Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis
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CRD summary
The authors concluded that there was some evidence that volatile anaesthetic agents protect the myocardium during coronary artery bypass graft surgery, but further research is required. The authors' cautious conclusions appear appropriate, but it is not possible to confirm their reliability given the incomplete reporting of review methods and study quality and the differences between the studies.

Authors' objectives
To compare the effects of volatile and non-volatile anaesthetic agents on myocardial protection during coronary artery bypass graft (CABG) surgery.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from 1985 to March 2005. The search terms were reported for the MEDLINE search and no language restrictions were applied. In addition, abstracts in major journals of anaesthesia and cardiac surgery and the reference lists of included studies and reviews were screened.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared volatile with non-volatile anaesthetic agents were eligible for inclusion. The included studies evaluated sevoflurane, isoflurane, desflurane, enflurane and halothane. These agents were administered pre-bypass and/or during and/or after bypass. Non-volatile agents included the following major intravenous hypnotic drugs: propofol, benzodiazepines, high-dose opioid and thiopentone.

Participants included in the review
Studies of adults undergoing on-pump or off-pump CABG surgery were eligible for inclusion in the review. Studies of patients undergoing valve surgery or with neuroaxial blockade were excluded.

Outcomes assessed in the review
The review assessed the following: myocardial ischaemia in the first 24 hours post-operatively; myocardial infarction (MI) during hospital admission; hospital mortality; cardiac index post-bypass; troponin I enzyme increase, inotrope requirement in the intensive care unit (ICU) or equivalent setting; stay in the ICU and hospital; and mechanical ventilation time. The included studies used different definitions for myocardial ischaemia and MI and different criteria for extubation and ICU discharge; the reviewers accepted the authors' definitions.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, double-blinding and the handling of withdrawals. The maximum possible score was 5 points. The level of blinding (single, double or triple) was also assessed. The authors did not state how many reviewers performed the validity assessment.
Data extraction
Two reviewers independently extracted the data and resolved any disagreements by consensus. The timing of anaesthesia administration in relation to surgery was extracted. For each study, the numbers of patients with events of interest, or the mean value with standard deviation (SD), were presented for each treatment group. Where required, means and SDs were calculated from median values and ranges; troponin I values were calculated from troponin T concentrations; cardiac indices were calculated from cardiac output; and numerical values were estimated from graphs.

Methods of synthesis
How were the studies combined?
Groups of volatile or non-volatile data were pooled within studies for those studies assessing multiple anaesthetics. The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for dichotomous data and the pooled weighted mean difference (WMD) and 95% CI for continuous data. A random-effects model was used in the presence of significant heterogeneity (p<0.05), otherwise a fixed-effect model was used.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics.

A subgroup analysis was used to examine the effect of timing of administration of volatile agent (during entire period of surgery or part of the period). Some potential causes of differing results amongst the studies were discussed.

Results of the review
Twenty-seven RCTs (n=2,979) were included.

Four studies scored 5 points on the Jadad scale, two scored 4, five scored 3, and the rest scored either 2 or 1. Three studies used triple-blinding, four used double-blinding, and the remainder used single-blinding.

There was no evidence of statistically significant heterogeneity for mortality, MI or myocardial ischaemia (p>0.10). Significant heterogeneity was found for hospital and ICU length of stay, duration of mechanical ventilation, cardiac index, troponin level and post-bypass inotrope administration.

There was no statistically significant difference between patients receiving volatile and non-volatile anaesthetic agents for MI (12 RCTs), mortality (5 RCTs), myocardial ischaemia (8 RCTs) or length of ICU stay (10 RCTs).

Patients receiving volatile anaesthetics compared with non-volatile anaesthetics had significantly higher cardiac indices (random-effects model, WMD 0.22, 95% CI: 0.06, 0.38, p<0.006); significantly lower troponin I serum concentrations (random-effects model, WMD -1.44, 95% CI: -2.34, -0.55, p<0.002); significantly lower requirements for inotropic support (random-effects model, OR 0.50, 95% CI: 0.31, 0.80, p<0.004); significantly shorter duration of mechanical ventilation (random-effects model, WMD -2.71 hours, 95% CI: -5.30, -0.12, p<0.04); and a significantly shorter hospital stay (random-effects model, WMD -1.05 days, 95% CI: -1.68, -0.43, p<0.001).

Authors' conclusions
There was some evidence that volatile anaesthetic agents protect the myocardium during CABG surgery, but further research is required.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and study design; the multiple outcomes assessed in the review were clearly stated but no primary outcomes were identified. Several relevant sources were searched and attempts were made to minimise language bias. No specific attempts to locate unpublished studies were reported, which raises the potential for publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was unclear whether similar steps were taken in the study selection and validity assessment processes. Validity was assessed, although only the level of blinding and the composite score was presented.
There was little information on the included patients. Statistical heterogeneity was assessed and forest plots were presented for most meta-analyses. However, using a meta-analysis to pool significantly heterogeneous studies might not have been appropriate; the authors acknowledged the limitations of these heterogeneous analyses in their discussion. The authors' cautious conclusions appear to appropriately reflect the results from a small number of trials, but incomplete reporting of review methods and study quality and differences between the studies meant it was not possible to confirm the reliability of the conclusions.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that large, adequately powered RCTs with agreed defined outcomes and protocols are required to fully assess the potential benefits of volatile anaesthetic agents on MI and mortality in patients undergoing a CABG.

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