

Isoflurane Causes Regional Myocardial Dysfunction in Dogs with Critical Coronary Artery Stenoses

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The effects of isoflurane-induced hypotension to mean aortic pressures of 70 and 55 mmHg on global and regional right and left ventricular performance (ultrasonic dimension technique) and on coronary hemodynamics (electromagnetic flow probes) were studied in 12 open-chest dogs (anesthetized and paralyzed by continuous infusions of fentanyl and pancuronium) with critical coronary artery stenoses (micrometer-controlled snares) of the right and left anterior descending coronary arteries. The stenoses reduced resting coronary blood flow by approximately 10% without affecting global or regional myocardial performance. During subsequent isoflurane administration, coronary blood flow fell markedly. In the areas supplied by the stenosed coronary arteries, segment length shortening decreased by 70% ($P < 0.01$), and regional akinesis, paradoxical motion, or postsystolic shortening developed in 9 of 12 animals. In contrast, in the areas supplied by normal coronary arteries, myocardial segment length shortening decreased significantly less and did not show signs of dysfunction. In these non-ischemic areas at both concentrations of isoflurane, end diastolic and systolic dimensions were greater in the right than in the left ventricle, probably related to differences in right (unchanged) and left (reduced) ventricular afterloads. The data indicate that in the presence of coronary artery stenoses, isoflurane-induced hypotension may cause regional myocardial dysfunction suggestive of ischemia. (Key words: Anesthetic, volatile: isoflurane. Heart: coronary artery stenosis; regional myocardial performance.)

CONTROVERSY EXISTS about which anesthetic agent or technique to use in patients with known or suspected coronary artery disease.^{1,2} While isoflurane may be beneficial because it reduces myocardial oxygen demand,³ it may also be detrimental because it tends to lower systemic arterial pressure and, thus, coronary perfusion pressure at concentrations necessary to achieve adequate levels of anesthesia.⁴ In addition, isoflurane may cause coronary "steal" in patients with coronary artery disease.^{5,6}

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While experimental data concerning the effects of isoflurane on the normal coronary circulation have been conflicting,^{7,8} no experimental data exist on the effects of isoflurane on coronary hemodynamics and regional myocardial function in the presence of coronary artery stenosis. When deliberately induced hypotension is employed to facilitate surgery, mean systemic arterial pressure may be lowered to 40-60 mmHg. Since uncontrolled intraoperative hypotension is associated with increased perioperative cardiac morbidity and mortality,⁹ ischemic heart disease is considered a contraindication to the technique of deliberately induced controlled hypotension.¹⁰ In the experimental animal, the combination of a moderate coronary artery stenosis (10% reduction in resting coronary blood flow) and deliberate hypotension to a mean arterial pressure of 50 mmHg induced by halothane failed to produce evidence of regional myocardial ischemia.¹¹ In contrast, in the same study, the combination of severe stenosis (40% reduction in resting coronary blood flow) and halothane-induced hypotension produced evidence of myocardial ischemia.¹¹

This study was designed to investigate the effects of two levels of isoflurane-induced hypotension on right and left ventricular myocardial function, and on coronary hemodynamics in the presence of a partially obstructed right and left coronary circulation.

Methods

INSTRUMENTATION

Twelve mongrel dogs of either sex weighing between 24 and 40 kg were premedicated with intramuscular fentanyl and droperidol, anesthetized and paralyzed with continuous iv infusions of pentobarbital, fentanyl, and pancuronium, and ventilated as previously described in detail.¹² Sodium bicarbonate was administered if the calculated base deficit exceeded 5 mEq/l. All dogs were in the supine 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®) positioned in the pulmonary artery. All animals received 4-6 ml · kg⁻¹ · h⁻¹ of normal saline.

Catheter-tip manometers (6F®, Millar Instruments Inc, TX) were advanced into the ascending aorta just above the aortic valve, and into the left (LV) and the right ventricles (RV), and calibrated as previously described.¹² The

chest was entered through a median sternotomy and 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 non-occlusive zero (Hellige Co., West Germany).

REGIONAL MYOCARDIAL FUNCTION

Regional myocardial performance was evaluated by sonomicrometry.^{13,14} Two 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, and another two pairs were inserted in an equatorial plane into the subendocardium of the LV distal to the first or second diagonal branch of the LAD and proximal to the first diagonal branch. Care was taken to place the crystals in the RV outflow tract and those proximal to the first diagonal branch outside the areas supplied by the RCA and LAD distal to the flow probes, and 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. This was done by occluding transiently RCA and LAD at the sites of the placement of the flow probes and observing the areas of developing cyanosis.

Myocardial segment lengths (SL) between each pair of crystals were determined at end diastole (SL_{ed}) and at the time of maximal shortening during systole (SL_{sys}). 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 end systole by the dicrotic notch in the aortic pressure signal as derived from the catheter-tip manometers. The ultrasonic signals were also assessed visually for qualitative changes such as akinesis, paradoxical systolic segment lengthening, or postsystolic segment shortening.¹⁵

CRITICAL STENOSIS

Critical coronary artery stenosis was defined as the minimum constriction necessary to prevent an increase in resting coronary blood flow (CBF) by more than 10% in response to an iv injection of the powerful coronary vasodilator acetate. Sutures were placed around the RCA and the LAD immediately distal to the respective flow probes. The sutures were attached to micrometer-controlled, spring-suspended snares which could be adjusted in 0.01 mm increments. While observing the maximally

amplified mean and phasic RCA and LAD flow signals on the oscilloscope, the snares were gradually tightened in 0.1 mm increments until dampening of the phasic flow signals and a tendency for the mean CBF to decline was observed. At this point, 0.02 ml/kg BW of a concentrated acetate solution (2.7 mMol/ml) was injected. If the injection of acetate resulted in a greater than 10% increase in resting CBF, the snare was tightened further by increments of 0.01 mm, and acetate was readministered. This procedure was continued until acetate failed to increase resting CBF by more than 10%. It required 2–4 injections of acetate to establish the critical stenoses (see also "Discussion").

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). Systemic (SVR) and pulmonary vascular resistances (PVR), right (RVSW) and left ventricular stroke work (LVSW), and stroke volume (SV) were derived from standard formulae.¹²

EXPERIMENTAL PROTOCOL

After the sternotomy, and approximately 2 h prior to the start of the experiment, pentobarbital was discontinued. 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. Critical stenoses were established under baseline anesthesia with fentanyl. With the introduction of isoflurane, the rate of fentanyl infusion was reduced by approximately 30% to 15 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. 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 control readings (C) had been obtained, critical stenoses of the RCA and LAD were induced. Measurements were made again 15–20 min after induction of the stenoses (S). Isoflurane was then administered through a precalibrated vaporizer at a concentration sufficient to reduce AoP_m to approximately 70 mmHg. Repeat measurements (ISO 1) were made after hemodynamic stabilization. The concentration of isoflurane was subsequently increased to lower AoP_m to approximately 55 mmHg, and measurements were repeated (ISO 2) after hemodynamic stabilization.

TABLE 1. Effects of Isoflurane-induced Hypotension on Systemic Hemodynamics, and on Left Ventricular Function and Coronary Blood Flow

Variable	C	S	ISO 1	ISO 2
AoP _m (mmHg)	95 ± 3	95 ± 2	70 ± 1*	55 ± 1*‡
LVSP (mmHg)	120 ± 4	119 ± 4	90 ± 3*	75 ± 3*‡
LVEDP (mmHg)	6.2 ± 0.5	6.3 ± 0.5	5.6 ± 0.4	6.2 ± 0.5
LVS _W (g · m)	29.4 ± 1.9	29.7 ± 1.7	16.6 ± 1.5*	9.9 ± 1.2*‡
LV _n SL _{ed} (mm)	10.9 ± 0.9	10.9 ± 0.9	10.6 ± 0.9†	10.9 ± 0.9*
LV _n SL _{sys} (mm)	8.2 ± 0.7	8.2 ± 0.7	8.2 ± 0.7	8.5 ± 0.7†§
ΔLV _n SL (%)	24.8 ± 2.1	24.5 ± 2.2	22.9 ± 1.9	21.8 ± 1.9‡
LV _s SL _{ed} (mm)	11.4 ± 0.9	11.4 ± 0.9	11.5 ± 0.9	12.1 ± 1.0†‡
LV _s SL _{sys} (mm)	8.5 ± 0.7	8.5 ± 0.7	9.9 ± 0.8*	11.4 ± 0.9*‡
ΔLV _s SL (%)	25.5 ± 2.1	25.1 ± 2.1	14.1 ± 1.2*	6.0 ± 1.4*‡
AoF (l/min)	2.3 ± 0.1	2.4 ± 0.1	2.2 ± 0.1†	1.7 ± 0.2*‡
HR (beats/min)	98 ± 6	100 ± 6	118 ± 7	114 ± 6
SV (ml/beat)	24 ± 2	25 ± 2	19 ± 2*	15 ± 2*‡
SVR (dyn · s · cm ⁻⁵)	3251 ± 257	3157 ± 245	2632 ± 226*	2793 ± 282§
CBF _{LAD} (ml/min)	29 ± 2	26 ± 2†	17 ± 2*	12 ± 1*‡

Values are means ± SE. C = control; S = post-induction of stenoses; ISO 1 and ISO 2 = concentrations of isoflurane (ISO) that reduced mean aortic pressure (AoP_m) to 70 mmHg (ISO 1) and 55 mmHg (ISO 2), respectively; LVSP = left ventricular (LV) systolic pressure; LVEDP = LV end-diastolic pressure; LVS_W ± LV stroke work; LVSL_{ed} = LV enddiastolic (ed) segment length (SL); LVSL_{sys} = LV systolic SL; ΔLVSL = LVSL shortening; The letters "n" and "s" in conjunction with measures of LV segments denote LV area supplied

by a nonstenosed (n) or the stenosed (s) coronary artery; AoF = aortic flow; HR = heart rate; SV = stroke volume; SVR = systemic vascular resistance; CBF_{LAD} = mean left anterior descending coronary artery blood flow.

* P < 0.01 when compared to preceding value.

† P < 0.05 when compared to preceding value.

‡ P < 0.01 when compared to stenosis value.

§ P < 0.05 when compared to stenosis value.

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 ON LV FUNCTION AND CORONARY BLOOD FLOW

It required mean inspired concentrations of 1.2% (range 0.7–2.0%) and 1.9% (range 1.25–2.5%) isoflurane to lower AoP_m to 70 mmHg (ISO 1) and 55 mmHg (ISO 2), respectively.

Induction of the LAD stenosis led to a small (10%) but significant reduction in LAD flow (CBF_{LAD}). Otherwise, there were no significant differences between control values (C) and those determined after induction of the coronary artery stenoses (S). Isoflurane caused dose-dependent decreases in LV systolic pressure (LVSP), LVS_W, AoF, stroke volume (SV), and CBF_{LAD}. LVEDP and heart rate (HR) did not change significantly. SVR decreased initially (ISO 1) by approximately 15%. It did not decrease further with the higher concentration of isoflurane (ISO

2). Whereas LV segment shortening (ΔLVSL) in the area supplied by the nonstenosed (n) coronary circulation fell insignificantly during ISO 1, and significantly by only 11% during ISO 2, ΔLVSL in the area supplied by the stenosed (s) LAD fell by approximately 45 and 75% during ISO 1 and ISO 2, respectively. In the nonstenosed area, LV end diastolic segment lengths (LV_nSL_{ed}) decreased initially and returned to baseline at ISO 2. In contrast, in the stenosed area, LV_sSL_{ed} remained unchanged at ISO 1, and increased at ISO 2. Similarly, systolic segment lengths in the nonstenosed area (LV_nSL_{sys}) remained unchanged at ISO 1 and increased by only 4% during ISO 2, but, in the area supplied by the stenosed LAD (LV_sSL_{sys}), they increased by approximately 15 and 35% during ISO 1 and ISO 2, respectively (table 1).

In addition, during ISO 2 in the area supplied by the stenosed LAD, akinesis and/or segment lengthening during systole (systolic bulge) and/or postsystolic shortening developed in 9 of 12 animals.

EFFECT OF ISOFLURANE ON PULMONARY HEMODYNAMICS, AND ON RV FUNCTION AND CORONARY BLOOD FLOW

There were no significant differences between control values (C) and those determined after induction of the stenoses (S). There were dose-dependent decreases in PAP_m, RV systolic pressure (RVSP), RVS_W, segment length shortening of RV outflow (ΔRVOTSL) and inflow tract (ΔRVITSL), and right coronary artery blood flow

TABLE 2. Effects of Isoflurane-induced Hypotension on Pulmonary Hemodynamics, and on Right Ventricular Function and Coronary Blood Flow

Variable	C	S	ISO 1	ISO 2
PAP _m (mmHg)	13 ± 1	14 ± 1	12 ± 1*	11 ± 1*‡
RVSP (mmHg)	27 ± 1	28 ± 1	23 ± 1†	20 ± 1†‡
RVEDP (mmHg)	2.5 ± 0.3	2.5 ± 0.3	2.8 ± 0.3	3.0 ± 0.3
RVS _W (g · m)	3.7 ± 0.3	3.7 ± 0.3	2.7 ± 0.3†	1.9 ± 0.3†‡
RVOTSL _{ed} (mm)	10.5 ± 0.8	10.5 ± 0.8	10.6 ± 0.8	10.9 ± 0.9
RVOTSL _{sys} (mm)	8.4 ± 0.7	8.3 ± 0.7	8.7 ± 0.7†	9.3 ± 0.7*†
ΔRVOTSL (%)	20.7 ± 1.7	20.3 ± 1.7	17.7 ± 1.4†	14.4 ± 1.2*†
RVITSL _{ed} (mm)	10.6 ± 0.8	10.5 ± 0.8	10.7 ± 0.9*	11.1 ± 0.9*†
RVITSL _{sys} (mm)	8.4 ± 0.7	8.4 ± 0.7	9.4 ± 0.7†	10.3 ± 0.8*†
ΔRVITSL (%)	20.2 ± 1.6	20.0 ± 1.7	12.0 ± 1.0†	6.5 ± 0.9†‡
PVR (dyn · s · cm ⁻⁵)	229 ± 27	231 ± 33	233 ± 30	222 ± 33
CBF _{RCA} (ml/min)	14 ± 2	13 ± 1	9 ± 1†	5 ± 1†‡

Values are means ± SE. PAP_m = mean pulmonary artery pressure; RVSP = right ventricular (RV) systolic pressure; RVEDP = RV end-diastolic pressure; RVS_W = RV stroke work; RVOTSL_{ed} = RV outflow tract (OT) enddiastolic (ed) segment length (SL); RVOTSL_{sys} = RVOT systolic SL; ΔRVOTSL = RVOTSL shortening; IT = inflow tract;

PVR = pulmonary vascular resistance; CBF_{RCA} = mean right coronary blood flow.

* $P < 0.05$ when compared to preceding value.

† $P < 0.01$ when compared to preceding value.

‡ $P < 0.01$ when compared to stenosis value.

(CBF_{RCA}), and dose-dependent increases in systolic (sys) segment lengths in both areas of the RV (RVOTSL_{sys}, RVITSL_{sys}), and in end diastolic segment lengths of RVIT (RVITSL_{ed}). RVEDP and end diastolic segment lengths of RVOT (RVOTSL_{ed}) did not increase significantly. As in the LV, changes in regional myocardial performance were more pronounced in the area (RVIT) supplied by the stenosed RCA, and during ISO 2 systolic segment lengthening and/or postsystolic shortening developed in seven animals in the RV inflow tract, *i.e.*, that area supplied by the stenosed right coronary artery. PVR remained unchanged throughout (table 2).

COMPARATIVE EFFECTS OF ISOFLURANE ON REGIONAL MYOCARDIAL PERFORMANCE

There were quantitative differences in regional myocardial function (a) within each ventricle between the areas supplied by a normal or a stenosed coronary artery, and (b) between the two ventricles. Within each ventricle, the increases in systolic segment lengths (fig. 1B) and the decreases in segment shortening (fig. 1C) were more pronounced in the areas supplied by the stenosed coronary arteries. As for the increase in end diastolic segment lengths, this difference was observed only in the LV (fig. 1A). Whereas, in the areas supplied by the stenosed coronary arteries, end diastolic and systolic segment lengths increased and segment shortening decreased to a similar extent in RV and LV, in the areas supplied by the unobstructed coronary circulations, these changes were more pronounced in the RV.

Figure 2 shows the effects of pronounced isoflurane-induced hypotension on LV function and CBF. Akinesis and postsystolic shortening can be seen in the area sup-

plied by the stenosed LAD when AoP_m had fallen to approximately 50 mmHg (see figure legend for further details).

There were no significant differences in pH_a, PaO₂, PaCO₂, Hct, and body temperature between any of the experimental periods.

Discussion

The protocol was designed to simulate the clinical situation in which patients with coronary artery disease, asymptomatic at rest, are premedicated and receive a baseline anesthetic during ongoing surgery, to which isoflurane is subsequently added to either deepen the anesthetic state or to deliberately induce hypotension. Type and amount of premedication and baseline anesthetic were selected to (a) ensure adequate sedation, analgesia, and anesthesia, and (b) to minimize myocardial depression. Premedication with fentanyl and droperidol have little effect on the cardiovascular system.¹⁶ Even in the presence of a critical coronary artery stenosis, administration of a high dose of fentanyl does not cause regional myocardial dysfunction.¹⁷ Effective premedication permitted a considerable reduction in induction and maintenance dose of pentobarbital. Its discontinuation at least 2 h prior to the start of the experiment should have minimized or even eliminated myocardial depression.¹⁸ However, some lasting effects of pentobarbital and a potential for later interaction with fentanyl cannot totally be excluded. It has, therefore, to be realized that the effect elicited by isoflurane occurred in the open-chest animal after premedication with fentanyl and droperidol, and during a baseline anesthesia with fentanyl. Negative inotropic in-

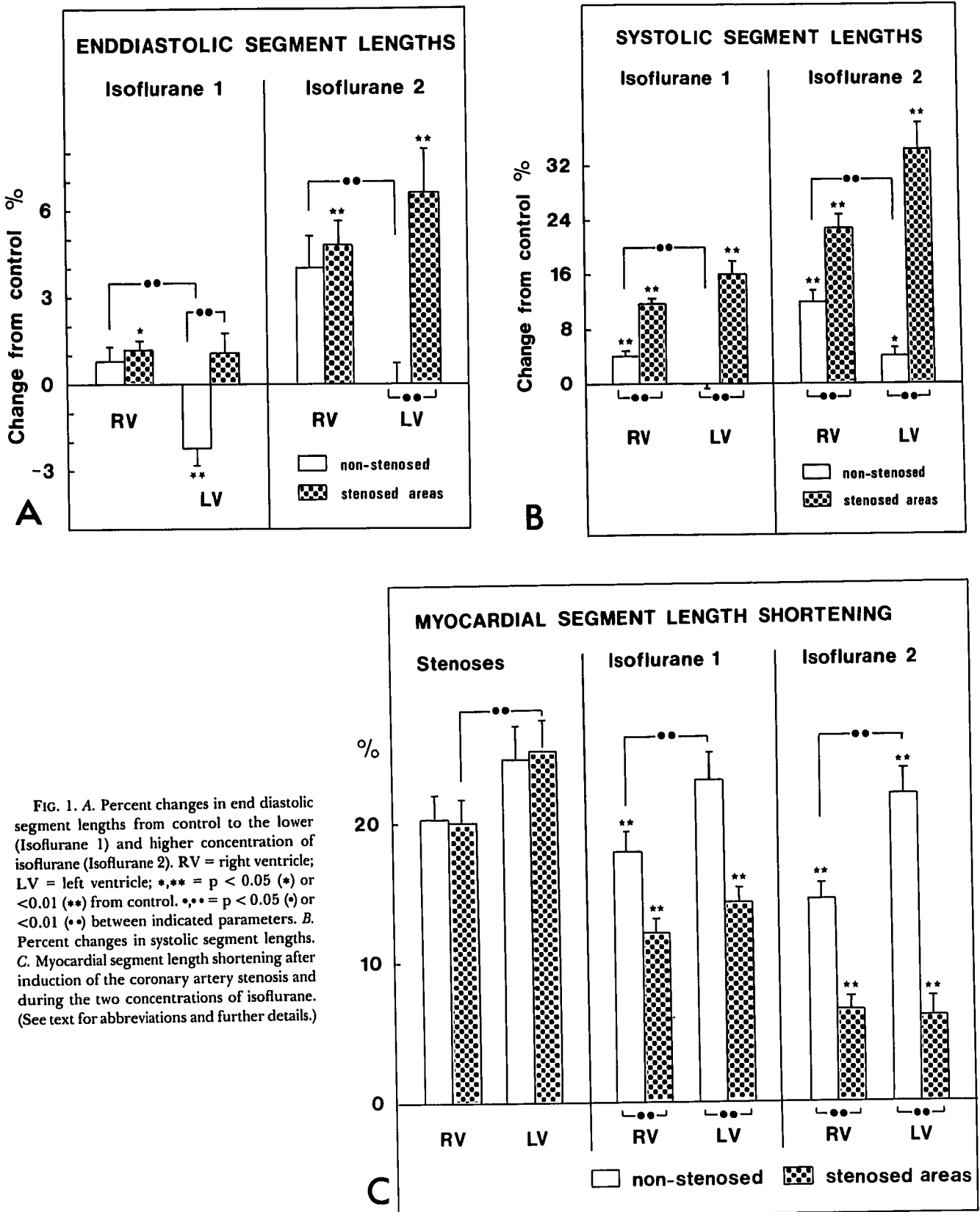


FIG. 1. A. Percent changes in end diastolic segment lengths from control to the lower (Isoflurane 1) and higher concentration of isoflurane (Isoflurane 2). RV = right ventricle; LV = left ventricle; *,** = $p < 0.05$ (*) or < 0.01 (**) from control. *,** = $p < 0.05$ (*) or < 0.01 (**) between indicated parameters. B. Percent changes in systolic segment lengths. C. Myocardial segment length shortening after induction of the coronary artery stenosis and during the two concentrations of isoflurane. (See text for abbreviations and further details.)

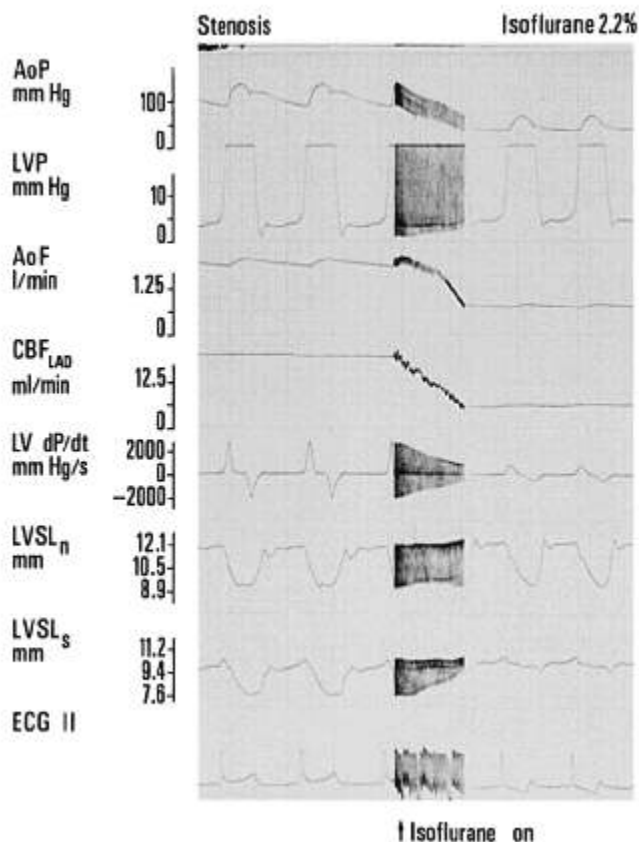


FIG. 2. When isoflurane was introduced (↑ Isoflurane on) during underlying coronary artery stenoses, there was an immediate pronounced fall in coronary blood flow through the stenosed left anterior descending coronary artery (CBF_{LAD}), STdepression occurred, and akinesis and postsystolic shortening developed in the area supplied by the stenosed LAD ($LVSL_s$). In contrast, in the area of the nonobstructed coronary circulation ($LVSL_n$), regional myocardial performance remained entirely unaffected, despite concomitant marked reductions in LV dP/dt and aortic flow (AoF). This recording is not entirely representative for the group as a whole because it shows the most severe form of regional dysfunction, and mean aortic pressure (AoP) fell to below 55 mmHg. However, it is evident that systolic shortening in the underperfused area ($LVSL_s$) started to decline at a considerably higher AoP.

fluences may be more pronounced in the open-chest than in the closed-chest animal.¹⁹

The degree of coronary artery stenosis aimed at has been termed "critical" in the literature.^{20,21} Critical stenosis has been defined as the minimum constriction required "to prevent an increase in flow over resting values in response to increased myocardial oxygen demands."²⁰ Resting CBF should hardly be affected, despite reductions in coronary artery diameter by as much as 75–93%.^{20,21} In the present study, critical stenosis was defined as the minimum constriction necessary to prevent an increase in resting CBF by more than 10% in response to an iv injection of acetate, which has been shown to be a pow-

erful coronary vasodilator.^{22,23} Our own preliminary studies have shown that it consistently increased resting CBF three- to five-fold, a response very similar to the two- to five-fold increases which we observed in this preparation following a 10 s occlusion of the RCA and LAD under baseline conditions. When, during progressive constriction of the coronary arteries, CBF failed to increase by more than 10% in response to acetate, it also failed to increase by more than 10% in response to a 10 s occlusion of the coronary arteries. The increase in CBF was not blunted after repeated injections of acetate, and CBF returned to baseline values within 1–2 min following injection. This is most likely related to rapid metabolism. Acetate was, therefore, utilized as a convenient means of repeatedly stimulating coronary vasodilation, thus avoiding mechanical damage to the coronary arteries and/or residual regional myocardial dysfunction, possibly associated with numerous vascular occlusions. The acetate injections did not produce myocardial dysfunction. Stenoses established this way resulted in reductions of resting coronary blood flow well within the range reported by other investigators.^{20,21}

Regional myocardial function was evaluated by the ultrasonic dimension technique,^{13,14} with which an excellent correlation between reduction in CBF and regional mechanical function has been demonstrated in dogs.¹⁵ This and other work^{24–26} indicates that regional myocardial dysfunction and systolic paradox are changes characteristic of myocardial ischemia.

Induction of the coronary artery stenoses *per se* did not result in regional myocardial dysfunction. Thus, the model simulates the clinical situation in which a patient with compromised coronary vascular reserve is asymptomatic in the absence of increased myocardial oxygen demands ($M\dot{V}O_2$) or reduced myocardial O_2 supply. Subsequent pronounced isoflurane-induced hypotension caused marked decreases in segment shortening in the areas supplied by the stenosed LAD and RCA. These decreases were three- to six-fold greater than those observed in the areas supplied by unobstructed coronary arteries. In several animals, akinesis and paradoxical systolic bulging, the most severe manifestations of myocardial ischemia,¹⁵ developed. Except for the moderate but mostly insignificant increases in heart rate and in RV preload, the other determinants of $M\dot{V}O_2$ ²⁷ were unchanged (LV preload) or decreased (LV afterload, segment shortening, stroke work) during ISO 1 and ISO 2. The development of dysfunction suggests that the decrease in O_2 demand was outweighed by the decrease in O_2 supply. The finding that regional contraction patterns indicative of ischemia did not occur in those areas supplied by the unobstructed coronary circulation confirms that even pronounced isoflurane-induced hypotension is well-tolerated in the pres-

ence of a presumed normal coronary circulation.¹² These differences in regional myocardial performance make it unlikely that the observed adverse effects of isoflurane are caused primarily by the experimented model (open-chest animal), or by potential interactions with the baseline anesthesia.

In the area of unopposed coronary blood supply, regional LV function was better maintained than RV function at both concentrations of isoflurane. It is possible that, in the presence of myocardial depression, the normally perfused LV segment benefited from the reduced afterload. This beneficial effect was not observed in the area supplied by the critical stenosis, possibly because further pressure-related reductions in coronary blood supply might well have outweighed the potential advantage of a decrease in $\dot{M}\dot{V}O_2$ associated with such a decrease in afterload.

We have shown previously that, in animals with an unobstructed coronary circulation, isoflurane is a potent coronary vasodilator.¹² Isoflurane may thus have the potential for inducing a coronary "steal" in which flow is diverted away from ischemic to nonischemic tissue.²⁸ However, our data do not allow the diagnosis of coronary steal, because distal coronary perfusion pressures and transmural blood flow distribution were not determined. Data from clinical studies suggest that myocardial ischemia may, indeed, develop in patients with coronary artery disease anesthetized with isoflurane.^{5,6} How isoflurane will affect regional myocardial performance in the individual patient depends on a variety of factors, the most important ones being degree of hypotension, degree of stenosis, kind of stenosis (fixed *vs.* functional), number of stenoses (single *vs.* multivessel lesions), status of the collateral system (immature *vs.* well-developed), and concomitant $\dot{M}\dot{V}O_2$ (reduced *vs.* increased by elevated pre- or afterload and heart rate). Such a multitude of diverse factors makes it very unlikely that isoflurane-induced hypotension in the presence of coronary artery stenosis will necessarily lead to myocardial ischemia in each patient.

In a recent experimental study,¹¹ the combination of a coronary artery stenosis of a similar degree (10% reduction in resting coronary blood flow) and halothane-induced hypotension to a similar AoP_m (50 mmHg) reduced total transmural myocardial blood flow by 40% and distal coronary perfusion pressure by almost 60%, but failed to produce evidence of regional myocardial ischemia. Only the combination of a more severe stenosis (40% reduction in resting coronary blood flow) and halothane-induced hypotension produced signs of myocardial ischemia.¹¹ Similar findings have been reported in another study.²⁹

In conclusion, our results indicate that the combination of isoflurane-induced hypotension and critical coronary

artery stenosis may result in regional myocardial dysfunction suggestive of ischemia. The cause of this dysfunction appears to be a localized decrease in coronary blood supply, due to a reduced pressure gradient across the stenosed coronary arteries, or perhaps due to coronary steal.

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