Nitrous oxide does not worsen myocardial ischaemia following beta-receptor blockade in isoflurane anaesthetized dogs

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The effect of nitrous oxide (N_2O) on ischaemic myocardium was investigated in the presence of beta-receptor blockade. Three anaesthetics were compared in each of six dogs: isoflurane 1.8% alone, isoflurane 1.4% with 50% N_2O, and isoflurane 1.8% with 50% N_2O. Heart rate (HR), systolic aortic blood pressure (SBP), and left atrial pressure (LAP) were held constant during the three treatments. The left anterior descending coronary artery (LAD) was cannulated and perfused with an autoperfusion circuit. Systolic segment length was measured with a sonomicrometer in the LAD and circumflex regions. Regional myocardial blood flow was measured using radioactive microspheres. Propranolol was administered intravenously and then measurements were made during imposition of a stenosis on the perfusion circuit sufficient to decrease systolic shortening by 30%. The substitution of 50% N_2O for 0.4% isoflurane had no effect on systolic shortening or transmural myocardial blood flow in the ischaemic or normal region. When N_2O was added to 1.8% isoflurane, systolic shortening decreased by 34.6% in the ischaemic and 57.3% in the normally perfused region, while transmural myocardial blood flow distribution did not change significantly. The decrease in shortening was therefore not due to increased ischaemia. These results were similar to those of a previous experiment which was identical except that beta-blockade was absent. It is concluded that beta-receptor blockade does not markedly alter the response of normal or ischaemic myocardium to N_2O.

L'effet du protoxyde d'azote (N_2O) sur le myocarde ischémique a été investigué en présence d'un bloc des récepteurs beta. Six chiens ont été étudiés et trois anesthésiques ont été comparés chez chacun: l'isoflurane 1,8% seul, l'isoflurane 1,4% avec N_2O 50%, et l'isoflurane 1,8% avec N_2O 50%. Le rythme cardiaque (HR), la tension artérielle systolique aortique (SBP), et la tension de l'oreillette gauche (LAP) ont été maintenus constants durant les trois traitements. L'artère coronaire antérieure descendante gauche (LAD) a été cannulée et perfusée à l'aide d'un circuit à autoperfusion. La longueur du segment systolique a été mesurée à l'aide d'un sonomicromètre pour la LAD et les régions de la circonflexe. Le débit sanguin myocardique régional a été mesuré à l'aide de microsphères radioactives. Suite à l'administration intraveineuse de propranolol, des mesures ont été prises pendant la création d'une sténose, au niveau du circuit de perfusion, suffisante pour diminuer le raccourcissement systolique de 30%. La substitution du N_2O 50% par de l'isoflurane 0,4% n'a eu aucun effet sur le raccourcissement systolique ou le débit sanguin myocardique transmural dans les régions ischémiques ou normales. Lorsque le N_2O était ajouté à l'isoflurane 1,8%, le raccourcissement systolique diminuait de 34,6% dans les régions ischémiques et de 57,3% dans les régions normalement perfusées, tandis que la distribution du débit sanguin myocardique transmural n'a pas changé de façon significative. La diminution du raccourcissement n'était donc pas due à une augmentation de l'ischémie. Ces résultats étaient semblables à ceux d'une expérience précédente, qui était identique à l'exception de l'absence de bloc beta. Nous concluons que le bloc des récepteurs beta n'altère pas de façon marquée la réponse du myocarde normal ou ischémique au N_2O.

Key words

ANAESTHETICS, GASES: nitrous oxide;
ANAESTHETICS, VOLATILE: isoflurane;
HEART: blood flow, ischaemia;
SYMPATHETIC NERVOUS SYSTEM: beta-adrenergic antagonists, propranolol.

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Previous studies[1,2] from this laboratory have investigated the effect of nitrous oxide (N_2O) on ischaemic and normally perfused regions of the heart in isoflurane anaesthetized dogs. When 1.8% isoflurane in 50% N_2/O_2 was replaced with 1.4% isoflurane in 50% N_2O/O_2 heart rate (HR) and blood pressure (BP) increased while systolic shortening and subendocardial/subepicardial (I/O) blood flow ratio decreased in an ischaemic region of myocardium.[1] When the same treatments were repeated but HR and BP were held constant, systolic shortening and I/O ratio did not change.[2] These results suggested that the worsening of ischaemia observed in the first series was due to the increased HR and BP associated with the substitution of 50% N_2O for 0.4% isoflurane. It was concluded that, so long as haemodynamic variables were controlled, N_2O per se would not have adverse effects on coronary arteriolar tone or myocardial function during myocardial ischaemia.

Many patients with coronary artery disease are treated with beta-blocking drugs which are usually continued up to the time of surgery. Often these agents are used to control heart rate intraoperatively. Beta-receptor blockade may unmask the direct myocardial depressant effects of N_2O which are normally balanced, in part, by increased sympathetic tone.[3–5] It is of interest to know if the results of the previous studies would be different in the presence of beta-blockade. The present results are from a series of experiments preliminary to the earlier study[1] where propranolol (rather than pacing) was used to prevent changes in heart rate when N_2O was substituted for or added to isoflurane in the same preparation. The data describe the effects of N_2O on ischaemic and normal myocardium in the presence of beta-blockade.

Methods

General preparation

In six dogs of either sex, weighing 20–30 kg, anaesthesia was induced with thiopentone. Following tracheal intubation, ventilation was controlled to maintain arterial PCO_2 between 35 and 40 mmHg. If required to maintain arterial PO_2 above 100 mmHg, PEEP of 2–5 cm H_2O was applied, before data collection began. Anaesthesia was maintained with isoflurane in oxygen during the surgical preparation. Inspired oxygen concentration was measured with a polarographic electrode and anaesthetic concentration at the endotracheal tube was continuously measured with an infrared analyzer (Datex model 222). Blood temperature was measured with a thermistor in the right atrium and maintained at 35–37° C with a water blanket.

Arterial blood pressure was measured with a Gould P23ID transducer via a fluid-filled catheter placed through the right brachial artery into the arch of the aorta (Figure 1). An 8F Fogarty catheter was inserted through the left femoral artery and the tip positioned in the thoracic aorta. A femoral arteriovenous shunt made of silastic tubing was inserted in the right groin and connected to a pressurized reservoir which was later filled with 300 ml of blood (see Protocol).

The chest was opened through an incision in the left fifth intercostal space and the heart suspended in a pericardial cradle. A catheter was placed directly in the left atrium to allow injection of radioactive microspheres as well as measurement of left atrial pressure with a Gould P23ID transducer. Left ventricular pressure was measured with a catheter-tip transducer (Millar MPC-500) placed in the left ventricle directly through the apex. Ringer's lactate was infused at 10 $ml \cdot kg^{-1} \cdot hr^{-1}$ into the left femoral vein throughout the experiment. Heparin 5 $mg \cdot kg^{-1}$ bolus followed by 2.5 $mg \cdot kg^{-1} \cdot hr^{-1}$ was started prior to coronary cannulation.

Coronary perfusion

The left anterior descending coronary artery (LAD) was cannulated near its origin with a specially designed stainless steel cannula. An autoperfusion circuit constructed of silastic tubing was used to bring blood from the left carotid artery to the LAD. A cannulating flow transducer was placed in the perfusion circuit and coronary blood flow measured with an electromagnetic flowmeter (Carolina Instruments FM501). Zero flow base lines were repeatedly determined throughout the experiment by diverting blood flow away from the probe through a parallel bypass shunt.

Downstream from the flow probe a shunt was constructed to allow the imposition of an artificial coronary stenosis (see Coronary Stenosis). The LAD pressure was measured at the cannula tip via a small stainless steel tube within the coronary cannula.

Myocardial blood flow

Radioactive microspheres, approximately 15 μ in diameter, and labelled with ^{113}Sn, ^{85}Sr, and ^{46}Sc were used to measure regional myocardial blood flow. After vigorous agitation and sonication to break up aggregates, approximately 2.5×10^6 spheres were injected into the left atrium. A syringe pump (Harvard 600) was used to withdraw blood from the left femoral artery at a rate of 14.5 $ml \cdot min^{-1}$ beginning 30 sec before and ending 90 sec after each microsphere injection. This reference sample was used to calculate tissue flow from counts by the method of Heymann *et al.*[6]

At the end of the experiment india ink was injected into the coronary cannula to define the ischaemic LAD region. Ventricular fibrillation was then induced, the heart removed and the left ventricular free wall excised and

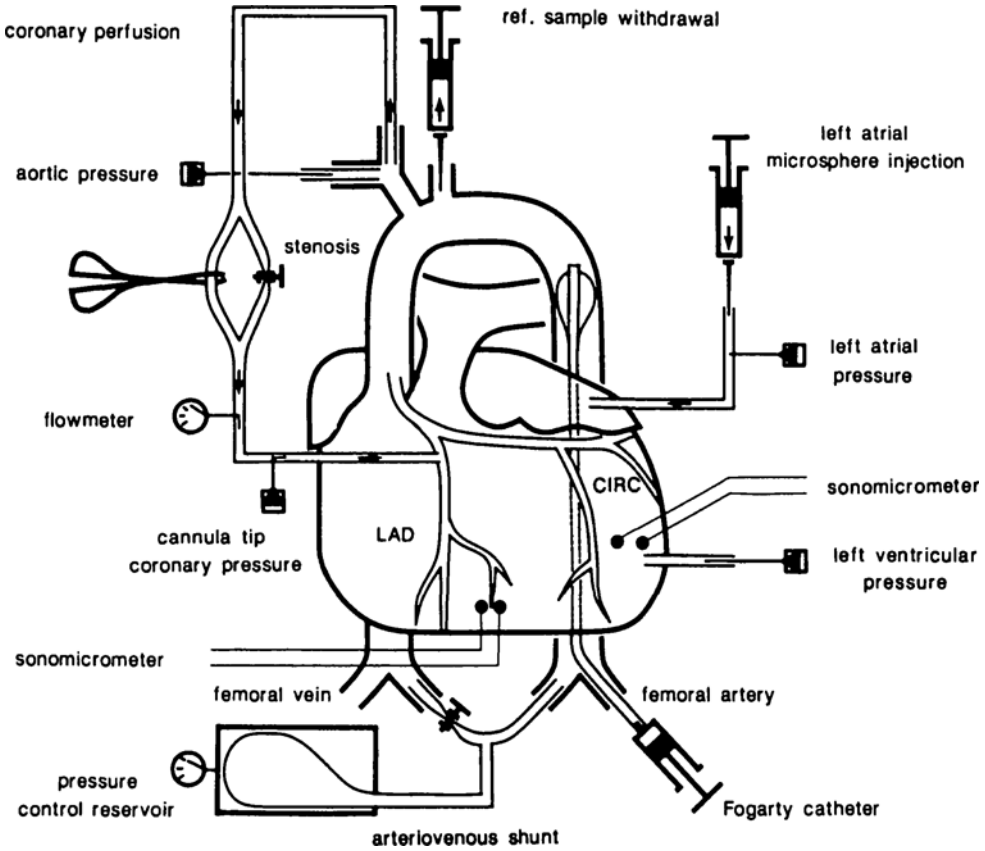

FIGURE 1 The experimental preparation. The LAD coronary artery was cannulated near its origin and perfused via an autoperfusion circuit. Coronary pressure was measured at the cannula tip. Coronary flow was measured with a cannulating flowmeter. A bypass shunt was constructed in the perfusion circuit, and on one limb a stenosis was produced by means of a modified screw clamp. This flow restriction was applied when required by occluding the parallel limb. Pairs of piezoelectric crystals were inserted into the subendocardium in the LAD and circumflex regions of the left ventricle to allow measurement of segment length by sonomicrometer. Regional myocardial blood flow was measured by injecting radio-active microspheres into the left atrium. Systolic aortic and left atrial pressure were held constant by adjusting a Fogarty catheter in the thoracic aorta and a pressurized reservoir connected to a femoral arteriovenous shunt.

placed in a 4% solution of formaldehyde in saline. The electromagnetic flow probe was calibrated with blood immediately following each experiment. Myocardial blood flow in the region of the heart perfused via the LAD cannula was determined by dividing the calibrated flow signal by the weight of tissue stained with india ink.

After four days the formalin fixed left ventricular free wall was divided into two regions: the stained area that had been perfused via the LAD cannula (ischaemic region), and an unstained area in the distribution of the circumflex coronary artery (control region). The central part of each region, always including the insertion sites of the ultrasonic transducers, were divided into four transmural (full thickness) cores each weighing at least 1.5 g. Each core was then sliced into three equal layers (subepicardial, middle, subendocardial), weighed, and then counted in a well-type NaI gamma counter (LKB model 1282) together with reference blood samples, isotope standards and blanks. After correction for background counts and Compton scatter the tissue counts were divided by tissue weight, and then flows computed using reference sample counts and flow.[7]

Regional systolic shortening

An ultrasonic dimension gauge (Sonomicrometer 120, Triton Technologies) was used to measure myocardial segment length in the LAD and LCA regions. In each region two piezo-electric crystals were inserted into the subendocardium 1–2 cm apart, parallel to the short axis of the heart. At the end of the experiment it was confirmed that the crystals were within the stained area and within the inner 15% of myocardium. The distance between the transducers was continuously recorded on the oscillograph along with aortic blood pressure and LV dP/dt. End diastolic length (EDL) was determined at the beginning of left ventricular contraction where the positive dP/dt signal

crossed the zero line. End systolic length (ESL) was determined 20 ms before peak negative dP/dt.[8] Systolic segment shortening (SS) was calculated as:

$$SS(\%) = \frac{EDL - ESL}{EDL} \times 100$$

Coronary stenosis

To test the experimental hypothesis it was necessary to restrict LAD coronary blood flow sufficiently to cause subendocardial ischaemia. To accomplish this a modified screw clamp was used to create a constriction in the silastic coronary perfusion circuit. A parallel bypass shunt could be clamped when the flow restriction was to be in effect. In this way the identical stenosis could be repeatedly imposed and released without manipulating the screw clamp.

When the surgical preparation was completed, propranolol given, and the animal stable and receiving 1.8% isoflurane in 50% oxygen/nitrogen, the bypass shunt was clamped and the screw clamp set. This was done by tightening the screw clamp until a decrease in systolic shortening of approximately 30% was noted in the LAD region. The bypass shunt was then opened and after a ten-minute recovery closed again to see if the same degree of dysfunction recurred. It was rarely necessary to readjust the setting. Once the final setting had been made the bypass shunt was reopened to restore normal flow. Typically, systolic shortening returned to pre-stenosis values within the first five minutes of the recovery period. The screw clamp was never again manipulated during the experiment.

Protocol

Propranolol 2 $mg \cdot kg^{-1}$ *iv* bolus was administered followed by a 1 $mg \cdot kg \cdot hr \cdot^{-1}$ infusion. In preliminary experiments it was found that this dose regimen was required to limit to less than 5% the increase in HR in response to a 20 μg *iv* bolus of isoproterenol for the entire data collection period.

Three anaesthetic treatments were compared in each animal in a randomized crossover design:

A Isoflurane 1.8% with 50% nitrogen in oxygen
B Isoflurane 1.4% with 50% N_2O in oxygen
C Isoflurane 1.8% with 50% N_2O in oxygen

Each of the six possible sequences (ABC, ACB, etc.) was included. The treatment sequence was randomly selected only after the final stenosis setting had been made.

Heart rate, systolic blood pressure (SBP), and left atrial pressure (LAP) were to be matched for the three treatments during application of the stenosis. Preliminary experiments showed that SBP was usually highest during treatment B (see above) and lowest during C. The strategy was therefore to try to match the values observed during setting of the stenosis when the animal was receiving treatment A. Thus, it was usually necessary to raise blood pressure slightly during C and lower it slightly during B. This was accomplished using the femoral arteriovenous fistula, the pressurized reservoir, and by inflating the Fogarty catheter in the aorta. Heart rate remained constant throughout the experiment without the need for pacing. Data were collected during three applications of the stenosis each separated by a 30-min recovery period. The stenosis was imposed by clamping the bypass shunt. Within two to three minutes the segment length trace and LAD coronary blood flow (EMF) became stable. Radioactive microspheres were then injected into the left atrium to measure regional myocardial blood flow. Data and sample collection could be completed in less than seven minutes after which the bypass shunt was reopened. Global haemodynamic measures (HR, SBP, LAP, LV dP/dt) and coronary flow and distal pressure were frequently recorded but changed little after the first three minutes of ischaemia. Variables that changed with respiration were measured at end expiration. During the second and third applications of the stenosis the ischaemic time was matched to that required for the first application.

Data analysis

The data were analyzed by a two-way analysis of variance for a repeated measures design using subject by treatment interaction as the error. When the ANOVA showed significant treatment effect comparisons were made using two-tailed paired t tests. Only two comparisons were of interest, A vs B and A vs C. The null hypothesis (no difference) was rejected if $P < 0.05$.

The percent change was calculated by subtracting the mean value during treatment A from the mean value during treatment B or C and dividing by the mean value during treatment A. Statistical tests were performed on raw differences only, the percent change is used only to facilitate description of the results. The results of the present experiment and previous experiment were compared using t tests for two samples.

Results

Heart rate, SBP, mean aortic pressure (MAP), and mean LAP were closely matched during the three treatments (Table I). There were no significant changes in haemodynamic variables when 50% N_2O was substituted for 0.4% isoflurane. The addition of 50% N_2O to 1.8% isoflurane resulted in decreases of 27.9% in LV dP/dt and 38% in cardiac index. This indicates that the increase from 1.3 MAC to 1.7 MAC was associated with additional depression of myocardial contractility. Mean coronary blood pressure and flow measured in the cannula in the LAD during application of the stenosis were similar

TABLE I Haemodynamic variables during application of stenosis

	A N_2 50% with isoflurane 1.8%	*B* N_2O 50% with isoflurane 1.4%	*C* N_2O 50% with isoflurane 1.8%	% Change $\frac{B-A}{A} \times 100$	% Change $\frac{C-A}{A} \times 100$
HR (beats·min^{-1})	111 ± 8	113 ± 9	112 ± 7	+1.8	+0.9
SBP (mmHg)	99 ± 10	101 ± 10	98 ± 9	+2.0	−1.0
MAP (mmHg)	80 ± 8	82 ± 10	81 ± 8	+2.5	+1.3
MLAP (mmHg)	11 ± 3	10 ± 3	10 ± 3	−9.1	−9.1
LV dP/dt (mmHg·S^{-1}·10^{-3})	0.68 ± 0.27	0.64 ± 0.23	0.49 ± 0.21	−6.0	−27.9†
CI (ml·min^{-1}·100 g^{-1})	100 ± 33	99 ± 27	62 ± 15	−1.0	−38.0*
MCBF (ml·min^{-1}·g^{-1})	0.44 ± 0.20	0.41 ± 0.17	0.43 ± 0.22	−6.8	−2.3
MCBP (mmHg)	43 ± 7	43 ± 6	48 ± 7	0	+11.6

HR = heart rate; SBP = aortic systolic pressure; MAP = mean arterial pressure; MLAP = mean left atrial pressure; LV dp/dt = first derivative of left ventricular pressure with respect to time; CI = cardiac index; MCBF = mean LAD blood flow measured by electromagnetic flowmeter; MCBP = mean LAD coronary artery pressure distal to stenosis. Values in the first three columns are mean ± SD.
*$P < 0.05$, †$P < 0.01$ by paired t test.

TABLE II Regional segment length measurements during stenosis

	A N_2 50% with isoflurane 1.8%	*B* N_2O 50% with isoflurane 1.4%	*C* N_2O 50% with isoflurane 1.8%	% Change $\frac{B-A}{A} \times 100$	% Change $\frac{C-A}{A} \times 100$	
Control (CCx)						
EDL (mm)	13.1 ± 2.7	13.2 ± 2.7	13.2 ± 27	+0.8	+0.8	
SS (%)	12.4 ± 8.5	10.7 ± 6.8	5.3 ± 6.3	−13.7	−57.3†	
Ischaemic (LAD)						
EDL (mm)	14.3 ± 1.7	14.4 ± 1.6	14.5 ± 1.5	+0.7	+4.2	NS
SS (%)	13.6 ± 9.6	11.6 ± 8.2	8.9 ± 8.5	−14.7	−34.6*	

EDL = end-diastolic length; SS = systolic segment shortening. Values in first three columns are mean ± SD.
*$P < 0.05$ by paired t test. †$P < 0.01$ by paired t test. NS, $P > 0.05$ by t test for 2 samples. The magnitude of the decrease in systolic shortening was not different in the ischaemic region compared with the control region.

during the three anaesthetic treatments. Thus, haemodynamic measures of myocardial oxygen supply and demand were unchanged when 50% N_2O was substituted for 0.4% isoflurane, whereas two measures of oxygen demand (LV dP/dt and CI) decreased when N_2O was added to 1.8% isoflurane.

Table II shows the regional segment length measurements made during application of the stenosis. End-diastolic length did not change during the three treatments in either the nonischaemic circumflex or ischaemic LAD region. This confirms the matching of preload suggested by the absence of significant change in left atrial pressure. Comparing the equipotent anaesthetics there was a small but insignificant decrease in systolic shortening with N_2O which was almost identical in magnitude in the two regions. When N_2O was added to 1.8% isoflurane, however, systolic shortening decreased significantly by 57.3% in the circumflex and 34.6% in the LAD region. Again, the magnitude of this depressant effect of N_2O was not significantly different in the nonischaemic and ischaemic regions.

The measurements of regional myocardial blood flow are given in Table III. Comparing 1.8% isoflurane in N_2 to 1.4% isoflurane with 50% N_2O there was no significant change in transmural distribution or blood flow in any layer in either region. When N_2O was added to 1.8% isoflurane, mean endocardial, epicardial and transmural (full thickness) blood flow decreased in the circumflex region but these changes did not reach statistical significance. Epicardial blood flow in the LAD region decreased significantly while the increase in mean I/O ratio did not reach statistical significance ($P = 0.14$, paired t test).

Discussion

The present experiment was designed to examine the effects of N_2O on myocardial blood flow and function in

TABLE III Regional myocardial blood flow during stenosis

	A N_2 *50% with isoflurane 1.8%*	*B* N_2O *50% with isoflurane 1.4%*	*C* N_2O *50% with isoflurane 1.8%*	*% Change* $\frac{B-A}{A} \times 100$	$\frac{C-A}{A} \times 100$
Control (CCx)					
Endo ($ml \cdot min^{-1} \cdot g^{-1}$)	1.28 ± 0.47	1.10 ± 0.24	0.96 ± 0.19	−14.1	−25.0
Epi ($ml \cdot min^{-1} \cdot g^{-1}$)	1.07 ± 0.35	0.89 ± 0.24	0.74 ± 0.29	−16.8	−30.8
Trans ($ml \cdot min^{-1} \cdot g^{-1}$)	1.16 ± 0.37	0.98 ± 0.22	0.83 ± 0.20	−15.5	−28.5
Endo/Epi	1.26 ± 0.31	1.31 ± 0.26	1.42 ± 0.36	+4.0	+12.7
Ischaemic					
Endo ($ml \cdot min^{-1} \cdot g^{-1}$)	0.49 ± 0.17	0.45 ± 0.17	0.50 ± 0.21	−8.2	+2.0
Epi ($ml \cdot min^{-1} \cdot g^{-1}$)	0.83 ± 0.21	0.78 ± 0.17	0.66 ± 0.13	−6.0	−20.5*
Trans ($ml \cdot min^{-1} \cdot g^{-1}$)	0.64 ± 0.17	0.61 ± 0.15	0.58 ± 0.16	−4.7	−9.4
Endo/Epi	0.60 ± 0.23	0.58 ± 0.21	0.78 ± 0.28	−3.3	+30.0

Endo = inner third of myocardium; Epi = outer third of myocardium; Trans = transmural, full thickness of myocardium; Endo/Epi = inner/outer (I/O) blood flow ratio. Values in the first three columns are mean ± SD.
*$P < 0.05$ by paired t test.

isoflurane anaesthetized dogs who were beta-blocked with propranolol. When 50% N_2O was substituted for 0.4% isoflurane, thereby keeping MAC constant, there was no significant change either in global cardiac function or function and blood flow in ischaemic and normal regions of myocardium. When 50% N_2O was added to 1.8% isoflurane, thereby increasing MAC from 1.3 to 1.7, direct myocardial depression was evident in normal and ischaemic myocardium. Changes in regional myocardial blood flow did not reach statistical significance except for a decrease in epicardial blood flow in the ischaemic region.

During the three anaesthetic treatments SBP and LAP were closely matched while HR, in the presence of beta-blockade, did not change. Blood flow and pressure in the LAD artery were constant as well. At equal MAC, where there were no changes in the haemodynamic determinants of myocardial oxygen supply and demand, any possible direct actions of N_2O on ischaemic or normal myocardium or on the coronary vessels were not powerful enough to cause significant changes in this preparation. When N_2O was added to 1.8% isoflurane CI and LV dP/dt decreased significantly. Systolic shortening decreased in both the circumflex and LAD regions of the heart. The magnitude of this direct depressant effect of N_2O was not significantly different in normal or ischaemic myocardium. Of the regional myocardial blood flow measurements only a decrease in blood flow in the epicardium of the ischaemic region reached statistical significance. Decreased blood flow to the outer layers and increased I/O ratio would be expected if MVO_2 decreased in a hypoperfused region of myocardium, indicating improved matching of supply and demand.

The present experiment was performed in an animal with open chest and pericardium and during anticoagulation with heparin. In contrast to a stenosis created by directly compressing a coronary artery, the stenosis was imposed on a silastic autoperfusion circuit which would not be subject to changes in coronary tone or vascular integrity at the constriction. Although such an artificial stenosis is different from the clinical entity, the fixed and reproducible nature of the obstruction to blood flow allows precise determination of distal coronary vasomotion. The dissection and cannulation of the LAD coronary artery may have interfered with the innervation of the vasculature in that region.[9,10] Using quantitative angiography in pentobarbitone/fentanyl anaesthetized closed chest dogs Wilkowski *et al.*[11] demonstrated constriction of large epicardial coronary conductance vessels but no effect on coronary arterioles or metabolic regulation. The mechanism of the vasoconstriction was not determined. The present preparation does not address the problem of patients with an eccentric coronary stenosis where it is possible that even a small amount of vasoconstriction of the intact media could lead to clinically significant reductions in coronary blood flow.[12]

The present study is similar in design to a previous study from this laboratory[2] where propranolol was not used. Differences between the studies could be ascribed to the effect of beta-blockade (Figure 2). Although haemodynamic conditions were not the same in both studies (HR was lower with propranolol), the changes occurring with change in anaesthetic treatment would still reflect the effect of N_2O with and without beta-blockade. Comparing 1.8% isoflurane and 1.4% isoflurane with 50% N_2O the response in CI, LV dP/dt, systolic shortening and I/O

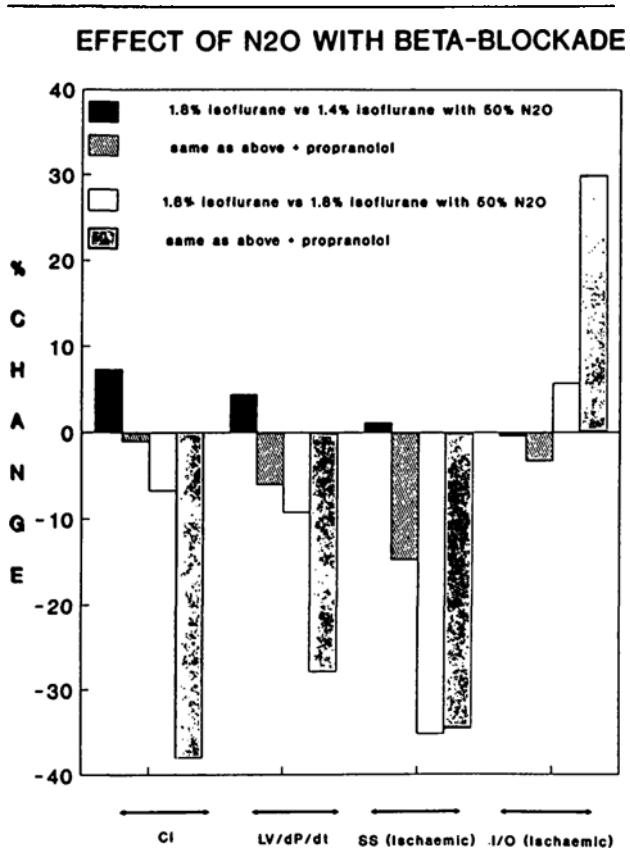

FIGURE 2 The effects of N_2O during regional myocardial ischaemia with and without β-receptor blockade. Heart rate and blood pressure were held constant during each experiment. Although the results suggest that N_2O causes a greater decrease in myocardial performance in the presence of beta-blockade, the differences did not reach statistical significance. Data without β-receptor blockade are from reference 2.

ratio (both in the ischaemic region) was similar with and without propranolol (Figure 1). The response was also similar when N_2O was added to 1.8% isoflurane. Although the magnitude of some changes appears to be larger with propranolol there were no statistically significant differences in the changes between the two groups (t test) possibly due to the small sample size. The direct myocardial depressant effects of N_2O are balanced by increased sympathetic outflow.[3-5] With beta-blockade more of the depressant effect of N_2O would be apparent and greater myocardial depression would be expected.

The laboratory and clinical experience with the effect of N_2O on the heart and vessels has recently been summarized.[2] The present study suggests that the presence of beta-blockade does not markedly alter the response of normal or ischaemic heart to N_2O except, perhaps, for some unmasking of its direct myocardial depressant effect. There was no evidence of any adverse effect on myocardial blood flow distribution. The lack of direct effect of nitrous oxide on coronary arteriolar tone observed in the present study is consistent with previous studies in animals despite the use of different preparations and background anaesthetics. Dottori,[13] who studied dogs receiving diazepam and nitrous oxide, and Wilkowski,[11] who anaesthetized dogs with pentobarbitone and fentanyl, and Thorburn,[14] who used pentobarbitone alone, all found that nitrous oxide had no effect on metabolic regulation. The relationship between coronary blood flow and myocardial oxygen consumption was unaffected by the presence of nitrous oxide. Recently transeosophageal echocardiography has been used to detect ischaemia during the administration of N_2O to patients with good[15,16] or poor[17] LV function. Most patients were receiving beta-blockers. Although only small numbers of patients were studied there was no evidence of a harmful effect of N_2O.

The present and previous data indicate that, so long as stable heamodynamic conditions can be maintained, the use of N_2O per se is unlikely to be harmful to the patient with coronary disease receiving beta-blocker therapy.

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