EFFECT OF NITROUS OXIDE ON THE CARDIOVASCULAR SYSTEM AND CORONARY CIRCULATION OF THE DOG

J. THORBURN, G. SMITH, J. P. VANCE AND D. M. BROWN

SUMMARY

A comparison was made in seven dogs anaesthetized with pentobarbitone of cardiovascular measurements during ventilation with 65–70% nitrous oxide in oxygen and ventilation with 65–70% nitrogen in oxygen. The substitution of nitrous oxide for nitrogen was found to be associated, after 15 min, with a significant decrease in cardiac output and significant increases in right atrial and left ventricular end-diastolic pressure and systemic vascular resistance. There was no significant change in mean coronary artery flow, coronary vascular resistance or myocardial oxygen consumption.

Previous laboratory studies of the systemic cardiovascular effects of nitrous oxide have yielded conflicting results. Lundborg, Milde and Theye (1966) and Smith and Corbascio (1966) found little cardiovascular effect, whereas Craythorne and Darby (1965) found evidence of myocardial depression. Results of clinical studies of the effect of nitrous oxide have been at variance also. For example, Bahlman and colleagues (1971) found no evidence of cardiovascular depression, whereas Eisele and Smith (1972) observed marked depression of cardiac function. Certainly different models, techniques and methods have been utilized and these may account for the divergent results.

There are relatively few studies of the effects of nitrous oxide on the coronary circulation. The present investigation was designed to study the effect of nitrous oxide on canine coronary blood flow together with any associated changes in the systemic circulation.

METHODS

Anaesthesia was induced in seven greyhounds (weight range 21–29 kg) with thiopentone 15–20 mg kg⁻¹ and pentobarbitone 30 mg kg⁻¹. Suxamethonium 50–100 mg was given i.v. to facilitate endotracheal intubation. Intermittent positive pressure ventilation with a mixture of oxygen in nitrogen was provided by a Palmer sine-wave pump, the ventilation being adjusted to produce $\frac{P}{\text{CO}_2}$ 5.2 kPa. The inspired oxygen mixture was adjusted to produce $\frac{P}{\text{O}_2}$ 12.0 kPa.

Catheters were inserted into the ascending aorta and left atrium via the left femoral vessels to permit pressure recording and blood sampling. Under radiographic control, a catheter was introduced into the coronary sinus via the internal jugular vein and a second catheter was inserted, via the carotid artery, into the left ventricle for the measurement of left ventricular end diastolic pressure (LVEDP) using an Elema–Schonander capacitance transducer. The frequency response of this catheter manometer system was found to be flat only to 25 Hz. Frequencies greater than this were filtered out electronically. Therefore, it is appreciated that, while this system produces acceptably accurate measurement of LVEDP, no great reliance can be placed on the accuracy of the measurement of $\frac{dp}{dt}$ max. In view of the small changes which were noted in this variable, the results are not significant and are not reported.

A Swan–Ganz catheter was introduced into the pulmonary artery under radiographic control for sampling of mixed venous blood. A left thoracotomy was performed, and after incision of the pericardium, a small length of the circumflex or anterior descending branch of the left coronary artery was dissected out carefully, and a suitable electromagnetic flow transducer with non-occlusive zero was applied and connected to a flow meter (Statham SP 2202). Similarly, a suitable flow probe was placed around the pulmonary artery. After satisfactory siting, the lung was reinflated and collapse minimized by the use of 5 cm H₂O positive end-expiratory pressure. Cardiac output was measured from the pulmonary artery flow probe. The accuracy of the Statham flow meter has been assessed against an absolute technique.
of measurement of flow and a correlation coefficient of 0.99 was found ($y = 1.134x - 9.00$) (Vance et al., 1979).

Blood-gas tensions and pH were measured using suitably calibrated electrodes (IL 213). Systemic arterial, pulmonary arterial and coronary sinus blood-gas tensions were corrected for the differences in temperature between the electrodes and the mid-oesophageal temperature of the animal. Blood oxygen content was calculated from the equation:

$$O_2 \text{ content (ml dl}^{-1} = \text{Hb concn (g dl}^{-1}) \times 1.36 \times \% \text{ satn} + P_{aO_2} \text{(kPa)} \times 0.0232$$

This has been found to correlate satisfactorily with the Van Slyke method of measurement of blood oxygen content as used in this laboratory (Ledingham et al., 1970).

The techniques used in the preparation, and the calculation of derived variables, have been discussed in greater detail in a recent publication (Vance et al., 1979).

After surgery, a control period of 30 min was observed to allow the preparation to stabilize and duplicate measurements were obtained during ventilation with 65-70% nitrogen in oxygen to ensure that a steady baseline had been obtained. After this, measurements were obtained following 15 min ventilation of the lungs with either 65-70% nitrogen in oxygen or 65-70% nitrous oxide in oxygen. Subsequently, the inspired gas was changed and after 15 min the measurements were repeated. In each dog, four sets of measurement were obtained for ventilation alternately with either nitrous oxide in oxygen or nitrogen in oxygen and the order of presentation of the gases was randomized over the seven experiments. Mean values of measurement were obtained for the two sets of corresponding data for each animal and the mean values for the seven animals compared by two-tailed Student’s $t$ test for paired data.

**RESULTS**

No statistically significant changes occurred in arterial, pulmonary arterial or coronary sinus blood-gas measurements during the various phases of the study.

Nitrous oxide produced a 21% increase in peripheral resistance but no change in heart rate or arterial pressure (table I). In addition, myocardial contractility was depressed as revealed by an 11% decrease in cardiac output, a 27% increase in LVDEP and a 12% increase in right atrial pressure (table II).

Nitrous oxide produced no significant changes in mean or systolic coronary blood flow or coronary artery resistance. There was a small but statistically significant increase in diastolic coronary artery flow (table III). This was associated with a significant increase in myocardial oxygen availability (table IV), although total body oxygen availability decreased as did total body oxygen consumption. There was no change in myocardial oxygen consumption or extraction (table III).

| TABLE I. Effect of nitrogen in oxygen and nitrous oxide in oxygen mixtures on heart rate, mean arterial pressure and total peripheral resistance (mean ± SEM; n = 7) |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | N$_2$/O$_2$     | N$_2$O/O$_2$    | % Change from nitrogen phase | Significance |
| Heart rate (beat min$^{-1}$)    | 156.0 ± 5.2     | 159.0 ± 4.8     | —                | n.s.         |
| Mean arterial pressure (mm Hg)  | 138.0 ± 6.7     | 139.0 ± 6.3     | —                | n.s.         |
| Total peripheral resistance (unit) | 47.4 ± 6.23     | 57.3 ± 8.7      | + 21%            | < 0.05       |

| TABLE II. Effect of nitrogen in oxygen and nitrous oxide in oxygen mixtures on cardiac function (mean ± SEM; n = 7) |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | N$_2$/O$_2$     | N$_2$O/O$_2$    | % Change from nitrogen phase | Significance |
| Cardiac output (litre min$^{-1}$) | 3.6 ± 0.43      | 3.2 ± 0.4       | -11%            | < 0.01       |
| Mean right atrial pressure (mm Hg) | 2.4 ± 0.3       | 2.8 ± 0.3       | + 12%           | < 0.01       |
| LVDEP (mm Hg)                   | 11.2 ± 1.9      | 14.2 ± 2.2      | 27%             | < 0.025      |
TABLE III. Effect of nitrogen in oxygen and nitrous oxide in oxygen mixtures on the coronary circulation (mean ± SEM; n = 7)

<table>
<thead>
<tr>
<th></th>
<th>N₂/O₂</th>
<th>N₂O/O₂</th>
<th>% Change from nitrogen phase</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean coronary artery flow</td>
<td>62 ± 7.8</td>
<td>64 ± 8.1</td>
<td>-</td>
<td>n.s.</td>
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<tr>
<td>(ml min⁻¹)</td>
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<tr>
<td>Mean coronary artery</td>
<td>255 ± 23.0</td>
<td>259 ± 24.0</td>
<td>-</td>
<td>n.s.</td>
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<tr>
<td>resistance (unit)</td>
<td></td>
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<tr>
<td>Systolic coronary artery</td>
<td>36 ± 6.5</td>
<td>36 ± 6.0</td>
<td>-</td>
<td>n.s.</td>
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<tr>
<td>flow (ml min⁻¹)</td>
<td></td>
<td></td>
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<tr>
<td>Diastolic coronary artery</td>
<td>88 ± 10.0</td>
<td>95 ± 10.0</td>
<td>+8</td>
<td>&lt;0.05</td>
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<td>flow (ml min⁻¹)</td>
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</table>

TABLE IV. Effect of nitrogen in oxygen and nitrous oxide in oxygen on myocardial and total body oxygenation (mean ± SEM; n = 7)

<table>
<thead>
<tr>
<th></th>
<th>N₂/O₂</th>
<th>N₂O/O₂</th>
<th>% Change from nitrogen phase</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Myocardial</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxygen availability</td>
<td>14.1 ± 1.8</td>
<td>14.8 ± 1.8</td>
<td>+7</td>
<td>&lt;0.05</td>
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<tr>
<td>(ml min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxygen extraction (%)</td>
<td>63.0 ± 2.2</td>
<td>61.0 ± 2.0</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Oxygen consumption (ml min⁻¹)</td>
<td>9.0 ± 1.0</td>
<td>9.0 ± 1.0</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total body</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oxygen availability</td>
<td>805.0 ± 98.0</td>
<td>724.0 ± 93.1</td>
<td>-10</td>
<td>&lt;0.05</td>
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<tr>
<td>(ml min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen extraction (%)</td>
<td>25.0 ± 1.9</td>
<td>26.0 ± 2.7</td>
<td>-</td>
<td>n.s.</td>
</tr>
<tr>
<td>Oxygen consumption (ml min⁻¹)</td>
<td>177.0 ± 14.1</td>
<td>151.0 ± 10.7</td>
<td>-15</td>
<td>&lt;0.05</td>
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</table>

DISCUSSION

The results of the present study reveal that nitrous oxide produced small but significant changes in cardiac output, mean right atrial pressure and left ventricular end-diastolic pressure which were consistent with a decrease in myocardial contractility. There were no significant changes in mean arterial pressure or heart rate, but nitrous oxide produced a significant increase in total systemic peripheral resistance.

Several earlier reports describing cardiovascular collapse in patients anaesthetized with oxygen and halothane in a closed circuit system following the introduction of nitrous oxide into the system suggested that nitrous oxide produced cardiovascular depression (Ap Ivor, 1959; Young and Lodge, 1959; Johnstone, 1961). However, the data in these earlier reports are difficult to interpret as a result of uncontrolled variables. Subsequently, there have been many controlled laboratory and clinical studies, some of which have indicated a dominant effect on myocardial contractility and some a dominant effect on the peripheral circulation (table V). These differences may be accounted for by the use of different species, different techniques of assessment of cardiovascular changes and myocardial contractility and the presence of different anaesthetic agents used for background anaesthesia. It is well known that myocardial contractility may be altered by inhalation anaesthetic agents, changes in arterial carbon dioxide tension and increased arterial oxygen tensions—factors which have varied in previous studies and which may have masked any changes produced by nitrous oxide. In table VI are listed the studies from table V in which myocardial contractility has been evaluated. In almost every instance there was a trend towards a reduction in myocardial contractility, although the authors’ analyses revealed that the trend was not statistically significant.
There is little doubt that the cardiovascular effects of nitrous oxide in the intact animal preparation or human are small (tables V and VI) and these may be obscured by other physiological changes or pharmacological effects. In vitro, there is good evidence that nitrous oxide produces a decrease in myocardial contractility (Price and Helrich, 1955; Price, 1976). Although Goldberg, Young and Phear (1972) observed a decrease in myocardial contractility with nitrous oxide in papillary cardiac muscle, similar changes were seen with the same concentration of nitrogen. However, the production of hypoxia was invoked as the mechanism accounting for this paradox (Price, 1976).
CARDIOVASCULAR EFFECTS OF NITROUS OXIDE

In the systemic circulation, nitrous oxide would appear to exert effects similar to those of an alpha-adrenergic agonist (Cullen, 1972; Leighton and Koth, 1973). Thus, a reduction in forearm blood flow was found in subjects anaesthetized with nitrous oxide and subsequently there was an increase in the urinary excretion of catecholamines (Smith et al., 1970). In addition, Eisele and colleagues (1976) observed an increase in plasma noradrenaline concentrations in association with the administration of nitrous oxide in patients. It is interesting that, although pentobarbitone is usually associated with a reduction in sympathetic responses, Eisele and colleagues (1969) observed that awake animals with chronically implanted aortic flow meters exhibited the same type of responses to nitrous oxide as did animals anaesthetized with pentobarbitone. In addition, Millar and co-workers (1970) found that pentobarbitone did not alter the sympathetic response of animals to nitrous oxide.

It would be anticipated that the small effects of nitrous oxide on both myocardial contractility and peripheral resistance would be associated with negligible changes in the coronary circulation and this is confirmed by the results of the present study. Although a small increase in diastolic coronary blood flow occurred, there was no significant change in mean coronary artery flow or mean coronary artery resistance. No change in myocardial blood flow was found by Dottori and colleagues (1976) during ventilation of dogs with either 50% nitrogen in oxygen or 50% nitrous oxide in oxygen. When the concentration of nitrous oxide was increased to 80%, a decrease in coronary vascular resistance occurred, permitting an increase in myocardial blood flow. It is well known that hyperoxia produces vasoconstriction in the coronary circulation so this change may be interpreted as a reduction in the vasocostrictive effect of oxygen rather than a vasodilator effect of nitrous oxide. In the present study, the concentration of nitrous oxide was 65–70%, and this value was chosen in order to produce a normal arterial oxygen tension. Under these circumstances, there was no change in mean coronary artery flow.

The systemic effects of nitrous oxide seen in the present study were similar to those found by previous investigators (table V) and comprise an increase in peripheral resistance and a reduction in cardiac output with an associated reduction in total body oxygen availability.

The clinical implications of the present study are small. However, it would be expected that in patients with impaired myocardial contractility and a high degree of resting sympathetic activity, the exhibition of nitrous oxide may be associated with detectable cardiovascular depression. Nitrous oxide would not be expected to have any direct effects on the coronary circulation, but changes in myocardial blood flow may occur secondary to alterations in myocardial contractility and external cardiac work.

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REFERENCES


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