Nitrous Oxide Worsens Myocardial Ischemia in Isoflurane-anesthetized Dogs

Howard J. Nathan, M.D.*

Two equipotent anesthetic regimens, isoflurane 1.8% in 50% nitrogen/oxygen and isoflurane 1.4% in 50% nitrous oxide/oxygen, were compared to test if nitrous oxide, without changing the depth of anesthesia, can affect myocardial function, blood flow, and metabolism in an ischemic region of the heart. In 14 dogs, anesthesia was induced with sodium thiopental. Following tracheal intubation, they were ventilated with isoflurane in oxygen. The chest was opened, the LAD coronary artery cannulated, and flow to it controlled with an autoperfusion circuit. Systolic shortening in the LAD and circumflex regions was measured with a sonomicrometer via pairs of piezo-electric crystals placed in the subendocardium. Regional myocardial blood flow was measured with radioactive microspheres injected into the left atrium. Regional myocardial lactate metabolism was assessed by withdrawing blood from a catheter placed in the anterior cardiac vein. Measurements were made during the imposition of a stenosis on the perfusion circuit sufficient to decrease systolic shortening by 10–20%. The same stenosis was imposed three times in a randomized and balanced crossover design. Treatment with nitrous oxide was associated with small increases in heart rate and systolic blood pressure (5 and 6%, respectively), as well as a 19% reduction in systolic shortening and a 30% fall in endo/epi blood flow ratio in the hypoperfused LAD region distal to the stenosis. Lactate extraction was low or negative during both anesthetics, but differences were not statistically significant. The data indicate that the substitution of 50% nitrous oxide for 0.4% isoflurane caused a reduction in mechanical function and a further maldistribution of blood flow in ischemic myocardium. The mechanism of this deleterious effect must be discovered in order to determine if it is safe to use nitrous oxide with isoflurane to anesthetize patients with ischemic heart disease. (Key words: Anesthesia, gases: nitrous oxide. Anesthetics, volatile: isoflurane. Artery: coronary. Heart: blood flow; ischemia; lactate metabolism.)

Nitrous oxide has been a favored anesthetic agent because of its nearly ideal pharmacokinetic properties and apparently benign physiologic effects. Recently, however, evidence has been presented that this gas may have adverse cardiac effects in animal models of coronary stenosis1,2 and in patients with coronary disease.3–6 When nitrous oxide is chosen as part of a patient’s anesthetic, the concentration of other agents needed to maintain the necessary depth of anesthesia is reduced.

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If nitrous oxide is simply added to an anesthetic, the specific physiologic effects of the gas are confounded by the concomitant effects of deepening anesthesia. There are no studies of the effect of nitrous oxide on the abnormal coronary circulation where anesthetic depth was kept constant.

The present study compares two anesthetic regimens, equipotent in the dog: isoflurane 1.8%, and isoflurane 1.4% with 50% nitrous oxide. In an ischemic region of the canine left ventricle, the substitution of 50% nitrous oxide for 0.4% isoflurane resulted in diminished myocardial contraction and maldistribution of regional myocardial blood flow.

Materials and Methods

GENERAL PREPARATION

In 14 dogs of either sex, weighing 22–40 kg, anesthesia was induced with sodium thiopental. Following tracheal intubation, ventilation was controlled to maintain arterial Pco2 between 35 and 40 mmHg. If required to maintain arterial Pao2 above 100 mmHg PEEP of 2–5 cm H2O 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® P231 transducer via a fluid-filled catheter placed through the right brachial artery into the arch of the aorta. Ringer's lactate was infused at 10 ml·kg⁻¹·h⁻¹ into the left femoral vein throughout the experiment.

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 into the left atrium to allow injection of radioactive microspheres, as well as measurement of left atrial pressure with a Gould® P231D transducer. Left ventricular pressure was measured with a Statham® mini-transducer via a short length of stiff tubing placed into the left ventricle through a pulmonary vein. Heparin 5 mg/kg bolus followed by 2.5 mg·kg⁻¹·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. This required a brief occlusion (mean = 49 s, SD = 29 s). An autoperfusor circuit constructed of silastic tubing was used to bring blood from the right femoral 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 repeatedly 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 (see 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 microns in diameter, and labeled with $^{141}$Ce, $^{85}$Sr, or $^{58}$Nb were used to measure regional myocardial blood flow. After vigorous agitation and sonication to break up aggregates, approximately $2.5 \times 10^6$ 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 counts by the method of Heymann et al.7

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, the formalin fixed 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 grams. 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.

**Myocardial Segment Length**

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 (fig. 1). At the end of the experiment, it was confirmed that the “ischemic 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 and left ventricular blood pressure. End-diastolic length (EDL) was measured at the onset of the steep upstroke in the LV pressure trace. End-systolic length (ESL) was measured at the dicrotic notch in the aortic pressure waveform. Systolic segment shortening (SS) was calculated:

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

**Regional Myocardial Lactate Extraction**

The anterior cardiac vein, distal to the perfusion cannula in the LAD, was cannulated with a 24-gauge catheter (fig. 1). A modified Seldinger technique was used to avoid occluding venous return. Venous blood was collected by holding the end of the catheter 2–3 cm below the left atrium and allowing blood to drip into a chilled test tube. At the same time, an arterial sample was obtained. Both samples were kept on ice and, within 10 min, the plasma was separated from the red cells by centrifugation. Plasma was frozen and later lactate concentration analyzed by enzymatic assay (DuPont® LA pack, day-to-day coefficient of variation < 5.6%):

\[ \% \text{Lactate extraction} = \frac{\text{arterial lactate} - \text{venous lactate}}{\text{arterial lactate}} \times 100 \]

**Coronary Stenosis**

To test the experimental hypothesis, 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 manipulating the screw clamp.

When the surgical preparation was completed and the animal’s condition stable, and during administration of the first anesthetic treatment to be tested (see Protocol), the bypass shunt was clamped and the screw clamp set. This was done by tightening the screw clamp until a 10–20% decrease in systolic shortening was noted in the LAD region. The bypass shunt was then opened and, after a 10-min recovery, closed again to see if the same degree of dysfunction occurred. 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 preconstriction values within 5 min of opening the shunt. The screw clamp was never again manipulated during the experiment.

**Protocol**

Two anesthetic treatments were compared in a randomized crossover design. In seven animals, the sequence was:

A. Isoflurane 1.8% with 50% nitrogen in oxygen,
B. Isoflurane 1.4% with 50% N₂O in oxygen,
C. Isoflurane 1.8% with 50% nitrogen in oxygen;

and, in seven animals, the sequence was:

B. Isoflurane 1.4% with 50% N₂O in oxygen,
C. Isoflurane 1.8% with 50% nitrogen in oxygen,
D. Isoflurane 1.4% with 50% N₂O in oxygen.

Isoflurane in oxygen was used to maintain anesthesia during the surgical preparation. The first anesthetic treatment (chosen randomly) was begun before setting the stenosis (see Coronary Stenosis). This strategy ensured that all animals experienced a similar degree of ischemia during the initial treatment. A 30-min recovery period was allowed once the final setting of the screw clamp had been made.

Data were collected during three applications of the stenosis, each separated by a 45-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. After collection of the reference sample was completed, the coronary venous cannula was opened and blood collected for lactate analysis. An arterial sample was withdrawn at the same time for arterial lactate and
blood gas analysis. Data and sample collection could be completed in less than 9 min, after which the bypass shunt was reopened. Global hemodynamic measures (heart rate, aortic pressure, left atrial pressure) 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

Two anesthetic treatments were tested (A and B). The stenosis was applied three times in each animal. Animals were randomly assigned to two treatment sequences: seven had ABA, and seven had BAB. The null hypothesis was that changes measured in each animal when the treatment was switched are due to random error. This was tested using two-way (treatment and sequence) analysis of variance for a crossover design. P values presented are the probability of finding a larger F value by chance. The null hypothesis was rejected when P < .05.

The data in the tables were calculated as follows: if the sequence was ABA, then the value during the first and last A were averaged, and similarly for sequence BAB. In this way, each variable was represented only once for treatment A and once for treatment B in each dog, the experimental unit. Thus, the means and standard deviations are calculated from 14 observations. The mean differences and standard errors of the mean differences were calculated in a similar way. The percent change was calculated by dividing each difference by the initial value.

RESULTS

The analysis of variance showed no significant effect of sequence on any measured variable. The tables show the pooled results of 21 administrations of treatment A (nitrogen 50% with isoflurane 1.8%) and 21 administrations of treatment B (nitrous oxide 50% with isoflurane 1.4%), ignoring sequence, but keeping n = 14 (see Data Analysis). Figures 2 and 3 show data collected in each animal and the mean for each treatment. The two treatment sequences are illustrated separately.

Arterial blood gas values and hematocrit did not change significantly during the experiments (table 1). Hemodynamic variables and lactate extraction measured during imposition of the stenosis under the two anesthetic treatments are presented in table 2. Heart rate was 5% and aortic systolic blood pressure 8% higher during isoflurane 1.4% with 50% N\textsubscript{2}O. This suggests that the use of nitrous oxide was associated with higher myocardial oxygen consumption. Mean coronary pressure measured at the tip of the cannula in the LAD and mean LAD coronary flow measured with the electromagnetic flowmeter were not significantly different during the two treatments. Coronary resistance was, therefore, similar during both anesthetics. In most animals, lactate extraction was low or negative; however, the values showed marked variability, and there was no significant difference in lactate metabolism.
Nitrous oxide worsens myocardial ischemia

Endocardial/Epicardial (I/O) Blood Flow Ratio

![Graph showing blood flow ratios](https://example.com/graph.png)

Fig. 3. The ratio of subendocardial/subepicardial blood flow was close to 1.0 in the LCA region confirming adequate perfusion. The ratio was lower in the LAD region due to the stenosis, and was further diminished significantly during administration of nitrous oxide (see legend for fig. 2).

between the two treatments (table 2). In three animals, there was a change from lactate extraction to lactate production with the change in anesthetic treatment. In all three, the lactate production was observed during administration of nitrous oxide.

Nitrous oxide use did not affect systolic shortening in the non-ischemic circumflex region of the heart, but was associated with a 19% decrease in systolic shortening in the ischemic LAD region (table 3; fig. 2). Thus, the anesthetic including nitrous oxide worsened myocardial mechanical function in the ischemic region of the heart.

The results of regional myocardial blood flow measurements made with radioactive microspheres during imposition of the stenosis are presented in table 4. In the circumflex region, mean transmural blood flow values were higher during nitrous oxide administration, but the differences were not statistically significant. The inner:outer blood flow ratio (fig. 3) was close to 1.0 during both treatments, indicating normal transmural blood flow distribution and adequate myocardial perfusion. In the LAD region, distal to the stenosis, epicardial blood flow was 15% higher during treatment with nitrous oxide, while small changes in endocardial and transmural blood flow did not reach statistical significance. The inner:outer blood flow ratio was low during both treatments, indicating the presence of ischemia. However, the ratio was 50% lower during isoflurane 1.4% with nitrous oxide than with isoflurane 1.8%, indicating a further maldistribution of myocardial blood flow associated with this treatment.

Discussion

The present study compared the effect on ischemic myocardium of two equipotent anesthetics: 50% nitrogen in oxygen with 1.8% isoflurane and 50% nitrous oxide in oxygen with 1.4% isoflurane. The data indicate

<table>
<thead>
<tr>
<th>Table 1. Arterial Blood Gas and Hematocrit during Stenosis</th>
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<tbody>
<tr>
<td><strong>Nitrogen 50% with Isoflurane 1.8%</strong></td>
</tr>
<tr>
<td>pH</td>
</tr>
<tr>
<td>P&lt;sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; (mmHg)</td>
</tr>
<tr>
<td>P&lt;sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt; (mmHg)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
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</tbody>
</table>

In all tables, the values in the first two columns are the mean ± SD for 14 dogs, ignoring sequence (see Data Analysis). The mean difference ± SE was calculated by subtracting, for each animal, the value during isoflurane 1.8% in 50% N<sub>2</sub> from the value during isoflurane 1.4% in 50% N<sub>2</sub>O and using the average of the two values from each animal to keep n = 14. Percent change was calculated by dividing each difference by the initial value. None of the differences in this table were statistically significant by analysis of variance for a crossover design.
HR = heart rate; SBP = aortic systolic pressure; MAP = mean arterial pressure; MLAP = mean left atrial pressure; MCBP = mean diastolic left anterior descending coronary artery (LAD) pressure; MCBF = mean LAD blood flow; LAD lactate EX = LAD regional lactate extraction. Calculations described in table 1.

* P < .05, †P < .01 from analysis of variance for crossover design.

Table 2. Hemodynamics and Myocardial Lactate Extraction during Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Nitrogen 50% w/ Isoflurane 1.8%</th>
<th>Nitrous Oxide 50% w/ Isoflurane 1.4%</th>
<th>Mean Difference</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>117 ± 11</td>
<td>123 ± 9</td>
<td>+5.7 ± 1.2†</td>
<td>5</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>102 ± 13</td>
<td>110 ± 14</td>
<td>+8.4 ± 1.6*</td>
<td>8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88 ± 13</td>
<td>94 ± 14</td>
<td>+6.7 ± 1.5</td>
<td>7</td>
</tr>
<tr>
<td>MLAP (mmHg)</td>
<td>8 ± 2</td>
<td>9 ± 3</td>
<td>+0.6 ± 0.3</td>
<td>4</td>
</tr>
<tr>
<td>MCBP (mmHg)</td>
<td>49 ± 8</td>
<td>50 ± 7</td>
<td>+1.0 ± 0.8</td>
<td>2</td>
</tr>
<tr>
<td>MCBF (ml·min⁻¹·g⁻¹)</td>
<td>0.87 ± 0.45</td>
<td>0.93 ± 0.55</td>
<td>+0.07 ± 0.04</td>
<td>6</td>
</tr>
<tr>
<td>LAD Lact Ex (%)</td>
<td>-4 ± 52</td>
<td>-13 ± 56</td>
<td>-9.2 ± 6.2</td>
<td>214</td>
</tr>
</tbody>
</table>

Table 3. Systolic Segment Shortening during Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Nitrogen 50% w/ Isoflurane 1.8%</th>
<th>Nitrous Oxide 50% w/ Isoflurane 1.4%</th>
<th>Mean Difference</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumflex (%)</td>
<td>14.6 ± 4.4</td>
<td>15.0 ± 3.5</td>
<td>+0.4 ± 0.5</td>
<td>3</td>
</tr>
<tr>
<td>LAD (%)</td>
<td>14.2 ± 4.0</td>
<td>12.6 ± 4.3</td>
<td>-2.3 ± 0.6*</td>
<td>-19</td>
</tr>
</tbody>
</table>

Circumflex = shortening in normally perfused region of myocardium served by left circumflex coronary artery; LAD = shortening in ischemic region perfused by left anterior descending artery. (See legend ends of tables 1 and 2).

* P < .05 from analysis of variance for crossover design.

that the substitution of 50% nitrous oxide for 0.4% isoflurane resulted in a reduction of systolic shortening and redistribution of myocardial blood flow.

The two anesthetic treatments were compared within each animal under carefully matched experimental conditions (pH, PaO₂, heparinization, etc.), so that the differences found could be ascribed to the change of anesthetic. However, it is possible that the results may have been affected by the use of an open-chest, heparinized preparation. The cannulation of the left anterior descending coronary artery may have disturbed the autonomic innervation of this vessel.

All data presented were collected during imposition of the stenosis, while a region of myocardium served by the left anterior descending coronary artery was ischemic. No comparison has been made with measurements made prior to imposition of the stenosis. Simultaneous measurement of myocardial blood flow and systolic shortening in the non-ischemic circumflex region provides the data necessary to distinguish the effects of the anesthetic on normally perfused myocardium from effects manifest only during ischemia.

Systolic segment shortening is a measure of systolic myocardial mechanical function. It is correlated with

Table 4. Regional Myocardial Blood Flow during Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Nitrogen 50% w/ Isoflurane 1.8%</th>
<th>Nitrous Oxide 50% w/ Isoflurane 1.4%</th>
<th>Mean Difference</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumflex</td>
<td>1.39 ± 0.52</td>
<td>1.83 ± 0.85</td>
<td>+.44 ± .19</td>
<td>23</td>
</tr>
<tr>
<td>Epi (ml·min⁻¹·g⁻¹)</td>
<td>1.39 ± 0.52</td>
<td>1.84 ± 0.97</td>
<td>+.45 ± .23</td>
<td>22</td>
</tr>
<tr>
<td>Trans (ml·min⁻¹·g⁻¹)</td>
<td>1.37 ± 0.52</td>
<td>1.83 ± 0.92</td>
<td>+.46 ± .21</td>
<td>24</td>
</tr>
<tr>
<td>Endo/Epi</td>
<td>1.03 ± 0.20</td>
<td>1.04 ± 0.21</td>
<td>+.01 ± .02</td>
<td>1</td>
</tr>
<tr>
<td>LAD</td>
<td>.49 ± 0.16</td>
<td>.45 ± 0.13</td>
<td>-.04 ± .02</td>
<td>-8</td>
</tr>
<tr>
<td>Epi (ml·min⁻¹·g⁻¹)</td>
<td>.92 ± 0.27</td>
<td>1.09 ± 0.33</td>
<td>+.17 ± .06*</td>
<td>15</td>
</tr>
<tr>
<td>Trans (ml·min⁻¹·g⁻¹)</td>
<td>.59 ± 0.20</td>
<td>.73 ± 0.21</td>
<td>+.05 ± .03</td>
<td>6</td>
</tr>
<tr>
<td>Endo/Epi</td>
<td>.58 ± 0.17</td>
<td>.43 ± 0.11</td>
<td>-.15 ± .09†</td>
<td>-50</td>
</tr>
</tbody>
</table>

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 of Endo, Epi, and Trans are based on 13 experiments (technical difficulty in one). Endo/Epi ratio from all 14 experiments. (See legend for table 1).

* P < .05, †P < .01 from analysis of variance for crossover design.
myocardial blood flow and is a sensitive index of myocardial ischemia. In the present experiment, two regions of the heart were simultaneously compared: the use of nitrous oxide was associated with a 19% reduction in systolic shortening in the ischemic LAD region, and no change in the normally perfused circumflex region. This lack of effect on normal myocardium suggests that the mechanism whereby the anesthetic including nitrous oxide worsened systolic function was not global myocardial depression. Both Philbin and Ramsay, in similar preparations, noted decreased systolic shortening with nitrous oxide in the LAD region, both before and during application of a critical stenosis. Those investigators, however, added 66% nitrous to a constant level of narcotic or halothane, thereby increasing anesthetic depth and making comparison with the present results difficult.

The ratio of subendocardial to subepicardial blood flow reflects the adequacy of myocardial perfusion. When blood flow distal to a coronary stenosis is inadequate, autoregulation is first lost in the inner layers of the heart because the force of myocardial compression inhibits systolic subendocardial blood flow. Dilation of subepicardial vessels will then cause a redistribution of blood flow from the subendocardium (where flow is pressure dependent) to the subepicardium. This subepicardial vasodilation may be caused by drugs that dilate coronary arterioles (pharmacologic steal) or by increased myocardial energy demand (metabolic regulation). The increase in subepicardial blood flow and decrease in I/O ratio observed with the use of nitrous oxide in the present experiment could be explained by three possible mechanisms: an increase in myocardial oxygen demand, constriction of epicardial conductance vessels, or direct nitrous oxide-induced dilation of subepicardial arterioles. In the present experiment, heart rate and systolic blood pressure were slightly, but significantly, higher during nitrous oxide administration; contractility was not estimated. The resulting increased oxygen demand may have caused subepicardial arteriolar dilatation by metabolic regulation. Measurement of coronary blood flow in dogs has not produced evidence of direct coronary vasodilation or vasoconstriction due to nitrous oxide. Using quantitative angiography to measure large epicardial coronary artery diameter in pentobarbital-anesthetized dogs, Wilkowski et al., however, have collected data suggesting that nitrous oxide causes large coronary vessel constriction. There was no change in the relationship between myocardial oxygen consumption and coronary blood flow, implying that, in the face of proximal vessel constriction, coronary arteriolar dilatation decreased total coronary resistance sufficiently to maintain flow. The results of the present experiment are consistent with this mechanism; constriction of the LAD artery beyond the cannulation site would induce compensatory dilatation of the arteriolar bed. Dilation of the subepicardial arterioles would result in a redistribution of blood flow from the subendocardium, where flow is pressure dependant to the subepicardium. This would occur with no change in the LAD pressure measured at the cannula tip. In a study of ten patients with ischemic heart disease, Reiz found that, when 70% nitrous oxide was added to 1% isoflurane, coronary sinus blood flow remained constant, despite a fall in myocardial oxygen consumption, suggesting that nitrous oxide may have caused coronary arteriolar vasodilation. Although there was little change in flow or pressure distal to the coronary stenosis when 50% nitrous oxide was substituted for 4% isoflurane, the present data are insufficient to distinguish between the three possible mechanisms. Nevertheless, the significant increases in heart rate and systolic blood pressure during administration of nitrous oxide make it very likely that the increased ischemia was mediated, at least in part, by an increase in myocardial oxygen demand.

Mean lactate extraction was negative during both anesthetic treatments, but it was not possible to show a significant difference between treatments. This may have been due to difficulties in collecting venous effluent representative of a small region of the heart, and due to the lack of a consistent relationship between the degree of ischemia and the lactate concentration of the venous effluent.

Diminished systolic shortening alone is not conclusive evidence of increased ischemia; however, the concurrent demonstration of a 15% decrease in systolic shortening with a 30% decrease in endo/epi ratio in hypoperfused myocardium argues strongly that a greater degree of ischemia was present during treatment with nitrous oxide. It seems reasonable to conclude that a further imbalance in the myocardial energy supply/demand ratio led to a deterioration in mechanical function.

This study was designed to compare two alternative anesthetic treatments that could be chosen for patients with ischemic heart disease. In the dog, MAC for nitrous oxide has been determined to be approximately 190%17 and MAC isoflurane 1.4%. To ensure that the animals were well anesthetized, 1.3 MAC was maintained either with isoflurane 1.8% in 50% nitrogen or isoflurane 1.4% in 50% nitrous oxide. An inspired oxygen concentration of 50% was chosen to minimize

† Eger EI: MAC. Isoflurane. Edited by Eger EI, Madison, Anaquest, 1985, p 11
changes in oxygen saturation through the course of the experiments.

Had nitrous oxide been added to a constant concentration of isoflurane, it would have been difficult to separate the effect of increasing anesthetic depth from specific actions of nitrous oxide. If isoflurane causes a dose-related transmural coronary steal, then decreasing the concentration of isoflurane by substituting nitrous oxide should increase the endo/epi ratio. The fall in endo/epi ratio observed in the present experiment would then be an underestimate of the adverse effect of using nitrous oxide during ischemia.

Isoflurane was chosen as the background agent because it has quickly become a popular drug for fragile patients, despite its potential for causing coronary steal. It is unclear if the present results can be extrapolated to the use of nitrous oxide with other agents. Only after the mechanism of the deleterious effect of nitrous oxide on ischemic myocardium described in the present experiment is discovered will it be possible to determine whether each combination of agents must be studied separately.

The effect of adding nitrous oxide to constant concentrations of halothane, enflurane, and isoflurane has been studied in patients with coronary disease. The results of these studies are similar, and demonstrate myocardial depression and, in some patients, evidence of worsened myocardial supply/demand ratio. Whether the mechanism is increased anesthetic depth, or direct effects of nitrous oxide on the cardiovascular system or coronary circulation is unclear. Two recent experiments examining the effect of adding nitrous oxide to narcotic anesthesia in patients with coronary disease failed to detect new wall motion abnormalities by transesophageal echocardiography. A factor in human coronary disease not addressed by the present preparation is the amplification of the increase in coronary resistance that occurs with vasoconstriction at the site of an eccentric stenosis.

The importance of the findings of the present study depend on mechanism. If the effects were due to increased demand because of increased heart rate and blood pressure or contractility, then control of these variables with anesthetic or cardiovascular drugs may allow use of nitrous oxide without adverse effect. If the mechanism involves direct coronary vasomotion, it may be more difficult to safely administer this anesthetic gas. Studies to determine mechanism are underway.

In conclusion, in a comparison of two equipotent anesthetics, the substitution of 50% nitrous oxide for 4% isoflurane caused a reduction in myocardial mechanical function and a further maldistribution of myocardial blood flow in an ischemic region of the heart. The mechanism of this deleterious effect must be discovered in order to determine if it is safe to use nitrous oxide with isoflurane to anesthetize patients with ischemic heart disease.

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