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## Regional Vasodilating Properties of Isoflurane in Normal Swine Myocardium

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**Background:** Studies of the coronary vasodilating properties of isoflurane have produced inconsistent results. Isoflurane has been reported to cause minimal or no coronary vasodilation, mild dose-related vasodilation, or even near-maximal coronary vasodilation. The current study was performed to clarify the direct coronary vasodilating potency of isoflurane.

**Methods:** We determined the vasodilating properties of isoflurane in regionally perfused swine myocardium. Six domestic swine were anesthetized with pentobarbital and fentanyl. The left anterior descending artery (LAD) was cannulated and perfused with blood drawn from the carotid artery and passed through a membrane oxygenator. LAD arterial flow was controlled by a calibrated roller pump with continuous digital readout, and LAD arterial pressure was measured directly. The anterior interventricular vein was cannulated and dimension crystals placed in the LAD-perfused myocardium. The vasodilation response to 0, 1, 2, and 3% isoflurane administered *via* the membrane oxygenator was determined and compared to maximal vasodilation produced by regional intracoronary administration of adenosine.

**Results:** Systemic blood pressure and heart rate remained constant throughout the experiment. With 3% isoflurane, systolic shortening and regional myocardial oxygen consumption decreased by 60 and 20%, respectively. The same concentration increased coronary blood flow by  $51 \pm 34\%$  and reduced coronary vascular resistance by  $32.9 \pm 11.0\%$ . Neither coronary blood flow nor coronary vascular resistance was affected with 1% isoflurane. Regional coronary administration of adenosine produced much greater changes in both coronary blood flow (+591%) and coronary vascular resistance (-92.5%). Isoflurane increased the venous oxygen content of the anterior interventricular vein in a dose-dependent fashion from 4.85 vol% at control to 6.17, 7.01, and 8.63 vol% at 1, 2, and 3% isoflurane, respectively.

**Conclusions:** We conclude that isoflurane is a mild dose-dependent coronary vasodilator. At a 1% concentration, the cor-

onary vasodilating properties of isoflurane are minimal. (Key words: Arteries, coronary; vasodilation. Anesthetics, volatile: isoflurane. Heart: regional perfusion.)

MOST studies of the coronary effects of isoflurane have reported that this anesthetic induces coronary vasodilation.<sup>1-9</sup> Some, however, have reported that isoflurane causes minimal or no coronary vasodilation,<sup>10,11</sup> mild and dose-related vasodilation,<sup>8,12</sup> or even near-maximal coronary vasodilation.<sup>13</sup> Controversy persists because the coronary and myocardial effects of isoflurane are complex. Isoflurane not only causes direct coronary vasodilation, but also may decrease aortic blood pressure, thereby inducing autoregulatory vasodilation. This tendency to cause coronary vasodilation is tempered, however, by the finding that isoflurane decreases myocardial oxygen consumption ( $M\dot{V}_{O_2}$ ), one of the prime determinants of coronary blood flow (CBF). By reducing  $M\dot{V}_{O_2}$ , isoflurane may induce metabolically mediated coronary vasoconstriction that offsets its direct coronary vasodilator effects.

To distinguish between the direct and indirect effects of isoflurane and to clarify its vasodilating potency, Crystal and coworkers administered isoflurane, *via* extracorporeal circulation, to the isolated, perfused coronary artery bed in a canine model.<sup>13</sup> One of the major advantages of their experimental design was the regional administration of isoflurane to the heart, which thus avoided systemic changes in heart rate and blood pressure and the subsequent confounding effects these variables could have on CBF. The results of their study suggest that isoflurane is an extremely potent coronary vasodilator, nearly equal in potency to adenosine, which dilates the coronary circulation maximally. In their model, 2% isoflurane increased CBF sixfold in 11 dogs, and moreover, concentrations as low as 0.5% increased CBF by more than 300%. This impressive vasodilating potency suggests that isoflurane probably produces vasodilator-induced coronary steal, as originally proposed by Reiz *et al.*<sup>3</sup> The results reported by Crystal and coworkers suggest a greater vasodilating

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## VASODILATING POTENCY OF INTRACORONARY ISOFLURANE

potency for isoflurane than that found in most other studies.

To clarify further the potency of isoflurane as a vasodilator and to confirm the provocative results of Crystal *et al.*,<sup>13</sup> we measured the effects of three concentrations of isoflurane on CBF and coronary vascular resistance (CVR) in a swine model of regional coronary perfusion.

### Materials and Methods

#### *Anesthesia*

This experimental protocol was approved by our Animal Welfare Committee and followed the guidelines for animal use by the American Physiological Society. Six domestic swine weighing 42–52 kg were premedicated with intramuscular ketamine hydrochloride (1.0 g) and then anesthetized *via* mask with isoflurane (1.0–2.5%) in oxygen. During general anesthesia, a tracheostomy was performed, and ventilation was controlled to maintain normal pH and arterial carbon dioxide partial pressure. To minimize ventricular arrhythmias, lidocaine hydrochloride was given as an intravenous bolus (3 mg · kg<sup>-1</sup>) followed by a constant intravenous infusion of 2 mg · min<sup>-1</sup> for the duration of the study. After the surgical preparation, isoflurane was discontinued, and anesthesia was maintained with sodium pentobarbital (a 15-mg · kg<sup>-1</sup> loading dose followed by a 60-μg · kg<sup>-1</sup> · min<sup>-1</sup> infusion) and fentanyl (a 50-μg · kg<sup>-1</sup> bolus followed by a 0.25-μg · kg<sup>-1</sup> · min<sup>-1</sup> infusion). End-tidal isoflurane could not be detected for at least 1 h before control measurements were made.

Central body temperature was maintained at 36.5–38.5°C by warmed intravenous fluids and surface warming. Arterial blood gases were measured using a Radiometer (Copenhagen, Denmark) ABL-II blood gas analyzer. Hemoglobin and oxyhemoglobin saturation were measured using a Radiometer hemoximeter OSM3 with internal correction for swine hemoglobin absorption characteristics.

After the experiment the animals were killed by anesthetic overdose.

#### *Surgical Preparation and Instrumentation*

The heart was exposed through a median sternotomy and suspended in a pericardial cradle. A calibrated micromanometer (Millar Instruments, Houston, TX) was inserted through the left atrium into the left ventricle

for measurement of the left ventricular pressure and its first derivative with respect to time (dP/dt). Epicardial pacing wires were sutured to the right atrium, and electrical pacing was begun after the preparation at a rate 20% higher than the intrinsic heart rate. Pacing then continued at the same rate throughout the experiment. Both carotid arteries were cannulated with 14-G catheters to supply blood to the extracorporeal circuit and to allow periodic arterial blood sampling and continuous systemic pressure monitoring. All transduced signals were recorded on a Grass Instruments polygraph (Quincy, MA). Both internal jugular veins were cannulated to provide intravenous access for drug and saline infusions. Finally, the anterior interventricular coronary vein was cannulated with a 20-G catheter to allow intermittent sampling of the blood draining the left anterior descending artery (LAD) perfusion bed.

#### *Cannulation and Perfusion of the Left Anterior Descending Artery*

Just before cannulation of the LAD, the pig's blood was anticoagulated with a 10,000-U intravenous bolus of heparin followed by a 5,000-U · h<sup>-1</sup> continuous infusion. The LAD was dissected free of surrounding tissue for a 2-cm length near its origin at the base of the heart. The coronary artery was then cannulated with a 3-mm (OD) plastic cannula and perfused with oxygenated blood pumped from the carotid artery with a rotary pump calibrated by timed collection for each experiment (Masterflex digital roller pump, Cole-Parmer, Chicago, IL). Before the heart was perfused, blood was passed through a 40-μm filter (Pall Biomedical, Glen Cove, NY) to trap air and particulate debris. Systolic shortening was measured to ensure adequacy of CBF. If systolic shortening did not return to the precannulation level within 3 min, cannulation was deemed unsuccessful and the pig was excluded from the study. One animal was excluded from this study.

LAD pressure was measured at the tip of the perfusion cannula through a 25-G catheter inside the cannula. Flow was measured continuously by digital readout for the calibrated roller pump and by an inline electromagnetic flowmeter (Transonic, Ithaca, NY), calibrated by timed blood collection in a graduated cylinder at the beginning of each experiment. LAD flow was determined by setting the pump output so that mean coronary artery pressure matched mean systemic pressure.

### Sonomicrometry

Myocardial contractile function was quantitated in the LAD perfusion zones using segmental systolic shortening. Systolic shortening was calculated as follows:

Systolic shortening (%)

$$= \frac{(\text{end-diastolic length} - \text{end-systolic length})}{\text{end-diastolic length}} \times 100$$

Diastolic and systolic segment lengths were measured using 2-mm lensed ultrasonic crystals (Dimension 3, La Jolla, CA) that were embedded in the subendocardial muscle through a small epicardial incision. The crystals were positioned approximately 11 mm apart, facing each other and parallel to the short axis of the heart. Electrical signals from the dimension crystals were displayed continuously on an oscilloscope. The position and orientation of the crystals were confirmed by examination of the function tracing and by direct inspection at necropsy. Systolic shortening readings were averaged over five heart beats. End diastole was defined as the onset of positive left ventricular  $dP/dt$ ; end systole was defined as the time of peak negative  $dP/dt$ .

### Perfusion Bed of the Left Anterior Descending Artery

The myocardium perfused by the LAD artery was delineated by a dye infusion technique: blood stained with Evans blue dye was infused into the cannulated LAD artery at normal aortic pressures, while the remainder of the heart was perfused at the same pressures with unstained blood from the aortic root. The blue area, representing myocardium perfused by the LAD artery, was excised and weighed.

### Perfusion Circuit and Membrane Oxygenator

The perfusion circuit is shown in figure 1. The day before each study, new silastic tubing and a new membrane oxygenator (Avecor Cardiovascular, Plymouth, MN) were assembled, filled with sterile saline containing 50 U/ml heparin, and debubbled. The perfusion circuit and the membrane oxygenator were aerated by oxygen (2.0 l/min) and carbon dioxide (0.1–0.125 l/min) while effluent gas was continuously sampled to measure the partial pressures of oxygen, carbon dioxide, and isoflurane (oxygen analyzer, Ohio; carbon dioxide and isoflurane analyzers, Puritan Bennet). Isoflurane was added to the circuit with a bubble-through vaporizer. The membrane oxygenator was warmed by

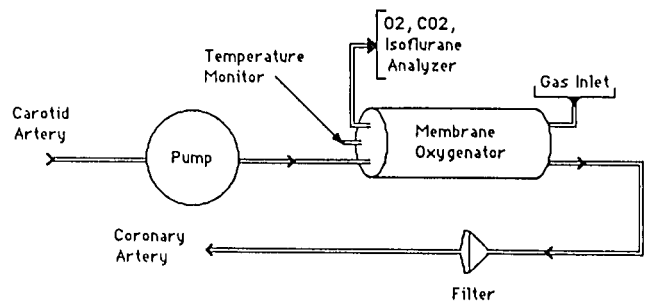


Fig. 1. The left anterior descending artery perfusion circuit. Not shown are the sampling site for blood and the injection site for adenosine.

an external heat source and its temperature measured and adjusted to match central body temperature.

### Blood Sampling

A T-connector was inserted into the LAD perfusion circuit immediately before the LAD cannula. Blood was withdrawn from this site at 12 ml/min by a calibrated rotary pump and reinfused into the pig's venous circulation. This allowed sampling of arterial blood for blood gases, oxygen saturation, hemoglobin concentration, and isoflurane concentration, without the need to change LAD CBF.

### Measurement of Isoflurane Concentration in the Blood

The partial pressure of isoflurane in the arterial blood was measured as detailed by Fink and Morikawa.<sup>14</sup> Briefly, 15 ml blood was withdrawn for analysis into a gas-tight, volume-calibrated syringe the dead space of which had previously been rinsed with the same blood. A volume of air equal to the volume of blood was drawn into the syringe, and the air–blood mixture was equilibrated in a 37°C rotary water bath for 2 h. A gas sample was measured by gas chromatography; the remaining gas was evacuated; and an additional 15 ml air was aspirated into the syringe. This new air–blood mixture was equilibrated in a 37°C rotary water bath for 2 h, and the gas was again analyzed by gas chromatography. The partial pressure of isoflurane in blood is calculated as follows:

$$\frac{P_0}{P_1} = \frac{P_1}{P_2}$$

where  $P_0$  = the partial pressure of the original anesthetic at body temperature;  $P_1$  = the partial pressure of anesthetic in the syringe after the first equilibration

## VASODILATING POTENCY OF INTRACORONARY ISOFLURANE

with air; and  $P_2$  = the partial pressure of anesthetic in the syringe after the second equilibration with air.

### Experimental Protocol

After LAD cannulation and a minimum of 60 min stabilization, control measurements of systemic blood pressure, heart rate, CBF (LAD perfusion bed), and systolic shortening were made. Arterial and coronary venous hemoglobin concentrations, oxygen saturation, and blood gases were measured to calculate  $\dot{M}\dot{V}_{O_2}$ . The latter measurements were repeated during administration of 1, 2, and 3% isoflurane. At all times during both control measurements and isoflurane administration, CBF was continuously adjusted so that mean coronary pressure and mean systemic pressure were equal. The order of administration of the three isoflurane concentrations was determined by restricted randomization, so that all possible computations were included. Fifteen minutes was allowed for stabilization at each concentration, before measurements were made. CBF remained constant for the last 5 min of the measurement period. Isoflurane was then eliminated, and control measurements were repeated. Adenosine (7.5 mM) dissolved in normal saline (2 mg/ml) was then administered directly into the LAD perfusion line and titrated to produce maximal CBF. The concentration of adenosine required to produce maximal CBF was 1.6–2.0 mg/min. All measurements were then repeated. The flow rate of adenosine solution necessary to produce maximal CBF was less than 0.5% of the LAD CBF.

### Calculations

**Coronary Blood Flow in the Left Anterior Descending Artery Perfusion Bed.** Regional CBF was calculated from the values measured by the calibrated roller pump and was expressed in milliliters per 100 g per minute, using the weight of the LAD perfusion bed. CVR equaled

$$\text{CVR} = \frac{\text{mean LAD pressure} - \text{left ventricular end-diastolic pressure}}{\text{LAD flow}}$$

**Myocardial Oxygen Consumption.**  $\dot{M}\dot{V}_{O_2}$  was calculated for the LAD-perfused zone, using the Fick Principle, as the product of the LAD blood flow and the difference between the coronary arterial and the anterior interventricular venous oxygen content.

**Data Analysis.** Values were compared using repeated-measures analysis of variance and, where indi-

cated by analysis of variance, by Scheffé's F test. Values reported are means  $\pm$  standard deviations.

### Results

Systemic arterial blood and blood from the membrane oxygenator had nearly identical pH values and carbon dioxide and oxygen partial pressures. For membrane oxygenator blood, oxygen partial pressure =  $501 \pm 53$ ; carbon dioxide partial pressure =  $40 \pm 2$ ; and pH =  $7.41 \pm 0.02$ . For systemic arterial blood, oxygen partial pressure =  $398 \pm 103$ ; carbon dioxide partial pressure =  $40 \pm 5$ ; and pH =  $7.42 \pm 0.04$ .

The paced heart rate ( $121.4 \pm 7.8$  beats/min) and the systemic blood pressure remained constant throughout the experiment (table 1). Regional administration of isoflurane had little effect on end-diastolic length or left-ventricular end-diastolic pressure, but did result in a dose-related decrease in systolic shortening, primarily by increasing end-systolic length. Regional isoflurane resulted in a dose-related increase in venous oxygen content at all doses studied (table 1). CBF and CVR were not affected by 1% isoflurane. Isoflurane at 2 and 3% increased CBF by 31 and 51%, respectively, while reducing CVR (table 1). Control measurements before and after administration of isoflurane were not different.

Effluent membrane oxygenator isoflurane concentrations and calculated blood isoflurane concentrations are shown in table 2.

### Discussion

Our results clearly indicate that isoflurane is a dose-dependent coronary artery vasodilator in the normal swine myocardium. One percent isoflurane did not cause an increase in CBF or a decrease in CVR, but did produce an increase in coronary venous oxygen content. However, a significant increase in CBF and reduction in CVR occurred at 2 and 3% isoflurane. The increase in CBF with 3% isoflurane was  $51 \pm 34\%$  (range 20–95%). Although this increase in CBF at this high concentration of isoflurane is small compared to the maximal increase produced by adenosine, it is substantial.

Many studies of the coronary effects of isoflurane are difficult to interpret because of the multiple, dose-dependent actions of this volatile anesthetic. Measurements of CBF and coronary perfusion pressure and cal-

**Table 1. Effects of 1%, 2%, and 3% Isoflurane and Adenosine on Systemic Blood Pressure, Left Ventricular Dimensions, Systolic Shortening, Venous Oxygenation, CBF, and CVR**

	Control (Before Isoflurane)	1% Isoflurane	2% Isoflurane	3% Isoflurane	Control (After Isoflurane)	Adenosine
Systemic blood pressure (mmHg)	66.2 ± 2.6	66.0 ± 2.3	65.3 ± 2.2	63.9 ± 3.8	63.9 ± 2.6	62.8 ± 3.8
LVEDP (mmHg)	4.5 ± 1.2	4.3 ± 1.2	4.8 ± 1.0	5.5 ± 0.8	4.2 ± 1.2	3.8 ± 1.0
EDL (mm)	14.2 ± 1.0	14.1 ± 2.2	14.3 ± 2.1	14.6 ± 2.1*	13.8 ± 2.0†	13.5 ± 1.9
ESL (mm)	11.0 ± 1.76	11.6 ± 2.0†	12.4 ± 2.1†	13.3 ± 2.2†	10.6 ± 1.8†	10.3 ± 1.8
Systolic shortening (%)	22.9 ± 2.32	17.9 ± 3.1†	13.9 ± 4.6†	8.9 ± 3.7†	21.4 ± 2.5†	23.2 ± 2.2
Venous oxygen content (vol%)	4.85 ± 1.54	6.17 ± 1.24†	7.06 ± 1.48†	8.63 ± 1.61†	4.98 ± 0.98	13.30 ± 1.24†
Venous oxygen saturation (%)	38.7 ± 10.1	46.7 ± 8.0	54.0 ± 10.9†	65.4 ± 19.6†	35.8 ± 6.4†	97.2 ± 1.45†
CBF (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	66.2 ± 15.7	71.2 ± 15.0	86.8 ± 22.2*	102.5 ± 42.6†	64.1 ± 12.6†	437.6 ± 47.3†
CVR (mmHg · ml <sup>-1</sup> · min · 100 g)	0.92 ± 0.17	0.89 ± 0.14	0.73 ± 0.17†	0.62 ± 0.15†	1.00 ± 0.21†	0.16 ± 0.02†

\* Significantly different at 95% from control.

† Significantly different at 95% from previous measurement.

culuation of CVR before and after administration of a drug provide information about that drug's effect on the coronary vasculature. However, this methodology provides only limited information about the mechanism of drug action. A drug can change CVR both by direct action on the arterial vasculature and by indirect effects. These two mechanisms may oppose and obscure each other. We define indirect effects as those produced by changing  $\dot{M}\dot{V}_{O_2}$  or perfusion pressure, and we hypothesize that the direct effect of any drug on coronary vascular tone can be determined only if the indirect effects are avoided or accounted for.

These indirect effects appear to operate *via* two established physiologic mechanisms. The first is the direct variation of CBF with  $\dot{M}\dot{V}_{O_2}$ .<sup>15</sup> Examination of the action of nitroglycerin, a drug generally considered a coronary vasodilator, provides an interesting example of direct *versus* indirect drug effects. The direct effect of nitroglycerin is to decrease CVR. However, because  $\dot{M}\dot{V}_{O_2}$  is reduced, CBF decreases, and CVR increases.<sup>16</sup> Thus, nitroglycerin, a "coronary vasodilator," can actually increase CVR by its indirect effect (reduction of  $\dot{M}\dot{V}_{O_2}$ ).

The second physiologic mechanism by which drugs may indirectly affect the coronary circulation is autoregulation of CBF. Autoregulation describes the physiologic mechanisms by which CBF is held relatively constant as coronary inflow pressure changes. If one direct effect of a drug is to decrease coronary inflow

pressure, then an expected indirect effect would be an autoregulatory decrease in CVR. These physiologic mechanisms act to keep coronary venous oxygen content relatively constant, whereas direct vasodilation decreases oxygen extraction and increases venous oxygen content. Several studies have found that oxygen extraction in the coronary circulation is about 60–70% at rest<sup>17–19</sup> and that CBF is matched to  $\dot{M}\dot{V}_{O_2}$ .<sup>15</sup> Coronary vasodilation increases the coronary supply–demand ratio, resulting in increased venous oxygenation. To allow comparison of our results to those of previous studies, we examined venous oxygenation after the administration of isoflurane. Table 3 summarizes the findings of 12 published studies that examined the coronary vasodilation properties of isoflurane based on venous oxygen content changes.

**Table 2. Effluent Membrane Oxygenator Isoflurane Concentrations and Calculated Blood Isoflurane Concentrations**

	1.03 ± 0.04	1.96 ± 0.10	2.96 ± 0.10
Oxygenator effluent gas concentration (% by infrared analysis)	1.03 ± 0.04	1.96 ± 0.10	2.96 ± 0.10
Partial pressure of isoflurane in arterial blood (%)	0.91 ± 0.11	1.69 ± 0.17	2.25 ± 0.17

## VASODILATING POTENCY OF INTRACORONARY ISOFLURANE

Table 3. Isoflurane and Coronary Venous Oxygenation

Species	Investigator	Isoflurane Concentration (%)	ml · 100 g <sup>-1</sup> · min <sup>-1</sup>		vol%		Increase in CV <sub>O<sub>2</sub></sub>	n	
			Control CBF*	Isoflurane CBF*	Control CV <sub>O<sub>2</sub></sub>	Isoflurane CV <sub>O<sub>2</sub></sub>			
Humans	Khambatta, 1988 <sup>4</sup>	1%	68†	56	5.7 ± 0.1	7.5 ± 0.1	1.8	10	
			131‡	153	7.6 ± 0.1	11.0 ± 0.1	3.4		
	Moffitt, 1986 <sup>5</sup>	1.76%	103‡	93	7.9	12.0	4.1	10	
			O'Young, 1987 <sup>20</sup>	0.75–1.0%	78.5†	69	6.4 ± 0.3		6.8 ± 0.3
	123.8‡	115.1			6.7 ± 0.1	7.1 ± 0.2	0.38		
	Dogs	Reiz, 1985, 1983 <sup>1,3</sup>	1.73%	100‡	74	7.54	13.9	5.33	13
1%			136†	126	5.16	8.3	3.09		
Abdel-Latif, 1992 <sup>21</sup>		2–4%	63	54	7.8 ± 0.8	8.7 ± 0.9	0.9	7	
			Cason, 1987 <sup>22</sup>	0.75	50	44	5.34		5.84
Conzen, 1992 <sup>7</sup>		2.25	96	87	7.9 ± 0.7	9.4 ± 0.6	1.5	13	
			1.5%	92	230	8.8 ± 0.5	15.4 ± 1.5		6.6
Crystal, 1991 <sup>13</sup>		0.5%	269	269		16.4 ± 0.9	7.6	11	
			2.0%	446	446		17.0 ± 0.9		8.2
Hickey, 1988 <sup>12</sup>		1.5%	92.5	119	§	§	2.43	6	
			Sill, 1987 <sup>8</sup>	0.75	60	65	§		§
Swine		Hickey (present study)	1% 2% 3%	200	160			0.34	6
				250	200			0.62	
	60			80	§	§	3.9		
	200			150			1.9		
	250			190			1.6		
	60			82	§	§	5.6		
	200			135			2.5		
	250			170			1.4		
Rats	Sahlman 1988 <sup>11</sup>	1.5%	195	225	3.6	5.1	1.48	10	

\* CBF is expressed in ml · 100 g<sup>-1</sup> · min<sup>-1</sup> except for human studies (ml/min).

† Flow measured in great cardiac vein.

‡ Flow measured in coronary sinus.

§ Presented data allow calculating only a change in venous oxygen content, rather than absolute values of venous oxygen content.

Each of these studies presented data that allowed us to determine venous oxygen content change with isoflurane administration. We note that in the 12 reports, isoflurane administration resulted in a decreased CBF in 15 measurements and an increased CBF in 14 measurements. However, in every measurement, venous oxygen content increased. With the exception of the work reported by Crystal and coworkers,<sup>1,3</sup> this increase was relatively small and did not appear to differ among species (table 3).

We considered two possible explanations for the difference between our findings and those of Crystal's group. The first they had suggested. In their experiment, the coronary circulation was abruptly exposed to blood already equilibrated with isoflurane. They

suggested that this abrupt exposure of the coronary circulation might produce a greater vasodilation than that seen in the steady state. Recently, Kenny and coworkers<sup>2,3</sup> provided support for that idea. They measured CBF continuously in instrumented dogs while inducing anesthesia with isoflurane administered *via* mask before and after autonomic blockade. Before autonomic blockade, CBF rose twofold during induction of anesthesia by mask with isoflurane. Prevention of increases in blood pressure, heart rate, and myocardial contractibility by autonomic blockade limited isoflurane's effect on CBF to a smaller but still significant increase. Thus, Crystal *et al.*'s suggestion that vasodilation may be increased by abrupt exposure to isoflurane is supported by Kenny *et al.*'s work and could

account for some of the differences between our work and Crystal *et al.*'s study.

The second possibility we considered is dependent on the known difference in collateral circulation between pigs and dogs. Dogs have a well-developed epicardial collateral circulation, whereas pigs have minimal innate coronary collateral circulation.<sup>24</sup> Perhaps abrupt exposure of the LAD perfusion bed to isoflurane (as in Crystal and coworkers' experiment) induced vasodilation, exposing the collateral circulation to a higher perfusion pressure. Collateral flow could then deliver to areas outside the LAD perfusion bed, previously supplied by the right coronary or circumflex coronary arteries. However, the limited vasculature of the coronary collateral circulation in the normal dog indicates that this proposed mechanism is inadequate to explain the difference between our study and that of Crystal *et al.*

Another experimental approach to determine the direct vasodilating properties of volatile anesthetics was recently reported by Larach and coworkers.<sup>2</sup> These investigators determined the dose response of CBF to isoflurane and halothane in arrested perfused rat hearts. They thus avoided any anesthetic-induced changes in  $\dot{M}\dot{V}_{O_2}$  and also controlled perfusion pressure. They reported a dose-related increase in CBF that was similar with both anesthetics. The highest concentration of anesthetic studied (2.0 MAC) increased CBF by about 100% over control. This response is greater than that found in the current study. The lack of vascular compression of the coronary circulation in the arrested heart could account for a portion of the increased CBF reported by these investigators.<sup>25</sup>

### Limitations

Although this swine model of selective coronary artery perfusion and oxygenation has many advantages, the invasive nature of the experiment and the use of a basal anesthetic raised some concerns. We choose fentanyl and pentobarbital to provide basal anesthesia because previous work indicated that neither fentanyl<sup>26</sup> nor pentobarbital<sup>27</sup> affect CVR. We believe our preparation was physiologically intact because function was normal before and after LAD cannulation, as evidenced by maintenance of systolic function and by its return to normal control after elimination of isoflurane. Moreover, anterior interventricular venous oxygen saturations of  $38.7 \pm 10.1$  and  $35.8 \pm 6.4\%$  in the control state (before and after isoflurane) confirm that auto-

regulation was present,<sup>28</sup> and the response to adenosine indicated the ability of the LAD artery to vasodilate.

Another potential limitation in application of the Fick Principle is the possibility of venous contamination. We determined LAD perfusion bed  $\dot{M}\dot{V}_{O_2}$  and venous oxygenation by sampling blood from the anterior interventricular vein. Recent work by Bier and coworkers<sup>29</sup> confirms the validity of use of this vein for determinations. These workers labeled LAD and right coronary and circumflex coronary arteries and indicated under conditions of equal perfusion pressures, and even when LAD pressure was reduced, that the anterior interventricular vein always was contaminated by less than 10%.

We thought it important to confirm the anesthetic concentrations delivered. We therefore measured both effluent membrane oxygenator isoflurane concentration and the partial pressure of isoflurane in the arterial blood perfusing the LAD. We found that the ratios of arterial blood to effluent gas isoflurane concentrations were 0.91, 0.85, and 0.75 at 1, 2, and 3% isoflurane, respectively. These ratios are similar to those reported by Nussmeier *et al.* after 20 min of isoflurane administered *via* a bubble oxygenator to patients undergoing cardiac surgery.<sup>30</sup> The isoflurane-mediated decreases in systolic shortening also indicate a significant anesthetic effect. The decrease in systolic shortening we found is similar to but slightly greater than that reported by Belo and Mazer at similar isoflurane concentrations.<sup>31</sup> Systemic blood pressure and heart rate were constant, but 3% isoflurane reduced  $\dot{M}\dot{V}_{O_2}$  only by about 20%, even though systolic shortening was markedly reduced (by 60%). Crystal *et al.* reported a reduction in  $\dot{M}\dot{V}_{O_2}$  of nearly 50% at 2% isoflurane. Support for our findings of a modest reduction of  $\dot{M}\dot{V}_{O_2}$  comes from the work of Gayheart *et al.*<sup>32</sup> These investigators reduced systolic shortening by regional intracoronary artery infusion of lidocaine. They found only a small reduction in  $\dot{M}\dot{V}_{O_2}$ , approximately 10%, when systolic shortening was reduced by 50%.

In summary, we were unable to confirm results of a study suggesting that intracoronary isoflurane causes near-maximal coronary vasodilation.<sup>13</sup> To the contrary, we found that 1% isoflurane did not increase CBF at all. CBF did increase by 31 and 51% at 2 and 3% isoflurane, respectively. By contrast, maximal coronary vasodilation with adenosine increased CBF by 591%. Our results, and the preponderance of reports in the literature, support the conclusion that isoflurane causes mild, dose-dependent coronary vasodilation.

## VASODILATING POTENCY OF INTRACORONARY ISOFLURANE

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