Cardiothoracic Anesthesia, Respiration and Airway

The effects of volatile anesthetics on cardiac ischemic complications and mortality in CABG: a meta-analysis

[Les effets des anesthésiques volatils sur les complications ischémiques et la mortalité cardiaques pendant le PAC : une méta-analyse]

Chun Hua Yu MD,* W. Scott Beattie MD PhD FRCPC†

Purpose: Coronary artery bypass graft surgery (CABG) is associated with cardiac complications, including ischemia, acute myocardial infarction (AMI), and death. Volatile anesthetics have been shown to have a preconditioning-like effect. This systematic review assesses the effects of volatile anesthetics on cardiac ischemic complications and morbidity after CABG.

Methods: Data were obtained, without language restriction, from searches of MEDLINE, Science Citation Index, PubMed, and reference lists. We included only prospective randomized controlled trials evaluating volatile anesthetics during CABG. Two reviewers independently abstracted data on myocardial ischemia, acute myocardial infarction (AMI), and death. Treatment effects were calculated as odds ratio (OR) with 95% confidence intervals (CI) for binary data, and weighted mean difference (WMD) with 95% CI for continuous data.

Principal findings: Thirty-two studies (2,841 patients) were included. In comparison with *iv* anesthesia, volatile anesthetics were associated with reduced all-cause mortality (OR, 0.65; 95% CI, 0.36–1.18; $P = 0.16$). Enflurane was associated with increased AMI (OR, 1.34; 95% CI, 0.68–2.64; $P = 0.40$), whereas sevoflurane and desflurane reduced cardiac troponin I (cTnI) at six hours, 12 hr, 24 hr [WMD, -1.45; 95% CI (-1.73, -1.16); $P < 0.00001$], and 48 hr after operation.

Conclusion: This meta-analysis demonstrates sevoflurane and desflurane reduce the postoperative rise in cTnI. Sevoflurane-mediated reduction in cardiac troponin was associated with improved long-term outcomes in one study. This meta-analysis was not able to show that these positive effects on troponin were translated into improved clinical outcomes. Well-designed large randomized control trials are needed to further elucidate the differential cardio-protective effects of volatile anesthetics.

Objectif *: Le pontage aortocoronarien (PAC) est associé à des complications cardiaques comme l'ischémie, l'infarctus aigu du myocarde (IAM) et la mort. Un effet semblable à celui du préconditionnement a été démontré avec les anesthésiques volatils. Dans la présente revue systématique, nous évaluons les effets des anesthésiques volatils sur les complications ischémiques et la morbidité cardiaques après un PAC.*

Méthode *: Les données obtenues, sans restriction de langue, proviennent de MEDLINE, Science Citation Index, PubMed et des listes de références. Seules les études prospectives, randomisées et contrôlées qui évaluent les anesthésiques volatils pendant le PAC ont été retenues. Deux réviseurs indépendants ont résumé les données sur l'ischémie myocardique, l'IAM et la mort. Les effets ont été calculés par le risque relatif approché (RRA) avec un intervalle de confiance (IC) de 95 % pour les données binaires et la différence moyenne pondérée (DMP) avec un IC de 95 % pour les données en continu.*

Constatations principales *: Trente-deux études, sur 2 841 patients, ont été retenues. Comparés aux anesthésiques iv, les anesthésiques volatils réduisent toutes les causes de mortalité (RRA de 0,65 ; IC de 95 %, 0,36 – 1,18 ; P = 0,16). L'enflurane*

From the Departments of Anesthesia, University Health Network,* and the University of Toronto,† Toronto, Ontario, Canada.
Address correspondence to: Dr. W. Scott Beattie, University of Toronto, EN 3-456, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada. E-mail: scott.beattie@uhn.on.ca
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augmente l'IAM (RRA de 1,34 ; IC de 95 %, 0,68 – 2,64 ; P = 0,40), tandis que le sévoflurane et le desflurane réduisent la troponine cardiaque I (cTnI) à six heures, 12 h, 24 h [DMP, -1,45 ; IC de 95 % (-1,73, -1,16) ; P < 0,00001] et 48 h après l'opération.

***Conclusion** : Cette méta-analyse démontre que le sévoflurane et le desflurane réduisent la hausse postopératoire de cTnI. La réduction de troponine cardiaque induite par le sévoflurane est associée à une meilleure évolution à long terme dans l'une des études. La méta-analyse n'a pu montrer que ces effets positifs sur la troponine présentaient des avantages cliniques. De grandes études bien définies randomisées et contrôlées devront élucider les effets cardio-protecteurs différentiels des anesthésiques volatils.*

DESPITE advances in surgical techniques and anesthetic management, coronary artery bypass graft surgery (CABG) remains associated with significant complications, including myocardial ischemia, acute myocardial infarction (AMI), and death. Strategies that reduce these events should therefore improve overall outcomes. Preconditioning is a powerful mode of reducing myocardial infarction size after ischemia[1,2] and represents an adaptive endogenous response to brief episodes of ischemia or to pharmacological interventions leading to paradoxical pronounced protection against subsequent ischemia. Pharmacological induction of preconditioning, in contrast to classical ischemic preconditioning, would therefore be greatly desirable, specifically in high-risk patients in whom an ischemic-type of preconditioning may further jeopardize diseased myocardium. Volatile anesthetics, which are known to improve post-ischemic recovery[3] and to decrease myocardial infarction size,[4] effectively activate protective cellular mechanisms. Notably, the protective effect of volatile anesthetics occurs even in the presence of already established cardioplegic protection.[5,6] Volatile anesthetics have been shown to have a preconditioning-like effect by selectively priming mitochondrial adenosine triphoshate-sensitive potassium (K_{ATP}) channels through multiple triggering protein kinase C-coupled signalling pathways.[1]

To date, no study of volatile anesthetics has possessed the statistical power to show altered morbidity. The purpose of this systematic review was to assess the effects of volatile anesthetics on cardiac ischemic complications and morbidity after CABG. We reasoned that if volatile mediated preconditioning was clinically significant, an effect should be demonstrated in trials that evaluated cardiac outcomes.

Methods

We conducted a systematic review according to the Quality of Reporting of Meta-analysis (QUOROM)[7] recommendations for improving the quality of meta-analyses.

Eligible studies were published randomized controlled trials (RCTs) that evaluated volatile anesthetics during CABG, and reported myocardial ischemia as outcomes. Acceptable definitions for ischemia included cardiac troponin I (cTnI) concentration elevation, ST segment deviation on an electrocardiogram, new wall-motion abnormalities on a transesophageal echocardiogram (TEE), creatine kinase myocardial band (CK-MB) enzyme elevation, myocardial lactate production, myocardial lactate extraction (%), and myocardial oxygen consumption ($MV0_2$) change. We collated the incidence of AMI, and death. Studies were excluded if they were not RCTs, if they exclusively recruited individuals younger than 18 yr, or if the control group did not receive *iv* anesthesia. When required, authors of included studies were contacted to provide additional data.

We identified published RCTs by searching MEDLINE (1966 to December 2005) for [(isoflurane OR sevoflurane OR desflurane OR enflurane OR halothane) AND (cardiac surgical procedures OR coronary artery OR cardiac surgery)] without language restriction. Titles and abstracts were screened to exclude obviously ineligible studies (Figure 1). Two reviewers independently read the remaining papers in full to determine final eligibility. Reasons for exclusion were documented for all excluded studies. Bibliographies were surveyed to identify any further eligible papers. Included papers were entered into the Science Citation Index and PubMed (related articles search) to identify other relevant studies. The reviewers evaluated the quality of included studies with regard to the adequacy of randomization, allocation concealment, blinding, and handling of dropouts.

The reviewers abstracted onto standardized data collection forms: demographics, preoperative data (cardiac function, prior medication), anesthesia intervention, hemodynamic changes, intraoperative data (number of grafts, aortic cross clamp time, cardiopulmonary bypass time, pH and potassium of the patient, lowest temperature during cardiopulmonary bypass, weaning temperature), myocardial ischemia, as well as perioperative complications, including myocardial infarction and death. We abstracted data for comparison of volatile anesthetics against *iv* anesthetics. All disagreements were resolved by consensus.

Statistical analyses were performed using RevMan 4.2 (Cochrane Collaboration, Oxford, UK).

Treatment effects were expressed as pooled odds ratio (OR) with 95% confidence intervals (CI) for binary data, and weighted mean difference (WMD) with 95% CI for continuous data. Initially, we assessed for heterogeneity using the Q-statistic, with the cutoff for statistically significant heterogeneity set at $P < 0.1$. Heterogeneity is defined as greater variation between the results of trials than would be expected by chance, assuming a single underlying treatment effect for all included trials. In the absence of significant heterogeneity, pooled ORs or WMDs were calculated under the fixed effects model. If there was statistically significant heterogeneity, the random effects model was used instead; in addition, we performed post hoc analyses to explain the observed heterogeneity. Statistical significance for treatment effects was defined by $P < 0.05$.

In the primary analyses, pooled ORs were calculated for the effects of volatile anesthetics on death, AMI, evidence of ischemia [e.g., electrocardiogram (ECG) ST-T change, myocardial lactate production]. Pooled WMDs were calculated for the effects of volatile anesthetics on evidence of ischemia (cardiac troponin change, CK-MB, myocardial lactate, and $MV0_2$ change). Secondary analyses were planned *a priori*. We calculated the effect of each anesthetic on myocardial ischemia, AMI, and mortality. Given that prior medication use may influence perioperative outcomes, we also compared the prior use of -adrenergic blocking drugs and calcium antagonists in the volatile anesthetics and control arms using meta-analytic methods. Medication use differences were expressed as pooled ORs using the fixed effects model.

Due to the small number of outcomes, we performed post hoc analyses that used combined outcomes: MI or death, (death due to an MI was counted once). We also analyzed the effects of volatile anesthetics on the combined outcome of major morbid events (MME) where MME was defined as death, MI, or congestive heart failure.

Additional sensitivity analyses were also planned *a priori*. The sensitivity analyses examined the influence of statistical model on estimated treatment effects. Analyses that used the fixed effects model were repeated using the random effects model.

Results

The search results are presented in Figure 1. Thirty-two studies,[8–39] encompassing 2,841 patients, were included (Table I). Four studies were double blinded. Six studies were evaluator blinded. Eleven studies evaluated isoflurane, nine studies evaluated sevoflurane, three studies evaluated desflurane, 11 studies evaluated enflurane, and four studies evaluated halothane. Two studies incorporated three arms: control, sevoflurane, and desflurane.[19,25] One study incorporated: control, isoflurane, and enflurane.[10] One study incorporated: control, isoflurane, and halothane.[9] One study incorporated four arms: control, isoflurane, enflurane, and halothane.[12] Some studies had more than one *iv* anesthetic group. In the event of more than one *iv* control, we arbitrarily chose the group in which opioid utilization was the least. Of the 32 studies, 93% were published in the English language.

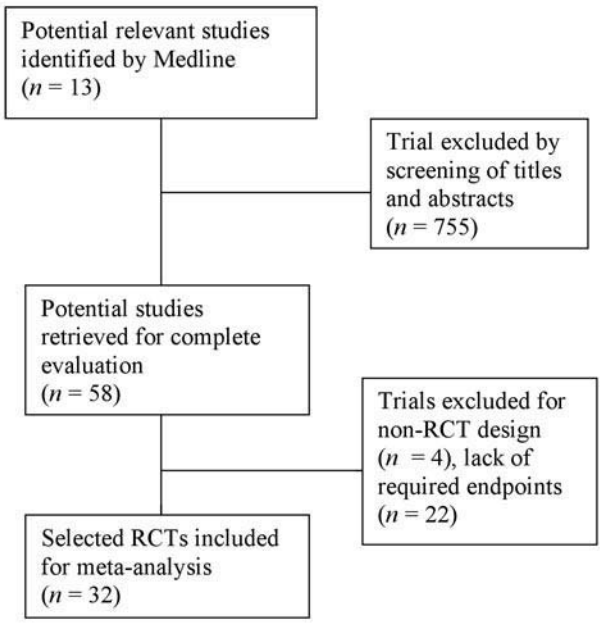

FIGURE 1 Flow (QUORUM) diagram of meta-analysis. RCT = randomized controlled trials.

The preoperative and operative characteristics of the study and control groups are presented in Table II. There were no differences in baseline characteristics including age, weight, preoperative ejection fraction, proportion of the population with three vessel disease, and the incidence of calcium channel blocker use. Beta-blocker utilization was 28% higher in the *iv* groups ($P = 0.03$). A post hoc analysis of narcotic utilization could not demonstrate a difference in the type or dose between treatment arms.

Ten studies reported mortality rates (Figure 2), for which the overall mortality among 2,338 patients was 2% ($n = 45$). The observed reduction in mortality did not achieve statistical significance (OR, 0.65;

TABLE I Characteristics of included studies

Study	*n*	*Inhalation group*	*Drug and dose*	*Control*	*Method ischemia detected*	*Blinded*	*Lang.*	*Year*
Haessler R (8)	58	Isoflurane	After induction, 0.4-1.2 vol% Isoflurane-N_2O until pre CPB. Fentanyl 10 $\mu g \cdot kg^{-1}$ for induction, 0.8-2.0 $mg \cdot hr^{-1}$ prebypass.	Propofol- N_2O Fentanyl 10 $\mu g \cdot kg^{-1}$ for induction, 0.8-2.0 $mg \cdot hr^{-1}$ prebypass.	ECG	+	English	1993
Urzua J (9)	25	Group 1: Isoflurane Group 2: Halothane	After induction, 0-2.0% Isoflurane throughout the case. Fentanyl 30 $\mu g \cdot kg^{-1}$ After induction, 0-1.5% Halothane throughout the case. Fentanyl 30 $\mu g \cdot kg^{-1}$ for induction	Fentanyl 30 $\mu g \cdot kg^{-1}$ for induction + Fentanyl 1.5 mg	ECG CPK-MB	+	English	1996
Ramsay JG (10)	75	Group 1: Isoflurane Group 2: Enflurane	Isoflurane, after induction until prebypass. Sufentanil 5 $\mu g \cdot kg^{-1}$ for induction. Enflurane, after induction until prebypass. Sufentanil 5 $\mu g \cdot kg^{-1}$ for induction.	Sufentanil 5 $\mu g \cdot kg^{-1}$ for induction. Dose after induction was not known.	ECG	Double blinded	English	1994
Leung JM (11)	18 6	Isoflurane	Isoflurane 0.88% ± 0.31%, after induction until prebypass. Fentanyl 7.5 $\mu g \cdot kg^{-1}$.	Sufentanil 5-10 $\mu g \cdot kg^{-1}$ followed by infusion 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$	ECG TEE	Double blinded	English	1991
Slogoff S (12)	10 12	Group 1: Isoflurane Group 2: Enflurane Group 3: Halothane	Isoflurane, from induction to the end. Fentanyl 10 $\mu g \cdot kg^{-1}$. Enflurane, from induction to the end. Fentanyl 10 $\mu g \cdot kg^{-1}$. Halothane, from induction to the end. Fentanyl 10 $\mu g \cdot kg^{-1}$.	Sufentanil 15-20 $\mu g \cdot kg^{-1}$ followed by Sufentanil 5 $\mu g \cdot kg^{-1}$	ECG CPK-MB	+		1989
Tomai F (13)	40	Isoflurane	Fentanyl 30 $\mu g \cdot kg^{-1}$ for induction. Before starting CPB, isoflurane was added to the inspired oxygen for about 15 min, followed by a 10-min wash-out period.	Fentanyl: 30 $\mu g \cdot kg^{-1}$ for induction, repeat before CPB	cTnI CK CK-MB	Not known	English	1999
Haroun-Bizri S (14)	49	Isoflurane	Midazolam 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + sufentanil 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ + Isoflurane 0.5-2.0%	Midazolam 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + sufentanil 1 $\mu g \cdot kg^{-1} \cdot hr^{-1}$	ECG	+	English	2001
Driessen JJ (15)	30	Isoflurane	Isoflurane 0.6% + fentanyl 70 $\mu g \cdot kg^{-1}$ (total)	Midazolam + fentanyl 70 $\mu g \cdot kg^{-1}$ (total)	ECG CK-MB	Not known	English	1997
Procaccini B (16)	20	Isoflurane	Isoflurane 1.0% + fentanyl 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during prebypass period, 0.11 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during postbypass period.	Propofol infusion + fentanyl 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during prebypass period, 0.11 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during postbypass period.	ECG	Not known	Italian	1996
Wang X (17)	34	Isoflurane	Same as control group + 5 min Isoflurane exposure after cannulation.	Induction: propofol 0.5-1.0 $mg \cdot kg^{-1}$ + sufentanil 0.8-1.0 $\mu g \cdot kg^{-1}$ Maintenance: propofol 4-8 $mg \cdot kg^{-1} \cdot hr^{-1}$ + sufentanil 0.03-0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$.	cTnI CK-MB	Not known	English	2004
Conzen PF (18)	20	Sevoflurane	2% sevoflurane + sufentanil 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Propofol 2-3 $\mu g \cdot mL^{-1}$ + sufentanil 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$	cTnI CK CK-MB	Not known	English	2003

TABLE I - *continued*

Study	*n*	*Inhalation group*	*Drug and dose*	*Control*	*Method ischemia detected*	*Blinded*	*Lang.*	*Year*
De Hert SG (19)	43	Group 1: Sevoflurane Group 2: Desflurane	0.5-2% sevoflurane + Remifentanil 0.3-0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 1-4% Desflurane + Remifentanil 0.3-0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Remifentanil 0.3-0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + TCI propofol	cTnI	Not known	English	2003
De Hert SG (20)	20	Sevoflurane	0.5-2% sevoflurane + Remifentanil 0.3-0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Remifentanil 0.3-0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + TCI propofol	cTnI ECG	Not known	English	2002
El Azab SR (21)	30	Sevoflurane	0.5-2% sevoflurane + sufentanil 0.7 $\mu g \cdot kg^{-1}$ + 0.2 $\mu g \cdot kg^{-1} \cdot hr^{-1}$	Sufentanil 7.0 $\mu g \cdot kg^{-1}$ + 1.0 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ + midazolam 0.12 $mg \cdot kg^{-1} \cdot hr^{-1}$	ECG	Not known	English	2000
De Hert SG (22)	100	Sevoflurane	0.5-2% sevoflurane + Remifentanil 0.2-0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Remifentanil 0.2-0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + TCI propofol	cTnI	Not known	English	2004
Pouzet B (23)	20	Sevoflurane	Sevoflurane before bypass	Midazolam + fentanyl	cTnI	+	English	2002
Julier K (24)	72	Sevoflurane	4% Sevoflurane for 10 min before cross clamp	Propofol + fentanyl (or remifentanil)	cTnI CK-MB ECG	Double blinded	English	2003
De Hert SG (25)	320	Group 1: Sevoflurane Group 2: Desflurane	0.5-2% sevoflurane + emifentanil 0.2-0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ 1-4% Desflurane + Remifentanil 0.2-0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Remifentanil 0.2-0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + TCI propofol	cTnI	Not known	English	2004
Nader ND (26)	21	Sevoflurane	Same as control group + sevoflurane 2% within the mixture used to oxygenate the cardioplegia solutions	Induction: etomidate 0.1-0.2 $mg \cdot kg^{-1}$ + fentanyl 5 $\mu g \cdot kg^{-1}$ Maintenance: propofol 100-150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ +fentanyl 2-3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$.	cTnI CK-MB TEE	Double blinded	English	2004
Helman JD (27)	200	Desflurane	1.0 MAC Desflurane + Sufentanil 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$	Sufentanil 5-10 $\mu g \cdot kg^{-1}$ + Sufentanil 0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$	ECG TEE	+	English	1992
Parsons RS (28)	51	Desflurane	1.0 MAC Desflurane + Fentanyl 10 $\mu g \cdot kg^{-1}$	Fentanyl 50 $\mu g \cdot kg^{-1}$	ECG	Not known	English	1994
Heikkila H (29)	24	Enflurane	Enflurane + Fentanyl 7.5 $\mu g \cdot kg^{-1}$	Fentanyl 100 $\mu g \cdot kg^{-1}$	ECG $Mv0_2$	Not known	English	1985
Underwood SM (30)	20	Enflurane	0.6-0.8% Enflurane + Fentanyl 20 $\mu g \cdot kg^{-1}$	Propofol + Fentanyl 20 $\mu g \cdot kg^{-1}$	MLE	Not known	English	1992
Myles PS (31)	124	Enflurane	0.2-1.0% Enflurane + Fentanyl 30 $\mu g \cdot kg^{-1}$	Propofol + Fentanyl 15 $\mu g \cdot kg^{-1}$	ECG CK-MB	Not known	English	1997
Mora CT (32)	47	Enflurane	0.25-2.0% Enflurane + Fentanyl 35 $\mu g \cdot kg^{-1}$	Propofol + Fentanyl 35 $\mu g \cdot kg^{-1}$	ECG	Not known	English	1995
Hall RI (33)	39	Enflurane	0.25-3.0% Enflurane + Sufentanil 7 $\mu g \cdot kg^{-1}$	Propofol + Sufentanil 0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$	MLP	Not known	English	1993
Heikkila H (34)	20	Enflurane	0.7% Enflurane + Fentanyl 100 $\mu g \cdot kg^{-1}$	Fentanyl 100 $\mu g \cdot kg^{-1}$	MLP MLE $Mv0_2$	Not known	English	1987
Samuelson PN (35)	35	Enflurane	1.0-2.0% Enflurane + 50% N_2O	Sufentanil 25 $\mu g \cdot kg^{-1}$	CK-MB	Not known	English	1986
Murphy T (36)	32	Enflurane	0-3.0% Enflurane + Sufentanil 10 $\mu g \cdot kg^{-1}$	Midazolam + Sufentanil 5 $\mu g \cdot kg^{-1}$	MLP ECG $Mv0_2$	Not known	English	1998
Hall RI (37)	47	Enflurane	0.25-3.0% Enflurane + Sufentanil 7 $\mu g \cdot kg^{-1}$	Propofol + Sufentanil 7 $\mu g \cdot kg^{-1}$	MLP MLE	Not known	English	1991
Moffitt EA (38)	18	Halothane	0-3.0% Halothane	Diazepam + Morphine 1 $mg \cdot kg^{-1}$	MLP MLE ECG $Mv0_2$	Not known	English	1982
Wilkinson PL (39)	26	Halothane	0.2-1.0% Halothane + 50% N_2O	Morphine 2 $mg \cdot kg^{-1}$ + 50% N_2O	ECG MLP	Not known	English	1981
Garcia C (40)	72	Sevoflurane	This is a long term follow-up of reference 24					

MLP = myocardial lactate production; MLE = myocardial lactate extraction (%); TCI = target-controlled infusion. For other abbreviations, refer to text.

TABLE II The preoperative and operative characteristics of the study and control groups

	WMD	*OR*	*95% CI*	*P value*
Age	-0.22	N/A	-0.71, 0.26	0.36
Weight	-0.33	N/A	-1.77, 1.12	0.66
Preoperative ejection fraction (%)	0.12	N/A	-0.55, 0.82	0.70
Proportion with three vessel disease	N/A	1.28	0.85, 1.93	0.23
Calcium channel blocker utilization	N/A	0.99	0.78, 1.26	0.96
β-blocker utilization	N/A	1.28	1.03, 1.60	0.03 *
α-adrenergic agonist utilization	N/A	1.14	0.80, 1.66	0.51
ACC time	-0.26	N/A	-0.91, 0.38	0.42

ACC = aortic cross clamp; OR = odds ratio; WMD = weighted mean difference; 95% CI = 95% confidence interval. $P < 0.05$; N/A = not applicable.

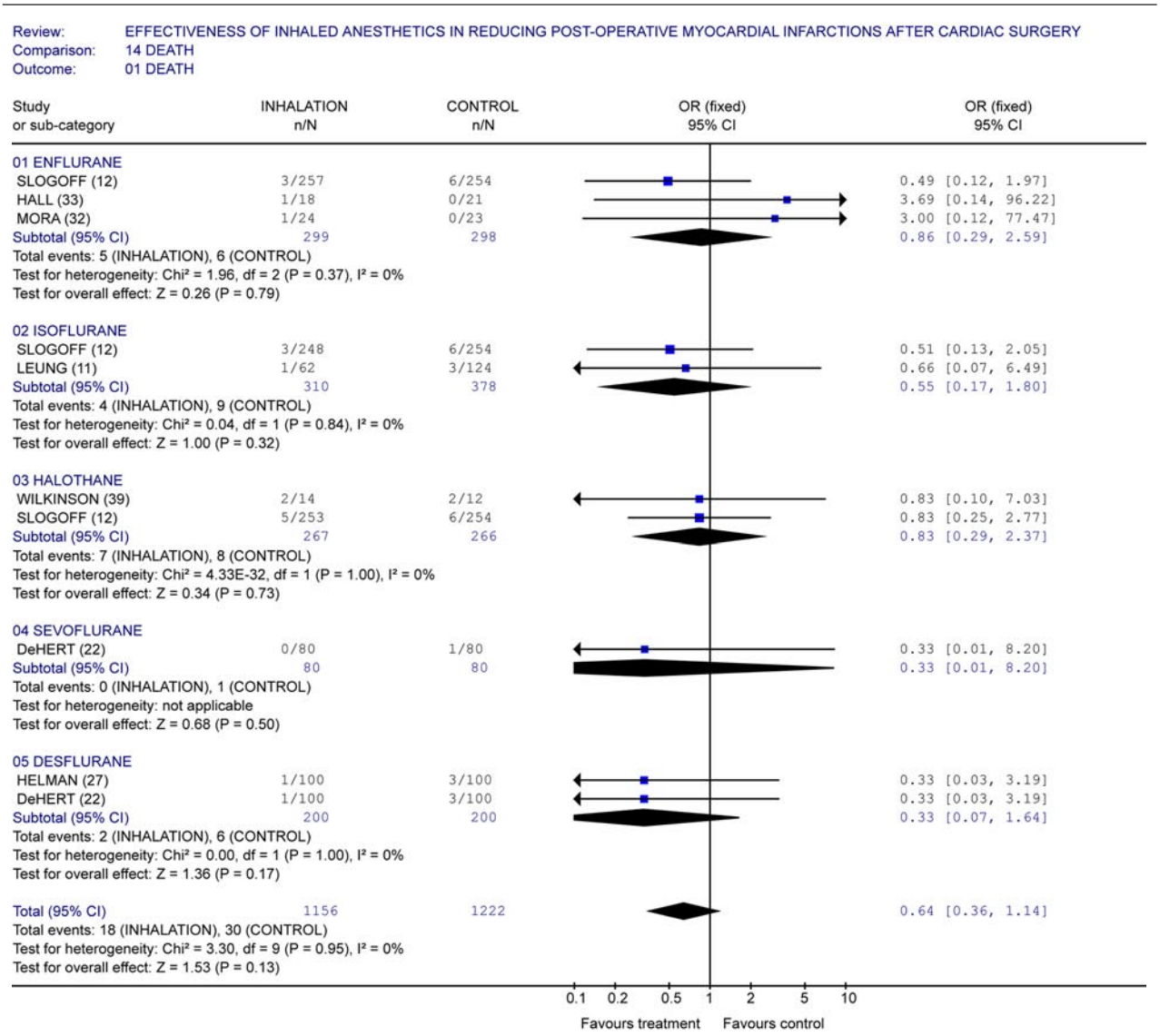

FIGURE 2 Forrest plot of the effect of volatile anesthetics on mortality. Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI). The diamonds represent overall summary estimates. RR = relative risk using the fixed effects model.

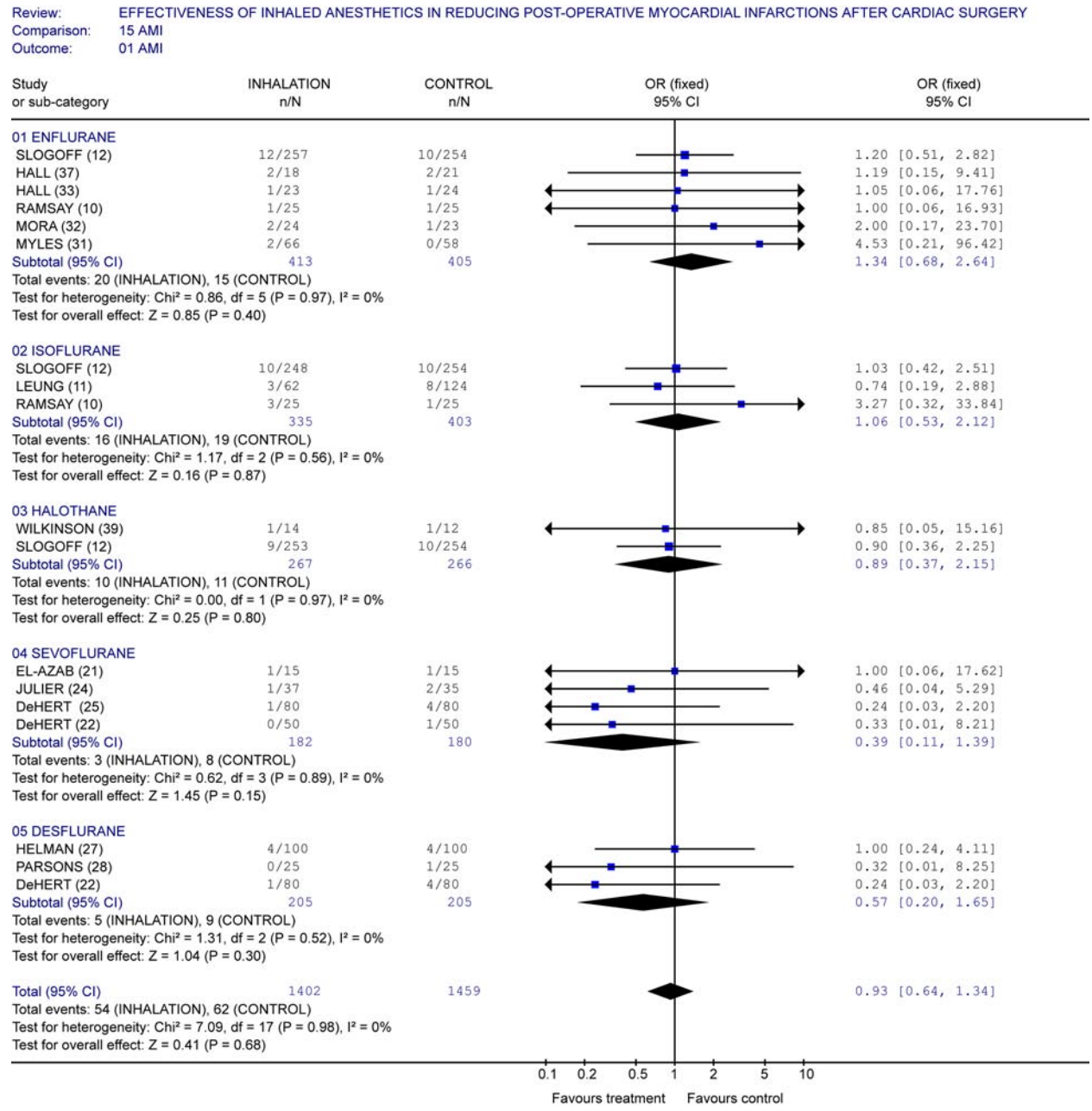

FIGURE 3 Forrest plot of the effect of volatile anesthetics on acute myocardial infarction (AMI). Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI). The diamonds represent overall summary estimates. RR = relative risk using the fixed effects model.

95% CI, 0.36–1.18; $P = 0.16$), without heterogeneity ($P = 0.96$). In the post-hoc analyses, combining sevoflurane, desflurane, and isoflurane did not show a significant reduction (OR, 0.45; 95% CI, 0.17–1.17; $P = 0.10$).

Eighteen studies reported postoperative AMI (as defined by the original authors), (Figure 3), with a 4% incidence ($n = 114$) among 2,861 patients. Volatile anesthetics did not reduce AMI (OR, 0.93; 95% CI, 0.64–1.34; $P = 0.68$) without heterogeneity (P

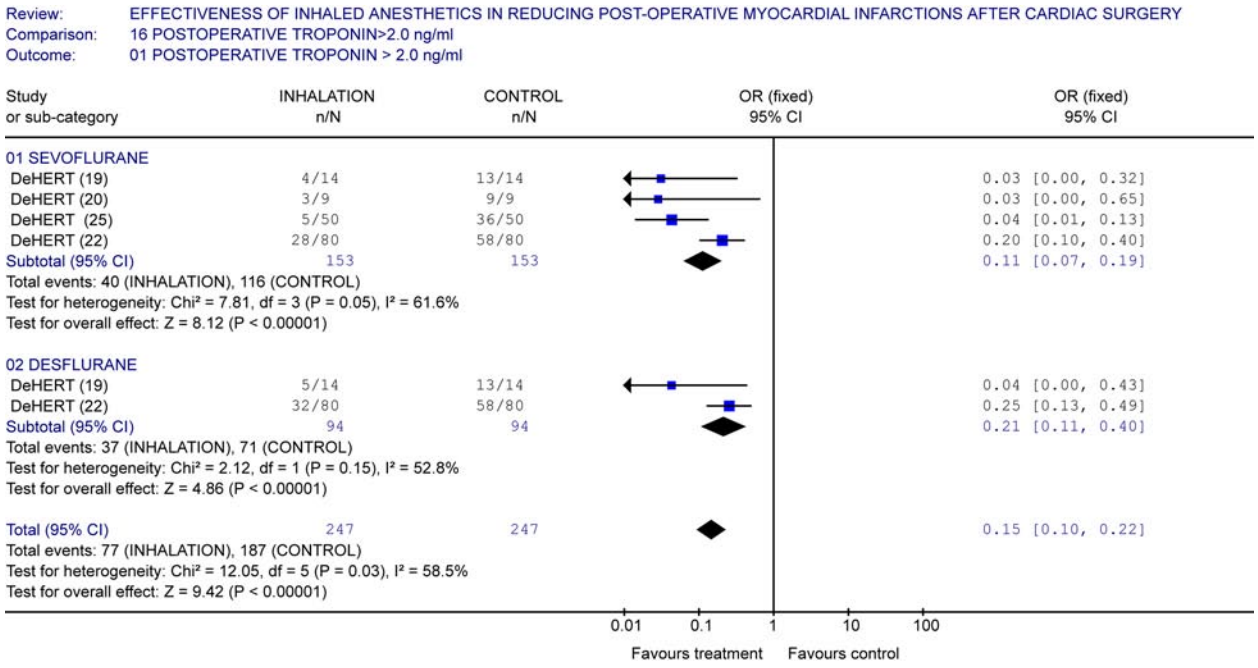

FIGURE 4 Forrest plot of the effect of volatile anesthetics on postoperative troponin I elevation (> 2 ng·mL^{-1}). Squares represent point estimates. The area of a square correlates with its contribution towards the weighted summary estimate. Horizontal lines denote 95% confidence intervals (CI), some of which extend beyond the limits of the scale. The diamonds represent overall summary estimates. RR = relative risk using the fixed effects model.

= 0.98). The pooled OR of all volatile anesthetics except enflurane was less than 1, however, enflurane was increased (OR, 1.34; 95% CI, 0.68–2.64; P = 0.40) without heterogeneity, P = 0.97). The post hoc analyses, where the newer agents sevoflurane and desflurane were combined, resulted in a reduced AMI rate (OR, 0.48; 95% CI, 0.21–1.09; P = 0.08). Sevoflurane and desflurane groups had significantly fewer patients whose postoperative troponin I increase exceeded 2 ng·mL^{-1} (Figure 4), (OR, 0.18; 95% CI, 0.12–0.26; P < 0.0001) without heterogeneity (P = 0.29).

Twelve studies reported alterations of cTnI. In five studies cTnI change occurred at the end of surgery, and in ten studies cTnI change occurred within six hours after the operation (T6). Details of the cTnI changes are presented in Table III. Sevoflurane and desflurane were associated with significant reductions of cTnI at T0, T6, T12, T24, and T48, whereas cTnI changes in association with isoflurane were not statistically significant. The heterogeneity, which we observed in this analysis, was significantly reduced when one study,[20] where all patients in the control group had significant elevations in postoperative troponin, was eliminated from the analysis. Exclusion of this study from the analysis did not negate the significant reduction in troponin [WMD, -1.31; 95% CI (-1.60, -1.01); P < 0.00001] heterogeneity (P = 0.21).

Nineteen studies reported ischemic ECG ST-T changes, with an incidence of 24% (n = 611) among 2,555 patients. Volatile anesthetics were not associated with an increased incidence of ST-T changes (OR, 1.15; 95% CI, 0.95–1.38; P = 0.15) without heterogeneity (P = 0.92).

Twelve studies reported perioperative CK-MB concentrations, with no effect of volatile anesthetics on CK-MB (WMD, 0.34; 95% CI, (-0.35, 0.83); P = 0.11). Three studies reported TEE changes (one study for desflurane, one study for isoflurane, and one study for sevoflurane), one study reported ECG ST segment changes (mm), and one study reported CK-MB elevation. There were insufficient data to perform statistical analyses.

Seven studies, assessing enflurane and halothane, reported myocardial lactate production, with an incidence of 28% (n = 108) among 389 patients. Enflurane was associated with increased myocardial lactate pro-

TABLE III Effect of volatile anesthetics on postoperative cTnI change

cTnI	*Sevoflurane*				*Desflurane*				*Isoflurane*				*Overall*			
Postop	*WMD*	*95% CI*	*P*	*HG*	*WMD*	*95% CI*	*P*	*HG*	*WMD*	*95% CI*	*P*	*HG*	*WMD*	*95% CI*	*P*	*HG*
0 hrs	-0.68	-0.88, -0.48	$P < .00001$*	+	-0.80	-1.13, -0.47	$P < .00001$*	N/A	-0.10	-0.63, 0.43	$P = 0.71$	N/A	-0.66	-0.82, -0.49	$P < .00001$*	+
6 hrs	-0.93	-1.03, -0.83	$P < .00001$*	+	-0.71	-1.15, -0.27	$P = 0.002$*	-	-1.27	-3.33, 0.78	$P = 0.22$	-	-0.92	-1.01, -0.83	$P < .00001$*	+
12 hrs	-2.38	-2.71, -2.05	$P < .00001$*	+	-0.90	-1.36, -0.44	$P = 0.0001$*	-	-0.40	-2.55, 1.75	$P = 0.72$	N/A	-1.70	-1.96, -1.45	$P < .00001$*	+
24 hrs	-1.67	-2.01, -1.43	$P < .00001$*	+	-0.91	-1.43, -0.38	$P = 0.0007$*	-	-0.48	-1.08, 0.12	$P = 0.12$	-	-1.27	-1.53, -1.01	$P < .00001$*	+
48 hrs	-1.76	-1.97, -1.55	$P < .00001$*	+	-0.80	-1.16, -0.44	$P < 0.0001$*	N/A	-0.20	-1.54, -1.14	$P = 0.77$	N/A	-1.49	-1.67, -1.31	$P < .00001$*	+

cTnI = cardiac troponin I; WMD = weighted mean difference; WMD < 0 favours volatile anesthetic, * $P < 0.05$ considered statistically significant; HG = heterogeneity. $P < 0.1$ considered statistically significant.

duction (OR, 4.63; 95% CI, (2.76, 7.76); $P < 0.00001$) without heterogeneity ($P = 0.41$). There was no apparent effect of halothane on lactate production.

Six studies reported myocardial lactate extraction. There was no significant effects on lactate extraction (WMD, 1.43; 95% CI, (-0.49, 3.34); $P = 0.14$) with significant heterogeneity ($P = 0.001$). In one study evaluating halothane, there was no difference in myocardial lactate extraction comparing halothane with a control group. Enflurane reduced $MV0_2$ (WMD, -1.87; 95% CI, -2.65, -1.08; $P < 0.00001$) with heterogeneity ($P = 0.007$).

When examining the composite outcome of death or AMI, volatile anesthetics did not appear to be associated with a reduced frequency of events (OR, 0.84; 95% CI, 0.61–1.15; $P = 0.28$), without heterogeneity ($P = 0.94$). However, enflurane appeared to increase death/AMI (OR, 1.20; 95% CI, 0.66–2.17; $P = 0.55$). Even if we eliminate enflurane from this post hoc analysis the result is not statistically significant (OR, 0.65; 95% CI, 0.41–1.04; $P = 0.07$) without heterogeneity.

In the planned sensitivity analysis, treatment effects were unaffected by the choice of statistical model (Table IV).

Discussion

This is the first published systematic review which examines the effects of volatile anesthetics on cardiac ischemic complications. The studies included in the meta-analysis were small, and undertaken in relatively low risk populations. Therefore, the meta-analysis lacks sufficient power to show effects on several important clinical endpoints. The meta-analysis does, however, demonstrate that sevoflurane and desflurane are associated with reduced postoperative cardiac troponin release. According to current best evidence, an association between reduced myocardial necrosis and overall mortality has not been clearly established. Only one study which assessed long-term outcome showed that a volatile anesthetic-mediated reduction in postoperative cardiac troponin was associated with improved long-term cardiac outcomes.[40]

An important finding of this analysis is that not all volatile anesthetics have cardioprotective effects. While sevoflurane and desflurane reduced postoperative TnI, this effect was not observed with enflurane. Troponin is a sensitive and specific marker of myocardial injury. Reduction in perioperative ischemia is clinically important.[41,42] Decreasing troponin release has been shown to lower the incidence of late adverse cardiac events.[40] The reduction in postoperative troponin concentrations occurred with significant het-

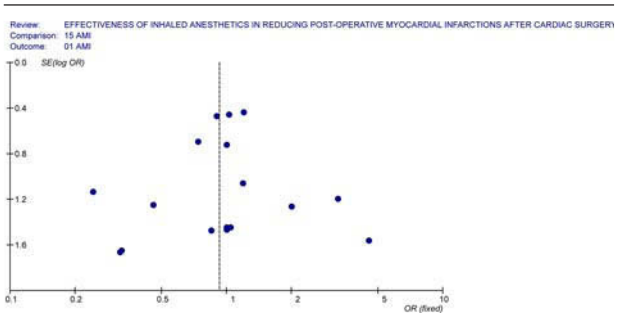

FIGURE 5 Funnel plot of effect of volatile anesthetics on acute myocardial infarction (AMI). The vertical dotted line indicates the overall odds ratio (OR).

erogeneity, weakening the reliability of this finding. In addition, four of the six studies included in this subgroup analysis were from the same author.[19,20,22,25] One result[20] was dramatically different from all other studies. If this study is eliminated from the analysis, the reduction in troponin is still significant, and there is no heterogeneity. Cardioprotection of desflurane was demonstrated without heterogeneity.

It is not possible to suggest which anesthetic is superior on the basis of this analysis. The second aspect of this analysis is that we have not found any evidence to suggest that enflurane is cardioprotective. In addition to the suggestion that enflurane may increase AMIs, we found that enflurane increased myocardial lactate production. The meta-analysis does not possess the statistical power to demonstrate an effect on myocardial infarction rates.

The results of ECG ST-T changes are at variance with the cTnI data. One possible explanation is that the ECG is not highly sensitive or specific for myocardial ischemia.[43] Further, ST-segment depression may occur in non-ischemic settings, including patients who are hyperventilating, taking digitalis, those with hypokalemia, and left ventricular strain.[44]

Previous research has shown that β-adrenergic blocking drugs reduce perioperative ischemia, major procedural complications, and long-term mortality.[45] The effects of volatile anesthetics seen in this meta-analysis were not attributable to concurrent β-blocker use. The incidence of beta-blocker use was 28% higher in the *iv* groups ($P = 0.03$) than in the inhalation groups. Some myocardial protective effects of the inhalation anesthetics may have been counteracted as β-blocker utilization was unequally distributed between the *iv* and inhalation groups.

Pharmacologic organ protection has been reported with numerous drugs including not just β-blockers, but also calcium channel blockers, alpha adrenergic agonists, and aspirin. The analysis shows that these medications were well balanced in both the treatment group and the control group (Table II). Moreover, opioid analgesics have been reported to induce a preconditioning effect in animal models. The data in humans is sparse (abstracts only). This analysis could not demonstrate a difference in the type or dose of opioid analgesics between treatment arms.

This analysis has several limitations. The meta-analytic tool is best used for hypothesis generation rather than hypothesis testing. Meta-analysis can be unreliable when multiple small studies, as seen in this analysis, are combined. Publication bias does not appear to be an issue in this study, as funnel plots show clearly that many negative studies have been included (Figure 5). Finally, the quality of included trials may have biased treatment effects.[46] Just four of the 32 studies were double blinded, and six of the 32 studies were evaluator blinded. The other 22 studies did not provide explicit description of the blinding. Unblinded trials have been found to bias an outcome result by 11 to 17%.[47,48] Allocation concealment was generally poorly described, which has been shown to increase estimates of treatment benefit.[46]

Meta-analysis is weakest and most controversial when studies disagree and there is heterogeneity. Heterogeneity was identified in this meta-analysis concomitantly with the reduction in postoperative tro-

TABLE IV Influence of statistical model on estimated treatment effects

Statistical model	*Death OR (95% CI)*	*AMI OR (95% CI)*	*Postoperative troponin I (> 2 ng·mL^{-1}) OR (95% CI)*	*Troponin I at T24 WMD (95% CI)*	*ECG ST-T OR (95% CI)*	*Death & AMI OR (95% CI)*
Fixed effects	0.65(0.36,1.18)	0.94(0.65,1.36)	0.18(0.12.0.26)	-1.27(-1.53,-1.01)	1.15(0.96,1.38)	0.84(0.61,1.15)
Random effects	0.65(0.35,1.19)	0.95(0.65,1.40)	0.17(0.11,0.28)	-1.84(-2.74,-0.94)	1.16(0.96,1.39)	0.85(0.61,1.18)

OR = odds ratio; AMI = acute myocardial infarction; WMD = weighted mean difference; 95% CI = 95% confidence interval; ECG = electrocardiogram.

ponin. Heterogeneity is defined as variation between studies that is greater than would be expected by chance alone. Many authors will elect to use a random effects model when faced with heterogeneity; however, use of the more conservative model does not circumvent the problem. In reality, authors are responsible for a search into reasons for this lack of uniformity between studies, but often a reason is not found. Reasons for heterogeneity are multi-factorial. The results of some studies may be due to an unknown bias or confounder that is never apparent. This may mean that it is inappropriate to combine studies. Other times, the reason is easily found.[49]

A further limitation of our analysis is that many studies were conducted at a time when the concept of pharmacological ischemic preconditioning was unknown. Since it is possible that pharmacological pre-conditioning was operational, any study that had MI as an outcome was potentially helpful. Of the 32 trials in this analysis, only eight controlled other factors that may negatively affect ischemic preconditioning. As a general rule, oral sulphonylureas and theophyllines, which are known to inhibit ischemic preconditioning by their action on K_{ATP} channels, were not discontinued; secondly we are unable to ascertain if these medications were balanced between study arms. This may partially explain the lack of protective effect seen in earlier studies of these drugs.

In conclusion, not all inhaled anesthetics possess myocardial protective effects. Sevoflurane and desflurane significantly reduce the postoperative rise in cTnI. The clinical significance of reduced troponin rises after cardiac surgery is debatable, but any positive effects may only be seen if long-term outcomes are considered. This meta-analysis lacks the statistical power to conclude that volatile anesthetics are associated with reduced death or AMI. However, the newer volatile anesthetics sevoflurane and desflurane appear promising. Adequately powered randomized control trials in both cardiac surgery patients and non-cardiac surgery populations at risk of ischemic events are needed to further elucidate the ischemic preconditioning effects of volatile anesthetics in patients at risk of cardiac morbidity.

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