Direct Myocardial Effects of Nitrous Oxide

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Eight isometrically contracting rat left ventricular trabeculae carnaeae muscle preparations were exposed to concentrations of 25, 50, and 75 vol per cent of both N₂O and N₂. Both gases depressed peak developed isometric tension and the maximum rates of tension development and relaxation in relation to the gas concentrations. In five other muscles, paired electrical stimulation reversed the negative inotropic effects of N₂O and N₂. The relative potentiation of contractility achieved with paired stimulation was the same in the presence of O₂, N₂O, and N₂. Since N₂O did not produce any additional depressant effects over and above those observed with N₂, and since the positive inotropic effects of paired stimulation were unchanged by this anesthetic, it was concluded that N₂O does not possess any direct myocardial depressant or stimulant properties. (Key words: Nitrous oxide; Nitrogen; Myocardial contractility; Paired electrical stimulation; Rat heart muscle.)

The analgesic properties of nitrous oxide (N₂O) have made it possible to reduce the minimum alveolar concentrations of halothane,¹ fluroxene,² and methoxyflurane³ necessary for surgical anesthesia. The decreased anesthetic concentrations permitted by the addition of N₂O may result in less cardiovascular depression than would otherwise exist.⁴ However, no data on the direct effects of N₂O on isolated mammalian heart-muscle preparations have been reported. The present study was under-

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taken to determine these direct inotropic effects of N₂O, and to compare them with those of nitrogen (N₂).

Methods

Thirteen rat left ventricular trabeculae carnaeae muscles were prepared for isometric contractions, as previously described.⁸ The muscles averaged 5.44 mm in length and 2.2 mg in dry weight. Field stimulation was carried out at a rate of 15/min with platinum electrodes placed parallel to the muscle, using square-wave pulses of 6 msec duration and voltages 10 per cent above threshold. All experiments were conducted at 37 C.

For the first hour, equilibration with isometric contractions was allowed to occur with a gas mixture of 95 per cent O₂ and 5 per cent CO₂ (P<sub>O₂</sub> 635 torr). During the first 30 minutes, each muscle was gradually stretched until peak isometric tension was reached. This length was maintained for the duration of the experiment.

Eight muscles were then exposed to three concentrations (25, 50, 75 vol per cent)§ of both N₂O and N₂. The effects of the experimental gases were computed as the differences between the observed measurements and the averages of two control observations obtained with 95 per cent O₂-5 per cent CO₂ before and after three administrations of N₂O or N₂. The order of administering these concentrations was based on a table of random numbers. Each concentration was administered for 15 minutes and was followed by a complete bath change.

In five additional muscles, the effects of sus-

§ Since all gases contained 5 per cent CO₂ plus N₂ or N₂O with the balance O₂, the actual concentrations were closer to 24, 48, and 71 per cent. The corresponding oxygen tensions were 478, 333, and 167 torr, respectively. Since the 25, 50, and 75 per cent values are within the limits of accuracy of our flowmeters, we used these designations for the sake of convenience.
tained paired electrical stimulation (PS) in the presence and absence of 75 per cent N₂O and 75 per cent N₂ were observed. PS was achieved by introducing a second stimulus just prior to the end of the absolute refractory period of the first stimulus. With this technique, two electrical events occur, but only one mechanical event occurs. The resulting contraction is a potentiated one.

The following measurements were made in all experiments: \( T_{\text{pdr}} \), peak developed tension (g/mm²); \( T_r \), resting tension (g/mm²); \( +dP/dt \), maximum rate of tension development (g/mm²/sec); \( -dP/dt \), maximum rate of tension relaxation (g/mm²/sec); TPT, time to peak isometric tension, the time from onset of tension development to the peak of the twitch (msec); RT₅₀₉₅, time for tension to decay 90 per cent of maximum, measured from the peak of the twitch (msec).

Statistical analysis was based on linear regression and analysis of variance methods, with \( P < 0.05 \) taken as the level of significance.

Results (Table 1)

With the standard "single" type of electrical stimulation, both N₂O and N₂ depressed \( T_{\text{pdr}} \) in relation to the concentration, and the effects ranged from -21 to -54 per cent in both cases. Similar changes occurred in the maximum rate of tension development, with the effects varying from 17 to 50 per cent depression. Comparable changes were observed in \( -dP/dt \); here the effects ranged from -21 to -55 per cent (fig. 1, table 1).

All these effects correlated directly with the gas concentrations. The regression coefficient values for \( T_{\text{pdr}} \), \( +dP/dt \), and \( -dP/dt \) on N₂O concentrations were -0.751 \( (P < 0.001) \), -0.476 \( (P < 0.01) \), and -0.544 \( (P < 0.01) \), respectively. On the N₂ concentrations, these values were -0.659 \( (P < 0.001) \), -0.461 \( (P < 0.01) \), and -0.429 \( (P < 0.05) \), respectively.

There were no statistically significant changes in TPT or RT₅₀₉₅ (fig. 2). Although an increase in \( T_r \) occurred with increasing gas concentrations (fig. 2), this trend did not achieve statistical significance until the 75 per cent concentrations were reached (fig. 2, table 1).

Analysis of variance revealed statistically significant differences among the subgroups (25, 50, 75 per cent N₂ or N₂O) within each treatment (N₂ or N₂O) for \( T_{\text{pdr}} \), \( +dP/dt \), and \( -dP/dt \) \( (P < 0.05) \). However, there were no significant differences between treatments for any of these variables. Thus, the changes produced by both N₂O and N₂ were dose-dependent, but were identical in both qualitative and quantitative terms.

In the absence of N₂O and N₂, sustained paired electrical stimulation (PS) increased \( T_{\text{pdr}} \), \( +dP/dt \), and \( -dP/dt \) by 126, 128, and 142 per cent, respectively (figs. 3, 4; table 2: 95 per cent O₂, single stimulus, vs. 95 per cent O₂, paired stimulus). When paired stimulation was applied in the presence of 75 vol per cent of these gases, the level of contractility was elevated above that which existed in their absence with single stimulation (95 per cent O₂, single stimulus, vs. 75 per cent N₂O, paired stimulus, and vs. 75 per cent N₂, paired stimulus).

Although the absolute potentiation of contractility was greatest in presence of O₂, the relative potentiation produced by paired stimulation was the same whether or not the muscles were depressed by N₂O or N₂ (fig. 4; table 2). In the presence of N₂O, paired stimulation increased \( T_{\text{pdr}} \) by 106 per cent, \( +dP/dt \) by 99 per cent, and \( -dP/dt \) by 150 per cent. Similar alterations were observed with 75 per cent N₂ and 95 per cent O₂. Analysis of variance indicated no statistically significant differences among these changes in the presence of O₂, N₂ and N₂O.

Discussion

The tissue preparation utilized in this study receives its oxygen supply by diffusion only, not by capillary perfusion. Nevertheless, since the cross-sections of our preparations are elliptical in shape, and since the maximum distance needed for diffusion of oxygen to the cores of these tissues is 0.5 mm or less, no hypoxia would be expected in the muscle with 95 per cent oxygen aerating the bath. However, a decrease in \( P_{O_2} \) of 25 per cent or more, especially at a temperature of 37°C, may result in some lack of oxygen at the muscle core, causing a modification in the muscles' mechanical performance. Such modifications were observed with N₂.
Table 1. Effects of N₂O and N₂ on Mechanical Properties of Heart Muscle: Per Cent Changes from Control (± SE)

<table>
<thead>
<tr>
<th></th>
<th>Peak Developed Tension (T₉₀)</th>
<th>Maximum Rate of Tension Development (+dP/dt)</th>
<th>Maximum Rate of Tension Relaxation (−dP/dt)</th>
<th>Resting Tension (T₀)</th>
<th>Time to Peak Isometric Tension (TFT)</th>
<th>Time for Tension to Decay 90 Per Cent of Maximum (R₁/T₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
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<tr>
<td>25 Per Cent</td>
<td>−21.3 ± 5.0</td>
<td>−19.8 ± 4.9</td>
<td>−23.5 ± 4.1</td>
<td>+4.8 ± 8.9</td>
<td>−0.04 ± 4.2</td>
<td>−1.71 ± 1.4</td>
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<tr>
<td>50 Per Cent</td>
<td>−36.0 ± 4.7</td>
<td>−43.4 ± 3.5</td>
<td>−53.1 ± 3.8</td>
<td>+22.9 ± 8.9</td>
<td>−0.03 ± 4.4</td>
<td>−7.93 ± 3.1</td>
</tr>
<tr>
<td>75 Per Cent</td>
<td>−54.1 ± 6.7</td>
<td>−49.7 ± 3.4</td>
<td>−57.8 ± 5.5</td>
<td>+35.1 ± 8.7</td>
<td>−3.29 ± 4.5</td>
<td>−3.85 ± 2.9</td>
</tr>
<tr>
<td>Nitrogen</td>
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<tr>
<td>25 Per Cent</td>
<td>−31.2 ± 6.4</td>
<td>−17.1 ± 2.9</td>
<td>−29.9 ± 2.2</td>
<td>−5.0 ± 2.4</td>
<td>−2.21 ± 4.2</td>
<td>−2.62 ± 6.2</td>
</tr>
<tr>
<td>50 Per Cent</td>
<td>−31.9 ± 5.4</td>
<td>−29.2 ± 2.3</td>
<td>−31.1 ± 3.9</td>
<td>−6.0 ± 3.7</td>
<td>−10.99 ± 2.7</td>
<td>−3.73 ± 2.9</td>
</tr>
<tr>
<td>75 Per Cent</td>
<td>−32.6 ± 4.0</td>
<td>−41.0 ± 3.2</td>
<td>−31.1 ± 4.3</td>
<td>−6.0 ± 4.2</td>
<td>−10.08 ± 4.3</td>
<td>−10.51 ± 4.4</td>
</tr>
</tbody>
</table>

*p* values indicate statistical significance of difference from control: *p* < 0.05; † *p* < 0.01; ‡ *p* < 0.001.

If N₂O directly depressed myocardial contractility, we would have expected additional changes in myocardial function over and above those seen with N₂. These additional alterations were not produced by N₂O. All changes in the performance of myocardial tissue observed in the presence of N₂O were duplicated exactly when the muscles were exposed to the same concentrations of N₂. Since the effects of N₂O and N₂ were identical, it would appear that N₂O does not have any inherent myocardial depressant properties.

The dose-related alterations in the measures of heart-muscle function which we did observe with N₂ and N₂O indicate a decrease in peak-active-state intensity of myocardial contractile elements. The basis of this conclusion is the reduction in the rate of tension development. An increase in the compliance of the series elastic component could have contributed to this effect. Although we did not study the series elastic component directly, others have done so, with the bath PO₂ equal to 15 torr. Since no alteration in series elastic characteristics was found in that study, we believe that it is not necessary to invoke changes in this component to explain the decreased developed tension.

The studies with paired stimulation were undertaken to determine whether N₂O had any influence on the muscles' maximum ability to contract. The maximum responses of T₉₀, +dP/dt, and −dP/dt to paired stimulation were less with 75 per cent N₂O than with 95 per cent O₂, but equivalent to the effects seen with 75 per cent N₂. However, the relative potentiations achieved in the presence of O₂, N₂O, and N₂ were all identical. Thus, even the positive inotropic effects of paired electrical stimulation are unchanged by N₂O compared with N₂ on an absolute basis, and are unchanged when compared with both O₂ and N₂ on a relative basis.

Other investigators have taken the point of view that N₂O does depress myocardial contractility. The first report of the effects of this anesthetic on myocardial performance appears to be that of Fisher *et al.*, in 1951. They stated only that 80 per cent N₂O produced "slight" cardiac dilation without changing pulmonary arterial or right atrial pressures in the dog heart-lung preparation. The possible contributions of hypoxia or altered myocardial compliance were not ruled out by the authors.

Price and Helrich also utilized the dog heart-lung preparation and observed changes in the slopes of the lines relating cardiac output and right atrial pressure. By extrapolation of their data, they calculated that a blood N₂O concentration that should just produce anesthesia in the dog would depress myocardial performance to the same degree as equianesthetic concentrations of diethyl ether and cyclopropane.

Crawthorne and Darby observed the effects of N₂O on myocardial contractile force as measured with a strain-gauge arch sutured to the right ventricular myocardium of the dog. They noted that 50 and 75 per cent N₂O produced exactly the same depression in contractile force. The experimental animals received halothane anesthesia while thoracic surgery and other procedures were carried out. Control values were recorded after halothane.
Fig. 1. Effects of N₂O (closed circles) and N₂ (open circles) on peak developed tension and maximum rates of tension development and relaxation (ordinates). Concentrations of both N₂O and N₂ are on the abscissa.
had been discontinued and the dogs had been allowed to awaken. Since these control data were obtained during the immediate postoperative period, it is possible that the values observed at this time were artificially increased owing to incisional pain and mechanical ventilation in awake animals. N₂O administered at this point could have decreased the con-
tractile-force readings merely by its analgesic properties and not necessarily because of myocardial depression.

Lundborg, Milde, and Theye also utilized dogs anesthetized with halothane. They observed that the substitution of 75 per cent N₂O for 75 per cent N₂ decreased left ventricular stroke volume, stroke work, and the peak rate of rise of ventricular pressure in spite of an increase in left ventricular end-diastolic pressure. If a change in myocardial compliance could be ruled out, these findings would indicate myocardial depression.

Eisele et al. evaluated myocardial contractility in dogs by examining the maximum acceleration of blood flow in the aorta. It appears from their data that 60 per cent N₂O, 80 per cent N₂O₂, and 3 per cent halothane were all equivalent in their ability to depress cardiac performance. However, since the data were presented only for the first minute following administration of N₂O, and were not analyzed statistically, it is difficult to formulate any firm conclusion regarding the inotropic effects of N₂O from this study.

Smith and Corbascio observed the effects of several concentrations of N₂O in dogs. They reported no change in any cardiovascular measurement, including the maximum rate of rise of left ventricular pressure and left ventricular ejection time. Also, there were no significant differences between halothane—oxygen and halothane—N₂O—O₂, except smaller decreases in systemic blood pressure and total peripheral resistance in the latter groups. These results do not imply myocardial depression. Rather, they suggest a sympathetic induced stimulation of the peripheral vascular system and no alteration in myocardial performance.

Three studies in man have recently been reported. Hornbein et al. added 70 per cent N₂O to 0.8 per cent or 1.5 per cent end-tidal concentrations of halothane in oxygen. The only statistically significant circulatory changes associated with the addition of N₂O were an increase in cardiac output at 0.8 per cent halothane and a decrease in the response of cardiac output to CO₂ at 1.5 per cent halothane. Also, central venous pressure at 1.5 per cent halothane and the response of central venous pressure to CO₂ at 0.8 per cent halo-
thene were increased. There were no changes in arterial blood pressure, stroke volume, heart rate, left ventricular stroke and minute work, or total peripheral resistance. These data are not sufficient to warrant a conclusion of depressed myocardial contractility due to \( \text{N}_2\text{O} \), especially since neither \( \text{PCO}_2 \) nor \( \text{PAO}_2 \) was the same in the presence of \( \text{N}_2\text{O} \) as in its absence.

Smith et al.\(^6\) compared the addition of either 70 per cent \( \text{N}_2\text{O} \) or air to 0.5 per cent to 2 per cent halothane-\( \text{O}_2 \). The results were not consistent with a myocardial depressant effect of \( \text{N}_2\text{O} \), but did indicate a sympathetic stimulating effect on the peripheral vasculature. This was confirmed by the demonstration of an increase in plasma norepinephrine levels with the addition of \( \text{N}_2\text{O} \).

**Table 2. Effects of Paired Electrical Stimulation with 95 Per Cent \( \text{O}_2 \), 75 Per Cent \( \text{N}_2\text{O} \), and 75 Per Cent \( \text{N}_2 \); Per Cent Changes (± SE)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Peak Developed Tension (( \text{T}_2 ))</th>
<th>Maximum Rate of Tension Development (+dp/dt)</th>
<th>Maximum Rate of Tension Relaxation (−dp/dt)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(1) Initial Conditions</strong></td>
<td><strong>(2) Final Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95 per cent ( \text{O}_2 ) single stimulus</td>
<td>95 per cent ( \text{O}_2 ) paired stimulus</td>
<td>+125.5( \pm ) 12.3</td>
<td>+127.8( \pm ) 18.7</td>
<td>+141.7( \pm ) 14.4</td>
</tr>
<tr>
<td>75 per cent ( \text{N}_2\text{O} ) single stimulus</td>
<td>75 per cent ( \text{N}_2\text{O} ) paired stimulus</td>
<td>+106.1( \pm ) 16.2</td>
<td>+ 98.7( \pm ) 25.2</td>
<td>+149.8( \pm ) 35.8</td>
</tr>
<tr>
<td>75 per cent ( \text{N}_2 ) single stimulus</td>
<td>75 per cent ( \text{N}_2 ) paired stimulus</td>
<td>+135.5( \pm ) 25.9</td>
<td>+133.3( \pm ) 19.2</td>
<td>+188.9( \pm ) 29.5</td>
</tr>
<tr>
<td>95 per cent ( \text{O}_2 ) single stimulus</td>
<td>75 per cent ( \text{N}_2\text{O} ) paired stimulus</td>
<td>+ 39.8*( \pm ) 39.3</td>
<td>+ 49.0*( \pm ) 21.9</td>
<td>+ 53.0( \pm ) 21.6</td>
</tr>
<tr>
<td>95 per cent ( \text{O}_2 ) single stimulus</td>
<td>75 per cent ( \text{N}_2 ) paired stimulus</td>
<td>+ 60.8*( \pm ) 21.3</td>
<td>+ 71.4*( \pm ) 27.0</td>
<td>+ 77.5*( \pm ) 20.6</td>
</tr>
</tbody>
</table>

\( \text{P} \) values indicate statistical significance of difference between 1 and 2; \( * \) \( P \) < 0.05; \( \dagger \) \( P \) < 0.01; \( \ddagger \) \( P \) < 0.001.
Bahlman et al. also found no evidence of a myocardial depressant effect of \( N_2O \). They reported less depression in several cardiovascular variables, including the left ventricular stroke and minute work, the rate of right ventricular ejection, and the J wave of the ballistocardiograph, at equianesthetic concentrations of halothane--\( N_2O-O_2 \) compared with halothane--\( O_2 \).

Thus, while some of the reported experimental results do indicate that \( N_2O \) may have the ability to depress myocardial contractility, most of the studies, including the three in man, are not compatible with this view. The conclusions of these studies, as well as ours, indicate that \( N_2O \) has no inherent myocardial depressant properties.

In the clinical usage of \( N_2O \), it seems reasonable to believe that the additional analgesia obtained with this anesthetic will not result in any additional myocardial depression if hypoxia is avoided. Nitrous oxide should thus be a useful adjunct to more potent anesthetic agents which do possess cardiovascular depressant characteristics, but only in the patient who does not require a high \( P_{\text{aO}_2} \) for adequate tissue oxygenation.

We conclude that \( N_2O \) does not possess any intrinsic myocardial depressant or stimulant properties. Any direct alteration in myocardial contractility associated with the use of \( N_2O \), therefore, should be related to variations in extraneous factors, such as oxygen delivery to the myocardium or the degree of myocardial sympathetic activation.

References


