

Effects of Halothane, Enflurane, and Isoflurane on Coronary Blood Flow Autoregulation and Coronary Vascular Reserve in the Canine Heart

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To investigate the effects of volatile anesthetics on coronary blood flow (CBF) autoregulation and coronary vascular reserve, studies were performed on chronically instrumented dogs, awake and during the administration of 1.0 MAC halothane, enflurane, and isoflurane. Coronary pressure-flow plots were generated by measuring left anterior descending coronary artery blood flow while varying coronary inflow pressure with a hydraulic occluder. Autoregulation was quantitated by two measures: the slope of the horizontal "autoregulated" portion of the pressure-flow relationship and the autoregulation index (Arl) of Norris. Slope values ($\text{ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1} \pm \text{SD}$) were: awake, 0.243 ± 0.043 ; halothane, 0.414 ± 0.044 ; enflurane, 0.587 ± 0.187 ; and isoflurane, 0.795 ± 0.246 . The increase in slope was statistically significant only for halothane and isoflurane ($P < .05$). The Arl approaches 1.0 when autoregulation is perfect, and approaches zero or is a negative number when autoregulation is absent. The authors found Arl values of: awake, 0.55; halothane, -0.08; enflurane, -0.01; isoflurane, -0.02. These values indicate good autoregulation while awake, but impaired autoregulation with all three anesthetics ($P < .05$). Coronary vascular reserve was calculated, at a diastolic coronary pressure of 40 mmHg, as the difference between resting flow and flow during maximal coronary vasodilation induced by intracoronary adenosine. Coronary vascular reserve, maximal coronary conductance, and coronary zero-flow pressure were not significantly altered by these anesthetics. The authors conclude that 1.0 MAC enflurane, halothane, and isoflurane mildly disrupt CBF autoregulation, increasing CBF out of proportion to myocardial demands. Under the conditions of this study, these anesthetics do not affect maximal CBF or coronary vascular reserve. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Autoregulation. Coronary Vascular Reserve. Heart: blood flow; myocardial.)

AUTOREGULATION OF CORONARY blood flow (CBF) is a vasoregulatory mechanism which maintains CBF nearly constant over a wide range of perfusion pressures.^{1,2} At a constant myocardial oxygen consumption, a decrease in coronary perfusion pressure causes autoregulatory coronary vasodilation, rapidly adjusting coronary vascular resistance to maintain constant myocardial perfusion (fig. 1).

The volatile anesthetics have complex effects on the coronary circulation which may interfere with the autoregulation of CBF: they may decrease coronary vascular resistance by direct vasodilation^{3,4} or by decreasing compressive forces on intramyocardial arteries;⁵ they may affect coronary perfusion pressure by decreasing systemic pressure and changing diastolic intraventricular chamber pressures and the "back pressure" to CBF;⁶ and they may alter myocardial oxygen consumption (MVO_2) by decreasing contractility, systemic arterial pressure, or heart rate. Although it is known that volatile anesthetics may impair coronary autoregulation,⁷ the magnitude of these effects has not been quantified.

Volatile anesthetics may also affect "coronary vascular reserve," which is the increment in CBF above resting level that can be produced by a maximal coronary vasodilating stimulus.⁸ Although coronary vascular reserve is currently being measured in humans to assess the physiological significance of coronary stenoses,⁸ the effects of volatile anesthetics on this index of coronary function have not been assessed.

To quantitate the effects of three volatile anesthetics on coronary autoregulation and coronary vascular reserve, we created a chronic model in which precise coronary pressure and flow measurements can be made. We measured coronary pressure-flow relationships and coronary vascular reserve in unanesthetized dogs, and repeated these measurements during anesthesia with halothane, enflurane, and isoflurane (1.0 MAC).

Materials and Methods

PREPARATORY SURGERY

Mongrel dogs weighing 25.2–34.1 kg were anesthetized with thiamylal ($5 \text{ mg} \cdot \text{kg}^{-1}$) and halothane (1–2% inspired concentration). Under sterile conditions, a left thoracotomy was performed in the fourth or fifth intercostal space, and the pericardium was opened. The left circumflex coronary artery (LCCA) was dissected free near its origin, and fitted with a 2.5–3.0-mm electromagnetic flow probe (Zepeda® Instruments, Seattle, Washington). Immediately distal to this, without intervening coronary arterial branches, an adjustable hydraulic occluder (manufactured in our laboratory) was positioned. The distal LCCA was then catheterized

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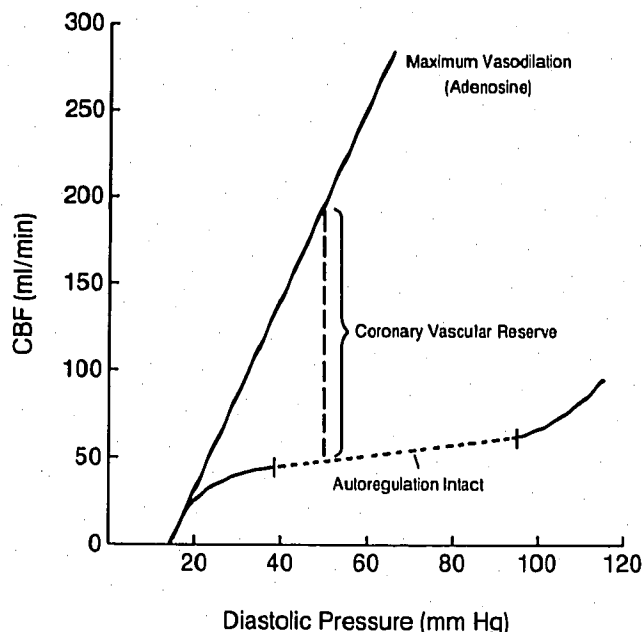


FIG. 1. Normal CBF autoregulation at a constant MVO_2 . The horizontal portion (broken line) of the lower curve illustrates the pressure range where CBF remains nearly constant as coronary diastolic pressure changes. Coronary vascular reserve is measured by the distance between the lower curve and the straight maximum vasodilation line. Note that coronary vascular reserve will increase as diastolic pressure increases.

using a small silastic catheter (0.30 mm id \times 0.64 mm od) and a modification of the technique of Herd and Barger.⁹ The undamped frequency response of this catheter system was uniform to 20–25 Hz, and the damping ratio was 0.30–0.50.¹⁰ Sixteen-gauge catheters were also inserted into the central aorta and the coronary sinus. The chest was then closed and any

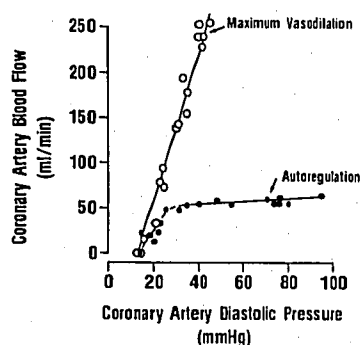


FIG. 2. The coronary blood flow-pressure relationship in an awake dog. The upper line, labeled "Maximum Vasodilation," is obtained after the circumflex coronary artery perfusion bed is maximally dilated with adenosine. The lower curve, labeled "Autoregulation," has a straight horizontal portion (solid line) with a curved portion (broken line) as flow becomes pressure-dependent.

Note that, during maximal vasodilation, coronary artery diastolic pressure was reduced so that the maximum flow shown in this illustration was obtained at a lower pressure (50 mmHg) than the diastolic pressure obtained in the resting state (autoregulation curve).

pneumothorax evacuated. All catheters and probe leads were exteriorized between the scapulae and protected by a snugly fitting jacket. Each dog received penicillin and streptomycin for 5 days postoperatively. Catheters were flushed daily with heparin to maintain patency. We report results only for those six animals whose instrumentation was successful. Our failure rate was 57%, primarily because of failure of coronary sinus and coronary artery catheters.

Beginning the day after surgery, each dog was brought daily to the laboratory for 6–10 h to become accustomed to the laboratory and personnel. Dogs were considered ready for study when they were afebrile, mobile, eating well, and had an arterial $P_{O_2} > 90$ mmHg while breathing room air. Studies were started 3–14 days post-surgery (mean = 3.9 days), and each study took a minimum of 3 days. Awake control measurements were obtained as follows.

AWAKE STUDIES

On the morning of the experiment, each dog was walked, then brought to the laboratory and placed in a restraining sling in the standing position. Catheters and flow probes were connected to measuring devices. After a variable period of quiet acclimatization (after which blood pressure, heart rate, and CBF were stable), the study was begun. If the dog became excited by an outside noise or some other stimulus, it was reassured until hemodynamic values returned to baseline. Simultaneous arterial and coronary sinus samples were drawn for measurement of oxygen content, and baseline blood pressure, heart rate, and CBF were measured.

To determine the baseline coronary pressure-flow relationship, we then obtained 20–30 paired values of CBF and pressure, over a wide range of pressures (fig. 2). By controlled inflation of the hydraulic occluder, the LCCA diastolic pressure was held transiently at values between 12 and 90 mmHg, and the CBF was recorded simultaneously. The duration of each partial occlusion was variable, but did not exceed 14 s. The criterion for acceptance of each point was 5 s of pressure-flow stability. After each measurement point, the hydraulic occluder was released and flow was allowed to return to baseline before obtaining the next measurements.

To cause maximal coronary vasodilation, adenosine (3.5 mM) was then infused directly into the LCCA, using a dose that was 1.5 times the dose necessary to produce maximal flow through the LCCA. This dose of adenosine caused no change in systemic blood pressure or heart rate. With the LCCA circulation maximally dilated, varying degrees of LCCA occlusion were applied, as described above, and multiple pressure-flow points were obtained (fig. 2).

ANESTHESIA STUDIES

Anesthesia was then induced by mask with either halothane, enflurane, or isoflurane. Each dog received each of the three anesthetics, but only one anesthetic was studied per day. The order of administration of anesthetics to individual dogs was controlled to avoid effects due to order of administration. Anesthetic end-tidal concentration was measured by mass spectrometry (Perkins-Elmer, Pomona, CA), and was adjusted to approximately 1.0 MAC of each of the three anesthetics studied (halothane, 0.87%; enflurane, 2.2%; isoflurane, 1.5%).¹¹ Sodium thiamylal 50–100 mg was also administered in most experiments for excitement during induction. After anesthesia was induced, the trachea was intubated and ventilation was controlled to keep P_{aCO_2} between 36 and 44 mmHg. Dogs remained in the prone position in the sling as in the awake studies.

All anesthetics were studied at constant end-tidal concentrations, maintained for a minimum of 20 min prior to the measurements. After 20 min of stability, hemodynamics, myocardial oxygen balance, and the coronary pressure-flow relationship were determined as in the awake state. Intracoronary adenosine was administered as described above, and the coronary pressure-flow relationship during maximal vasodilation was determined.

At the conclusion of the final day of study, dogs were killed by an overdose of pentobarbital. Their hearts were excised and inspected to confirm that the coronary sinus catheters were appropriately placed and that there was no macroscopic evidence of myocardial damage.

DATA ANALYSIS

Coronary Pressure-Flow Plots. For pressure-flow plots, we used paired values of *end-diastolic* coronary artery pressure and *mean* coronary flow. We chose end-diastolic pressure as it is relatively unaffected by the artifact due to systolic compression of coronary arteries, which may be seen in mean pressure measurements, and because nearly all coronary flow occurs during diastole. While mean diastolic coronary pressure might be a preferable alternative for pressure-flow plots, the direct measurement of mean diastolic pressure presents significant problems, and this pressure is, therefore, most often calculated *post hoc* after planimetric measurements. For the above reasons, and because our experimental design required that we use a coronary pressure which could be measured and controlled "on-line," we chose end-diastolic pressure rather than the difficult-to-measure mean diastolic pressure. Although it is recognized that the use of mean flows does not show the phasic contributions of coronary capacitance and extra-

vascular compressive forces,² the pairing of mean coronary flows with diastolic coronary pressures for pressure-flow plots is, nevertheless, justifiable because almost all left ventricular coronary flow occurs in diastole.

Quantitation of Coronary Autoregulation. The degree of coronary artery autoregulation was quantitated by two indices. Pressure-flow plots obtained during autoregulation were divided by inspection into two parts, a horizontal autoregulated portion and a steeper pressure-dependent portion (fig. 2). A regression equation for the horizontal portion of this curve was obtained by least-squares linear regression analysis. The slope of this regression line provided one measure of autoregulation. A second measure of autoregulation was obtained by calculation of the autoregulation index (ArI) of Norris.¹² This index was originally developed for quantitation of autoregulation in mesenteric arteries, and has more recently been used by Dole as a measure of autoregulation in the coronary circulation.¹³ To calculate the ArI, a measured change in coronary vascular conductance ($\Delta F/\Delta P$) is divided by the change in coronary vascular conductance which would be expected if autoregulation had been perfect and CBF had remained constant. Mathematically, the expression is:

$$ArI = \left[\frac{F_1}{P_1} - \frac{F}{P} \right] \times \left[\frac{F_1}{P_1} - \frac{F_1}{P} \right]^{-1},$$

where F_1 = CBF at starting pressure P_1 and F = CBF at a new steady-state reduced pressure, P . The first bracketed term in this equation is the actual measured change in coronary conductance. The second bracketed term is the expected change in coronary conductance if CBF remained constant at F_1 as pressure was reduced from P_1 to P . This second term thus represents "perfect autoregulation," or constant flow across a range of pressures, and is used to normalize the observed change found in coronary conductance. To calculate ArI, we chose minimum and maximum values of flow and pressure from the horizontal portion of the CBF autoregulation curve determined by regression analysis. In each instance, the ArI was calculated over the entire measurable range of autoregulated flow.

Zero-flow pressure intercepts were determined by direct measurement. The coronary pressure-flow relationship during adenosine administration was determined using linear regression. An example of data points and curve fit is shown in figure 2. Oxygen content was determined by measurement of P_{O_2} (ABL-2, Radiometer, Copenhagen), oxygen saturation, and hemoglobin (OSM-2, Radiometer, Copenhagen), and was calculated as: (% Saturation \times 1.34 \times Hb(g \cdot 100 ml)) + (.003 \times P_{O_2} mmHg).

TABLE 1. Systemic and Coronary Hemodynamics

Status	Blood Pressure (mmHg)				Heart Rate (bpm)
	Systemic Systolic	Systemic Diastolic	LCCA Systolic	LCCA Diastolic	
Awake	125 ± 7	84 ± 9	113 ± 9	83 ± 7	111 ± 5
Halothane	99 ± 6*	72 ± 6	90 ± 9*	65 ± 7*	82 ± 14*†
Enflurane	96 ± 4*	74 ± 7	84 ± 8*	66 ± 11*	104 ± 15
Isoflurane	96 ± 10*	68 ± 11*	84 ± 7*	62 ± 10*	112 ± 15

Values are mean ± SD, n = 6.

* Significantly reduced compared to awake, $P < 0.05$.

† Significantly reduced compared to enflurane and isoflurane.

Quantitation of Coronary Vascular Reserve. Coronary vascular reserve is defined as the difference between CBF at rest and during maximal coronary vasodilation at a given pressure. In this experiment, we developed coronary pressure-flow diagrams at rest and during maximal coronary vasodilation, and measured the difference between these two lines at a coronary diastolic pressure of 40 mmHg. Lines were determined by linear regression, as previously described.

Statistical Analysis. Repeated-measures analysis of variance was used to analyze hemodynamics, coronary blood flow-pressure slopes, ArI, and myocardial oxygen consumption. For multiple comparisons among groups where indicated by ANOVA results, paired t tests with the Bonferroni correction were used.

Results

HEMODYNAMICS

Blood pressures were normal and heart rates slightly increased in the awake animals. Heart rate fell during halothane administration, but was no different than control during isoflurane and enflurane studies. At 1 MAC, all three anesthetics reduced blood pressure in both the systemic and coronary circulation, as expected. There was no significant diastolic pressure gradient be-

tween the aorta and circumflex coronary artery in awake or anesthetized dogs, indicating that the instrumentation caused no significant coronary stenosis (table 1).

CORONARY BLOOD FLOW-PRESSURE RELATIONSHIPS

In awake dogs, CBF was well-autoregulated, and typically changed little over the pressure range from 35 to 80 mmHg (fig. 2). The mean slope of this autoregulated portion of the pressure-flow line, determined by linear regression, was $0.243 \text{ cc} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$. All three volatile anesthetics tended to increase this slope, with the order of increase being: awake slope < halothane < enflurane < isoflurane. The increased autoregulatory slope was significantly different during halothane and isoflurane administration ($P < 0.05$), but did not reach statistical significance during enflurane ($0.10 > P > 0.05$) (table 2).

In awake dogs, the mean autoregulation index (ArI) was 0.55, confirming good autoregulation in the awake state. The calculated ArI decreased during administration of all three anesthetics ($P < 0.05$) when compared to awake, but there was no significant difference in ArI among the anesthetics studied.

Mean coronary (LCCA) blood flow in awake dogs was $32.6 \text{ ml} \cdot \text{min}^{-1}$ at coronary diastolic pressure of 40

TABLE 2. CBF Autoregulation

Status	Autoregulation Slope ($\text{ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$)	r	ArI	Coronary Blood Flow ($\text{ml} \cdot \text{min}^{-1}$)	
				At $P_d = 40 \text{ mmHg}$	At $P_d = 60 \text{ mmHg}$
Awake	0.243 ± 0.043	0.83	0.55 ± 0.16	32.6 ± 9.4	37.8 ± 9.3
Halothane	$0.414 \pm 0.044^*$	0.97	$-0.08 \pm 0.14^*$	$16.0 \pm 5.1^{\S}$	$24.5 \pm 5.4^{\S}$
Enflurane	$0.587 \pm 0.187^{\ddagger}$	0.94	$-0.01 \pm 0.35^*$	21.6 ± 7.4	32.0 ± 9.5
Isoflurane	$0.795 \pm 0.246^{*\ddagger}$	0.93	$-0.02 \pm 0.11^*$	30.5 ± 10.64	47.6 ± 18.6

ArI is the autoregulation index described in Methods. r = mean correlation coefficient of the autoregulation line derived by linear regression; P_d = coronary artery diastolic pressure.

* Significantly different from awake, $P < 0.05$.† Significantly different from awake, halothane, and enflurane, P

< 0.05.

‡ Not significantly different from awake, $0.10 > P > 0.05$.§ Significantly different from corresponding awake and isoflurane values, $P < 0.05$.

TABLE 3. Maximum Coronary Vasodilation and Coronary Vascular Reserve

Status	Maximum Vasodilation (Adenosine)		Coronary Vascular Reserve (ml · min ⁻¹)	Coronary Blood Flow at P _d = 40 mmHg (ml · min ⁻¹)
	Slope (ml · min ⁻¹ · mmHg ⁻¹)	r		
Awake	5.32 ± 2.18*	0.980	97.3 ± 63	128.3 ± 28.9
Halothane	5.20 ± 2.3*	0.989	115.8 ± 80†	132.5 ± 32.9
Enflurane	4.57 ± 1.7*	0.977	93.7 ± 47†	114.5 ± 20.4
Isoflurane	5.30 ± 2.02*	0.985	91.3 ± 54†	121.5 ± 24.7

r = mean correlation coefficient of the pressure-flow relationship derived by linear regression.

* Significantly different from both awake and anesthetized autoreg-

ulation values.

† Not significantly different than corresponding awake values, *P* > 0.05.

mmHg, and was 37.8 ml · min⁻¹ at coronary diastolic pressure of 60 mmHg. Halothane decreased CBF significantly at both pressures. Neither enflurane nor isoflurane changed CBF significantly at either pressure (*P* > 0.20).

MAXIMUM CORONARY VASODILATION, CORONARY VASCULAR RESERVE, AND ZERO-FLOW PRESSURE

Adenosine-induced maximum coronary vasodilation increased CBF significantly in all dogs, and increased the slope of the coronary blood flow-pressure relationship from 0.243 ± 0.043 cc · min⁻¹ · mmHg⁻¹, in awake autoregulating dogs, to 5.32 ± 2.18 cc · min⁻¹ · mmHg⁻¹. The three anesthetics studied did not significantly change the slope of the coronary blood flow-pressure relationship during maximal vasodilation with adenosine. Coronary vascular reserve was calculated, at coronary diastolic pressure = 40 mmHg, as the difference between baseline CBF and adenosine-induced maximum CBF. Coronary vascular reserve was not changed by any of the three anesthetics tested (table 3).

Mean LCCA blood flow during adenosine administration in awake dogs was 128.3 ml · min⁻¹ at a coronary diastolic pressure of 40 mmHg. Neither halothane, enflurane, or isoflurane significantly changed CBF during maximum coronary vasodilation.

The coronary zero-flow pressure (*P_{zf}*) is the measured coronary pressure at which forward, non-collateral flow stops (table 4). *P_{zf}* was 15.5 ± 2.4 mmHg in awake dogs, and was not changed significantly by any of the anesthetics tested. Maximal vasodilation by adenosine did not alter *P_{zf}*.

MVO₂ AND CORONARY SINUS OXYGEN SATURATIONS

MVO₂ was calculated for the zone of myocardium supplied by the LCCA, as the product of LCCA blood flow and the aorta-coronary sinus oxygen content difference. All three anesthetics decreased MVO₂, as ex-

pected. There was no significant difference in MVO₂ among the anesthetics (table 5).

Coronary sinus hemoglobin-O₂ saturation was 27.3 ± 6.8% in awake dogs. All three anesthetics increased coronary sinus hemoglobin-O₂ saturation when compared to the awake state (*P* < 0.05), with the order of increase being: awake saturation < halothane < enflurane < isoflurane. Among the three anesthetics, the only significant difference found was that coronary sinus O₂ saturation during halothane was less than that during isoflurane administration (*P* < 0.05) (table 5).

Discussion

AUTOREGULATION

Autoregulation of CBF normally serves to keep CBF relatively constant over a wide range of coronary perfusion pressures. The basic finding of this study is that

TABLE 4. Coronary Zero-flow Pressures*

Status	P _{zf} during Autoregulation (mmHg)	P _{zf} during Maximal Vasodilation (mmHg)
Awake	15.5 ± 2.4	15.6 ± 2.8
Halothane	14.6 ± 3.6	15.3 ± 1.9
Enflurane	14.5 ± 3.3	15.5 ± 3.1
Isoflurane	15.0 ± 1.7	15.4 ± 3.0

* No significant differences were found.

TABLE 5. Myocardial Oxygen Balance

Status	MVO ₂ (ml · min ⁻¹)	Arterial O ₂ Saturation (%)	Coronary Sinus O ₂ Saturation (%)
Awake	4.26 ± 1.09	96.3 ± 0.1	27.3 ± 6.8
Halothane	2.12 ± 0.72*	98.8 ± 0.1	48.7 ± 7.8*†
Enflurane	2.79 ± 0.11*	99.7 ± 0.2	57.7 ± 7.8*
Isoflurane	2.47 ± 0.18*	99.8 ± 0.1	68.5 ± 10.2*

* Significantly different from awake, *P* < 0.05.

† Significantly different from isoflurane, *P* < 0.05.

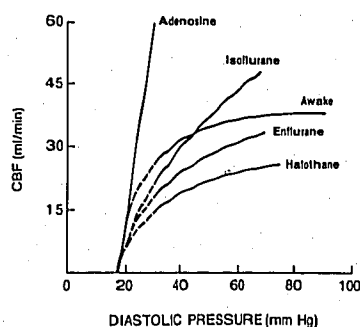


FIG. 3. This figure provides a qualitative description of the effects of volatile anesthetics on the CBF-pressure relationship, and demonstrates the effect of adenosine-induced maximal coronary vasodilation in awake and anesthetized dogs. Solid lines are drawn from mean slopes determined by linear regression analysis. Dashed lines represent

the non-linear portion of the curve and are estimates. Note that, compared to values determined in awake dogs, the anesthetics affect absolute CBF variably but do tend to increase the slope of the CBF-pressure plots. During maximal coronary vasodilation by intracoronary adenosine, CBF becomes completely pressure-dependent (*i.e.*, autoregulation is lost), and CBF is greatly increased over a wide range of pressures. CBF-pressure relationships during maximal coronary vasodilation were not different in awake and anesthetized dogs, so both states are equally well-represented by the single adenosine line. (Please see tables 2-4 and text for actual data and statistical comparisons.)

1.0 MAC anesthesia with halothane, enflurane, or isoflurane reduces autoregulation of CBF, both by increasing flow out of proportion to the reduced myocardial oxygen demand, and by making flow more pressure-dependent (fig. 3). We found, however, that these anesthetics do not significantly affect maximum coronary conductance, coronary vascular reserve, or coronary zero-flow pressures.

We found that, in awake dogs, CBF remained nearly constant as coronary pressure was reduced, until a diastolic coronary pressure of about 30 mmHg was reached (fig. 2). Although this finding was expected, to our knowledge, autoregulation of CBF has not been previously described in awake dogs. Our finding of good coronary autoregulation in awake dogs is similar to results reported from previous studies of dogs anesthetized with pentobarbital and α -chloralose: CBF is constant over a wide range of pressures, although there is a slightly positive slope.¹⁴⁻¹⁷ (If autoregulation were perfect, slope of the flow-pressure relationship would be zero.)

Both measures of autoregulation employed in this study (autoregulatory slope and ArI) indicate that all three volatile anesthetics blunt coronary autoregulation. However, these two measures of autoregulation provide contrasting results and problems of interpretation. The ArI of Norris approaches 1.0 when autoregulation is perfect, and approaches zero or is a negative number when autoregulation is absent.¹² In this study, the ArI was decreased significantly ($P < 0.001$) by all three volatile anesthetics: awake ArI = 0.55, halothane ArI = -0.08, enflurane ArI = -0.01, and isoflurane

ArI = -0.02. Statistical testing revealed no significant difference among the three anesthetics. By contrast, if the slope of the most horizontal portion of the coronary pressure-flow plot is used as the index of autoregulation, isoflurane appears to inhibit autoregulation most: awake slope = 0.243, halothane slope = 0.414 ($P < 0.05$ vs. awake), enflurane slope = 0.587, and isoflurane slope = 0.795 ($P < 0.05$ vs. awake). Methods of calculation indicate the reason for these contrasting results. The ArI is calculated by dividing a measured change in coronary conductance ($F \cdot P^{-1}$) by the ideal change in coronary conductance as if autoregulation were perfect (*i.e.*, no change in flow over the pressure range). The ArI thus normalizes the initial measured conductance to the conductance required to maintain perfect autoregulation and, as such, is a function of an "ideal" calculated number. Autoregulatory slope, on the other hand, describes only the absolute rate of change of flow as pressure is varied.

Parallel autoregulated pressure-flow plots of different baseline height have identical slopes, because slope is dependent only on the absolute change in flow over a given pressure range (*i.e.*, slope is sensitive to the absolute change in flow, but insensitive to the resting level of flow, or to percent change in flow). However, parallel pressure-flow plots have different ArIs, because ArI depends not only on the absolute change in flow over a given pressure range, but also on the absolute level of flow measured (*i.e.*, ArI is sensitive to the percent change in flow, slope is not). Given two parallel pressure-flow lines of identical slope, the line with the highest baseline autoregulated flow will have an ArI indicating superior autoregulation, because the percentage change in conductance over a given pressure range will be least.

An illustration of this difference is found in our study when comparing autoregulation in awake *versus* halothane-anesthetized animals. Although the slope of the autoregulated pressure-flow plot increased only slightly (awake slope = 0.243, halothane slope = 0.414), the ArI fell substantially (awake ArI = 0.55, halothane ArI = -0.08). This is because halothane substantially decreased MVO₂ and resting levels of CBF. Subsequently, small pressure-induced decrements in CBF represented a greater percent change from baseline flow in animals anesthetized with halothane; hence the small increase in slope and the greater change in ArI.

Which of these anesthetics disturbs coronary autoregulation most? Based on the autoregulatory slope, the calculated ArI, and the coronary sinus O₂ content (a measure of the matching of myocardial oxygen supply to demand), all three anesthetics disturb autoregulation significantly, but isoflurane causes the greatest blunting of autoregulation and the highest CBF when compared

to the awake state. In our experiment, CBF during 1.0 MAC isoflurane was 126% of the value determined in awake dogs, although this finding did not reach statistical significance. Gelman *et al.* have also reported that 1.0 MAC isoflurane increases CBF to a comparable degree (129% of values measured in awake dogs).⁴ Thus, our findings are very similar to Gelman's. We attribute the lack of statistical significance in the present study to the relatively small number of experimental animals. The small or insignificant increase in CBF caused by isoflurane in these studies is in marked contrast to the effects of the potent coronary vasodilator, adenosine, which increased absolute CBF in awake dogs by nearly 400% (tables 2, 3).

CORONARY VASCULAR RESERVE

Coronary vascular reserve measures the capacity of the coronary circulation to increase blood flow during maximal coronary vasodilation, which is usually produced pharmacologically. In this experiment, coronary vascular reserve was measured as the increment of flow above resting levels produced by adenosine-induced maximum coronary vasodilation at a coronary diastolic pressure of 40 mmHg (fig. 2). Coronary vascular reserve was not different in the awake and anesthetized dog.

The finding that the volatile anesthetics do not change coronary vascular reserve differs from one previous report. Verrier *et al.*¹⁸ found greater coronary vascular reserve in open-chest dogs during halothane anesthesia when compared to a nitrous oxide-pentobarbital control state. In that study, the animals anesthetized with nitrous oxide and pentobarbital had higher heart rates (171 *vs.* 146 bpm) and increased dp/dt (1879 *vs.* 1079 mmHg/sec), compared to those anesthetized with halothane. Both increased contractility and increased heart rate, as found in Verrier's study, have been shown to reduce maximum coronary conductance,^{19,20} and, therefore, to diminish coronary vascular reserve. Therefore, coronary vascular reserve may have been diminished in the nitrous oxide-barbiturate control group in that experiment. Additionally, resting left ventricular blood flow was 41% lower in the dogs anesthetized with halothane in Verrier's study, so the maximum attainable increase in CBF due to vasodilation was greater during halothane anesthesia. We believe that these substantial hemodynamic differences account for the reported increase in coronary vascular reserve due to halothane in that study.

In our study, coronary vascular reserve was calculated at a diastolic pressure of 40 mmHg. This relatively low diastolic pressure was chosen because, during maximal coronary vasodilation, the maximum diastolic pressure measured in the circumflex artery during anesthe-

sia was seldom much greater than 40 mmHg. We believe that calculation of coronary vascular reserve at this pressure is valid, since 40 mmHg is still within the autoregulated range of the pressure-flow relationship (fig. 2).

ZERO-FLOW PRESSURE INTERCEPTS

P_{zf} , or the pressure at which forward, non-collateral CBF stops, is held to be a measure of the true back-pressure to CBF, and is, therefore, an important determinant of coronary vascular resistance.² Anesthetic-induced changes in P_{zf} could, therefore, substantially alter CBF dynamics. We found values of P_{zf} (mean = 15.5, \pm 2.4 mmHg) in awake dogs, which are similar to values reported in prior studies of anesthetized and awake dogs,²¹⁻²³ in which P_{zf} was determined by extrapolation of coronary blood flow-diastolic pressure curves to zero flow. Our study differs from the above studies in that P_{zf} values were measured directly rather than extrapolated, but the results are comparable.

We found no significant change in P_{zf} during administration of any of the three anesthetic agents, or during maximum coronary vasodilation by adenosine. This finding suggests that, at 1.0 MAC concentration, the anesthetics studied do not change the apparent back-pressure to CBF, despite their multiple effects on cardiac chamber pressures, ventricular wall tension, extravascular compressive forces, and coronary vascular resistance.

During conditions of increased heart rate and contractility, P_{zf} is reported to range from 27-50 mmHg.^{21,22,24} The difference in P_{zf} under such conditions may be due to differences in coronary tone and capacitance, but this phenomenon has yet to be fully explained. Prior work by Verrier *et al.* suggests that, under such conditions, halothane may decrease P_{zf} to the levels found in our study in awake, resting animals.¹⁸

The values of P_{zf} found in this experiment and those reported in the literature are, however, greater than either normal coronary sinus pressure or left ventricular diastolic pressure. Pantely *et al.*²⁵ found that, in pigs, which have little native coronary collateral circulation, P_{zf} is 5-6 mmHg, approximating the coronary sinus pressure. This group suggested that the high P_{zf} in dogs is caused by back pressure transmitted through the relatively good native collaterals present in this species.²⁶

MYOCARDIAL OXYGEN CONSUMPTION AND CORONARY SINUS OXYGEN CONTENT

The decreases in myocardial oxygen consumption observed in this study due to the administration of the volatile anesthetics are directionally similar to those re-

ported by other workers.²⁷⁻²⁹ Coronary sinus O₂-hemoglobin saturation rose with all three anesthetics, indicating that myocardial oxygen supply was increased out of proportion to demand (table 5). This increase in coronary sinus O₂-hemoglobin saturation was greatest for isoflurane, confirming that this agent increased flow the most, relative to demand.

The increased coronary sinus oxygen saturation observed during administration of these volatile anesthetics provides an interesting area for speculation and further investigation. It is commonly believed that the primary mechanism for increasing oxygen delivered to the myocardium is by coronary vasodilation, which increases CBF.³⁰ This is believed because CBF can normally increase four- to sixfold,^{31,32} whereas increases in myocardial oxygen extraction are limited: coronary venous saturation is "normally" about 20–30% of arterial saturation.³³⁻³⁵ During the administration of the volatile anesthetics, however, oxygen extraction is not maximal and may be substantially less than "normal." If the relative increase in CBF caused by these agents is not due to intramyocardial shunting, this "excess flow" may allow oxygen consumption to increase during times of increased demand, without increases in CBF. This would only be applicable if the increased flow is available as nutrient flow and if myocardial cells are capable of increasing their oxygen extraction. Gelman *et al.*⁴ have addressed the question of intramyocardial shunting, and did not find a significant increase in the shunting of 9-micron microspheres, a measure of non-nutritive flow through the myocardium during anesthesia with isoflurane or halothane at 1.0 or 2.0 MAC. This suggests that these drugs do not open direct arteriovenous anastomoses or create thoroughfare channels, and that the excess myocardial blood flow may be available for nutritive needs during periods of increased demand. However, the availability of this "excess flow" for increased oxygen extraction during stress has not yet been systematically tested in any animal or human model.

METHODOLOGICAL LIMITATIONS

Autoregulation of the coronary circulation has most often been studied in perfused heart preparations. After cannulation of the left main coronary artery, coronary pressure can be controlled by a separate perfusion circuit, while systemic pressure and MVO₂ remain constant.¹⁴⁻¹⁷ Mosher, in a classic study of CBF autoregulation, described the limitations of this methodology,¹⁷ which include the use of anesthesia in the "control" state, open chest technique, and the partial use of non-phasic perfusion pressure. Since our goal was to measure the effects of the volatile anesthetics on coronary

autoregulation and vascular reserve, it was necessary to obtain control measurements in awake animals. Our experimental preparation allowed us to vary coronary pressure and to measure CBF in awake, closed-chest dogs during phasic coronary perfusion, thus avoiding the limitations of perfused-heart preparations. However, this experimental preparation did present other problems in data-gathering and analysis.

First, the demanding technical nature of this preparation led to frequent failures and prohibited data-gathering in a much larger number of experimental animals. The study design did, however, enable us to obtain all data in every animal studied. It does appear likely that changes in two of the experimental variables (enflurane autoregulatory slope and isoflurane CBF at P_a60) might have reached statistical significance if we had performed more experiments. Given the magnitude of the measured changes in these variables, however, the finding of statistical significance would not alter our interpretations.

A second limitation of our methods is that coronary blood flow-pressure relationships were difficult to obtain in awake animals. Extraneous laboratory stimuli could cause near-instantaneous changes in heart rate, blood pressure, myocardial oxygen consumption, and in the coronary pressure-flow relationship. Patient conditioning of dogs to the laboratory environment was, therefore, essential to obtain meaningful data. Multiple measurements in awake animals on separate days helped to minimize variability, but curves were always more exact in anesthetized animals and during maximal vasodilation, as shown by higher correlation coefficients of the regression lines obtained under these conditions.

Third, we report only the effects of these anesthetics at 1.0 MAC, although we originally had planned to test their effects at multiple concentrations. We found that, because these chronically instrumented animals had no surgical stimulation at the time of study, anesthetic-induced reductions in blood pressure made determination of pressure-flow relationships at deeper levels of anesthesia impractical. We are, thus, unable to report dose-response curves for the agents studied.

Fourth, this preparation only allowed us to reduce coronary artery pressure; we could not increase coronary pressure to further define the upper limits of coronary autoregulation in awake dogs, or to determine the effects of the volatile anesthetics at high coronary pressures. This limitation is not found in studies where CBF is controlled by external perfusion apparatus in anesthetized animals,¹⁴⁻¹⁷ but such experiments do not permit awake control measurements. Infusion of peripheral vasoconstrictors or the use of an aortic compression cuff can raise coronary pressures in awake ani-

mals, but these interventions can also rapidly change myocardial oxygen consumption, thus altering the pressure-flow relationship. As stated earlier, this preparation was selected to permit study of awake animals, so it was necessary to accept measurements of coronary autoregulation over a more limited pressure range.

Similarly, during adenosine-induced maximal coronary vasodilation, coronary blood pressure was lowered considerably compared to the awake resting state (fig. 2). Thus, the coronary flow-pressure relationships during maximal vasodilation were also determined over a reduced pressure range. The maximum pressures at which pressure-flow values were obtained were only slightly greater than 40 mmHg. We found this to be an acceptable limitation of our preparation, as it permitted determination of pressure-flow relationships during maximal vasodilation in awake dogs.

A final limitation of this experiment is that we report only total CBF measured at an epicardial coronary artery, and are not able to describe transmural differences in autoregulation. It is known that there may be significant transmural differences in coronary autoregulation and vasodilator reserve, especially in the canine heart, which has a good, primarily epicardial, collateral circulation.³⁶ Although transmural differences in CBF can be measured by the radionuclide-labeled microsphere method, current methodology only allows for, at most, six to eight flow measurements in any one animal. Since such few measurements are insufficient to characterize completely the transmural differences in coronary autoregulation, we thought it more important to obtain a larger number of associated pressure-flow points in each experiment by using the epicardial flow probe method.

SUMMARY AND IMPLICATIONS

In summary, we found that 1.0 MAC anesthesia with halothane, enflurane, or isoflurane diminishes, but does not abolish, autoregulation of CBF in this chronically instrumented canine model. CBF is increased out of proportion to the reduced myocardial oxygen demand caused by these agents, and this effect is most evident with isoflurane. However, absolute regional blood flow did not increase significantly when any of these agents was administered at this dosage (table 4). In fact, absolute CBF decreased with halothane. Therefore, none of these agents can be considered to be a powerful coronary vasodilator, when compared to a drug like adenosine, which increased CBF nearly 400% in this model. None of the three anesthetics, halothane, enflurane, nor isoflurane, significantly affected maximum coronary conductance, coronary vascular reserve, or coronary zero-flow pressure.

The implications of anesthetic-induced coronary vasodilation are several. This vasodilation may be beneficial if myocardial oxygen delivery is enhanced, or detrimental if these anesthetics can cause a coronary "steal" effect. Under the conditions of this study, none of the three anesthetics was found to be a very potent coronary vasodilator, based on the considerations described above. We, therefore, speculate that their ability to induce coronary steal should be limited under these circumstances. However, this experiment was not designed to test the potential of these anesthetics to induce coronary steal.

The results of this experiment can be extrapolated to humans with coronary atherosclerosis, but, for several reasons, this should be done with great caution. First, there might be significant species differences in responsiveness to the drugs tested. Dogs have, however, often been found to have responses to coronary vasodilators that are similar in direction and magnitude to normal human responses.³⁷ Second, we were unable to test the effects of these drugs during conditions of hypertension or tachycardia, which may be more relevant clinical scenarios than the conditions employed in this experiment. For instance, although isoflurane did not increase CBF significantly when measured at a coronary diastolic pressure of 40 or 60 mmHg, this does not rule out a possibly significant increase at much higher diastolic pressures. Finally, atherosclerotic arteries may have responses to some drugs which are different in magnitude from those of normal arteries.³⁸⁻⁴⁰ If this is true for the volatile anesthetics, then the most relevant experiments must necessarily be performed on humans with coronary artery disease.

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