The Cardiovascular Effects of Nitrous Oxide During Halothane Anesthesia in the Dog

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Nitrous oxide-oxygen, halothane-oxygen, and nitrous oxide-oxygen-halothane were administered in random order to each of 12 dogs. Thirteen cardiovascular parameters—cardiac output, stroke volume, heart rate, mean arterial pressure, systolic arterial pressure, total peripheral resistance, mean transit time, left ventricular pressure, right ventricular pressure, the time derivatives of the pressures, and the left ventricular ejection time—were plotted against concentrations of nitrous oxide and halothane. Except for a greater decrease in systemic pressure and resistance with halothane-oxygen anesthesia, there was no significant difference between the performance of the cardiovascular system with halothane-oxygen and nitrous oxide-halothane-oxygen anesthesia. Since considerably greater analgesia was achieved when nitrous oxide was added to a given concentration of halothane, nitrous oxide used with halothane spares the cardiovascular system, in a relative way.

Saidman and Eger, have reported that the use of 70-75 per cent nitrous oxide with halothane reduces by 2/3 the minimum alveolar concentration of halothane necessary to prevent movement in response to surgical incision. Young and Lodge, Apivar, Johnstone, and Bloch observed that the addition of nitrous oxide to halothane-oxygen can decrease blood pressure to markedly low levels, while discontinuation of nitrous oxide leads to an increase in blood pressure. This work suggests that the advantage of additional analgesia offered by nitrous oxide may be offset by the disadvantage of cardiovascular depression. This question was examined in dogs by studying the cardiovascular effects of combining nitrous oxide with halothane under controlled conditions.

Methods

Twelve mongrel dogs, weighing from 20-25 kg., were studied. Anesthesia was induced with 15-20 mg./kg. thiopental intravenously. After insertion of an endotracheal tube, surgical preparation of the animal was done during administration of nitrous oxide-oxygen-succinylcholine. Intermittent positive pressure ventilation was maintained throughout an experiment with a Harvard nonrebreathing respirator. “Deep breaths” were administered every 10 minutes by occluding the outlet of the ventilator. Rate and tidal volume were adjusted to maintain an arterial pH of 7.40-7.42, as measured with a Beckman glass pH electrode.

Central aortic pressure was obtained via a Teflon catheter inserted through a carotid artery. The contralateral artery was used for withdrawal of blood during determinations of cardiac output and for blood sampling. Number 9 Courmand catheters were advanced blindly via the right jugular vein into the right ventricle, and the left femoral artery into the left ventricle. Pressure curves were used to determine the presence of the catheters in the ventricles. In addition, lead 2 of the electrocardiogram was recorded.

Pressures were measured with Statham P23Gb strain gauges. Mean aortic pressure was obtained by electrical damping. Electronic differentiating circuits linear to 100 cps were used to obtain the first derivative (dP/dt) of each pressure curve. To obtain left ventricular ejection time, the recorder paper was run at 100 mm./sec. Ejection time was measured on an amplified central aortic pres-
TABLE 1. Experimental Plan for the Administration of Anesthetic Agents

<table>
<thead>
<tr>
<th>Group 1 (Nitrous oxide-oxygen)</th>
<th>Group 2 (Halothane-Oxygen)</th>
<th>Group 3 (Nitrous oxide-oxygen-halothane)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixture</strong></td>
<td><strong>Time Administered (minutes)</strong></td>
<td><strong>Mixture</strong></td>
</tr>
<tr>
<td>100% O₂</td>
<td>15</td>
<td>100% O₂</td>
</tr>
<tr>
<td>Room air</td>
<td>15</td>
<td>Halothane-0% O₂ (0.5% O₂)</td>
</tr>
<tr>
<td>N₂O-O₂:20-80</td>
<td>15</td>
<td>Halothane-0% O₂ (1.0% O₂)</td>
</tr>
<tr>
<td>N₂O-O₂:40-60</td>
<td>15</td>
<td>Halothane-0% O₂ (1.5% O₂)</td>
</tr>
<tr>
<td>N₂O-O₂:60-10</td>
<td>15</td>
<td>Halothane-0% O₂ (2.0% O₂)</td>
</tr>
<tr>
<td>N₂O-O₂:80-20</td>
<td>15</td>
<td>Halothane-0% O₂ (2.5% O₂)</td>
</tr>
</tbody>
</table>

sure curve as the interval between the sharp upstroke and the incisura of the pulse wave. Ten pressure waves were measured for each determination, and the mean computed to the nearest msec. Pressures, pressure derivatives, and the ECG were recorded on a multichannel direct-writing Offner oscillograph.

Cardiac output was determined by the Stewart-Hamilton method, using indocyanine green dye as an indicator. The dye was injected directly into the right ventricle with a Cornwall spring-loaded injection syringe, while blood was continuously withdrawn from a carotid artery by means of a Harvard infusion-withdrawal pump, and passed through a Beckman Cardio-Densitometer. The output of the densitometer was integrated by a disk integrator and cardiac output calculated by extrapolation of the down curve and correction for the dead space of the catheter. Blood withdrawn was reinfused after each determination. Calibration of the densitometer was performed after each study with serial dilutions of dye in previously drawn aliquots of the dog’s own blood. Dextran in normal saline was used to replace this blood.

Heart rate was calculated over a 30-second period. Stroke volume was obtained by dividing the cardiac output by the heart rate. Mean transit time was calculated by the method described by Eistien. Total peripheral resistance was calculated by the formula:

\[
TPR \text{ (dyne-sec. cm.}^{-5}) = \frac{1332 \times AP}{CO \text{ ml./sec.}}
\]

* Beckman Spinco, Palo Alto, California. Courtesy Mr. Conrad Rader.

Left ventricular work was calculated according to the formula: \( LVW \text{ (kg.-m./minute)} = 0.0135 \times CO \text{ (liters/minute)} \times AP \).

Three studies were performed on the same animal on the same day. The sequence of the three studies was randomly varied, as were the concentrations of anesthetic agents. Table 1 shows the experimental plan for each study.

Relative flows of nitrous oxide and oxygen from a Forreger anesthetic machine were used to determine their respective inspired concentrations. The flowmeters were calibrated with a bubble meter system. Halothane was vaporized with a Forreger Copper Kettle (R), and the inspired concentration monitored with an Analytic Systems ultraviolet halothane analyzer. Concentrations of halothane in arterial blood were measured on a Perkin-Elmer gas chromatograph (N1801) equipped with Perkin-Elmer DC350 columns (6 feet \( \times \frac{1}{8} \) inches), the solvent packed on 80-100 mesh GC22. Samples were injected directly into a glass injection port and analysis carried out by an electron capture detector.

Cardiac output was determined following the periods of room air and oxygen, as well as at the end of each concentration of anesthetic agent. All other cardiovascular parameters were simultaneously recorded. At the same time, if halothane was being administered, an arterial sample was withdrawn for analysis of halothane.

Cardiovascular parameters were converted to per cent of change, using those values obtained before the administration of anesthetic agents as controls. The inspired concentration
of nitrous oxide and both the inspired and arterial concentrations of halothane were plotted against each of the converted cardiovascular parameters. To compare data from the various parameters, the BIMD06 and BMD05 programs were used on an IBM 7090 digital computer. Seven types of regression equations were obtained for each parameter vs. each anesthetic agent: linear, polynomial to the fifth degree, and transformation of the anesthetic concentrations to log_{10} and square root. F (Fisher) values were used to determine the significance of each equation. None of the parameters changed significantly during nitrous oxide-oxygen anesthesia. Therefore, it was decided to compare only the equations of halothane vs. each parameter in the halothane-oxygen with the nitrous-oxygen-halothane groups. The lowest pooled mean error square was used to choose the pairs of equations for each parameter. In order to determine any significant difference between the two anesthetic groups, the differences between variances (H-test), slopes (S-test), and Y intercepts (T-test) were analyzed. The 0.05 per cent level was chosen in all statistical analyses.

Results

The results obtained by plotting the inspired concentrations and the arterial concentrations of halothane against each parameter are similar. Hence only the results of the latter are presented in this paper.

There was no statistically significant change in any parameter during nitrous oxide-oxygen anesthesia, although total peripheral resistance did show a moderate increase with increas-

Fig. 1. Best-fit curves plotting percentage change in total peripheral resistance against per cent inspired nitrous oxide (top scale) or arterial concentration of halothane (bottom scale). In the nitrous oxide-halothane group, only halothane is plotted against the total peripheral resistance.

Fig. 2. Percentage change in heart rate vs. per cent inspired nitrous oxide or mg. per cent arterial halothane. See figure 1.

Fig. 3. Percentage change in cardiac output vs. per cent inspired nitrous oxide or mg. per cent arterial halothane. See figure 1.
ing concentrations of nitrous oxide. During halothane anesthesia, there was significant depression in every parameter, except total peripheral resistance in the nitrous oxide-oxygen-halothane group (fig. 1) and heart rate in both groups (fig. 2). Mean aortic pressure, systolic aortic pressure, and total peripheral resistance decreased more rapidly with increasing halothane concentrations in the halothane-oxygen group than in the nitrous oxide-oxygen-halothane group, the difference being statistically significant. When the data were analyzed using room air or oxygen as a base for the percentage change the results did not change qualitatively.

The following sections summarize the results obtained during halothane anesthesia administered with nitrous oxide and without nitrous oxide.

**Cardiac Output and Stroke Volume.** Both of these parameters decreased markedly \( (P < 0.001) \). There was no significant difference between the two anesthetic groups (fig. 3) \( (P > 0.05) \).

**Left Ventricular Minute Work.** Left ventricular minute work showed extreme depression with halothane anesthesia \( (P < 0.001) \), slightly greater in the halothane-oxygen group, but with no significant difference between the two groups \( (P > 0.05) \).

**Mean Aortic Pressure, Systolic Aortic Pressure and Total Peripheral Resistance.** Mean aortic pressure and systolic aortic pressure declined significantly in both groups \( (P < 0.01) \). The decline was somewhat greater in the halothane-oxygen group (fig. 4). Total peripheral resistance declined significantly in the halothane-oxygen group \( (P < 0.01) \), but not in the dogs receiving nitrous oxide-oxygen-halothane (fig. 1) \( (P > 0.05) \). The difference was significant for all three parameters \( (P < 0.05) \).

**Left and Right Ventricular Pressures.** Both parameters declined in both anesthetic groups, the left ventricular pressure slightly more in the nitrous oxide-oxygen-halothane group (fig. 5) \( (P < 0.01) \) and the right ventricular pressure in the halothane-oxygen group \( (P < 0.05) \). The differences were not significant \( (P > 0.05) \).

**Left Ventricular Ejection Time.** Ejection time was increased in both groups \( (P < 0.05) \) with no significant difference between the two groups \( (P > 0.05) \). At a given heart rate, a decreased ejection time reflects increased myocardial “contractility,” and vice versa.
FIG. 6. Percentage change in the first derivative of the right ventricular pressure vs. inspired nitrous oxide or mg. per cent arterial halothane. See figure 1.

The First Derivatives of the Pressures. The pressure derivatives measure the peak slope or rate of rise of the corresponding pressure curve. Although, as with any other similar measurements, the pressure derivatives are affected by a number of factors, they do reflect one segment of myocardial “contractility.” 16-18 Each derivative decreased considerably in both groups (P < 0.001). The derivatives of the left ventricular and central aortic pressures decreased slightly more in the nitrous oxide-oxygen-halothane group, and the derivative of the right ventricular pressure in the halothane-oxygen group (fig. 6). The differences were not significant (P > 0.05).

Discussion

The changes in cardiovascular parameters noted in this study agree qualitatively with most previous studies in the intact animal: halothane is a cardiovascular depressant drug, while nitrous oxide has no important cardiovascular effects. The use of a neuromuscular blocking agent and intermittent positive pressure ventilation did not alter this picture. Their use was necessary in order to be able to (1) obtain good “conscious” controls, (2) obtain cardiovascular data in animals at light levels of nitrous oxide anesthesia, and (3) avoid the effects of decreased pH on the circulation. Residual thiopental may have produced a cardiovascular effect of its own, but after several hours of preparation, the effect should have been slight.

The addition of nitrous oxide to halothane in our studies did not significantly affect the cardiovascular system, except as manifested in the mean aortic pressure, systolic aortic pressure, and total peripheral resistance. This indicates that the major difference between the two techniques—halothane with nitrous oxide and halothane without nitrous oxide—lies in the peripheral vascular system. This assumption has two implications. First, any apparent improvement in cardiovascular function with the addition of nitrous oxide, which would be noted clinically only with the routinely measured blood pressure, comes at the expense of decreased peripheral resistance. If one believes that the peripheral vasodilating effects of halothane are important, especially as a protection against shock, the removal of this mechanism might not be desirable, particularly in the presence of continued myocardial depression. Second, this finding helps to explain the discrepancies previously noted in the circulatory effects of halothane. There has been disagreement on the peripheral vascular effects of halothane, although most investigators now agree that the agent causes a decrease in cardiac output and myocardial contractility.19-21 Every investigator who used nitrous oxide with halothane recorded no change 22-23 or a rise 19 in total peripheral resistance. Black and McArle 24 noted a decrease in forearm resistance with a nitrous oxide-oxygen-halothane combination, but did not measure systemic resistance. Those who used only oxygen as a diluent described a decrease in total peripheral resistance.25-26

No matter what the views on the desirability of vasodilation in shock, the difference between the circulatory effects of halothane with and without nitrous oxide are minor. This suggests that the combination of nitrous oxide-oxygen-halothane may be useful. Saidman and Eger 1 found that the addition of 70-75 per cent nitrous oxide to halothane anesthesia reduced to ½ the amount of halothane necessary for light anesthesia. The curves observed
in the present studies indicate the possible benefit to be derived from the administration of nitrous oxide with halothane. To attain a given level of surgical anesthesia, a lesser concentration of halothane is necessary with nitrous oxide, hence there is less cardiovascular depression. This assumes, of course, adequate oxygenation of the blood.

There remains to be explained the phenomenon noted by the British workers: a decrease in blood pressure with the addition of nitrous oxide to halothane-oxygen anesthesia. Although species differences between our studies and their reports can explain all the differences, other factors may be important. It is possible that there is enough vasoconstriction with nitrous oxide to give a false low indirect blood pressure reading. Bloch described a shivering and increased muscle tension in many of his patients. Johnstone noted a considerable diminution of the digital pulse wave in his subjects. Accidental hypothermia does occur during halothane anesthesia, particularly in cold operating rooms.

We have observed that, during hypothermia of 25–30°C, withdrawal of halothane and substitution of nitrous oxide produced a disappearance of Korotkoff sounds by ear and a marked decrease by microphone, a profound decrease of the digital plethysmograph pulse, but an increase in blood pressure as recorded with an intra-arterial needle. Withdrawal of nitrous oxide and addition of halothane reversed the picture. Without the direct pressure measurement, this would have been interpreted as cardiovascular collapse. It must be admitted that tissue perfusion was probably quite poor under these circumstances.

Johnstone ascribes the phenomenon to the effects of acute hypoxia under conditions in which the adrenalin-sympathetic system is unable to respond to the stimulus of acute hypoxia—that is, during halothane anesthesia. The rapid onset and reversal of the hypotension are in favor of this interpretation. Also, the original case reports described closed anesthetic systems, in which hypoxia with nitrous oxide easily occurs. However, a later report of Johnstone involved a partial rebreathing system, with total gas flows of 8 liters/minute used when nitrous oxide was added. When a concentration of nitrous oxide:oxygen of 4 liters:1 liter is administered to normal human subjects after breathing room air, arterial $P_{O_2}$ actually increases the first few minutes. Eger noted no low arterial $P_{O_2}$ when nitrous oxide was added to halothane-oxygen anesthesia in dogs or man. Adequate ventilation, of course, must be present. Most observers, including Johnstone, attest to adequate ventilation. Therefore, hypoxia may not explain every episode of hypotension.

Summary

The cardiovascular effects of $N_2O-O_2$, halothane-O$_2$, and $N_2O-O_2$-halothane anesthesia were studied in dogs. $N_2O-O_2$ caused no significant cardiovascular changes. Mean and systolic arterial pressure decreased more rapidly during halothane-O$_2$ anesthesia than during $N_2O-O_2$-halothane. Total peripheral resistance decreased significantly during halothane-O$_2$ anesthesia, but not during $N_2O-O_2$-halothane. The difference between the two types of anesthesia in these three parameters was statistically significant. Cardiac output, stroke volume, left ventricular minute work, left and right ventricular pressures, and the first derivatives of the pressures all decreased with both anesthetic combinations. Mean transit time increased, and heart rate did not change.

Except for the greater decrease in systemic pressure and resistance with halothane-O$_2$ anesthesia, there is no essential difference between the performance of the cardiovascular system with halothane-O$_2$ and $N_2O-O_2$-halothane anesthesia. This would indicate that, since considerably greater analgesia is achieved when $N_2O$ is added to a given concentration of halothane, $N_2O$ used with halothane spares the cardiovascular system, in a relative way. The only exception could be the protection allegedly given by halothane during shock. This protection would be lost with the disappearance of peripheral vasodilation.

The results of the present studies explain the differences noted in previous studies on the peripheral vascular effects of halothane. All studies showed a systemic vasodilation with halothane-O$_2$, and no effect or a slight vasoconstriction with $N_2O-O_2$ halothane.

1 Personal communication.
The studies conflict with the reports of British workers, who noted a decrease in blood pressure upon addition of \( N_2O \) to halothane-O\(_2\) anesthesia in surgical patients.

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References

13. BMD06: Multiple regression and correlation analysis No. 1, Computer Programs Manual, Division of Biostatistics, Department of Preventive Medicine and Public Health, School of Medicine, University of California, Los Angeles, 1961, pp. 1-6 and Appendix.
14. BMD05R: Polynomial regression, Computer Programs Manual, Division of Biostatistics, Department of Preventive Medicine and Public Health, School of Medicine, University of California, Los Angeles, 1964, pp. 289-290.