

# Differential Effects of Isoflurane on Regional Right and Left Ventricular Performances, and on Coronary, Systemic, and Pulmonary Hemodynamics in the Dog

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The effects of isoflurane-induced hypotension to mean aortic pressures of 70 and 55 mmHg on global and regional right (RV) and left (LV) ventricular performance (ultrasonic dimension technique), and on coronary, systemic, and pulmonary hemodynamics (electromagnetic flow probes) were studied in 12 open-chest dogs anesthetized and paralyzed by continuous infusions of fentanyl and pancuronium. Isoflurane caused dose-dependent decreases in LV and RV dP/dt, and in myocardial segment shortening in the presence of unchanged heart rate, unchanged or increased (RV) preload, and unchanged (RV) or decreased (LV) afterload. RV and LV functions were affected differently: at a mean aortic pressure of 70 mmHg (mean inspired isoflurane 1.2%), RV end diastolic dimensions and pressure remained unchanged, whereas those of the LV decreased. At a mean aortic pressure of 55 mmHg (mean inspired isoflurane 1.8%), RV end diastolic dimensions and pressure increased above control, whereas those of the LV remained unchanged. Within the RV, inflow and outflow tract were affected quantitatively similarly, but dyssynchrony developed in four animals. Isoflurane caused dose-dependent decreases in coronary and systemic vascular resistances, but no change in pulmonary vascular resistance. At the lower concentration of isoflurane, coronary blood flow did not fall despite decreased LV and RV dP/dt, unchanged heart rate, unchanged or decreased preload, and unchanged or reduced afterload. The data indicate that isoflurane is a myocardial depressant and a potent coronary vasodilator. At both concentrations, LV function was better preserved than RV function, most likely due to the different effects of isoflurane on RV (unchanged) and LV (reduced) afterload. (Key words: Anesthetics, volatile; isoflurane. Heart: coronary hemodynamics; regional myocardial performance.)

WHEREAS THE NEGATIVE inotropy of isoflurane has been established,<sup>1,2</sup> comparative data on the simultaneous effects of isoflurane on regional performances of right *versus* left ventricle, and of right ventricular inflow *versus* outflow tract, do not exist. Similarly, systemic arterial vasodilation

has been reported,<sup>1,2</sup> but comparative data on the simultaneous effects of isoflurane on the coronary, systemic, and pulmonary circulations are lacking.

Experimental data concerning the effects of isoflurane on the coronary circulation have been conflicting. Both decreases in canine coronary vascular resistance with no change in coronary blood flow<sup>1</sup> and unaltered coronary vascular resistance with a decrease in coronary blood flow<sup>2</sup> have been reported. It was the objective of this study to compare the effects of two levels of isoflurane-induced hypotension on right and left ventricular global and regional myocardial function, and on coronary, systemic, and pulmonary hemodynamics.

## Methods

### INSTRUMENTATION

Sixteen mongrel dogs of either sex weighing between 26 and 48 kg were premedicated with intramuscular Innovar-Vet® 0.1 ml/kg (0.04 mg/kg fentanyl and 2 mg/kg droperidol). Endotracheal anesthesia was induced with small incremental doses of iv pentobarbital, up to a maximum total of 10 mg/kg, and maintained by continuous iv infusions of pentobarbital (1 mg · kg<sup>-1</sup> · h<sup>-1</sup>) and fentanyl (20 µg · kg<sup>-1</sup> · h<sup>-1</sup>). Additional fentanyl was administered as indicated by increases in heart rate and blood pressure. Controlled ventilation with a Harvard constant-volume ventilator (Harvard Apparatus Co, South Natick, MA) was facilitated by a continuous iv infusion of pancuronium (0.04 mg · kg<sup>-1</sup> · h<sup>-1</sup>). Tidal volume was set at 15 ml/kg. Respiratory rates and inspired oxygen concentrations were adjusted to maintain the arterial carbon dioxide tension (PaCO<sub>2</sub>) between 30 and 40 mmHg, and the arterial oxygen tension (PaO<sub>2</sub>) between 150 and 350 mmHg. Positive end-expiratory pressure (2 cm H<sub>2</sub>O) was applied to prevent major airway collapse in the open-chest animals. Sodium bicarbonate (NaHCO<sub>3</sub>, 1 mEq/kg) was given at the beginning of the surgical preparation. Additional NaHCO<sub>3</sub> was administered if the calculated base deficit exceeded 5 mEq/L. All dogs were in the supine

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position and placed on a heating element incorporated in the operating table. Body temperature was continuously monitored by a thermistor of a flow-directed thermodilution catheter (Edwards Laboratory, Model 93-132-5F) inserted through the right jugular vein and advanced into the pulmonary artery. All animals received 4–6 ml · kg<sup>-1</sup> · h<sup>-1</sup> of normal saline.

Catheter-tip manometers (6F, Millar Instruments Inc, TX) were inserted through an internal mammary artery, the left carotid artery and the right jugular vein, and advanced into the ascending aorta just above the aortic valve, and into the left (LV) and the right ventricles (RV), respectively. Stiff polyethylene tubing (ID 1.0 mm, OD 1.6 mm) was advanced into the aortic arch *via* the left femoral artery. The catheter-tip manometers were prewarmed in a water bath at 37° C for several hours, and were calibrated simultaneously and immediately prior to insertion. Calibration was performed by actuating a switch incorporated in the connection cable that produced an electrical output corresponding to a pressure of 100 mmHg. Baseline stability of the high-fidelity signals was checked repeatedly during the experiment by superimposing the manometer-derived pressures on those derived from either the separate fluid-filled catheter in the aortic arch, or from the fluid-filled lumina incorporated in the RV and LV catheter-tip manometers using Statham transducers (P23 ID).

Following median sternotomy, the heart was suspended in a pericardial cradle. Precalibrated electromagnetic flow probes (Stölzer Messtechnik, West Germany) of appropriate sizes to ensure a snug fit were placed around the ascending aorta, the right coronary artery (RCA) approximately 1–2 cm distal to its origin, and the left anterior descending coronary artery (LAD) distal to its first large diagonal branch. The flow probes were connected to flow meters with incorporated nonocclusive zero (Hellige Co., West Germany).

#### REGIONAL MYOCARDIAL FUNCTION

Regional myocardial performance was evaluated by sonomicrometry.<sup>3,4</sup> Pairs of piezoelectric crystals (5 MHz, 1.5–2.0 mm diameter) were inserted into the subendocardium of the inflow (longitudinal direction) and outflow tract (transverse direction) of the RV. A third pair was inserted in an equatorial plane into the subendocardium of the LV distal to the first or second diagonal branch of the LAD. Care was taken to place the crystals in the inflow tract of the RV and those in the apical region of the LV within the areas supplied by the RCA and LAD, respectively. Myocardial segment lengths (SL) between each pair of crystals were determined at end diastole (SL<sub>ed</sub>) and at

the time of maximal shortening during systole (SL<sub>sys</sub>). From these values, percent segment shortening during systole (ΔSL) was derived:

$$\Delta SL (\%) = (SL_{ed} - SL_{sys}) / SL_{ed} \cdot 100$$

End diastole was defined as the beginning of the sharp upslope in the expanded LV and RV pressure tracings, and endsystole by the dicrotic notch in the aortic pressure signal as derived from the catheter-tip manometers. Analysis of aortic flow and pressure signals in several animals showed that zero aortic flow and dicrotic notch occurred within 40 ms of each other. The ultrasonic signals were also assessed visually for qualitative changes, such as akinesis, paradoxical systolic segment lengthening, or postsystolic segment shortening.

#### HEMODYNAMIC MEASUREMENTS

A multichannel recorder (Hellige Co., West Germany) was used for the continuous recording of all signals. RV dP/dt and LV dP/dt were derived from RV and LV high-fidelity signals using operational amplifiers connected to a differentiator (Hellige Co., West Germany). For direct calibration of the dP/dt signals, a triangular wave signal of known slope was substituted for the pressure signal. Systemic (SVR), pulmonary (PVR), and right (CVR<sub>R</sub>) and left anterior descending (CVR<sub>LAD</sub>) coronary artery vascular resistances, right (RVSW) and left ventricular stroke work (LVSW), and stroke volume (SV) were derived from the following formulae:

$$\begin{aligned} SVR(\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}) &= \frac{AoP_m(\text{mmHg}) - RVEDP(\text{mmHg})}{AoF(\text{l}/\text{min})} \cdot 80 \end{aligned}$$

$$\begin{aligned} PVR(\text{dyn} \cdot \text{s} \cdot \text{cm}^{-5}) &= \frac{PAP_m(\text{mmHg}) - LVEDP(\text{mmHg})}{AoF(\text{l}/\text{min})} \cdot 80 \end{aligned}$$

$$\begin{aligned} CVR_R(\text{kdyn} \cdot \text{s} \cdot \text{cm}^{-5}) &= \frac{AoP_m(\text{mmHg}) - RVEDP(\text{mmHg})}{CBF_R(\text{ml}/\text{min})} \cdot 80 \end{aligned}$$

$$\begin{aligned} CVR_{LAD}(\text{kdyn} \cdot \text{s} \cdot \text{cm}^{-5}) &= \frac{AoP_d(\text{mmHg}) - LVEDP(\text{mmHg})}{CBF_{LAD}(\text{ml}/\text{min})} \cdot 80 \end{aligned}$$

$$\begin{aligned} RVSW(\text{g} \cdot \text{m}) &= \frac{1.36 \cdot [PAP_m(\text{mmHg}) - RVEDP(\text{mmHg})]}{100} \\ &\quad \times SV(\text{ml}) \end{aligned}$$

TABLE 1. Effects of Isoflurane-induced Hypotension on Systemic Hemodynamics and Left Ventricular Function (n = 12)

Variable	C	ISO 1	ISO 2
AoP <sub>m</sub> (mmHg)	94 ± 3	70 ± 1*	55 ± 1*†
LVSP (mmHg)	113 ± 1	85 ± 2*	70 ± 2*†
LV dP/dt <sub>max</sub>	1970 ± 101	1388 ± 66*	1075 ± 71*†
LVEDP (mmHg)	5.5 ± 0.3	4.8 ± 0.3	5.2 ± 0.3
LVS <sub>w</sub> (g · m)	32.3 ± 2.0	20.2 ± 7*	14.3 ± 1.4*†
LVSL <sub>ed</sub> (mm)	10.4 ± 0.6	10.1 ± 0.6	10.2 ± 0.6
LVSL <sub>sys</sub> (mm)	8.0 ± 0.5	8.0 ± 0.6	8.5 ± 0.6*‡
ΔLVSL (%)	23.5 ± 1.9	21.3 ± 1.7*	17.3 ± 1.7*†
AoF (l/min)	2.8 ± 0.2	2.4 ± 0.2*	2.0 ± 0.2*†
HR (beats/min)	103 ± 5	105 ± 4	99 ± 4
SV (ml/beat)	27 ± 2	23 ± 2*	21 ± 2*‡§
SVR (dyn · s · cm <sup>-5</sup> )	2729 ± 193	2374 ± 218*	2158 ± 186*†

Values are means ± SE. C = control; ISO 1 and ISO 2 = concentrations of isoflurane (ISO) that reduced mean aortic pressure (AoP<sub>m</sub>) to 70 mmHg (ISO 1) and 55 mmHg (ISO 2), respectively; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end diastolic pressure; LVS<sub>w</sub> = left ventricular stroke work; LVSL<sub>ed</sub> = left ventricular end diastolic segment length; LVSL<sub>sys</sub> = left ventricular systolic segment length; ΔLVSL = left ventricular segment shortening; AoF = aortic flow; HR = heart rate; SV = stroke volume; SVR = systemic vascular resistance.

\* P < 0.01 when compared to preceding value.

† P < 0.01 when compared to control value.

‡ P < 0.05 when compared to control value.

§ P < 0.05 when compared to preceding value.

$$\text{LVS}_w(\text{g} \cdot \text{m}) = \frac{1.36 \cdot [\text{AoP}_m(\text{mmHg}) - \text{LVEDP}(\text{mmHg})]}{100}$$

× SV(ml)

$$\text{SV}(\text{ml}/\text{beat}) = \frac{\text{AoF}(\text{ml}/\text{min})}{\text{HR}(\text{beats}/\text{min})}$$

where AoP<sub>m</sub> = mean aortic pressure, RVEDP = right ventricular end diastolic pressure, AoF = mean aortic flow, PAP<sub>m</sub> = mean pulmonary artery pressure, LVEDP = left ventricular end diastolic pressure, CBF<sub>R</sub> = mean right coronary artery blood flow, AoP<sub>d</sub> = end diastolic aortic pressure, and CBF<sub>LAD</sub> = mean left anterior descending coronary artery blood flow, HR = heart rate (as derived from the R-R intervals of the ECG).

#### EXPERIMENTAL PROTOCOL

Following sternotomy and the various cut-downs required for insertion of catheters, pentobarbital was discontinued, and no pentobarbital was administered during the 2 h prior to the start of the experiment. With the introduction of isoflurane, the rate of fentanyl infusion was reduced by approximately 30%. Any adjustments in ventilation, acid base status, depth of anesthesia, and fluid administration were made no later than 30 min prior to the start of the experiment. At the end of the surgical

preparation, at least 30 min were allowed for stabilization. Body temperature (T), hematocrit (Hct; Microcentrifuge Compur, Model M1100), arterial blood gases, and arterial pH (Instrumentation Laboratory, Model 613) were recorded at the end of each experimental period. After hemodynamic stabilization, control readings (C) were obtained in 12 animals. Isoflurane was then administered through a precalibrated vaporizer at a concentration sufficient to reduce AoP<sub>m</sub> to approximately 70 mmHg. Repeat measurements (ISO 1) were made 15–20 min after hemodynamic stabilization. The concentration of isoflurane was subsequently increased to lower AoP<sub>m</sub> to approximately 55 mmHg. Measurements were repeated (ISO 2) 15–20 min after hemodynamic stabilization.

In four additional animals, the effects of time on the stability of the surgical preparation were evaluated during baseline (fentanyl, pentobarbital) and isoflurane anesthesia. The surgical preparation was performed as described earlier. In two of the four animals, no interventions were undertaken after control readings had been obtained, and repeat measurements were made 3 h later. In the other two animals, isoflurane was administered at a concentration to reduce AoP<sub>m</sub> to approximately 55 mmHg while the infusion rate for fentanyl was reduced by approximately 30%. After baseline measurements had been obtained, no interventions were undertaken, and repeat measurements were made 2 h later.

#### STATISTICAL ANALYSIS

The data were statistically analyzed by Friedman's statistic, followed by Wilcoxon signed-rank test where appropriate (comparisons between experimental periods), or Mann-Whitney test (comparisons within experimental periods). A P value of <0.05 was considered statistically significant.

#### Results

##### EFFECTS OF ISOFLURANE ON SYSTEMIC HEMODYNAMICS AND LV FUNCTION

It required mean inspired concentrations of 1.2% (range 0.75–2.2%) and 1.8% (range 1.25–2.75%) isoflurane to lower AoP<sub>m</sub> to 70 mmHg (ISO 1) and 55 mmHg (ISO 2), respectively. Isoflurane caused dose-dependent decreases in LV systolic pressure (LVSP), LVS<sub>w</sub>, LV segment length shortening (ΔLVSL), AoF, and SV. LV systolic segment length (LVSL<sub>sys</sub>) increased only during ISO 2. LVEDP, LV end diastolic segment length (LVSL<sub>ed</sub>), and HR remained unchanged. SVR fell in a dose-dependent fashion (table 1).

EFFECTS OF ISOFLURANE ON PULMONARY HEMODYNAMICS AND RV FUNCTION

There were dose-dependent decreases in PAP<sub>m</sub>, RV systolic pressure (RVSP), RVSW, and in segment length shortening of RV inflow (ΔRVITSL) and outflow (ΔRVOTSL) tract. RVEDP, as well as end diastolic segment lengths in RV inflow tract (RVITSL<sub>ed</sub>), remained unchanged. In contrast, end diastolic segment lengths in the RV outflow tract (RVOTSL<sub>ed</sub>) increased during ISO 2. Systolic segment lengths (SL<sub>sys</sub>) increased in a dose-dependent fashion in both areas of the RV. PVR did not change (table 2).

EFFECTS OF ISOFLURANE ON CORONARY HEMODYNAMICS

During ISO 1, neither CBF<sub>LAD</sub> nor CBF<sub>R</sub> were significantly reduced. Only during ISO 2 did they fall significantly, by approximately 15%. Consequently, there were marked dose-related reductions in CVR<sub>LAD</sub> and CVR<sub>R</sub>. CBF as a fraction of aortic flow (CBF/AoF) increased in a dose-dependent fashion. There were no qualitative differences between RCA and LAD hemodynamic behavior (table 3).

EFFECTS OF ISOFLURANE ON SYSTEMIC, CORONARY AND PULMONARY CIRCULATIONS

Isoflurane exerted quantitatively and qualitatively different effects on the three circulations. Whereas PVR remained unchanged during both concentrations of isoflurane, there were dose-dependent decreases in CVR and SVR. In addition, there were quantitative differences between the coronary and the systemic circulations: the decreases in CVR during ISO 1 (-22.5% ± 1.3) and during ISO 2 (-31.7% ± 1.6) were significantly greater than those in SVR (-13.7% ± 3.1 and -21.3% ± 3.1, respectively) (fig. 1).

EFFECTS OF ISOFLURANE ON REGIONAL MYOCARDIAL PERFORMANCE

Isoflurane had quantitatively similar effects on regional function within the RV. The respective increases in end diastolic lengths of RVIT and RVOT during ISO 1 (0.3% ± 0.3 vs. 2.0% ± 0.8) and during ISO 2 (2.0% ± 0.4 vs. 4.8% ± 0.9), the increases in systolic segment lengths during ISO 1 (4.1% ± 1.2 vs. 5.9% ± 1.7) and during ISO 2 (10.3% ± 1.4 vs. 12.2% ± 2.2), and the decreases in segment shortening during ISO 1 (-18.2% ± 4.6 vs. -13.8% ± 4.2) and during ISO 2 (-35.6% ± 5.5 vs. -30.7% ± 6.7), were not significantly different from each other (figs. 2, 3).

TABLE 2. Effects of Isoflurane-induced Hypotension on Pulmonary Hemodynamics and Right Ventricular Function (n = 12)

Variable	C	ISO 1	ISO 2
PAP <sub>m</sub> (mmHg)	13 ± 1	12 ± 1*	11 ± 1†‡
RVSP (mmHg)	29 ± 1	25 ± 1*	23 ± 1*†
RV dP/dt <sub>max</sub>	425 ± 31	355 ± 25*	315 ± 29*†
RVEDP (mmHg)	3.1 ± 0.3	3.1 ± 0.3	3.4 ± 0.4
RVSW (g · m)	3.4 ± 0.3	2.6 ± 0.3*	2.0 ± 0.3*†
RVITSL <sub>ed</sub> (mm)	11.7 ± 0.9	11.7 ± 0.9	11.9 ± 0.9
RVITSL <sub>sys</sub> (mm)	9.6 ± 0.7	9.9 ± 0.7*	10.5 ± 0.8*†
ΔRVITSL (%)	18.2 ± 1.4	14.7 ± 1.1*	11.7 ± 1.0*†
RVOTSL <sub>ed</sub> (mm)	11.2 ± 0.9	11.4 ± 0.9	11.7 ± 0.9*†
RVOTSL <sub>sys</sub> (mm)	9.2 ± 0.8	9.7 ± 0.8*	10.3 ± 0.9*†
ΔRVOTSL (%)	18.3 ± 1.7	15.4 ± 1.3*	12.7 ± 1.4*†
PVR (dyn · s · cm <sup>-5</sup> )	235 ± 23	260 ± 30	238 ± 31

Values are means ± SE. PAP<sub>m</sub> = mean pulmonary artery pressure; RVSP = right ventricular systolic pressure; RVEDP = right ventricular end diastolic pressure; RVSW = right ventricular stroke work; RVITSL<sub>ed</sub> = RV inflow tract (RVIT) end diastolic segment length; RVITSL<sub>sys</sub> = RVIT systolic segment length; ΔRVITSL = RVIT segment shortening; RVOTSL<sub>ed</sub> = RV outflow tract (RVOT) end diastolic segment length; RVOTSL<sub>sys</sub> = RVOT systolic segment length; ΔRVOTSL = RVOT segment shortening; PVR = pulmonary vascular resistance.

\* P < 0.01 when compared to preceding value.

† P < 0.05 when compared to preceding value.

‡ P < 0.01 when compared to control value.

However, in four of the 12 animals, isoflurane exerted qualitatively different effects on regional performance of the RV inflow and outflow tract. In the control state, onset of shortening and occurrence of maximal systolic shortening did not differ by more than 10–30 ms between inflow and outflow tract. At the higher concentration of isoflurane (ISO 2), dyssynchrony between inflow and outflow tract developed in four animals: in early systole, there was now lengthening of the inflow tract and shortening of the outflow tract, and, in late systole, there was shortening of the inflow tract and lengthening of the outflow

TABLE 3. Effects of Isoflurane-induced Hypotension on Left and Right Coronary Hemodynamics (n = 12)

Variable	C	ISO 1	ISO 2
CBF <sub>LAD</sub> (ml/min)	27 ± 2	26 ± 2	23 ± 2*†
CBF <sub>R</sub> (ml/min)	17 ± 2	16 ± 2	14 ± 2*§
CVR <sub>LAD</sub> (kdyn · s · cm <sup>-5</sup> )	241 ± 24	174 ± 16*	148 ± 15*§
CVR <sub>R</sub> (kdyn · s · cm <sup>-5</sup> )	496 ± 69	371 ± 40*	327 ± 38†§
CBF <sub>LAD</sub> /AoF · 100 (%)	0.99 ± 0.06	1.15 ± 0.15†	1.23 ± 0.18†‡
CBF <sub>R</sub> /AoF · 100 (%)	0.62 ± 0.07	0.70 ± 0.08†	0.74 ± 0.09‡

Values are means ± SE. CBF<sub>LAD</sub> = mean left anterior descending coronary artery blood flow; CBF<sub>R</sub> = mean right coronary artery blood flow; CVR<sub>LAD</sub> = left anterior descending coronary artery vascular resistance; CVR<sub>R</sub> = right coronary artery vascular resistance.

\* P < 0.01 when compared to preceding value.

† P < 0.05 when compared to preceding value.

‡ P < 0.05 when compared to control value.

§ P < 0.01 when compared to control value.

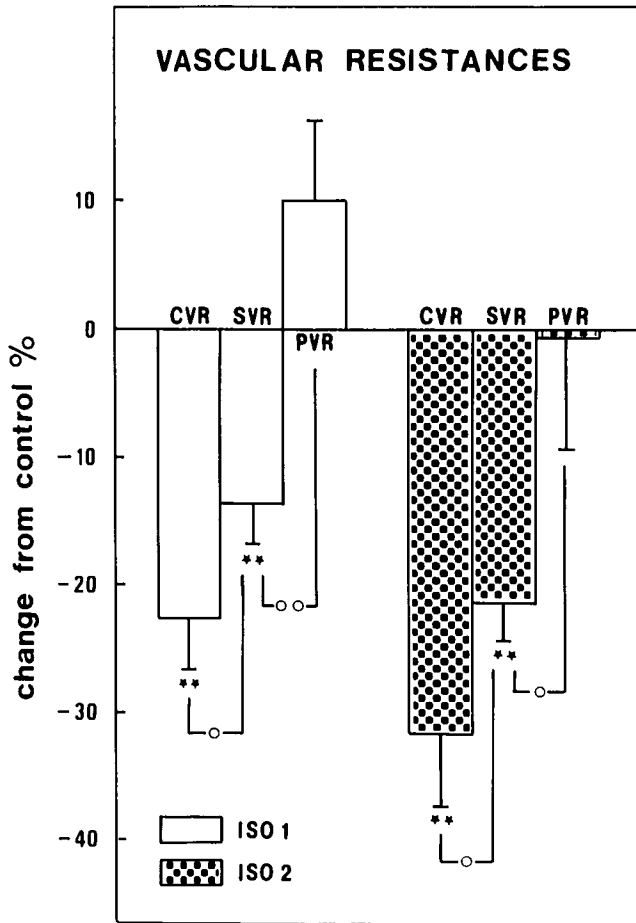


FIG. 1. Percent change in coronary (CVR), systemic (SVR), and pulmonary vascular resistance (PVR) from control to the lower (ISO 1) and higher concentration (ISO 2) of isoflurane. \*\*\* =  $p < 0.05$  (\*) or  $< 0.01$  (\*\*) from control. °, °° =  $p < 0.05$  (°) or  $< 0.01$  (°°) between indicated parameters.

tract. Onset of shortening and maximal shortening during systole now occurred as much as 70 ms after those in the outflow tract. This regional dysfunction in the inflow tract was not accompanied by changes in RV pressure tracings or by signs of regional myocardial underperfusion: CBF was well maintained, and, macroscopically, the myocardium appeared well perfused. Such dyssynchrony between inflow and outflow tract was not observed during ISO 1.

There were also differences between RV and LV regional performance. The decreases in LV end diastolic segment lengths during ISO 1 ( $-2.9\% \pm 1.2$ ) and during ISO 2 ( $-1.7\% \pm 1.3$ ), and the increase in LV systolic segment length during ISO 1 ( $0.2\% \pm 1.4$ ), were significantly different from the respective changes in RVIT and RVOT. In contrast, the decreases in LV segment shortening during ISO 1 ( $-9.0\% \pm 2.7$ ) and during ISO 2 ( $-26.1\% \pm 4.8$ ), although somewhat less, were not significantly different from those of RVIT and RVOT.

**EFFECTS OF ISOFLURANE ON INTRAVENTRICULAR PRESSURES**

Similar to RV and LV end diastolic segment lengths, the increase in RVEDP during ISO 1 ( $0.9\% \pm 4.8$ ) and during ISO 2 ( $7.8\% \pm 4.9$ ) were significantly different from the respective decreases in LVEDP ( $-11.0\% \pm 4.3$  and  $-4.1\% \pm 5.4$ ) (fig. 4).

**HEMODYNAMIC RECORDINGS**

These recordings were taken simultaneously. As in almost all the experiments, there were very pronounced increases in  $CBF_{LAD}$  and  $CBF_R$  within 30 s of starting isoflurane. These initial increases in CBF occurred with either no or only little change in AoF, LVEDP, and HR,

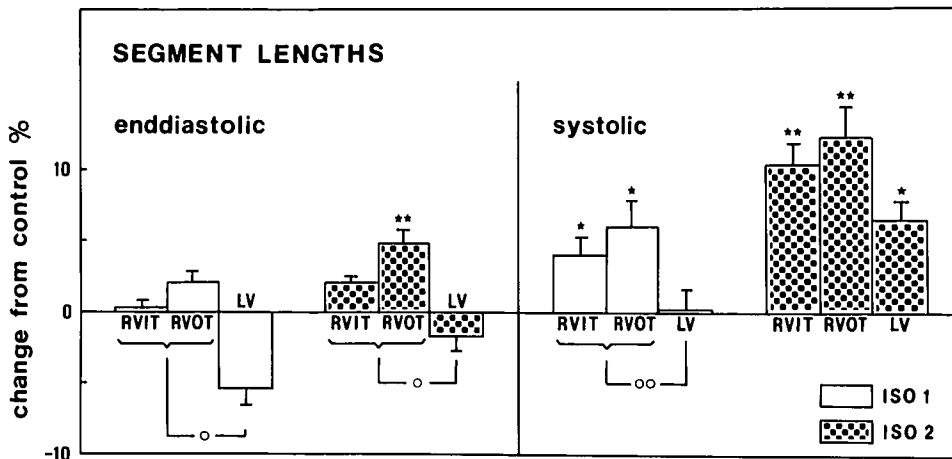


FIG. 2. Percent change in end diastolic and systolic segment lengths. (See figure 1 and text for further abbreviations and details.)

and with decreases in AoP, LV segment shortening, and LV dP/dt (fig. 5), and with no change in RV systolic pressure or mean PAP (fig. 6). In this particular example only, when compared to the control state, CBF remained as high (CBF<sub>LAD</sub>) or even higher (CBF<sub>R</sub>) during the steady-state conditions of ISO 2 (figs. 5, 6; right-hand panels), despite a clearly lower systemic perfusion pressure (AoP), LV dP/dt, and RV systolic pressure, and less shortening in LV, and in RVIT and RVOT. Dyssynchrony between inflow and outflow tract during isoflurane 2.1% (as described earlier) can be seen in this recording. (See figure legends for further details.)

**EFFECTS OF EXPERIMENTAL PROCEDURE ON GENERAL HOMEOSTASIS**

*p*Ha, PaO<sub>2</sub>, PaCO<sub>2</sub>, Hct, and body temperature did not change significantly throughout the experimental procedure (table 4).

**EFFECT OF TIME ON THE STABILITY OF THE SURGICAL PREPARATION DURING BASELINE AND ISOFLURANE ANESTHESIA**

All parameters could essentially be maintained during the 2- (t<sub>2h</sub>) and 3- (t<sub>3h</sub>) h periods (table 5).

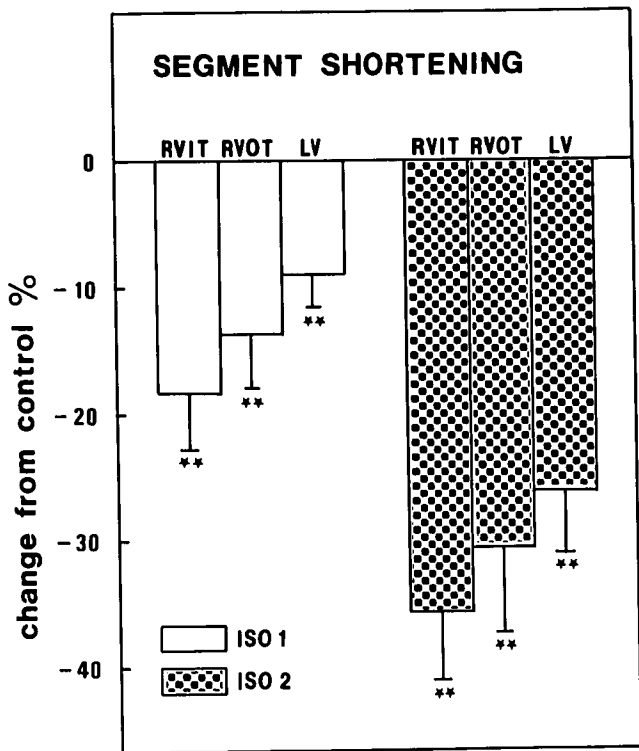


FIG. 3. Percent changes in segment shortening. (See figure 1 and text for further abbreviations and details.)

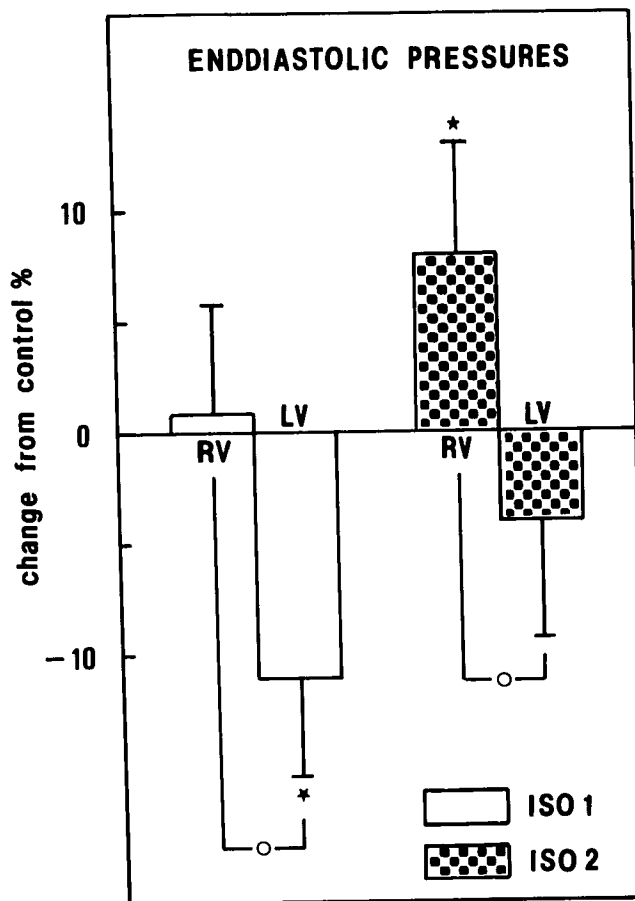


FIG. 4. Percent change in right (RV) and left ventricular (LV) end diastolic pressures. (See figure 1 and text for further abbreviations and details.)

**Discussion**

The principal findings of this study are: 1) isoflurane is a myocardial depressant; 2) isoflurane affects regional performance of RV and LV differently; 3) isoflurane affects regional performance of RV inflow and outflow tract quantitatively similarly, but may induce dyssynchrony between them; 4) isoflurane is a potent coronary artery vasodilator; and 5) isoflurane affects coronary, systemic, and pulmonary circulations differently.

**CRITIQUE OF METHODS**

The protocol employed simulates the clinical situation in which premedicated patients receive a baseline anesthetic during ongoing surgery, to which isoflurane is subsequently added to either deepen the anesthetic state or to deliberately induce hypotension. Accordingly, all measurements were taken during both anesthesia and acute

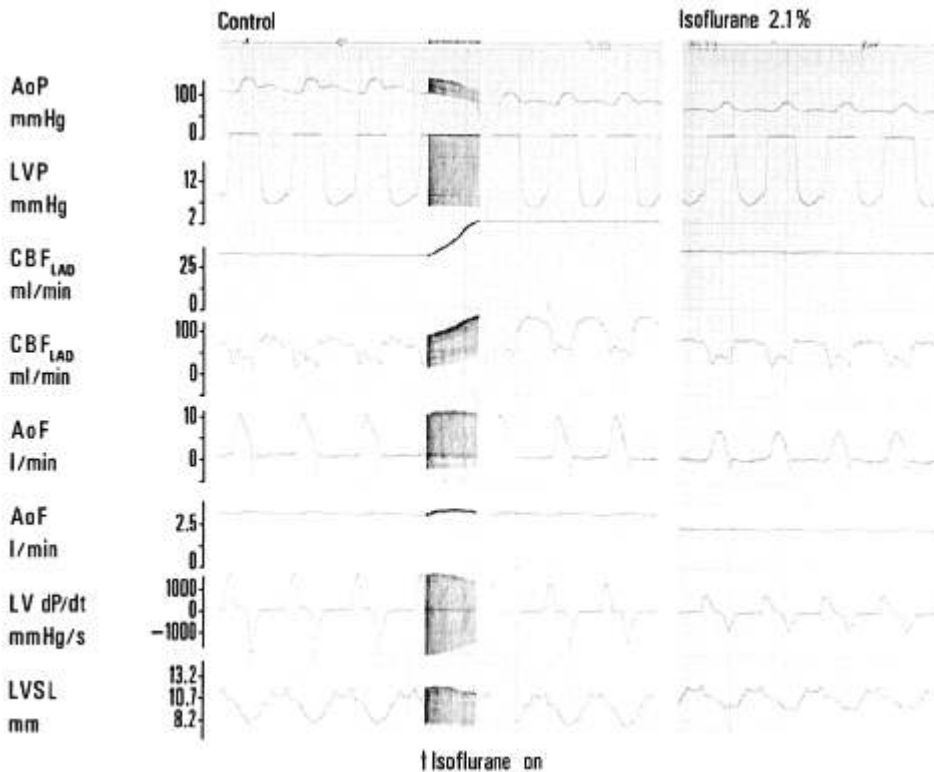


FIG. 5. When isoflurane was introduced ( $\uparrow$  Isoflurane on), there was an immediate increase in mean (channel 3) and in systolic and diastolic (channel 4) left anterior descending coronary blood flow ( $CBF_{LAD}$ ) without any change in aortic flow (AoF). Note the initial decrease in LV end diastolic segment length and the unchanged systolic segment length (LVSL). During the steady-state conditions of ISO 2 (Isoflurane 2.1%, right hand side), CBF remained as high as during the control state despite markedly lower aortic pressure (AoP), AoF, LV  $dP/dt_{max}$  and reduced segmental shortening. LVP = expanded LV pressure. (See text for further details.)

preparation. Although it has to be taken into consideration that anesthesia and acute operative interventions may alter normal physiologic responses,<sup>5</sup> this is, however, what is to be expected in patients undergoing anesthesia and surgery.

The type and amount of premedication and baseline anesthetic were selected to (a) ensure adequate sedation, analgesia, and anesthesia, and (b) to avoid myocardial depression. Premedication with fentanyl and droperidol have little effect on the cardiovascular system.<sup>6</sup> Even large doses of those agents do not impair myocardial contractility.<sup>7</sup> Effective premedication permitted a considerable reduction in the induction dose of pentobarbital. Administration of only low-dose pentobarbital and its discontinuation at least 2 h prior to the start of the experiment should have minimized, or even eliminated,<sup>8</sup> myocardial depression. However, some lasting effects of pentobarbital and a potential for later interaction with fentanyl cannot totally be excluded. The amount of fentanyl as administered by continuous infusion and the supplemental boli are sufficient to provide adequate analgesia in the dog.<sup>9</sup> The infusion rate of fentanyl was reduced at the start of isoflurane to avoid possible accumulation of fentanyl due to a decrease in hepatic metabolism.<sup>10</sup> On the other hand, fentanyl was not entirely discontinued upon introduction

of isoflurane, because this would have resulted in decreasing drug levels throughout the experiment. It has, therefore, to be realized that isoflurane elicited the described effects in the open-chest animal after premedication with fentanyl and droperidol, and in the presence of a baseline anesthesia with fentanyl.

The protocol required extensive surgical preparation. Both baseline anesthesia and surgery might have resulted in spontaneous deterioration of the preparation over time, and may thus have influenced the results. However, the results of the four control animals indicate that significant spontaneous deterioration of the preparation is unlikely. Nevertheless, the effects of negative inotropic influences may be more pronounced in the open-chest than in the closed-chest animal.

#### MYOCARDIAL PERFORMANCE

The results of this study document the negative inotropy of isoflurane. Because heart rate stayed constant, end diastolic pressures and dimensions remained unchanged (LV) or increased (RV), and because afterload decreased (LV) or remained unchanged (RV), the reductions in LV and RV  $dP/dt_{max}$ , as well as the reductions

in segmental shortening, in systolic pressures and in stroke volume, and the increases in systolic dimensions for both right and left ventricle can only be attributed to the negative inotropy of isoflurane. This is in accordance with previous studies.<sup>1,2,11</sup>

The effects of isoflurane on regional function of RV inflow tract (RVIT) and RV outflow tract (RVOT) were quantitatively very similar. In both areas of the RV, systolic segment lengths increased, and segment shortening decreased similarly in a dose-dependent fashion. End diastolic segment lengths also tended to increase in both areas of the RV, but this increase was significant only in the RV outflow tract. However, in 4 of the 12 animals, isoflurane affected the two areas of the RV qualitatively differently. In the RVIT, onset of shortening became clearly delayed, and contraction continued, so that maximal shortening occurred at a time when relaxation could already be observed in the RVOT.

The RV outflow tract is an anatomically and physiologically distinct region of the RV, which usually begins to contract 20–25 ms later than the RVIT,<sup>12–14</sup> and which remains contracted longer than the remainder of the RV.<sup>15</sup> An explanation for why isoflurane, in some animals, reversed this normal pattern cannot be provided on the basis of this investigation. CBF was always well maintained, and the myocardium in the area of the RVIT appeared macroscopically well perfused; therefore, it is highly unlikely that RVIT dysfunction developed on the basis of underperfusion. Placement of piezoelectric crystals, inspired concentrations of isoflurane, and overall hemodynamic responses were not notably different in these four animals.

Isoflurane affected RV and LV quantitatively differently (fig. 7); at the lower concentration of isoflurane (ISO 1), end diastolic segment lengths remained unchanged (RVIT) or increased slightly (RVOT), and end diastolic pressure also remained unchanged in the RV, but both end diastolic dimension and pressure tended to decrease in the LV. At the higher concentration of isoflurane (ISO 2), end diastolic dimensions and pressures now tended to increase in both ventricles. However, whereas, in the RV, both parameters tended to be above control values, they still tended to be lower than control values in the LV. Similarly, at the lower concentration of isoflurane, systolic segment lengths increased in the RV, but remained unchanged in the LV, whereas, at the higher concentration, they increased in both ventricles. Thus, LV dimensions and end diastolic pressure at the higher concentration of isoflurane in a way resembled those of the RV at the lower concentration.

The LV generated its output from a lower preload than the RV. This suggests that LV function was better

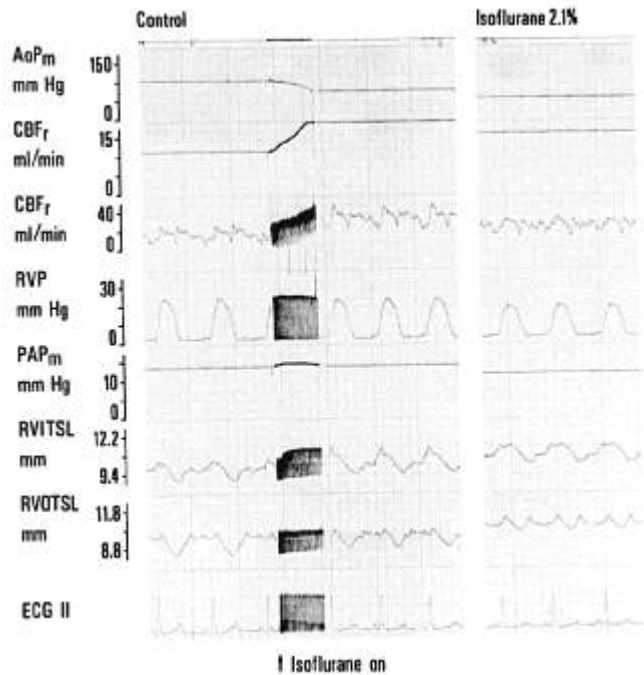


FIG. 6. (Simultaneously recorded with figure 5.) As in the case of LAD flow, there was an immediate increase in right coronary blood flow (CBF<sub>R</sub>) upon introduction of isoflurane. In contrast to the LV, end diastolic and systolic segment lengths increased in both right ventricular inflow (RVITSL) and outflow tract (RVOTSL). In the control state, onset of shortening and maximal shortening occurred almost simultaneously in inflow and outflow tract. During ISO 2 (Isoflurane 2.1%, right hand side), CBF remained above control. In the inflow tract, onset of shortening now became delayed by approximately 60 ms, and maximal shortening occurred approximately 70 ms after that in the outflow tract, i.e., dyssynchrony had developed between inflow and outflow tract. This dyssynchrony is not representative for the group as a whole because it developed in only four animals, and because this recording depicts the most extreme form. RVP = RV pressure; PAP<sub>m</sub> = mean pulmonary artery pressure.

maintained than RV function at both concentrations of isoflurane. It is likely that these differences in RV and LV performance existed, because, in the presence of myocardial depression, the RV faced an unchanged af-

TABLE 4. Effects of Experimental Procedure on General Homeostasis (n = 12)

Variable	C	ISO 1	ISO 2
pHa	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01
PaO <sub>2</sub> (mmHg)	210 ± 21	229 ± 15	225 ± 17
PaCO <sub>2</sub> (mmHg)	35 ± 1	35 ± 1	35 ± 1
Hct (%)	34 ± 1	34 ± 1	33 ± 1
T (°C)	37.4 ± 0.1	37.5 ± 0.1	37.3 ± 0.1

Values are means ± SE. (See text and table 1 for further abbreviations.)



TABLE 5. Effect of Time on Stability of Surgical Preparation during Baseline and Isoflurane Anesthesia (n = 4)

	Baseline Anesthesia				Isoflurane Anesthesia			
	Dog 1		Dog 2		Dog 3		Dog 4	
	t <sub>0</sub>	t <sub>3h</sub>	t <sub>0</sub>	t <sub>3h</sub>	t <sub>0</sub>	t <sub>3h</sub>	t <sub>0</sub>	t <sub>3h</sub>
AoP <sub>m</sub> (mmHg)	85	85	85	80	60	60	55	55
LVEDP (mmHg)	5.5	6	6.5	6.5	7	7	6	6
AoF (l/min)	3.3	3.4	2.5	2.4	1.7	1.8	2.0	1.8
HR (beats/min)	91	86	80	79	80	88	108	115
SV (ml/beat)	36	40	31	30	21	20	19	16
ΔLVSL (%)	27.5	26.8	24.6	24.3	18.0	15.0	24.0	23.7
ΔRVITSL (%)	21.2	19.6	14.2	13.1	11.9	10.9	18.3	19.1
ΔRVOTSL (%)	24.0	22.6	—	—	—	—	13.6	11.3
RVSP (mmHg)	24	27	21	22	21	23	21	20
RVEDP (mmHg)	2	3	3	3	4	4	3	3
PAP <sub>m</sub> (mmHg)	18	18	12	13	12	13	9	10
CBF <sub>R</sub> (ml/min)	17	18	12	13	13	13	12	13
CBF <sub>LAD</sub> (ml/min)	25	30	16	15	24	25	34	35
T (°C)	37.8	37.7	36.9	36.9	36.8	36.7	37.6	37.8
Hct (%)	23	24	30	32	31	32	38	39
pHa	7.45	7.42	7.39	7.38	7.40	7.38	7.35	7.35
PaCO <sub>2</sub> (mmHg)	37	37	37	36	35	35	37	37
PaO <sub>2</sub> (mmHg)	59	58	253	280	216	318	235	210

t<sub>0</sub> = control values; t<sub>3h</sub>, t<sub>2h</sub> = repeat measurement after 3 and 2 h, respectively. (See text and Tables 1 and 2 for abbreviations.)

terload, whereas the LV faced a decreased afterload. The finding of similar percent increases in systolic segment lengths and decreases in segment shortening in LV and RV during ISO 2 might suggest that, at the higher concentration of isoflurane, myocardial depression now overcame some of the functionally opposing effect of the decrease in LV afterload.

CORONARY HEMODYNAMICS

In this study, isoflurane proved to be a potent coronary vasodilator. Except for the moderate increase in RV preload at the higher concentration of isoflurane, the otherwise unchanged LV preload, RV afterload, and heart rate, and the decrease in LV afterload, segment short-

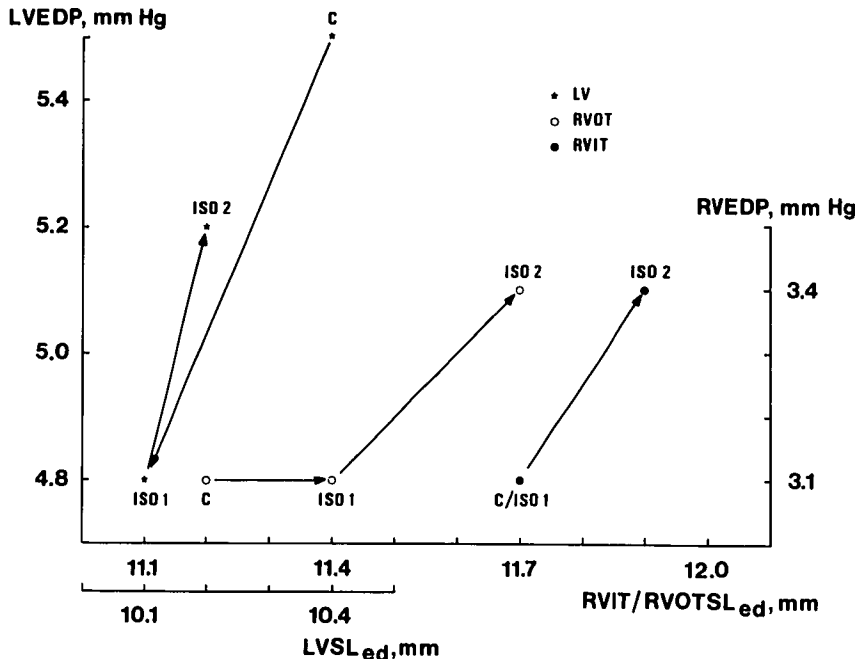


FIG. 7. Plot of end diastolic segment lengths (SL<sub>ed</sub>) vs. end diastolic pressures (EDP). RV inflow (RVITSL<sub>ed</sub>) and outflow (RVOTSL<sub>ed</sub>) tract end diastolic segment lengths are plotted against RVEDP, and LVSL<sub>ed</sub> is plotted against LVEDP. The arrows indicate the directional changes from control (C), to isoflurane 1 (ISO 1) and isoflurane 2 (ISO 2).

ening and stroke work are very likely to have markedly reduced myocardial  $O_2$  demands ( $M\dot{V}O_2$ ) during ISO 1 and ISO 2. This should have led to a decrease in CBF and an increase in CVR.<sup>16,17</sup> However, CVR decreased in a dose-dependent fashion, and CBF decreased significantly only during ISO 2. The potent coronary vasodilatory properties of isoflurane become even more striking if one considers that CBF was maintained almost at control values not only in the presence of what was likely a markedly reduced  $M\dot{V}O_2$ , but also at markedly reduced perfusion pressures. During ISO 2, coronary perfusion pressure (when calculated from mean aortic pressure minus LVEDP) had dropped to approximately 50 mmHg. This is below the normal autoregulatory range,<sup>18</sup> where CVR should not decrease any further, and where CBF becomes pressure-dependent.

It thus appears that coronary autoregulation is not preserved during isoflurane anesthesia. This is in agreement with findings of increased  $O_2$  content in coronary sinus blood with a concomitant decrease in myocardial  $O_2$  extraction.<sup>1,19</sup>

Data on the effects of isoflurane on coronary hemodynamics are conflicting. Decreases in CBF,<sup>2,11,20</sup> as well as unchanged<sup>1</sup> or increased CBF,<sup>21</sup> have been reported in the experimental animal. Some of the discrepancies can be explained on the basis of differences in species (dog vs. pig), preparation (acute vs. chronically instrumented; intact vs. open-chest animal), technique to determine myocardial blood flow (electromagnetic flow probes vs. microspheres vs. <sup>133</sup>Xe washout vs. coronary sinus catheter), and differences in the "control" state (awake vs. baseline anesthetic with opiates, opiates plus  $N_2O$ , or isoflurane itself).

Merin and Basch<sup>2</sup> found no evidence of coronary vasodilation and concluded that, under isoflurane, CBF is determined by the functional demands of the heart. In contrast to the present study, Merin studied dogs with a closed chest, CBF was determined by <sup>133</sup>Xenon washout, and there were no control values for CBF without isoflurane. Merin showed that, under these conditions, CBF was lower at an end-tidal concentration of 3.3% than at 1.7% isoflurane without changes in coronary vascular resistance. Manohar<sup>20</sup> reported a dose-dependent decrease in CBF, as determined by microspheres in the chronically instrumented, closed-chest pig. However, at 1 MAC isoflurane, total CBF had not fallen significantly, despite a significant decrease in aortic pressure. This would suggest that CVR had decreased at the lower concentration of isoflurane. In contrast, and in accordance with our own results, in the closed-chest dog during basal anesthesia with a synthetic opiate and 67% nitrous oxide, Tarnow *et al.*<sup>1</sup> found unchanged CBF (as determined by coronary

sinus catheter) at 0.5 and 1 MAC isoflurane with decreased myocardial  $O_2$  extraction indicating coronary vasodilation. Similarly, Gelman<sup>21</sup> reported an increase in CBF (as determined by microspheres) in the open-chest dog. Despite the many differences in methodology and in results, the majority of data suggests that, initially, there is a decrease in CVR in response to isoflurane. As isoflurane concentration is increased to above 1.5 MAC and as mean arterial pressure falls to below 65 mmHg, CBF also tends to fall with or without a concomitant further decrease in CVR.

#### SYSTEMIC AND PULMONARY CIRCULATIONS

There were quantitative as well as qualitative differences in the effects of isoflurane on various circulations. Whereas isoflurane did not significantly change pulmonary vascular resistance, it reduced systemic vascular resistance (SVR). This confirms previous studies.<sup>1,2</sup> In addition, the dose-dependent increase in CBF as a fraction of aortic flow, and the greater decreases in CVR than in SVR during both concentrations of isoflurane, indicate that isoflurane is a less powerful systemic arterial than coronary artery vasodilator.

The difference in change of SVR and PVR caused by isoflurane will result in clearly different afterloads for LV and RV. This is of special significance for regional myocardial performance in the presence of a myocardial depressant, such as isoflurane (as discussed earlier).

In conclusion, this study confirms the negative inotropy of isoflurane and its potent coronary vasodilating properties. It demonstrates quantitatively similar, but at times qualitatively different, effects of isoflurane on regional performances of RV inflow and outflow tract. Differences were also observed between RV and LV dimensions and end diastolic pressures during identical concentrations of isoflurane which were most likely related to the different effect of isoflurane on RV (unchanged) and LV (reduced) afterloads. The data suggest that moderate, and even pronounced, isoflurane-induced hypotension is well tolerated by a heart with a presumed normal coronary circulation.

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#### References

1. Tarnow J, Eberlein HJ, Oser G, Patschke D, Schneider E, Schweichel E, Wilde J: Hämodynamik, Myokardkontraktilität, Ventrikelvolumina und Sauerstoffversorgung des Herzens unter

- verschiedenen Inhalationsanästhetika. *Anaesthesist* 26:220-230, 1977
2. Merin RG, Basch S: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? *ANESTHESIOLOGY* 55:398-408, 1981
  3. Bugge-Asperheim B, Leraand S, Kiil F: Local dimensional changes of the myocardium measured by ultrasonic technique. *Scand J Clin Lab Invest* 24:361-371, 1969
  4. Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N: The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res Cardiol* 72:344-364, 1977
  5. Vatner S, Braunwald E: Cardiovascular control mechanisms in the conscious state. A comparison of the effects of physiological and pharmacological stimuli in the presence and absence of general anesthesia. *N Engl J Med* 293:970-976, 1975
  6. Muggenburg BA, Mauderly JL: Cardiopulmonary function of awake, sedated, and anesthetized beagle dogs. *J Appl Physiol* 37:152-157, 1974
  7. Ostheimer GW, Shanahan EA, Guyton RA, Daggett WM, Lowenstein E: Effects of fentanyl and droperidol on canine left ventricular performance. *ANESTHESIOLOGY* 42:288-291, 1975
  8. Newman WH, Pruett JK: Myocardial contractility during induction and steady-state pentobarbital anesthesia. *Arch Int Pharmacodyn Ther* 199:139-143, 1972
  9. Arndt JO, Mikat M, Parasher C: Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. *ANESTHESIOLOGY* 61:355-361, 1984
  10. Van Wijngaarden I, Soudijn W: The metabolism and excretion of the analgesic fentanyl (R 4263) by Wistar rats. *Life Sci* 7:1239-1244, 1968
  11. Theye RA, Michenfelder JD: Individual organ contributions to the decrease in whole-body  $\dot{V}O_2$  with isoflurane. *ANESTHESIOLOGY* 42:35-40, 1975
  12. March HW, Ross JK, Lower RR: Observations on the behaviour of the right ventricular outflow tract, with reference to its developmental origins. *Am J Med* 32:835-845, 1962
  13. Armour JA, Pace JB, Randall WC: Interrelationship of architecture and function of the right ventricle. *Am J Physiol* 218:174-179, 1970
  14. Santamore WP, Meier GD, Bove AA: Effects of hemodynamic alterations on wall motion in the canine right ventricle. *Am J Physiol* 236:H254-H262, 1979
  15. Raines RA, LeWinter MM, Covell JW: Regional shortening patterns in canine right ventricle. *Am J Physiol* 231:1395-1400, 1976
  16. Berne RM: Regulation of coronary blood flow. *Physiol Rev* 44:1-29, 1964
  17. Braunwald E: Control of myocardial oxygen consumption: physiologic and clinical considerations. *Am J Cardiol* 27:416-432, 1971
  18. Braunwald E, Ross J Jr, Sonnenblick EH: Regulation of coronary blood flow, Mechanisms of Contraction of the Normal and Failing Heart. 2nd edition. Boston, Little Brown, 1976, p 200
  19. Reiz S, Bolfors E, Sørensen MB, Ariola S Jr, Friedman A, Truedsson H: Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. *ANESTHESIOLOGY* 59:91-97, 1983
  20. Manohar M, Parks C: Regional distribution of brain and myocardial perfusion in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia produced without or with 50% nitrous oxide. *Cardiovasc Res* 18:344-353, 1984
  21. Gelman S, Fowler KC, Smith LR: Regional blood flow during isoflurane and halothane anesthesia. *Anesth Analg* 63:557-565, 1984