Nitrous oxide decreases shivering threshold in rabbits less than isoflurane

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\textbf{Background.} Comparable minimum alveolar concentration (MAC) fractions of volatile anaesthetics produce similar thermoregulatory impairment. Nitrous oxide, however, decreases the vasoconstriction threshold less than sevoflurane or isoflurane. We tested the hypothesis that nitrous oxide also decreases shivering threshold less than isoflurane alone or in combination.

\textbf{Methods.} Twenty-four rabbits were assigned randomly to one of three 0.3 MAC anaesthetic regimens: (i) nitrous oxide 69%; (ii) nitrous oxide 35% and isoflurane 0.3%; or (iii) isoflurane 0.6%. Body temperature was lowered by perfusing 10°C water through a U-shaped thermode positioned in the colon. Shivering was evaluated by inspection.

\textbf{Results.} The rabbits anaesthetized with nitrous oxide alone shivered at 37.0 (0.5)°C (P<0.01 vs other groups). In those given the nitrous oxide and isoflurane combination, the shivering threshold was 36.4 (0.5)°C and that in the isoflurane group was 35.9 (0.4)°C.

\textbf{Conclusion.} This study indicates that nitrous oxide reduces the shivering threshold less than isoflurane.

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The extent to which anaesthetics inhibit thermoregulatory control depends on both drug type and plasma concentration. Opioids\textsuperscript{1} and i.v. anaesthetics\textsuperscript{2} reduce the threshold for vasoconstriction and shivering as a linear function of dose. In contrast, volatile anaesthetics produce non-linear inhibition, the threshold reduction being proportionately greater at higher end-tidal concentrations.\textsuperscript{3, 4} However, the amount of inhibition with various volatile anaesthetics is similar at comparable minimum alveolar concentration (MAC) fractions.

Nitrous oxide decreases the vasoconstriction threshold less than the volatile anaesthetics sevoflurane and isoflurane.\textsuperscript{5} We therefore tested the hypothesis that nitrous oxide also decreases shivering threshold less than isoflurane alone or the combination of isoflurane with nitrous oxide.

\textbf{Methods and results}

With approval of our institutional Committee on Animal Research, we studied 24 male Japanese white rabbits, with mean weight 3.6 (range 2.7–4.0) kg. Ambient temperature was maintained near 24°C throughout the procedure.

The animals were anaesthetized by inhalation of isoflurane 1.0–2.5% (end-tidal concentration) and nitrous oxide 67% in oxygen. A femoral venous catheter was inserted and lactated Ringer’s solution 2–3 ml kg\textsuperscript{−1} h\textsuperscript{−1} was infused throughout the procedure. Each rabbit was intubated with a 3-mm tracheal tube and subsequently allowed to breathe spontaneously. Core temperature was cooled at a rate of 2–3°C h\textsuperscript{−1} by perfusing water at 10°C through a U-shaped thermode positioned in the colon.\textsuperscript{6} Twenty-four
rabbits were assigned randomly to one of three 0.3 MAC anaesthetic regimens: (i) nitrous oxide 69%; (ii) nitrous oxide 35% and isoflurane 0.3%; or (iii) isoflurane 0.6%. The MAC of nitrous oxide has not been reported in rabbits; we therefore assumed that MAC in rabbits is similar to that in rats.7 Nitrogen was added to keep $F_{IO2}$=0.3 in each group.

Core temperatures were recorded from the distal oesophagus at 1-min intervals. Shivering was evaluated by inspection by an observer blinded to group assignment.6 Sustained, vigorous shivering was considered physiologically significant. The core temperature triggering significant shivering identified the thermoregulatory threshold for this response. Arterial blood was sampled for gas analysis at the shivering threshold in each rabbit.

Morphometric characteristics, arterial oxygen partial pressures, shivering thresholds and haemodynamic and respiratory responses at the time of shivering were compared using one-way ANOVA and Student–Newman–Keuls tests. Data are expressed as mean (SD); $P$<0.05 identified statistically significant differences.

Weights did not differ among the three groups. Haemodynamic and respiratory responses at the time of shivering were also comparable (Table 1). Two of the rabbits receiving 0.3 MAC isoflurane did not shiver. Rabbits in the 0.3 MAC nitrous oxide group shivered at 37.0 (0.5)$^\circ$C. In contrast, the shivering threshold in the other two groups was significantly ($P$<0.01) reduced, to 36.4 (0.5)$^\circ$C during the combination of nitrous oxide and isoflurane, and 35.9 (0.4)$^\circ$C during isoflurane alone. Each anaesthetic or anaesthetic combination totalled 0.3 MAC. Individual thresholds are shown together with the mean and SD. The threshold during nitrous oxide alone differed significantly ($P$<0.01) from those in the other two groups.

**Comment**

Anaesthetic-induced thermoregulatory inhibition is the primary cause of intraoperative hypothermia.8 Hypothermia can be prevented by active warming, but is also limited by re-emergence of thermoregulatory vasoconstriction in patients who become sufficiently hypothermic. Once triggered, vasoconstriction prevents further core hypothermia by constraining metabolic heat to the core thermal compartment. Because thermoregulatory vasoconstriction is so effective, few anaesthetized patients become sufficiently hypothermic to shiver. However, anaesthetized humans who become sufficiently hypothermic do shiver,2,3 and shivering is common during recovery.

The first thermoregulatory defence against cold is vasoconstriction; the vasoconstriction threshold is defined by the core temperature triggering constriction. While all opioids1 and anaesthetics2–4 impair thermoregulatory control, they do not do so comparably. Previous work, for example, demonstrates that nitrous oxide impairs vasoconstriction less than equal MAC fractions of isoflurane.5 Our present results extend this finding by showing that nitrous oxide also reduces the shivering threshold less than equal MAC fractions of isoflurane.

Nitrous oxide was initially reported to have a subadditive contribution to MAC.9 However, this conclusion was based on a MAC for nitrous oxide in rats that was subsequently shown to be too low.7 Using the correct MAC for nitrous oxide, the contribution was indeed linear. Our results indicate that inhibition of thermoregulatory control is also a linear function of nitrous oxide and isoflurane dose. Linear responses for nitrous oxide and isoflurane suggest that various concentrations of nitrous oxide will inhibit thermoregulation less than equal MAC fractions of isoflurane.

A clear limitation of the present work is that we studied rabbits rather than humans. Nonetheless, thermoregulatory control systems are remarkably well preserved among mammalian species.10 It is thus unlikely that relative responses in humans would differ significantly. We con-

| Table 1 Weight and haemodynamic and respiratory responses at the time of shivering |
|---------------------------------|-----------------|-----------------|
|                                 | Nitrous oxide   | Nitrous oxide and isoflurane | Isoflurane |
| Shivered (n=8)                  | 8               | 8               | 6          |
| Weight (kg)                     | 3.6 (0.4)       | 3.6 (0.4)       | 3.7 (0.3)  |
| MAP (mm Hg)                     | 105 (10)        | 98 (7)          | 91 (9)     |
| Heart rate (beats min$^{-1}$)   | 245 (22)        | 246 (16)        | 232 (18)   |
| Arterial pH                     | 7.43 (0.05)     | 7.47 (0.04)     | 7.45 (0.05) |
| $P_{aco2}$ (kPa)                | 4.1 (0.9)       | 3.9 (0.8)       | 4.2 (0.8)  |
| $P_{ao2}$ (kPa)                 | 22.8 (1.6)      | 21.8 (1.7)      | 21.7 (1.3) |

MAP=mean arterial pressure; $P_{aco2}$=arterial carbon dioxide partial pressure; $P_{ao2}$=arterial oxygen partial pressure.
clude that nitrous oxide reduces the shivering threshold less than isoflurane.

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