The variable effect of low-dose volatile anaesthetics on the acute ventilatory response to hypoxia in humans: a quantitative review

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Authors' objectives
To examine the effect of an anaesthetic dose (less than or equal to 0.2 minimal alveolar concentration, MAC) of halothane, isoflurane, enflurane and sevoflurane on the acute hypoxic ventilatory response in healthy people.

Searching
MEDLINE and PubMed Central were searched for articles published from January 1966 to August 2001. The searches were conducted using the terms 'anaesthetics', 'anesthetics', 'hypoxia', 'ventilation', 'breathing' and 'human' separately for each anaesthetic. The reference lists from the retrieved published papers, reference articles and correspondence were used to manually search the papers in listed journals. The authors of the publications retrieved through the electronic searches were also searched to identify further relevant publications. The following journals were manually searched: the British Journal of Anaesthesia, Anesthesiology, Anesthesia and Analgesia, Anaesthesia, Canadian Journal of Anaesthesia, Acta Anaesthesiologica Scandinavica, Journal of Physiology, Journal of Applied Physiology, Japanese Journal of Physiology and Respiration Physiology. In addition, abstracts from a range of relevant professional meetings and symposia, and unpublished doctoral theses were also searched; further details were provided in the review.

Study selection
Study designs of evaluations included in the review
The mention of control groups in the study inclusion criteria suggests that only controlled trials were eligible for inclusion in the review.

Specific interventions included in the review
Studies in which the anaesthetic dose of halothane, isoflurane, enflurane or sevoflurane was no higher than 0.2 MAC were included. Anaesthetic agents studied in only one article were excluded.

Participants included in the review
The participants were reported as being healthy human individuals only.

Outcomes assessed in the review
The acute hypoxic ventilatory response (in L/minute) had to be reported as one of the end points for both the intervention (anaesthetic) and control groups. The other outcomes reported were background carbon dioxide (CO2) and participant stimulations (audiovisual or painful).

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

Assessment of study quality
The author does not report the method used to assess validity, or how the validity assessment was performed.

Data extraction
The author does not state how the data were extracted for the review.

The following data were extracted: the anaesthetic employed; whether hypoxic stimulus was ramp (progressive hypoxia induced through rebreathing) or step (wherein the end-tidal pressure of oxygen failed to reach a nadir within 1 minute of the inspired hypoxic challenge); the level of background CO2 (normocapnia or hypercapnia); whether the
participants were stimulated (audiovisual input or pain); MAC; the number of participants; and the acute hypoxic ventilatory response. Standardised hypoxic response rates were calculated by dividing the acute hypoxic ventilatory response for the intervention by that for the control. In articles that published a standard error of the mean, this was converted into a standard deviation (SD), or pooled SD where appropriate.

Methods of synthesis
How were the studies combined?
The studies were combined in four ways.

1. The standardised hypoxic responses were grouped according to agent, and an average value calculated for each of the four anaesthetics. An analysis of variance was used to calculate the statistical significance of differences between the mean values for the different agents.

2. The standardised hypoxic responses were grouped according to the speed of hypoxic stimulus (step or ramp, ignoring all other factors), and an average value was calculated for each of the two speeds of hypoxic stimulus. Student's t-test was used to assess the statistical significance of the difference between the means values for the two groups.

3. The standard hypoxic responses were grouped according to the two levels of background CO2 (ignoring all other factors), and an average value was calculated for normocapnia and hypercapnia. Student's t-test was used to assess the statistical significance of the difference between the mean values for the two groups.

4. The standardised hypoxic responses were grouped according to the two levels of stimulation, and an average value was calculated for the two scenarios (stimulation and no stimulation). Student's t-test was used to assess the statistical significance of the difference between the mean values for the two groups. A p-value of less than 0.05 was considered to be statistically significant.

The effect of anaesthetic dose was explored by a linear regression analysis of the standardised hypoxic response versus dose.

Publication bias was assessed by plotting the standardised hypoxic response against the year of publication of the study for each agent. The plots were assessed visually for evidence of a marked trend in the results over time.

How were differences between studies investigated?
The author does not report using a formal test for heterogeneity. The values for the standardised hypoxic response were used to explore variability in the complete data set. Steps (2) to (4) (see 'How Were The Studies Combined') were repeated for each anaesthetic, to assess the factors that might contribute to the variability of the results. A sensitivity analysis was also performed by plotting the size of the study against each of the values of the standardised hypoxic response. This was used to assess any bias as a result of study size influencing the outcome.

Results of the review
A total of 37 studies (21 published articles, n=390) were included in the analysis.

Publication bias was found to be insignificant.

The mean standardised hypoxic response of all results was 0.56 (95% confidence interval, CI: 0.48, 0.64), suggesting a reduction in the control hypoxic ventilatory response by anaesthetic of 44%. The main factor influencing standardised hypoxic response was anaesthetic agent (p<0.002). The results for sevoflurane were more consistent than for the other agents but, on average, halothane depressed acute hypoxic ventilatory response the most (0.42, 95% CI: 0.32, 0.52). This was followed by enflurane (0.52, 95% CI: 0.25, 0.79), then isoflurane (0.71, 95% CI: 0.55, 0.87), and finally sevoflurane (0.72, 95% CI: 0.64, 0.80). The analysis of variance suggested that significant differences existed between these means (p<0.0001); post hoc Student's t-tests suggested that these differences were between the means for halothane and isoflurane (p<0.001) and halothane and sevoflurane (p<0.001).

Stimulation of the participants was found to be significant (p<0.014). However, the interaction term of agent and
stimulation was also significant (p<0.039), which suggested that the influence of the stimulation varied with the agent used. Anaesthetic dose and background CO2 were not significant.

Other groups of findings were also reported in the review.

**Authors' conclusions**
In contrast to previous reports that study conditions have a major impact upon the acute ventilatory response to hypoxia, the main determinant is actually the anaesthetic agent employed.

**CRD commentary**
The review question and the study selection criteria were stated clearly. The literature search was restricted to electronic searches of MEDLINE and PubMed Central, although extensive manual searches were also carried out. Language restrictions were apparently not applied. The author provided no information on the selection, validation or data extraction processes, and noted that there was no attempt to screen publications on the grounds of quality. Consequently, as the author admits, misleading data from 'poor quality' studies may have been included. The author stated that the reason for this was to include as many studies as possible in order to meet the objectives, which were to assess the influence of study conditions. The author states that relevant publications may have been missed on account of the data being contained within publications not specifically addressing the study question, rather than through the limitations of the electronic searches. The author offers a sound critique of the review in which the reasons for some of the generalisations or methods used are explained.

The range of statistical tests employed seem appropriate. The author's conclusions appear to be valid, but are appropriately cautious given the data presented and the limitations discussed.

**Implications of the review for practice and research**
Practice: The author states that the main influence on the acute ventilatory response to hypoxia in humans is that of the agent used, with halothane being the most effective. The state of arousal of patients to be anaesthetised should be taken into account.

Reviewer's comment: As this review was of experimental studies in healthy humans, implications for practice should be appropriately cautious.

Research: The author states that the action of volatile agents upon the human acute ventilatory response is worthy of further investigation. The influence of the effects of audiovisual stimulation and pain upon anaesthetic-induced depression of the acute hypoxic ventilatory response when different anaesthetic agents are employed should be investigated further; in particular, whether audiovisual stimulation will have no effect on the degree of depression of acute hypoxic response by halothane or sevoflurane.

There is apparently no research on the interaction of hypercapnia on acute hypoxic ventilatory response with halothane and few studies performed on enflurane, whilst all studies using sevoflurane have used background hypercapnia. Additional data are therefore needed to address these imbalances and to afford valid comparisons.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.