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Direct Vasodilation by Sevoflurane, Isoflurane, and Halothane Alters Coronary Flow Reserve in the Isolated Rat Heart

David R. Larach, M.D., Ph.D., H. Gregg Schuler, B.A.†*

Direct vasodilation of coronary resistance vessels by anesthetics may reduce coronary flow reserve and interfere with myocardial flow–metabolism coupling. This study was performed to evaluate the potential for the halogenated anesthetic agents sevoflurane, isoflurane, and halothane to alter the regulation of coronary flow *via* a direct action on coronary resistance vessels. Coronary flow and flow reserve were measured in the quiescent isolated perfused rat heart at anesthetic concentrations between 0 and 3 × MAC. In order to minimize anesthetic-induced secondary changes in coronary resistance, constant coronary perfusion pressure was maintained; the left ventricular cavity was vented; and tetrodotoxin was used to achieve cardiac arrest. These conditions permitted the dissociation of direct anesthetic actions from indirect regulatory processes affecting coronary vascular resistance (CVR). Coronary flow reserve was defined as the difference between coronary flow prior to and during administration of a maximally vasodilating dose of adenosine. Each anesthetic significantly reduced the magnitude of both CVR and coronary flow reserve in a concentration-dependent manner. Sevoflurane reduced coronary flow reserve significantly less than did halothane and isoflurane. At high concentrations (3.0 × MAC), coronary flow reserve was abolished by halothane and was decreased to near zero by isoflurane; however, flow reserve was reduced only 48% from control by sevoflurane. This difference among anesthetics is explained primarily by variations in the magnitude of direct coronary vasodilation produced by each anesthetic, rather than by effects on maximal vasodilator capacity. These data show that sevoflurane's intrinsic vasodilator action on coronary resistance vessels differs substantially from that of halothane and isoflurane. (Key words: Adenosine. Anesthetics, volatile: halothane; isoflurane; sevoflurane. Heart, isolated perfused: coronary hemodynamics. Tetrodotoxin. Vascular smooth muscle: vasodilation; resistance-vessel.)

THE CORONARY CIRCULATION displays a high degree of regulation that maintains an appropriate coronary flow despite changes in myocardial O_2 consumption ($M\dot{V}O_2$) and perfusion pressure. Because halogenated anesthetics depress myocardial contractility and alter systemic hemodynamics, marked secondary changes in coronary vascular resistance (CVR) often are induced through the indirect processes of coronary flow–metabolism coupling and pressure–flow autoregulation.[1–3] These indirect vascular effects can obscure the direct actions of the anesthetic on the resistance vessels of the coronary circulation, even in the isolated heart.[4]

It is important to understand how anesthetics directly affect coronary resistance vessels. These small arteries and arterioles regulate regional myocardial flow; also, drug-induced relaxation of these vessels is responsible for the phenomenon of coronary "steal" when coronary artery stenoses of a particular configuration are present.[5,6] Recently, we developed a method for isolating the direct coronary microvascular effects of halogenated anesthetics and other negative inotropic drugs, using the isolated, perfused, tetrodotoxin (TTX)-arrested rat heart.[7] Using this technique, we quantified the direct vasodilating effects of halothane and isoflurane on coronary resistance vessels *in situ*.[7]

The ability of the myocardium to increase its blood supply in response to increased nutrient demand can be assessed by measuring coronary flow reserve. Coronary flow reserve is the increment in flow that can be induced by a maximal vasodilator stimulus such as intracoronary adenosine.[8] Stresses affecting the balance between myocardial O_2 supply and demand, such as coronary artery stenosis or myocardial hypertrophy, can decrease the coronary flow reserve, indicating increased vulnerability of the myocardium to ischemia.[2,3] Thus, preservation of a large coronary flow reserve may be beneficial to the heart, because substantial increments in blood flow will be achievable during stress. Hickey *et al.*[9] measured coronary flow reserve in the beating hearts of chronically instrumented dogs at a coronary inlet pressure of 40 mmHg. They found that neither halothane, isoflurane, nor enflurane affected coronary flow reserve compared with the awake state, although each agent did attenuate autoregulation. In contrast, Gilbert *et al.*[10] showed in open-chest pigs that coronary flow reserve was unaffected by isoflurane, but that halothane at a MAC fraction (F_{MAC}) $\geq$ 1.25 markedly reduced flow reserve, compared with a control state at F_{MAC} = 0.5. In those investigations, the hearts performed mechanical work and were subject to indirect regulatory changes in coronary resistance, which prevented the determination of the anesthetics' *direct* vascular actions.

Sevoflurane is an investigational fluorinated methyl-isopropyl-ether anesthetic that is receiving increased attention due, in part, to its low blood/gas partition coefficient (0.60), lack of pungency, apparent low incidence

* Associate Professor of Anesthesia.

† Research Assistant.

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Address reprint requests to Dr. Larach: Department of Anesthesia, University Hospital, P.O. Box 850, Hershey, Pennsylvania 17033.

of toxicity, and recent approval for clinical use in Japan.[11,12] Preliminary data from our laboratory using the isolated, perfused, *working* rat heart shows that sevoflurane causes myocardial depression and coronary vasodilation.[13] However, the direct vascular effects of sevoflurane on coronary resistance vessels have not been reported previously.

A limitation of our prior study[7] of halothane and isoflurane was the appearance of a small but significant time-dependent decrease in the magnitude of maximal adenosine vasodilation. Because our protocol included an anesthetic washout phase, adenosine was not administered simultaneously with anesthetic, and this time-dependence prohibited us from calculating coronary flow reserve. In the current study, we expanded our prior investigation of direct anesthetic actions on coronary resistance vessels by formally measuring coronary flow reserve and in addition by studying the effects of sevoflurane. We tested the hypothesis that halothane, isoflurane, and sevoflurane each reduce coronary flow reserve equally *via* direct coronary resistance vessel dilation. We found that significant differences exist among these three anesthetics in their direct coronary vasodilating effects and consequently in their influences on coronary flow reserve in the arrested heart.

Materials and Methods

This research was carried out in accordance with the Guide for the Care and Use of Laboratory Animals (as adopted and promulgated by the National Institutes of Health) and with procedures approved by our Institutional Animal Use and Care Committee. Male Sprague-Dawley rats (body weight 381 ± 7 [mean ± standard error of the mean (SEM)], range 264–547 g; Charles River Laboratories) were used for these studies.

The procedures for obtaining and perfusing the rat hearts have been described in detail by us previously.[7] Briefly, rats were killed instantaneously by decapitation in the absence of anesthetic to ensure a valid anesthetic-free control state. For each experiment, four to six hearts were perfused simultaneously in randomly assigned perfusion chambers using a modified Langendorff technique. Initially, a modified Krebs-Henseleit bicarbonate "drip-out" buffer was used, composed of (in millimolar concentrations): NaCl 118, KCl 4.7, EDTA 0.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 3.0, and $NaHCO_3$ 25.0, and heparin sodium 1.0 U · ml^{-1} (porcine); glucose 10.0 mM was added as the only exogenously supplied oxidizable substrate. The buffer was equilibrated with an O_2:CO_2 mixture (95:5% vol/vol) maintained at 37° C and *p*H 7.40. Hearts underwent an initial retrograde aortic perfusion using non-recirculating buffer at a mean pressure of approximately 50–60 mmHg. Coronary flow was allowed to stabilize for 10 min.

After equilibration, recirculating perfusion commenced at a constant pressure (90 mmHg) for the duration of the experimental protocol. The buffer volume for each heart was 15 ml. The recirculating buffer differed from that described above by the addition of 0.1% bovine serum albumin (fraction V, radioimmunoassay grade, U. S. Biochemical, Cleveland, Ohio), insulin (400 $\mu U \cdot ml^{-1}$, bovine), and pyruvate (2 mM), and by the absence of heparin. After stabilization of coronary flow, TTX citrate (Calbiochem) 9.0 $\mu g \cdot ml^{-1}$ (28 μM) was added to each perfusion circuit to induce cardiac arrest. A 20-g apical vent was placed in the left ventricular (LV) cavity to prevent LV distension and to permit identification of aortic valve insufficiency. Constant perfusion pressure was maintained by continually adjusting the rate of buffer flow provided to the coronary circulation of each heart using individual, calibrated occlusive peristaltic pumps (model 7550-60, Cole-Parmer, Chicago, Illinois). Aortic valve competence and aortic integrity were documented in each heart, which ensured accurate coronary flow measurement as described previously.[7]

Volatile anesthetic agents were administered by diversion of the CO_2:O_2 mixture through calibrated vaporizers for halothane and isoflurane (Vapor 19.1, Dräger) or sevoflurane (Sevotec 3, Ohmeda, Madison, WI) proximal to the humidification chambers and glass oxygenators. Gas-phase anesthetic concentrations were monitored in the oxygenator effluent gas using a Raman spectrometer (Rascal®, Ohmeda) specially modified for analysis of sevoflurane.

The efficiency of transfer of each anesthetic from the gas phase to the buffer was quantified using samples of recirculating perfusion buffer and gas chromatography with flame ionization detection (model 5890II, Hewlett-Packard). Both analytical instruments were calibrated using gravimetric standards. We calibrated the gas chromatograph by injecting distilled water samples that had been equilibrated previously at 37° C with gas containing known gas-phase anesthetic concentrations. A standard curve then was constructed using the relationship of chromatographic peak area *versus* gas-phase anesthetic concentration (at 37° C), which was linear. In this manner, the peak area generated by anesthetic dissolved in any buffer sample could be related to the equivalent gas-phase anesthetic concentration.

Preliminary experiments showed that tonometry of anesthetics with recirculating buffer generated peak areas indistinguishable from those obtained with water, over the range studied. The anesthetic concentrations (mean ± SD) that we measured in buffer samples during the heart perfusions were equivalent to 95 ± 4, 96 ± 9, and 87 ± 3% of the concentration measured in the gas phase at the oxygenator outlet for halothane, isoflurane, and sevoflurane, respectively. Thus, the oxygenators displayed high efficiency for transfer of anesthetic into liquid buffer.

There were no significant differences among these anesthetic concentrations ($P = 0.09$). The following values of MAC in the rat for each anesthetic were used: halothane 1.0,[14] isoflurane 1.64 ± 0.02,‡ and sevoflurane 2.4%.[15]

Each heart received only one anesthetic agent at one concentration. Coronary flow was recorded 15 and 30 min after commencing anesthetic administration. At 30 min, in the continued presence of anesthetic, adenosine 5×10^{-5} M was administered to achieve maximal coronary vasodilation. In order to test the hypothesis that this adenosine concentration produces maximal vasodilation, we added additional adenosine to achieve 1×10^{-4} M in each heart and found only a trivial (mean 1.9%) flow increase ($P = 0.30$). Thus, 5×10^{-5} M adenosine produces maximal coronary vasodilation in this preparation. Finally, the hearts were removed from the perfusion apparatus, trimmed of atria and connective tissue, blotted, and weighted. Heart tissue was then dried *in vacuo* at 80° C to a constant weight and reweighed to obtain the "dry" heart weight. The mean dry heart weight was 0.208 ± 0.003 g, which was 17.7 ± 0.1% of the wet weight. Certain hearts were designated *a priori* as control hearts; these were perfused simultaneously in the same manner except that anesthetic was omitted.

In order to investigate a possible effect of the order of administration of adenosine and anesthetic, an additional study ($n = 6$) was performed with adenosine and with isoflurane as a representative anesthetic. In all of these TTX-arrested rat hearts, maximal adenosine vasodilation was induced (5×10^{-5} M and then 10^{-4} M) first without anesthetic. In one half of the hearts (designated the isoflurane group), isoflurane then was administered at $F_{MAC} = 3.0$, and after 15 min of anesthetic wash-in, coronary flow was recorded. The other hearts comprised a simultaneous time-control group, receiving only adenosine.

Data Analysis

Criteria for the exclusion of hearts were developed *a priori:* these were 1) visible air emboli entering perfusion cannula or coronary arteries; 2) lack of decrease in coronary flow after TTX arrest; 3) baseline coronary flow after TTX outside two standard deviations (SD) from the mean flow (49 ± 2 SD yields a range of 8–90 $ml \cdot min^{-1} \cdot g^{-1}$; see ref. 7); or 4) maximal adenosine coronary flow of magnitude less than two times that of the TTX baseline flow. These criteria were devised in response to data obtained in this laboratory during previous studies and are applicable to data from the current investigation (see Discussion). The presence of any one criterion was sufficient to exclude a heart from analysis. According to these criteria, 20 of the 140 hearts (14%) were excluded.

‡ Skeehan TM, Greiner AS, Larach DR: Unpublished data.

The coronary flow reserve was calculated for each heart as the difference between the flow attained after 30 min anesthetic administration alone and the maximal flow induced by adenosine plus anesthetic. In addition, the coronary flow reserve ratio ("relative flow reserve"[8]) was calculated as the ratio of flow with maximal adenosine to flow during anesthetic alone. CVR in $dyn \cdot s \cdot g \cdot cm^{-5}$ was calculated as aortic pressure × (coronary flow/heart weight)$^{-1}$. We believed it reasonable to assume zero coronary back pressure because the LV cavity was drained, the LV wall was flaccid, and the coronary sinus pressure was atmospheric.

Coronary flow reserve data were analyzed using analysis of covariance (ANCOVA) in which the covariates were baseline flow (after TTX arrest but before anesthetic administration), body weight (as an indicator of age, $P = 0.91$ by ANCOVA), anesthetic agent and concentration, and agent–concentration interaction. Therefore, the flow reserve analysis reported below adjusts for the influence of these covariates. Note that data points are independent, since each is derived from one heart. The anesthetic concentrations causing 50% reductions in coronary flow reserve (ED_{50}) were calculated by interpolation or extrapolation using linear regression. The absolute coronary flow data were analyzed by linear regression (excluding control data) and analysis of variance (ANOVA). Flow increments above baseline were compared among groups using ANOVA. *Post hoc* testing and point comparisons were made with the *t* test. Significance was determined at the $\alpha = 0.05$ level. All data are reported as mean ± SEM, unless specified otherwise. All heart weights are dry weights.

Halothane (thymol-free) was a gift from Halocarbon Laboratories, (Hackensack, New Jersey); isoflurane was purchased from Anaquest; and sevoflurane was supplied by Maruishi Pharmaceutical Co., Ltd. (Osaka, Japan). Unless specified, all chemicals were supplied by Fisher, Sigma, or Baker, at the highest available purity. Adenosine and TTX were dissolved in distilled water.

Results

Coronary hemodynamic data were obtained at three times prior to the start of anesthetic administration; these baseline data, pooled from all experimental groups, are presented in table 1. CVR first decreased with institution of recirculating perfusion at the higher pressure ($P < 0.0001$) and then increased after cardiac arrest ($P < 0.0001$).

The derived coronary flow reserve data, all measured at 90 mmHg pressure, are depicted in figure 1 and table 2. Note that coronary flow reserve decreased significantly with each anesthetic as the concentration increased ($P = 0.0001$). However, the three anesthetics produced dif-

TABLE 1. Baseline Coronary Hemodynamic Data

Perfusion Condition	Coronary Perfusion Pressure (mmHg)	Coronary Flow ($ml \cdot min^{-1} \cdot g^{-1}$)	CVR ($dyn \cdot s \cdot g \cdot cm^{-5}$)
Nonrecirculating (beating)	50–60	65 ± 1	115 ± 2*
Recirculating (beating)	90	90 ± 2	86 ± 2*
Recirculating (arrested, vented)	90	48 ± 1	167 ± 6*

CVR = coronary vascular resistance.

* $P < 0.0001$ among perfusion conditions.

ferent quantitative changes in coronary flow reserve ($P < 0.0001$): sevoflurane administration was associated with significantly higher coronary flow reserve values than was halothane or isoflurane. When averaged over all anesthetic concentrations, coronary flow reserve values with sevoflurane were 24.7 ± 4.9 $ml \cdot min^{-1} \cdot g^{-1}$ higher than with halothane ($P = 0.0001$) and 24.9 ± 5.2 $ml \cdot min^{-1} \cdot g^{-1}$ higher than with isoflurane ($P = 0.0002$). In contrast, halothane and isoflurane each caused similar reductions in coronary flow reserve ($P = 0.96$).

At the highest concentration, $F_{MAC} = 3.0$, coronary flow reserve with halothane (7.6 ± 4.5 $ml \cdot min^{-1} \cdot g^{-1}$) was statistically indistinguishable from zero ($P = 0.23$). Similarly, isoflurane at $F_{MAC} = 3.0$ reduced flow reserve to near zero (9.2 ± 2.1, $P = 0.03$). With sevoflurane, however, there was a markedly higher coronary flow reserve at $F_{MAC} = 3.0$ (53 ± 6), which was significantly different from zero ($P = 0.0001$).

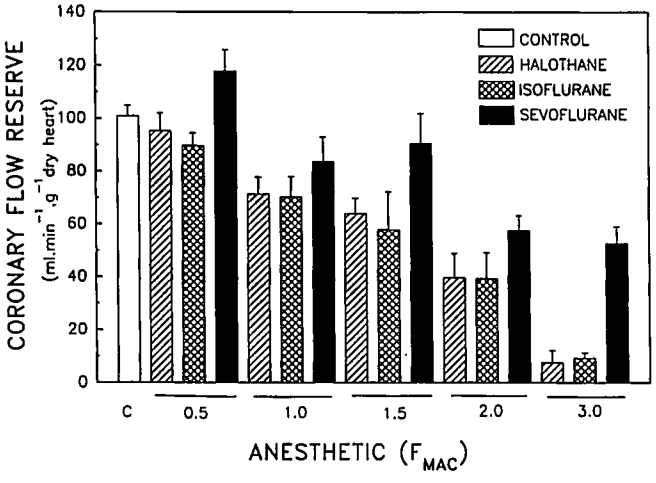

FIG. 1. Effects of anesthetic and anesthetic concentration on coronary flow reserve in the isolated, perfused, arrested, vented rat heart. Coronary perfusion pressure was constant at 90 mmHg during all studies. Control data (C) were obtained in the absence of anesthetic. Coronary flows are reported per gram dry heart weight. F_{MAC} = the fraction of MAC for specified anesthetic. Sevoflurane demonstrates a greater coronary flow reserve at all anesthetic concentrations ($P < 0.0002$), whereas halothane and isoflurane responses were equivalent ($P = 0.96$). Analysis of covariance revealed significant effects of anesthetic concentration ($P = 0.0001$), anesthetic agent ($P = 0.0001$), and baseline coronary flow after arrest ($P < 0.002$) on coronary flow reserve. The apparent difference in flow reserve between sevoflurane $F_{MAC} = 0.5$ and the control group was not significant ($P = 0.07$).

The flow reserve ED_{50} values were 1.74 ± 0.53, 1.70 ± 0.70, and 3.39 ± 1.22 × MAC for halothane, isoflurane, and sevoflurane, respectively (the last value by extrapolation). The differences among these ED_{50} values did not achieve statistical significance ($P > 0.20$), but whereas the halothane and isoflurane data were best fitted by straight lines, the sevoflurane data showed borderline evidence of curvature by polynomial regression ($P = 0.058$).

Table 3 contains selected data using alternative computation techniques in order to permit comparison with the literature. Thus, the coronary flow reserve is also reported as a flow ratio, and CVR values during baseline, anesthetic, and maximal adenosine vasodilation are provided.

We examined the hemodynamic mechanism responsible for anesthetic-induced reduction in coronary flow reserve. Figure 2 shows the absolute coronary flows during the arrested baseline state, during anesthetic, and during maximal vasodilation, each plotted *versus* anesthetic concentration. Linear regression of the baseline flow data revealed slopes that were not significantly different from zero for each anesthetic ($P > 0.40$). Administration of each anesthetic agent resulted in a dose-dependent coronary vasodilator response, as indicated by the increased absolute coronary flows during constant-pressure perfusion (middle curve in each panel of fig. 2). The slopes of the absolute coronary flow data were 37.4 ± 1.1 (halothane), 25.5 ± 1.2 (isoflurane), and 15.2 ± 0.6 (sevoflurane) $ml \cdot min^{-1} \cdot g^{-1} \cdot F_{MAC}^{-1}$; each slope was significantly different from zero ($P < 0.001$).

During maximal adenosine vasodilation, coronary flow averaged 150 ± 2 $ml \cdot min^{-1} \cdot g^{-1}$, and CVR averaged 49.2 ± 0.8 $dyn \cdot s \cdot g \cdot cm^{-5}$ when pooled over all conditions. The slopes of the curves relating maximal vasodilated flow *versus* anesthetic concentration were not significantly different from zero for halothane (3.0 ± 0.6 $ml \cdot min^{-1} \cdot g^{-1} \cdot F_{MAC}^{-1}$; $P = 0.58$) and isoflurane (−7.1 ± 1.0; $P = 0.22$); for sevoflurane, a significant negative slope existed (−7.7 ± 0.6; $P = 0.035$).

The additional adenosine–isoflurane study was performed to determine whether the addition of anesthetic alters the magnitude of adenosine vasodilation. Adding

TABLE 2. Coronary Hemodynamic Data

F_{MAC}	Agent	Anesthetic Concentration (vol %)	n	Flow ($ml \cdot min^{-1} \cdot g^{-1}$)		
				Baseline	During Anesthetic	Reserve
0.0	Control	0.0	19	47 ± 3	47 ± 4	101 ± 4
0.5	Halothane	0.5	5	51 ± 4	62 ± 5	95 ± 7
	Isoflurane	0.8	3	61 ± 5	72 ± 8	90 ± 5
	Sevoflurane	1.2	5	40 ± 8	54 ± 12	118 ± 8
1.0	Halothane	1.0	6	38 ± 4	61 ± 7	71 ± 6
	Isoflurane	1.6	5	49 ± 7	74 ± 11	70 ± 8
	Sevoflurane	2.4	4	55 ± 6	75 ± 8	84 ± 9
1.5	Halothane	1.5	5	52 ± 6	73 ± 4	64 ± 6
	Isoflurane	2.4	7	49 ± 3	104 ± 17	58 ± 14
	Sevoflurane	3.6	5	47 ± 3	78 ± 5	90 ± 11
2.0	Halothane	2.0	8	44 ± 7	108 ± 16	40 ± 9
	Isoflurane	3.2	6	39 ± 4	98 ± 13	39 ± 10
	Sevoflurane	4.8	11	50 ± 4	96 ± 4	57 ± 6
3.0	Halothane	3.0	6	53 ± 3	146 ± 7	8 ± 5
	Isoflurane	4.8	9	60 ± 7	133 ± 10	9 ± 2
	Sevoflurane	7.2	16	42 ± 3	98 ± 5	53 ± 6

Baseline flow data were obtained after inducing cardiac arrest. Data during anesthesia were recorded at steady-state after a 30-min exposure. Flow reserve is the difference between flow during anesthetic and maximal flow induced by adenosine. Weights are dry heart weights. Values are mean ± SEM.

F_{MAC} = fraction of MAC.

isoflurane (F_{MAC} = 3.0) to previously established maximal adenosine vasodilation produced no change in coronary flow. The concurrent time-control group showed a trivial, 0.14% increase in coronary flow ($P > 0.9$) after 15 min, demonstrating that adenosine-induced vasodilation in the presence or absence of added anesthetic was stable.

Further analysis was performed to examine the hypothesis that isoflurane produced higher anesthetic flow values than did the other agents. The anesthetic-induced increment in absolute flow above baseline (the flow increment) was calculated for each heart, and the following significant differences were found. Isoflurane produced a greater flow increment than did halothane or sevoflurane only at F_{MAC} = 1.5 and 3.0 ($P < 0.05$), and halothane induced greater vasodilation than did sevoflurane only at F_{MAC} = 2.0 ($P < 0.05$) and 3.0 ($P < 0.0001$). One heart

TABLE 3. Additional Coronary Hemodynamic Data

F_{MAC}	Agent	Flow Reserve Ratio	CVR ($dyn \cdot s \cdot g \cdot cm^{-5}$)		
			Baseline	During Anesthetic	Adenosine
0.0	Control	3.48 ± 0.27	168 ± 12	176 ± 18	50 ± 2
0.5	Halothane	2.59 ± 0.22	146 ± 12	118 ± 9	46 ± 2
	Isoflurane	2.27 ± 0.07	119 ± 9	103 ± 11	45 ± 3
	Sevoflurane	3.78 ± 0.70	221 ± 50	164 ± 37	42 ± 2
1.0	Halothane	2.29 ± 0.23	203 ± 24	128 ± 18	55 ± 3
	Isoflurane	2.10 ± 0.25	160 ± 25	107 ± 16	50 ± 2
	Sevoflurane	2.13 ± 0.10	135 ± 14	100 ± 12	47 ± 6
1.5	Halothane	1.90 ± 0.12	145 ± 17	99 ± 5	53 ± 1
	Isoflurane	1.74 ± 0.24	150 ± 10	78 ± 10	45 ± 3
	Sevoflurane	2.21 ± 0.21	156 ± 14	94 ± 6	43 ± 2
2.0	Halothane	1.47 ± 0.13	197 ± 32	78 ± 12	52 ± 5
	Isoflurane	1.47 ± 0.13	196 ± 20	78 ± 8	53 ± 3
	Sevoflurane	1.62 ± 0.08	155 ± 14	76 ± 3	47 ± 2
3.0	Halothane	1.06 ± 0.04	140 ± 9	50 ± 2	47 ± 2
	Isoflurane	1.05 ± 0.01	137 ± 18	57 ± 4	54 ± 4
	Sevoflurane	1.60 ± 0.09	191 ± 20	77 ± 4	49 ± 2

Flow reserve ratio is the ratio of maximal adenosine flow to the flow during anesthetic only. Coronary vascular resistance (CVR) data were calculated assuming zero back pressure to coronary flow in the drained arrested hearts. Adenosine CVR was obtained during maximal adenosine vasodilation.

F_{MAC} = fraction of MAC.

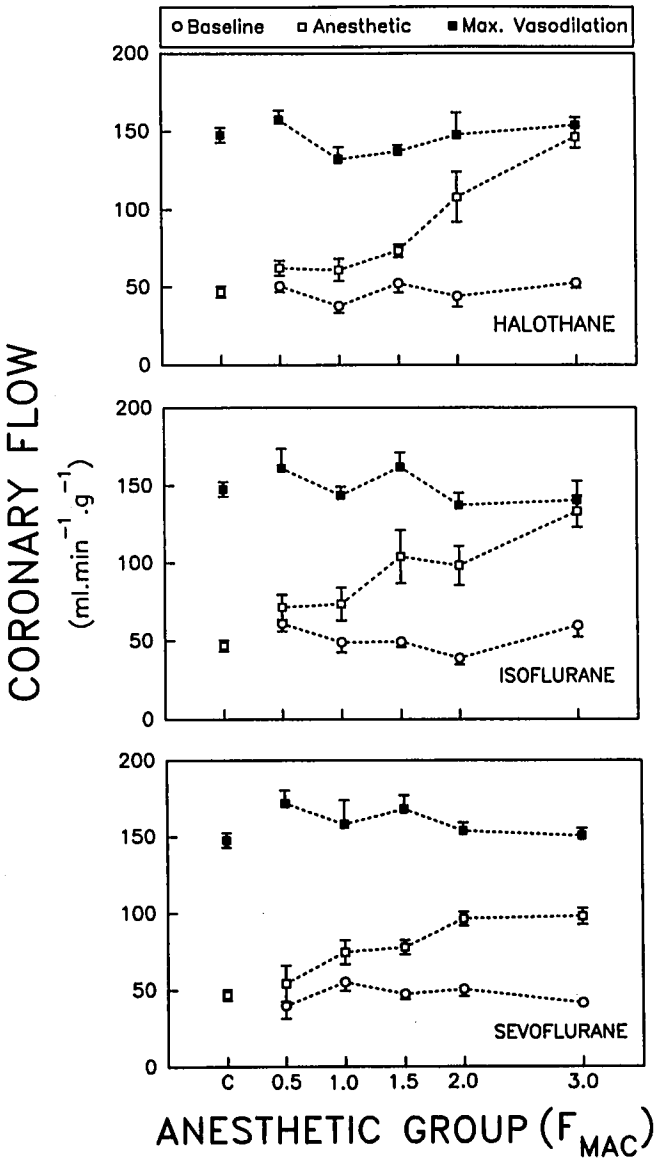

FIG. 2. Absolute coronary flow rates obtained for each anesthetic and concentration group. The data for each group are associated vertically, with the experimental conditions proceeding from bottom to top for each anesthetic. The dashed lines connecting points are provided for clarity; each heart was exposed only to one anesthetic at one concentration. Within each panel, the bottom curve represents baseline flow in the arrested heart without anesthetic. Middle curves are data obtained during anesthetic administration only; top curves are data obtained during simultaneous administration of a maximally vasodilating adenosine concentration and the anesthetic. Coronary flow reserve for each condition is the vertical distance between the middle and top curve. Control group data (C) were obtained in the absence of anesthetic, and the data from this single group are duplicated on each panel for clarity. Coronary flows are reported per gram dry heart weight. F_{MAC} = the fraction of MAC for the specified anesthetic.

in the isoflurane F_{MAC} = 1.5 group was an outlier (flow = 197 ml · min^{-1} · g^{-1}), but it was retained because it did not meet any of the *a priori* exclusion criteria.

Discussion

The primary finding of this study is that sevoflurane, over a range of concentrations, preserved significantly higher levels of coronary flow reserve than did equianesthetic concentrations (F_{MAC}) of halothane or isoflurane (fig. 1). These differences were most pronounced at the highest concentration (F_{MAC} = 3.0), at which halothane and isoflurane reduced coronary flow reserve by 92 and 91%, respectively, whereas sevoflurane lowered flow reserve by only 48%. The hemodynamic explanation for these responses is apparent from figure 2. The coronary flow reserve for a given condition is the vertical distance between the middle and upper coronary flow curves (before and during adenosine) shown in each panel of figure 2. Halothane and isoflurane caused significant and dose-related direct coronary vasodilation that led to a convergence of the anesthetic flow (middle curve) and maximally vasodilated flow (upper curve), because the latter flow was relatively constant. This convergence manifests itself as a marked reduction in coronary flow reserve.

In contrast, coronary flow reserve was higher with sevoflurane than with the other anesthetics due to an apparent limitation (a "plateau") in the absolute coronary flow achievable at F_{MAC} values greater than 1.5. This qualitative difference in coronary flow reserve with sevoflurane occurred despite the small but significant downward slope of the maximal vasodilation curve in the sevoflurane hearts, which would have tended to decrease flow reserve further at higher anesthetic concentrations. This negative slope was explained primarily by the large adenosine flow value during sevoflurane F_{MAC} = 0.5; we believe it was not due to an anesthetic/adenosine interaction because the maximally vasodilated flows at sevoflurane F_{MAC} = 2.0 and 3.0 were very close to the control values (fig. 2). Furthermore, evidence for a lack of direct effect of anesthetic on maximal vasodilator capacity was provided by the additional adenosine–isoflurane experiment. Thus, the anesthetic and maximally vasodilated curves converge less with sevoflurane than with the other anesthetics, explaining the relative preservation of coronary flow reserve with higher doses of sevoflurane.

To examine further whether coronary flow with sevoflurane demonstrates a plateau at higher concentrations, we performed a limited experiment using a toxic, nonclinical dose of anesthetic. With sevoflurane at F_{MAC} = 3.7 (8.9%), we found coronary flow reserve remained substantially greater than zero at 20.1 and 23.9 ml · min^{-1} · g^{-1} (n = 2). Therefore, even at a very high concentration, sevoflurane did not abolish coronary flow reserve. These data at F_{MAC} = 3.7 also indicate that sevoflurane's unique coronary flow responses were not a consequence of the minor and nonsignificant differences in

anesthetic transfer into buffer from the gas ventilating the oxygenators.

Isolation of Direct Coronary Effects

In this study, the indirectly mediated components of coronary tone were dissociated from the direct pharmacologic actions of the anesthetics on the coronary circulation. We have shown previously that the isolated arrested rat heart with controlled hemodynamic conditions is an appropriate model system for determining the direct coronary resistance vessel actions of drugs possessing negative myocardial inotropic activity.[7] In this preparation, $M\dot{V}O_2$ is reduced to the basal levels of the quiescent heart, as shown by the lack of a further decrease in $M\dot{V}O_2$ during the administration of negative inotropic anesthetics. Because the indirect modulators of coronary tone are kept constant, we infer that the changes we observed in coronary flow are due primarily to the direct anesthetic action on coronary resistance vessels. Our prior study documents that the direct anesthetic vasodilator responses are stable and fully reversible. However, those data do not define the capacity of the vascular bed for further vasodilation in the presence of anesthetic, which prompted performance of the current investigation.

Critique of Methods

The isolated perfused heart preparation that we used has many advantages and several limitations, which have been reviewed recently.[7,16] To induce cardiac arrest, we used the Na^+-channel blocker TTX for its inhibitory action on cardiomyocytes, which cause reductions in both the metabolic demand of the myocardial contractile apparatus and in the adenosine triphosphate utilization required to maintain the appropriate cyclical ion gradients within cellular compartments. Interpretation of our results depends upon a lack of effect by TTX on vascular smooth muscle, and there is considerable support for this assertion, as described in reference 7. In addition, recently we have shown that TTX (28 μM) does not alter the vasoconstrictor dose responses either of isolated porcine coronary artery segments to prostaglandin $F_{2\alpha}$ or of rat aortic segments to phenylephrine.§ Obviously, our findings in rat heart cannot be extrapolated directly to the clinical situation, due to species differences and the artificial nature of the preparation. However, this methodology permitted us to achieve the mechanistically important isolation of direct from indirect anesthetic vasomotor effects. CVR did change with institution of recirculating perfusion and cardiac arrest (table 1), as expected from the elevation in perfusion pressure and the consequent alterations in $M\dot{V}O_2$.[17] This indicates preservation of flow–metabolism coupling in the hearts.

The study's exclusion criteria were chosen *a priori* to help ensure that only viable hearts were analyzed. Each criterion has a physiologic basis. Thus, with intact coronary flow–metabolism coupling, decreased $M\dot{V}O_2$ occurring with arrest should lead to decreased coronary flow (table 1). Also, inability of the heart to double its baseline arrested flow with TTX may imply impaired maximal vasodilation due to loss of total vascular cross-sectional area. Finally, we believe it is reasonable to compare baseline arrested coronary flow values with the prior values established in this laboratory, because low flows can be caused by visually unapparent air or by particulate embolization, and because high flows can be caused by small aortic leaks. Use of those historic data to exclude outliers induced negligible error; analysis of *all* hearts studied in this series demonstrated a mean baseline arrested flow of 52 ± 2 ($n = 140$), which is nearly identical to the 49 ± 3 reported previously.[7]

Coronary Flow Reserve

The nonworking heart possesses a relatively high degree of intrinsic vascular tone associated with its low nutrient requirements. Normally, increases in O_2 demand are linked closely with an increase in coronary flow through autoregulatory processes intrinsic to the myocardium and coronary vessels.[2,17] A useful measure of the heart's vasodilator capacity is the coronary flow reserve, defined as the increment in coronary flow induced by a maximal vasodilator stimulus. Various factors can decrease the magnitude of coronary flow reserve and thereby reduce the ability of intrinsic regulatory processes to appropriately distribute flow to the myocardial regions having the greatest nutrient demand (see below). As coronary flow reserve is exhausted regionally, with further flow increases rendered impossible, the heart's vulnerability to myocardial ischemia in response to stress increases.

Pharmacologic interference with autoregulation by direct vasodilation of resistance vessels can reduce coronary flow reserve by raising baseline flow toward maximal flow rates. Examples of deleterious consequences of resistance-vessel vasodilation are coronary steal[18] and passive narrowing of a compliant arterial stenosis due to reduced transmural pressure.[19] Additional factors that can diminish flow reserve include coronary stenosis, reduced coronary perfusion pressure, myocardial hypertrophy, tachycardia, increased inotropism, elevated diastolic ventricular wall stress, decreased perfusate O_2 or substrate content, and hyperviscosity.[8] Because in this study we sought to directly quantify anesthetic actions on resistance vessels, we attempted to eliminate the influences of these

§ Larach DR: Unpublished data.

factors by using healthy young-adult rats and by perfusing arrested hearts under constant hemodynamic conditions (*i.e.*, constant perfusion pressure, inotropic state, and preload) using a uniform buffer composition. The effects of halothane, enflurane, and isoflurane on coronary flow reserve in the *in vivo* working hearts of the dog and pig have been reported previously.[9,10,20] However, the concurrent indirect effects of the anesthetics on coronary autoregulatory function in those experiments did not allow the separation of the agents' direct and indirect coronary actions. In a preliminary report using the isolated perfused beating rat heart, halothane, enflurane, and isoflurane caused submaximal vasodilation that suggested preservation of some coronary flow reserve.[21]

Various methods have been used to induce maximal coronary vasodilation. "Endogenous" flow reserve can be measured using the reactive hyperemic flow that follows transient myocardial ischemia, whereas "pharmacologic" flow reserve is determined by administering a potent vasodilator such as adenosine.[2,22] It has been known for some time that maximal global coronary flows obtained by pharmacologic means with adenosine tend to exceed those obtained endogenously with ischemia.[23] Recently, analysis of the spatial distribution of coronary flow during autoregulated and maximally vasodilated conditions with and without ischemia has shown, within small myocardial regions, that adenosine administration generally does not increase flow further in ischemic zones.[22] The increased global tissue flow produced by adenosine may be a response generated in less ischemic areas that still possess flow reserve. Thus, exogenous adenosine appears to be an appropriate means of inducing maximal coronary vasodilation that is at least as effective as ischemia. These reports indicate that the determination of pharmacologic flow reserve with adenosine, as in our study, is a technique that may have relevance to the endogenous conditions that result in coronary vasodilation during ischemia.

In our study, two types of hemodynamic changes could have reduced coronary flow reserve: 1) a decrease in the maximal vasodilating potential of the coronary resistance vessels or 2) a drug-induced elevation in flow prior to eliciting maximal vasodilation.[8] The first mechanism implies a reduction in total recruitable resistance-vessel cross-sectional area per unit cardiac mass and occurs with cardiac hypertrophy.[24] The relative constancy of maximal adenosine coronary flow that we observed in the presence or absence of anesthetic and the lack of influence of the order of adenosine and anesthetic administration suggest that the second hemodynamic mechanism listed above is responsible for the reduction in coronary flow reserve with all three anesthetics. Our data also agree with the data of Hickey *et al.*[9] in the dog showing that anesthetics do not alter maximal coronary flows induced by adenosine. Also, the current investigation confirms our earlier finding that these two anesthetics are equipotent in their *direct* vasodilating action.[7]

Sevoflurane and Coronary Hemodynamics

Few studies have examined the coronary hemodynamics of sevoflurane. Manohar and Parks,[25] in chronically instrumented pigs, found that sevoflurane significantly lowered blood pressure and that myocardial blood flow decreased in a dose-dependent manner in proportion to the reduction in rate–pressure product. Bernard *et al.*[26] examined sevoflurane's systemic and coronary hemodynamic actions in chronically instrumented dogs with an awake baseline state. They found that sevoflurane caused hemodynamic changes similar to isoflurane, including systemic vasodilation and myocardial contractile depression, although sevoflurane at F_{MAC} = 1.2 produced greater tachycardia than did isoflurane. Their data showed a linear decrease in CVR with isoflurane; in contrast, sevoflurane's dose–response curve for CVR demonstrates a plateau, with no change in CVR between the low and high doses (F_{MAC} = 1.2 and 2.0).

Our sevoflurane and isoflurane data in the perfused arrested rat heart (fig. 2 and tables 2 and 3) demonstrate anesthetic-induced direct coronary vasodilation and agree with the findings of Bernard *et al.*[26] in the working dog heart *in vivo*. Both their and our studies suggest the presence of a plateau in the sevoflurane dose–response curve for CVR. However, it is not possible to deduce the direct *versus* the indirect actions of this anesthetic on coronary resistance vessels from either of the two prior coronary hemodynamic studies,[25,26] because of differences in coronary perfusion pressure, myocardial contractility, and heart rate among these studies' experimental conditions. Indeed, the reported rate–pressure product values imply that $M\dot{V}O_2$ did decrease as the sevoflurane dose increased. This effect would invoke indirect coronary vasoconstriction that could obscure direct vasomotion induced by the anesthetic.

Prior Studies of Halothane, Isoflurane and Coronary Hemodynamics

Isolated preparations

Several studies in large epicardial coronary artery segments *in vitro* show that halothane and isoflurane each can cause vascular relaxation.[27,28] Two studies that analyzed equianesthetic concentrations revealed that halothane is a more potent vasodilator than is isoflurane in porcine[29] and canine[30] large coronary arteries.

Large coronary arteries perform primarily a conduit function, and their responses to anesthetics do not necessarily reflect the reactions either of smaller arteries[30]

or of resistance vessels.[31] There are only limited data concerning volatile anesthetic actions on coronary resistance vessels in the isolated heart (see ref. 7 for a review). In the rat, Sahlman *et al.*[4] demonstrated that CVR was increased significantly with halothane but was minimally decreased with isoflurane in the isolated perfused working rat heart. They observed that halothane increased CVR in association with a large decrement in $M\dot{V}O_2$, whereas isoflurane significantly reduced stroke volume (and presumably, stroke work), but did not change either CVR or $M\dot{V}O_2$. It is not clear why the rats in those investigators' isoflurane group demonstrated a significant reduction in stroke volume at constant preload, afterload, and heart rate, without a comparable decrease in $M\dot{V}O_2$. These data of Sahlman *et al.*[4] suggest, in the working heart, that the negative inotropic actions of anesthetics invoke an indirect coronary vasoconstriction in proportion to the degree of alteration in myocardial work. Our findings in the arrested heart are compatible with those of Sahlman *et al.* by considering that metabolic vasoconstriction in the working heart masks the anesthetics' direct vasodilating action on coronary resistance vessels. Cronau *et al.*[32] also studied the isolated perfused working rat heart; they found that halothane decreased CVR and reduced O_2 extraction. It is possible that the CVR data of Cronau *et al.* differ from those of Sahlman *et al.*[4] with halothane because of the reduced perfusion pressure during anesthetic in the former study.

In vivo *Preparations*

Many investigators have examined the actions of halogenated anesthetics on coronary flow using *in vivo* preparations, in which important determinants of myocardial metabolism and coronary flow have been controlled to variable degrees, and in the presence or absence of coronary artery disease, according to the specific aims of each study. Generally, in humans halothane causes little change in CVR,[33,34] whereas isoflurane can reduce CVR,[34,35] sometimes associated with ischemia.[36]

In the dog, halothane has been reported to cause either no change in CVR[6,18,37-39] or a net vasoconstriction response.[40] In contrast, isoflurane has produced no change in CVR[6,41,42] or a vasodilator response.[18,31,39,43] Only a few studies were designed to compare equianesthetic concentrations of halothane and isoflurane in the dog without background anesthesia: Gelman *et al.*[40] found a significant difference between anesthetics at $F_{MAC} = 2$, with halothane decreasing coronary flow and isoflurane increasing it; Hickey *et al.*[9] showed that halothane ($F_{MAC} = 1$) significantly increased CVR but that isoflurane caused a nonsignificant decrease in CVR.

Administration of halothane to the pig is reported to generate an increase in CVR[44] and a decrease in coronary flow reserve.[10] In contrast, isoflurane produces no change in either CVR[45] or coronary flow reserve.[10] Using the isolated rabbit heart perfused at constant pressure, Kaukinen[46] found that halothane did not alter CVR.

It is apparent that there are qualitative differences in the effects of halothane and isoflurane on CVR among several species during *in vivo* studies. Thus, halothane usually causes either net vasoconstriction or no CVR change, and isoflurane characteristically produces either net vasodilation or no change in CVR. It is difficult to make conclusions regarding specific anesthetic responses in a given species, however, because of the substantial differences in the preparations and protocols. Important methodologic factors that vary among studies include: the use of a background anesthetic or an awake control group; maintenance of constant coronary perfusion pressure, heart rate, and preload; variations in autonomic activation and the inotropic state; and the presence of coronary artery stenoses with variable collateral circulation. Each factor can substantially affect the coronary vascular responses of anesthetics and should be taken into account when future studies are designed. Use of the isolated perfused heart preparation can be beneficial for such studies, by permitting the careful control of these variables.

Significance

Our data demonstrate that the halogenated anesthetics tested generate distinct direct vasodilation responses in coronary resistance vessels. The direct coronary vascular actions of the three anesthetics reduced coronary flow reserve, with a rank order of potency of halothane $\approx$ isoflurane $>>$ sevoflurane, when doses are expressed in multiples of MAC. The hemodynamic change responsible for the reduction in coronary flow reserve, in each case, was primarily an anesthetic-induced coronary resistance vessel vasodilation rather than a reduction in maximal adenosine coronary vasodilation. Our data help to define the pharmacologic actions of anesthetics directly on the coronary microcirculation and will be important in efforts to understand the mechanisms of anesthetic action on vascular tissue. Obviously, species differences in coronary vascular regulation may exist, and the data from our rat study should be extrapolated to other species with caution.

The higher incidence of myocardial ischemia with isoflurane than with halothane reported in some studies is difficult to reconcile with our data, which show that halothane and isoflurane have similar flow reserves. Potential explanations include: the more pronounced depression of myocardial function and $M\dot{V}O_2$ with halothane compared with isoflurane; the overriding of the anesthetics' direct coronary actions by the various *indirect* determinants of CVR in the working heart; or species differences in coronary vascular responses among the different stud-

ies. It is possible that the greater preservation of coronary flow reserve by sevoflurane may reduce its potential for inducing myocardial ischemia by coronary steal or other mechanisms; however, this hypothesis will require formal testing.

Future studies should be directed to determining why anesthetics appear to exert different actions on coronary resistance vessels in the arrested and working heart 1) by examining these effects under controlled conditions of mechanical work in which both direct vasodilation and indirect vasoregulatory processes are present and 2) by examining multiple perfusion pressures. The observed differences in the absolute coronary flow *versus* anesthetic concentration curves for sevoflurane, compared with halothane and isoflurane, suggest that sevoflurane may possess a distinct vasodilation mechanism. Further research is needed to define the cellular mechanisms responsible for the microcirculatory actions of the individual volatile anesthetics.

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References

1. Merin RG, Verdouw PD, de Jong JW: Dose-dependent depression of cardiac function and metabolism by halothane in swine (*Sus scrofa*). ANESTHESIOLOGY 46:417–423, 1977
2. Dole WP: Autoregulation of the coronary circulation. Prog Cardiovasc Dis 29:293–323, 1987
3. Hoffman JIE, Spaan JAE: Pressure-flow relations in coronary circulation. Physiol Rev 70:331–390, 1990
4. Sahlman L, Henriksson BÅ, Martner J, Ricksten SE: Effects of halothane, enflurane, and isoflurane on coronary vascular tone, myocardial performance, and oxygen consumption during controlled changes in aortic and left atrial pressure: Studies on isolated working rat hearts *in vitro*. ANESTHESIOLOGY 69:1–10, 1988
5. Becker LC: Is isoflurane dangerous for the patient with coronary artery disease? (editorial). ANESTHESIOLOGY 66:259–261, 1987
6. Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF: Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: Their capacity to induce coronary steal. ANESTHESIOLOGY 67:665–675, 1987
7. Larach DR, Schuler HG, Skeehan TM, Peterson CJ: Direct effects of myocardial depressant drugs on coronary vascular tone: Anesthetic vasodilation by halothane and isoflurane. J Pharmacol Exp Ther 254:58–64, 1990
8. Hoffman JIE: Maximal coronary flow and the concept of coronary vascular reserve. Circulation 70:153–158, 1984
9. Hickey RF, Sybert PE, Verrier ED, Cason BA: Effects of halothane, enflurane, and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. ANESTHESIOLOGY 68:21–30, 1988
10. Gilbert M, Roberts SL, Mori M, Blomberg R, Tinker JH: Comparative coronary vascular reactivity and hemodynamics during halothane and isoflurane anesthesia in swine. ANESTHESIOLOGY 68:243–253, 1988
11. Wallin RF, Regan BM, Napoli MD, Stern IJ: Sevoflurane: A new inhalational anesthetic agent. Anesth Analg 54:758–766, 1975
12. Jones RM: Desflurane and sevoflurane: Inhalation anaesthetics for this decade. Br J Anaesth 65:527–536, 1990
13. Skeehan TM, Schuler HG, Riley J, Larach DR: Sevoflurane produces modest depression of the isolated perfused working rat heart (abstract). FASEB J 4:A321, 1990
14. Larach DR, Schuler HG, Skeehan TM, Derr JA: Mass spectrometry for monitoring respiratory and anesthetic gas waveforms in rats. J Appl Physiol 65:955–963, 1988
15. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI: Renal effects and metabolism of sevoflurane in Fischer 344 rats. ANESTHESIOLOGY 43:70–77, 1975
16. Jennings RB, Morgan HE: Strategy of experimental design in metabolic experiments, The Heart and Cardiovascular System: Scientific Foundations. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven Press, 1986, pp 130–132
17. Feigl EO: Coronary physiology. Physiol Rev 63:1–205, 1983
18. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH: Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. ANESTHESIOLOGY 66:280–292, 1987
19. Schwartz JS, Bache RJ: Pharmacologic vasodilators in the coronary circulation. Circulation 75(Suppl I):I-162–I-167, 1987
20. Verrier ED, Edelist G, Consigny PM, Robinson S, Hoffman JIE: Greater coronary vascular reserve in dogs anesthetized with halothane. ANESTHESIOLOGY 53:445–459, 1980
21. Villeneuve E, Blaise GA, Vinay P, Hollmann C, Meloche R: Persistance of coronary flow reserve with volatile anesthetics (abstract). FASEB J 3:A896, 1989
22. Coggins DL, Flynn AE, Austin RE, Aldea GS, Muehrcke D, Goto M, Hoffman JIE: Nonuniform loss of regional flow reserve during myocardial ischemia in dogs. Circ Res 67:253–264, 1990
23. Warltier DC, Gross GJ, Brooks HL: Pharmacologic- vs. ischemia-induced coronary artery vasodilation. Am J Physiol 240:H767–H774, 1981
24. Tomanek RJ: Response of the coronary vasculature to myocardial hypertrophy. J Am Coll Cardiol 15:528–533, 1990
25. Manohar M, Parks CM: Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anesthesia without and with 50% nitrous oxide. J Pharmacol Exp Ther 231:640–648, 1984
26. Bernard J-M, Wouters PF, Doursout M-F, Florence B, Chelly JE, Merin RG: Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. ANESTHESIOLOGY 72:659–662, 1990
27. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM: Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. ANESTHESIOLOGY 67: 513–517, 1987
28. Blaise GA, Hughes JM, Sill JC, Buluran JN, Caille G: Attenuation of contraction of isolated canine coronary arteries by enflurane and halothane. Can J Anaesth 38:111–115, 1991
29. Bollen BA, Tinker JH, Hermsmeyer K: Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. ANESTHESIOLOGY 66:748–752, 1987
30. Hatano Y, Nakamura K, Yakushiji T, Nishiwada M, Mori K:

Comparison of the direct effects of halothane and isoflurane on large and small coronary arteries isolated from dogs. ANESTHESIOLOGY 73:513–517, 1990

31. Sill JC, Bove AA, Nugent M, Blaise GA, Dewey JD, Grabau C: Effects of isoflurane on coronary arteries and coronary arterioles in the intact dog. ANESTHESIOLOGY 66:273–279, 1987
32. Cronau LH, Merin RG, de Jong JW: Effect of halothane on glucose metabolism in the perfused working rat heart. J Cardiovasc Pharmacol 12:116–121, 1988
33. Sonntag H, Merin RG, Donath U, Radke J, Schenk H-D: Myocardial metabolism and oxygenation in man awake and during halothane anesthesia. ANESTHESIOLOGY 51:204–210, 1979
34. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D: Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 67:936–942, 1988
35. Reiz S, Bålfors E, Sørensen MB, Ariola S, Friedman A, Truedsson H: Isoflurane: A powerful coronary vasodilator in patients with coronary artery disease. ANESTHESIOLOGY 59:91–97, 1983
36. Priebe H-J: Isoflurane and coronary hemodynamics. ANESTHESIOLOGY 71:960–976, 1989
37. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. Circ Res 34:155–167, 1974
38. Merin RG, Kumazawa T, Luka N: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. ANESTHESIOLOGY 44:402–415, 1976
39. Priebe H-J: Isoflurane causes more severe regional myocardial dysfunction than halothane in dogs with a critical coronary artery stenosis. ANESTHESIOLOGY 69:72–83, 1988
40. Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 63:557–565, 1984
41. Merin RG: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? ANESTHESIOLOGY 55:398–408, 1981
42. Hartman JC, Kampine JP, Schmeling WT, Warltier DC: Alterations in collateral blood flow produced by isoflurane in a chronically instrumented canine model of multivessel coronary artery disease. ANESTHESIOLOGY 74:120–133, 1991
43. Conzen PF, Hobbhahn J, Goetz AE, Gonschior P, Seidl G, Peter K, Brendel W: Regional blood flow and tissue oxygen pressures of the collateral-dependent myocardium during isoflurane anesthesia in dogs. ANESTHESIOLOGY 70:442–452, 1989
44. Manohar M, Parks CM: Porcine regional brain and myocardial blood flows during halothane-O_2 and halothane-nitrous oxide anesthesia: Comparisons with equipotent isoflurane anesthesia. Am J Vet Res 45:465–473, 1984
45. Lundeen G, Manohar M, Parks CM: Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide. Anesth Analg 62:499–512, 1983
46. Kaukinen S: The combined effects of antihypertensive drugs and anaesthetics (halothane and ketamine) on the isolated heart. Acta Anaesthesiol Scand 22:649–657, 1978