A randomized clinical trial comparing hemodynamic responses to ketamine-propofol combination (ketofol) versus etomidate during anesthesia induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft surgery

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Abstract

Introduction: Anesthesia induction is often accompanied by a period of hemodynamic instability, which could be a significant problem in patients with compromised ventricular function. The aim of this study is to compare the hemodynamic responses to etomidate versus a combination of ketamine and propofol (ketofol) for anesthetic induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft (CABG) surgery.

Material and methods: In a double-blind randomized clinical study, a total of 84 patients with ischemic left ventricular dysfunction (EF < 40%) were randomly assigned to two groups (A and B). Patients in group A received etomidate 0.2 mg/kg and a placebo (normal saline); group B received a combination of ketamine (1 mg/kg) and propofol (1.5 mg/kg) at the induction of anesthesia. Two minutes after induction, hemodynamic variables, including systolic, diastolic, mean arterial pressure (SAP, DAP, MAP) and heart rate (HR), were measured immediately before and after the laryngoscopy, and before intubation and post-intubation at 1, 2, and 3 min.

Results: The decrease in all hemodynamic parameters (SBP, DBP, MAP and HR) from induction time to laryngoscopy was greater in the ketofol group (group B) than in the etomidate group (group A) ($p < 0.05$). The ephedrine prescription rate due to hemodynamic changes was 24.4% (10 patients) and 5% (2 patients) in group B and group A, respectively ($p = 0.03$).

Conclusions: We found that etomidate provides superior hemodynamic stability as compared to ketofol in patients with left ventricular dysfunction undergoing CABG surgery under general anesthesia.

Key words: ketofol, etomidate, hemodynamics, propofol, ketamine, ventricular dysfunction.

Introduction

Anesthesia induction is one of the most critical periods in cardiac anesthesia, especially for patients with left ventricular dysfunction undergoing coronary artery bypass graft (CABG) surgery, who constitute a high-risk group [1, 2]. Anesthetics often interfere with cardiovascular function through direct myocardial depression and/or altering cardiovascular control mechanisms [3]. Anesthesia induction is often accompanied by a period of hemodynamic instability, especially hypotension, which could be a significant problem in patients with compromised ventricular function, because these patients cannot tolerate such depression [3, 4]. On the other hand, laryngoscopies and orotracheal intubations are potent noxious stimuli provoking untoward hemodynamic responses such as hypertension and tachycardia, which can be detrimental to patients with poor myocardial reserve [2, 5]. Such variations in hemodynamic status may change the fine balance between myocardial oxygen demand and supply, thus accelerating myocardial ischemia in these patients. Therefore, preserving hemodynamic stability during anesthesia induction is critically important [2, 3, 6]. Numerous studies have evaluated the effects of a wide variety of induction agents and their combinations used to attain hemodynamic stability during anesthesia induction. However, there is no single anesthetic agent suitable for all patients [1, 2, 4, 7].

Etomidate, a commonly used anesthetic agent with minimal depressant effects on the cardiovascular and respiratory systems, is suitable for patients with compromised ventricular function [8]. Although etomidate has a reputation for hemodynamic stability, studies have found that a single bolus of etomidate can blunt the hypothalamic–pituitary–adrenal (HPA) axis response for more than 24 h after cardiac surgery, a response which is an essential component of general adaptation to illness and stress [2, 9, 10]. Studies have also shown that administration of etomidate during anesthesia induction may lead to postoperative vasopressor dependency, as well as substantially unfavorable outcomes such as mortality, cardiovascular morbidity, and prolonged hospital stays [9, 11].

Ketamine and propofol are two well-known anesthetic agents, and using these two drugs together is a well-known combination that makes use of the specific properties of each. Ketamine, a dissociative anesthetic agent with cardiac stimulatory properties, increases blood pressure, heart rate, and cardiac output [2, 12]. In contrast, propofol, as a widely used sedative-hypnotic anesthetic agent, has potent cardiovascular depressant effects that produce hypotension [1, 13]. Theoretically, the divergent hemodynamic effects of these two drugs might be neutralizing and reduce the incidence of overall adverse effects. In balanced anesthesia, a combination of small doses of multiple anesthetics is concurrently administered, which aggregates the benefits, but not the unfavorable effects, of each agent in the mixture [14–16]. Although many studies have delineated the beneficial effects of ketofol in procedural sedation as well as non-cardiac procedures [17–25], we found only one study evaluating the use of ketofol during anesthesia induction in patients undergoing cardiac surgery with compromised ventricular function [16]. We hypothesized that using ketofol for anesthesia induction in patients undergoing cardiac surgery with compromised ventricular function provides better hemodynamic stability as compared to etomidate, without any important side effects.

Considering the paucity of information, this study aims to compare the hemodynamic responses to etomidate versus ketofol for anesthetic induction in patients with left ventricular dysfunction who are undergoing CABG surgery.

Material and methods

We obtained approval from the institutional ethics committee and received written informed consent from each participant, enrolling a total of 84 patients of both sexes, aged 40 to 70 years, in a double-blind randomized clinical study. All participants had a physical status class II and III, as defined by the American Society of Anesthesiologists (ASA), and suffered from ischemic left ventricular dysfunction (ejection fraction (EF) < 40%). Each patient was scheduled for a first-time isolated on-pump elective CABG surgery. This study was carried out between February 2014 and April 2015 at Mazandaran Heart Center, a teaching hospital affiliated with Mazandaran University of Medical Sciences, Sari, Iran. Excluded from the study were patients with a known history of adrenal insufficiency, steroid therapy during the preceding 6 months, congestive heart failure (CHF), renal or hepatic insufficiency and use of propofol, ketamine, or etomidate one week prior to surgery. Also excluded were those with known allergies to egg or soy and known allergies or contraindication to propofol, ketamine, or etomidate. Finally, patients who had had tracheal intubations that required more than 30 s, or who had had combined cardiac valve surgery with CABG were excluded.

Patients who met the eligibility criteria were randomly allocated by sealed envelope to group A and group B, with 42 patients in each group. Patient allocation was performed by a nurse who was unaware of the study groups, using numbers from a computer generated list. In the operating room and before anesthesia induction, all patients were infused with 5 cc/kg Ringer lactate via an

intravenous line. Each participant also received an electrocardiogram (ECG), and invasive arterial blood pressure, pulse oximeter, baseline systolic and diastolic arterial blood pressure (SAP, DAP), mean arterial pressure (MAP) and heart rate (HR) were measured and recorded. Intra-arterial cannulae in the left radial artery were used for the invasive arterial blood pressure measurement.

Each patient then received intravenous standardized premedication of midazolam (0.03 mg/kg) and fentanyl (2 µg/kg). One minute later, patients in group A were induced with etomidate at 0.2 mg/kg and a placebo (normal saline). Those in group B were induced with a combination of ketamine (1 mg/kg) and propofol (1.5 mg/kg). All drugs were prepared by an anesthesiology resident who was not involved in the study, and all syringes were covered with opaque tape to conceal their content, thus ensuring that the study drug was blinded from all investigators and healthcare providers. Within 30 s after drug administration, each patient received atracurium (0.2 mg/kg) for muscle relaxation to facilitate intubation. Two minutes after anesthesia induction, the hemodynamic variables SAP, DAP, MAP and HR were measured immediately before and after the laryngoscopy and before intubation, and post-intubation at 1, 2, and 3 min by a trained research nurse. ECGs were monitored continuously during the study period. Laryngoscopy and anesthesia administration were performed by an anesthesiologist who was blinded from the study groups. The durations of laryngoscopy and intubation were recorded for each patient. If the blood pressure decreased to less than 20% of a patient's baseline, ephedrine (10 mg) was administered and then recorded. Occurrences of muscle twitching were also noted. All events were recorded by a trained research nurse, who was unaware of the study groups. Also, intra-operative characteristics such as cardiopulmonary bypass (CPB) time, aortic cross-clamp time, duration of surgery and number of grafts were recorded for each patient. The primary outcome measure of the study was comparison of hemodynamics changes between the two groups. This study is registered in the Iranian Registry of Clinical Trials Database (IRCT201207184365N14; http://www.irct.ir).

Statistical analysis

Data were tested for normal distribution using the Shapiro-Wilk test. Comparative descriptions of baseline characteristics for the two groups (ketofol and etomidate) were tabulated as mean (SD) or as percentages. Comparisons between the two groups for categorical data were statistically analyzed using the χ^2 or Fisher's exact test, and were statistically analyzed using the *t*-test for continuous data. When necessary, we used the *t*-test and the Mann-Whitney tests to evaluate percentage changes of hemodynamic parameters before laryngoscopies. In order to control the effects of age and previous blood pressure medications, we used linear regression models. The times to hemodynamic failure and the need for ephedrine were compared using the Kaplan-Meier method, and we compared the two groups using the log-rank test. We examined the primary efficacy data on hemodynamic failure and the need for ephedrine using intention-to-treat analysis. The general linear model (GLM) hemodynamic parameters between the two groups were compared using the ANOVA test. We also considered time of evaluation as a within-subject factor, and the intervention state (ketofol and etomidate) as a between-subject factor. The time groups (interaction terms) were considered group differences between ketofol and etomidate groups in their responses over time. We used Mauchly's sphericity test for compound symmetry assumption; a *p*-value of 0.05 or less was considered statistically significant. Missing data were imputed by the last observation carried forward. One of the advantages of a mixed effects model is its flexibility in dealing with missing data, which occur frequently in clinical trials. Data were analyzed using IBM SPSS statistics software, version 16, and Stata version 12.

Sample size calculation

Study sample sizes were determined to detect a difference of 105 between the two study groups, with a power of 80% and a standard deviation (SD) of 13 and a type I error of 5%. The sample size calculation was 36 patients in each group; we therefore recruited 42 patients to account for any dropouts.

Results

Participants

A total of 96 patients were referred for CABG surgery to our hospital and screened during the study period. Of these, 7 patients did not meet the inclusion criteria and 5 patients declined to participate in the study. Of the 84 patients allocated to the two groups, 1 patient was lost during follow-up from group B, and two were lost from group A. In total, 81 patients completed the present study, and data from all these patients were analyzed (Figure 1). There was no significant difference between the two groups in epidemiological and clinical characteristics (age, gender ratio, body mass index (BMI), EF, history of hypertension, diabetes mellitus, hypercholesterolemia, number of grafts, cardiopulmonary bypass (CPB) time, aortic cross-clamp time, duration of surgery, number of grafts,

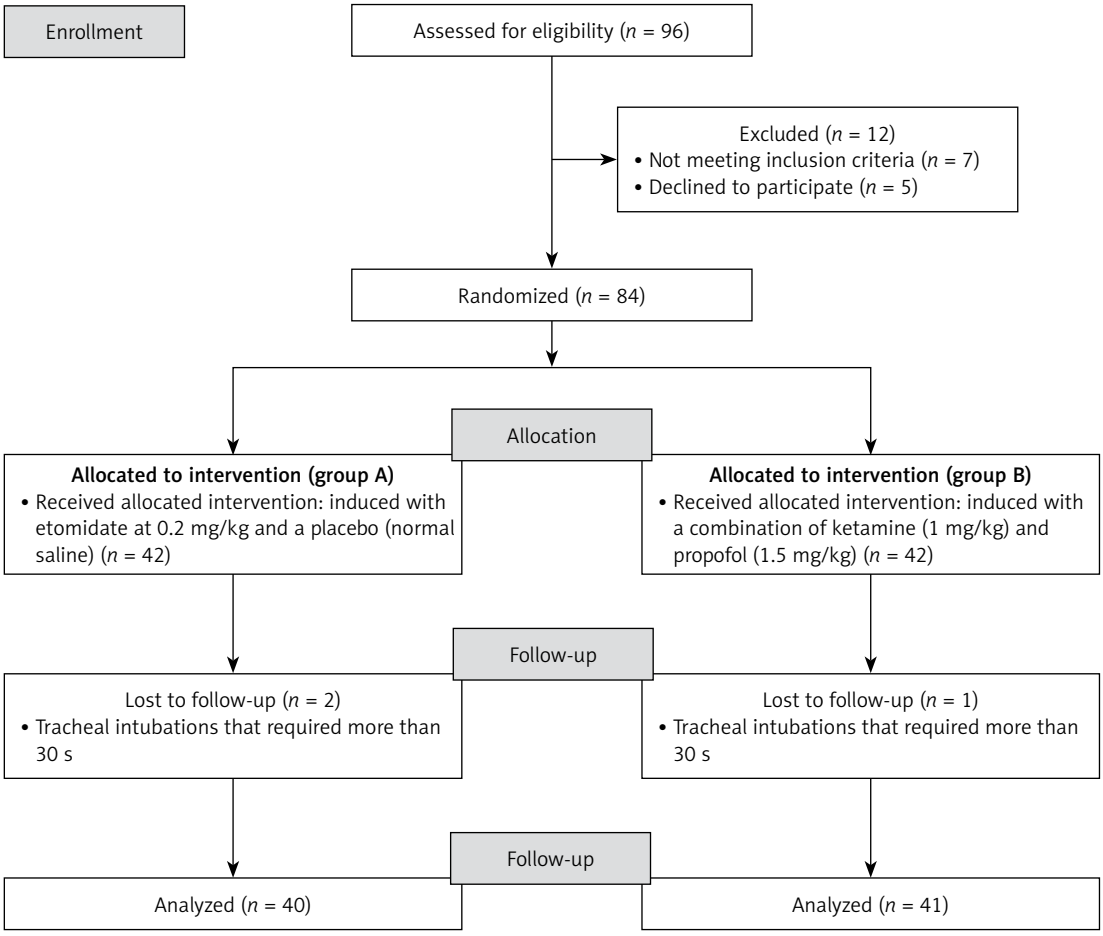

Figure 1. Flow diagram of the study

baseline SAP, baseline DAP, baseline MAP, and baseline HR) (Table I).

Hemodynamic changes after induction and before laryngoscopy

At the laryngoscopy time, the hemodynamic parameters' (SAP, DAP, MAP, and HR) percentage reduction was significantly greater in the ketofol group than the etomidate group ($p < 0.05$) (Table II). The regression model showed that after adjusting for age and the effect of prescribed antihypertensive drugs, the association between percentage decrease from the induction time to the time of laryngoscopy and the prescribed anesthetic drug (ketamine and propofol combination or etomidate) was statistically significant (Table III).

Ephedrine prescription rate

The ephedrine prescription rate due to hemodynamic changes was 24.4% (10 patients) and 5% (2 patients) in the ketofol and etomidate groups, respectively ($p = 0.03$). The mean ± SD ephedrine prescription time was 284.36 ±13.6 and 321.75 ±5.9 s. The log-rank test revealed a statistically significant difference between these rates over time ($p = 0.014$).

Trend of hemodynamic parameter changes

Table III show the mean values of the pre- and post-intervention hemodynamic parameters of each group.

Systolic arterial blood pressure trend

As shown in Table IV, there was a statistically significant time effect ($p = 0.001$), indicating that when the two groups were combined the average SAP at baseline was higher than the average after induction times. Table II shows that there was no significant group effect ($p = 0.07$) or group by time interaction effect ($p = 0.2$) (power, 82%).

Diastolic arterial blood pressure trend

As shown in Table IV, there was a statistically significant time effect ($p < 0.001$), indicating that when the two groups were combined, the average DAP at baseline was higher than the average after induction times. The diastolic arterial blood pressure in the ketofol group was lower than that

Table I. Basic demographic and clinical characteristics of patients in the two groups

Variable	Groups		*P*-value
	A (ketamine + propofol, *N* = 41)	B (etomidate, *N* = 40)	
Age, mean ± SD	58.71 ±9.2	62.23 ±6.3	0.126
Sex (female/male)	16/25	12/28	0.496
BMI, mean ± SD [kg/m^2]	26.85 ±3.89	25.23 ±4.02	0.073
Hypertension, *n* (%)	21 (51.2)	24 (60)	0.501
Diabetes mellitus, *n* (%)	14 (34.1)	17 (42.5)	0.493
Hypercholesterolemia, *n* (%)	22 (53.7)	19 (47.5)	0.655
CPB time, mean ± SD [min]	66.07 ±8.95	65.38 ±9.25	0.734
Aortic cross-clamp time, mean ± SD [min]	41.22 ±7.85	42.80 ±7.79	0.363
Duration of surgery, mean ± SD [min]	193.48 ±22.35	189.36 ±26.51	0.372
Number of grafts, *n* (%):			
One	3 (7.3)	2 (5)	0.752
Two	7 (17.1)	5 (12.5)	
Three	12 (29.3)	16 (40)	
Four	19 (46.3)	17 (42.5)	
EF (mean ± SD)	32.2 ±4.88	33.75 ±6.18	0.168
Baseline SAP	140.46 ±22.49	136.45 ±23.93	0.581
Baseline DAP	66.61 ±10.22	64.45 ±11.94	0.463
Baseline MAP	90.98 ±12.73	90.75 ±14.03	0.975
Baseline HR	81.68 ±15.28	76.13 ±16.49	0.117

BMI – body mass index, CPB – cardiopulmonary bypass, EF – ejection fraction, SAP – systolic arterial blood pressure, DAP – diastolic arterial blood pressure, MAP – mean arterial pressure, HR – heart rate.

Table II. Percent change in hemodynamic variables after induction and before laryngoscopy

Variable	Groups		*P*-value
	A (ketamine + propofol, *N* = 41)	B (etomidate, *N* = 40)	
Percent change in SAP	39 ±18	30 ±14	0.014
Percent change in DAP	31 ±2	20 ±16	0.011
Percent change in MAP	34 ±17	26 ±14	0.036
Percent change in HR	11 ±8	4 ±12	0.004

SAP – systolic arterial blood pressure, DAP – diastolic arterial blood pressure, MAP – mean arterial pressure, HR – heart rate.

Table III. The effect of prescribed drugs on hemodynamic parameters after adjustment for age and antihypertensive drugs in multiple linear regression models

Variable	B* (95% CI)	SE	*P*-value
SAP	–0.09 (–0.16, –0.02)	0.04	0.013
DAP	–0.11 (–0.19, –0.02)	0.04	0.016
MAP	–0.08 (–0.15,–0.02)	0.03	0.011
HR	–0.06 (–0.11, –0.005)	0.03	0.038

*****Regression coefficient. SAP – systolic arterial blood pressure, DAP – diastolic arterial blood pressure, MAP – mean arterial pressure, HR – heart rate.*

in the etomidate group, but there were no statistically significant differences between groups (between-subject differences or group effect) ($p = 0.2$) (power, 85%). Significant group-by-time interaction effects were also present ($p = 0.007$).

Mean arterial blood pressure

As shown in Table IV, there was a statistically significant time effect ($p = 0.001$), indicating that when the two groups were combined, the average MAP at baseline was higher than the average after induction times. Table II shows that there were

no statistically significant differences between groups (between-subject differences or group effects) (p = 0.09) or group-by-time interaction effects (p = 0.19) (power, 87%).

Heart rate

Table IV shows that there were no statistically significant time effects (p = 0.83) (power, 95%), between-subject differences, or group effects (p = 0.43) (power, 82%), or group-by-time interaction effects (p = 0.75) (power, 76%).

Muscle twitching was not observed in the two groups. One patient in each group experienced an episode of postoperative bleeding, which required re-exploration.

Discussion

The number of patients with compromised left ventricular function undergoing CABG is increasing. Researchers believe that CABG is a safe and effective treatment for patients with severely compromised left ventricular function with coronary artery disease [26]. Cardiovascular stability is a crucial prerequisite for any anesthetic agent used for anesthesia induction in patients undergoing CABG surgery, specifically patients with a poor cardiovascular reserve [2, 16]. Several studies have investigated the effects on these patients of a wide variety of induction agents. In our study, we compared the hemodynamic responses to etomidate versus ketofol for anesthetic induction in the participants. The results show more hemodynamic stability during anesthesia induction and intubation using etomidate compared with ketofol. Also, the incidence of post-induction hypotension requiring rescue IV ephedrine administration was significantly higher in patients who received ketofol compared with the other group.

Aghdaii *et al.* evaluated the effect of etomidate-midazolam versus propofol-ketamine combination during induction of anesthesia on hemodynamic responses in patients with left ventricular dysfunction undergoing CABG. The results of this study demonstrate a similar hemodynamic response at different time intervals in the two groups, except for the cardiac index (CI) and systemic vascular resistance (SVR), at one and three minutes after intubation. Patients who received the propofol-ketamine combination had a significantly higher CI and lower SVR compared with the other group [16]. Another study conducted with patients undergoing on-pump CABG/valve plasty using general anesthesia showed that using etomidate during anesthesia induction provides more hemodynamic stability compared with propofol [27]. Pandey *et al.* found that etomidate provides more stable hemodynamic values when used for anesthesia induction compared with propofol in

Table IV. Change trends of hemodynamic parameters in the two groups during follow-up

Variable		Time						*P*-value		
		T1	T2	T3	T4	T5	T6	Time effect	Group effect	Time* group effect (interaction)
SAP	A	139.93 ±20.6	91.07 ±18.8	118.3 ±34.1	120.3 ±32.6	120.2 ±31.6	117.8 ±34.9	0.001	0.071	0.221
	B	136.45 ±23.8	95.39 ±21.9	121.6 ±33.4	128.8 ±35.4	127.9 ±29.4	124.1 ±24.99			
DAP	A	66.53 ±10.4	50.1 ±15.3	66.2 ±23.5	65.6 ±21.41	67.03 ±19.9	68.1 ±18.6	< 0.001	0.243	0.007
	B	64.11 ±12.15	51.6 ±13.3	68.7 ±21.2	71.4 ±21.8	69.6 ±17.6	64.9 ±14.1			
MAP	A	91.4 ±12.5	63.9 ±16.7	84.6 ±27.3	84.5 ±26.3	85.8 ±23.4	85.3 ±23.6	< 0.001	0.092	0.191
	B	90.7 ±14.35	67.53 ±17.1	88.8 ±25.4	90.6 ±30.7	88.7 ±20.9	85.7 ±17.9			
HR	A	81.8 ±15.8	72.9 ±11.9	74.9 ±15.3	77.7 ±12.3	77.5 ±12.4	75.8 ±13.9	0.835	0.438	< 0.001
	B	74.8 ±15.8	71.3 ±11.9	81 ±14.7	82.4 ±14.2	78.9 ±13.9	75.6 ±12.5			

SAP – systolic arterial blood pressure, DAP – diastolic arterial blood pressure, MAP – mean arterial pressure, HR – heart rate. T1 – before induction of anesthesia, T2 – before performing laryngoscopy and tracheal intubation, T3 – immediately after laryngoscopy and tracheal intubation, T4 – 1 min after tracheal intubation, T5 – 2 min after tracheal intubation, T6 – 3 min after tracheal intubation.

patients with normal left ventricular function undergoing on-pump CABG surgery [28]. Other studies have confirmed that using etomidate during anesthesia induction in elective procedures results in greater hemodynamic stability compared with propofol [29, 30]. In addition, studies have demonstrated that etomidate provides hemodynamic stability without requiring any rescue drug, as compared to the need for a rescue drug with propofol during induction and intubation [31].

In our previous study, we found that using a ketamine-thiopental combination for anesthesia induction in patients with impaired ventricular function undergoing CABG was associated with greater hemodynamic stability compared with etomidate [2]. However, in the present study we found that etomidate provides better hemodynamic values compared with the ketamine-propofol combination. A study by Yang *et al.* confirmed that anesthesia induction with propofol reduces myocardial systolic and diastolic function in patients with prior normal left ventricular function who underwent non-cardiac surgery [32]. Furthermore, propofol can cause vasodilation and hypotension by decreasing sympathetic tone and decreasing SVR, and has a direct effect on intracellular smooth muscle calcium mobilization. Additionally, its myocardial depressant effect may be related to alterations in intrinsic myocyte contractile function [32, 33]. Regardless of any underlying conditions, studies indicate that anesthesia induction with propofol at a dose of 2 mg/kg to 2.5 mg/kg can reduce blood pressure by 25% to 40% [33]. Theoretically, it seems that concurrent administration of propofol and ketamine with divergent hemodynamic effects might be neutralizing and reduce the overall adverse effects [14, 15]. This assumption has not been completely confirmed by our study. A study by Abbasivash *et al.* revealed that propofol-midazolam-ketamine co-induction in patients scheduled for elective non-cardiac surgery provides more hemodynamic stability than etomidate [34].

Singh *et al.* evaluated the hemodynamic effects of anesthesia induction with propofol, etomidate, midazolam, and thiopentone in patients with coronary artery disease and compromised left ventricular function who underwent elective CABG. The results of their study show that there were no significant differences in hemodynamic changes between the groups [1]. Researchers believe that the route, dose, and speed of injection of anesthetic induction agents, as well as the differing experience levels of anesthesiologists, are factors that may affect the outcome of anesthesia induction [1, 32]. In the present study, all patients received the induction agents according to their body weight intravenously by the same anesthesiology resident. However, the research evidence regarding the effects of different injection rates of propofol on hemodynamic parameters is controversial [35–39]. In spite of the potential benefits of using etomidate as an induction agent, one area of concern exists regarding its use in anesthesia. Researchers believe that etomidate could possibly lead to profound and persistent adrenocortical steroid synthesis [40]. However, the evidence surrounding this concern is conflicting, and the effect of a single bolus of etomidate on patient morbidity and mortality remains unclear [41]. Basciani *et al.* found that relative adrenocortical insufficiency after administering a single dose of etomidate during anesthesia induction was higher than that of patients undergoing cardiac surgery following propofol induction. However, no significant differences between groups were found in terms of vasopressor requirements and other patients' outcomes [42]. In line with this, Morel *et al.* observed that in patients undergoing elective cardiac surgery, a single bolus of etomidate blunts the HPA axis response for more than 24 h, without an increase in vasopressor requirements [9]. However, a prospective cohort study found that using etomidate is a changeable risk factor for the occurrence of relative adrenal insufficiency development in cardiopulmonary bypass surgery patients, and therefore should be avoided [10]. Muscle twitching was not observed in the two groups. One possible explanation for this is pretreatment with midazolam in the present study. In considering the study limitations, we recognize that although the two groups were given the same premedication of midazolam (0.03 mg/kg) and fentanyl (2 µg/kg), the dosages per kilogram body weight may have been unequally distributed between the groups, and thus the dosing of these premedication drugs may be a confounding variable. Another limitation we recognize is that we did not measure blood cortisol level changes in patients over time.

In conclusion, although the beneficial effects of the ketamine and propofol combination in non-cardiac procedures have been confirmed, in patients with left ventricular dysfunction undergoing CABG surgery under general anesthesia, etomidate may be recommended as an effective and safe agent during anesthesia induction. We found that etomidate provides superior hemodynamic stability as compared to ketofol. Further well-designed randomized clinical trials confirming the safety and efficacy of this modality are warranted.

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Conflict of interest

The authors declare no conflict of interest.

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