

## Preconditioning by isoflurane as a volatile anesthetic in elective coronary artery bypass surgery

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### Original Article

#### Abstract

**BACKGROUND:** Some pharmacological preconditioning approaches are utilized as an effective adjunct to myocardial protection, particularly following cardiac procedures. The current study addressed the potential clinical implications and protective effects of isoflurane as an anesthetic most applicable on postoperative myocardial function measured by cardiac biomarkers.

**METHODS:** 46 patients were included in the study. In 23 of them, preconditioning was elicited after the onset of cardiopulmonary bypass via a 5-minute exposure to isoflurane (2.5 minimum alveolar concentration), followed by a 10-minute washout before aortic cross clamping and cardioplegic arrest. 23 case-matched control patients underwent an equivalent period (15 minutes) of pre-arrest isoflurane-free bypass. Outcome measurements included creatine phosphokinase (CPK) and creatine kinase-MB (CK-MB) levels until 24 hours after the surgery.

**RESULTS:** None of the differences in enzyme levels at baseline and 24 hours after surgery between the two groups reached the threshold of statistical significance. The level of CPK was significantly reduced 24 hours after surgery compared with the baseline in the two groups. However, the postoperative release of CPK was consistently smaller in the isoflurane-preconditioned group than in the control group. The release of CK-MB displayed a statistically similar pattern. Multivariate linear regression analysis showed the effect of isoflurane regimen on reducing CPK level within the 24 hours after surgery compared with placebo.

**CONCLUSION:** Our study supports the cardio protective effect of isoflurane and the role of pharmacological preconditioning of the human heart by this volatile anesthetic during elective coronary artery bypass surgery.

**Keywords:** Preconditioning, Isoflurane, Volatile Anesthetic, Coronary Artery Bypass Surgery

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#### Introduction

The increase in cardiac biomarkers appearance following cardiac invasive procedures has been known as accepted indicatives of cell death. Some of these chemical markers, such as creatine phosphokinase (CPK) and creatine kinase-MB (CK-MB), can specifically reflect myocardial necrosis.<sup>1</sup> Therefore, they can predict the outcome of acute coronary syndrome and heart failure, and different cardiac procedures such as bypass surgery

or coronary stenting.<sup>2-6</sup> The use of cardiac protecting strategies can improve the tolerance of the myocardium to myocardial ischemia and necrosis; and therefore, lead to reducing cardiac damages. Some approaches, including pharmacological preconditioning, can be utilized as an effective adjunct to myocardial protection. In this context, volatile anesthetics that are commonly used in general anesthesia for inducing hypnosis, analgesia, amnesia, and mild muscle relaxation are effective

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adjuncts, which provide protection against reperfusion injury.<sup>7</sup> Some researches on animal models showed an improving post-ischemic recovery at the cellular level in isolated hearts.<sup>8</sup> In addition, a reduction in the release of cardiac damage biomarkers in those receiving volatile anesthetics as a part of their anesthesia plan has been documented after cardiac surgery, along with reduction in incidences of perioperative myocardial infarction and death.<sup>9</sup> On the other hand, volatile anesthetics can provide protection against reperfusion injury when administered after myocardial ischemia. However, a few studies have assessed the importance of the myocardial protective effects of these anesthetics when administered before ischemia or during reperfusion. Moreover, a few small randomized controlled studies have yielded conflicting results with respect to the effects of volatile anesthetics on the extent of myocardial damage as assessed by measuring postoperative cardiac biomarker release after cardiac revascularization.

The current study addressed the potential clinical implications and protective effects of isoflurane as a most applicable anesthetic on postoperative myocardial function with the measurement of CPK and CK-MB markers.

### Materials and Methods

The current study was a double-blind, placebo-controlled, randomized clinical trial. It was conducted on forty six consecutive patients with two or three diseased coronary arteries confirmed by coronary angiography, and scheduled for isolated elective coronary artery bypass grafting. Patients with active heart failure, previous unusual response to anesthetics, and those who experienced myocardial infarction during the preceding 6 weeks or any cardiac or non-cardiac surgical procedures during current admission were excluded. The other exclusion criteria were the following: concomitant aortic or valvular surgery, elevated CK or CK-MB concentrations within 24 hours before surgery, unstable angina, angina within 24 hours before surgery, haemodynamic instability with the need for medical or mechanical inotropic support, re-intervention, preoperative values of creatinine > 2.0 mg/dl, chronic obstructive pulmonary disease, age of over 70 years, preoperative ejection fraction inferior to 40%, or preoperative hepatopathy. The participants were also excluded if they had used theophylline, sulfonyleureas, allopurinol, or anti-diabetics within the one month before surgery because of their inhibiting effects on

pharmacological preconditioning. Study protocol was performed according to the principles of the Declaration of Helsinki and approved by the ethics committee of the Isfahan University of Medical Sciences, Iran. Written informed consents were obtained from all participants. Baseline characteristics and periprocedural data were collected from the hospital recorded files or via face to face interviewing by a trained, blinded, observer nurse who did not participate in patient care. This information included demographics, general risk factors for coronary artery disease, used drugs, the number of diseased coronary arteries, and left main lesions. Patients were randomly divided into two groups by opening of a sealed envelope the evening before the surgical procedure, and then allocated to receive either isoflurane or placebo. Both groups received general anesthesia (diazepam, fentanyl, pan chromium in a closed circuit). Preconditioning was achieved with a 5-minute exposure to isoflurane (2.5 minimum alveolar concentration), followed by 10 minutes of isoflurane-free bypass before aortic cross-clamping. Isoflurane was added to the gas mixture in the oxygenator. Control patients underwent a time-matched (15-minute) period of isoflurane-free cardiopulmonary bypass and air and oxygen without isoflurane was administered. The type of anesthesia was similar in both groups during cardiopulmonary bypass. The randomization management was delegated to a person unconnected to the clinical experimentation. No operator involved in the care of the patients in every phase had any knowledge of the group to which each single patient belonged; apart from the person who collected the data and the individual who carried out the statistical analysis. No other volatile anesthetics were administered at any time during the study. Blood samples to evaluate CPK and CK-MB chemical parameters were obtained from peripheral venous blood preoperatively and 24 hours after the end of surgery. Blood was collected in plastic tubes with clot activator and was centrifuged before chemical analysis. Myocardial infarction was detected by both enzyme and ECG. In the present study, we tested the hypothesis that the volatile anesthetic isoflurane, given before coronary artery bypass grafting (CABG) will reduce perioperative myocardial damage, as assessed by CPK and CK-MB enzymes, when compared with placebo. Therefore, the main endpoint of the study was the postprocedural release of these two enzymes.

Results were reported as mean  $\pm$  standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the Mann-Whitney or

Wilcoxon tests for the continuous variables and the chi-squared test (or Fisher's exact test if required) for the categorical variables. Changes in cardiac enzymes were determined primarily by comparing the change between the baseline and final measurements of these enzymes. We also used a multivariate linear regression analysis to evaluate the relationship between cardiac enzyme change and type of treatment schedule with the presence of other variables as cofounders. Beta ( $\beta$ ) and standard error for  $\beta$  were calculated. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS for Windows version 16 (SPSS Inc., Chicago, IL) and SAS for Windows version 9.1 (SAS Institute Inc., Cary, NC).

## Results

The baseline characteristics and clinical data for the patients are summarized in table 1. The two groups were similar with respect to study parameters,

including demographics, medical history, drug history, the number of involved coronary arteries as well as left main lesion. As presented in table 2, none of the differences in enzyme levels at baseline and 24 hours after surgery between the two groups reached the threshold of statistical significance. The level of CPK was significantly reduced 24 hours after surgery compared with the baseline, however, the postoperative release of CPK was consistently smaller in the isoflurane-preconditioned group than in the control group. The release of CK-MB displayed a statistically similar pattern. Multivariable linear analysis showed the effect of isoflurane regimen on reducing CPK level within the 24 hours after surgery compared with placebo (Table 3).

There were no isoflurane-related side effects. Postoperatively, there were no deaths and no patient had a transmural myocardial infarction. Inotropic support was required in none of the patients of the control and isoflurane-preconditioned groups.

**Table 1.** Baseline characteristics and clinical data of patients who received isoflurane or placebo

Characteristics	Isoflurane group (n = 23)	Placebo group (n = 23)	P
Gender (male)	18 (87.5)	15 (71.4)	0.454
Age (year)	61.6 $\pm$ 5.4	58.7 $\pm$ 9.1	0.198
Body mass index (kg/m <sup>2</sup> )	27.4 $\pm$ 2.9	27.2 $\pm$ 4.3	0.904
Cigarette smoking	3 (13.0)	8 (34.8)	0.084
Opium addiction	3 (13.0)	4 (17.4)	0.678
Myocardial infarction	5 (21.7)	4 (17.4)	0.713
Serum creatinine	0.96 $\pm$ 0.23	0.99 $\pm$ 0.21	0.594
Drug history			
Aspirin	8 (34.8)	6 (26.1)	0.522
Warfarin	0 (0.0)	1 (4.3)	0.315
Beta-blocker	4 (17.4)	3 (13.0)	0.678
Ca-blocker	3 (13.0)	2 (8.7)	0.639
Diuretic	1 (4.3)	2 (8.7)	0.545
ACE inhibitor	3 (13.0)	2 (8.7)	0.639
Digoxin	0 (0.0)	1 (4.3)	0.315
Statins	0 (0.0)	1 (4.3)	0.315
Insulin	2 (8.7)	0 (0.0)	0.198
Diseased vessels			
Two coronaries	2 (8.7)	3 (13.0)	0.998
Three coronaries	21 (91.3)	20 (87.0)	
Left main lesion	6 (26.1)	8 (34.8)	0.522
Ejection fraction	53.6 $\pm$ 11.1	53.1 $\pm$ 10.3	0.964

Data are presented as mean  $\pm$  SD or number (%); ACE: Angiotensin converting enzyme

**Table 2.** Cardiac enzymes concentrations at the baseline and 24 hours after the coronary artery bypass surgery

Characteristics	Isoflurane group median (mean $\pm$ SD) (n = 23)	Placebo group median (mean $\pm$ SD) (n = 23)	P
CPK			
At baseline	410 (487.4 $\pm$ 264.8)	410 (401.7 $\pm$ 182.9)	0.091
24 hours after CABG	277 (267.7 $\pm$ 44.6)	277 (314.9 $\pm$ 184.2)	0.120
P	< 0.001	0.043	
CK-MB			
At baseline	44 (52.4 $\pm$ 34.0)	46 (71.1 $\pm$ 67.0)	0.132
24 hours after CABG	35 (44.3 $\pm$ 23.6)	43.5 (46.3 $\pm$ 19.7)	0.250
P	0.351	0.096	

Data are presented as median (mean  $\pm$  SD); CPK: Creatine phosphokinase; CK-MB: creatine kinase-MB; CABG: Coronary artery bypass grafting

**Table 3.** Multivariate lineae regression analysis of the effect of isoflurane regimen on change in serum CPK level within the 24 hours after coronary artery bypass surgery

Variables	Beta	Standard error	P
Baseline CPK	0.036	0.08	0.665
Isoflurane therapy	-126.5	57.3	0.011
Male gender	15.12	37.9	0.694
Age (year)	3.142	2.5	0.226
Body mass index (kg/m <sup>2</sup> )	5.128	4.5	0.268
Diabetes mellitus	2.907	44.3	0.948
Cigarette smoking	70.99	4.9	0.104
Opium addiction	66.95	42.1	0.126
Myocardial infarction	106.91	45.1	0.027
Serum creatinine	51.07	91.9	0.584
Three vessel disease	84.76	69.8	0.237
Left main lesion	58.32	43.5	0.193
Ejection fraction	-3.873	1.40	0.011

R square: 0.510; CPK: Creatine phosphokinase

## Discussion

The major finding of the current study is that CPK, as an applicable marker of cardiac damage, reduced significantly more in patients receiving isoflurane according to a preconditioning protocol than the placebo group. Our result was consistent with some other similar studies. In a study by Belhomme et al. a consistently smaller release of troponin I was revealed following administration of isoflurane in comparison with the control group, and the release of creatine kinase-MB followed a similar pattern.<sup>10</sup> In another study by Lee et al. a consistently lower release of troponin I was observed in the isoflurane group compared to the control group, and the mean troponin I level was significantly reduced in the isoflurane group 24 hours after surgery.<sup>11</sup> Moreover, Tomai et al. showed that isoflurane could reduce myocardial injury only in patients with impaired left ventricular function undergoing CABG. In their study, when the comparisons were restricted to those patients with preoperative LVEF < 50%, 24 hours after the surgery the isoflurane-treated

patients exhibited a smaller release of troponin I and of CK-MB than controls.<sup>12</sup> However, some studies contrarily could not demonstrate the cardioprotective effect of isoflurane following CABG. In the study by Wang et al. although patients released slightly less CK-MB and troponin I than the controls postoperatively, the difference was not significant.<sup>13</sup> Some mechanisms of isoflurane in protecting the heart from procedural damages have been considered. Recent studies using animal models of regional ischemia have shown that isoflurane can duplicate the infarct-limiting effects of ischemic preconditioning. On the other hand, this drug causes potassium channel activation, as suggested by the abolishment of its infarct-limiting effects with potassium channel blockers.<sup>14-16</sup> It has also been confirmed that isoflurane increases the probability of potassium channel opening for any given concentration of ATP.<sup>17</sup> This opening could then account for the increase in ecto-5 $\beta$ -ectosomal activity that has been reported after pharmacological activation of the potassium channels.<sup>17</sup> It was also demonstrated that isoflurane-induced preconditioning

can be dependent on the release of some free radicals such as mercaptopropionyl glycine (MPG) and Mn (III) tetrakis (4-benzoic acid) porphyrin chloride (MnTBAP) that can be markers of infarct size.<sup>18</sup> Recent researches have studied the effect of intravenous and thoracic epidural analgesia after coronary artery bypass graft surgery, and the exact role of inflammatory markers and oxidative stress.<sup>19-22</sup>

Because the primary effect of preconditioning is to reduce infarct size, the outcome analysis focused on the sensitive markers of cellular necrosis such as CPK, CK-MB, and troponin I.<sup>23,24</sup> Although increases in creatine kinase (CK-MB) or troponin levels following CABG are common and are an indicator of myocardial necrosis, it seems that preconditioning with isoflurane and morphine, as general anesthesia drugs, decreased the enzyme level. We could confirm that the postoperative release of CPK enzyme was consistently lower in preconditioned patients than in their control counterparts. This is consistent with the cardio-protective effects of isoflurane. However, the between-group difference in CK-MB level which failed to achieve statistical significance can be explained by the small sample size of our study. Therefore, further studies are recommended to confirm the cardio-protective effect of isoflurane via reducing the release of CK-MB and troponin I using a greater sample size.

### Conflict of Interests

Authors have no conflict of interests.

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