

Control of Hemodynamics Prevents Worsening of Myocardial Ischemia When Nitrous Oxide is Administered to Isoflurane-Anesthetized Dogs

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This study was designed to determine if nitrous oxide can worsen myocardial ischemia by directly affecting coronary tone in the absence of changes in myocardial oxygen consumption. Three anesthetics were compared in each animal: isoflurane 1.8% alone, isoflurane 1.4% with 50% nitrous oxide, and isoflurane 1.8% with 50% nitrous oxide. Heart rate, systolic aortic pressure and left atrial pressure were held constant during the three treatments. In 12 isoflurane-anesthetized dogs the chest was opened and the left anterior descending (LAD) coronary artery cannulated and perfused with an autoperfusion circuit. Systolic segment shortening was measured in the LAD and circumflex regions of the heart with a sonomicrometer. Regional myocardial blood flow was measured with radioactive microspheres. Measurements were made during imposition of a stenosis on the perfusion circuit sufficient to decrease systolic shortening by 30-50%. The same stenosis was imposed three times in a randomized and balanced crossover design. When heart rate, blood pressure, and left atrial pressure were held constant, the substitution of 50% nitrous oxide for 0.4% isoflurane had no effect on myocardial blood flow or function in the ischemic or normal region. When nitrous oxide was added to 1.8% isoflurane, systolic shortening decreased by 35% in the ischemic and 27% in the normally perfused region, but myocardial blood flow was unaffected. The decrease in shortening was therefore not due to increased ischemia. The effects of nitrous oxide on ischemic myocardium can be explained by its well-known hemodynamic and direct myocardial actions. These results suggest that nitrous oxide does not have important direct effects on the coronary circulation. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, volatile: isoflurane. Artery, coronary: steal. Heart, blood flow: ischemia; myocardial; regional ventricular function.)

In 1985 PHILBIN *et al.*¹ reported that regional wall motion abnormalities occurred upon adding nitrous oxide to an opioid anesthetic in dogs with critical coronary stenoses. That observation stimulated further research, and conflicting evidence has now been produced in both humans and animals supporting or discouraging the use of this gas for patients with coronary artery disease.

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Received from the Department of Anesthesia, Ottawa Civic Hospital, University of Ottawa Heart Institute, Ottawa, Ontario, Canada. Accepted for publication June 5, 1989. Supported by a grant from the Heart and Stroke Foundation of Ontario and a Career Scientist Award from the Ontario Ministry of Health. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1988, San Francisco, California.

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A previous report from this laboratory² documented worsening of ischemia when the anesthetic was changed from 1.8% isoflurane to 1.4% isoflurane with 50% nitrous oxide; equipotent anesthetics in the dog. It was unclear, however, if the adverse effect was due to the small increases in heart rate and blood pressure that accompanied the use of nitrous oxide or if nitrous oxide was directly affecting coronary tone or ischemic myocardial function. Heart rate and blood pressure can be easily monitored and controlled in the operating room. However, changes in coronary tone not caused by changes in these variables would be difficult to detect and treat. If such direct coronary effects were powerful enough to worsen myocardial ischemia, it would discourage the use of nitrous oxide for patients with coronary artery disease. In the present experiment the same two anesthetics were compared, but heart rate and blood pressure were held constant to determine the mechanism whereby nitrous oxide worsened ischemia in the previous study. The effect of adding 50% nitrous oxide to a constant level of isoflurane (1.8%) was also investigated.

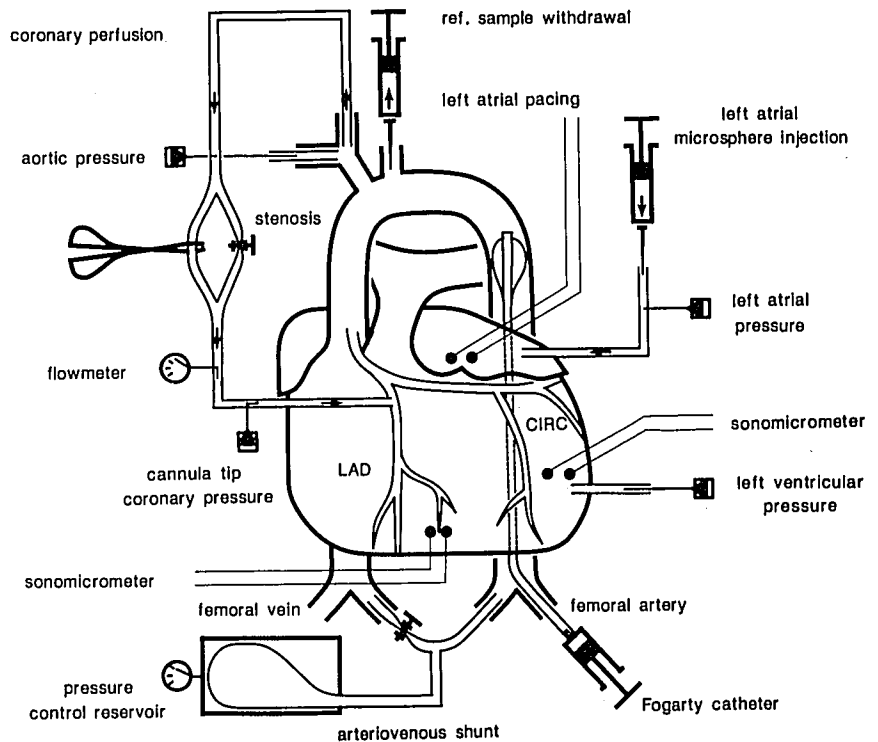
Methods

GENERAL PREPARATION

In 12 dogs of either sex, weighing 19.5-30 kg, anesthesia was induced with sodium thiopental. Following tracheal intubation ventilation was controlled to maintain arterial P_{CO_2} between 35 and 40 mmHg. If required to maintain arterial P_{O_2} above 100 mmHg, PEEP of 2-5 cmH_2O was applied before data collection began. Anesthesia was maintained with isoflurane in oxygen during the surgical preparation. Inspired oxygen concentration was measured with a polarographic electrode, and anesthetic 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.

Figure 1 illustrates the surgical preparation. Arterial blood pressure was measured with a Gould P23ID transducer *via* a fluid filled catheter placed through the right

FIG. 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 radioactive microspheres into the left atrium. The heart was paced via wires attached to 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.



brachial artery into the arch of the aorta. An 8-Fr 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.

The chest was opened through an incision in the left fifth intercostal space and the heart suspended in a pericardial cradle. A catheter was inserted into 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 through the apex and the signal differentiated using an analog circuit. The left atrium was paced with an electrical stimulator. Ringer's lactate was infused at $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ into the left femoral vein throughout the experiment. Heparin 5 mg/kg bolus followed by $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was started prior to coronary cannulation.

CORONARY PERFUSION

The left anterior descending coronary artery 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 (fig. 1). A cannulating flow transducer was placed in the perfusion circuit and coronary blood flow measured with an electromagnetic flowmeter (Carolina Instruments FM501). Zero flow baselines were re-

peatedly determined throughout the experiment by diverting blood flow away from the probe through a parallel bypass shunt (not illustrated).

Downstream from the flow probe a shunt was constructed to allow the imposition of an artificial coronary stenosis. Left anterior descending coronary artery pressure was measured at the cannula tip via a small stainless steel tube within the coronary cannula.

MYOCARDIAL BLOOD FLOW

Radioactive microspheres, approximately $15 \mu\text{m}$ in diameter, and labeled 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/min beginning 30 s before and ending 90 s after each microsphere injection. This reference sample was used to calculate tissue flow from tissue counts and cardiac output from total counts injected by the method of Heymann *et al.*³

At the end of the experiment india ink was injected into the coronary cannula to define the ischemic LAD region. Ventricular fibrillation was then induced, the heart removed, and the left ventricular free wall excised and 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 4 days in formalin the left ventricular free wall was divided into two regions: the stained area that had been perfused *via* the LAD cannula (ischemic 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 were computed using reference sample counts and flow.³

REGIONAL SYSTOLIC SHORTENING

An ultrasonic dimension gauge (Sonomicrometer 120, Triton Technologies) was used to measure myocardial segment length in the LAD and circumflex (CCX) regions. In each region two piezoelectric crystals were inserted into the subendocardium 1–2 cm apart, parallel to the short axis of the heart (fig. 1). An attempt was made to keep both pairs of crystals in the same equatorial plane. 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.⁴ Systolic segment shortening (SS) was calculated as:

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

CORONARY STENOSIS

To test the possibility of transmural coronary steal, it was necessary to restrict LAD coronary blood flow sufficiently to cause subendocardial ischemia. To accomplish this, a modified screw clamp was used to create a constriction in the silastic coronary perfusion circuit (fig. 1). 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 changing the screw clamp setting.

When the surgical preparation was completed, the an-

imal's condition was stable, and the anesthetic was 1.8% isoflurane in 50% oxygen/nitrogen, the heart was paced at a rate 20% greater than the intrinsic rate. The bypass shunt was then 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 10-min recovery closed again to determine if the same degree of dysfunction recurred. It rarely was 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 prestenosis values within the first 5 min of the recovery period. The screw clamp was never again manipulated during the experiment.

PROTOCOL

Three anesthetic treatments were compared in each animal in a randomized crossover design: A) isoflurane 1.8% with 50% N₂ in O₂; B) isoflurane 1.4% with 50% N₂O in O₂; C) isoflurane 1.8% with 50% N₂O in O₂. Each of the six possible sequences (ABC, ACB, etc.) was replicated twice for a total of 12 experiments. The treatment sequence was randomly selected only after the final stenosis setting had been made.

Heart rate, systolic blood pressure (BP), and left atrial pressure were to be matched for the three treatments during application of the stenosis. Preliminary experiments showed that heart rate and systolic BP were usually highest during treatment B 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. Through use of these techniques, it was possible to closely match both systolic BP and left atrial pressure as well. Heart rate was kept constant throughout the experiment by atrial pacing at a rate approximately 20% higher than the intrinsic rate present before setting the stenosis.

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 (fig. 1). Within 2–3 min 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 reference sample collection could be completed in less than 7 min after which the bypass shunt was reopened. Global hemodynamic measures (heart rate, aortic pressure, left atrial pressure, LV dP/dt) and coronary flow and distal

pressure were frequently recorded but changed little after the first 3 min of ischemia. Variables that changed with respiration were measured at end-expiration. During the second and third applications of the stenosis the ischemic 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 versus B and A versus C. The null hypothesis (no difference) was rejected if *P* < 0.05. Because the comparisons were chosen *a priori*, no correction for multiple testing was made.

The percent change was calculated separately for each animal by subtracting the value during treatment A from the value during treatment B or C and dividing by the value during treatment A. The mean percent change was then computed and the results presented in the last two columns of the tables. These values are not the same as the percent difference between the means.

In one animal heart rate increased above the paced rate before the second treatment began. The pacing rate was raised and the second and third treatments were matched. The first treatment was 50% nitrous oxide with 1.8% isoflurane and the data were not included in the analysis. Thus, in all tables the number of observations for this treatment is 11; for the other two anesthetic treatments the number of observations was 12.

Results

Heart rate, systolic aortic BP, and mean left atrial pressure were closely matched during the three treatments, as were *pH* and *P*_{O₂} (table 1). There were small changes in systolic blood pressure and hematocrit that were sta-

tistically significant but not likely important physiologically.

Although not directly manipulated experimentally, mean arterial pressure, cardiac index, mean LAD coronary blood flow, and mean LAD pressure measured distal to the stenosis were similar during the three treatments (table 2). The addition of 50% nitrous oxide to 1.8% isoflurane did result, however, in a decrease of 9.2% in left ventricular *dP/dt*, indicating that the increase from 1.3 MAC to 1.7 MAC was associated with additional depression of myocardial contractility.

Table 3 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 nonischemic circumflex or the ischemic LAD region. This confirms at a regional level the matching of preload suggested by the lack of significant change in left atrial pressure. Comparing the two equipotent anesthetics, systolic shortening did not change in either region. However, when nitrous oxide was added to 1.8% isoflurane, systolic shortening decreased 26.5% in the nonischemic and 35.2% in the ischemic region. The magnitude of this depressant effect of nitrous oxide was not significantly different in the two regions. In four animals postsystolic shortening was observed during all three treatments. The changes in this measure between treatments were small and inconsistent.

Regional myocardial blood flow was unchanged during the three anesthetic treatments (table 4). The probability of failing to detect a true 25% change in transmural blood flow or endocardial:epicardial blood flow ratio in the ischemic region was less than 10%. The type II error calculation for this within subject comparison is based on the standard error of the mean of the differences between treatments B and A (*SEM*_{B-A}) or C and A (*SEM*_{C-A}) calculated for each animal. The values of *SEM*_{B-A} and *SEM*_{C-A} for transmural blood flow in the LAD region were both 0.03 ml · min⁻¹ · g⁻¹. The corresponding values for endocardial/epicardial ratio were also both 0.03. The

TABLE 1. Controlled Variables during Application of Stenosis

	A N ₂ O 50% with Isoflurane 1.8%	B N ₂ O 50% with Isoflurane 1.4%	C N ₂ O 50% with Isoflurane 1.8%	% Change	
				$\frac{B-A}{A} \times 100$	$\frac{C-A}{A} \times 100$
HR (beats/min)	136 ± 12	136 ± 12	135 ± 11	+0.11	0
SBP (mmHg)	105 ± 12	107 ± 13	104 ± 12	+1.44*	-0.57
MLAP (mmHg)	6.9 ± 1.9	6.7 ± 2.4	7.2 ± 2.2	-4.47	+4.07
<i>pH</i>	7.38 ± 0.3	7.37 ± 0.03	7.38 ± 0.02	-0.16	+0.04
<i>P</i> _{O₂} (mmHg)	148 ± 50	147 ± 52	150 ± 51	+2.3	+2.6
Hematocrit (%)	32 ± 3.6	33 ± 3.1	33 ± 2.9	+3.8	+5.7*

HR = heart rate; SBP = aortic systolic pressure; MLAP = mean left atrial pressure.

Values in the first three columns are mean ± SD, n = 12 for treat-

ments A and B and n = 11 for treatment C in this table and in tables 2-4.

* *P* < 0.05.

TABLE 2. Hemodynamic Variables during Application of Stenosis

	A N ₂ 50% with Isoflurane 1.8%	B N ₂ O 50% with Isoflurane 1.4%	C N ₂ O 50% with Isoflurane 1.8%	% Change	
				$\frac{B-A}{A} \times 100$	$\frac{C-A}{A} \times 100$
MAP (mmHg)	87 ± 9.6	87 ± 10.0	87 ± 12.3	+1.0	+0.5
CI (ml · min ⁻¹ · 100 g ⁻¹)	127 ± 39	130 ± 36	122 ± 78	+7.3	-6.7
LV dP/dt (mmHg · s ⁻¹ · 1,000 ⁻¹)	1.01 ± 0.26	1.03 ± 0.20	0.85 ± 0.17	+4.4	-9.2*
MCBF (ml · min ⁻¹ · g ⁻¹)	0.57 ± 0.17	0.56 ± 0.17	0.55 ± 0.17	-1.1	-1.4
MCBP (mmHg)	45 ± 6	44 ± 7	46 ± 8.5	-3.1	+3.3

MAP = mean arterial pressure; CI = cardiac index; LV dP/dt = first derivative of left ventricular pressure with respect to time; MCBF = mean LAD blood flow measured by electromagnetic flowmeter; MCBP

= mean LAD coronary artery pressure distal to the stenosis. Values in the first three columns are mean ± SD.

* $P < 0.05$ by paired t test.

effect of the stenosis was to reduce transmural blood flow in the LAD region to 45% of the flow in the control region. The endocardial:epicardial blood flow ratio was above 1.0 in the control region, indicating normal perfusion. The ratio was low in the LAD region distal to the stenosis, indicating hypoperfusion, but did not change with the three different anesthetics. Thus, the substitution of nitrous oxide for 0.4% isoflurane and the addition of nitrous oxide to a constant level of isoflurane both had no effect on coronary blood flow when heart rate, systolic BP, and left atrial pressure were held constant.

Discussion

The present experiment completes a study of the cardiac effects of nitrous oxide during regional myocardial ischemia in isoflurane-anesthetized dogs. The earlier series² (fig. 2) compared the effects of two equipotent anesthetics in the dog: 50% nitrogen/oxygen with 1.8% isoflurane and 50% nitrous oxide/oxygen with 1.4% isoflurane. The substitution of 50% nitrous oxide for 0.4% isoflurane caused a 5% increase in heart rate and an 8% increase in systolic BP and was associated with a 19% reduction in systolic shortening and a 30% decrease in endocardial:epicardial blood flow ratio in an ischemic region

of the left ventricle. The present experiment was designed to test if the worsening of ischemia with nitrous oxide observed in the first series was due to the changes in heart rate and BP. When heart rate, BP, and left atrial pressure were held constant in the same preparation, there was no change in myocardial function or blood flow in the ischemic region. This indicates that in the absence of changes in myocardial metabolism, the two equipotent anesthetics have similar effects on the myocardium and coronary circulation. The worsening of ischemia observed in the earlier experiment was therefore caused by increased myocardial oxygen demand in the setting of a supply limited by an artificial coronary stenosis. The present experiment also revealed the effect of adding 50% nitrous oxide to 1.8% isoflurane, thereby increasing anesthetic dose from 1.3 MAC to 1.7 MAC. With heart rate, BP, and left atrial pressure held constant, systolic shortening in the ischemic region declined by 35% when nitrous oxide was added. However, there was no change in coronary blood flow and myocardial blood flow distribution (I/O ratio). Systolic shortening decreased by a similar amount (27%) in the normally perfused control region. This indicates that the decrease in systolic function was not due to ischemia but was likely caused by direct depression of myocardial contractility associated with an increase in anesthetic dose.

TABLE 3. Regional Segment Length Measurements during Stenosis

	A N ₂ 50% with Isoflurane 1.8%	B N ₂ O 50% with Isoflurane 1.4%	C N ₂ O 50% with Isoflurane 1.8%	% Change	
				$\frac{B-A}{A} \times 100$	$\frac{C-A}{A} \times 100$
Control (CCx)					
EDL (mm)	13.2 ± 6.1	13.2 ± 6.1	13.8 ± 6.1	-0.4	+0.5
SS (%)	18.1 ± 8.3	18.5 ± 8.0	13.7 ± 8.2	+5.4	-26.5*
Ischemic (LAD)					
EDL (mm)	14.2 ± 3.7	14.0 ± 3.7	14.8 ± 3.5	-1.8	+1.2
SS (%)	11.8 ± 7.2	11.8 ± 7.5	7.8 ± 5.8	+1.1	-35.2†

EDL = end-diastolic segment length; SS = systolic segment shortening.

Values in the first three columns are mean ± SD.

* $P < 0.01$ by paired t test.

† $P < 0.05$ by paired t test.

‡ The magnitude of the decrease in systolic shortening comparing C with A was not different in the control ischemic regions by paired t test.

TABLE 4. Regional Myocardial Blood Flow during Stenosis

	A N ₂ O 50% with Isoflurane 1.8%	B N ₂ O 50% with Isoflurane 1.4%	C N ₂ O 50% with Isoflurane 1.8%	% Change	
				$\frac{B-A}{A} \times 100$	$\frac{C-A}{A} \times 100$
Control (CCx)					
Endo (ml · min ⁻¹ · g ⁻¹)	1.53 ± 0.60	1.47 ± 0.56	1.50 ± 0.76	-2.6	-3.9
Epi (ml · min ⁻¹ · g ⁻¹)	1.45 ± 0.52	1.52 ± 0.71	1.44 ± 0.75	+4.0	-3.1
Trans (ml · min ⁻¹ · g ⁻¹)	1.48 ± 0.54	1.47 ± 0.60	1.45 ± 0.76	-0.2	-3.7
Endo/Epi	1.08 ± 0.13	1.02 ± 0.17	1.08 ± 0.15	-5.4	-0.2
Ischemic (LAD)					
Endo (ml · min ⁻¹ · g ⁻¹)	0.41 ± 0.16	0.41 ± 0.19	0.42 ± 0.19	-1.6	+10.2
Epi (ml · min ⁻¹ · g ⁻¹)	0.95 ± 0.27	0.96 ± 0.38	0.96 ± 0.29	-0.2	+2.3
Trans (ml · min ⁻¹ · g ⁻¹)	0.65 ± 0.19	0.66 ± 0.25	0.67 ± 0.21	-1.1	+3.2
Endo/Epi	0.46 ± 0.20	0.44 ± 0.18	0.46 ± 0.19	-0.4	+5.7

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. None of the changes were significant.

When changes in myocardial metabolism were limited by holding heart rate and blood pressure constant, nitrous oxide did not cause detectable coronary arteriolar vasodilation or vasoconstriction. This lack of direct coronary effect was observed when nitrous oxide replaced 0.4% isoflurane and also when it was added to a constant concentration of isoflurane. Nitrous oxide did not cause coronary steal.

LIMITATIONS

The present experiment was performed in an animal with an 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 more precise determination of distal coronary vasomotion.

The dissection and cannulation of the LAD coronary artery may have interfered with the adrenergic innervation of the vasculature in that region.^{5,6} In a closed chest canine preparation Wilkowski and Sill⁷ found coronary arterial but not arteriolar vasoconstriction with the administration of nitrous oxide. Adrenergic coronary arteriolar vasoconstriction has been found to improve subendocardial perfusion by lessening transmural steal in an ischemic region of the canine left ventricle.⁸ Nevertheless, the present experimental preparation may not demonstrate a possible effect of nitrous oxide-induced adrenergic coronary vasoconstriction because of interference with the sympathetic supply to the LAD vasculature. The possible effect of sympathetic vasoconstriction at the site of a coronary stenosis in patients is considered later.

Myocardial oxygen consumption was not directly measured in the present or previous experiment. The change in oxygen consumption can be estimated using the pressure-work index developed by Rooke and Feigl.⁹ This index is sensitive to changes in stroke volume and contractility, the determinants of myocardial oxygen consumption not controlled in the present experiment (Appendix). In the first series when the effects of isoflurane 1.8% were compared with those of isoflurane 1.4% with 50% nitrous oxide without controlling heart rate and systolic BP, calculated MVO₂ rose by 11.8% (*P* < 0.05, ANOVA). When heart rate and systolic BP and LA pressure were held constant, this substitution of 50% nitrous oxide for 0.4% isoflurane resulted in a statistically insignificant 2.5% increase in MVO₂. Addition of 50% nitrous oxide to 1.8% isoflurane was associated with a 3.2% decline in MVO₂, which also was not statistically significant. It is noteworthy that increases in MVO₂ of less than 12% result in significant worsening of ischemia. This indicates that in a region where subendocardial ischemia is already present, small changes in the myocardial oxygen supply/demand relationship can cause large changes in myocardial function and blood flow distribution.

COMPARISON WITH PREVIOUS WORK

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 anesthetics. Dottori *et al.*,¹⁰ who studied dogs receiving diazepam and nitrous oxide, Wilkowski *et al.*,⁷ who anesthetized dogs with pentobarbital and fentanyl, and Thorburn *et al.*,¹¹ who used pentobarbital 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. Studies

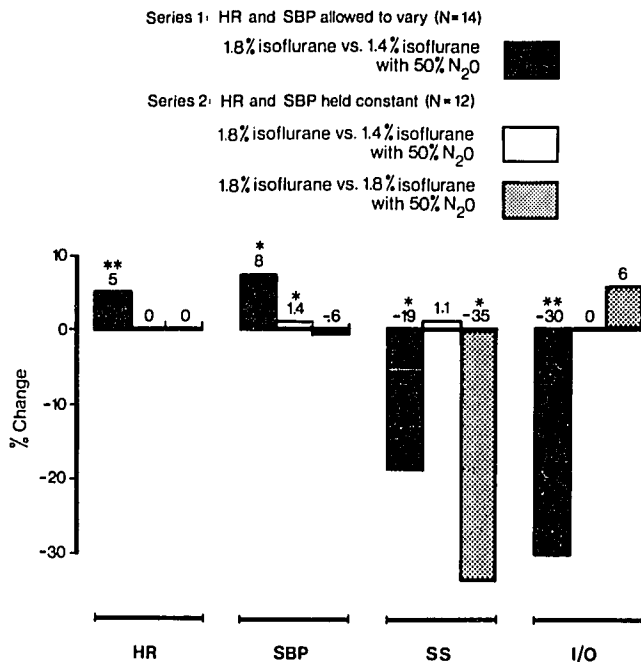


FIG. 2. The effect of anesthetic treatment during ischemia. In series 1 (solid bars) the substitution of 0.4% isoflurane with 50% N₂O was associated with increases in heart rate (HR) and systolic aortic pressure (SBP), and decreases in percent systolic shortening (SS) and inner/outer blood flow ratio (I/O), indicating worsening of myocardial ischemia. When the same two anesthetics were compared in series 2 (white bars), but holding HR, SBP, and left atrial pressure constant, there was no change in systolic shortening or I/O ratio, indicating that the worsening of ischemia in series 1 was due to increased myocardial oxygen demand. When 50% N₂O was added to 1.8% isoflurane (stippled bars) and HR, SBP, and left atrial pressure were held constant, systolic shortening declined by 35% but I/O ratio was unchanged. This indicates that N₂O had a myocardial depressant effect not associated with changes in myocardial blood flow or ischemia. * $P < 0.05$, ** $P < 0.01$.

of normally perfused myocardium consistently demonstrate mild myocardial depression when nitrous oxide is added to different background anesthetics.^{1,11-13} When 75% nitrous oxide was added to 1% halothane in dogs,¹² peak LV dP/dt decreased by 9.7%, similar to the 9.2% decrease observed when 50% nitrous oxide was added to 1.8% isoflurane in the present experiment.

Regional myocardial function has been studied using the ultrasonic dimension gauge (sonomicrometer) in animals with induced coronary stenosis. Philbin *et al.*¹ administered nitrous oxide to dogs anesthetized with sufentanil or fentanyl and found decreased systolic shortening both in a normally perfused region of myocardium as well as in a region distal to a critical coronary stenosis. Nitrous oxide caused postsystolic shortening only in the poststenotic region. This change in pattern of contraction was associated with a small decrease in coronary perfusion pressure but no change in coronary blood flow measured with an electromagnetic flow probe around the LAD cor-

onary artery. It is not known if this change was caused by a worsening of ischemia because regional myocardial blood flow and metabolism were not measured. Ramsay *et al.*¹³ added 66% N₂O to 1% halothane in a preparation similar to that of Philbin *et al.*¹ and found postsystolic shortening both during application of a critical stenosis and during normal perfusion. The findings of Ramsay *et al.*¹³ and the results of the present experiment suggest that a decrease in regional function can occur without an adverse change in the myocardial supply/demand relationship. The diagnosis of ischemia would require confirmation with simultaneous measurement of regional myocardial blood flow or regional myocardial metabolism. Buffington *et al.*¹⁴ found no effect of nitrous oxide on coronary resistance in a preparation designed to demonstrate intercoronary steal.

Using quantitative angiography in closed chest dogs anesthetized with pentobarbital and fentanyl, Wilkowski *et al.*⁷ 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. Vasoconstriction in the epicardial portion of the LAD coronary artery powerful enough to alter regional myocardial blood flow was not observed in the present experiment.

Hemodynamic studies in both normal humans and patients about to undergo cardiac surgery describe effects of nitrous oxide similar to those demonstrated in the present experiment. When nitrous oxide is added to a constant level of background anesthetic, there is usually little hemodynamic change because the direct myocardial depressant effect of nitrous oxide is balanced by the cardiac and peripheral effects of increased sympathetic outflow. When the concentration of background agent is reduced, thereby maintaining MAC constant, the use of nitrous oxide leads to increased BP because the direct myocardial depression caused by nitrous oxide is balanced by the withdrawal of background agent and there is a net increase in performance due to increased sympathetic outflow. The sympathetic effect of nitrous oxide is most pronounced with isoflurane and halothane,¹⁵⁻¹⁷ less with enflurane,¹⁸ and least with narcotics.¹⁹⁻²²

Moffitt *et al.*²³ studied 13 patients prior to coronary artery surgery and found marked myocardial depression and evidence of an adverse myocardial oxygen supply/demand relationship when 50% nitrous oxide was added to 0.5% inspired halothane. All 13 patients had left ventricular ejection fractions greater than 50%, and so these findings were unexpected. Six patients were receiving beta-adrenergic blocking drugs, and it may be possible that this could inhibit the increase in contractility due to the increase in sympathetic tone seen with nitrous oxide, thereby revealing the direct depressant effect of the agent. Fischerstrom *et al.*²⁴ however, used either halothane or

fentanyl with 50% nitrous oxide in a similar group of patients and found little difference between the two anesthetics. Nineteen of the 20 patients were receiving beta-adrenergic blocking drugs. Nitroprusside or fluid volume was used as needed to maintain normal pulmonary artery and systemic blood pressures. The benign response to both combinations is in contrast to the findings of Moffitt *et al.*²³ The careful hemodynamic control in the study by Fischerstrom *et al.*²⁴ may explain the discrepant results.

Moffitt *et al.*²⁵ also studied the effect of adding 50% nitrous oxide to fentanyl or enflurane in 20 patients of whom 19 had previously received beta-adrenergic blocking drugs. The combination of nitrous oxide with enflurane was found to be more depressant. There was some compromise of myocardial oxygenation with enflurane but no evidence of coronary arteriolar dilation.

Reiz²⁶ examined the effect of adding 70% nitrous oxide to 1% isoflurane in ten patients prior to coronary artery surgery. Adding nitrous oxide was associated with a decrease in heart rate, MAP, MVO_2 , and myocardial O_2 extraction but little change in coronary sinus blood flow. If the coronary sinus flow measurement accurately reflects myocardial blood flow, then these data are unusual in that they imply that nitrous oxide caused further direct coronary arteriolar dilation. These patients were hypotensive, and six showed signs of ischemia prior to adding nitrous oxide. It would be important to determine if a similar effect was found if BP and heart rate were better controlled.

Cahalan *et al.*²⁷ investigated the effect of administering 60% nitrous oxide to 18 patients with ischemic heart disease anesthetized with a moderate dose of fentanyl. The addition of nitrous oxide caused a decline in heart rate of 8 beats/min. There was no evidence of ischemia caused by nitrous oxide either on 12-lead ECG or transesophageal echocardiogram. The patients studied were receiving beta-adrenergic blocking drugs or calcium entry blocking drugs, and all had good left ventricular systolic function. These data suggest that nitrous oxide is safe for this population. These findings are supported by a similar study of only seven patients anesthetized with sufentanil for coronary artery surgery.²⁸ There was no hemodynamic, ECG, or echocardiographic evidence of ischemia associated with the use of nitrous oxide in this small group.

It is important to consider three issues in interpreting studies of patients with coronary artery disease. First, it is possible that few or none of the patients have physiologically critical stenoses during the administration of nitrous oxide; with low heart rates and normal blood pressures coronary reserve may be maintained despite the presence of significant stenoses. Coronary steal can only occur in regions of myocardium where coronary flow is pressure-dependent. Second, if an adverse effect of nitrous oxide on ischemic myocardium is to be demonstrated, the

presence of an ischemic region must be confirmed. Third, in patients with an eccentric coronary stenosis, it is possible that even a small amount of vasoconstriction of the intact media could lead to clinically significant reductions in coronary blood flow.²⁹

The present study of isoflurane-anesthetized dogs indicates that the effects of nitrous oxide on myocardial function and blood flow in an ischemic region of the heart can be explained by its well-known hemodynamic and direct myocardial actions. Direct effects on coronary tone powerful enough to alter regional myocardial blood flow or function were not observed. A consideration of the evidence from both humans and animals suggests that if heart rate and BP are controlled, nitrous oxide can be used safely in the presence of coronary stenoses. If the administration of nitrous oxide contributes to the ability of the anesthesiologist to maintain stable hemodynamic conditions, then its use may benefit the patient with coronary artery disease.

The author wishes to thank Vera Temple, R.N., and Keith Sheldrick for expert technical assistance, Mary O'Shaughnessy for typing the manuscript, and Anaquest Canada for supplying isoflurane.

Appendix

PRESSURE-WORK INDEX⁹

$$MVO_2 = K1(SBP \cdot HR) + K2((0.8SBP + 0.2DBP) \cdot HR \cdot SV) / BW + 1.43$$

where

$$MVO_2 = \text{left ventricular myocardial oxygen consumption (ml } O_2 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}\text{);}$$

SBP = systolic blood pressure (mmHg);
 DBP = diastolic blood pressure (mmHg);
 HR = heart rate (beats/min);
 SV = stroke volume (ml);
 BW = body weight (kg);
 K1 = 4.08^{-4} ; and
 K2 = 3.25^{-4} .

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