off-pump coronary artery bypass grafting were prospectively studied. The adenosine group received an infusion of Adenoscan at a rate of 50 µg/kg/min for 15 min. The control group received normal saline at the same rate and volume calculated. Pulmonary artery catheter was introduced through the right internal jugular vein. Cardiac output measurements were obtained. Cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular resistance, right ventricular stroke work index, and left ventricular stroke work index were derived. Hemodynamic measurements were recorded together with blood levels of troponin I and CK-MB fraction to detect perioperative myocardial necrosis. Postoperative duration of mechanical ventilation, ICU stay together with inotropic support quantification using inotropic score were recorded.

Results: Fifty patients were included in the study. In the adenosine group, the infusion of adenosine resulted in a significant reduction in mean pulmonary artery pressure after stopping drug infusion (18 ± 2.2 mmHg versus 31 ± 4.1 mmHg). There was a recorded increase in cardiac index in the adenosine group that started 15 min after adenosine infusion and lasted for 12 h postoperatively ($p < 0.001$). Also, adenosine infusion resulted in a reduction in pulmonary vascular resistance that exceeded the reduction in systemic vascular resistance which resulted in a decrease in pulmonary vascular resistance/systemic vascular resistance ratio (0.14 in adenosine group 15 min after injection versus 0.28 in control group) and (0.11 in adenosine group 12 h postoperatively versus 0.26 in control group). The cTroponin I measured 6 h postoperatively was less in the adenosine group compared with the control group (5.8 ± 2.8 ng/ml versus 16.5 ± 3.9 ng/ml).

Conclusion: Adenosine infusion during off-pump coronary artery surgery may improve cardiac index, reduce the need for inotropes, and have cardioprotective effect.

Keywords: Adenosine, Cardioprotective, Off-pump coronary artery surgery, Cardiac index, Ischemic preconditioning

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Background

The off-pump coronary artery bypass (OPCAB) graft surgery has been largely extended because of the benefit of avoiding bypass-related cardiopulmonary complications. OPCABG requires a period of coronary artery occlusion to provide a bloodless field. This temporary occlusion of the target arteries may be superimposed on pre-existing ischemia, especially in patients with acute infarction in which blood flow is totally occluded. The off-pump surgical techniques have limited the strategies to protect the heart from ischemia or reperfusion injury, where extracorporeal circulation and cardioplegia are not options. Although many studies have identified effective cardioprotective agents to attenuate ischemia-reperfusion injury, a useful strategy has not been developed for these types of surgeries. Among the various cardioprotective drugs, adenosine has been extensively investigated both in clinical and experimental studies (Vinten-Johansen et al. 2003; Murak et al. 2001). The A1 and A3 adenosine receptors are involved in the endogenous cardioprotective response of adenosine, and their activation reproduces the infarct-limiting effect of ischemic preconditioning (Lasley et al. 1990; Randhawa Jr et al. 1995; Jordan et al. 1997; Auchampach et al. 1997). The present prospective, randomized study was designed to investigate the effect of adenosine pretreatment on hemodynamic instability and myocardial recovery from reperfusion injury in patients undergoing off-pump coronary artery bypass surgery.

Methods

After approval of the local ethics committee and informed written consent was obtained from all patients entering the study, 50 patients undergoing off-pump coronary artery bypass grafting were prospectively studied. Only elective operations were included in the study. Patients who were in hemodynamically unstable condition, with poor left ventricular function (ejection fraction < 30%), or who showed evidence of acute ischemia before surgery were excluded from the study. The conduct of anesthesia and operation was similar in all patients. Anesthesia was induced with fentanyl 5–10 µg/kg administered slowly and titrated according to response and sodium thiopental 3–5 mg/kg, and muscular relaxation was obtained with pancuronium bromide 0.1 mg/kg. After sternotomy, the adenosine group (A) patients received an infusion of Adenoscan (Sanofi; Winthrop, France) through a central venous catheter. The adenosine infusion was started at a rate of 50 µg/kg/min, and the infusion lasted for 15 min. During infusion of the drug, if severe hypotension (systolic blood pressure < 60 mmHg) or bradycardia (< 50 bpm) developed, the infusion was interrupted, vasopressor drugs were administered, and patient was excluded from the study. The

control group (C) received normal saline at the same rate and volume calculated. A standard off-pump coronary artery bypass grafting was undertaken with the left internal mammary artery (LIMA) harvested and from one to three peripheral vein grafts taken in each case from the lower extremities. After systemic heparinization (1 mg/kg), the pericardium was opened. A silastic tape was placed around the left anterior descending (LAD) to produce proximal coronary occlusion, and the epicardial stabilizing device was placed. The LIMA-to-LAD anastomosis was completed. Then, saphenous vein graft was anastomosed to the right coronary artery with the silastic tape and the epicardial stabilizing device. The partial cross-clamp was applied to the aorta for the placement of the proximal anastomoses. Each patient was monitored with five-lead ECG, a radial artery cannula for invasive blood pressure monitoring, and a pulmonary artery catheter (Abbot Laboratories, Chicago, IL) introduced through the right internal jugular vein. The CO measurements were obtained using a thermo dilution catheter. The cardiac index, stroke volume, systemic vascular resistance, pulmonary vascular resistance, right ventricular stroke work index, and left ventricular stroke index were derived. Hemodynamic measurements were recorded after induction of anesthesia, 15 min after stopping injection of the drug, after complete revascularization (removal of the partial clamp), 6 h postoperatively and 12 h after the surgery. To detect perioperative myocardial necrosis, blood levels of troponin I and CK-MB were serially measured by commercially available enzyme-linked immunosorbent assay (Pe-likine Compact; CLB; Amsterdam, Netherlands) after induction of anesthesia, and 6, 12, 24, and 48 h after surgery. At ICU postoperative, data were collected for all patients and this includes the duration of mechanical ventilation and ICU length of stay. The inotropic support for the first 48 h after operation is quantified by the inotropic score; this is calculated as dopamine (× 1) + dobutamine (× 1) + amrinone (× 1) + milrinone (× 15) + epinephrine (× 100) + norepinephrine (× 100) + isoprenaline (× 100) (Wernovsky et al. 1995; Shore et al. 2001; Jin et al. 2007; Jin et al. 2008). The primary outcomes for this study were the effect of adenosine infusion on myocardial protection, the effect on the cardiac index, and inotropic support assessed by inotropic score. The secondary outcome was the effect on the duration of mechanical ventilation and ICU stay in the postoperative period.

Statistical analysis

Analysis of data was performed by using SPSS version 16 (Chicago IL, USA). Quantitative data were presented as mean ± SD and were statistically analyzed by unpaired student *t* test. Qualitative data were presented as number and percentages and were statistically analyzed

Table 1 Preoperative data and clinical characteristics

		Adenosine group (n = 24)	Control group (n = 25)	p value
Age (year)		55 ± 12.3	53 ± 11.2	0.55
Sex	♂	20 (83.3%)	19 (76%)	0.52
	♀	4 (16.7%)	6 (24%)	
BMI (kg/m ²)		27.8 ± 4.1	28.5 ± 5.04	0.59
Number of grafts	Single graft	13 (54.17%)	12 (48%)	0.9
	Two grafts	7 (29.6%)	8 (32%)	
	Three grafts	4 (16.7%)	5 (20%)	
Incidence of	Pre-op MI	18 (75%)	17 (68%)	0.58
	Diabetes	9 (37.5%)	11 (44%)	
	Hypertension	15 (62.5%)	16 (64%)	
Preoperative EF (%)		59 ± 9.5	55 ± 11.1	0.18

Data were presented as mean ± SD except for qualitative data were presented as number and percentages. p value > 0.05

by Chi-square, Fisher's exact, and Z tests. p value < 0.05 was considered statistically significant, while p value < 0.01 was considered statistically highly significant. Sample size was calculated according to a pilot study on the first 5 patients. By assuming α error = 0.05 (two-tailed) and a power of 80% to detect an assumed clinically significant difference (effect size $d = 1.0068$) between the measurements of the level of NGAL after 2 h (primary outcome). Twenty-one patients in each group were found to be satisfactory. We considered 24 patients in each group to overcome the dropout.

Results

The study was conducted on 50 patients, 25 patients in each group. Only one patient in the adenosine group, due to some surgical technical reason, was converted to

on-pump surgery. The preoperative data and clinical criteria for all patients were similar (Table 1). In adenosine group, there was a slight decrease in the heart rate and in systemic blood pressure which was of no clinical significance as none of the patients experienced a significant hypotension (systolic blood pressure < 60mmhg) or bradycardia (< 50 bpm) during or after infusion of the drug (Figs. 1 and 2). The infusion of adenosine resulted in significant reduction in mean pulmonary artery pressure after stopping drug infusion (18 ± 2.2 mmHg versus 31 ± 4.1 mmHg), after revascularization (17 ± 1.4 mmHg versus 30 ± 3.2 mmHg), after 6 h in ICU (16 ± 2.1 mmHg versus 32 ± 4.5 mmHg), and after 12 h in ICU (19 ± 2.2 mmHg versus 30 ± 3.3 mmHg) compared with control group (Fig. 3). There was a transient decrease in CVP (15 min after drug injection) and in

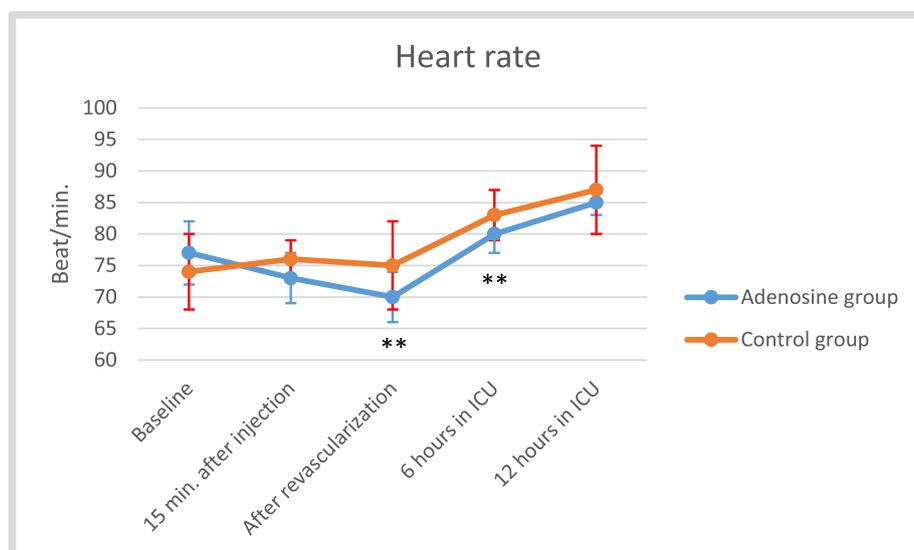


Fig. 1 Effect of adenosine on heart rate. Data were presented as mean ± SD. **p value is highly significant

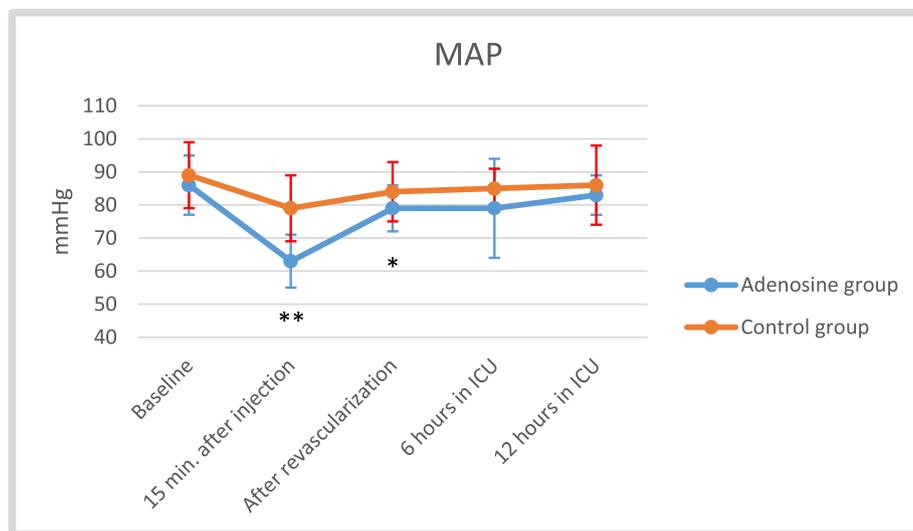


Fig. 2 Effect of adenosine on mean arterial blood pressure (MAP). Data were presented as mean \pm SD. ** p value is highly significant. * p value is significant

PCWP in adenosine group (after removal of the partial clamp and complete revascularization) (Figs. 4 and 5). The cardiac index was comparable in both groups after induction of anesthesia ($p = 0.57$), but a slight increase in cardiac index occurred 15 min after adenosine infusion and continued until 12 h postoperatively ($p < 0.001$) (Fig. 6). The need for inotropic support was significantly lower after adenosine infusion with a much lower inotropic score calculation throughout the study in the adenosine group (Table 2). There was a significant decrease in SVR in adenosine group after injection

of drug compared with control group (1142 ± 155 dyne/sec/cm⁻⁵ versus 1803 ± 185 dyne/sec/cm⁻⁵), after revascularization (1374 ± 155 dyne/sec/cm⁻⁵ versus 1880 ± 176 dyne/sec/cm⁻⁵), after 6 h in ICU (1343 ± 163 dyne/sec/cm⁻⁵ versus 1886 ± 180 dyne/sec/cm⁻⁵), and 12 h in ICU (1430 ± 143 dyne/sec/cm⁻⁵ versus 1894 ± 168 dyne/sec/cm⁻⁵) (Fig. 7). Adenosine has a pulmonary vasodilator effect as there was a significant decrease in PVR after adenosine infusion and this continued until 12 h in ICU when compared with the control group ($p < 0.001$) (Fig. 8). The adenosine infusion

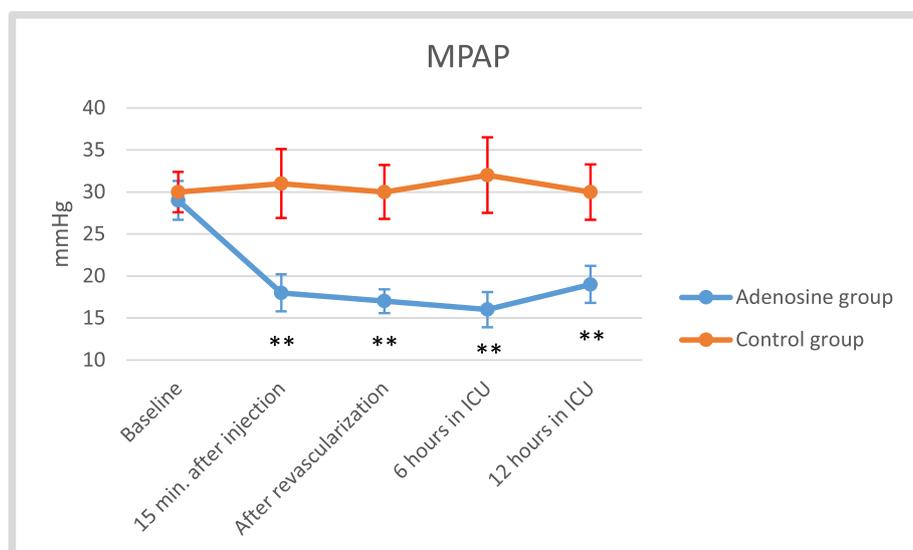


Fig. 3 Effect of adenosine on mean pulmonary artery pressure (MPAP). Data were presented as mean \pm SD. ** p value is highly significant

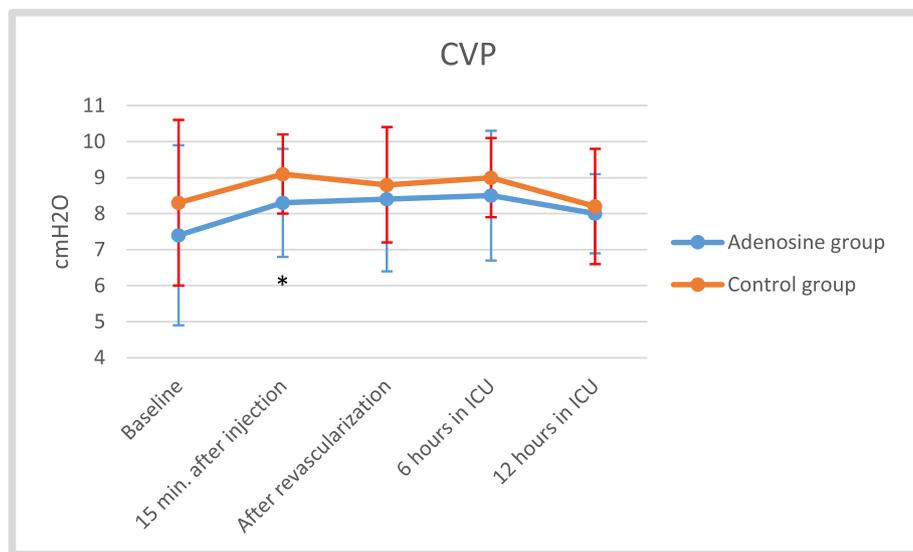


Fig. 4 Effect of adenosine on central venous pressure (CVP). Data were presented as mean \pm SD. **p* value is significant

produced much more pulmonary vasodilation than systemic; thus, the PVR/SVR ratio decreased 15 min after adenosine infusion until 12 h postoperatively (Table 3). At the postoperative period, the cTroponin I was less in adenosine group compared with control group (5.8 ± 2.8 ng/ml versus 16.5 ± 3.9 ng/ml) in ICU after 6 h, at 12 h (6.0 ± 1.9 ng/ml versus 18.2 ± 1.5 ng/ml), until 48 h (8.9 ± 1.3 ng/ml versus 20.1 ± 0.4 ng/ml) (Fig. 9). Respectively, the CK-MB also was less in adenosine group after 6 h in ICU (40 ± 10 ng/ml versus 75 ± 20 ng/ml), at 12 h (45 ± 12 ng/ml versus 80 ± 15 ng/ml) until the

first 24 h (32 ± 17 ng/ml versus 63 ± 19 ng/ml) when compared with control group (Fig. 10).

Discussion

The results of the present study have shown that pretreatment of adenosine infusion in OPCAB graft surgery resulted in less cTroponin I and CK-MB release, and improved post-bypass CI after the operations. Off-pump coronary artery bypass (OPCAB) graft surgery has been shown to be feasible and effective with nearly comparable postoperative morbidity and mortality rates compared

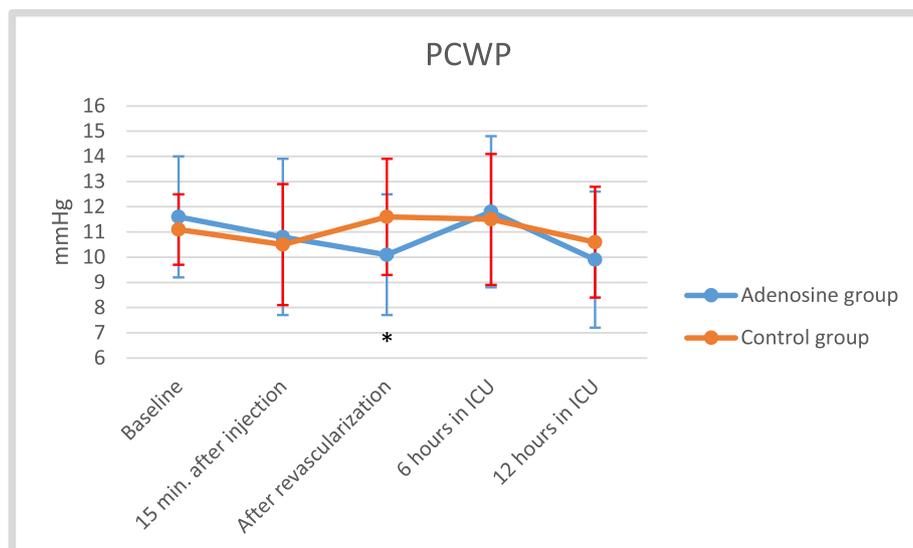


Fig. 5 Effect of adenosine on pulmonary capillary wedge pressure (PCWP). Data were presented as mean \pm SD. **p* value is significant

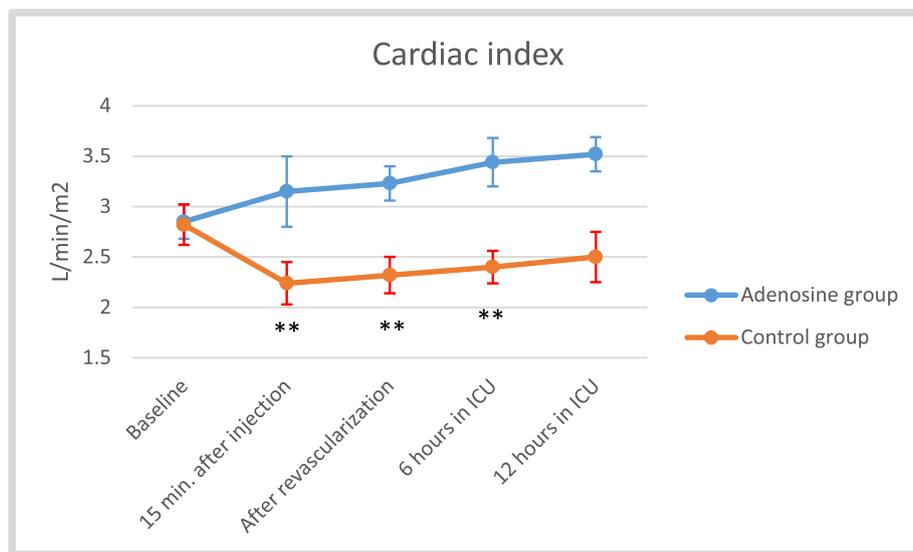


Fig. 6 Effect of adenosine on cardiac index (CI). Data were presented as mean \pm SD. ** *P* value highly significant

with on-pump cardiac surgery. During OPCABG, reperfusion after a period of coronary artery occlusion is established without any active cardio-protection (i.e., cardioplegia, hypothermia). The main cause of myocardial injury in off-pump surgery is the ligation of the target vessel for 10 to 12 min. In normal myocardium, this transient period of ischemia causes only reversible injury and modest contractile dysfunction; however, in myocardium with preexisting ischemia, it may cause acutely irreversible changes. The myocardial damage may occur during the ligation period or during the post-ligation period when blood flow through the lesion (i.e., stenosis) is restored (Guyton et al. 2000; Cooper et al. 2003). Adenosine has multiple cardioprotective effects on the myocardium and inflammatory response. Cardiologists have introduced the therapeutic use of adenosine to protect the human heart during acute myocardial infarct. Mahaffey and colleagues (Mahaffey et al. 1999) examined the effect of an intravenous adenosine infusion of 70 μ g/kg/min for 3 h during

acute myocardial infarction. There was a significant reduction in the infarct size in the adenosine group. Quintana and colleagues (Quintana et al. 2003) also demonstrated that an intravenous adenosine infusion reduced cardiac complications in patients with acute anterior wall myocardial infarction. The A1, A2a, and A3 ADO receptors are involved in these cardioprotective effects (Louttit et al. 1999; Shalaby et al. 2008). ADO A1 receptors and possibly A3 receptors are also known to confer protection through inhibitory G-protein-coupled pathways, which is linked to the opening of sarcolemma ATP-sensitive K⁺ channels (Miura et al. 2000). The mechanism by which opening of these channels elicits cardio-protection is not yet fully elucidated but could involve the reduction of calcium overload or better control of mitochondrial volume and energetics (Peart and Headrick 2007). Other authors (Lasley and Mentzer 1995) have reported that adenosine reduces oxygen-derived free radical production by neutrophils, an effect that could minimize the free radical-

Table 2 Postoperative variables

	Adenosine group (n = 24)	Control group (n = 25)	<i>p</i> value
Mechanical ventilation (hours)	8 \pm 2	9 \pm 2	0.08
ICU stay (days)	3.2 \pm 1.1	2.9 \pm 1.2	0.36
Inotropic score:			
At arrival to ICU	4.7 \pm 2.2	8.8 \pm 3.8	< 0.001**
6 h	4.4 \pm 2.1	8.0 \pm 2.9	< 0.001**
12 h	3.9 \pm 2.0	8.5 \pm 3.2	< 0.001**
24 h	3.3 \pm 1.8	7.9 \pm 4.4	< 0.001**
48 h	3.0 \pm 1.6	6.6 \pm 3.7	< 0.001**

Data were presented as mean \pm SD. ***p* value highly significant

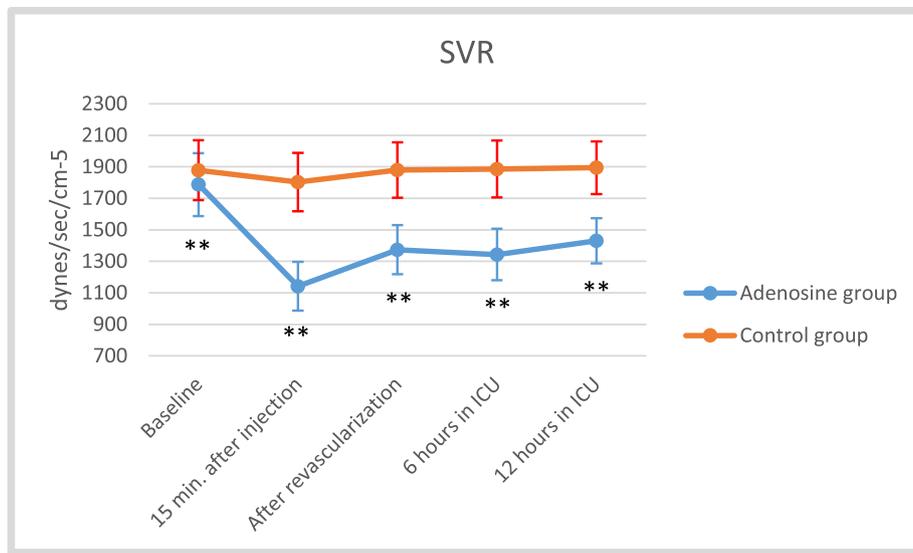


Fig. 7 Effect of adenosine on systemic vascular resistance (SVR). Data were presented as mean ± SD. ***p* value is highly significant.

induced damage that occurs during reperfusion. Thus, adenosine has a broad spectrum of physiologic effects, which make it suitable as a cardioprotective agent with efficacy in all three windows of opportunity (pretreatment, and during ischemia and reperfusion) and against numerous targets, including the neutrophils (Jin et al. 2007; Lee et al. 1995; Wei et al. 2001; Mentzer Jr et al. 1999; Mentzer Jr et al. 1997; Chauhan et al. 2000; Belhomme et al. 2000). The present results were in line with these previous studies, that adenosine pretreatment exerts a myocellular

protective effect against ischemic reperfusion injury, as adenosine pretreatment here resulted in lower release of CK-MB and cTroponin I during the first 48 h of the recovery period with improved recovery in myocardial performance postoperatively, as indicated by faster recoveries of CI. Because of the varied adenosine administration protocols that were applied in different researches designs, there was controversy over the benefits of using adenosine as a cardioprotective agent during these clinical settings. Jin and his colleagues found that 1.5 ml/kg bolus

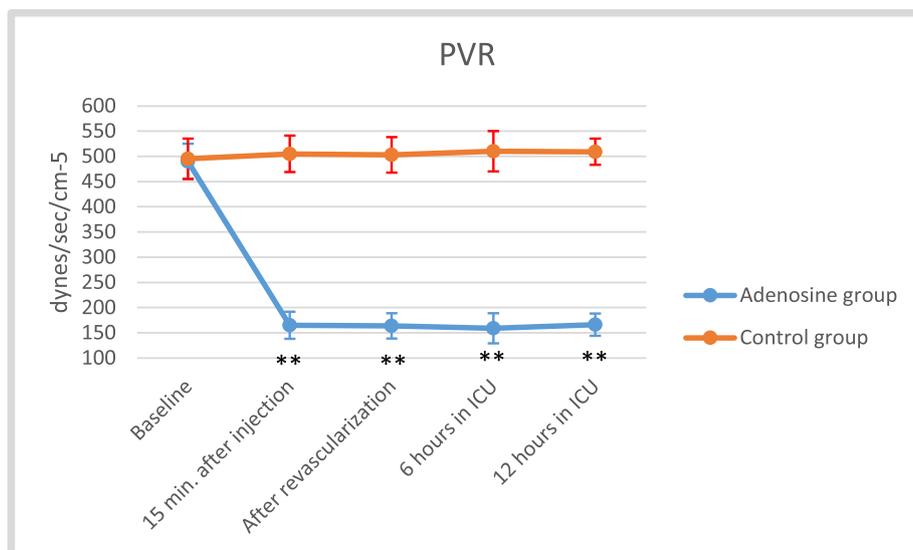


Fig. 8 Effect of adenosine on pulmonary vascular resistance (PVR). Data were presented as mean ± SD. ***p* value is highly significant

Table 3 The ratio of pulmonary vascular resistance (PVR) to the systemic vascular resistance (SVR)

PVR/SVR (ratio)	Adenosine group (n = 24)	Control group (n = 25)	p value
Baseline	0.27	0.26	0.68
15 min after injection	0.14	0.28	< 0.001**
After revascularization	0.12	0.26	< 0.001**
6 h in ICU	0.11	0.27	< 0.001**
12 h in ICU	0.11	0.26	< 0.001**

Data are presented as ratio (PVR/SVR) **p value highly significant

adenosine after the aorta clamp off resulted in less cTnI release and lesser inotropic drug use with shorter ICU stay in a patient undergoing valve replacement (Jin et al. 2007). A study on 30 patients undergoing CABG by Wei et al. proved that the infusion of adenosine (total of 650 µg/kg) before CPB decreased CK-MB release and improved post-bypass CI (Wei et al. 2001). A smaller dose of adenosine (250–350 µg/kg) followed by 5 min of washout before clamp removal in cardiac surgery improved postoperative cardiac function (Lee et al. 1995). Administration of 12 mg or 24 mg adenosine, half before clamp on and half after clamp in CABG patients resulted in greater improvement in postoperative CI and SVI (Chauhan et al. 2000). In this study, the increase in the CI in adenosine is associated with less inotropic agent requirement which indicates that adenosine has a significant myocardial protection effect. This goes in line with previous results (Mentzer Jr et al. 1999; Mentzer Jr et al. 1997) that found a decrease in the requirement of inotropic drugs in adenosine groups. However, contrary to this, Belhomme and his colleagues found no benefit for adenosine 140 mg/kg/min followed

by 10 min of washout in CABG patients (Belhomme et al. 2000). The pulmonary vasodilator effect of adenosine is based on the fact that adenosine is metabolized by adenosine deaminase found in vascular endothelial cells and in erythrocytes. Adenosine produced pulmonary vasorelaxation and then metabolized during the passage through the lungs before reaching the systemic circulation (Utterback et al. 1994). The pulmonary clearance of adenosine is dose dependent, at low concentration the adenosine clearance is nearly complete but infusion at high concentration produced systemic vasodilatation. When infused at 75 µg/kg/min, the extraction ratio of adenosine through the pulmonary circulation is approximately 80%, and this ratio fell at higher concentration (Fullerton et al. 1996). Previous study on patients with primary pulmonary hypertension infusion of 50 µg/kg/min adenosine lowered the PVR without significantly fall in SVR (Morgan et al. 1991). Larger dose of adenosine (100 µg/kg/min) was used to produce controlled deliberate systemic hypotension in peripheral vascular surgery and in neurosurgical procedures (Owall et al. 1988; Owall et al. 1987). Because the

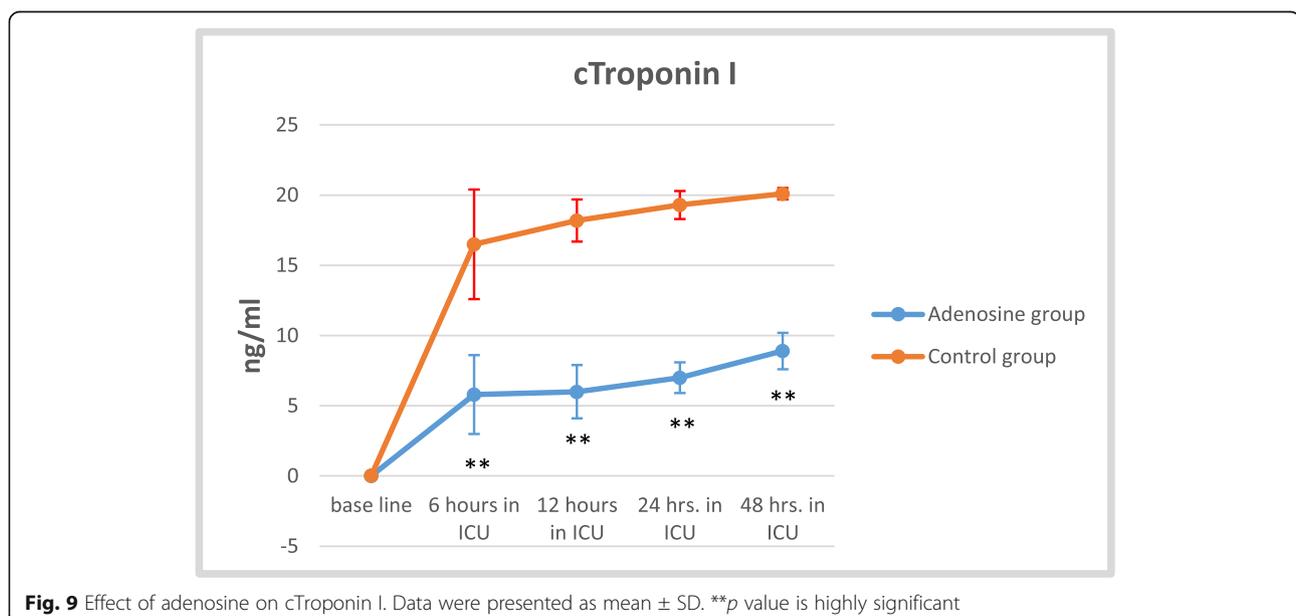


Fig. 9 Effect of adenosine on cTroponin I. Data were presented as mean ± SD. **p value is highly significant

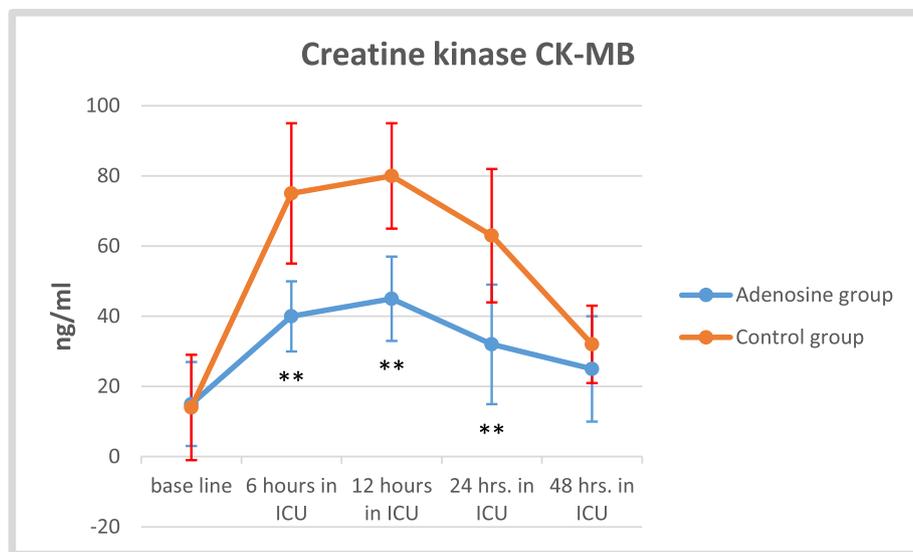


Fig. 10 Effect of adenosine on creatine kinase (CK-MB). Data were presented as mean \pm SD. ***p* value is highly significant

cardiac index increased after adenosine infusion, the calculated systemic vascular resistance was significantly decreased throughout the study despite transient decreases in mean arterial pressure. However, it would appear that adenosine preferentially vasodilates the pulmonary system, as the ratio of PVR to SVR fell significantly in the adenosine group.

Conclusion

This study concludes that the use of adenosine infusion during off-pump coronary artery bypass surgery may have a cardioprotective effect and may improve myocardial recovery from reperfusion injury.

Abbreviations

OPCAB: Off-pump coronary artery bypass; LIMA: Left internal mammary artery; LAD: Left anterior descending artery; CO: Cardiac output; ICU: Intensive care unit; CVP: Central venous pressure; PCWP: Pulmonary capillary wedge pressure; CI: Cardiac index; SVR: Systemic vascular resistance; PVR: Pulmonary vascular resistance; PVR/SVR: Pulmonary vascular resistance to systemic vascular resistance ratio; CK-MB: Creatine kinase isoenzyme; CPB: Cardiopulmonary bypass; SVI: Stroke volume index

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Authors' contributions

MMAA, AMAH, and HMAH conceived the study and performed literature search, clinical studies, data collection, data analysis, and manuscript preparation. AMAH performed statistical analysis and manuscript revision. All authors read and approved the final manuscript.

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Availability of data and materials

Data supporting findings can be obtained from the corresponding author.

Ethics approval and consent to participate

Local ethics approval committee has been obtained, and written informed consent has been obtained from all patients enrolled in the study. This study has been approved by "Ain Shams University, Faculty of Medicine Research Ethics Committee" (REC).

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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