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Safe Inhalational Anesthetics in Patients With Coronary Artery Disease: Effects of Sevoflurane and Desflurane on Ischemia-Modified Albumin levels

Celaleddin Soyalp[1], Omer Turk[2], Ersoy Oksüz[3], Nureddin Yuzkat[1], Canan Demir[4], Halit Demir[5]

[1]Van Yuzuncu Yil University School of Medicine, Department of Anaesthesiology and Reanimation, Van, Türkiye
[2]Van Training and Research Hospital Department of Training Clinic, Van, Türkiye
[3]Malatya Turgut Ozal University , Medical Faculty, Department of Medical Pharmacology, Malatya , Türkiye
[4]Van Yuzuncu Yil University Vocational School of Healthcare, Van, Türkiye
[5]Van Yil University, Faculty of Science, Department of Biochemistry, Van, Türkiye

Abstract

Introduction: Sevoflurane and desflurane are commonly used anesthetic agents with known cardiac side effects. Ischemia-modified albumin (IMA) is a useful biomarker that increases in cardiac conditions. This study investigates the effects of desflurane and sevoflurane on cardiac parameters and IMA levels in patients with coronary artery disease (CAD).

Materials and Methods: Sixty CAD patients aged over 18 years scheduled for elective surgery were enrolled. Patients were randomly divided into two groups: group I, desflurane (D) (n=30) and group II, sevoflurane (S) (n=30). Pre- and post-operative cardiac parameters were recorded for each patient. IMA measurement in serum was determined spectrophotometrically.

Results: Postoperative IMA levels were significantly higher than preoperative IMA levels in both groups. The rate of change between post- and pre-operative IMA levels was significantly lower in group S than in group D . Postoperative heart rate (HR) and mean arterial pressure (MAP) levels were significantly lower than preoperative HR and MAP levels in both groups, whereas no significant differences were found between the two groups with regard to pre- and post-operative HR and MAP levels.

Conclusions: Sevoflurane is safer and has fewer cardiac side effects in CAD patients than desflurane. However, there is a need for comprehensive new studies evaluating large patient groups investigating this situation.

Key words: Sevoflurane; desflurane; ischemia-modified albumin; coronary artery disease; anesthesia.

Introduction

Coronary artery disease (CAD) is a clinical condition characterized by myocardial injury, resulting from reduced blood supply associated with abnormalities in the structure of coronary arteries. CAD is highly prevalent and also a leading cause of death around the world (1). Cardiac events associated with CAD include a wide range of clinical conditions varying from ischemia to myocardial necrosis caused by infarction Patients with CAD have an increased risk of mortality and complications during surgical procedures than normal individuals. Utmost care is needed in the anesthetic management of patients with CAD. Conversely, myocardial injury in such patients leads to increased perioperative complications and postoperative hospital length of stay (2). Considering that almost all pharmacological agents used for general anesthesia have varying degrees of side effects, the anesthetic management of patients with CAD is of paramount importance. Of these agents, sevoflurane and desflurane are frequently used inhalational anesthetics. Sevoflurane has cardiac side effects it has protective effects on myocardial cells and reduces myocardial infarction (MI) size (3,4,5). The cardiac effects of sevoflurane have been shown to vary according to patient characteristics. For instance, sevoflurane has been reported to have beneficial effects on the myocardium such as reduced, a reduction of myocardial infarction, myocardial tissue damage and motalty in patients undergoing cardiac surgery and no such effects in patients undergoing noncardiac procedures (6,7). Sevoflurane has been indicated to have a cardioprotective effect in younger patients and no such effects in the

*Corresponding Author: Celaleddin Soyalp. Van Yuzuncu Yil University 65080, Tusba/Van E-mail: c.soyalp@hotmail.com. **Orcid:** Celaleddin Soyalp 0000-0002-2687-5329, Omer Turk 0000-0003-2644-8842, Ersoy Öksüz 0000-0002-8088-1009, Nureddin Yuzkat 0000-0002-8218-1217, Canan Demir 0000-0002-4204-9756, Halit Demir 0000-0001-5598-2601

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elderly, although the effects of sevoflurane on myocardial cells are associated with age (8,9). Similar to sevoflurane, desflurane has also been reported to have cardiac side effects, particularly at high doses (10). For all these reasons, close monitoring of CAD patients and the selection of anesthetic agents with minimum side effects both pre- and post-operatively is extremely important.

Cardiac complications in CAD patients are commonly assessed with highly sensitive biochemical markers, such as creatine kinase-MB (CK-MB) and troponin (11). However, these markers are secreted from cells within several hours after the initial symptoms of acute MI and mostly used in the diagnosis of MI. The effectiveness of these markers is limited in clinical conditions with no cellular necrosis, such as ischemia. In contrast, ischemia-modified albumin (IMA) is a highly sensitive serum marker of myocardial ischemia that increases within minutes after the onset of ischemia and remains elevated for up to 12 h; it has a reported sensitivity of 80% (11). The N-terminal end of albumin binds drugs, toxic substances, and various elements, such as copper, zinc, and cobalt in the body. The N-terminal end of albumin is modified by ischemia and increased reactive oxygen species (ROS) production, and as a result, its metal-binding capacity is reduced. This novel albumin with reduced metal-binding capacity is termed as IMA, which is practically measured by the albumin cobalt-binding assay (12). IMA has been shown to be elevated in various conditions, including acute coronary syndrome, coronary angioplasty, percutaneous coronary intervention (PCI), bypass surgery, and myocardial ischemia, and IMA is also reported to be a useful biomarker of myocardial injury (13,14). The present study was designed to investigate the effects of desflurane and sevoflurane on heart rate, arterial pressure and SpO2 parameters and IMA levels in CAD patients.

Materials and Methods

Study population: The study included 60 CAD patients aged over 18 years who presented to the our University Medical School Anesthesia and Reanimation outpatient clinic and were scheduled for elective surgery. Written and verbal consent was obtained from each participant. The 60 patients were randomly divided into two groups using a sealed envelope method: group I, desflurane (D) (n=30) and group II, sevoflurane (S) (n=30). All the patients were informed about the surgical procedure one day prior to the surgery and demographic characteristics were recorded for each patient. Patients who were excluded from the study were those who underwent operations under emergency conditions, were taken to surgery intubated, were operated on because of multiple trauma, were pregnant, were aged <18 years, underwent coronary artery surgery, received intraoperative transfusion of blood and blood products, underwent thoracic surgery, and did not provide a written consent. General anesthesia was induced after collecting a 4 mL of blood sample through an intravenous access established on the dorsum of the left hand. Throughout the anesthesia period, hemodynamic parameters (heart rate [HR], mean arterial pressure [MAP], and peripheral capillary oxygen saturation [SpO2]) were recorded every 10 min using noninvasive monitoring. Immediately after the termination of anesthesia, an additional 4 mL blood sample was obtained from each patient. Both pre- and post-operative serum samples were centrifuged and then stored at -80 °C for until the IMA assay could be performed.

IMA assay: IMA measurement in serum was determined spectrophotometrically. For serum IMA measurement, 50 µL of cobalt chloride was added over 200 µL of serum, followed by incubation for 10 min and the addition and mixture of 50 µL dithiothreitol to the measurement cuvette. After two min, 1 mL of saline was added. The resulting colored complex was measured spectrophotometrically at a wavelength of 470 nm (15).

General anesthesia procedure: In both groups, the patients were intubated after inducing general anesthesia with 2 mg kg-1 propofol, 2 µg kg-1 fentanyl, and 0.6 mg kg-1 rocuronium intravenously (IV). Anesthetic maintenance was achieved with 8% desflurane, O2/air (40/60), and 1 µg kg-1 fentanyl in group D and with 2% sevoflurane, O2/air (40/60), and 1 µg kg-1 fentanyl in group S. at the end of the surgery, residual muscle relaxation was antagonized with atropine 0.02 mg kg-1 IV and neostigmine 0.04 mg kg-1 IV. Subsequently, the patients were transferred to the post-anesthesia care unit (PACU) and those with a Modified Aldrete score of 10 were transferred to the general ward.

Ethical approval: The study was approved by Van Yuzuncu Yil University Clinical Research Ethics Committee (Approval Date: January 16, 2019; No: 03).

Statistical analysis: Data were analyzed using SPSS 25.0 for Windows (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Distribution of univariate data was determined using the Shapiro-Wilk test. For continuous variables, independent

groups were compared using independent-samples t-test and using Mann-Whitney U test. Two

Table 1: Demographic characteristics

		Total (N=60)	Sevoflurane (n=30)	Desflurane (n=30)	p
		n (%)	n (%)	n (%)	
Gender	Female	29 (48.3)	13 (43.3)	16 (53.3)	0.606 p
	Male	31 (51.7)	17 (56.7)	14 (46.7)	
ASA	II	32 (53.3)	13 (43.3)	19 (63.3)	0.195 p
	III	28 (46.7)	17 (56.7)	11 (36.7)	
		Mean±SD	Mean±SD	Mean±SD	
Age		64.57±9.05	63.33±8.90	65.80±9.19	0.295 t
		Median (Min / Max)	Median (Min / Max)	Median (Min / Max)	
BMI		24.46 (19.03 / 47.61)	26.18 (20.55 / 35.16)	23.77 (19.03 / 47.61)	0.133 u
Operative time (min)		80.00 (35.00 / 150.00)	77.50 (50.00 / 150.00)	80.00 (35.00 / 130.00)	0.794 u

p Pearson's Chi-Square Test (Exact),t Independent samples t-test, u Mann-Whitney U test, **SD:** Standard deviation, **Min.:** Minimum, **Max.:** Maximum, **BMI:** Body mass index

Table 2: IMA levels

	Total (N=60)	Sevoflurane (n=30)	Desflurane (n=30)	p ga
IMA	Median (Min / Max)	Median (Min / Max)	Median (Min / Max)	
Preoperative	1.30 (1.11 / 1.81)	1.30 (1.11 / 1.81)	1.30 (1.15 / 1.44)	0.588 u
Postoperative	2.70 (2.03 / 3.94)	2.62 (2.35 / 3.57)	2.83 (2.03 / 3.94)	0.001 u
Difference (Post - Pre)	1.42 (0.67 / 2.58)	1.31 (0.87 / 2.31)	1.53 (0.67 / 2.58)	0.001 u
P gi	<0.001 w	<0.001 w	<0.001 w	

u Mann-Whitney U test, w Wilcoxon Signed-Rank Test, **Min.:** Minimum, **Max.:** Maximum, **P gi:** intragroup value, **P ga :** intergroup value

Table 3: Cardiac parameters

		Total (N=60)	Sevoflurane (n=30)	Desflurane (n=30)	p ga
		Median (Min / Max)	Median (Min / Max)	Median (Min / Max)	
SPO2	Preoperative	95.00 (80.00 / 98.00)	94.50 (80.00 / 98.00)	95.00 (88.00 / 98.00)	0.256 u
	Postoperative	96.79 (89.67 / 99.80)	96.50 (89.67 / 99.20)	97.52 (94.00 / 99.80)	0.131 u
	Difference (Post - Pre)	2.50 (-2.33 / 12.42)	2.31 (-2.33 / 12.42)	2.75 (-2.18 / 9.92)	0.942 u
	P gi	<0.001 w	<0.001 w	<0.001 w	
		Mean±SD	Mean±SD	Mean±SD	
HR	Preoperative	82.83±16.67	82.23±18.12	83.43±15.37	0.756 t
	Postoperative	77.22±13.91	75.31±15.27	79.14±12.37	0.289 t
	Difference (Post - Pre)	-5.61±13.35	-6.92±11.71	-4.29±14.89	0.450 r
	P gi	0.002 r	0.003 r	0.125 r	
MAP	Preoperative	107.77±15.75	106.87±15.43	108.67±16.28	0.663 t
	Postoperative	89.58±12.33	86.86±10.84	92.30±13.29	0.106 t
	Difference (Post - Pre)	-18.19±14.81	-20.01±15.02	-16.37±14.63	0.346 r
	P gi	<0.001 r	<0.001 r	<0.001 r	

t Independent samples t-test, u Mann-Whitney U test, w Wilcoxon Signed-Rank Test, r Paired t test, SD: Standard deviation, **Min.:** Minimum, **Max.:** Maximum, **P gi :**Intragroup value, **P ga :**Intergroup value, **HR:** Heart rate, **MAP:** Mean arterial pressure

repeated measurements of dependent variables were compared using the nonparametric Wilcoxon signed-rank test and parametric paired t test. For determining relationships between categorical

variables, Pearson Chi-square test was used. Continuous variables were expressed as mean ± standard deviation (SD) and median (Minimum/Maximum) and categorical variables were expressed as frequencies (n) and percentages (%). A p value of <0.05 was considered significant.

Results

Table 1 presents the demographic characteristics of the patients in both groups. No significant differences were found between the two groups with regard to age, sex, body mass index (BMI), and operative time (p>0.05). The postoperative IMA level was significantly higher than the preoperative IMA level in both groups (p<0.001 for both). Moreover, the rate of change between post- and pre-operative IMA level was significantly lower in Group S than in Group D (p<0.001) (Table 2). Postoperative SpO2 levels were significantly higher than preoperative SpO2 levels in both groups (p<0.001). However, no significant differences were found between the two groups with regard to pre- and post-operative SpO2 levels. Conversely, postoperative HR and MAP levels were significantly lower than preoperative HR and MAP levels in both groups (p<0.001), whereas no significant difference was found between the two groups with regard to pre- and post-operative HR and MAP levels (Table 3).

Discussion

Accumulating evidence suggests that IMA has a higher sensitivity in coronary ischemia and patients undergoing cardiac surgery compared to other biomarkers. A previous study evaluated 19 patients undergoing PCI and revealed that IMA was elevated in the presence of chest pain and ST elevation during percutaneous coronary angioplasty and suggested that IMA was more sensitive than other markers such as 8-iso prostaglandin F2-A (12). Bar-or et al. evaluated 41 patients undergoing PCI and reported that IMA was elevated earlier than other markers including CK-MB, myoglobin, and cTn-I (14). Another study evaluated 114 CAD patients undergoing coronary angiography and indicated that IMA was elevated earlier than other markers such as high-sensitivity C-reactive protein and natriuretic peptide and proposed that IMA was a relatively more specific marker in patients with ischemia (16). A study by Mishra et al. evaluated 50 patients with acute coronary syndrome and revealed that IMA showed better diagnostic performance compared to other markers, including troponin I and CK-MB (17). To the best of our knowledge, our study is the first of its kind to investigate the effects of sevoflurane and desflurane on IMA levels in CAD patients. Our results indicated that the postoperative IMA level was significantly higher than the preoperative IMA level in both groups (p<0.001). Moreover, the postoperative IMA level was significantly higher in group D than in group S (p<0.001). These findings indicate that IMA, which has been shown to be a significant marker of ischemia and myocardial injury, was elevated by these two drugs, and that the administration of these drugs could result in coronary artery occlusion, and thereby lead to ischemia in patients with CAD. Moreover, it was noted that desflurane is more likely to cause ischemia than sevoflurane. Accordingly, we consider that sevoflurane could be a better option than desflurane in patients with CAD and similar cardiac diseases. However, there is a need for comprehensive new studies evaluating large patient groups investigating this situation. Halogenated inhalational anesthetics, such as sevoflurane and desflurane became popular particularly in the 1990s and have recently become the mainstay anesthetic agents. However, these anesthetics have been shown to have adverse effects on the central nervous system and various disadvantages, including respiratory depression. These agents have been reported to cause frequent postoperative side effects, such as pain, nausea, vomiting, headache, cognitive impairment, and delirium (18,19). Conversely, halogenated inhalational anesthetics are known to exert their most critical and remarkable effects on the cardiovascular system. Notably, these agents have been shown to reduce vascular resistance, MAP, and cardiac output dependent on the dosage (10,20). Conversely, halogenated inhalational anesthetics, particularly desflurane, are known to cause tachycardia and shown to have significant cardiac side effects, such as impairment of diastolic myocardial relaxation (20). It has been reported that there are a number of factors that could modify the emergence of cardiac side effects of these agents. To illustrate, these agents may not modify the cardiac output at lower concentrations and healthy individuals whereas they may reduce cardiac output in elderly patients with comorbidities and multiple drug use (10). There are numerous other studies suggesting that halogenated inhalational anesthetics exert cardioprotective effects and have no detrimental effect on the heart tissue. These agents have no effect on HR and cardiac output when administered at clinical concentrations in humans (18). Further, sevoflurane reduced myocardial

injury in patients undergoing coronary artery revascularization surgery (9). Similarly, a previous meta-analysis revealed that halogenated inhalational anesthetics, including sevoflurane and desflurane have beneficial effects on ischemia/reperfusion damage *in vivo*. The study also noted that the administration of sevoflurane improved postoperative output, reduced cardiac troponin I concentrations, atrial fibrillation, and intensive care unit stay and also decreased mortality and morbidity (18). Based on the findings of the abovementioned studies, we believe that our study is of high value since it sheds light on the cardiac effects of sevoflurane and desflurane, both of which have been reported to have different effects. Our study supports the results of previous studies indicating that halogenated inhalational anesthetics have cardiac side effects and lead to hypotension. Our findings revealed that postoperative HR and MAP levels were significantly higher than preoperative HR and MAP levels in both groups and there was no significant difference between the two groups with regard to pre- and post-operative HR and MAP levels ($p<0.05$ for both). Although no significant difference was found between pre- and post-operative HR levels in group D, postoperative HR levels were significantly lower than preoperative HR levels in Group S ($p>0.05$ and $p<0.05$, respectively). Postoperative SpO2 levels were significantly higher than preoperative SPO2 levels in both groups, no significant difference was found between the two groups with regard to pre- and post-operative SpO2 levels ($p<0.05$ and $p>0.05$, respectively). These findings confirm that IMA elevation as an important biomarker and also indicates that both sevoflurane and desflurane may have cardiac side effects in CAD patients, although the effect of desflurane on MAP is lower than that of sevoflurane. Based on the above evidence, we suggest that a meticulous evaluation of CAD patients prior to anesthetic induction and close monitoring of such patients are of paramount importance. Moreover, further large-scale studies comparing CAD patients and patients without comorbidities are needed to provide additional evidence on the cardiac effects of these two anesthetics.

Study limitations: The limited number of cases and the fact that ECG and cardiac markers results before and after surgery were not evaluated are the limitations of our study.

Conclusions

Our findings indicated that halogenated inhalational anesthetics may lead to ischemia and alterations in vital parameters, such as MAP in CAD patients. Further, sevoflurane may be considered safer and with fewer cardiac side effects in CAD patients than desflurane. Large-scale studies evaluating other ischemic markers at different IMA concentrations are needed.

Conflict of interest: The authors report no conflict of interest.

Ethical approval: The study was approved by Van Yuzuncu Yil University Clinical Research Ethics Committee (Approval Date: January 16, 2019; No: 03).

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Author contributions: Study design, analyze and writing (C.S.,ÖT.,E.Ö), Data collection and processing
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Availability of data and materials: The authors confirm that the data supporting the findings of this study are available within the article.

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