EFFECT OF NITROUS OXIDE ON MYOCARDIAL CONTRACTILITY OF DOGS*

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INTRODUCTION

NITROUS OXIDE (N_2O) is commonly used in clinical anaesthesia, usually in conjunction with other more potent agents. This practice is based in major part on the clinical observation that N_2O is a readily reversible, potent analgesic with minimal-to-absent effects on the cardiovascular system.¹ However, surprisingly little information on the cardiovascular effects of N_2O has been available,² other than the report of depression of left ventricular function in canine heart-lung preparations.³ This paucity of information about a drug in such wide use has prompted the present study of the cardiovascular effects of addition or removal of N_2O during halothane (1%) anaesthesia in dogs.

MATERIALS AND METHODS

Forty-three experiments were performed on eight unpremedicated dogs (surface area 0.61 to 0.93 sq. m.) in the right lateral position. Anaesthesia was induced and maintained with halothane (1%) in 25 per cent O_2 and N_2 (four dogs) or N_2O (four dogs). Succinylcholine was administered prior to intubation (30 mg.) and continuously thereafter at a rate of 150 mg./hr. Carrier gases containing halothane‡ (Vernitrol vaporizer) were passed through a humidifier and into a reservoir bag supplying the ventilator (Harvard pump). Ventilation was constant at a low rate (7 to 9 per min) and with a tidal volume that was adjusted initially to maintain an arterial P_{aCO_2} below 35 mm. Hg. The inspired mixture was maintained at 25 per cent O_2 ($\pm 0.2\%$) and 1 per cent halothane ($\pm 0.05\%$) with the aid of a P_{O_2} electrode and gas chromatographic halothane analyser. Additional preparations included placement of electrocardiographic leads, an oesophageal thermistor, and catheters (left ventricle, left common carotid artery, pulmonary trunk, and right atrium, with positions confirmed at autopsy).

Control observations (duplicate) were made about one hour after induction of anaesthesia. Each set of observations included measurements of cardiac output (dye dilution); arterial, right atrial, left ventricular systolic, and left ventricular end-diastolic pressures (strain gauge); arterial blood pH, P_{O_2} , P_{CO_2} (electrodes at body temperature); heart rate (E.C.G. lead II); arterial and mixed venous

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blood oxygen saturations (reflection oximetry); and haemoglobin concentration (cyanmethaemoglobin) as previously described in detail.⁴⁻⁶ In addition, the peak rate of rise of the left ventricular pressure pulse (dP/dT) was determined. The differentiating circuit for dP/dT and its calibration and recording characteristics have been previously described.⁷ Stroke work was calculated as the product of mean left ventricular systolic pressure, stroke volume, and a constant (0.0144). Mean left ventricular systolic and end-diastolic pressures were determined on three consecutive ventricular pressure pulse tracings. Systemic vascular resistance was calculated by conventional means. Oxygen uptake calculations were based on the Fick Relationship.

Following the control set of observations, N_2 was replaced by N_2O (four dogs) or N_2O was replaced by N_2 (four dogs). After a 30-minute wait for equilibration and haemodynamic stabilization, the above procedures were repeated. Approximately five such switches, waiting periods, and observations were carried out in this manner during a three- to four-hour period in each dog. The differences between values for measurements before and after each switch were used to provide one estimate of the change due to N_2O .

RESULTS

Only small and, in general, statistically insignificant differences existed between mean values during halothane anaesthesia with 75 per cent N_2O and halothane anaesthesia with 75 per cent N_2 (Table I). Although this indicates that N_2O probably does not greatly alter haemodynamics and myocardial contractility, the

TABLE I
HAEMODYNAMICS DURING ANAESTHESIA WITH 1% HALOTHANE IN
75% NITROGEN (N_2) OR IN 75% NITROUS OXIDE (N_2O)
Based on a single average value for N_2O and for N_2 from each of eight dogs

	N_2O (mean $\pm$ S.E.)		N_2 (mean $\pm$ S.E.)		N_2O-N_2
Cardiac output (L./min./sq.m.)	3.0	0.3	2.9	0.3	+0.1
Stroke volume (ml./beat/sq.m.)	28	4	31	4	-3
Heart rate (beats/min.)	113	7	99	8	+14
Stroke work (gram-metres)	27	4	28	4	-1
LV systolic pressure (mean mm. Hg)	83	4	80	3	+3
LV end-diastolic pressure (mean mm. Hg)	10.2	0.8	7.0	1.1	+3.2*
Right atrial pressure (mean mm. Hg)	2.5	0.4	1.7	0.6	+0.8
Systemic vascular resistance (dynes-cm.sec. ⁻⁵)	3,550	400	3,500	400	+50
Arterial pressure (mean mm. Hg)	97	3	91	3	+6
Peak dP/dT (mm. Hg/sec.)	1,900	200	2,100	200	-200
Oxygen uptake (ml./min./sq.m.)	144	8	139	9	+5

*Significant difference ($p < 0.05$) by t -test.

TABLE II
CHANGE IN HAEMODYNAMICS WITH REPLACEMENT OF NITROGEN (N₂)
BY NITROUS OXIDE (N₂O) OR OF N₂O BY N₂ IN INSPIRED MIXTURE
DURING HALOTHANE (1%) ANAESTHESIA

Based on 43 switches in eight dogs

	Change (N ₂ O-N ₂) mean $\pm$ S.E.	
Cardiac output (%)	+3.3	1.8
Stroke volume (%)	-11.2*	1.6
Heart rate (%)	+14.2*	1.8
Stroke work (%)	-5.9*	2.3
LV systolic pressure (mean, %)	+4.6*	1.4
LV end-diastolic pressure (mean mm. Hg)	+2.6*	0.7
Right atrial pressure (mean mm. Hg)	+0.9*	0.2
Systemic vascular resistance (%)	+5.3*	1.8
Arterial pressure (%)	+8.8*	1.4
Peak dP/dT (%)	-9.7*	2.0
Oxygen uptake (%)	+4.3*	1.2

*Significant difference ($p < 0.05$) by *t*-test.

FIGURE 1. Changes in three commonly used indices of myocardial contractility—stroke work, peak dP/dT, and stroke volume—are related to change in left ventricular end-diastolic filling pressure (LVEDP). A reduction in value of each index in the presence of an augmented LVEDP is considered to indicate myocardial depression. By these terms, replacement of nitrogen (N₂) by nitrous oxide (N₂O) was associated with depression of myocardial contractility.

TABLE III
ARTERIAL BLOOD VALUES: ALL OBSERVATIONS

	Mean	Range
P _{O₂} (mm. Hg)	94	70-127
O ₂ saturation (%)	94	89-97
P _{CO₂} (mm. Hg)	28	21-35
pH	7.42	7.31-7.55

FIGURE 2. Changes in haemodynamics with replacement of nitrogen (N_2) by nitrous oxide (N_2O) during 1% halothane anaesthesia in dogs. The reduction in stroke volume with N_2O was associated with an increase in heart rate such that cardiac output was not reduced.

lack of a significant difference between mean values is undoubtedly influenced by the variability inherent in comparing absolute values observed in different dogs. Influence of absolute-value variability in individual dogs is lessened by the treatment of data used in preparing Table II. In this approach, each dog served as its own control, and only the differences between succeeding observations in the same dog are evaluated. Small statistically significant differences attributable to N_2O are now evident in all measurements other than those of cardiac output. Directional differences between means are nevertheless identical in the two

tables. Myocardial contractility was apparently lessened by the presence of N_2O , since stroke volume, stroke work and peak dP/dT were all decreased in the presence of increased left ventricular end-diastolic and right atrial pressures (Fig. 1). An increase in heart rate similar in magnitude to the reduction in stroke volume accounts for cardiac output remaining essentially unchanged (Fig. 2). Arterial blood P_{O_2} , O_2 saturation, P_{CO_2} , and pH values were essentially the same with N_2O as with N_2 . Over-all mean values and ranges are listed in Table III. Oesophageal temperature averaged $38.9^\circ C$. in each group.

DISCUSSION

The results of the present study support the general clinical impression that haemodynamics are little affected by N_2O administration in the absence of hypoxia.¹ Cardiac output was little changed with N_2O despite a significant reduction in stroke volume. The basis for the increased heart rate that accompanied the switch to N_2O and compensated for the reduction in stroke volume was not established in the present studies. It seems unlikely that the increase in heart rate was based on increased activity of the sympathetic nervous system with release of catecholamines in view of the apparent suppression of the catecholamine-release mechanisms with halothane anaesthesia.⁸ An explanation based on altered baroreceptor-reflex activity appears untenable since changes in blood pressure were small in magnitude and were directionally opposite to what would be required to result in an increase in heart rate. The most plausible hypothesis is that the analgesia provided by N_2O lessened vagal tone through a central nervous system mechanism and thereby allowed the heart rate to increase. An over-all reduction in the activity of the parasympathetic nervous system of this variety may be the basis for the observed increase in systemic vascular resistance.

Nitrous oxide has now been demonstrated to be capable of depressing myocardial contractility by various experimental techniques. Results of different approaches are important since no single method of evaluation has universal acceptance. Originally, in heart-lung preparation studies,⁸ the effect of N_2O on myocardial contractility was assessed by a comparison of the slopes of ventricular function curves (right or left ventricular output versus right or left atrial pressure) obtained in the absence of N_2O with those obtained at various N_2O concentrations. Using this index, myocardial contractility was found to be reduced by N_2O . The degree of myocardial depression with N_2O was similar to that observed with equi-anaesthetic concentrations of ethyl ether and cyclopropane. In studies of intact dogs with a Brodie-Walton strain gauge sutured to the right ventricle,⁹ a decrease in contractile force was observed to accompany the administration of N_2O . The magnitude of reduction was similar with 50 per cent N_2O and 75 per cent N_2O in O_2 . Again, although by the use of a different index, it was concluded that N_2O is capable of depression of myocardial contractility. In the present study, depression of myocardial contractility with N_2O was indicated by the association of a reduction in stroke work and peak dP/dT with increased ventricular end-diastolic (filling) pressures.¹⁰ This interpretation seems particularly

well-founded since the increase in heart rate, peripheral resistance, or end-diastolic pressure associated with the switch to N_2O is known to result in an increase in dP/dT without an apparent increase in contractility.¹¹ A decrease in peak dP/dT in these circumstances is unusually good evidence that, in fact, myocardial contractility has lessened.

The consistency of these findings seems to justify the conclusion that N_2O is indeed a myocardial depressant even when administered in clinically useful concentrations and in the absence of hypoxia. However, the clinical implications of this information are not easy to assess. Depression of myocardial contractility with N_2O only implies that for a given ventricular end-diastolic fibre length, the amount of energy released with systole is less than would have been released in the absence of N_2O . Depression of contractility cannot be equated with reduction in cardiac output since many factors are interposed between systolic energy release and cardiac output, including heart rate, arterial pressure, and stroke volume. This is, of course, evident in the present study wherein well-established depression of myocardial contractility was associated with unchanged cardiac output.

Another perspective emerges when these observations are viewed in the context of the O_2 system. As emphasized previously,⁶ whole-body O_2 levels depend on the relationship of arterial O_2 levels, cardiac output, and rate of metabolic consumption of O_2 . Circumstances conducive to the lowering of whole-body O_2 levels include one or more of the following: reduced arterial O_2 content, reduced cardiac output, and increased rate of metabolic consumption of O_2 . It would be expected, therefore, that the clinical use of N_2O is ordinarily associated with a reduction in whole-body O_2 levels since the lowered inspired O_2 concentration gives rise to a reduced arterial O_2 content, whereas cardiac output and metabolism are little affected.

SUMMARY

The effect of nitrous oxide on myocardial contractility and haemodynamics has been studied in unpremedicated, closed chest, anaesthetized dogs (1% halothane). Substitution of N_2O (75%) for the N_2 (75%) in the inspired mixture (O_2 , 25%) was associated with minor or insignificant changes in cardiac output, arterial blood pressure, oxygen uptake, and blood O_2 or CO_2 levels. Myocardial contractility, however, was reduced by the presence of N_2O , and both stroke work and peak dP/dT were decreased in the presence of concurrent increased end-diastolic ventricular pressures. In the clinical use of N_2O , the advantages of potent, reversible analgesia must be considered along with the potential disadvantages of reduced myocardial contractility and, ordinarily, lower levels of arterial O_2 .

RÉSUMÉ

On a étudié l'effet du protoxyde d'azote sur la contractilité du myocarde et l'hémodynamique en prenant comme sujets des chiens anesthésiés (halothane à 1%) à thorax fermé, sans prémédication. Le remplacement de N_2 (75%) par N_2O

(75%) dans le mélange inspiré (O_2 , 25%) a été associé à des changements minimes ou sans importance dans le débit cardiaque, la pression artérielle, la consommation d'oxygène, et les niveaux sanguins d'oxygène ou d'acide carbonique. Cependant, la contractilité du myocarde a été diminuée par la présence du protoxyde d'azote, et le travail systolique ainsi que le sommet dP/dT ont été diminués en présence de pressions ventriculaires de fin de diastole concurrentes et augmentées. Dans l'usage clinique du protoxyde d'azote, on doit considérer les avantages d'une analgésie puissante et réversible en regard des désavantages possibles d'une contractilité diminuée du myocarde et, généralement, de niveaux plus bas d'oxygène artériel.

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