

A pilot study of perioperative esmolol for myocardial protection during on-pump cardiac surgery

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Abstract. The protective effects of preprocedural esmolol on myocardial injury and hemodynamics have not, to date, been investigated in patients who were scheduled for cardiac surgeries under a cardiopulmonary bypass (CPB). A pilot randomized controlled trial was performed at The First Affiliated Hospital of Dalian Medical University (Dalian, China). Patients scheduled for elective open-heart surgeries under CPB were included, and were randomized to esmolol and control groups. For patients in the esmolol groups, intravenous esmolol (70 $\mu\text{g/kg/min}$) was administered at the time of incision until CPB was performed. For patients assigned to the control group, equal volumes of 0.9% saline were administered. Markers of myocardial injury and hemodynamic parameters were observed until 12 h post surgery. A total of 24 patients were included in the present study. No significant differences in hemodynamic parameters, including the central venous pressure and heart rate, were detected between patients in the two groups during the perioperative period or within the first 12 h post-surgery ($P>0.05$), except for the mean arterial pressure, which was higher in the esmolol group compared with the control group at 5 and 12 h post-surgery ($P<0.05$). However, the serum level of cardiac troponin I was higher in patients of the control group compared with those of the esmolol group during the preoperative period ($P<0.05$). Although creatinine kinase was significantly different at T2 between the two groups, its MB isoenzyme was not significantly different between the groups ($P>0.05$). In addition, administration of esmolol was not associated with an increased risk for severe complications and adverse events in these patients. In conclusion, preoperative esmolol may be an effective and safe measure of myocardial protection for patients who undergo elective cardiac surgeries under CPB.

Introduction

Perioperative myocardial injury remains one of the most serious complications of cardiac surgery (1-3), and numerous factors have been implicated during the pathogenesis process, including the technique of cardiac surgery, induction of cardioplegia and period of cardiac arrest (4-6). The primary mechanisms underlying myocardial dysfunction in this process are ischemic-reperfusion injury and the associated inflammatory responses (6-9). Several cardioprotective agents have been investigated for preventing iatrogenic myocardial injury. However, the majority of these agents affect only a single aspect of the pathogenesis of ischemic-reperfusion injury, and results of pilot studies are not consistent (10,11). β -adrenergic receptor blockers (β -blockers) have been extensively used as cornerstone medications in the management of ischemic heart disease, most likely by reducing myocardial oxygen demands and mitigating the ischemia-induced injury (12,13). However, to the best of our knowledge, the direct effect of preprocedural administration of esmolol on the markers of myocardial injury, as well as hemodynamic characteristics, have rarely been evaluated in Asian patients who were scheduled for elective open-heart surgery. Therefore, the present study describes a pilot single-center randomized controlled trial that was performed in order to evaluate the potential myocardial protective effects of esmolol, as well as its impact on hemodynamic parameters, in Chinese patients who underwent elective open-heart cardiac surgery under a cardiopulmonary bypass (CPB).

Patients and methods

Study design. The study protocol was approved by the Local Ethics Committee of The First Affiliated Hospital of Dalian Medical University (KY2009-38; Dalian, China), and written informed consent was obtained from all the participating patients. The present investigation was designed as a single-center, randomized controlled trial on patients scheduled to undergo open-heart cardiac surgery with CPB at the Department of Cardiovascular Surgery in the First Affiliated Hospital of Dalian Medical University.

Patient inclusion and exclusion criteria. Patients were included in the current study if they met the following criteria: i) Age between 40 and 80 years; ii) patients undergoing

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elective primary cardiac surgery, including coronary artery bypass graft (CABG) or heart valvular replacement (HVR); iii) a cardiac function of New York Heart Association class II or III; and iv) no evidence of myocardial ischemia or elevation of serum levels of myocardial markers (troponin I [TnI], creatine kinase [CK] or CK-MB fraction [CK-MB]) within the last 24 h prior to surgery. The exclusion criteria were as follows: i) A diagnosis of acute myocardial infarction within the last 4 weeks prior to the scheduled surgery; ii) an activated phase of rheumatic diseases; iii) left ventricular ejection fraction of <40%; iv) preoperatively confirmed intra-cardiac shunt; v) a hematocrit of <30%; and vi) severe systemic diseases, including pulmonary diseases, hepatic, renal, musculoskeletal diseases or immune system illnesses. Additionally, patients receiving oral hypoglycemic agents or theophyllines were excluded since these medications are known to influence the process of ischemia-reperfusion injury (14).

Patient groups. Eligible patients were assigned to one of the two study arms on the basis of a computer-generated randomization list: One group was administered the conventional care (control group; n=12), while the other was administered conventional care plus intravenous esmolol infusion (esmolol group; n=12; Sanlian Pharmacy, Harbin, China). The mean age of the patients was 60.5 years old and 14 of the enrolled patients were male.

Anesthetic protocols. All patients included were administered intramuscular injections of scopolamine (0.6 µg/kg; Minsheng Pharmacy, Hangzhou, China), morphine (0.1 mg/kg) and pethidine (1 mg/kg) (both purchased from Shenyang 1st Pharmacy of Northeastern China, Shenyang, China) 30 min prior to the induction of anesthesia. Preoperative sedation and anesthesia were achieved with the intravenous injection of midazolam (0.1 mg/kg; Enhua Pharmacy, Jiangsu, China), fentanyl (10 µg/kg; Renfu Pharmacy, Yichang, China), etomidate (0.2-0.3 mg/kg; Enhua Pharmacy) and cisatracurium besilate (0.2 mg/kg; Hengrui Pharmacy, Jiangsu, China), and these drugs were administered during the surgery in order to maintain a stable hemodynamic status. Following tracheal intubation, the patients were placed on artificial ventilation such that the end-tidal carbon dioxide pressure was maintained at 30-35 mmHg and the airway pressure at 8-18 cm H₂O. Anesthesia was maintained using the standard method with continuous administration of propofol at 3-6 mg/kg/h.

Patients in the esmolol group were administered intravenous esmolol (70 µg/kg/min) during the incision until the initiation of CPB, and the dosages of esmolol were titrated every 2 min to maintain the heart rate (HR) of each patient within 80% of the baseline level. Patients assigned to the control group were administered equal volumes of 0.9% saline.

CPB and surgical protocols. All patients underwent cardiac surgery under CPB according to the standard method using a roller pump and a membrane oxygenator with a priming solution (Jinyao Pharmacy, Tianjin, China). During CPB, pump flow was set such that the mean arterial pressure (MAP) was maintained between 50 and 80 mmHg. The blood temperature was allowed to drop to <30°C and restored back to 36°C with active rewarming at the end of CPB. Myocardial protection

was ensured with the induction of cardioplegia by administration of cold potassium solution (10-15 ml/kg) and by placement of ice chips in the pericardial region to maintain the heart in a hypothermic condition. Moreover, cardioplegia was achieved using the single-clamp technique in an antegrade fashion. Following the establishment of CPB, vasoactive medications, including dopamine, nitroglycerin and norepinephrine, were administered to maintain the arterial blood pressure at a relatively stable level.

The aortic cross-clamp was completely released, followed by the placement of the epicardial atrial or ventricular pacing wires. The aortic and venous cannulas were removed following the administration of the appropriate test dose of protamine such that the activated clotting time was maintained at 110-140 sec, and the surgery was continued with the closure of the pericardium and sternum. Following surgery, the patients were closely monitored during their stay in the intensive care unit (ICU) at The First Affiliated Hospital of Dalian Medical University for at least 12 h.

Study outcomes. The primary outcomes analyzed in the present study were perioperative changes in the concentrations of the serum markers of myocardial injury, including TnI, CK and CK-MB. Briefly, arterial blood samples (3 ml for each time point) of the patients were collected from the radial artery or from the arterial catheters during CPB at the following time points: Baseline (prior to the start of the CPB procedure), prior to aortic cannulation, 30 min prior to the placement of the aortic cross-clamp at the time of releasing the aortic cross-clamp, and 120 min after the release of the aortic cross-clamp. The levels of the markers of myocardial injury were measured using the Roche Biochemical Analyzer (ADVIA centaur-CP; Siemens AG, Munich, Germany) according to the manufacturer's instructions. The secondary outcomes analyzed were the changes in the levels of the hemodynamic parameters, including HR, MAP and central venous pressure (CVP), during the surgery and during the 12-h ICU follow-up. In addition to the abovementioned parameters, other related clinical outcomes were also evaluated, including the characteristics of CPB, usage of vasoactive medications, rebeating status of the heart and the incidence of postoperative adverse events.

Statistical analysis. The results are presented as mean values with standard deviation. Significant intergroup differences at the different time points were analyzed using the Student's t-test. Moreover, one-way analysis of variance was used for intragroup comparison of the values of the hemodynamic parameters if the data were normally distributed; if the distribution was abnormal, the Friedman test was used. $P < 0.05$ was used to indicate a statistically significant difference. All the statistical analyses were performed using SPSS Software (version 13.0; SPSS, Inc., Chicago, IL, USA).

Results

Patient baseline characteristics. In total, 14 patients enrolled underwent CABG, while 10 patients underwent HVR. All the surgical procedures were executed successfully, and the patients were closely monitored during their 12-h postoperative

Table I. Baseline characteristics of patients enrolled in the esmolol and control groups.

Characteristics	Esmolol group (n=12)	Control (n=12)
Male (n, %)	8 (66.7)	6 (50)
Age, years	58.9±9.8	62.1±7.1
Height, cm	166.3±9.8	164.9±8.6
BW, kg	69.9±9.0	66.8±8.9
LVEF, %	52.7±6.0	55.8±3.2
Hypertension (n, %)	8 (66.7)	8 (66.7)
Diabetic (n, %)	4 (33.3)	3 (25.0)
Smokers (n, %)	7 (58.3)	6 (50)
Preoperative		
β blockers (n, %)	1 (8.3)	0 (0.0)
Surgery		
CABG (n, %)	7 (58.3)	7 (58.3)
HVR (n, %)	5 (41.7)	5 (41.7)
NYHA classification		
Class II (n, %)	4 (33.3)	4 (33.3)
Class III (n, %)	8 (66.7)	8 (66.7)

BW, body weight; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; HVR, heart valvular replacement; NYHA, New York Heart Association.

ICU follow-up period. The baseline characteristics of the patients included are listed in Table I. The two study groups were well balanced in terms of the demographic characteristics, prevalence of hypertension, diabetes, types of surgery and class of cardiac function.

Effects of preprocedural esmolol administration on outcomes related to surgical and perioperative care of the enrolled patients. The two groups did not differ significantly in terms of the characteristics of the surgery and CPB procedure (CPB time, aortic cross-clamp time, surgical duration and quantity of potassium cardioplegic solution used) (Table II). Furthermore, no significant differences were detected between the two groups with respect to the following parameters: Perioperative fluid infusion, urinary volumes, usage of vasoactive medications during the surgery and status of the heart rebeating. Similarly, no significant intergroup differences were noted in the length of the ICU stay, decannulation times and urinary volumes during the ICU stay (Table II).

Effects of preprocedural esmolol on hemodynamic parameters during the perioperative period of the patients included. The mean MAP of the patients in both groups was gradually reduced from the baseline levels (esmolol group, 105.4±18.9 mmHg; control group, 106.1±17.1 mmHg; $P=0.464$ between groups), and remained at relatively low levels throughout the surgical procedures (60-70 mmHg for both groups) (Fig. 1A). Furthermore, no significant differences were noted between the two groups in the measurement of MAP at the aforementioned 6 time points of assessment. Although CVP (at the time of

tracheal intubation) in the patients of the esmolol group was found to be significantly greater than that in the control group (6.4 ± 3.5 vs. 4.2 ± 2.2 cm H₂O; $P=0.039$), the values at the other time points did not show any significant difference (Fig. 1B). Moreover, the HR in the esmolol group appeared to be lower than that in the control group at the majority of time-points, which may partially reflect the potential negative chronotropic effects of esmolol; however, these differences were not statistically significant (Fig. 1C). These observations suggest that preprocedural administration of esmolol did not induce any significant changes in the levels of venous and arterial hemodynamic parameters during the perioperative period in patients who underwent elective cardiac surgery with CPB.

Effects of preprocedural administration of esmolol on serum markers of myocardial injury in patients undergoing on-pump cardiac surgeries. As shown in Fig. 2A, the baseline levels of serum TnI did not differ significantly in the two groups (esmolol group, 0.048 ± 0.064 ng/ml; control group, 0.064 ± 0.056 ng/ml; $P=0.282$). However, prior to aortic cannulation (~30 min after esmolol administration) and at 120 min after the release of the aortic cross-clamp, the serum TnI levels were significantly lower in the esmolol group than in the control group (esmolol group, 6.114 ± 2.864 ng/ml and 0.072 ± 0.058 ng/ml, respectively; control group, 9.709 ± 6.146 ng/ml and 0.188 ± 0.094 ng/ml, respectively; $P=0.039$ and $P<0.001$, respectively). Similarly, the TnI levels in the esmolol group were lower than those in the control group at 30 min prior to the aortic cross-clamp and at the time of release of the aortic cross-clamp, although the difference was not significant ($P=0.099$ and $P=0.163$, respectively). The serum levels of CK (Fig. 2B) did not show any significant difference between the two groups at four of the five time points (baseline, before aortic cannulation, before aortic cross-clamp and 120 min after the release of aortic cross-clamp); however, the levels were significantly higher in the esmolol group compared with the control group (esmolol group, 125.67 ± 30.81 IU/ml; control group, 89.67 ± 23.31 IU/ml; $P=0.002$). With regard to the serum levels of CK-MB, which is an isoenzyme considered to be more specifically reflective of myocardial injury than CK, no significant intergroup differences were detected (Fig. 2C).

Effects of preprocedural esmolol on hemodynamic parameters during the first 12 postoperative hours in ICU. The dynamic changes in the MAP, CVP and HR in both groups during the 12-h ICU follow-up period are presented in Fig. 3A-C, respectively. The levels of all three parameters were similar in the two groups, except for significantly higher levels of MAP at the 5th and the 10th hour in the esmolol group compared with the control group ($P=0.026$). This indicates that the preprocedural administration of esmolol did not have any significant effect on the postoperative hemodynamic status.

Complications and adverse events. The incidences of the most common complications and adverse events occurring in the two groups are provided in Table III. Postoperative pulmonary infection was noted in two patients in the esmolol group and in three patients in the control group. Furthermore, one patient in the control group had neurological complications manifesting as delayed postoperative recovery. No other instances

Table II. Surgical and perioperative care-related outcomes of patients in the esmolol and control groups.

Outcomes	Esmolol group (n=12)	Control group (n=12)	P-value
Surgical characteristics			
CPB time, min	136.2±26.0	126.2±33.8	0.318
Aortic cross-clamp time, min	96.7±23.5	94.8±30.1	0.424
Surgery duration, min	317.9±77.5	302.1±66.1	0.298
Potassium cardioplegic solution, ml	1729.8±147.8	1716.7±153.6	0.420
Perioperative fluid volumes			
Total fluid infusion, ml	966.7±206.7	933.3±250.7	0.363
Urinary volume, ml	1329.2±689.7	1208.3±520.4	0.316
Medication dosages			
Nitroglycerin, mg	3.0±3.0	5.4±9.7	0.211
Dopamine, mg	34.0±15.4	30.6±24.0	0.344
Esmolol, mg	233.3±77.9	0	-
Heart rebeating status			
Spontaneous rebeating (n, %)	6 (50)	6 (50)	1.00
Atrial fibrillation (n, %)	8 (66.7)	7 (58.3)	0.67
Normal ventricular rate (n, %)	10 (83.3)	11 (91.7)	0.54
Postoperative care			
Time to decannulation, h	22.4±17.2	30.7±22.6	0.188
ICU stay, h	59.5±23.7	45.7±37.4	0.385
Fluid infusion within 20 h, ml	3882.9±1104.1	4072.5±953.6	0.327
Urinary volume within 20 h, ml	3350.1±1081.4	3041.3±609.5	0.199

CPB, cardiopulmonary bypass; ICU, intensive care unit.

of infection of incision, pericardial tamponade, open-chest hemostasis or mortality were recorded in the present study.

Discussion

One of the most important observations of the present randomized controlled trial on Chinese patients scheduled for elective open-heart cardiac surgery under CPB was that esmolol administration was able to maintain the HR within 80% of the pre-bypass levels that resulted in a marked reduction in the serum levels of a TnI-a specific marker of myocardial injury. In addition, the results of the present study revealed that preoperative esmolol administration did not induce any significant changes of the hemodynamic parameters, including MAP, CVP and HR, during the surgery and during the first 12 postoperative hours in ICU. These results suggest that the preoperative administration of esmolol may be an effective strategy for myocardial protection in patients scheduled for elective cardiac surgery under CPB, without increasing the risk of hemodynamic disorders. In addition, administration of esmolol was not associated with increased risks for severe complications and adverse events in these patients, thereby indicating that this preventative strategy is safe.

Injury due to surgical maneuvers and ischemia-reperfusion injury induced by CPB and hypothermia are considered the most important mechanisms underlying the occurrence of perioperative myocardial injury (7). The early phase of perioperative myocardial ischemia is characterized by a lack

of oxygen supply, resulting in the upregulation of anaerobic metabolism in the myocardium to cope with the anoxic environment. If the anoxic condition is maintained for long, cellular dysfunction occurs as a result of decreased adenosine 5' phosphate supply and the resultant changes in the internal environment homeostasis lead to structural damage to cardiomyocytes. The damage to cardiomyocytes has been attributed to several pathophysiological processes, including oxidative stress (15), overactivated inflammatory responses (16,17) and calcium overload (18) in the plasma of the cardiomyocytes. Therefore, interventional strategies targeting these processes may help identify cardioprotective agents that may be useful for administration during the procedures of CPB and open-heart cardiac surgery. Although β -blockers are known to lower the oxygen demand by eliciting an inotropic response (19), they have been shown to have numerous other potential cardioprotective actions (20). It has been suggested that the tonic activation of the beta-adrenergic system associated with proinflammatory and proapoptotic changes in the heart may be alleviated by β -blockers (21). Metoprolol, a regular β -blocker, has been demonstrated to cause a reduction in oxidative stress and an increase in the antioxidant activity in patients undergoing elective angioplasty, thereby highlighting the antioxidative action of β -blockers (22). In addition, it has been reported that propranolol, another commonly used β -blocker, is likely to exert its protective effect on mitochondrial function in the ischemic heart by attenuating the calcium overload in cardiomyocytes (23). Therefore, the potential protective action

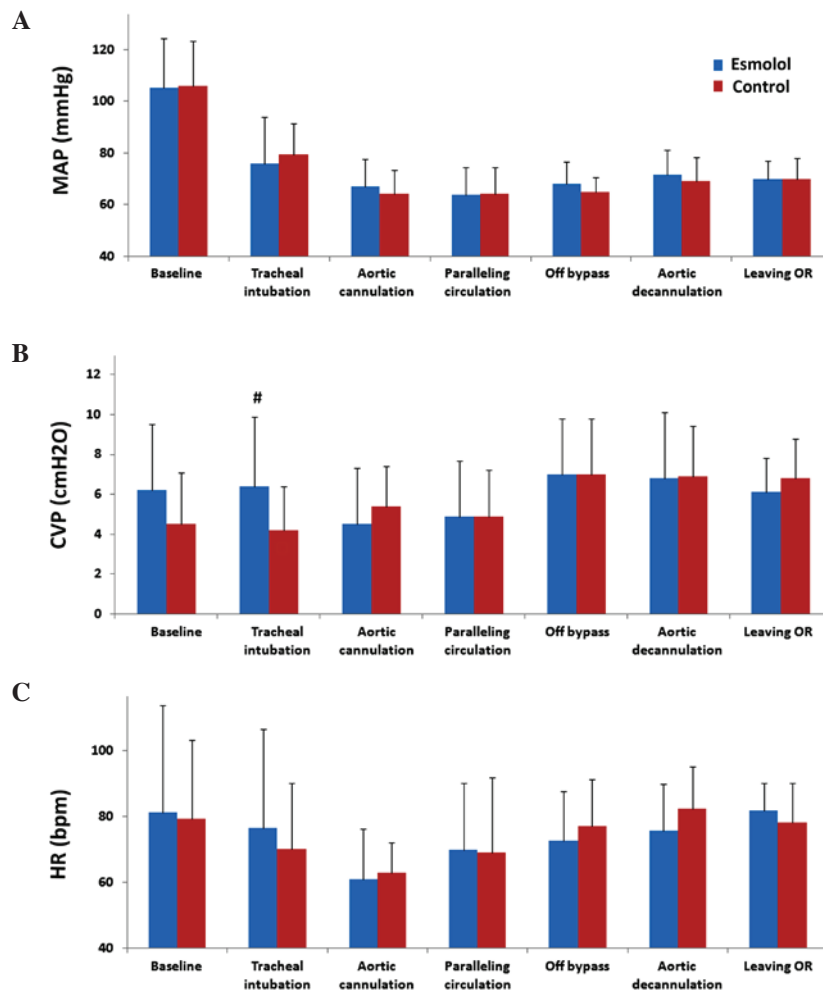


Figure 1. Changes in the (A) MAP, (B) CVP and (C) HR during the perioperative period of the patients in the esmolol and control groups. [#]P<0.05 vs. the control group. MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate; OR, operating room.

of perioperative β -blockers against myocardial injury may be attributed to their widespread beneficial effects, which may render them more effective than the other agents that only influence limited aspects of the pathophysiological process.

Consistent with our observations, early studies in humans have provided evidence of the protective effect of β -blockers against myocardial injury during CPB and open-heart surgery. However, their use in cardiac surgery has been limited by their potential negative inotropic effects and their unfavorable effects on hemodynamics (24-26). To overcome this problem, the ultra-short-acting β -blocker esmolol appeared to be an attractive agent in the current settings, since it is rapidly metabolized, and is expected to have little impact on the hemodynamic parameters. The half-life of esmolol is ~2 min, the time to peak effect is ~6-10 min after administration and the washout time is 9 min after stopping the infusion (27). Due to these properties, this β -blocker is the first-choice drug in critical patients in whom the possible adverse effects of β -blockers, including cardiac failure, hypotension and bradycardia, may necessitate immediate discontinuation of the drug.

A number of pilot studies have explored the potential benefits of esmolol in patients undergoing cardiac surgeries. Deng *et al* (28) reported that in a direct vision of an intracardiac beating-heart surgery, esmolol protects the myocardium

and facilitates the operation, as demonstrated by the maintenance of the myocardial ultrastructure. In addition, Scorsin *et al* (29) measured the transmural gradient of the oxygen content and revealed that esmolol provides potent myocardial protection in hypertrophied hearts, at least partly, by reducing the myocardial oxygen metabolism. In addition, a meta-analysis revealed that esmolol reduces the incidence of myocardial ischemia and arrhythmias when administered prior to cardiac surgery, although it does cause an increase in bradycardia (30). However, none of the above studies have systematically analyzed the dynamic changes in the levels of the markers of myocardial injury and hemodynamic parameters and compared the levels of these markers prior to, during and within the first number of hours following the surgery.

The results of the present study indicated that the preoperative administration of esmolol for the maintenance of the HR within 80% of the baseline levels before CPB led to a significant reduction in the serum TnI levels, without causing any disturbances in the hemodynamic parameters at least for the first 12 postoperative hours. This reveals the cardioprotective effect of the drug and suggests that the preoperative administration of esmolol may be effective and safe for patients undergoing cardiac surgery under CPB.

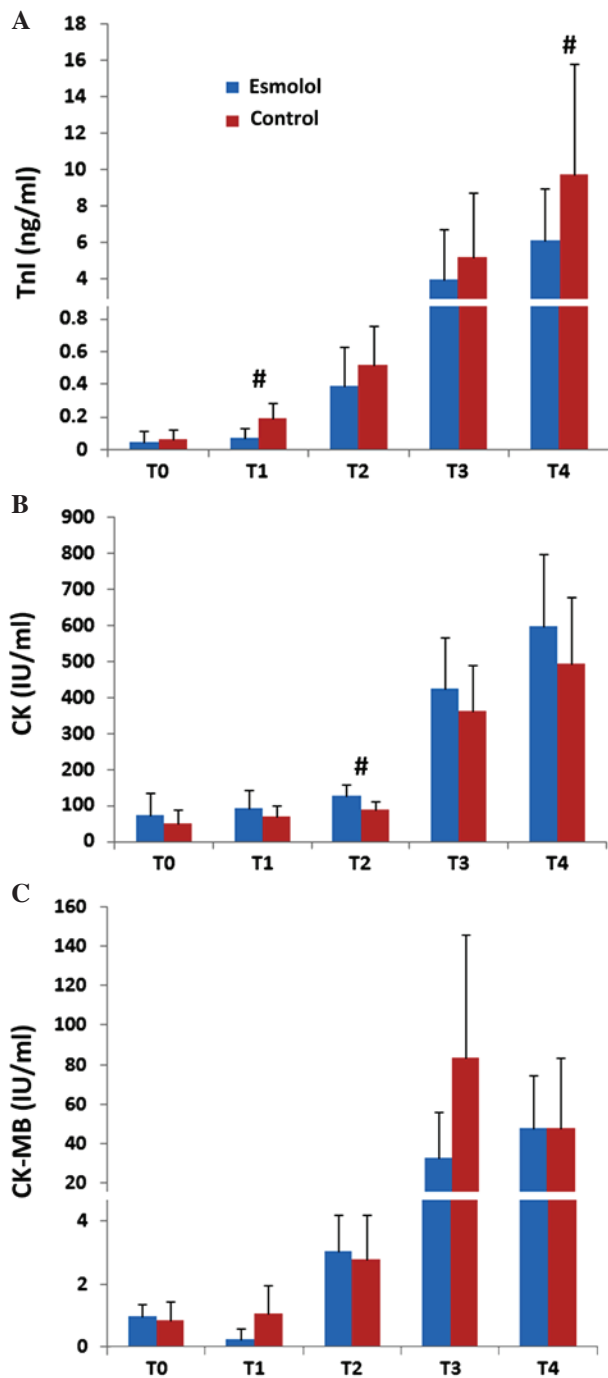


Figure 2. Perioperative changes in the levels of (A) TnI, (B) CK and (C) CK-MB in the esmolol and control groups. T0, at baseline; T1, before aortic cannulation; T2, 30 min before aortic cross-clamp; T3, release of aortic cross-clamp; T4, 120 min after release of aortic cross-clamp. #P<0.05 vs. the control group. TnI, troponin I; CK, creatine kinase; CK-MB, creatine kinase MB.

The observations of the present study should be interpreted in the light of a number of limitations. Initially, it is a pilot study that included only 24 patients from a single medical center in China. The potential effects of perioperative administration of esmolol on the clinical outcomes and adverse events in this situation should be demonstrated in future studies. In addition, due to the small sample size of the study population, it is difficult to detect whether the benefits of esmolol were more remarkable in certain subgroups of patients, such as those

Table III. Incidences of complications and adverse events of included patients in esmolol and control group.

Complications and adverse events	Esmolol group (n=12)	Control group (n=12)
Neurological complications (n)	0	1
Pulmonary infection (n)	2	3
Infection of incision (n)	0	0
Pericardial tamponade (n)	0	0
Open-chest hemostasis (n)	0	0
Death (n)	0	0

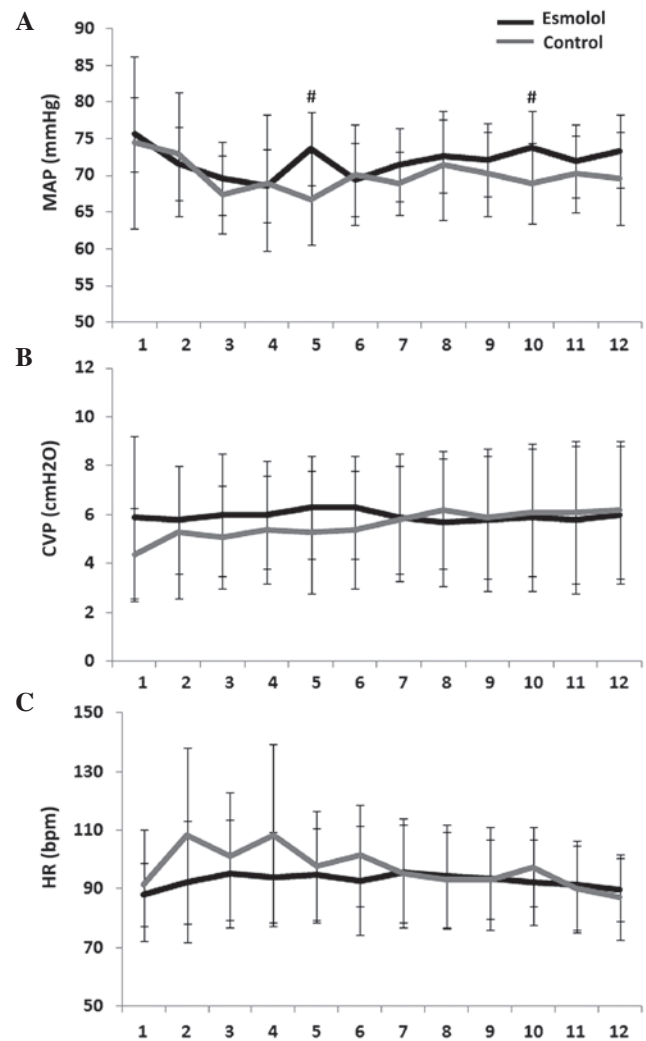


Figure 3. Changes in the (A) MAP, (B) CVP and (C) HR during the first 12 postoperative hours in the esmolol and control groups in the Intensive Care Unit. #P<0.05 vs. the control group. MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate.

with diabetes. The clinical applicability of the observations of the present study need to be verified in a multi-center study comprising a large number of patients. In addition, although TnI has been established as a reliable marker of myocardial injury, the potential benefits of esmolol on the myocardium should be verified by other assessment criteria, including

histopathological examinations. In addition, the present study did not include any blinding strategy, which may induce bias in the results. Finally, the effects of esmolol on the perioperative levels of the markers of myocardial injury and the changes in the hemodynamic parameters for the first 12 postoperative hours were evaluated. The long-term outcomes, such as the cardiac function and mortality data, need to be addressed in future studies to further confirm the beneficial effects of administering preoperative esmolol to patients.

In conclusion, the present study indicates that the administration of esmolol prior to starting the surgical procedure may be an effective and safe strategy for myocardial protection in the case of patients undergoing elective cardiac surgery under CPB. However, further studies on a larger sample population are required in order to confirm the long-term beneficial effects of preoperative administration of esmolol in such patients.

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