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REVIEW ARTICLE

Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis

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Previous studies have investigated the role of volatile anaesthetic agents in myocardial protection during coronary artery bypass graft (CABG) surgery, and some have identified beneficial effects. However, these studies have been too small to identify a significant effect on myocardial infarction (MI) or mortality. We undertook a systematic overview and meta-analysis of all randomized trials comparing volatile with non-volatile anaesthesia in CABG surgery. We identified 27 trials that included 2979 patients. There was no significant difference in myocardial ischaemia, MI, intensive care unit length of stay or hospital mortality between the groups (all $P>0.05$). Post-bypass, patients randomized to receive volatile anaesthetics had 20% higher cardiac indices ($P=0.006$), significantly lower troponin I serum concentrations ($P=0.002$) and lesser requirement for inotropic support ($P=0.004$) compared with those randomized to receive i.v. anaesthetics. Duration of mechanical ventilation was reduced by 2.7 h ($P=0.04$), and there was a 1 day decrease in hospital length of stay ($P<0.001$). Some of these outcomes were based on a smaller number of trials because of incomplete data, largely because the individual trials focused on one or more surrogate endpoints. We found some evidence that volatile anaesthetic agents provide myocardial protection in CABG surgery, but larger adequately powered trials with agreed, defined outcomes need to be done to fully assess a possible beneficial effect of volatile anaesthetic agents on the risk of MI and mortality.

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Myocardial ischaemia–reperfusion injury, which commonly occurs during and after coronary artery bypass grafting (CABG) surgery, can lead to marked myocardial dysfunction and, possibly, myocardial infarction (MI) and prolonged hospitalization. The concept of pharmacologically protecting the myocardium to prevent this type of injury is an attractive concept. Since 1985, when Freedman and colleagues[15] reported that enflurane could improve postischaemic myocardial recovery in the isolated rat heart, there has been a body of research into the potential benefits of anaesthetic myocardial protection in both animal and human models.

Volatile anaesthetic agents may afford myocardial protection by minimizing ischaemia–reperfusion injury or by having a preconditioning effect on the myocardium (preconditioning is a treatment before an ischaemic event). The mechanisms of volatile anaesthetic protection and preconditioning have been extensively studied *in vivo* and *in vitro*. These include: opening mitochondrial K_{ATP} channels[12 19 20 40 62 63] increasing mitochondrial reactive oxygen species,[12 36 58] and activation or translocation of protein kinase C, tyrosine kinases and p38 mitogen-activated protein kinase.[12 16 42 56] These mechanisms decrease cytosolic and mitochondrial calcium loading.[60] Volatile anaesthetic agents may also protect endothelial coronary cells by mediating nitric oxide release.[41] Finally, some volatile agents suppress neutrophil activation and the neutrophil–endothelium interactions that cause myocardial dysfunction.[24 32] For a more complete review of myocardial protection by anaesthetic agents, the reader is referred to Kato and Foëx U.[29]

Many studies have explored various endpoints as surrogate markers of myocardial protection by volatile anaesthetic agents during CABG surgery. In all cases, these studies have been underpowered to identify a significant effect on MI or mortality. We, therefore, did a

systematic overview and meta-analysis of randomized trials to better define the role of volatile agents in myocardial protection during CABG surgery.

Materials and methods

We included all randomized control trials of adult cardiac patients undergoing on-pump or off-pump CABG surgery that compared volatile with non-volatile anaesthetic agent(s). Patients having valve surgery, and those who had central neuraxial blockade were excluded.

Search strategy for identification of studies

A systematic search for all relevant randomized control trials, in all languages, was conducted. Relevant trials were obtained from the following sources between January 1985 and March 2005: electronic databases (MEDLINE and EMBASE), the Cochrane Controlled Trials Register, abstracts in major journals related to anaesthesia and cardiac surgery, and reference lists of relevant randomized trials and review articles. In addition, the following medical subject headings and text words in various combinations were included in a MEDLINE electronic search: *propofol, isoflurane, sevoflurane, desflurane, anaesthetics, volatile agents, inhalational, ischaemic preconditioning, protection, myocardial, cardiac surgery, coronary artery bypass surgery, human, postoperative complications, fast-track, early extubation, tracheal extubation, intensive care, morbidity and mortality*. Studies which did not include both a volatile anaesthetic and a non-volatile control group were excluded. In studies which had both CABG and valve surgery in the study groups, the valve surgery data were excluded. We also recorded the temporal relationship of the administration of the volatile anaesthetic agent to the commencement of cardiac bypass, and whether the study was single-blind (patient, but not staff or researchers), double-blind (patient plus staff but not researchers) or triple-blind (patient, staff and researchers). In studies in which there was more than one volatile or non-volatile group, these groups were combined for the pooled analyses. The quality (validity) of individual trials was quantified by the Jadad scale,[26] using five criteria (one point each): (i) proper randomization, (ii) double blind, (iii) withdrawals documented, (iv) randomization adequately described, (v) blindness adequately described.

Outcome measures

Our outcome measures included: myocardial ischaemia in the first 24 h after surgery, MI during hospital admission, hospital mortality, cardiac index post-bypass, troponin I enzyme increase, inotrope requirement in intensive care unit (ICU) (or in the operating theatre, post-bypass, where no ICU data were available), ICU and hospital length of stay, and mechanical ventilation time. Because the definitions of myocardial ischaemia and MI varied between studies, all were accepted. The criteria for tracheal extubation and ICU discharge also varied between studies and all were accepted.

For studies where the median and range were reported, the mean and SD were estimated by using the O'Rourke method[44] whereby the median was used as the estimate of the mean, and the SD was a quarter of the range. Troponin T concentrations were converted to troponin I concentrations using a conversion factor of 2/0.65, based on the ratio of the upper limit of their respective reference ranges. Cardiac output was converted to a cardiac index by either dividing the cardiac output by the body surface area (if reported) or otherwise assuming a value of 1.7 m^2 (the mean value of pooled studies reporting body surface area). Variables which were not reported numerically in the original papers were estimated from the published figures.

Statistical analysis

All data were abstracted and verified by both authors independently, and differences resolved by consensus. Data were then entered into a Rev Man 3.1 (Cochrane Collaboration) database. Trials with no events in both groups for a particular endpoint were excluded from the relevant meta-analysis. The pooled OR and 95% CI were estimated for dichotomous endpoints: mortality, MI, ischaemia and inotrope use. The weighted mean difference and 95% CI were estimated for numerical variables: ICU and hospital length of stay, mechanical ventilation time, cardiac index and troponin level. We tested each endpoint for heterogeneity[23] and used random-effects models if significant ($P<0.05$) heterogeneity was detected; all other comparisons were done with fixed-effects models.

Subgroup analyses were done to explore a possible differential effect if the volatile agent was administered throughout the entire CABG surgery or for only a portion of the procedure. In a previous study,[11] one group (50 patients) received volatile agent throughout the entire procedure, the other two groups (100 patients) received volatile at 'any time' and therefore all data for the volatile group from this trial were included in the volatile 'any time' group to avoid double-counting of data in the non-volatile group.

Results

Our literature search identified 43 studies, 16 of which were excluded because volatile agent was not used at all, the study population was restricted to valve surgery, no relevant outcomes were reported, the study was retrospective, or dealt with long-term outcome (list available from the authors). This left 27 studies,[1 2 6 8–11 13 17 18 21 28 31 33 35 37 39 45–50 53–55 59] with 2979 patients, included in the analysis. Most of the studies only reported some of the endpoints which were the focus of this review, in which case each meta-analysis included fewer patients.

The characteristics of the study populations are summarized in Table 1. There was no evidence of statistical

Table 1 Characteristics of the trials included in the meta-analysis. Blinding: single-blind (patient, but not staff or researchers); double-blind (patient plus staff but not researchers); triple-blind (patient, staff and researchers). Volatile administration: 1, pre-bypass; 2, during bypass; 3, post-bypass

Study	Blinding	Jadad scale[26]	Major i.v. hypnotic drug	Volatile	Volatile administration
Bein and colleagues[1]	Single	2	Propofol (*n*=26)	Sevoflurane (*n*=24)	1,2,3
Parker and colleagues[45]	Double	5	Propofol (*n*=118)	Isoflurane(*n*=118)	1,2,3
				Sevoflurane(*n*=118)	1,2,3
De Hert and colleagues[11]	Double	5	Propofol (*n*=50)	Sevoflurane (*n*=50)	1
				Sevoflurane (*n*=50)	3
				Sevoflurane (*n*=50)	1,2,3
De Hert and colleagues[10]	Double	5	Propofol (*n*=80)	Sevoflurane (*n*=80)	1,2,3
			Benzodiazepine (*n*=80)	Desflurane (*n*=80)	1,2,3
Nader and colleagues[39]	Triple	5	Propofol (*n*=10)	Sevoflurane (*n*=11)	2
Kendall and colleagues[31]	Single	3	Propofol (*n*=10)	Isoflurane (*n*=10)	1,2,3
Conzen and colleagues[6]	Single	1	Propofol (*n*=10)	Sevoflurane (*n*=10)	1,2,3
De Hert and colleagues[8]	Single	2	Propofol (*n*=15)	Desflurane (*n*=15)	1,2,3
				Sevoflurane (*n*=15)	1,2,3
Julier and colleagues[28]	Triple	2	Propofol (*n*=35)	Sevoflurane (*n*=37)	2
Lu and colleagues[33]	Single	1	High-dose opioid (*n*=53)	Isoflurane (*n*=54)	1,2,3
De Hert and colleagues[9]	Single	2	Propofol (*n*=10)	Sevoflurane (*n*=10)	1,2,3
El-Shobaki and colleagues[13]	Single	1	Propofol (*n*=25)	Isoflurane (*n*=25)	1
Pouzet and colleagues[49]	Single	1	High-dose opioid (*n*=10)	Sevoflurane (*n*=10)	2
Haroun-Bizri and colleagues[21]	Single	1	High-dose opioid, benzo (*n*=21)	Isoflurane (*n*=28)	1
Belhomme and colleagues[2]	Single	1	High-dose opioid, benzo (*n*=10)	Isoflurane (*n*=10)	2
Tomai and colleagues[59]	Single	1	High-dose opioid (*n*=20)	Isoflurane (*n*=20)	1
Gravel and colleagues[17]	Single	4	Propofol (*n*=15)	Sevoflurane (*n*=15)	1,2,3
Penta de Peppo and colleagues[47]	Single	1	High-dose opioid (*n*=8)	Enflurane (*n*=8)	1
Sakaida[53]	Single	1	High-dose opioid (*n*=20)	Isoflurane (*n*=20)	Not reported
Myles and colleagues[37]	Double	4	Propofol (*n*=58)	Enflurane (*n*=66)	1
Mora and colleagues[35]	Single	2	High-dose opioid (*n*=22)	Enflurane (*n*=24)	1,2,3
			Propofol (*n*=23)		
			Thiopentone (*n*=21)		
Phillips and colleagues[48]	Single	1	Propofol (*n*=22)	Isoflurane (*n*=20)	1
Parsons and colleagues[46]	Single	3	High-dose opioid, benzo (*n*=25)	Desflurane (*n*=25)	1,3
Ramsay and colleagues[50]	Triple	3	High-dose opioid (*n*=25)	Isoflurane (*n*=25)	1
				Enflurane (25)	1
Hall and colleagues[18]	Single	1	Propofol (24)	Enflurane (23)	1,2,3
Slogoff and colleagues[55]	Single	3	High-dose opioid (254)	Enflurane (257)	1,3
				Halothane (253)	1,3
				Isoflurane (248)	1,3
Samuelson and colleagues[54]	Single	3	High-dose opioid (10)	Isoflurane (21)	1,2,3
			High-dose opioid (14)		

heterogeneity for the endpoints of mortality, MI, or myocardial ischaemia ($P>0.1$), but there was evidence of heterogeneity for the endpoints of hospital length of stay, ICU length of stay, duration of mechanical ventilation, cardiac index, troponin level and post-bypass inotrope administration.

Five trials reported an effect on mortality,[8 10 35 45 55] 12 trials reported an effect on MI,[8 10 11 18 28 31 35 37 45 46 50 55] and 8 trials reported an effect on myocardial ischaemia.[1 28 35 37 39 46 50 55] There was no significant difference between volatile and non-volatile anaesthetic groups with respect to MI (Fig. 1), mortality, myocardial ischaemia or ICU length of stay (Fig. 2).

Patients randomized to receive volatile anaesthetics had 20% higher cardiac indices (Fig. 3) ($P<0.006$), significantly lower troponin I serum concentrations ($P<0.002$) (Fig. 4), lesser requirement for inotropic support ($P<0.004$) (Fig. 5), shorter duration of mechanical ventilation ($P<0.04$) (Fig. 6) and a shorter length of hospital stay ($P<0.001$) (Fig. 7) compared with those randomized to receive intravenous anaesthetics.

Timing of volatile anaesthetic agent administration

The subgroup analyses of the timing of volatile anaesthetic agent administration with respect to cardiopulmonary bypass showed no statistically significant difference between those groups in which volatile anaesthetic agent was administered throughout the procedure or at intermittent periods of the procedure for the endpoints of mortality, MI, myocardial ischaemia, troponin I level or ICU length of stay (Figs 1–7).

Discussion

Our systematic overview and meta-analysis has demonstrated some evidence of volatile anaesthetic agent protection in CABG surgery, with a significant increase in post-bypass cardiac index, and a reduction in troponin I levels, inotrope use, duration of mechanical ventilation and hospital length of stay (Table 2, Fig. 7). There was no significant difference in MI or hospital mortality between the volatile and non-volatile groups.

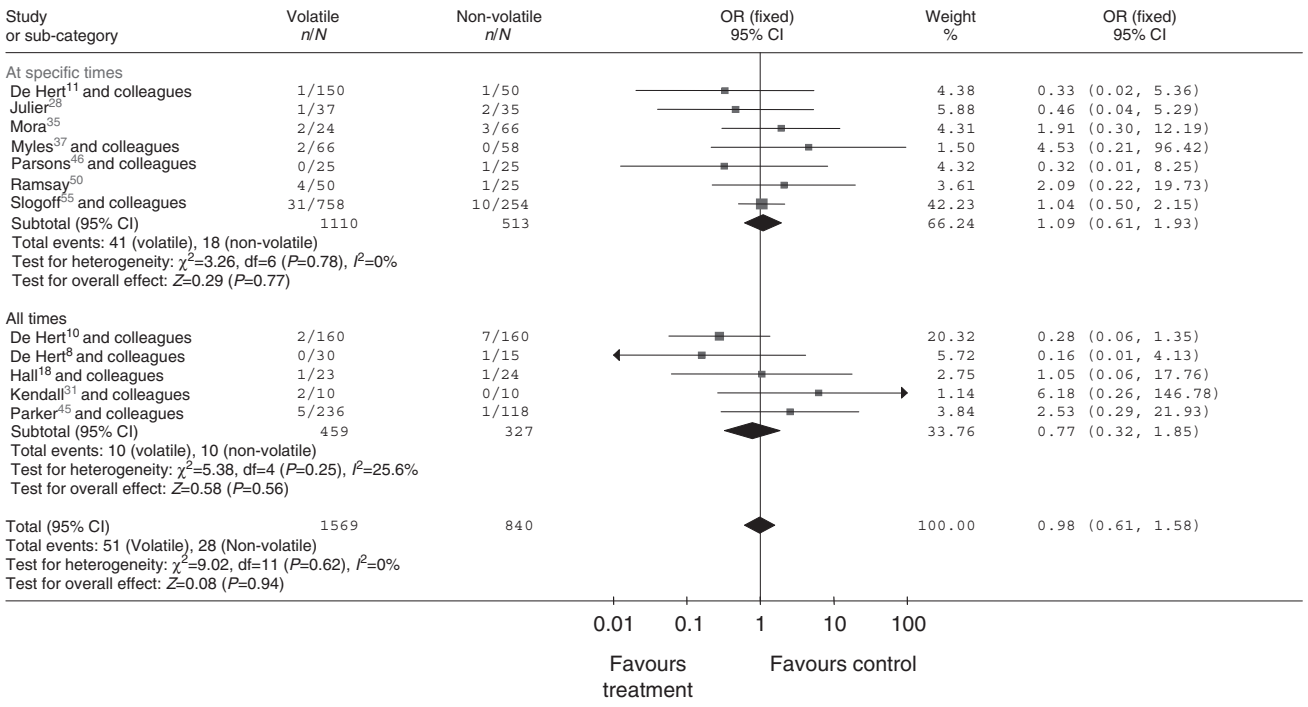

Fig 1 Myocardial infarction.

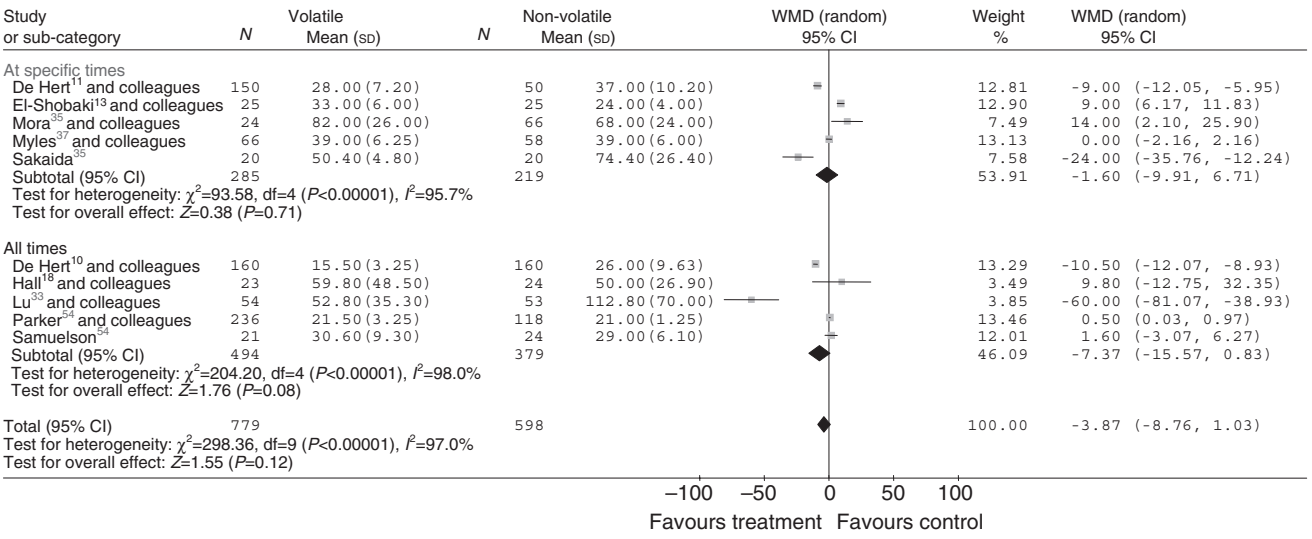

Fig 2 Intensive care length of stay.

The reduction in mechanical ventilation time in the volatile group was about 2.5 h. Although significant, this difference needs to be interpreted with caution for a number of reasons. First, there was heterogeneity in the data, perhaps reflecting the varied practices in postoperative ventilatory management in CABG patients. Second, the studies most likely used different criteria for tracheal extubation. Third, studies varied widely in their adjuvant anaesthetic drug administration(s), in particular different opioid dose administration and this is known to affect the time to patient awakening. In one study,[45] in whom all patients received low-dose (<15 $\mu g\ kg^{-1}$) fentanyl, they found no difference in extubation time between their isoflurane and sevoflurane groups, but a significantly longer extubation time in the propofol group. Volatile anaesthetic agent was administered for the entire duration of surgery in the volatile group. Myles and colleagues,[37] however showed that a propofol-based regimen led to a decrease in ventilation time compared with a volatile (enflurane) anaesthetic technique. Two major differences in the aforementioned studies could explain the discrepant findings: the latter study[37] did not administer volatile agent during bypass, and the volatile

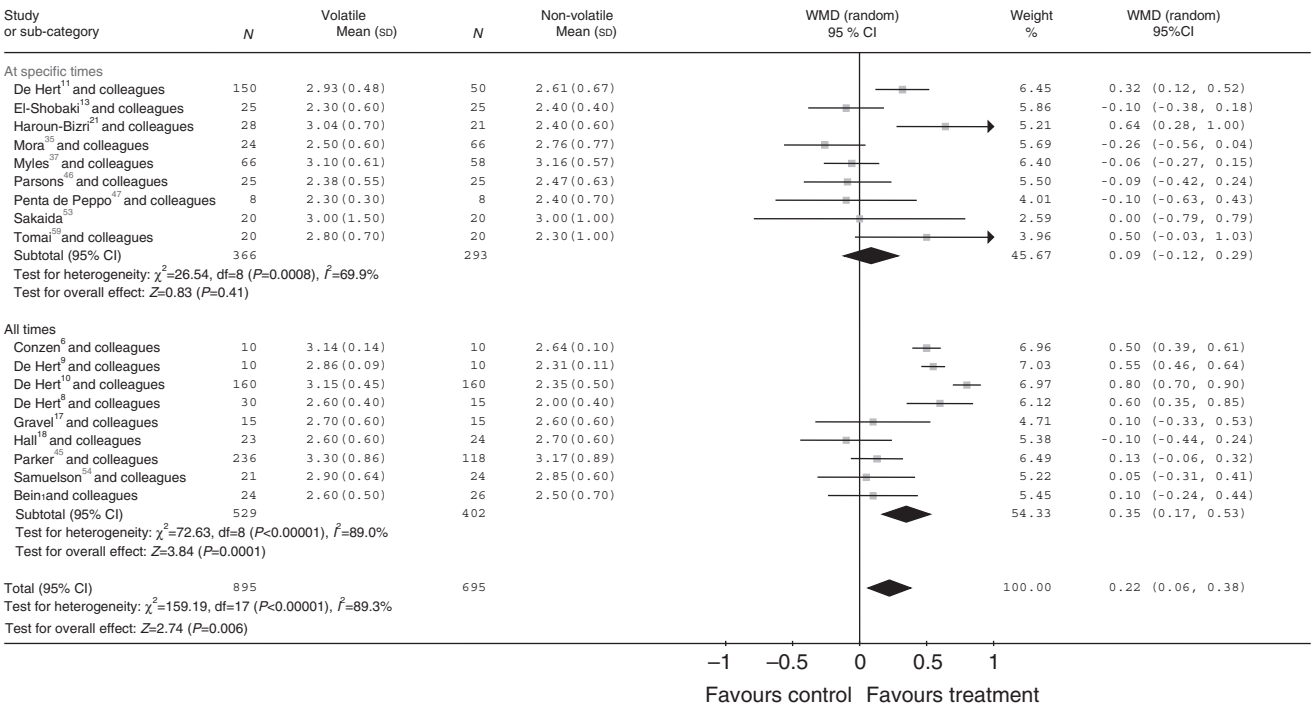

Fig 3 Cardiac index.

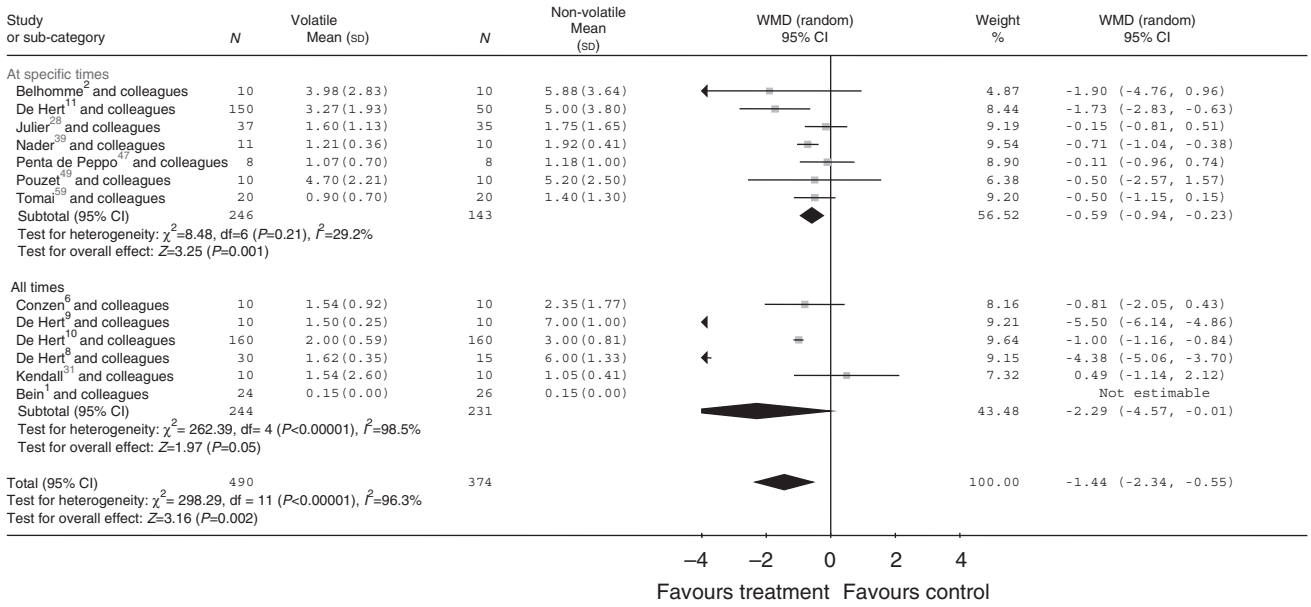

Fig 4 Troponin I concentration.

group received a higher dose of fentanyl compared with the non-volatile group (30 μg *vs* 15 μg). Low-dose opioid regimens reduce tracheal extubation times in CABG surgery.[4 38] However, a specific effect of volatile anaesthetic agent administration on postoperative mechanical ventilation and tracheal extubation time has been unclear.

There was a decrease in length of hospital stay of 1 day in the volatile group. Although this result needs to be interpreted with caution in view of the heterogeneity and limited amount of data (four studies with a total of 600 patients), it does represent a potentially important outcome for patients and clinicians, as it is usually associated with a reduced number of serious complications and hospital costs. In a systematic review on fast-track cardiac anaesthesia, there was no significant difference in hospital length of stay between low-dose and high-dose opioid groups.[38] DeHert and colleagues[10] conducted a randomized study of 320 elective CABG patients, in which 80 patients received

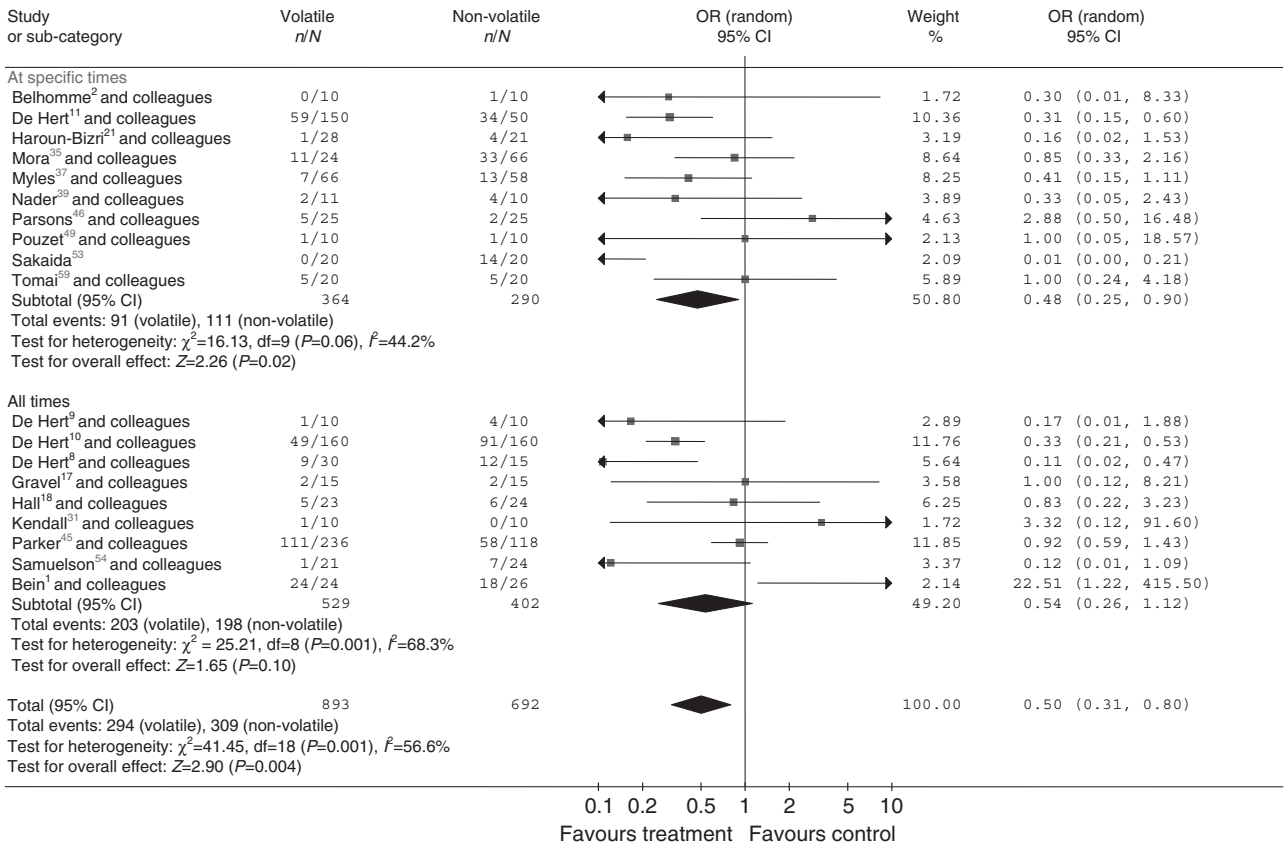

Fig 5 Inotrope use.

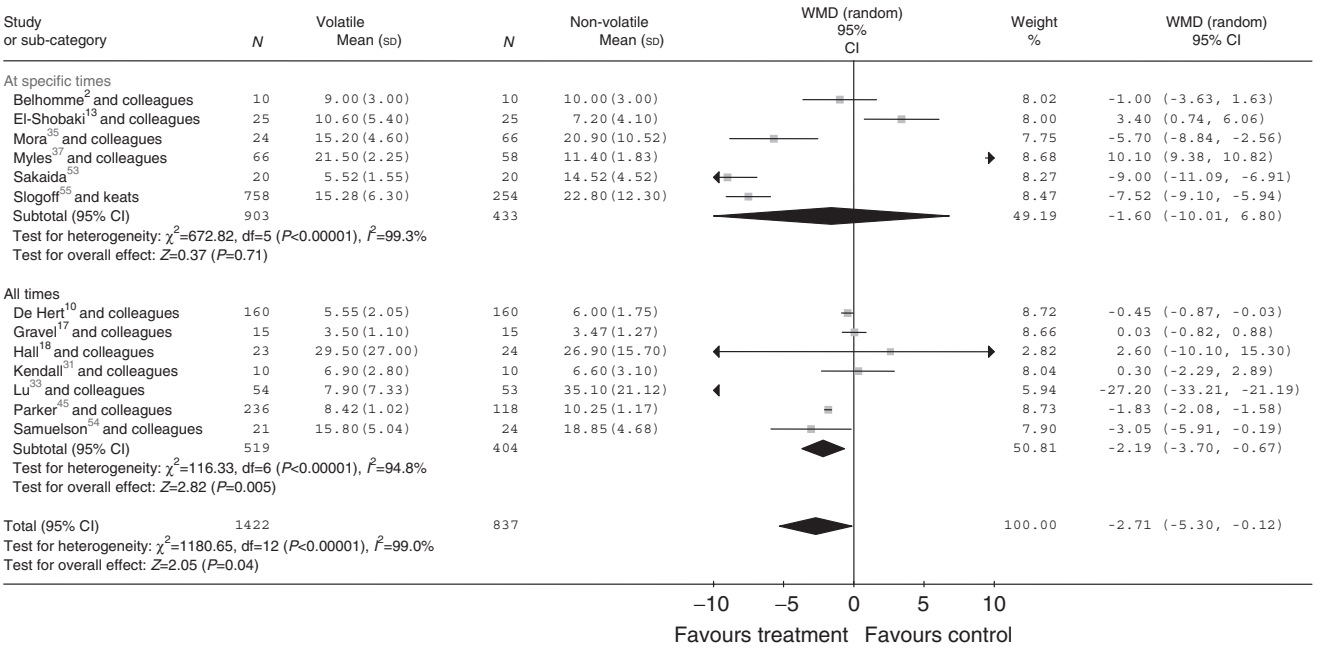

Fig 6 Mechanical ventilation time.

propofol, 80 midazolam, 80 sevoflurane and 80 desflurane. All patients received a remifentanil-based anaesthetic regimen. They found a significant decrease in ICU and hospital length of stay in the volatile groups when compared with the non-volatile groups. Postoperative troponin I and inotropic support was significantly lower in the volatile group. The occurrence of atrial fibrillation, a postoperative troponin I concentration of >4 ng ml^{-1}, and the need for prolonged

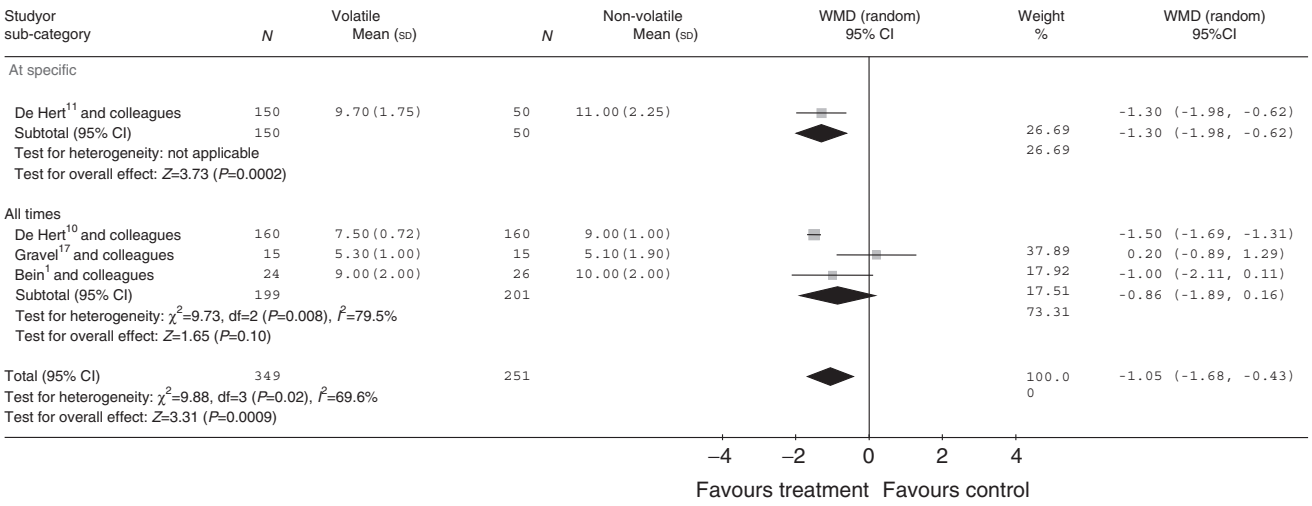

Fig 7 Hospital length of stay.

Table 2 Variables comparing volatile agent with a non-volatile agent regimen in CABG surgery. *OR, odds ratio; †WMD, weighted mean difference; CI, confidence interval

Variable	Volatile No. (%)	Non-volatile No. (%)	OR or WMD (95% CI)	*P*-value
At specific times				
Mortality	12/782 (1.53)	7/320 (2.19)	0.73 (0.28 to 1.90)*	0.52
Myocardial infarction	41/1110 (3.69)	18/513 (3.51)	1.09 (0.61 to 1.93)*	0.77
Myocardial ischaemia	279/971 (28.73)	111/473 (2.33)	1.09 (0.84 to 1.43)*	0.51
Inotrope use	91/364 (25.00)	111/290 (38.28)	0.48 (0.25 to 0.90)*	0.02
ICU length of stay (h)			−1.60 (−9.91 to 6.71)†	0.71
Cardiac index			0.09 (−0.12 to 0.29)†	0.41
Troponin I (ng ml^{-1})			−0.59 (−0.94 to −0.23)†	0.001
Mechanical ventilation time (h)			−1.60 (−10.01 to 6.80)†	0.71
Hospital length of stay (days)			26.69 (−1.98 to −0.62)†	0.0002
All times				
Mortality	4/426 (0.94)	4/293 (1.37)	0.6 (0.16 to 2.19)*	0.44
Myocardial infarction	10/459 (2.18)	10/327 (3.06)	0.77 (0.32–1.85)*	0.56
Myocardial ischaemia	5/24 (20.83)	8/26 (30.77)	0.59 (0.16 to 2.15)*	0.43
Inotrope use	203/529 (38.37)	198/402 (49.25)	0.54 (0.26 to 1.12)*	0.10
ICU length of stay (h)			−7.37 (−15.57 to 0.83)†	0.08
Cardiac index			0.35 (0.17 to 0.53)†	0.0001
Troponin I (ng ml^{-1})			−2.29 (−4.57 to −0.01)†	0.05
Mechanical ventilation time (h)			−2.19 (−3.70 to −0.67)†	0.005
Hospital length of stay (days)			−0.86 (−1.89 to 0.16)†	0.10
Pooled studies				
Mortality	16/1208 (1.32)	11/613 (1.79)	0.68 (0.32 to 1.47)*	0.33
Myocardial infarction	51/1569 (3.25)	28/840 (3.33)	0.98 (0.61 to 1.58)*	0.94
Ischaemia	284/995 (28.54)	119/499 (23.85)	1.07 (0.82 to 1.38)*	0.63
Inotrope use	294/893 (32.92)	309/692 (44.65)	0.50 (0.31 to 0.80)*	0.004
ICU length of stay (h)			−3.87 (−8.76 to 1.03)†	0.12
Cardiac index			0.22 (0.06 to 0.38)†	0.006
Troponin I (ng ml^{-1})			−1.44 (−2.34 to −0.55)†	0.002
Mechanical ventilation time (h)			−2.71 (−5.30 to −0.12)†	0.04
Hospital length of stay (days)			−1.05 (−1.68 to −0.43)†	0.0009

inotropic support were identified as risk factors for a prolonged ICU stay.[10] They concluded that a better preservation of early postoperative myocardial function with volatile anaesthetic agents resulted in a shorter ICU and hospital length of stay. This study was notable, in that volatile anaesthetic agent was used for the entire duration of surgery. However, the study was not adequately powered to show a decrease in mortality or postoperative MI with volatile agents.

The increase in post-bypass cardiac index, and reduced troponin flux, in the volatile group in our study supports a myocardial protection effect. It has been suggested that in order for preconditioning to be effective, the volatile should be administered throughout the entire procedure.[11] Our subgroup analyses are equivocal, and neither support nor refute this assertion. Nevertheless, volatile myocardial protection seems to be concentration-dependent and time-dependent,[30 43] and volatile agents preserve myocardial

energy stores during ischaemia (through a decrease in afterload, contractility and heart rate), thereby allowing the myocardium to recover.[51] Each of these proposed mechanisms should be detected by troponin flux, a sensitive marker of myocardial damage.[14 34] Volatile anaesthetic agents may also prevent reperfusion injury, a concept which has been raised previously.[11] Other mechanisms whereby volatile agents prevent myocardial reperfusion injury include suppression of neutrophil activation and the neutrophil–endothelium interaction.[22 24 25 32] This effect may also be concentration dependent.[30 43] Reduction in dysrrhythmias[3 61] and decrease in infarct size[7] may be additional mechanisms.

Limitations of the study

There was no difference in the rates of MI between the volatile and non-volatile groups. These results would seem to weaken the proposed role of volatile anaesthetic agents in myocardial protection. However, in order to detect a clinically important (e.g. >20%) difference would require many thousands of patients to be studied, considering that postoperative MI is an uncommon event. Detection of perioperative myocardial ischaemia is probably best done with continuous Holter ST-segment monitoring,[27] and a uniform definition of ischaemia is used.

The heterogeneity in our data for post-bypass inotrope use is not surprising given the differences in inotrope usage and the thresholds for commencing inotropic support in various institutions. Sevoflurane may protect the myocardium against stunning,[5 57] an effect not reported with propofol.[52] Another explanation for decreased inotrope usage in ICU could be the result of volatile agents preserving myocardial energy stores, thereby allowing the myocardium to recover.[51] Our subgroup analyses could not identify a variable effect according to the timing of volatile agent administration (before, during, and/or after bypass) nor whether any particular volatile agent, if any, has superior myocardial protection effects. More standardized protocols, including agreed, defined endpoints, need to be developed in future studies. This study has potential weaknesses inherent in meta-analyses. Being able to pool many smaller studies increases the power of the analyses, but varied clinical practices and lack of uniformity of definition and reporting of endpoints limit the certainty of our findings. The results need to be interpreted taking into account the different practices with regard to anaesthesia, surgery and ICU management of CABG patients between various institutions. This uncertainty is best dealt with by a large prospective randomized trial in order to establish the true role of volatile anaesthetic agents in myocardial protection. We believe such a trial is warranted, and recommend that common endpoint definitions should be established.

In conclusion, this systematic overview and meta-analysis has found some evidence of volatile agent protection in CABG surgery, with increased cardiac index and a reduction in mechanical ventilation time, hospital length of stay, troponin flux and inotrope use in ICU. These findings support the conduct of a large definitive trial.

Acknowledgements

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References

1 Bein B, Renner J, Caliebe D, *et al*. Sevoflurane but not propofol preserves myocardial function during minimally invasive direct coronary artery bypass surgery. *Anesth Analg* 2005; **100**: 610–16

2 Belhomme D, Peynet J, Louzy M, Launay J-M, Kitakaze M, Menasché P. Evidence for preconditioning by isoflurane in coronary artery bypass graft surgery. *Circulation* 1999; **100** (Suppl. II): 340–44

3 Buljubasic N, Stowe DF, Marijic J, Roerig DL, Kampine JP, Bosnjak ZJ. Halothane reduces release of adenosine, inosine, and lactate with ischaemia and reperfusion in isolated hearts. *Anesth Analg* 1993; **76**: 54–62

4 Cheng DCH. Anesthetic techniques and early extubation: does it matter? *J Cardiothorac Vasc Anesth* 2000; **14**: 627–30

5 Coetzee JF, le Roux PJ, Genade S, Lochner A. Reduction of postischaemic contractile dysfunction of the isolated rat heart by sevoflurane: comparison with halothane. *Anesth Analg* 2000; **90**: 1089–97

6 Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *Anesthesiology* 2003; **99**: 826–33

7 Davis RF, DeBoer LWV, Rude RE, Lowenstein E, Maroko PR. The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. *Anesthesiology* 1983; **59**: 402–11

8 De Hert SG, Cromheecke S, ten Broecke PW, *et al*. Effects of propofol, desflurane and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. *Anesthesiology* 2003; **99**: 314–23

9 De Hert SG, ten Broecke PW, Mertens E, *et al*. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. *Anesthesiology* 2002; **97**: 42–9

10 De Hert SG, Van der Linden PJ, Cromheecke S, *et al*. Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. *Anesthesiology* 2004; **101**: 9–20

11 De Hert SG, Van der Linden PJ, Cromheecke S, *et al*. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology* 2004; **101**: 299–310

12 de Ruijter W, Musters RJP, Boer C, Stienen GJM, Simonides WS, de Lange JJ. The cardioprotective effect of sevoflurane depends on protein kinase C activation, opening of mitochondrial K^+_{ATP} channels, and the production of reactive oxygen species. *Anesth Analg* 2003; **97**: 1370–6

13 El-Shobaki A, Abd El Aal WAM, Tahoun HM, Abdel-Rashid A. Comparative study between isoflurane and propofol in fast-track cardiac anesthesia for patients undergoing CABG. *Egypt J Anesth* 2002; **18**: 37–43

14 Etievent J-P, Chocron S, Toubin G, *et al*. Use of cardiac troponin I as a marker of perioperative myocardial ischaemia. *Ann Thorac Surg* 1995; **59**: 1192–4

15 Freedman BM, Hamm DP, Everson CT, Wechsler AS, Christian CM, II. Enflurane enhances postischaemic functional recovery in the isolated rat heart. *Anesthesiology* 1985; **62**: 29–33

16 Fujimoto K, Bosnjak ZJ, Kwok W-M. Isoflurane-induced facilitation of the cardiac sarcolemmal K_{ATP} channel. *Anesthesiology* 2002; **97**: 57–65

17 Gravel NR, Searle NR, Taillefer J, Carrier M, Roy M, Gagnon L. Comparison of the hemodynamic effects of sevoflurane anesthesia induction and maintenance vs TIVA in CABG surgery. *Can J Anaesth* 1999; **46**: 240–6

18 Hall RJ, Murphy JT, Moffitt EA, Landymore R, Pollak PT, Poole L. A comparison of the myocardial metabolic and haemodynamic changes produced by propofol-sufentanil and enflurane-sufentanil anaesthesia for patients having coronary artery bypass graft surgery. *Can J Anaesth* 1991; **38**: 996–1004

19 Hanouz J-L, Yvon A, Massetti M, *et al*. Mechanisms of desflurane-induced preconditioning in isolated human right atria *in vitro*. *Anesthesiology* 2002; **97**: 33–41

20 Hara T, Tomiyasu S, Sungsam C, Fukusaki M, Sumikawa K. Sevoflurane protects stunned myocardium through activation of mitochondrial ATP-sensitive potassium channels. *Anesth Analg* 2001; **92**: 1139–45

21 Haroun-Bizri S, Khoury SS, Chehab IR, Kassas CM, Baraka A. Does isoflurane optimize myocardial protection during cardiopulmonary bypass? *J Cardiothorac Vasc Anesth* 2001; **15**: 418–21

22 Heindl B, Reichle FM, Zahler S, Conzen PF, Becker BF. Sevoflurane and isoflurane protect the reperfused guinea pig heart by reducing postischaemic adhesion of polymorphonuclear neutrophils. *Anesthesiology* 1999; **91**: 521–30

23 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003; **327**: 557–60

24 Hu G, Vasiliauskas T, Salem MR, Rhone DP, Crystal GJ. Neutrophils pretreated with volatile anesthetics lose ability to cause cardiac dysfunction. *Anesthesiology* 2003; **98**: 712–18

25 Hu G, Vinten-Johansen J, Salem MR, Zhao Z-Q, Crystal G. Isoflurane inhibits neutrophil-endothelium interaction in the coronary circulation: lack of role for adenosine triphosphate-sensitive potassium channels. *Anesth Analg* 2003; **94**: 849–56

26 Jadad AR, Moore RA, Carroll D, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12

27 Jain U, Laflamme CJA, Aggarwal A, *et al*. Electrocardiographic and hemodynamic changes and their association with myocardial infarction during coronary artery bypass surgery. *Anesthesiology* 1997; **86**: 576–91

28 Julier K, da Silva R, Garcia C, *et al*. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. *Anesthesiology* 2003; **98**: 1315–27

29 Kato R, Foëx P. Myocardial protection by anaesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists. *Can J Anaesth* 2002; **49**: 777–91

30 Kehl F, Krolikowski JG, Mraovic B, Pagel PS, Warltier DC, Kersten JR. Is isoflurane-induced preconditioning dose related? *Anesthesiology* 2002; **96**: 675–80

31 Kendall JB, Russell GN, Scawn NDA, Akrofi M, Cowan CM, Fox MA. A prospective, randomised, single-blind pilot study to determine the effect of anaesthetic technique on troponin T release after off-pump coronary artery surgery. *Anaesthesia* 2004; **59**: 545–9

32 Kowalski C, Zahler S, Becker BF, *et al*. Halothane, isoflurane, and sevoflurane reduce postischaemic adhesion of neutrophils in the coronary system. *Anesthesiology* 1997; **86**: 188–95

33 Lu C-C, Ho S-T, Wang J-J, *et al*. Minimal low-flow isoflurane-based anesthesia benefits patients undergoing coronary revascularization via preventing hyperglycemia and maintaining metabolic homeostasis. *Acta Anaesthesiol Sin* 2003; **41**: 165–72

34 Maynard SJ, Menown IBA, Adgey AAJ. Troponin T or troponin I as cardiac markers in ischaemic heart disease. *Heart* 2000; **83**: 371–3

35 Mora CT, Dudek C, Torjman MC, White PF. The effects of anesthetic technique on the hemodynamic response and recovery profile in coronary revascularization patients. *Anesth Analg* 1995; **81**: 900–10

36 Müllenheim J, Ebel D, Fräβdorf J, Preckel B, Thämer V, Schlack W. Isoflurane preconditions myocardium against infarction via release of free radicals. *Anesthesiology* 2002; **96**: 934–40

37 Myles PS, Buckland MR, Weeks AM, *et al*. Haemodynamic effects, myocardial ischaemia, and timing of tracheal extubation with propofol-based anesthesia for cardiac surgery. *Anesth Analg* 1997; **84**: 12–19

38 Myles PS, Daly DJ, Djaiani G, Lee A, Cheng DCH. A systematic review of the safety and effectiveness of fast-track cardiac anaesthesia. *Anesthesiology* 2003; **99**: 982–7

39 Nader ND, Li CM, Khadra WZ, Reedy R, Panos AL. Anesthetic myocardial protection with sevoflurane. *J Cardiothorac Vasc Anesth* 2004; **18**: 269–74

40 Nakae Y, Kohro S, Hogan QH, Bosnjak ZJ. Intracellular mechanism of mitochondrial adenosine triphosphate-sensitive potassium channel activation with isoflurane. *Anesth Analg* 2003; **97**: 1025–32

41 Novalija E, Fujita S, Kampine JP, Stowe DF. Sevoflurane mimics ischaemic preconditioning effects on coronary flow and nitric oxide release in isolated hearts. *Anesthesiology* 1999; **91**: 701–12

42 Novalija E, Kevin LG, Camara AKS, Bosnjak ZJ, Kampine JP, Stowe DF. Reactive oxygen species precede the **ϵ**-isoform of protein kinase C in the anesthetic preconditioning signaling cascade. *Anesthesiology* 2003; **99**: 421–8

43 Obal D, Preckel B, Scharbatke H, *et al*. One MAC of sevoflurane provides protection against reperfusion injury in the rat heart *in vivo*. *Br J Anaesth* 2001; **87**: 905–11

44 O'Rourke K. Mixed means and medians: a unified approach to deal with disparate outcome summaries. In: *Proceedings of the Symposium on Systematic Reviews: Pushing the Boundaries*. Oxford: 2002; 49

45 Parker FC, Story DA, Poustie S, Liu G, McNicol L. Time to tracheal extubation after coronary artery surgery with isoflurane, sevoflurane, or target-controlled propofol anesthesia: a prospective, randomized, controlled trial. *J Cardiothorac Vasc Anesth* 2004; **18**: 613–19

46 Parsons RS, Jones RM, Wrigley SR, MacLeod KGA, Platt MW. Comparison of desflurane and fentanyl-based anaesthetic techniques for coronary artery bypass surgery. *Br J Anaesth* 1994; **72**: 430–8

47 Penta de Peppo A, Polisca P, Tomai F, *et al*. Recovery of LV contractility in man is enhanced by preischaemic administration of enflurane. *Ann Thorac Surg* 1999; **68**: 112–18

48 Phillips AS, McMurray TJ, Mirakhur RK, Gibson FM, Elliott P. Propofol-fentanyl anesthesia: a comparison with isoflurane–fentanyl anesthesia in coronary artery bypass grafting and valve replacement surgery. *J Cardiothorac Vasc Anesth* 1994; **8**: 289–96

49 Pouzet B, Lecharny J-B, Dehoux M, *et al*. Is there a place for preconditioning during cardiac operations in humans? *Ann Thorac Surg* 2002; **73**: 843–8

50 Ramsay JG, DeLima LGR, Wynands JE, O'Connor JP, Ralley FE, Robbins GR. Pure opioid versus opioid-volatile anesthesia for coronary artery bypass graft surgery: a prospective, randomized, double-blind study. *Anesth Analg* 1994; **78**: 867–75

51 Ross S, Foëx P. Protective effects of anaesthetics in reversible and irreversible ischaemia–reperfusion injury. *Br J Anaesth* 1999; **82**: 622–32

52 Ross S, Munoz H, Piriou V, Ryder WA, Foëx P. A comparison of the effects of fentanyl and propofol on left ventricular contractility during myocardial stunning. *Acta Anaesthesiol Scand* 1998; **42**: 23–31

53 Sakaida K. Isoflurane anaesthesia with combined use of low dose fentanyl for open heart surgery. *Masui* 1998; **47**: 576–84

54 Samuelson PN, Reves JG, Kirklin JK, Bradley E, Wilson KD, Adams M. Comparison of sufentanil and enflurane-nitrous oxide anesthesia for myocardial revascularization. *Anesth Analg* 1986; **65**: 217–26

55 Slogoff S, Keats AS. Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. *Anesthesiology* 1989; **70**: 179–88

56 Stadnicka A, Kwok W-M, Warltier DC, Bosnjak ZJ. Protein tyrosine kinase-dependent modulation of isoflurane effects on cardiac sarcolemmal K_{ATP} channel. *Anesthesiology* 2002; **97**: 1198–208

57 Takahata O, Ichihara K, Ogawa H. Effects of sevoflurane on ischaemic myocardium in dogs. *Acta Anaesthesiol Scand* 1995; **39**: 449–56

58 Tanaka K, Weihrauch D, Kehl F, *et al*. Mechanism of preconditioning by isoflurane in rabbits: a direct role for reactive oxygen species. *Anesthesiology* 2002; **97**: 1485–90

59 Tomai F, De Paulis R, Penta de Peppo A, *et al*. Beneficial impact of isoflurane during coronary bypass surgery on troponin I release. *G Ital Cardiol* 1999; **29**: 1007–14

60 Varadarajan SG, An J, Novalija E, Stowe DF. Sevoflurane before or after ischaemia improves contractile and metabolic function while reducing myoplasmic Ca^{2+} loading in intact hearts. *Anesthesiology* 2002; **96**: 125–33

61 Warltier DC, Al-Wathiqui MH, Kampine JP, Schmeling WT. Recovery of contractile function and stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**: 552–65

62 Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K_{ATP} channels via multiple signalling pathways. *Anesthesiology* 2002; **97**: 4–14

63 Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Garcia C, Schaub M. Differential effects of anesthetics on mitochondrial K_{ATP} channel activity and cardiomyocyte protection. *Anesthesiology* 2002; **97**: 15–23