Nitrous Oxide Constricts Epicardial Coronary Arteries Without Effect on Coronary Arterioles

Deborah Ann W. Wilkowski, M.D.,* J. Christopher Sill, M.B.B.S.,† William Bonta, B.S.,‡ Robert Owen, B.S.,‡ Alfred A. Bove, M.D., Ph.D.§

The authors sought to determine the effects of nitrous oxide on both epicardial coronary artery dimensions and intramyocardial coronary arteriolar tone. Nine dogs were anesthetized with fentanyl-pentobarbital-oxygen. High resolution angiograms of the left coronary system were obtained, and cross-sectional areas of the proximal, mid, and distal left anterior descending and proximal circumflex coronary arteries were quantitated using a computerized analysis system. Measurements were made at three coronary perfusion pressures before nitrous oxide administration, and then repeated following the addition of both 30% and 60% nitrous oxide. At the same time, coronary arteriolar tone was assessed by measuring coronary blood flow using 125I-Xenon washout. Sixty percent nitrous oxide was accompanied by constriction of the epicardial coronary arteries. Thirty percent nitrous oxide had a less marked effect. At 70 mmHg coronary perfusion pressure, following 60% nitrous oxide, mid left anterior descending cross-sectional area decreased from 4.6 ± 0.3 mm² (mean ± SD) to 3.5 ± 0.3 mm². At 90 mmHg, area decreased from 4.57 ± 0.3 mm² to 3.69 ± 0.4 mm², and, at 110 mmHg, from 4.7 ± 0.4 mm² to 3.9 ± 0.4 mm² (P < 0.01). Nitrous oxide had no effect on the relationship between coronary blood flow and myocardial oxygen consumption, indicating an absence of effect on coronary arteriolar tone. It is concluded that intramyocardial coronary arteriolar and epicardial coronary arteries are dissimilar in their response to nitrous oxide. In the intact, anesthetized, normal dog, nitrous oxide does not affect coronary arteriolar tone. Sixty percent nitrous oxide produces constriction of epicardial coronary arterioles. (Key words: Anesthetics: gases; nitrous oxide. Arteries: coronary. Heart: blood flow.)

Nitrous oxide was introduced into clinical practice about 120 yr ago. Since then, it has been given to more patients than any other inhaled anesthetic. Its actions on the heart and peripheral circulation have been extensively investigated, and are well understood.1-4 Although its effects on coronary arteriolar tone and myocardial blood flow are well understood,5-7 little is known concerning the effect of nitrous oxide on proximal coronary arteries. The purpose of this investigation was to determine the effects of nitrous oxide on the coronary vasculature, especially upon the proximal coronary vessels, using intact normal dogs.

When assessing the effects of drugs on coronary vessels, it is important to distinguish between epicardial coronary arteries and intramyocardial coronary arterioles.8 They not only differ in structure and function, but they may also respond differently to the same vasoactive stimulus.9-11 Epicardial coronary arteries are conduit vessels that lie on the surface of the heart and conduct blood from the aorta to the intramyocardial network of coronary arterioles. They normally contribute little to either the regulation of coronary blood flow or to the total vascular resistance of the heart.8 Coronary arterioles are small vessels that ramify throughout the myocardium. They deliver blood to the heart tissue and, by constricting and dilating, regulate coronary blood flow and its distribution.12 Both types of vessels contain abundant smooth muscle in their walls. In dogs and humans, both types of vessels are capable of considerable physiologic and drug-induced changes in dimensions. Epicardial coronary artery vasomotion has recently been recognized as important in humans with coronary artery disease.8,13 Dilatation of these vessels may improve blood flow across stenoses, while constriction may increase the degree of stenosis resistance.8,18 Paradoxically, coronary arteriolar dilatation is thought to induce myocardial ischemia in susceptible patients by a steal mechanism.8,15

In humans8-4 and dogs,5 nitrous oxide increases both systemic and pulmonary vascular resistance. The mechanism of this effect is not known, but nitrous oxide has been shown to increase norepinephrine release from dog pulmonary artery segments,14 perhaps suggesting that vasoconstriction is mediated via the adrenergic system. Nitrous oxide has been shown to have no effect on coronary arterioles,8-7 however, its effects on epicardial coronary arteries are unknown.

Methods

Nine dogs were anesthetized with fentanyl 1 mg/kg and pentobarbital 10 mg/kg administered intravenously. Anesthesia was maintained with an intravenous infusion of fentanyl 0.5 mg/kg at approximately 0.1 mg·kg⁻¹·hr⁻¹, and pentobarbital 15 mg/kg at approximately 3 mg·kg⁻¹·hr⁻¹. Following endotracheal intubation, the dogs were mechanically ventilated with an oxygen-air mixture, FiO₂, 0.5. The left carotid artery, left and right femoral arteries, right external jugular vein, and left femoral vein were dissected. Using fluoroscopy,
a No. 6F Lehman catheter was introduced via the right external jugular vein into the coronary sinus for pressure monitoring and blood sampling. A No. 6F bipolar pacing catheter was also placed into the coronary sinus and was connected to a pulse generator set at approximately 80 beats/min. A catheter was placed in the left ventricle by passing it from the right external jugular vein via the atrial septum into the left ventricle. A coronary guide catheter was advanced under fluoroscopy retrograde through the left carotid artery into the ascending aorta. The left coronary ostium was identified by injections of radiopaque contrast medium, and a 1 mm balloon dilatation catheter (USCI) was advanced through the coronary guide catheter and positioned in the proximal left anterior descending coronary artery (LAD) just proximal to the first large branch. 133 Xenon was injected through this intracoronary catheter to measure blood flow in the left anterior descending artery. The guide catheter was used for measuring proximal coronary artery pressure and for the injection of radio-opaque contrast medium. A 10F Fogarty balloon catheter was placed in the descending thoracic aorta. Inflation of the balloon permitted the arterial pressure to be increased as needed.

Statham P23DG pressure transducers were balanced and calibrated with a fluid-filled manometer system at the beginning and during each experiment. Proximal coronary artery, coronary sinus, left ventricular, and femoral artery pressures were transmitted, along with the electrocardiogram (lead II) to a digital computer (PDP 11/34, Digital Equipment Corporation). Data was displayed in real time. Graphic records were obtained as needed.

LAD and circumflex coronary artery dimensions were obtained in nine dogs. The dimensions were quantitated using computerized analysis of high resolution angiograms. Angiography was performed using 5–7 ml of meglumine diatrizoate (Renografin 76) injected via the guide catheter in the left main coronary artery. Exposures were made in mid-diastole using an R-wave triggering x-ray switch set to trigger midway in the T-P segment of the electrocardiogram. Images were recorded on x-ray film using a cassette-type film holder. The angiograms were obtained in a right anterior oblique projection. Dimensions of the epicardial coronary arteries were obtained by placing the angiogram on a digitizing board connected to the PDP 11/34 computer. The outlines of three segments of the LAD and one segment of the circumflex artery were manually traced using an electronic cursor also connected to the computer. The computer then calculated luminal diameter and cross-sectional area at 1-mm intervals along the vessel segments. Several scans of each segment were performed and the results averaged. This method of quantitative angiography has been described in detail elsewhere,\textsuperscript{10,15} and is used by a number of laboratories.\textsuperscript{13}

Coronary blood flow was determined by selective injection of 0.2 ml of 133Xe (0.25 mCi, Xeneisol; Mallinkrodt) into the LAD.\textsuperscript{16} A single crystal detector was positioned using fluoroscopy over the left ventricle and used to detect the isotope washout. Data were processed by the PDP 34/11 computer. Myocardial blood flow was calculated using the first 60 s of the washout curve and monoexponential log-linear least squares calculation for the slope (K). Flow (ml·min⁻¹·g⁻¹) was calculated as 0.72 k/1.05, where 0.72 is the myocardium-blood partition coefficient for xenon and 1.05 is the density of myocardium.\textsuperscript{17}

Hemoglobin oxygen saturation was measured using a Co-oximeter (Instrument Laboratory Model 122). The oxygen content of arterial and coronary sinus blood was used to calculate arteriovenous oxygen difference. Myocardial oxygen consumption (MVO₂) was calculated by multiplying the AV O₂ difference by the coronary blood flow.

**Experimental Procedure**

The animals were anesthetized, the catheters placed, and then hemodynamic, oxygen saturation, and coronary blood flow measurements made and an angiogram performed. Control measurements were made during ventilation with oxygen-air (FI O₂ 0.5). Arterial pressure was next increased by inflating the balloon of the Fogarty catheter in the descending aorta. Measurements and angiogram were repeated. Arterial pressure was then lowered by deflating the balloon and then adding 10–20 cm H₂O PEEP to the breathing circuit. Measurements and angiogram were repeated. Thirty percent nitrous oxide in oxygen (FI O₂ 0.7) was then administered for 20 min, and the sequence of measurements was repeated. Sixty percent nitrous oxide in oxygen (FI O₂ 0.4) was then introduced for 20 min, and again the measurement protocol was repeated. A calibrated oxygen analyzer (Instrumentation Laboratories) in the inspiratory limb of the breathing circuit was used to measure oxygen concentration. At the end of the experiment, the dogs were killed with intravenous potassium chloride while still anesthetized.

**Statistical Analysis**

Cross-sectional dimensions of coronary arteries are dependent, to some degree, upon perfusion pressure. In order to analyze nitrous oxide effects on dimensions at constant perfusion pressure, vessel areas were first normalized to three standard coronary perfusion pressures: 70 mmHg, 90 mmHg, and 110 mmHg (coronary perfusion pressure = diastolic arterial pressure minus mean coronary sinus pressure). Regression lines of vessel area versus perfusion pressure were drawn for each individual dog, and vessel areas at the three standard perfusion pres-
NITROUS OXIDE AND CANINE CORONARY VASOMOTION

Table 1. Hemodynamics and Myocardial Oxygenation During Control State and Following Nitrous Oxide Administration

<table>
<thead>
<tr>
<th>Nitrous Oxide Concentration</th>
<th>Intervention</th>
<th>Proximal Coronary Artery Pressure (mmHg)</th>
<th>CSP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>HR Beats/Min</th>
<th>A-V O₂, ml O₂</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>PEEP</td>
<td>88 ± 10</td>
<td>16 ± 6</td>
<td>14 ± 5</td>
<td>101 ± 91</td>
<td>7.4 ± 1.3</td>
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<tr>
<td></td>
<td>None</td>
<td>102 ± 11</td>
<td>2 ± 3</td>
<td>6 ± 4</td>
<td>80 ± 9</td>
<td>6.2 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>Balloon</td>
<td>142 ± 12</td>
<td>5 ± 4</td>
<td>8 ± 4</td>
<td>79 ± 10</td>
<td>5.3 ± 1.3</td>
</tr>
<tr>
<td>30%</td>
<td>PEEP</td>
<td>95 ± 11</td>
<td>14 ± 5</td>
<td>15 ± 7</td>
<td>89 ± 24</td>
<td>7.3 ± 1.4</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>101 ± 7</td>
<td>4 ± 3</td>
<td>10 ± 11</td>
<td>81 ± 9</td>
<td>5.8 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>Balloon</td>
<td>139 ± 9</td>
<td>6 ± 4</td>
<td>8 ± 4</td>
<td>82 ± 8</td>
<td>6.4 ± 0.8</td>
</tr>
<tr>
<td>60%</td>
<td>PEEP</td>
<td>95 ± 10</td>
<td>17 ± 4</td>
<td>13 ± 4</td>
<td>102 ± 28</td>
<td>7.0 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>102 ± 6</td>
<td>6 ± 4</td>
<td>7 ± 8</td>
<td>81 ± 11</td>
<td>6.4 ± 1.2</td>
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<tr>
<td></td>
<td>Balloon</td>
<td>138 ± 12</td>
<td>6 ± 3</td>
<td>9 ± 3</td>
<td>82 ± 9</td>
<td>6.1 ± 1.8</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. CSP = coronary sinus pressure; LVEDP = left ventricular end diastolic pressure; S = saturation; PEEP = positive end expiratory pressure; Balloon = inflation of Fogerty catheter balloon in the descending aorta.

Pressures were then calculated. Mean values were obtained. Statistical analysis of nitrous oxide effects was performed by repeated measures analysis of variance. For additional testing of nitrous oxide effect, the Kruskal-Wallis non-parametric rank sum analysis was used. Control vessel cross-sectional areas were compared to areas measured following administration of both concentrations of nitrous oxide. A P value < 0.05 was considered statistically significant. Myocardial blood flow is regulated by myocardial oxygen consumption. In order to analyze nitrous oxide effects on coronary blood flow at constant MVO₂, statistical analysis was performed by first normalizing values for myocardial blood flow to three standard values of MVO₂. Values used were 7, 11, and 15 ml O₂·100 gm⁻¹·min⁻¹. Regression lines of coronary blood flow versus MVO₂ were drawn for each individual dog, and coronary flow at the three standard values of MVO₂ was then calculated. Mean values were obtained. Statistical analysis of nitrous oxide effects was performed by repeated measures analysis of variance. A P value < 0.05 was considered statistically significant.

Results

Hemodynamic Parameters

Table 1 displays mean values of mean coronary artery pressure, coronary sinus pressure, left ventricular end diastolic pressure, heart rate, and arterio-venous oxygen content difference. Inspired nitrous oxide concentration is indicated as are manipulations of the arterial pressure.

Large Coronary Dimensions

Sixty percent nitrous oxide constricted both the LAD and circumflex epicardial coronary arteries. This effect is illustrated in figure 1, where the mid segment of the LAD is shown prior to nitrous oxide administration and then following ventilation with 60% nitrous oxide (coronary perfusion pressure was unchanged). A decrease in diameter is apparent. Actual cross-sectional area (mean ± SE) of the three segments of LAD and the proximal segment of circumflex coronary arteries are shown in figure 2. Vessel area has been plotted against coronary perfusion pressure. Following 60% nitrous oxide, a downward displacement of the lines can be seen. At any given perfusion pressure, vessel area is smaller following 60% nitrous oxide. Cross-sectional vessel areas were calculated at standard perfusion pressures and are plotted in figure 3. Again, a downward displacement of the points following 60% nitrous oxide is apparent. In both figure 2 and figure

FIG. 1. Coronary angiograms of the mid left anterior descending coronary artery. The x-ray on the left was obtained under control conditions. The x-ray on the right was obtained following 60% nitrous oxide. Coronary perfusion pressure was unchanged. The vessel cross-sectional area is decreased on the right, demonstrating constriction.
Fig. 2. Mean values of vessel area plotted against coronary perfusion pressure; proximal, mid, and distal left anterior descending and proximal circumflex are shown. Lines represent vessel areas throughout a range of perfusion pressures. Three lines are shown on each graph, one indicating control data, and two lines representing data following 30% nitrous oxide and 60% nitrous oxide. The 60% nitrous oxide line falls below the control line demonstrating constriction of the coronary artery. Values are mean ± SE (n = 9).

Fig. 3. Cross-sectional area of coronary artery versus coronary perfusion pressure. Proximal, mid, and distal left anterior descending, and proximal circumflexes are shown. Lines represent vessel areas calculated at three standard perfusion pressures; 70 mmHg, 90 mmHg, and 110 mmHg. Three lines are shown on each graph, one representing control data, and two representing data following 30% nitrous oxide and 60% nitrous oxide. The nitrous oxide lines fall below the control lines, demonstrating constriction of the coronary artery. P values are indicated. Values are mean ± SE (n = 9).

3, the effects of 30% nitrous oxide are also shown. Consistent epicardial coronary constriction was not observed at this concentration. Significant vasoconstriction was also demonstrated using Kruskal-Wallis analysis. At 70 mmHg, the statistical significance of the 60% nitrous oxide effect was: proximal LAD, P < 0.02; mid LAD, P < 0.01; distal LAD, P < 0.02; and proximal circumflex, P < 0.02. At 90 mmHg, the significance of nitrous oxide effect was, respectively, P < 0.05, <0.05, <0.02, and <0.02. At 110 mmHg, the significance was P < 0.05, <0.05, <0.02, and <0.05.

Coronary Arteriolar Tone

Nitrous oxide had no effect on coronary arteriolar tone throughout the range of values of myocardial oxygen consumption and nitrous oxide concentrations investigated. Absence of effect can be appreciated from figure 4, where coronary blood flow has been plotted against myocardial oxygen consumption. The control and nitrous oxide plots not only run close together, but are, at times, superimposed. If nitrous oxide had been a coronary arteriolar constrictor, then, at any given value for MVO₂,
coronary blood flow would have been reduced following nitrous oxide. The plot would have been displaced downwards from control. No such displacement occurred. In figure 5, values for coronary blood flow have been calculated at standardized values of MVO₂. Coronary blood flow versus MVO₂ has been plotted. There was no significant difference between control blood flow and blood flow following nitrous oxide administration.

**Discussion**

Nitrous oxide had distinctly different effects on the two components of the coronary arterial system. Proximal epicardial coronary arteries were constricted by nitrous oxide. No effect was observed on the distal resistance arteries.

Epicardial coronary arteries are normally maintained in a relaxed state by an interplay of numerous vasoconstrictor and vasodilator influences. Although the autonomic nervous system undoubtedly has a role in regulating epicardial coronary tone,21,22 other systems also participate in determining vessel diameter. Serotonergic and neuropeptidergic nerves are present in the walls of coronary arteries.23 In experimental studies, serotonin produces marked reduction in coronary cross-sectional area,10 while neuropeptides may provide vasodilatory tone.23 Prostaglandins may also participate in vasomotion regulation.24

The mechanism whereby nitrous oxide induces vasoconstriction is not known. A number of endogenous vasactive substances, such as norepinephrine,9 the eicosanoid-thromboxane A₂,25 the amines-serotonin10 and histamine,11 and the peptides-angiotensin,26 vasopressin, and neuropeptide Y27 have been shown to be vasoconstrictors. Whether or not nitrous oxide augments their activity is unknown. Nitrous oxide has been shown to increase norepinephrine release from isolated pulmonary artery strips;14 however, whether or not a similar effect occurs in coronary arteries has not been determined. Even if coronary artery catecholamine turnover were altered by nitrous oxide, such an effect would not necessarily be responsible for vasoconstriction as norepinephrine and alpha agonists are only modest constrictors of normal coronary arteries.10,28

Nitrous oxide may augment endogenous constrictor activity or, alternatively, may inhibit endogenous vasodilator tone. Prostaglandins,24 neuropeptides,25 and substances released from the vascular endothelium29 may modulate dilatation. Nitrous oxide may inhibit activity of such substances. Little is known concerning regulation of epicardial coronary artery vasodilatation, and even less concerning nitrous oxide’s mechanism of action; therefore, this suggestion is entirely speculation.

The relationship between myocardial oxygen consumption and coronary blood flow remained unchanged following nitrous oxide administration, indicating that nitrous oxide had no effect on intramyocardial arteriolar tone. Our results are in keeping with those of previous investigations, where an absence of nitrous oxide effect on coronary blood flow has also been demonstrated.5-7 Regulation of coronary arteriolar tone is probably determined by locally produced metabolic products and by adenosine release.12,30 These substances have ready access to the arterioles, as the arterioles are completely surrounded by myocardium. Normally, coronary blood flow

![Coronary blood flow vs. myocardial oxygen consumption](image-url)

**Fig. 4.** Effects of nitrous oxide on coronary blood flow. Lines represent coronary blood flow versus myocardial oxygen consumption. 3 lines are shown, one indicating control data, the other two representing data obtained following 30% nitrous oxide and 60% nitrous oxide. All three lines are nearly superimposed, demonstrating that nitrous oxide has no effect on coronary arteriolar tone. Values are mean ± SE.

![Coronary blood flow vs. myocardial oxygen consumption](image-url)

**Fig. 5.** Effects of nitrous oxide on coronary blood flow. Lines represent calculated coronary blood flow at three standard values for myocardial oxygen consumption: 7, 11, and 15 ml O₂·100 gm⁻¹·min⁻¹. Three lines are shown, one representing control data, the other two representing data following 30% nitrous oxide and 60% nitrous oxide. Values are mean ± SE.
matches the metabolic needs of the heart. We have shown this close coupling to remain intact following nitrous oxide administration.

In this experiment, a closed-chest canine preparation was used, and epicardial coronary dimensions were determined using quantitative angiography. Absence of instrumentation via a thoracotomy minimized surgical stress on the animal. Quantitative coronary angiography was used, and is a versatile technique. It has proven accurate when assessed by measuring test objects of known dimensions inserted into intact anesthetized dogs' coronary arteries. A similar technique has also been shown to be accurate when used in humans. Angiography permits visualization of the whole of the left coronary tree, and multiple cross-sectional measurements are possible. In this experiment, 20 measurements were made from each angiogram. One hundred and eighty measurements were made in each dog. Contrast medium used to visualize the epicardial vessels is known to transiently dilate intramyocardial coronary arterial segments. However, dilatation lasts only 4–6 min, and, by 10 min, no effect can be demonstrated. This experiment was carefully designed to ensure that blood flow measurements always preceded the angiogram, and, in this way, vasodepressor effects of contrast were minimized. Both coronary blood flow and epicardial coronary artery dimensions have previously been shown to remain stable, despite repeated angiograms.

It was necessary to provide background anesthesia for the dogs during this experiment. Pentobarbital and fentanyl were used. It is possible that these anesthetics altered vascular responsiveness to nitrous oxide. However, fentanyl does not alter isolated epicardial coronary artery rings' contractile response to vasoconstrictors. The effects of pentobarbital on coronary artery tone are unknown. In addition, the coronary vasculature does remain sensitive to both constrictors and dilators when this background anesthetic is used.

Although we have shown nitrous oxide to constrict epicardial coronary arteries in normal dogs, its effects in humans are, for the moment, speculative. Normal coronary arteries in both humans and animals possess considerable reserve capacity, and their constriction would have little impact on blood flow to the heart. However, in the presence of atherosclerotic stenoses, this reserve is lost. In this situation, epicardial coronary artery vasoconstrictors would be disadvantageous, as many atherosclerotic stenoses are capable of constriction. The majority of stenoses contain an arc of relatively normal wall that is free of atheroma. Even small degrees of circumferential shortening of smooth muscle in this arc will dramatically decrease lumen size and increase resistance to blood flow. If nitrous oxide constricts epicardial coronary arteries in patients as well as dogs, then dynamic narrowing superimposed upon atherosclerotic narrowing may unfavorably effect the blood supply to the heart.

References

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