Cardiovascular effects of 50% nitrous oxide in older adult patients anaesthetized with isoflurane or halothane

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Summary

We have studied the cardiovascular effects of equipotent concentrations of halothane or isoflurane, with or without 50% nitrous oxide in oxygen, in 80 patients, aged 60 yr or more, during 20 min of stable equipotent anaesthesia. Non-invasive measurement techniques were used, with suprasternal Doppler ultrasonography for estimating cardiac output. Both isoflurane and halothane reduced heart rate and systemic arterial pressure. With isoflurane, mean rate decreased from 72 (so 9.7) to 67 (10.4) beat min⁻¹ and with halothane from 76 (10.1) to 65 (9.1) beat min⁻¹ (P<0.05). Mean diastolic arterial pressure decreased from 81 (11.3) to 58 (17.0) mm Hg with isoflurane and from 86 (14.7) to 70 (13.3) mm Hg with halothane (P<0.05). Cardiac index decreased from 3.1 (1.03) to 2.7 (0.71) litre min⁻¹ m⁻² with isoflurane and from 3.1 (0.98) to 2.5 (0.57) litre min⁻¹ m⁻² with halothane (P<0.05). Systemic vascular resistance decreased significantly in all groups except those receiving halothane with nitrous oxide. Nitrous oxide resulted in significantly less depression of cardiac index when given with isoflurane than when given with halothane. The mean percentage change in cardiac index during isoflurane anaesthesia without nitrous oxide was 16.7%; with nitrous oxide there was a 0.5% increase. Halothane, in combination with nitrous oxide, resulted in greater depression of cardiac index than isoflurane with nitrous oxide. The mean percentage change with halothane was 20.4% (22.2%); with isoflurane there was a 0.5% (27.1%) increase (P<0.05). Hypotension was more pronounced in patients anaesthetized with isoflurane (n=40) than those anaesthetized with halothane (n=40), irrespective of the presence of nitrous oxide. The mean percentage decrease with isoflurane was 29.7% (21.1%) compared with 16.8% (16.78%) with halothane (P<0.05). (Br. J. Anaesth. 1998; 80: 169–173)

Keywords: anaesthetics volatile, halothane; anaesthetics volatile, isoflurane; anaesthetics gases, nitrous oxide; heart, cardiac output; measurement techniques, Doppler ultrasonography; age factors

Previously published work by our group showed that cardiac output was less well maintained in elderly patients compared with their younger counterparts during isoflurane anaesthesia.² We attributed this to reduced cardiovascular sensitivity to sympathetic stimulation.

We report on the cardiovascular effects of nitrous oxide when given with halothane or isoflurane in the elderly.

Patients and methods

After obtaining approval from the University Research Ethics Committee and written, informed consent, we studied 80 ASA I or II patients, aged 60 yr or more, within 20% of their predicted lean body mass. Patients were not included if they were receiving cardioactive medication or had a history of cardiovascular disease, had recently received halothane or had a history of malignant hyperpyrexia. Temazepam 10–20 mg orally was given 1 h before the study commenced.

Patients were allocated randomly to one of four groups (n=20 in each) to receive isoflurane or halothane at 1 MAC end-tidal concentration in 100% oxygen (1.05% or 0.65%, respectively) or the same agents in a 50% mixture of nitrous oxide in oxygen at 1 MAC (0.55% or 0.35%, respectively). Cardiac output was measured using a Dataspoke Accucom cardiac output monitor. This device uses the Doppler principle to measure blood velocity in the ascending aorta. Measurements were obtained in duplicate from the suprasternal notch. Baseline measurements of cardiac output, systemic arterial pressure and heart rate were made after a 10-min period of stabilization in the anaesthetic room. Systemic arterial pressure and heart rate were measured by a Dataspoke Accutorr and the ECG was monitored throughout the study. All the data were collected before surgery commenced.

Anaesthesia was induced with etomidate 0.3 mg kg⁻¹ followed by 1-mg increments for initial maintenance. Atracurium 0.5 mg kg⁻¹ was given at the same time to facilitate tracheal intubation with a Portex gas sampling tube, performed 90 s after induction. Two minutes after intubation (time 0) the

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A volatile agent was introduced at an inspired concentration chosen to attain 1 MAC (end-tidal) within 2 min. The lungs were ventilated to an end-tidal carbon dioxide partial pressure of 4.5 kPa. Measurements of arterial pressure, heart rate, cardiac output and volatile agent were made at time 0 and every 2 min for 20 min. During this time the patient remained undisturbed and the inspired volatile agent concentration was adjusted to maintain 1 MAC expired concentration, as measured by a Datex Normac.

Data were collected on-line using a BBC microcomputer which was interfaced with the Accucom and the Normac.* The computer collected and stored data on arterial pressure, heart rate and cardiac output, together with other Doppler information (ejection time, signal strength and heart rate). It also sampled intermittently the concentration of volatile agent over a 10-s period from the Normac and calculated peak and trough concentrations of volatile agent. The Normac/computer system was calibrated with a standard gas before each study. Data were stored on diskette for later retrieval. Cardiac index, stroke distance and minute distance were calculated for each measurement using a nomogram-derived estimate for body surface area.

Results were analysed using two- or three-factor repeated measures analysis of variance to give a broad perspective. To improve the power of the factorial design of the study, summary measures were made for each of the measured variables. Two-factor ANOVA was then used to compare the effects of volatile agent or nitrous oxide, or both, using contrast analyses, with the Newman–Keul’s test for appropriate individual comparisons. Chi-square and Mann-Whitney U tests were applied to non-parametric data. P < 0.05 was considered statistically significant.

### Results

Table 1 shows patient characteristics, ventilatory and other data for the elderly patients anaesthetized with halothane or isoflurane in 100% oxygen or 50% nitrous oxide in oxygen (mean (SD)). *P < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Isoflurane</th>
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<tbody>
<tr>
<td></td>
<td>100% Oxygen</td>
<td>50% Nitrous oxide</td>
</tr>
<tr>
<td>Sex (M/W)</td>
<td>11/9</td>
<td>7/13</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>72 (5.8)</td>
<td>71 (5.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 (14.2)</td>
<td>71 (12.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 (8.1)</td>
<td>163 (13.0)</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.75 (0.206)</td>
<td>1.74 (0.196)</td>
</tr>
<tr>
<td>Etomidate (mg)</td>
<td>24.7 (3.69)</td>
<td>27.1 (5.35)</td>
</tr>
<tr>
<td>Atracurium (mg)</td>
<td>36.3 (8.76)</td>
<td>36.3 (6.77)</td>
</tr>
<tr>
<td>Minute volume (litré)</td>
<td>5.23 (1.219)</td>
<td>5.48 (1.045)</td>
</tr>
<tr>
<td>Tidal volume (ml)</td>
<td>665 (101.4)</td>
<td>680 (96.5)</td>
</tr>
<tr>
<td>P&lt;sub&gt;i&lt;/sub&gt; (cm H₂O)</td>
<td>16.1 (3.82)</td>
<td>19.1 (3.24)*</td>
</tr>
<tr>
<td>Cutaneous weals (n)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1 Mean (so) heart rate (HR) in all subjects receiving isoflurane or halothane.

Figure 2 Mean (so) heart rate (HR) in all subjects receiving either volatile agent and 50% nitrous oxide (N₂O) in oxygen or 100% oxygen (O₂).

Figure 3 Mean (so) systolic (SAP) and diastolic (DAP) arterial pressures in patients receiving 1 MAC of isoflurane or halothane.

Table 1 Patient characteristics, ventilatory and other data for the elderly patients anaesthetized with halothane or isoflurane in 100% oxygen or 50% nitrous oxide in oxygen (mean (so)). P<sub>i</sub> = peak airway inflation pressure. *P < 0.05
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Systemic vascular resistance was reduced to a greater extent by isoflurane than halothane (\(n=40\)) \((P<0.05)\) (fig. 7). There was little change when nitrous oxide was added to either agent \((n=40)\) \((P>0.05)\) (fig. 8).

**Discussion**

Ventilation to an end-tidal carbon dioxide value of 4.5 kPa was based on previous work\(^7\) which demonstrated that this value resulted in normocapnia in this age group of patients. Indeed, arterial blood samples showed that mean arterial \(P_{CO_2}\) was 4.9 kPa.

Atracurium was chosen because of its minimal effect on the cardiovascular system. Other neuromuscular blocking agents have been associated with vagal reactions and altered pharmacokinetics in the elderly.

Most studies on the cardiovascular effects of nitrous oxide alone would suggest that it exhibits a sympathomimetic action\(^8,9\) and these effects have also been demonstrated when nitrous oxide is used in conjunction with other anaesthetic agents, with an increased systemic vascular resistance being the most consistent finding.\(^4,10,11\)

Reports on the effect of nitrous oxide in combination with volatile anaesthetic agents on heart rate have been inconsistent.\(^11–13\) In the older adult, isoflurane in oxygen was associated with a decrease in heart rate\(^5\) and the addition of nitrous oxide (with equal anaesthetic potency) has now been shown to increase this effect. Halothane in oxygen was also associated with a reduced heart rate but nitrous oxide did not change this effect. These findings, attributed to the limited responsiveness of the aged cardiovascular system to sympathomimetic effects,\(^14–19\) may explain the absence of an increase in heart rate in this study.

It has been demonstrated previously that nitrous oxide reduces the decline in arterial pressure associated with isoflurane\(^12,20\) and halothane\(^21,22\) in healthy young adults, a finding corroborated by these results. The use of 100% oxygen in the control group may itself have contributed to some cardiovascular changes, although oxygen alone has been shown to increase arterial pressure and systemic vascular resistance.\(^23\)

Systemic vascular resistance was increased by the addition of nitrous oxide to halothane but was reduced similarly in both groups receiving isoflurane anaesthesia. As a sole agent or in conjunction with halothane, nitrous oxide has been shown to exert a peripheral vasoconstricting effect in healthy adults and animals.\(^3,10,11,24\) However, these effects were not replicated during isoflurane anaesthesia; indeed, Dolan and colleagues\(^20\) indicated that systemic vascular resistance was higher in the absence of nitrous oxide, although they did not compensate for altered anaesthetic potency.

Isoflurane, halothane and nitrous oxide exhibit dose-dependent myocardial depression by interacting with Ca\(^{2+}\) effects in the myocyte;\(^25–27\) although the exact mechanisms may differ between halothane and isoflurane.\(^28–30\) Reducing the concentration of the volatile agent by adding a less potent myocardial depressant drug (nitrous oxide)\(^26\) should reduce depression of cardiac function, but we found that this occurred only with isoflurane. Lawson, Frazer and Lynch\(^27\) found that nitrous oxide, in common with halothane, reduced Ca\(^{2+}\) release from the sarcoplasmic reticulum of the myocyte but that the effects of isoflurane were of a different character. However, they found that the addition of nitrous oxide to either halothane or isoflurane caused simple additive depression of myocardial function with both agents. There is evidence that uptake of Ca\(^{2+}\) by sarcoplasmic reticulum of aged myocytes is deficient\(^31\) and this
alone; there was, however, greater depression of heart rate. Systemic vascular resistance was unaffected. Nitrous oxide with halothane resulted in a greater decrease in cardiac output, increased systemic vascular resistance and no alteration in heart rate. This suggests that, in terms of cardiovascular responses, nitrous oxide supplementation may be beneficial during isoflurane, and detrimental during halothane anaesthesia in older age groups.

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References
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