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Coronary Vasodilation by Isoflurane

Abrupt Versus *Gradual Administration*

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Background: **Under certain circumstances, isoflurane is associated with coronary artery vasodilation. The objective of the current study was to ascertain whether the rate of administration of isoflurane influences its vasodilating effect in the coronary circulation.**

Methods: **Seven open-chest dogs anesthetized with fentanyl and midazolam were studied. The left anterior descending coronary artery was perfused *via* either of two pressurized (80 mmHg) reservoirs; reservoir 1 (control) was supplied with arterial blood free of isoflurane, and reservoir 2 was supplied with blood from an extracorporeal oxygenator, which was provided with 95% O_2/5% CO_2 gas that passed through calibrated vaporizer. Coronary blood flow (CBF) was measured with Doppler flow transducer. In each dog, isoflurane was administered according to two protocols; abrupt (isoflurane-A) or gradual (isoflurane-G). In isoflurane-A, the left anterior descending coronary artery was switched from reservoir 1 to reservoir 2 after the latter was filled with blood previously equilibrated with 1.4% (1 MAC) isoflurane. In isoflurane-G, the left anterior descending coronary artery was switched to reservoir 2 with vaporizer set at 0% isoflurane; then the vaporizer was adjusted to 1.4% isoflurane, which produced a gradual increase in isoflurane concentration within reservoir 2 that reached a level equivalent to that in isoflurane-A (as evaluated by gas chromatography) by 30 min. CBF during maximally dilating, intracoronary infusion of adenosine served as a reference to assess effects of isoflurane.**

Results: **Isoflurane-A caused marked increases in CBF, which at constant perfusion pressure, reflected pronounced reductions in vascular resistance. These increases in CBF were 80% of those with adenosine. Although isoflurane-G also caused increases in CBF, the increases were only 45% of those caused by isoflurane-A.**

Conclusions: **The current findings demonstrate that the extent of coronary vasodilation by isoflurane was not dependent only on its blood concentration but also on the rate at which this blood concentration was achieved; a gradual increase in blood concentration blunted the vasodilator effect. Differences in the rate of administration of isoflurane likely contributed to its widely variable coronary vasodilating effects in previous studies. (Key words: Anesthetics, volatile: isoflurane. Heart: coronary blood flow; myocardial contractility; myocardial oxygen consumption.)**

ALTHOUGH studies conducted in both humans and experimental animals have agreed that inhaled isoflurane has a coronary vasodilating effect, the potency of this effect has shown wide variation.[1–5] For example, Abdel-Latif *et al.*[1] found that coronary blood flow (CBF) remained nearly proportional to myocardial oxygen demand during inhalation of isoflurane (as evidenced by a small 13% increase in coronary sinus oxygen saturation), implying a weak vasodilator effect. On the other hand, Hickey *et al.*[2] found that CBF significantly increased relative to myocardial oxygen demand during inhalation of isoflurane (as evidenced by a pronounced 156% increase in coronary sinus oxygen saturation), implying a potent vasodilator effect. Much of the variation in the coronary vasodilating effect of inhaled isoflurane has been attributed to the systemic hemodynamic changes accompanying inhalation of isoflurane, *e.g.*, aortic hypotension, which themselves have been demonstrated to have profound influence on myocardial oxygen demand and CBF.[6]

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To evaluate the direct coronary vasomotor effects of isoflurane without the complication of unstable hemodynamic conditions, Crystal *et al.*[7] used an extracorporeal system equipped with an oxygenator to perfuse selectively the left anterior descending coronary artery (LAD) of *in situ* canine hearts with arterial blood previously equilibrated with isoflurane. The results of this study demonstrated that isoflurane was a potent, concentration-dependent coronary vasodilator; blood equilibrated with 2% isoflurane was capable of increasing CBF to approximately 80% of the maximal adenosine-induced response. In a more recent study, Hickey *et al.*[8] used the same basic model as Crystal *et al.* to investigate the effects of selective intracoronary isoflurane on CBF in *in situ* swine hearts. Hickey *et al.* also demonstrated that isoflurane was a concentration-dependent coronary vasodilator; however, they showed that the vasodilator potency of isoflurane was much less than that reported by Crystal *et al.* Although the use of a different species (swine *vs.* dog) may have contributed to the much attenuated isoflurane-induced coronary vasodilation in the study of Hickey *et al.*, a more likely factor was the use of a different method of administration of isoflurane, which resulted in a gradual increase in isoflurane concentration within the coronary artery. Recent findings from Kenny *et al.*[3] and Crystal *et al.*[9] have demonstrated that the coronary circulation adapts to the vasodilator effects of isoflurane over time. If this mechanism were operating during the period that isoflurane concentration was increasing gradually in the coronary blood, it could explain the blunted coronary vasodilation observed in the steady-state by Hickey *et al.*

The current study tested the hypothesis that the direct coronary vasodilator effect of isoflurane is not a simple function of its blood concentration but is also dependent on the rate with which this blood concentration is achieved. A model of regional coronary perfusion was used to compare coronary vasodilation during an abrupt and gradual administration of isoflurane in the same *in situ* canine hearts.

Methods

Canine Preparation

The study was conducted in compliance with the Institutional Animal Research Committee. Experiments were performed on seven conditioned, healthy mongrel dogs of either sex (weight, range 20.5–25.0 kg). Anesthesia was induced with intravenous bolus injection of thiopental 15 $mg \cdot kg^{-1}$. Anesthesia was maintained by continuous intravenous infusion of fentanyl and midazolam at rates of 12 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 0.6 $mg \cdot kg^{-1} \cdot h^{-1}$, respectively. Adequacy of this anesthesia regimen was demonstrated by lack of muscle movement and hemodynamic responses during surgical preparation. After tracheal intubation and left thoracotomy in the fourth intercostal space, the lungs were mechanically ventilated (Air Shields, Hatboro, PA) with an inspired oxygen fraction equal to 1.0. The volume and rate of the ventilator were established to maintain arterial P_{CO_2} at physiologic levels. P_{O_2}, P_{CO_2}, and *p*H of arterial blood samples as well as coronary perfusate and venous samples (see below) were measured electrometrically (model 413, Instrumentation Laboratories, Lexington, MS). After surgical preparation, 0.1 $mg \cdot kg^{-1}$ vecuronium bromide, with supplements at 0.05 $mg \cdot kg^{-1} \cdot h^{-1}$, was administered to facilitate mechanical ventilation. Body temperature was maintained at 38°C with a heating pad. Lactated Ringer's solution was administered continuously at a rate of 5 $ml \cdot kg^{-1} \cdot h^{-1}$ intravenously to compensate for evaporative fluid losses. Heparin (400 $U \cdot kg^{-1}$ with supplementation) was used for anticoagulation.

The LAD was perfused *via* an extracorporeal system at 80 mmHg. This system was identical to that used in our previous studies,[7] except that a membrane oxygenator rather than a bubble oxygenator was used. In brief, a thin-wall stainless-steel cannula (2.5 mm ID) was introduced into the LAD just distal to its first major diagonal branch. This cannula was connected with tubing to two pressurized reservoirs, which served as alternate sources of blood for the LAD. Reservoir 1 was supplied with isoflurane-free blood withdrawn directly from the left femoral artery. Reservoir 2 was supplied with blood from the right femoral artery that was pumped through a new hollow-fiber membrane oxygenator (Capiox 300 series, Terumo, Tokyo, Japan) supplied with a 95% O_2/5% CO_2 gas mixture, which passed through a calibrated Fortec vaporizer (Cyprane, Yorkshire, UK) providing 1.4% (1 MAC) isoflurane.

The LAD perfusion tubing was equipped with (1) a heat exchanger to maintain the temperature of the coronary perfusate at 38°C, (2) a Doppler flow transducer (Transonic System, Ithaca, NY) to measure CBF, (3) ports for collecting samples of coronary perfusate, and (4) a mixing chamber for drugs infused into the LAD perfusion tubing. Coronary perfusion pressure was

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monitored through a small-diameter tube positioned at the orifice of the perfusion cannula.

Measurements of arterial pressure, left atrial pressure, left ventricular pressure, left ventricular dP/dt max, and heart rate were obtained using standard methods.[7] A continuous record of these variables and CBF was obtained on an eight-channel physiologic recorder (model 2800S, Gould, Cleveland, OH).

Experimental Measurements

Myocardial Oxygen Consumption. To distinguish direct vascular effects of isoflurane from those secondary to changes in oxygen demand, measurements of myocardial oxygen consumption (MV_{O_2}) were obtained in the LAD-perfusion territory. The anterior interventricular vein was cannulated to obtain samples of venous effluent from the LAD-perfused myocardium.[7] The venous cannula was allowed to drain freely into a beaker to prevent venous stagnation and interstitial edema. This venous blood was returned intermittently to the dog to maintain isovolumic conditions. At specified times in the study, 1-ml blood samples were collected from the coronary venous cannula under mineral oil to maintain anaerobic conditions. These venous blood samples were paired with 1-ml arterial blood samples obtained from the LAD perfusion tubing, so that the arteriovenous oxygen difference for oxygen could be determined. Hemoglobin concentration and percent hemoglobin oxygen saturation of the coronary blood samples was measured with a CO-Oximeter (model 482, Instrumentation Laboratories, Lexington, MS) and used to calculate oxygen bound to hemoglobin assuming an oxygen carrying capacity for hemoglobin of 1.39 ml $O_2 \cdot g^{-1}$.[10] The oxygen dissolved in the blood was computed (O_2 dissolved = 0.003 ml $O_2 \cdot 100$ ml $blood^{-1} \cdot mmHg^{-1}$) and added to the bound component to compute total oxygen content. MV_{O_2} was computed from the product of the coronary arteriovenous oxygen difference and CBF at the time that blood samples were obtained.

Blood Isoflurane Concentration. Isoflurane concentration in samples of coronary perfusate was determined using a modification of the equilibration method described in detail by Yamamura *et al.*[11] Briefly, 2-ml samples of arterial blood were obtained from the LAD perfusion tubing using an air-tight glass syringe and introduced into a 5-ml glass vial. The vial was placed in a constant-temperature chamber at 38°C for 30 min. After equilibration, 100 μl of the gas in the vial was introduced into a gas chromatograph (model 5890, Hewlett Packard) equipped with a flame ionization detector, and the area under the curve was measured. Anesthetic concentration in blood was determined by means of a calibration curve derived from appropriate standards. All analyses were performed in triplicate and mean values calculated.

Experimental Protocol

After cannulation, the LAD was allowed to recover for at least 45 min before measurements of CBF and MV_{O_2} were obtained. In each dog, isoflurane was administered according to two protocols; abrupt (isoflurane-A) or gradual (isoflurane-G). In isoflurane-A, the LAD was switched from reservoir 1 to reservoir 2 after the latter was filled with blood previously equilibrated with isoflurane. The blood was recirculated at least three times through the oxygenator to ensure complete equilibration at the desired isoflurane concentration. Measurements of CBF and associated parameters (including coronary arterial isoflurane concentration) were obtained at the peak vasodilator effect, which occurred 5–10 min after switching reservoirs. The LAD was returned to reservoir 1, and at least 45 min were allowed for recovery before a second set of control measurements was obtained. (During this period, blood in reservoir 2 was recirculated at least three times through the oxygenator with the vaporizer set at 0% isoflurane to remove isoflurane from this limb of the circuit.) The LAD was switched to reservoir 2, and a third set of control measurements was obtained. By comparing the second and third control measurements for CBF, it was possible to evaluate whether the membrane oxygenator *per se* released vasoactive substances into the LAD blood supply. The vaporizer setting was adjusted from 0% to 1.4% isoflurane, which produced a gradual increase in isoflurane concentration within reservoir 2 and LAD inflow tubing over 30 min (fig. 1). Preliminary studies demonstrated that a single pass of blood through the membrane oxygenator could not produce complete equilibration; thus, a partial recirculation of the outflow from reservoir 2 was initiated after 15 min of isoflurane-G to ensure that isoflurane concentration in the coronary blood perfusate reached a level equivalent to that in isoflurane-A (as evaluated by gas chromatography) within 30 min. In isoflurane-G, measurements of CBF and isoflurane blood concentration were obtained before turning on the vaporizer (control) and at 5-min intervals during the isoflurane administration, whereas measurements of MV_{O_2} were

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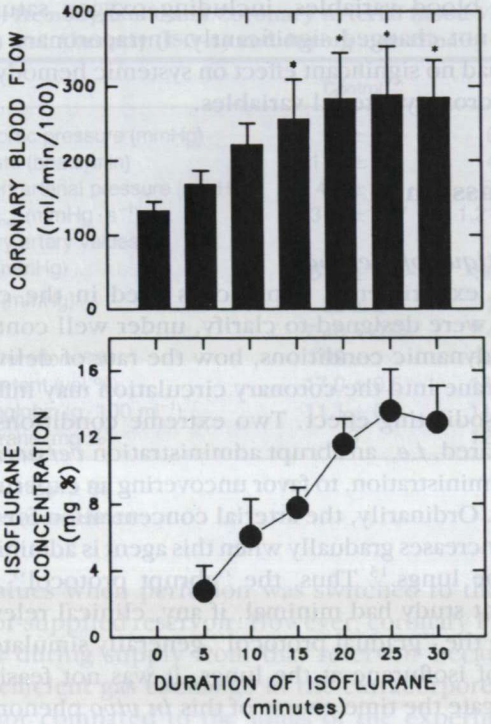

Fig. 1. Changes in coronary blood flow and coronary arterial isoflurane concentration during gradual administration of isoflurane. *$P < 0.05$ *versus* control.

obtained during control and after 30 min of isoflurane. After isoflurane-G, the LAD was returned to reservoir 1. After at least 45 min for recovery, a fourth set of control measurements was obtained, and adenosine in isotonic saline (8 mg/ml) was infused directly into the perfusion line at a dose sufficient to cause steady-state maximal coronary vasodilation (10.3 ± 0.6 mg/min corresponding to an infusion rate of 1.3 ± 0.1 ml/min). Preliminary studies indicated that infusion of the saline vehicle at this rate had no effect on CBF or associated parameters. Maximal vasodilation was indicated by failure of an increase in the rate of infusion of adenosine to cause a further increase in CBF. The rate of CBF during adenosine served as a reference for assessing the extent of coronary vasodilation by intracoronary isoflurane. To rule out time-dependent factors, the conditions of coronary perfusion (isoflurane-A, isoflurane-G, and adenosine) were performed in random order.

At the completion of each experiment, Evans blue dye was injected into the perfusion tubing, with perfusion pressure maintained at the normal level, to identify the LAD perfusion field. After the heart was stopped with KCl, it was removed, trimmed, and frozen to facilitate sampling. The dyed tissue was excised and weighed so that CBF could be expressed on a per 100 g basis. The average weight of the LAD perfusion field was 28 ± 2 g.

Statistical Analyses

Individual effects of isoflurane-A, isoflurane-G, and adenosine were evaluated using the Student's *t* test for paired samples.[12] These effects were compared using a completely randomized analysis of variance with repeated measurements in conjunction with the Student-Newman-Keuls test.[12] A $P < 0.05$ was considered significant throughout this study.

Results

Figure 1 presents time-dependent changes in CBF and coronary arterial isoflurane concentration during isoflurane-G. Isoflurane concentration increased progressively to reach a maximum within 25–30 min after beginning anesthetic administration. The increase in CBF during isoflurane-G tended to parallel the increase in blood isoflurane concentration. The maximal level of CBF during isoflurane-G was approximately double the control value.

Figure 2 compares the maximal change in CBF, as well as the accompanying changes in MV_{O_2} and coronary venous P_{O_2}, during isoflurane-G to those during isoflurane-A and adenosine. The preisoflurane and preadenosine control values did not differ significantly. Thus, for the sake of brevity and simplicity, the pooled means for all controls are presented. The increase in CBF during isoflurane-G was only 45% of that caused by isoflurane-A, even though the peak coronary arterial blood concentrations for isoflurane were not significantly different (table 1). The level of CBF during isoflurane-A was approximately 80% of that during adenosine. Isoflurane-G and isoflurane-A both caused reductions in MV_{O_2} (20–25%), which did not differ significantly. The more pronounced increase in CBF during isoflurane-A combined with a similar reduction in MV_{O_2} to cause a more marked increase in coronary venous P_{O_2} than during isoflurane-G. Isoflurane-A caused similar increase in CBF when instituted before (n = 3) or after (n = 4) isoflurane-G. Switching to the oxygenator-supplied reservoir with the vaporizer off (control 2 *vs.* control 3) had no significant effect on CBF.

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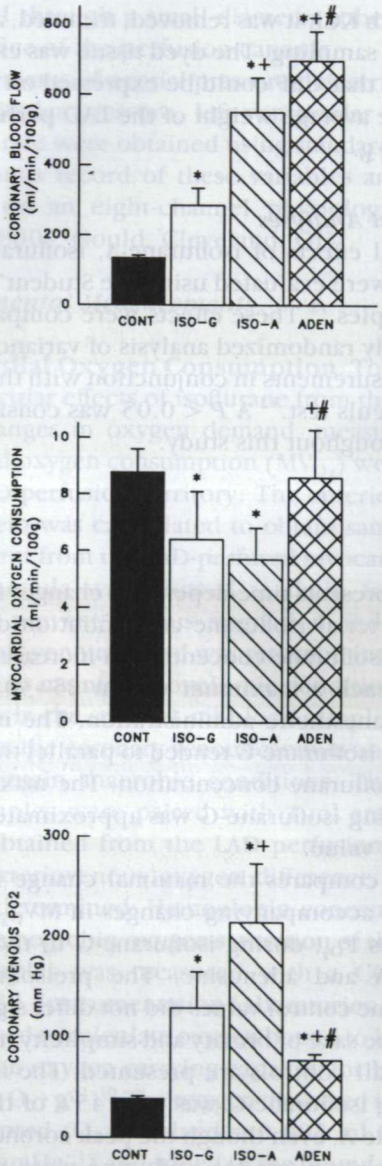

Fig. 2. Effects of intracoronary isoflurane administered gradually (ISO-G) or abruptly (ISO-A) and of adenosine (ADEN) on coronary blood flow, myocardial oxygen consumption, and coronary venous P_{O_2}. Pooled control values are presented. Values are mean ± SE. $P < 0.05$; **versus* pre-isoflurane control; +*versus* ISO-G; #*versus* ISO-A.

Table 1 presents effects of isoflurane-G, isoflurane-A, and adenosine on values for systemic hemodynamic and coronary arterial variables. Neither isoflurane-G nor isoflurane-A caused significant changes in systemic hemodynamic variables. Isoflurane-A caused a small but significant increase in coronary arterial oxygen content (secondary to an increase in arterial P_{O_2}), although other blood variables, including oxygen saturation, were not changed significantly. Intracoronary adenosine had no significant effect on systemic hemodynamic and coronary arterial variables.

Discussion

Critique of Methods

The experimental approaches used in the current study were designed to clarify, under well controlled hemodynamic conditions, how the rate of delivery of isoflurane into the coronary circulation may influence its vasodilating effect. Two extreme conditions were compared, *i.e.*, an abrupt administration *versus* a gradual administration, to favor uncovering an experimental effect. Ordinarily, the arterial concentration for isoflurane increases gradually when this agent is administered *via* the lungs.[13] Thus, the "abrupt protocol" in the current study had minimal, if any, clinical relevance. While the "gradual protocol" generally simulated uptake of isoflurane at the lungs, it was not feasible to duplicate the time course of this *in vivo* phenomenon precisely. Thus, caution should be exercised in extrapolating these findings to the clinical situation in which isoflurane is used for anesthesia.

The objective of the current study was to compare abrupt and gradual exposures to isoflurane in the same preparation. The validity of our findings depended on the responses to isoflurane under the two conditions being independent of one another. In our previous study using a similar model, we demonstrated that the coronary vasodilating effect of isoflurane waned when isoflurane was continued for 3 h after an abrupt exposure,[9] implying vascular adaptation. The length of time after washout required to restore responsiveness of the coronary circulation to isoflurane was not evaluated. To minimize the possibility that the gradual exposures to isoflurane would attenuate responses to the subsequent abrupt exposures to isoflurane in the current study, we limited the duration of the gradual exposures to 30 min and permitted at least 45 min for recovery. The finding that abrupt exposures caused similar increases in CBF when they were before and after gradual exposures demonstrated that our experimental design was successful in avoiding the complication of residual impaired responsiveness to isoflurane.

A 95% O_2/5% CO_2 gas mixture was used to ensure that the coronary arterial P_{CO_2} and *p*H remained at nor-

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Table 1. Hemodynamic and Coronary Arterial Blood Variables during Intracoronary Isoflurane Administered Gradually (ISO-G) and Abruptly (ISO-A) and during a Maximally Dilating Intracoronary Infusion of Adenosine (ADEN)

	Control	ISO-G	Control	ISO-A	Control	ADEN
Mean aortic pressure (mmHg)	69 ± 6	68 ± 8	70 ± 7	67 ± 8	79 ± 7	70 ± 8
Heart rate (beats/min)	143 ± 11	140 ± 9	146 ± 8	143 ± 9	142 ± 12	136 ± 15
Mean left arterial pressure (mmHg)	4.2 ± 1.1	5.8 ± 1.4	5.9 ± 1.2	5.9 ± 1.2	4.7 ± 1.3	5.6 ± 1.5
LV_{dP}/dt_{max} (mmHg · s^{-1})	1,314 ± 167	1,214 ± 141	1,300 ± 179	1,171 ± 143	1,471 ± 139	1,450 ± 143
Coronary artery values						
Pa_{O_2} (mmHg)	572 ± 32	566 ± 24	249 ± 79	538 ± 34*	206 ± 54	213 ± 41
Pa_{Co_2} (mmHg)	32 ± 2	29 ± 2	34 ± 2	31 ± 2	36 ± 1	38 ± 1
*p*H	7.46 ± 0.04	7.47 ± 0.03	7.45 ± 0.04	7.45 ± 0.02	7.41 ± 0.04	7.38 ± 0.01
O_2 saturation (%)	99 ± 1	99 ± 1	98± 1	99 ± 1	98 ± 1	97 ± 1
O_2 content (vol %)	17.0 ± 0.5	17.5 ± 0.4	15.7 ± 0.5	17.2 ± 0.8*	15.3 ± 0.7	15.6 ± 0.7
Hemoglobin (g · 100 ml^{-1})	11.1 ± 0.4	11.5 ± 0.3	11.0 ± 0.3	11.4 ± 0.6	10.9 ± 0.5	11.4 ± 0.5
Isoflurane (mg %)	0	12.9 ± 2.2	0	13.2 ± 2.2	0	0

Values are mean ± SE.

* $P < 0.05$ *versus* control.

mal values when perfusion was switched to the oxygenator-supplied reservoir. However, coronary P_{O_2} was higher during supply from that reservoir because of more efficient gas exchange in the extracorporeal oxygenator compared to the lungs of the experimental animal. It is highly unlikely that this factor influenced our conclusions for two reasons. First, coronary arterial P_{O_2} was sufficient under all conditions for essentially complete saturation of hemoglobin, so that the increase in coronary arterial oxygen content when perfusion was switched to the oxygenator-supplied reservoir resulted primarily from an increased quantity of dissolved oxygen and was small (table 1). Second, the P_{O_2} in the coronary arterial blood was the same during the abrupt and gradual administrations of isoflurane.

In our previous studies assessing the effects of abrupt administrations of isoflurane on CBF, bubble oxygenators were used to add isoflurane to the coronary blood perfusate.[7,9] To more closely approximate the study of Hickey *et al.*,[8] we substituted membrane oxygenators in the current study. Noteworthy is that the peak increases in CBF during isoflurane in the current study were similar to those in our previous studies, implying no influence of oxygenator type on the vasodilator response. The lack of change in CBF when the LAD was switched to the oxygenator-supplied reservoir with the vaporizer off provided evidence that the membrane oxygenator used in the current study did not itself elaborate a substance with coronary vasorelaxing effects.

While the LAD was perfused with isoflurane-equilibrated blood, venous effluent containing isoflurane (the portion not collected *via* the implanted coronary venous catheter) returned directly to the systemic circulation. Sufficient time was permitted between isoflurane exposures (at least 45 min) to permit complete removal of this systemic isoflurane at the lungs. This was confirmed by the absence of isoflurane in blood samples obtained from the perfusion tubing during the subsequent control period.

Coronary Effects of Isoflurane

CBF normally is matched to the prevailing myocardial oxygen demands by local adjustments in coronary vasomotor tone mediated by metabolic control mechanisms.[6] This local control of CBF functions to maintain coronary Pv_{O_2} essentially constant. An increase in coronary Pv_{O_2} indicates uncoupling of coronary oxygen supply from the myocardial oxygen demands and is the hallmark of a coronary vasodilating drug.[6] With coronary perfusion pressure maintained constant, abrupt administration of isoflurane into the coronary circulation caused approximately a fivefold increase in CBF reflecting a proportional decrease in local vascular resistance. The magnitude of these effects was nearly equal to that achievable with adenosine. Because isoflurane also reduced MV_{O_2}, coronary Pv_{O_2} values increased remarkably, providing evidence that isoflurane has a potent direct vasodilating action in the *in situ* canine heart. This observation confirms previous findings obtained using the same preparation and protocol.[7,9] It must be emphasized that, although isoflurane retains a significant coronary vasodilating effect when administered rapidly *via* the lungs, this effect is much smaller than that evident during the abrupt adminis-

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trations of isoflurane in the present study. Kenny *et al.* reported that rapid induction with a high concentration of isoflurane (5%) in chronically instrumented dogs caused a maximum 118% increase in CBF, which could be reduced substantially by autonomic blockade.

The current study also demonstrated that, when a comparable increase in coronary arterial concentration for isoflurane was attained gradually over 30 min, the coronary vasodilator effect of isoflurane was greatly attenuated. We speculate that the mechanism responsible for this effect was the same as that causing a recovery of coronary vascular tone during a prolonged administration of isoflurane.[9] The period required for the gradual increase in isoflurane blood concentration would have provided an opportunity for the time-dependent factor(s) to moderate the coronary vasodilator response. Because the molecular mechanisms underlying coronary vasodilation by isoflurane remain poorly understood, it is difficult to envision with any specificity how this response may be blunted over time. However, we can postulate two general mechanisms that may account for this phenomenon: (1) The coronary vascular smooth muscle becomes tachyphylactic to the relaxing action of the isoflurane. (2) A vasoconstrictor mechanism, *e.g.*, metabolic factors secondary to a reduced local oxygen demand,[6] antagonizes the direct coronary vasorelaxing effects of isoflurane. Further studies are required to clarify the relative contributions of these mechanisms.

The maximal increase in CBF during a gradual intracoronary administration of isoflurane in the present study was greater than that reported in the study of Hickey *et al.*,[8] who used a similar experimental approach in swine. One factor contributing to this quantitative discrepancy may be a species difference in coronary vascular responsiveness to isoflurane. Another possibility relates to the rate of increase in coronary arterial blood concentration for isoflurane. Hickey *et al.* provided no information in this regard; but if the rate of increase in coronary arterial blood concentration were slower in the study of Hickey *et al.*, there may have been greater opportunity for counteracting mechanisms to antagonize or reverse the relaxing effect of isoflurane on coronary vascular smooth muscle.

Although we have not compared abrupt *versus* gradual administrations of other volatile anesthetics, insight into this question may be gained from our findings comparing the time-related changes in CBF after abrupt exposures to isoflurane, halothane, and enflurane.[14] The findings indicated that, although halothane, enflurane, and isoflurane all had direct coronary vasodilating effects that diminished over time, the magnitude and time-course of these responses varied: The maximal increase in CBF was greater for isoflurane and enflurane than for halothane, whereas the time required for maximal recovery of tone was greater for isoflurane than for halothane and enflurane. On the basis of the findings during the prolonged exposures to halothane and enflurane, it might be expected that gradual administrations of these agents would result in less pronounced coronary vasodilation than would abrupt administrations. Our previous study demonstrating a sustained increase in CBF during 3- and 4-h intracoronary infusions of adenosine[15] suggests that the ability of the coronary circulation to overcome pharmacologic vasodilation is drug specific.

The major determinants of myocardial oxygen demand are myocardial contractility, wall tension, and heart rate.[16] Because mean aortic pressure, mean left atrial pressure, and heart rate were constant, the isoflurane-induced decreases in MV_{O_2} in the current study can be ascribed to reduced myocardial contractility by isoflurane. The ability of isoflurane to cause direct cardiac depression is consistent with previous work from our laboratory[17] and others[8] demonstrating impaired segmental shortening in the LAD-perfusion field during local exposure to isoflurane.

In summary, the current study demonstrated that the extent of coronary vasodilation by isoflurane was not dependent simply on its blood concentration but also on the rate at which this blood concentration was increased; a gradual increase in isoflurane blood concentration blunted the vasodilator effect. This phenomenon may reflect a time-dependent vascular adaptation to isoflurane, which is possible when the blood isoflurane concentration increases slowly. Differences in the rate of administration of isoflurane may have contributed to the widely variable coronary vasodilator effects accompanying inhalation of isoflurane in previous clinical and experimental studies.[1–5]

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