

Effects of Isoflurane on Coronary Arteries and Coronary Arterioles in the Intact Dog

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To determine the site of isoflurane-associated coronary vasodilatation, the authors measured epicardial coronary artery diameter and examined the effects of isoflurane on coronary arteriolar tone. Angiograms of the left coronary system were obtained in seven fentanyl-pentobarbital anesthetized dogs and quantitated with a computerized analysis system. Cross-sectional areas of the proximal, mid, and distal left anterior descending and proximal circumflex coronary arteries were obtained at three arterial pressures, and then the measurement repeated following administration of 0.75%, 1.5%, and 2.25% end-tidal isoflurane. At the same time coronary blood flow was measured using a ^{133}Xe washout technique. Isoflurane was found to have no effect on epicardial coronary artery dimensions. No dilatation was observed throughout the range of isoflurane concentrations and coronary perfusion pressures investigated. However, despite the absence of epicardial coronary effects, coronary arterioles were dilated by both 1.5% and 2.25% isoflurane. Coronary blood flow corresponding to a myocardial oxygen consumption of 7.5 ml oxygen $\cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ was calculated as $99 \pm 17 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ (mean \pm SD) during control conditions, and it increased to $150 \pm 26 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ at 1.5% isoflurane ($P < .004$) and to $197 \pm 35 \text{ ml} \cdot 100 \text{ gm}^{-1} \cdot \text{min}^{-1}$ at 2.25% isoflurane ($P < .001$). Although higher concentrations of isoflurane dilated intramyocardial arterioles, isoflurane had no effect on epicardial coronary arteries. (Key words: Anesthetics: volatile; isoflurane. Arteries: coronary. Heart: blood flow.)

THERE ARE TWO MAJOR TYPES of coronary artery—the large proximal coronary arteries that lie predominantly on the surface of the heart and the small coronary arterioles that ramify throughout the cardiac muscle.¹ These two vessel types differ considerably in structure and function. The large coronary arteries are conductance vessels and offer little resistance to blood flow, while the arterioles impose a highly variable resistance and regulate distri-

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bution of blood flow within the myocardium.² The effects of isoflurane on coronary arterioles in man and animals is controversial, as both absence of vasodilating effects^{3,4} and arteriolar dilatation⁵⁻⁷ have been reported. The effects of isoflurane on coronary arteries are unknown.

The action of drugs on the coronary vasculature is important in coronary artery disease (CAD). CAD involves the coronary arteries^{8,9} and not the coronary arterioles. It has recently become apparent that atherosclerotic coronary stenoses behave in a dynamic fashion.^{1,10} The resistance they impose to coronary blood flow is not fixed, but depends upon underlying vascular smooth muscle tone.^{1,10} Nitroglycerin^{11,12} and, to a lesser degree, nitroprusside¹³ have been shown to dilate both normal and diseased segments of coronary arteries, and this dilatation is thought to be a major component of nitroglycerin's therapeutic effect.¹⁴ Isoflurane is a known potent peripheral vasodilator.^{15,16} Whether or not it also dilates coronary arteries is unknown. Such an effect would be a definite attribute for isoflurane.

Although drugs that dilate coronary arteries are beneficial for patients with CAD, paradoxically, coronary arteriolar dilators may provoke angina.¹⁷ Regulation of coronary blood flow is performed by coronary arterioles.^{1,2} If the coronary arteriolar resistance bed is dilated, then intramyocardial distribution of coronary blood flow may be disturbed. Isoflurane has proven to be a safe anesthetic for patients with CAD¹⁸; however, there are disturbing reports that isoflurane is a coronary arteriolar dilator and may cause myocardial ischemia.^{19,20}

In this experiment, we examined the effects of isoflurane on both the large proximal coronary arteries and on the distal coronary arterioles. Proximal and distal vessels differ from one another in terms of structure, function, and regulation;¹ therefore, isoflurane might affect them differently. In addition, in clinical practice, vasodilatation of the two vessel types would have distinctly different consequences.¹⁷

Methods

Eight adult mongrel dogs were anesthetized with an intravenous bolus of fentanyl 1 mg/kg and pentobarbital 10 mg/kg, their tracheas were intubated, and they were mechanically ventilated with a volume ventilator supplying an oxygen air mixture, FiO_2 0.6. Anesthesia was then

maintained with intravenous fentanyl 0.5 mg/kg and pentobarbital 5 mg/kg, infused throughout the experiment. The left carotid artery, left and right femoral arteries, the right external jugular vein, and the left femoral vein were dissected. Under fluoroscopic monitoring, the coronary sinus was catheterized *via* a branch of the right external jugular vein with a No. 6F Lehman catheter for pressure monitoring and blood sampling. Through another external jugular branch vein, a No. 6F bipolar pacing catheter was also placed into the coronary sinus to produce atrial pacing, and was connected to a pulse generator set at approximately 80 beats/min. The left ventricle was catheterized, also from the right external jugular vein, by passing a catheter and dilator with needle into the left atrium *via* a transeptal approach and on into the left ventricle. After a single intravenous bolus of 2% lidocaine to suppress cardiac arrhythmias, a coronary guide catheter was advanced under fluoroscopy retrograde through the left carotid artery to the ascending aorta. The left coronary ostium was identified by injections of radio-opaque contrast medium, and a 1 mm balloon dilatation catheter (USCI) was advanced through the coronary guide catheter and positioned in the proximal portion of the left anterior descending coronary artery (LAD) just proximal to the first large diagonal branch. This intracoronary catheter was used for ^{133}Xe injection to measure blood flow in the LAD. The large 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 passed from the right femoral artery, and the balloon segment was placed in the descending thoracic aorta. This balloon was inflated at stages during the experiment in order to increase coronary perfusion pressure.

Statham P23DG pressure transducers were balanced and calibrated with a fluid-filled manometer system at the beginning of each experiment, and calibrations were checked periodically during the procedure. Pressures were monitored from the proximal coronary artery, the coronary sinus, the left ventricle, and the femoral artery, and were transmitted along with the electrocardiogram (lead II) directly into a digital computer (PDP 11/34, Digital Equipment Corporation), which displayed the data in real time and produced graphic records as needed. Pressures and electrocardiogram were monitored continuously and recorded during each stage of the experiment.

Dimensions of the left coronary system were obtained in seven dogs and were quantitated with a computerized angiographic analysis system.^{21,22} Angiographic examination was performed by injection of 5–7 ml meglumine diatrizoate (Renografin 76) through the guide catheter into the left main coronary artery. To ensure well-defined coronary images, exposures were made in mid-diastole with an R wave-triggering x-ray switch with the delay 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. Exposure was 85 kV, 75–100 mA for 35 msec. Angiograms were acquired in a constant right anterior oblique projection in each animal. The opacified edges of the coronary artery lumens were manually traced and digitized with a quantitative angiography program in a PDP 11/34 computer (Digital Equipment Corp). The program calculated luminal diameter and cross-sectional area at 1 mm intervals along the artery measured. Three segments of LAD and one segment of the circumflex artery were scanned. Several scans of each segment were performed, and the results were averaged.

This quantitative analytical method had been evaluated for accuracy by measuring dimensions from x-ray images of tubular models with known dimensions.^{21,22} These models included metal wire, contrast-filled polyethylene tubing, and accurately machined hollow plastic cylinders that were inserted into the LAD of intact, anesthetized dogs with a catheter guidewire technique. The regression of calculated *versus* actual dimensions gave a slope of .986, a correlation coefficient of .997, and a standard error of estimate of 0.062 mm. This small standard error of the estimate allows a high degree of accuracy. The method has also been validated in other laboratories.²³

Coronary blood flow was determined by injection of 0.2 ml of ^{133}Xe solution (0.25 mCi, Xenexol; Mallinckrodt) selectively into the LAD.²⁴ The isotope washout was detected with a single crystal detector placed over the left chest and positioned at midventricular level under fluoroscopic guidance. Data were transferred directly to a PDP 11/34 computer and processed to determine flow by means of the first 60 s of washout curve and monoexponential log-linear least squares calculation for the slope (k). Flow ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) was calculated as $0.72 k / 1.05$, where 0.72 is the myocardium-blood partition coefficient and 1.05 is the density of myocardium.²⁵

Arteriovenous oxygen differences (ml/dl) were calculated by taking the difference between arterial and coronary sinus blood oxygen content. Hemoglobin oxygen saturation was measured using a Co-oximeter (Instruments Laboratory Model 122). Oxygen content was calculated as hemoglobin (g/100 ml) \times 1.35 ml O_2 /g \times oxygen saturation. Myocardial oxygen consumption (MVO_2) was calculated by multiplying the A- VO_2 difference by the coronary blood flow.

EXPERIMENTAL PROCEDURE

After positioning the catheters, baseline hemodynamics, coronary flow, and coronary dimension measurements were made. Arterial pressure was increased by inflating the Fogarty catheter balloon and, after approximately 5 min, the measurements were repeated and then the bal-

TABLE 1. Hemodynamics and Myocardial Oxygenation During Control State and Following Isoflurane Administration

Isoflurane Concentration	Intervention	Proximal Coronary Artery Pressure (mmHg)	CSP (mmHg)	LVEDP (mmHg)	HR Beats/Min	SaO ₂ %	SvO ₂ %	A-VO ₂ ml O ₂
Control	PEEP	65 ± 13	15 ± 7	10 ± 3	105 ± 21	96 ± 2	31 ± 6	8.8 ± 1.0
	None	100 ± 9	5 ± 3	4 ± 2	86 ± 7		46 ± 10	6.7 ± 1.0
	Balloon	129 ± 16	7 ± 4	7 ± 5	86 ± 10		54 ± 10	6.2 ± 0.9
0.75%	PEEP	54 ± 11	11 ± 3	8 ± 3	89 ± 16	96 ± 1	44 ± 5	8.0 ± 1.2
	None	74 ± 10	5 ± 2	4 ± 3	88 ± 11		52 ± 3	6.3 ± 0.7
	Balloon	113 ± 11	7 ± 1	7 ± 4	86 ± 9		63 ± 5	5.4 ± 1.1
1.50%	PEEP	51 ± 12	12 ± 1	8 ± 4	93 ± 13	96 ± 1	52 ± 9	6.2 ± 1.5
	None	63 ± 5	4 ± 3	4 ± 4	87 ± 6		59 ± 5	4.8 ± 0.8
	Balloon	108 ± 19	7 ± 2	7 ± 4	85 ± 6		65 ± 8	4.5 ± 0.9
2.25%	PEEP	48 ± 8	11 ± 3	8 ± 4	86 ± 11	96 ± 1	53 ± 9	5.3 ± 1.3
	None	51 ± 8	5 ± 3	5 ± 4	90 ± 13		62 ± 5	4.3 ± 0.8
	Balloon	87 ± 12	7 ± 3	8 ± 3	78 ± 5		69 ± 6	3.7 ± 0.8

Values are mean ± SD (pressure measurements n = 7, saturation and A-VO₂ values n = 8).

loon deflated. Arterial pressure was then decreased by adding approximately 10–20 cm H₂O PEEP to the breathing circuit and, after about 5 min, the measurements were repeated. In this way measurements were made at three different coronary perfusion pressures—normal pressure, induced hypertension, and induced hypotension. Isoflurane was then administered for 25–30 min and the inspired concentration adjusted to produce an end-tidal value of 0.75% measured by a Beckman LB-2 infrared analyzer (isoflurane MAC in the dog is 1.5%).²⁶ Hemodynamic and coronary measurements were now repeated, first at normal pressure and then during induced hypertension and induced hypotension. End-tidal isoflurane concentration was then increased to 1.5% and, after 25–30 min, the measurement was repeated, again at three coronary perfusion pressures. Finally, end-tidal isoflurane was increased to 2.25% and the protocol was repeated. Coronary blood flow measurements were always made before the angiogram so that the angiographic dye would not interfere with coronary arteriolar tone. At the end of the experiment, the dogs were killed with intravenous potassium chloride, administered while they were still anesthetized.

STATISTICAL ANALYSIS

Increasing pressure distends the epicardial coronary arteries and increases their cross-sectional area; therefore, in order to assess isoflurane's effects at constant pressure, statistical analysis was performed by first normalizing vessel areas to standard perfusion pressures. Regression lines of vessel area *versus* perfusion pressure were drawn for each individual dog, and vessel areas at three standard perfusion pressures were then calculated. Pressures of 40 mmHg, 70 mmHg, and 100 mmHg were used and mean vessel area was obtained at each standard pressure. Effects

of isoflurane were determined by comparing areas following isoflurane administration to control area using paired *t* testing. The effect of change in perfusion pressure on vessel cross-sectional area was considered significant if the regression slope was significantly greater than zero.

The rate of myocardial oxygen consumption has an effect on coronary blood flow independent of isoflurane. Therefore, in order to assess isoflurane's effects at constant MVO₂, statistical analysis was performed by first normalizing coronary flow rates to standard rates of MVO₂. Regression lines of coronary flow *versus* MVO₂ were drawn for each individual dog, and the flow at each standard MVO₂ was calculated. Rates of oxygen consumption of 5, 7.5, and 10 ml · 100 gm⁻¹ · min⁻¹ were chosen. Mean coronary flow was obtained at each standard oxygen consumption rate. Effects of isoflurane were determined by comparing flow following isoflurane to control flow using paired *t* testing. *P* < 0.05 was considered significant except when repeated comparisons were performed, at which time the Bonferroni correction was applied.

Results

HEMODYNAMIC PARAMETERS

Mean values of coronary artery pressure, coronary sinus pressure, left ventricular end diastolic pressure, and values for heart rate are shown in table 1. Mean values of arterial and coronary sinus oxygen saturation and the arteriovenous oxygen content differences are also given. Data (mean ± SD) are shown both in relation to end-tidal isoflurane concentration and to perfusion pressure intervention, *i.e.*, normal blood pressure, induced hypertension, and induced hypotension.

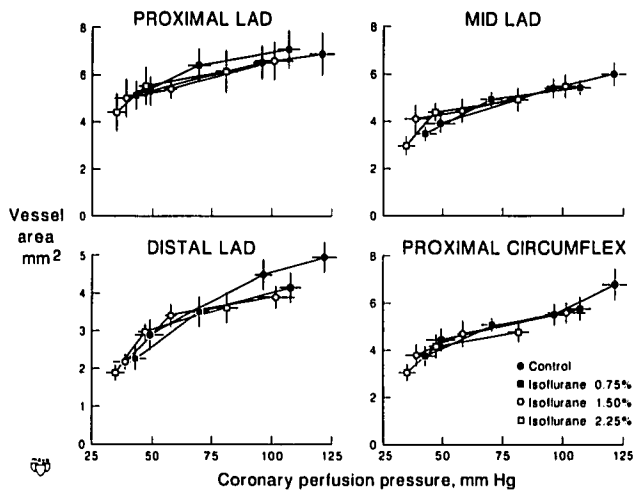


FIG. 1. Cross-sectional area of coronary artery versus coronary perfusion pressure; proximal left anterior descending (LAD), mid LAD, distal LAD, and proximal circumflex. Lines represent vessel areas throughout a range of perfusion pressures. Four lines on each graph are shown, one indicating control data and the other three representing data following 0.75%, 1.50%, and 2.25% isoflurane. All four lines are close together and are, at times, superimposed, demonstrating that isoflurane neither dilated nor constricted the coronary artery. Values are mean \pm SE ($n = 7$).

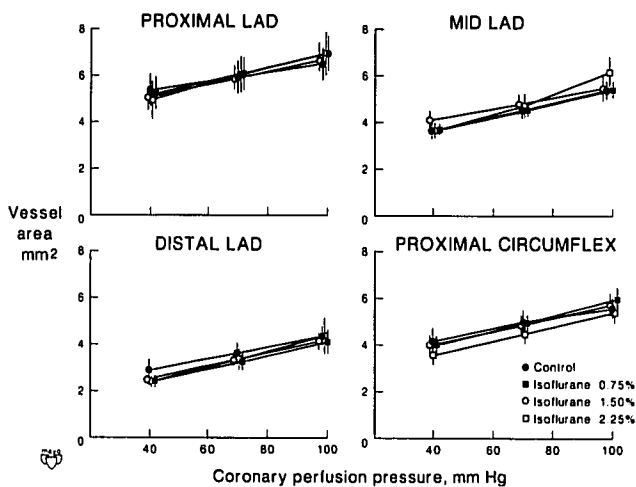


FIG. 2. Cross-sectional area of coronary artery versus coronary perfusion pressure; proximal, mid, and distal LAD, and proximal circumflex. Lines represent vessel areas calculated at the three standard perfusion pressures, 40 mmHg, 70 mmHg, and 100 mmHg. Four lines on each graph are shown, one indicating control data and the other three representing data following 0.75%, 1.50%, and 2.25% isoflurane. (The line representing 2.25% isoflurane was extrapolated to the 100 mmHg point, as not all dogs achieved this pressure.) All four lines are close together and are at times superimposed, demonstrating that isoflurane neither dilated nor constricted the coronary artery. Values are mean \pm SE ($n = 7$).

LARGE CORONARY DIMENSIONS

Isoflurane had no effect on epicardial coronary artery dimensions. No dilatation was observed throughout the range of isoflurane concentrations and coronary perfusion pressures investigated. Absence of effect can be appreciated in figure 1, where coronary vessel area versus coronary perfusion pressure has been plotted. If isoflurane had been a coronary dilator, then, at any given perfusion pressure, vessel area would be greater following isoflurane. Isoflurane would have shifted the area pressure lines upwards from control. Not only do the control and isoflurane area-pressure lines run close to one another, but they are, at times, superimposed. In figure 2, coronary dimensions have been calculated at standard perfusion pressures. Again, area-pressure lines are virtually superimposed. There is no significant difference between control areas and areas following isoflurane at all pressures analyzed.

Vessel cross-sectional area increased with increase in coronary perfusion pressure ($P < 0.001$). Figures 3 and 4 illustrate this pressure effect. Here, typical coronary angiograms are shown, both taken at the same isoflurane concentration; however, figure 3 was obtained during induced hypotension and figure 4 was taken during induced hypertension.

ARTERIOLAR VASOMOTION

Coronary arterioles were dilated by higher concentrations of isoflurane. This effect is apparent in both figures 5 and 6, where myocardial blood flow has been plotted against myocardial oxygen consumption. In figure 5, mean actual values are shown, while in figure 6 calculated mean flows have been plotted against standard values of MVO_2 . As would be expected, as MVO_2 increased, so did coronary blood flow. With the addition of isoflurane, this relationship is shifted upwards and to the left. At any given value of MVO_2 , coronary blood flow is increased following isoflurane. Coronary arteriolar vasodilatation has occurred.

Discussion

The purpose of this study was to determine coronary artery and coronary arteriolar responses to isoflurane. We have shown that, although isoflurane produced a dose-dependent arteriolar dilatation, it did not dilate coronary arteries. Isoflurane failed to exert an effect on the coronary arteries throughout a wide range of end-tidal isoflurane concentrations and coronary perfusion pressures.

The coronary circulation in dogs and in man consists of both coronary arteries and coronary arterioles.¹ The coronary arteries are large-diameter, low-resistance vessels

whose role is simply to conduct blood. In normal man, they contribute little to either regulation of coronary blood flow or to the total vascular resistance of the heart.^{1,27} Coronary arteries are capable of considerable dilatation and constriction.^{1,10} In dogs, dilatation occurs during high coronary blood flow states,²⁸ and, in man, normal segments of coronary arteries dilate during exercise.¹² Atherosclerotic segments do not dilate and may constrict during exercise.^{12,29} Drugs can induce major changes in coronary artery dimensions. Nitroglycerin and nitroprusside have been shown to dilate coronary arteries in dogs,³⁰ and both normal and stenosed segments of coronary arteries in man.^{11,12} We studied the entire length of the LAD coronary artery, as well as the proximal circumflex, but observed no coronary dilatation in response to isoflurane administration.

Coronary arterioles are small vessels with a well-developed media that ramify throughout the myocardium.^{1,2} By constricting and dilating, they regulate coronary blood flow and its distribution. Modulation of their tone is not well understood. A number of vasoactive substances, including adenosine and locally released potassium ions, are thought to link coronary blood flow to the metabolic requirements of the heart.^{2,31} The effects of isoflurane on coronary arteriolar tone in both man and dogs are controversial.³⁻⁷ We have shown higher isoflurane doses to produce marked arteriolar dilatation. Merin, in a carefully conducted experiment, found no isoflurane-induced arteriolar dilatation.³ However, in his experiment, measurements of flow were made at relatively low values of MVO_2 that were achieved following 1.66% and 3.30% isoflurane administration. From figures 5 and 6, it can be seen that the probability of detecting a significant difference in flow between isoflurane concentrations is decreased at low MVO_2 because regression lines for flow *versus* MVO_2 converge. We used lower, perhaps more clinically relevant isoflurane concentrations—0.75, 1.50, and 2.25%, and, unlike Merin, we were able to compare coronary flows throughout a broader MVO_2 range. In addition, we used fentanyl-pentobarbital as a background anesthetic and, although these drugs are thought to have little effect on coronary tone, they may be partially responsible for differences in results. However, this basal anesthetic did permit us to compare the effects of three isoflurane concentrations to a control state without isoflurane.

A dose-related decrease in myocardial blood flow in isoflurane-anesthetized pigs has been reported by Manohar,⁴ but, as measurements of MVO_2 were not made, it is difficult to assess the relationship between coronary flow, MVO_2 , and isoflurane effect. Coronary vasodilatation,⁵ decrease in coronary vascular resistance,⁷ and increase in myocardial blood flow despite decrease in blood

FIG. 3. Typical left coronary angiogram taken during induced hypotension. The small intracoronary catheter is just visible in the proximal left anterior descending coronary artery. The larger coronary guide catheter can be seen in the coronary ostium. ICC = intracoronary catheter; CGC = coronary guide catheter; P = proximal left anterior descending; D = distal left anterior descending; C = circumflex. A pacing catheter and coronary sinus catheter can also be seen. End-tidal isoflurane concentration was 0.78%.



pressure⁶ have been reported in dogs by other workers. In man, arteriolar dilatation accompanied by myocardial lactate production has been reported in some patients with CAD^{19,20}; however, these findings remain controversial, as isoflurane has not only been shown to be free of major adverse myocardial effects in CAD,³² but also increases myocardial tolerance of pacing-induced tachycardia.¹⁸

It is possible that this experimental method failed to detect small changes in large coronary artery dimensions. However, quantitative angiography has proven to be accurate when assessed by measuring test objects of known dimensions inserted into intact anesthetized dogs' coronary arteries.^{21,22} In addition, angiography offers several advantages. Using angiography, all the left coronary tree

FIG. 4. Typical left coronary angiogram taken during induced hypertension in the same animal (fig. 3). An increase in epicardial coronary size is evident. The small intracoronary catheter is just visible in the proximal left anterior descending coronary artery. The larger coronary guide catheter can be seen in the coronary ostium. ICC = intracoronary catheter; CGC = coronary guide catheter; P = proximal left anterior descending; D = distal left anterior descending; C = circumflex. A pacing catheter and coronary sinus catheter can also be seen. End-tidal isoflurane concentration was 0.78%.



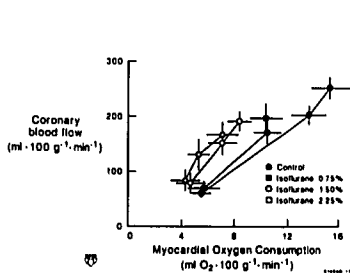


FIG. 5. Effects of isoflurane on coronary blood flow. Lines represent coronary blood flow versus myocardial oxygen consumption. Four lines are shown, one indicating control data and the other three representing data following 0.75%, 1.50%, and 2.25% isoflurane. Values are mean \pm SE ($n = 8$).

can be visualized and multiple cross-sectional measurements are possible. We made 20 individual measurements of coronary cross-section at each stage of the experiment, resulting in a total of 60 at each isoflurane concentration. Quantitative angiography has also been used to demonstrate drug effects on coronary artery dimensions in man.^{11,12,33} This method has been shown to be accurate to within 80 μm ,³⁴ and a good correlation between calculated luminal areas and postmortem measurements has been demonstrated.²³

Radio-opaque dye was used to image the coronary arteries, and this dye is known to reduce coronary arteriolar tone. However, dye effects are transient, and last only 4–6 min.²¹ This experiment was designed to ensure that coronary flow measurements were made at least 10 min or longer following the last contrast injection. Coronary blood flow has been shown to remain stable following repeated angiograms when this precaution is applied.³⁵

It is possible that the basal fentanyl-pentobarbital anesthetic reduced coronary tone, resulting in a vasculature less susceptible to further dilatation by isoflurane. However, neither pentobarbital nor fentanyl reduce coronary tone in isolated coronary rings.[†] Reduction in sympathetic activity following loss of consciousness may have an effect on the coronary vasculature; however, control mechanisms other than the adrenergic system probably participate in regulating large coronary tone.^{21,36} In addition, using a similar background anesthetic and this experiment technique, coronary arteries have been shown to remain sensitive and dilate following nitroglycerin administration.³⁵ Although no dilatation was seen in these animals with normal coronary tone, it remains possible that isoflurane may be a coronary artery dilator in the presence of elevated coronary tone.

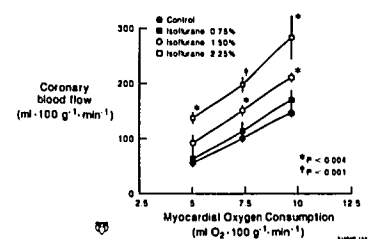
We were surprised to discover that fentanyl 1.5 mg/kg failed to prevent the animals from moving during arterial cutdown. We and others suggest that the fentanyl

dose required to anesthetize dogs is higher than 1.5 mg/kg, and may approach 3.0 mg/kg.³⁷ We were obliged to add pentobarbital. Our results indicate that isoflurane does not have a nitroglycerin-like vasodilatory effect on normal coronary arteries. We do not know the effects of isoflurane on coronary dimensions in the presence of elevated vascular tone. We are, therefore, unwilling to speculate on its effects in man with CAD as a vasospastic component may contribute to the degree of vessel narrowing in this condition.³⁸

In summary, we have demonstrated the site of isoflurane's coronary vasodilating property in normal dogs anesthetized with pentobarbital and fentanyl. Isoflurane dilates coronary arterioles, but does not dilate coronary arteries.

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