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Comparative Study between Halothane, Isoflurane and Sevoflurane in Ischemic Patients Undergoing Non-Cardiac Surgery

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ABSTRACT

Background: Volatile anesthetics offer myocardial protection during cardiac surgery by reducing ischemia-reperfusion injury and surgical stress response. Their impact on outcomes in ischemic heart disease (IHD) patients remains under investigation, with agents like sevoflurane showing favorable cardiac effects compared to older anesthetics.

Objective: To compare and clinically evaluate the use of halothane, isoflurane and sevoflurane in ischemic heart diseases patients undergoing non-cardiac surgery.

Patients and methods: This prospective clinical study was carried out on 75 patients known to have IHD scheduled for non-cardiac elective surgery. They were randomized into 3 equal groups which received either halothane, isoflurane or sevoflurane as maintenance anesthesia. Hemodynamics and cardiac enzymes were monitored perioperatively.

Results: Sevoflurane maintained a steady heart rate, while halothane caused a slight decrease and isoflurane a mild increase. Postoperative CK-MB levels were significantly elevated in the halothane group, with lower levels observed in the isoflurane and sevoflurane groups. Troponin levels increased with halothane but remained unchanged with isoflurane and sevoflurane, suggesting improved cardiac protection with the latter agents.

Conclusion: In cardiac patients undergoing non cardiac surgery, sevoflurane and isoflurane were comparable with respect to the incidence and severity of intra- and postoperative myocardial ischemia and in the frequency of adverse cardiac outcomes while halothane was linked to increased cKMB and troponin levels, indicating higher cardiac stress.

Keywords: halothane; isoflurane; sevoflurane; ischemic heart disease; troponin.

INTRODUCTION

Inhalation anesthetics are substances that are brought into the body via the lungs and are distributed with the blood into different tissues. The main target of inhalation anesthetics (or so-called volatile anesthetics) is the brain [(1)].

Inhalation anesthetics act either by amplifying inhibitory function or decreasing excitatory transmission at the nerve endings in the brain. Volatile anesthetics are seldom used alone nowadays. A combination of inhalation anesthetics and intravenous drugs is called balanced anesthesia. Currently used inhalation anesthetics include enflurane, halothane, isoflurane, sevoflurane, desflurane, and nitrous oxide [(2)].

Volatile anesthetics reduce postoperative mortality after cardiac surgery. Nonetheless, whether volatile anesthetics improve the outcome of cardiac surgical patients is still a matter of debate. The authors investigated whether the use of volatile anesthetics reduces mortality in cardiac surgery [(3)].

It was reported that volatile anesthetics can suppress the cardiovascular response to surgical stress. They also exert preischemic effects and protect the myocardium against ischemic and reperfusion injury [(4)].

The choice of anesthetic agents in patients with IHD is of paramount importance due to their vulnerability to perioperative myocardial ischemia. Patients with underlying coronary artery disease may not adequately increase myocardial oxygen supply in response to increased demand during surgical stress, making hemodynamic stability crucial [(5)]. Volatile anesthetics have been studied extensively for their myocardial protective effects, particularly through mechanisms such as preconditioning. This phenomenon involves a transient ischemic episode that renders the myocardium more resistant to subsequent prolonged ischemia. Inhalational agents like isoflurane and sevoflurane have been shown to mimic this protective effect, potentially reducing myocardial injury in high-risk patients [(6)]. Among volatile agents, halothane has a known tendency to cause myocardial depression and sensitize the heart to catecholamines, increasing the risk of arrhythmias, particularly in patients with ischemic heart disease. In contrast, isoflurane and sevoflurane are associated with better maintenance of cardiac output and myocardial oxygen balance [(7)].

Furthermore, studies have suggested that certain volatile anesthetics may attenuate the release of cardiac biomarkers such as troponin and creatine kinase-MB, indicators of myocardial injury, thus serving not only as anesthetic agents but also as modulators of perioperative cardiac risk [(8)].

Therefore, this study aimed to clinically assess and compare the effects of halothane, isoflurane, and sevoflurane in patients with ischemic heart disease undergoing noncardiac surgery.

PATIENTS AND METHODS

This prospective randomized clinical study was carried out at Anesthesia, Intensive Care and Pain management Department, Faculty of Medicine, Zagazig University Hospitals for one year from January 2024 to January 2025.

This study included a total of 75 patients with known ischemic heart disease (IHD). Patients were

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randomly assigned into three equal groups (25 patients each): Group I: Received halothane (MAC ≤ 1.5), Group II: Received isoflurane (MAC ≤ 1.5) Group III: Received sevoflurane (MAC ≤ 1.5).

The method of randomization was computer-generated random numbers with the use of sealed opaque envelopes for allocation concealment.:

Inclusion criteria:

- Provided informed written consent for participation
- Known diagnosis of ischemic heart disease (IHD).
- Classified as American Society of Anesthesiologists (ASA) physical status II or III.
- Aged between 40 and 70 years.
- Body weight ranging from 60 to 90 kg.
- Scheduled for elective, noncardiac surgery under general anesthesia.
- Expected surgical duration between 60 and 120 minutes.

Exclusion criteria:

Patients were excluded from the study if they were classified as ASA physical status IV or V, had a history of unusual response or complications related to anesthesia, or suffered from severe comorbidities such as hepatic or renal failure. Additional exclusion criteria included a history of coronary artery bypass surgery, presence of severe arrhythmias, ejection fraction less than 40% as assessed by Echo Doppler, or elevated cardiac enzyme concentrations within 24 hours prior to surgery. Patients with unstable angina, acute coronary syndrome, mean arterial pressure (MAP) below 60 mmHg or above 150 mmHg at the time of the study, or coagulopathy with an INR greater than 2 were also excluded.

Withdrawal criteria: Patients had the right to withdraw from the study at any time without any negative consequence on their medical or surgical treatment plan.

Preoperative Assessment

All selected patients underwent thorough history taking, complete clinical examination, and routine preoperative investigations after obtaining informed written consent. Preoperative assessments were performed 24 hours prior to surgery and included laboratory tests, imaging studies, and 12-lead electrocardiography (ECG).

Anesthetic Management and Monitoring

Upon admission, an 18G intravenous cannula was inserted into the dorsum of the hand. All patients received intravenous midazolam at a dose of 0.05–0.07 mg/kg approximately 30 minutes before surgery. In the operating room, prior to induction, a radial arterial line was inserted under local anesthesia while patients remained sedated. Continuous monitoring included:

- 5-lead ECG.
- Capnography.
- Pulse oximetry.
- Invasive arterial blood pressure monitoring.

Induction and Maintenance of Anesthesia

Anesthesia was induced using propofol (1.5 mg/kg), fentanyl (1.5 µg/kg), and atracurium (0.5 mg/kg), followed by endotracheal intubation. Anesthesia was maintained using one of the studied inhalational agents (halothane, isoflurane, or sevoflurane), in addition to supplemental doses of fentanyl and atracurium as required.

Intraoperative Monitoring and Measurements

The following parameters were monitored and recorded:

1. Heart rate and rhythm – at baseline (pre-induction) and every 10 minutes until the end of surgery
2. Invasive mean arterial pressure (MAP) – at baseline and every 10 minutes
3. Continuous ST segment analysis – from pre-induction to end of surgery
4. Oxygen saturation and end-tidal CO_2 – from pre-induction and every 10 minutes intraoperatively
5. Cardiac biomarkers (CPK, CKMB, Troponin) – sampled preoperatively (day before surgery)

Fluid Therapy

Intraoperative fluid management was performed using lactated Ringer's solution, calculated according to the patient's body weight.

Emergence and Postoperative Period

At the conclusion of surgery, inhalational agents were discontinued at the time of skin closure. Patients received 100% oxygen, and neuromuscular blockade was reversed with neostigmine (0.07 mg/kg) and atropine (0.01 mg/kg). Extubation was performed once the patient met standard clinical criteria.

Postoperative measurements of CPK, CKMB, and troponin were taken in the recovery room and repeated on the second postoperative day.

Ethical approval

The study had the approval of the Institution Review Board (IRB) at Zagazig University. Also, approved from Anesthesia, ICU and Pain Management Department of Zagazig University. Scientific committee obtained patients or first-degree relatives' written consent. This work has been performed by The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All statistical analyses were performed using SPSS version 27. Normality was tested using the Shapiro-Wilk test and the Kolmogorov-Smirnov Normality Test. ANOVA, Kruskal-Wallis test, followed by the Mann-Whitney test, Chi-square test, Fisher's Exact test and General Linear Model were used. The statistical significance level was set at $P<0.05$.

RESULTS

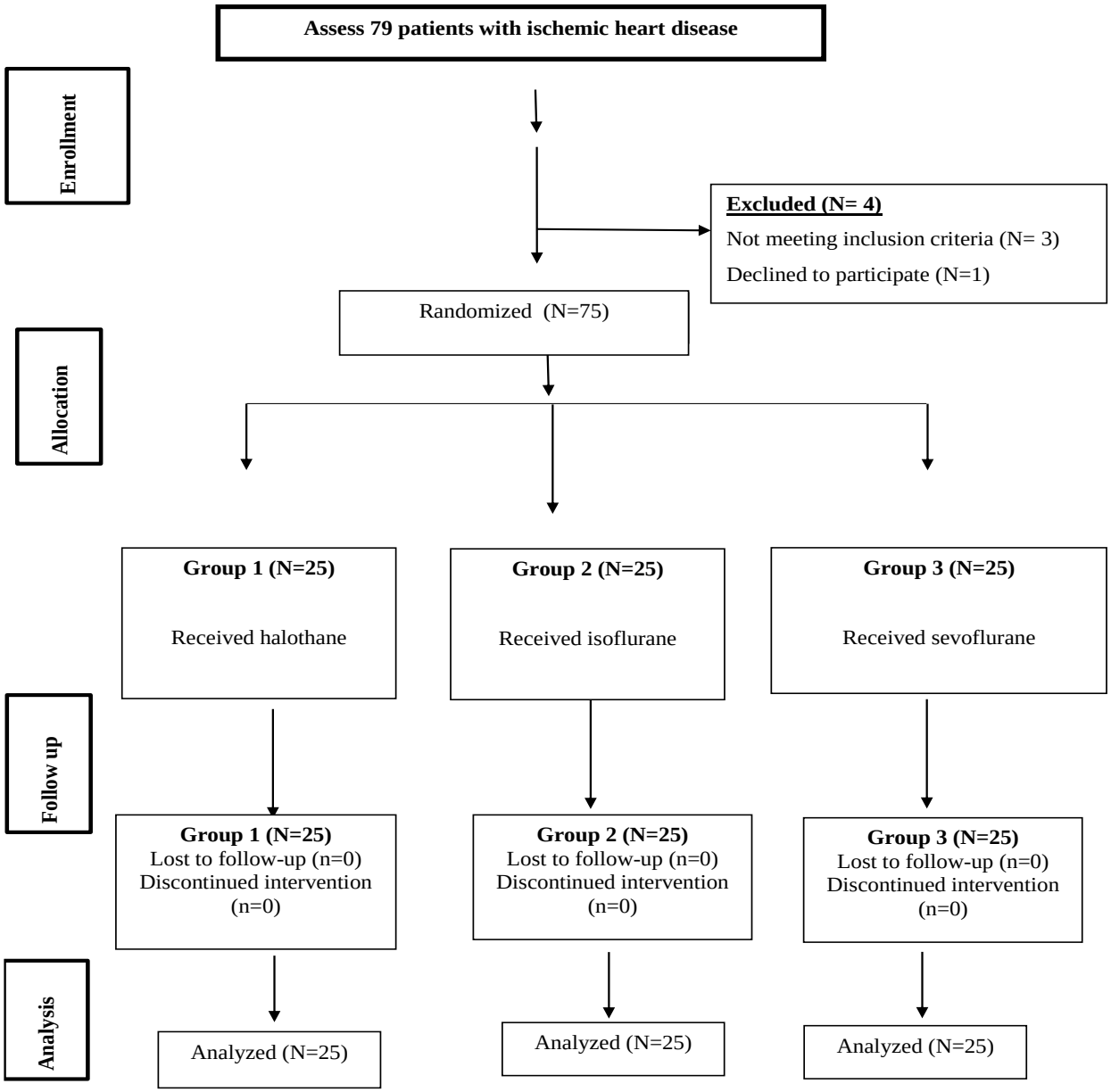

Figure (1): Study flowchart.

The study included 75 patients, 25 in each group of ASA grade II or III of both sexes. The duration of the study was from 1 to 2 years (fig 1).

The study was conducted on 75 patients, consisting of 56 male patients and 19 female patients. The patients' body weight ranged from 60 to 90 kgs and their age ranged from 40 to 70 years old.

Table (1): Patient characteristics, duration of anesthesia and type of operation.

		Halothane	Isoflurane	Sevoflurane
Number of patients		25	25	25
Sex: Male/Female		18/7	19/6	19/6
Age (year)		56.5 ± 8.5	54.7 ± 7.6	57 ± 3.1
Body weight (kg)		79.7 ± 7.8	75.3 ± 9.6	70 ± 8.6
Duration of anesthesia (min)		95.8 ± 7.8	99.3 ± 9.6	101.3 ± 9.6
Type of operation	Umblilical hernia	7	8	7
	Open cholecystectomy	6	6	5
	Thyroidectomy	5	4	4

*This table is expressed as mean ± standard deviation (SD).

Table (2): End Tidal CO_2 (mmHg) recorded at different times of the study for all groups.

	Halothane	Isoflurane	Sevoflurane	(P. value)
Preinuduction	35.5 ± 1.1	35.3 ± 0.9	35.9 ± 1.2	0.23
10 minutes	36.1 ± 1.18	36.5 ± 0.8	36.8 ± 0.6	0.08
20 min	37.3 ± 0.76	37 ± 0.8	37.1 ± 1.2	0.53
30 min	37.3 ± 0.7	37.1 ± 0.9	37.1 ± 0.7	0.52
40 min	37.7 ± 1.3	37.6 ± 0.8	36.5 ± 0.7	0.24
50 min	36.7 ± 0.9	36.7 ± 1.1	37.5 ± 1.3	0.63
60 min	37 ± 0.8	37.6 ± 1.3	37.7 ± 0.6	0.13
70 min	37.2 ± 0.9	37.5 ± 0.9	37.5 ± 0.8	0.67
80 min	38 ± 1.1	37.8 ± 1.4	37.5 ±1.2	0.67
90 min	37.5 ± 0.85	37.7 ± 1.3	38 ± 1.1	0.77
100 min	38.1 ± 0.85	38.5 ± 0.7	38.3 ± 0.8	0.76
110 min	38.2 ± 1.1	37.6 ± 1.3	37.6 ± 0.7	0.68
120 min	40 ± 0.8	40 ± 0.8	40 ± 0.08	0.66

*This table is expressed as mean ± SD. P value >0.05 is considered non-significant.

Table 2 shows that there was no significant difference between the 3 groups at different times of the study regarding End Tidal CO2 values.

Table (3): O2 saturation recorded at different times of the study for all groups.

	Halothane	Isoflurane	Sevoflurane	(P. value)
Preinuduction	98.5 ± 1.2	98.2 ± 1	98.1 ± 1.1	0.49
10 minutes	98.5 ± 1.1	99.1 ± 0.85	98.3 ± 1.2	0.66
20 min	99 ± 1	99.8 ± 0.4	98.6 ± 0.9	0.67
30 min	98.6 ± 1.1	99.1 ± 0.7	98.6 ± 0.9	0.76
40 min	98.5 ± 1	98.9 ± 0.8	99.1 ± 0.8	0.08
50 min	98.6 ± 0.9	98.8 ± 0.76	98.9 ± 0.85	0.53
60 min	98.6 ± 1.3	98.9 ± 0.06	98.5 ± 0.7	0.36
70 min	98.5 ± 1.2	98.8 ± 0.6	98.5 ± 0.09	0.66
80 min	98.7 ± 1.1	99.2 ± 0.8	98.9 ± 0.97	0.27
90 min	98.5 ± 0.9	98.9 ± 0.7	99.2 ± 1	0.66
100 min	98.8 ± 1.1	98.9 ± 0.86	99 ± 1	0.81
110 min	98.7 ± 0.9	99.3 ± 0.08	98.9 ± 0.97	0.73
120 min	99.5 ± 1.1	99.3 ± 0.5	99.8 ± 0.4	0.74

*This table is expressed as mean ± SD, P value >0.05 is considered non-significant.

Table 3 shows that there was no significant difference between all groups regarding the peripheral oxygen saturation (Spo2) recorded at different times of the study.

Table (4): Heart rate recorded at different times of the study for all groups.

	Halothane	Isoflurane	Sevoflurane	(P. value)
Preinuduction	79.2 ± 4.7	78.8 ± 2.3	77.9 ± 1.2	0.389
10 minutes	78.2 ± 4.9	80 ± 2.4	77.5 ± 1.5	0.056
20 min	78.2 ± 4.8	80.2 ± 2.5	78.4 ± 1.4	0.062
30 min	77.9 ± 3.1	81.2 ± 1.9	79.8 ± 1.1	0.083
40 min	79.6 ± 3.8	80.5 ± 2.8	79.3 ± 1.1	0.075
50 min	78.7 ± 3 .7	80.2 ± 3	78.5 ± 1.5	0.054
60 min	78.1 ± 4.6	80.2 ± 2.5	78.5 ± 1.4	0.054
70 min	80 ± 4.3	79.9 ± 4.4	78.3 ± 1.4	0.143
80 min	80.8 ± 3.2	80.5 ± 4.4	80.5 ± 1.7	0.085
90 min	80.3 ± 3.6	81.2 ± 3.2	80.9 ± 1.9	0.145
100 min	81.1 ± 3.6	81.2 ± 3.4	80.9 ± 1.9	0.144
110 min	81.4 ± 4.8	81 ± 4.1	80.3 ± 1.4	0.153
120 min	80 ± 2.7	81 ± 3.2	80.2 ± 1.4	0.022

*This table is expressed as mean ± SD, P value > 0.05 is considered non-significant.

As compared to *Pre-induction* values, the heart rate(beats/min) was slightly lower than post induction values in halothane group, slightly higher in isoflurane group. But slightly constant in sevoflurane group (table 4).

Table (5): cKMB values during different times of study for all groups.

cKMB (mg/ml)	Halothane	Isoflurane	Sevoflurane	(P. value)
Pre-operative	2.05 ± 0.2	2.01 ± 0.2	2 ± 0.24	0.08
Postoperative in recovery room	2.63 ± 0.6	2.01 ± 0.3	2.01 ± 0.2	**0.001**
Post-operative in the day of surgery	2.67 ± 0.56	1.98 ± 0.2	1.93 ± 0.1	**0.001**

*This table is expressed as mean ± SD. P value > 0.05 is considered non-significant.

Although there was no significant difference between the groups regarding preoperative levels of cKMB, post-operative assessments in the recovery room showed a significant increase in halothane group compared to isoflurane and sevoflurane group. On the day of surgery, cKMB levels remained elevated in halothane group, while isoflurane and sevoflurane groups showed slight decreases respectively, with the difference still being statistically significant (table 5).

Table (6): Tropnin quantity results during different times of study for all groups.

Tropinin quantity (mg/ml)	Halothane	Isoflurane	Sevoflurane	P value
Preoperative	0.006 ± 0.004	0.013 ± 0.01	0.06 ± 0.05	0.09
Postoperative in recovery room	0.016 ± 0.02	0.014 ± 0.06	0.058 ± 0.056	0.013
Postoperative in 2nd day of surgery	0.045 ± 0.08	0.014 ± 0.07	0.06 ± 0.057	0.016

*This table is expressed as mean ± SD. P value > 0.05 is considered non-significant.

Halothane shows a rising troponin quantity, while Isoflurane and Sevoflurane exhibits stable levels upon times of study (table 6).

DISCUSSION

In the present study, there was no statistically significant difference in end-tidal carbon dioxide ($EtCO_2$) values among the halothane, isoflurane, and sevoflurane groups at various intraoperative time points. These results align with the findings of **Soliman and Abukhudair** [9], who similarly observed no significant difference in $EtCO_2$ levels between isoflurane and sevoflurane groups ($P > 0.05$). Similarly, peripheral oxygen saturation (SpO_2) remained consistent across all three anesthetic groups, with no significant intraoperative fluctuations. These observations are supported by both **Soliman and Abukhudair** [9] and **Jones *et al.*** [10] who found no significant difference in SpO_2 between sevoflurane and isoflurane during general anesthesia.

Regarding hemodynamic responses, we observed a slight reduction in heart rate after induction in the halothane group, a modest increase in the isoflurane group, and relative stability in the sevoflurane group. These findings are consistent with a prospective study by **Hama *et al.*** [11] which found no significant differences in heart rate or mean blood pressure between sevoflurane and isoflurane during various intraoperative intervals.

Similarly, **Mai *et al.*** [12] demonstrated comparable hemodynamic stability—heart rate and blood pressure—between sevoflurane and isoflurane in adult patients undergoing off-pump coronary bypass surgery, with sevoflurane showing slightly more stable parameters.

Preconditioning effects have also been observed: **Dharmalingam *et al.*** [13] reported similar intraoperative hemodynamic indices in patients receiving sevoflurane versus isoflurane during cardiac surgery, with no meaningful intergroup differences in heart rate or mean arterial pressure. These recent findings reaffirm that sevoflurane and isoflurane produce comparable cardiovascular effects intraoperatively, both in cardiac and non-cardiac settings, echoing earlier conclusions based on modern clinical data.

Soliman and Abukhudair [9] reported that isoflurane was associated with increases in heart rate, mean arterial pressure, cardiac index, and systemic and pulmonary vascular resistance, potentially increasing myocardial oxygen demand and exacerbating ischemia.

Conversely, sevoflurane was associated with reductions in these parameters, decreasing cardiac workload and preserving myocardial oxygen balance. This protective mechanism was supported by electrocardiographic findings and lower elevations of troponin I and CK-MB. These outcomes are consistent with the findings of **Sarkar *et al.*** [14], **Venkatesh *et al.*** [15], and **Jones *et al.*** [10], who found no significant differences in heart rate, blood pressure, central venous pressure, systemic vascular resistance, or cardiac index among the three volatile anesthetics. **Diana *et al.*** [16], using transesophageal echocardiography and coronary sinus lactate sampling, also reported no difference in intraoperative myocardial ischemia incidence between sevoflurane and isoflurane.

In the present study, no significant differences were found in preoperative CK-MB levels among the

halothane, isoflurane, and sevoflurane groups. However, postoperative measurements revealed a significant elevation in CK-MB levels in the halothane group, while the isoflurane and sevoflurane groups showed only minor changes.

These findings are supported by **Patel *et al.*** [17], who demonstrated that patients receiving sevoflurane during non-cardiac surgery had significantly lower postoperative CK-MB and troponin-I levels compared to those given isoflurane, reflecting a more favorable cardiac enzyme profile.

Similarly, **Zhang *et al.*** [18] observed that isoflurane was associated with modest elevations in CK-MB relative to sevoflurane, though without reaching clinical significance in myocardial infarction rates. **Nguyen *et al.*** [19] also reported that sevoflurane maintained more stable intraoperative heart rates and reduced myocardial oxygen consumption compared to isoflurane, resulting in diminished postoperative CK-MB levels.

A meta-analysis by **Kumar *et al.*** [20] of 12 randomized controlled trials concluded that sevoflurane significantly reduced postoperative CK-MB and troponin I levels compared to both isoflurane and total intravenous anesthesia. These findings reinforce the cardioprotective advantage of sevoflurane over isoflurane and halothane regarding cardiac enzyme release.

Li *et al.* [21] and **Yang *et al.*** [22] showed that sevoflurane was associated with lower troponin I levels and improved cardiac output compared to propofol. **Landoni *et al.*** [23] further demonstrated that both sevoflurane and desflurane reduce postoperative myocardial infarction, mortality, and cardiac biomarker release, while also shortening ICU and hospital stays.

Although **Patel *et al.*** [17] reported slightly lower postoperative troponin T levels in patients receiving isoflurane, the difference was not clinically significant, as no differences in major outcomes such as myocardial infarction or mortality were observed. Moreover, a 2022 meta-analysis by **Li *et al.*** [24] found that sevoflurane significantly reduced cardiac troponin T levels 12–24 hours postoperatively compared with propofol, and was associated with a reduced incidence of atrial fibrillation and shorter ICU stays.

The mechanisms underlying sevoflurane's myocardial protection include the absence of the coronary steal phenomenon [25], lower intraoperative heart rates [26], enhanced myocardial depression during surgical stress, ischemic preconditioning, ATP preservation during reperfusion, and anti-inflammatory effects during cardiopulmonary bypass [27].

A study by **Kiani *et al.*** [28] supports that isoflurane preconditioning also reduces postoperative cardiac enzyme release, while **Hemmerling *et al.*** [29] suggested that both isoflurane and sevoflurane offer comparable protection in off-pump coronary artery bypass surgery. Based on this growing body of evidence, the American College of Cardiology and American Heart Association recommend volatile anesthetics for maintaining anesthesia in patients at risk of myocardial infarction during non-cardiac surgery (Class IIa, Level of Evidence B) [23].

A meta-analysis by **Fochi *et al.*** [30], involving 79 randomized trials and over 6000 patients, found no reported myocardial infarctions or deaths associated with either volatile anesthetics or TIVA during non-cardiac surgery, confirming the safety of both. However, **Testa *et al.*** [31] reported significantly lower postoperative troponin I levels in patients receiving sevoflurane compared to propofol, highlighting a possible myocardial protective benefit even in smaller-scale randomized studies.

CONCLUSION

For patients with underlying cardiac disease undergoing non-cardiac surgery, sevoflurane and isoflurane appear to offer comparable intraoperative respiratory and hemodynamic profiles. However, sevoflurane demonstrates a more favorable cardiac enzyme response and a stronger cardioprotective effect, making it a potentially safer choice in reducing myocardial stress and injury in this high-risk population.

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