Isoflurane Causes More Severe Regional Myocardial Dysfunction Than Halothane in Dogs with a Critical Coronary Artery Stenosis

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The effects of 1) isoflurane (ISO)- and halothane (HAL)-induced hypotension to a mean aortic pressure (AoP) of 55 mmHg, and 2) of substituting ISO and HAL for each other at a mean AoP of 55 mmHg on global and regional left ventricular performance (ultrasonic dimension technique) and on coronary hemodynamics (electromagnetic flow probes) were studied in eight open-chest dogs (anesthetized and paralyzed by continuous infusions of fentanyl and pancuronium) with a critical coronary artery stenosis (micrometer-controlled snare) of the left anterior descending coronary artery (LAD). The stenosis reduced resting coronary blood flow by 5% (P < 0.05) without affecting global or regional myocardial performance. HAL- and ISO-induced hypotension caused comparable decreases in global cardiac function, but regional myocardial dysfunction in the area of stenosis and the reduction in coronary flow through the stenosed LAD were more pronounced during ISO. Substitution of HAL for ISO at constant mean AoP, heart rate, end-diastolic dimensions and pressures, and stroke volume resulted in significant (P ≤ 0.05) amelioration of regional myocardial dysfunction (improvement in contraction amplitude, disappearance of paradoxical systolic lengthening and akinesis), a 20% increase in flow through the stenosed LAD, and a 20% decrease in flow through the unobstructed left circumflex coronary artery. These data suggest that, in the presence of a critical coronary artery stenosis: 1) ISO- and HAL-associated hypotension result in comparable decreases in global cardiac function, 2) ISO-associated hypotension is more likely to cause severe regional myocardial dysfunction suggestive of ischemia than equal degrees of HAL-associated hypotension, and 3) the different effects of HAL and ISO on ischemic myocardial segments at equally reduced coronary perfusion pressure are primarily related to their different effects on coronary vasomotor tone. (Key words: Anesthetics, volatile: halothane, isoflurane. Heart: coronary artery stenosis; coronary hemodynamics; regional myocardial performance.)

CONTROVERSY CONTINUES over whether it is safe to use isoflurane (ISO) in patients with coronary artery disease (CAD).[1–4] Several clinical studies have indicated that ISO may cause myocardial ischemia in patients with CAD, possibly by the mechanism of coronary steal.[5–8] This possibility is supported by experimental evidence.[9,10] However, in most cases there was a concomitant marked reduction in systemic arterial pressure, and, in addition, ISO has been successfully used in patients with CAD to treat intraoperative hypertension.[11,12] On the other hand, under clinical[13] and experimental conditions[9,14] of comparable severity of stenosis, and of comparable reductions in coronary perfusion pressure and coronary blood flow (CBF), halothane (HAL) failed to produce evidence of myocardial ischemia.

The question, thus, remains whether myocardial ischemia during ISO is primarily due to a specific drug effect (i.e., coronary vasodilation with subsequent redistribution of CBF), whether it is due to cardiovascular side effects (i.e., decrease in coronary perfusion pressure), or whether it is due to a combination of both.

This study was performed to try to separate the effects of HAL and ISO on coronary perfusion pressure from those on coronary vasomotor tone. For this purpose, mean aortic pressure (AoP$_m$) was first reduced by either HAL or ISO to 55 mmHg. Severe myocardial ischemia has been shown to develop at this degree of ISO-induced hypotension.[10] Comparison of the initial effects of HAL- and ISO-induced hypotension on global and regional myocardial performance should allow some estimate on the relative contribution of a reduction in coronary perfusion pressure to the development of myocardial dysfunction.

Subsequently, HAL and ISO were to be substituted for each other at concentrations necessary to maintain AoP$_m$ at 55 mmHg. Any differences between HAL and ISO on myocardial performance should now no longer be attributable solely to a reduction in coronary perfusion pressure, and some estimate on the relative contribution of changes in coronary vasomotor tone to the development of myocardial dysfunction should become possible.

Materials and Methods

INSTRUMENTATION

Eight mongrel dogs of either sex weighing between 25 and 36 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.[15] For determination of end-tidal concentrations of halothane and isoflurane, the tip of a small-bore catheter was placed close to the carina via the endotracheal tube and connected to a precalibrated infrared gas analyzer (Beckman, Medical Gas Analyzer LB-2). After an initial iv bolus dose (1 mEq·kg^{-1}), sodium bicarbonate (NaHCO$_3$) was administered by con-

tinuous iv infusion (maximally $0.5 \ mEq \cdot kg^{-1} \cdot h^{-1}$) throughout the experiment.

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 $ml \cdot kg^{-1} \cdot h^{-1}$ 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 ventricle (LV), and calibrated as previously described.[15] The chest was entered through a median sternotomy, and the heart was suspended in a pericardial cradle. Precalibrated electromagnetic flow probes (Stölzer Messtechnik, Waldkirch, West Germany) of appropriate sizes to ensure a snug fit were placed around the ascending aorta, the left anterior descending (LAD) coronary artery distal to its first large diagonal branch, and the proximal left circumflex (Cfx) coronary artery. The flow probes were connected to flow meters with incorporated nonocclusive zero (Hellige Co., Freiburg i. Br., West Germany).

REGIONAL MYOCARDIAL FUNCTION

Regional myocardial performance was evaluated by sonomicrometry.[16,17] Two pairs of piezoelectric crystals (5MHz, 1.5–2.0 mm diameter) were inserted in an equatorial plane into the subendocardium of the LV. One pair was placed distal to the first or second diagonal branch and in close proximity to the LAD, and the other pair was placed in close proximity to the Cfx. Care was taken to ensure that the crystals in the apical region of the LV had been placed within the area supplied by the LAD distal to the flow probe, and that those crystals close to the Cfx had been placed outside that area. This was done by occluding transiently the LAD at the site of the attached flow probe and observing that cyanosis and changes in the ultrasonic signals typical of myocardial ischemia (see below) develop only in the apical region of the LV.

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 pressure or in the LV dP/dt tracing, and end systole by the dicrotic notch in the aortic pressure signal as derived from the catheter-tip manometers. The ultrasonic signals derived from the piezoelectric crystals were also assessed visually for qualitative changes suggestive of myocardial

ischemia such as akinesis, paradoxical systolic segment lengthening, or post-systolic segment shortening.[18]

CRITICAL STENOSIS

Details regarding the definition and induction of the critical stenosis have been provided previously.[10] In brief, critical coronary artery 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 the powerful coronary vasodilator acetate.[19,20] A suture was placed around the LAD immediately distal to the flow probe. The suture was attached to a micrometer-controlled, spring-suspended snare that could be adjusted in 0.01-mm increments. While observing the maximally amplified mean and phasic LAD flow signal on the oscilloscope, the snare was gradually tightened in 0.1-mm increments until dampening of the phasic flow signal and a tendency for the mean CBF to decline was observed. At this point, 0.02 $ml \cdot kg^{-1}$ BW of a concentrated acetate solution (2.7 $mMol \cdot ml^{-1}$) 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 one to three injections of acetate to establish the critical stenosis.

HEMODYNAMIC MEASUREMENTS

A multichannel recorder (Hellige Co., Freiburg i. Br., West Germany) was used for the continuous recording of all signals. LV dP/dt was derived from a LV high-fidelity signal using an operational amplifier connected to a differentiator (Hellige Co., Freiburg i. Br., West Germany). Systemic (SVR) and left circumflex coronary artery (CVR_{Cfx}) vascular resistances, and stroke volume (SV) were derived from standard formulae as described previously.[15]

EXPERIMENTAL PROTOCOL

After 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. The critical stenosis was established during baseline anesthesia with fentanyl. With the introduction of ISO or HAL, the rate of fentanyl infusion was reduced by approximately 30% to 15 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Body temperature (T), hematocrit (Hct; Microcentrifuge Compur, Model M1100), arterial blood gases, and arterial pH (Instrumentation

Control (n = 8)

Stenosis (n = 8)

(n = 4)   (n = 4)

AoP$_m$ ~ 55 mmHg

HAL   ISO

ISO   (◄— 1st substitution —►)   HAL

HAL   (◄— 2nd substitution —►)   ISO

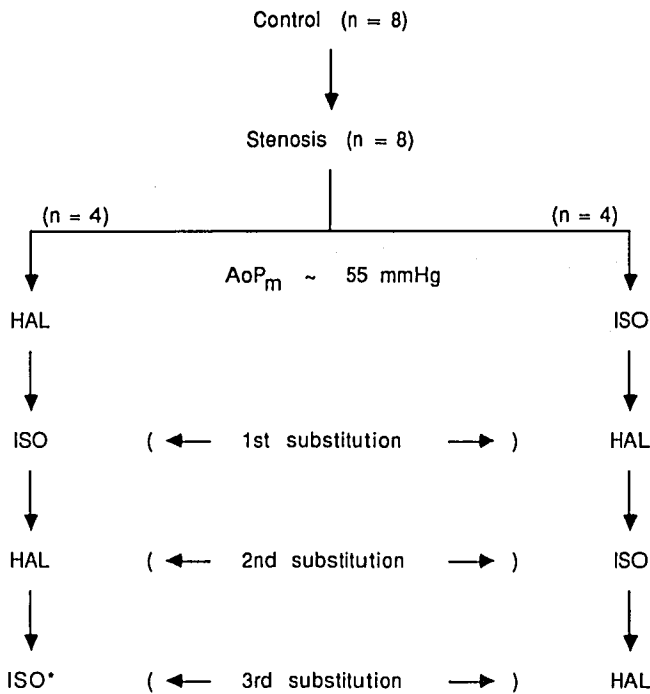ISO*   (◄— 3rd substitution —►)   HAL

FIG. 1. Diagram of experimental protocol. *This final substitution was carried out in only three animals.

Laboratory, Model 613) were recorded at the end of each experimental period.

The experimental sequence is shown in figure 1. After control readings (C) had been obtained, critical stenosis of the LAD was induced. Measurements were made again after induction of the stenosis (S). Subsequently, either ISO or HAL (in four animals each) were introduced first at concentrations sufficient to lower AoP$_m$ to approximately 55 mmHg. Baseline measurements were taken after hemodynamic stabilization. Subsequently, ISO and HAL were substituted for each other at concentrations sufficient to maintain AoP$_m$ at 55 mmHg. Before taking repeat measurements, at least 20 min were allowed for hemodynamic stabilization and for wash-out of the previously administered anesthetic. By this time, end-tidal concentrations of HAL or ISO had fallen to 0.1% or less. In four dogs, HAL was substituted for ISO first, and, in four dogs, ISO was substituted for HAL first. Except for one animal that had two substitutions, a total of three substitutions was made in each experiment, resulting in a total of 23 substitutions. HAL was substituted for ISO 12 times, and ISO was substituted for HAL 11 times.

STATISTICAL ANALYSIS

The data were statistically analyzed by Friedman's statistic followed by Wilcoxon signed-rank test where appropriate (for comparisons between experimental pe-

riods), by Mann-Whitney test (for comparisons within the same experimental period), and by Chi-square test with Yates correction (for comparison of incidence of myocardial dysfunction). Since differences were less than 5%, values determined after the initial exposure to a respective inhalational anesthetic (n = 4) were pooled with those determined after the first substitution of that same inhalational anesthetic for the other one (n = 4). Thus, it became possible to compare the initial effects of HAL and ISO in all eight animals.

In order to document reproducibility of results, to exclude that residual effects of the preceding anesthetic agent might have modified subsequent findings, and to exclude time-related spontaneous deterioration of the surgical preparation, data of the first (n = 8), the last (n = 8), the means of identical substitutions within the same animal (n = 8), and of all substitutions (n = 23) were analyzed separately and compared with each other. Only if the difference of an individual parameter between each of the four evaluations was less then 5%, and only if the P value was ≤0.05 in all four analyses, was a difference between HAL and ISO considered statistically significant.

Results

INITIAL EFFECTS OF HAL AND ISO ON GLOBAL LV AND RV FUNCTION, AND ON PULMONARY HEMODYNAMICS

Induction of the LAD stenosis led to a small but significant reduction in LAD flow (table 1). Otherwise, there were no significant differences between control values (C) and those determined after induction of the LAD stenosis (S). It required mean end-tidal concentrations of 1.9% HAL (range 1.3–2.6%) and of 1.9% ISO (range 1.1–3.0%) to lower AoP$_m$ to 55 mmHg. ISO and HAL caused comparable decreases in LV dP/dt, SVR, SV, and aortic flow (AoF), they had no significant effect on LV end diastolic pressure (LVEDP), and they caused significant increases in heart rate (HR) (fig. 2). Although there was a tendency for a lesser decline of SV and AoF, and a greater decline of SVR following ISO when compared to HAL, these differences did not reach statistical significance.

INITIAL EFFECTS OF HAL AND ISO ON REGIONAL MYOCARDIAL PERFORMANCE

HAL, as well as ISO, had no significant effects on end-diastolic segment lengths (SL) in either the area supplied by the stenosed LAD or in the area of no coronary artery stenosis (fig. 3).

In contrast, the effects on systolic SL were more pronounced, and they differed between areas. Following

TABLE 1. Cardiovascular and Respiratory Parameters during Control State and Induction of Coronary Artery Stenosis (n = 8)

Variable	Control	Stenosis
LV and systemic hemodynamics		
AoP_m (mmHg)	97 ± 3	97 ± 3
LVEDP (mmHg)	8.0 ± 0.8	8.1 ± 0.8
LV dP/dt (mmHg·s^{-1})	2125 ± 180	2125 ± 201
LV_nSL_{ed} (mm)	10.1 ± 1.0	10.1 ± 1.0
LV_nSL_{sys} (mm)	7.5 ± 0.8	7.5 ± 0.8
ΔLV_nSL (%)	25.8 ± 2.5	25.8 ± 2.5
LV_sSL_{ed} (mm)	10.1 ± 0.8	10.1 ± 0.8
LV_sSl_{sys} (mm)	7.4 ± 0.7	7.4 ± 0.7
ΔLV_sSL (%)	27.6 ± 2.0	27.3 ± 2.1
AoF (1·min^{-1})	2.2 ± 0.3	2.2 ± 0.3
HR (min^{-1})	76 ± 4	78 ± 4
SV (ml)	29 ± 4	28 ± 4
SVR (units)	48 ± 6	48 ± 6
Coronary hemodynamics		
CBF_{LAD} (ml·min^{-1})	24 ± 3	23 ± 3*
CBF_{LAD} (μl·beat^{-1})	309 ± 32	286 ± 34*
CBF_{Cfx} (ml·min^{-1})	32 ± 6	33 ± 6
CBF_{Cfx} (μl·beat^{-1})	411 ± 67	415 ± 71
CVR_{Cfx} (units)	2.8 ± 0.5	2.8 ± 0.5
Miscellaneous		
pH	7.42 ± 0.01	7.42 ± 0.01
Pa_{O_2} (mmHg)	295 ± 15	292 ± 17
Pa_{CO_2} (mmHg)	34.7 ± 0.2	34.3 ± 0.5
Hct (%)	32 ± 1	32 ± 1
T (C°)	37.4 ± 0.4	37.4 ± 0.4

Values are means ± SE. LV = left ventricular; AoP_m = mean aortic pressure; LVEDP = LV end-diastolic pressure; LVSW = LV stroke work; $LVSL_{ed}$ = LV end-diastolic (ed) segment length (SL); $LVSL_{sys}$ = LV systolic (sys) SL; $\Delta LVSL$ = LV systolic SL shortening (the letters "n" and "s" in conjunction with measures of LV segments denote LV area supplied by the non-stenosed [n] circumflex or the stenosed [s] left anterior descending coronary artery); AoF = aortic flow; HR = heart rate; SV = stroke volume; SVR = systemic vascular resistance; CBF = coronary blood flow; LAD = left anterior descending coronary artery; Cfx = left circumflex coronary artery; CVR = coronary vascular resistance; Hct = hematocrit; T = body temperature.
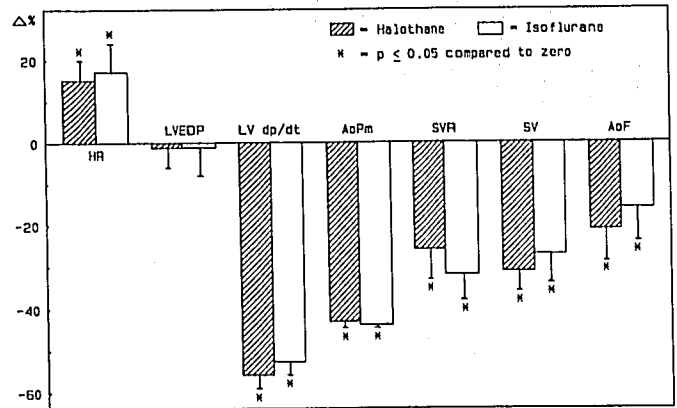
* $P < 0.05$ when compared to control.

FIG. 2. Percent changes from values determined after induction of coronary artery stenosis following administration of halothane and isoflurane. See table 1 for abbreviations.

developed in five animals during ISO, but in none during HAL ($P < 0.05$). Post-systolic shortening developed in five animals during ISO, and in only three (and less pronounced) during HAL. In the area supplied by the unobstructed coronary circulation, neither HAL nor ISO caused qualitative abnormalities in contraction pattern.

both HAL and ISO, systolic SL in the area supplied by the stenosed LAD increased significantly more than those in the area of no stenosis. ISO tended to increase systolic SL in the area of no stenosis less, and systolic SL in the area of stenosis more, than HAL, but these differences did not reach statistical significance.

Similarly, both HAL and ISO decreased systolic segment shortening (ΔSL) significantly more in the area of stenosis than in the area of no stenosis. Due to the somewhat different effects on systolic SL, ISO tended to decrease ΔSL in the area of no stenosis less, and ΔSL in the area of stenosis more, than HAL. In the case of ΔSL in the area of stenosis, this difference reached borderline statistical significance ($P = 0.058$).

Despite the lack of statistically significant differences between HAL and ISO on quantitative aspects of regional myocardial performance, there were marked qualitative differences in the area supplied by the stenosed LAD. Paradoxical systolic lengthening or akinesis
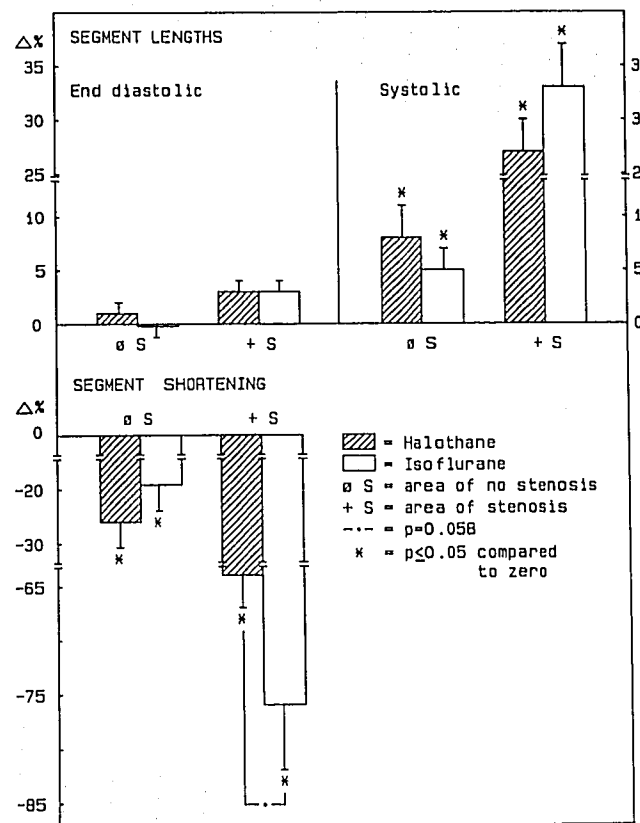

FIG. 3. Percent changes from values determined after induction of coronary artery stenosis following administration of halothane and isoflurane.
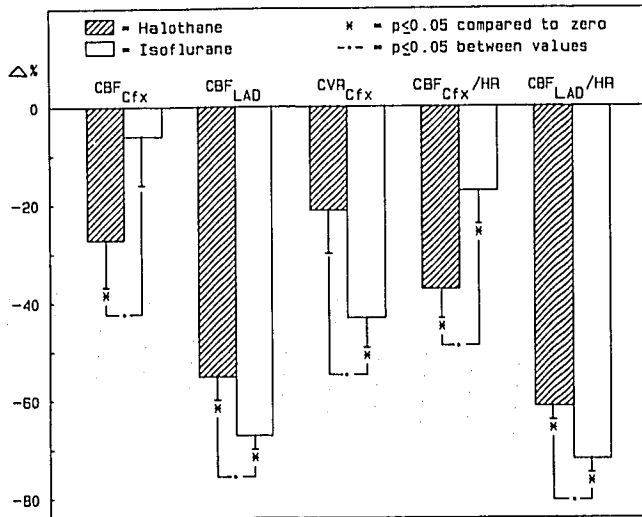
FIG. 4. Percent changes from values determined after induction of coronary artery stenosis following administration of halothane and isoflurane. CBF/HR = coronary blood flow per heart beat. See table 1 for further abbreviations.

TABLE 2. Cardiovascular and Respiratory Parameters during Halothane (HAL)- and Isoflurane (ISO)-induced Hypotension

Variable	HAL	ISO
LV and systemic hemodynamics		
AoP$_m$ (mmHg)	55.2 ± 0.3	54.7 ± 0.5
AoP$_d$ (mmHg)	45.1 ± 1.1	44.3 ± 1.1
LVEDP (mmHg)	8.3 ± 0.6	7.8 ± 0.6
LV dP/dt (mmHg·s^{-1})	896 ± 87	974 ± 100
AoF (1·mm^{-1})	1.6 ± 0.2	1.7 ± 0.2
HR (min^{-1})	89 ± 4	91 ± 4
SV (ml)	19 ± 2	19 ± 2
SVR (units)	33 ± 3	31 ± 2*
Miscellaneous		
[C]$_{ET}$ (%)	1.8 ± 0.1	1.8 ± 0.2
pH	7.40 ± 0.02	7.41 ± 0.02
Pa$_{O_2}$ (mmHg)	284 ± 20	290 ± 16
Pa$_{CO_2}$ (mmHg)	34.5 ± 0.9	34.8 ± 0.8
Hct (%)	30 ± 1	31 ± 1
T (C°)	37.2 ± 0.3	37.2 ± 0.3

Values are means ± SE. [C]$_{ET}$ = end-tidal concentration (see table 1 for further abbreviations).
* $P < 0.05$ between HAL and ISO.

INITIAL EFFECTS OF HAL AND ISO ON CORONARY HEMODYNAMICS

There were significant differences between 1) HAL and ISO, and 2) between LAD and Cfx hemodynamics (fig. 4). HAL caused decreases in both LAD and Cfx flow. During ISO, LAD flow also decreased, but Cfx flow decreased only when expressed in μl·beat^{-1}. Although HAL tended to decrease CVR$_{Cfx}$ (in six of the eight animals), this decrease did not reach statistical sig-

nificance. In contrast, ISO decreased CVR$_{Cfx}$ significantly. The effects of HAL and ISO on all evaluated parameters of coronary hemodynamics were significantly different from each other. In addition, during both HAL and ISO, the effects on LAD flow were more pronounced than those on Cfx flow.

EFFECTS OF SUBSTITUTIONS ON GLOBAL CARDIAC PERFORMANCE

Values presented in figures 5 and 8, and in table 2 represent means as derived from averaging the results of identical substitutions within each animal (see Statistical analysis in Materials and Methods section). Thus, statistical analysis is based on n = 8 (the number of individual animals), rather than on the total number of substitutions (n = 23).

It required mean end-tidal concentrations of 1.8% HAL (range 1.3–2.2%) and of 1.8% ISO (range 1.2–2.6%) to maintain AoP$_m$ close to 55 mmHg. Following substitutions, LV dP/dt, LVEDP, AoF, HR, SV, pH, Pa$_{O_2}$, Pa$_{CO_2}$, Hct, and temperature remained unchanged. Only SVR was slightly but significantly lower during ISO.

EFFECTS OF SUBSTITUTIONS ON REGIONAL MYOCARDIAL PERFORMANCE

End-diastolic segment lengths in both the area of no stenosis and the area of stenosis remained unaffected, and there were no significant differences between either the area of no stenosis and the area of stenosis, or between the effects of HAL and ISO (fig. 5).

In contrast, systolic SL were affected very differently depending on 1) the location and 2) the anesthetic. Sys-
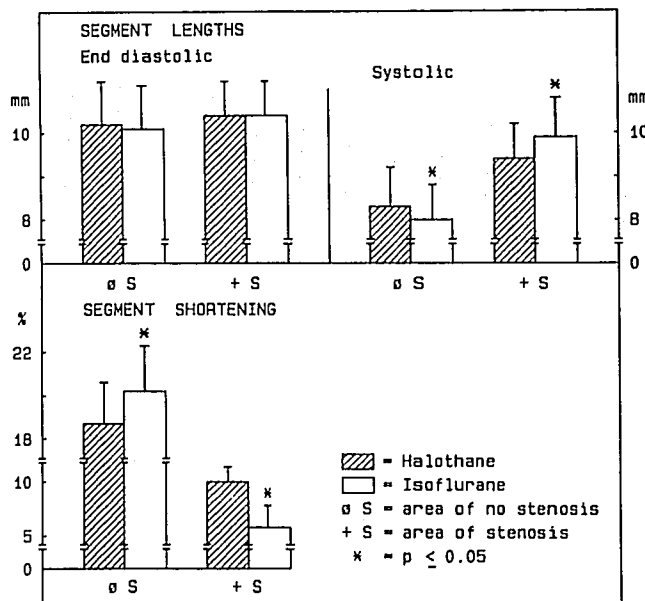

FIG. 5. Bars represent mean values and SE following the substitution of either halothane for isoflurane □, or isoflurane for halothane □. *Indicates significant difference between halothane and isoflurane.
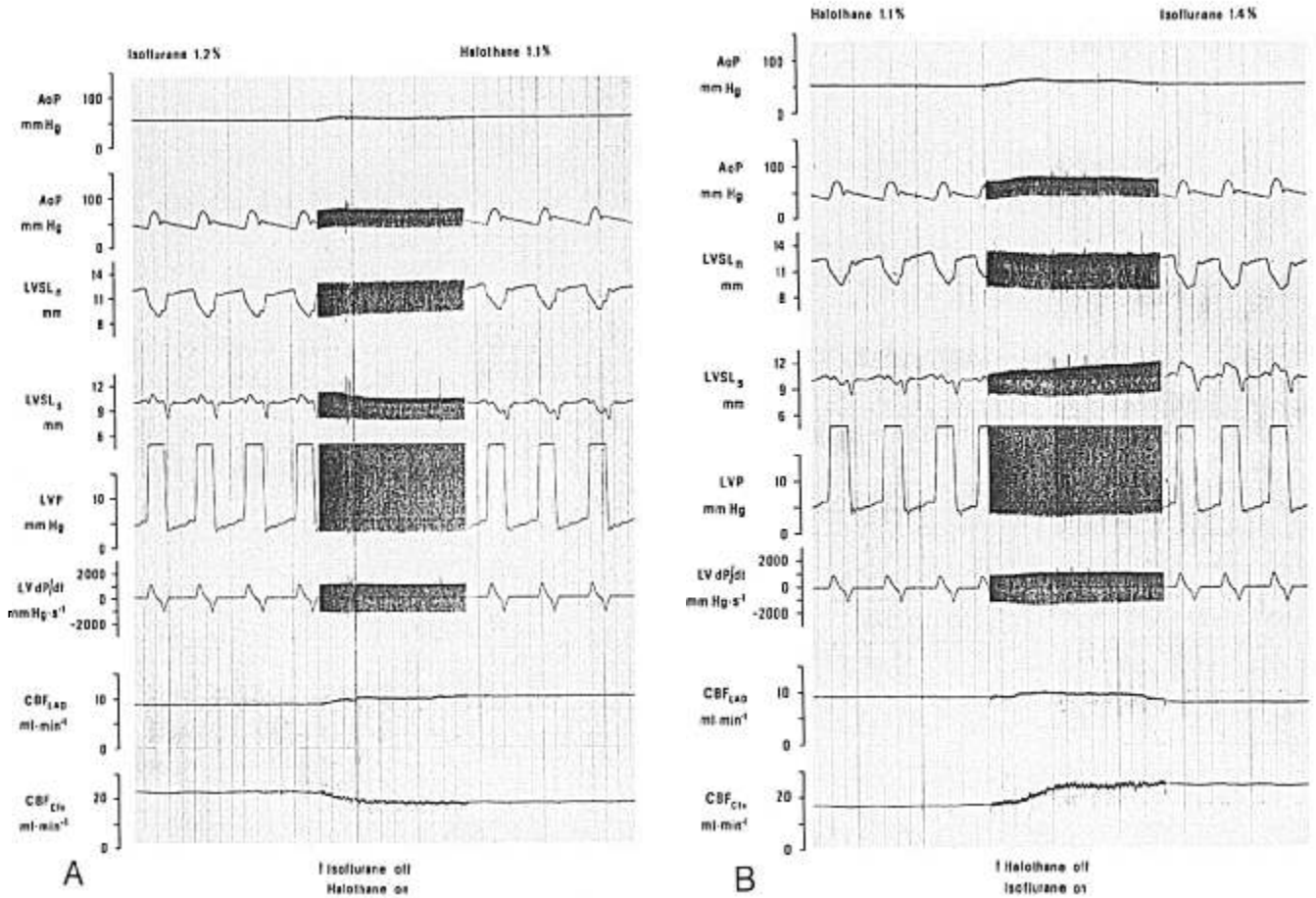
FIG. 6. A. During isoflurane 1.2% (left hand side), systolic bulging and post-systolic shortening can be seen in the area supplied by the stenosed (LVSL$_s$) left anterior descending (LAD) coronary artery. When isoflurane was discontinued and halothane substituted at constant aortic pressure (AoP), systolic bulging disappeared, and post-systolic shortening became less pronounced. At the same time, there was a slight increase in flow through the stenosed LAD (CBF$_{LAD}$) and a decrease in flow through the left circumflex coronary artery (CBF$_{Cfx}$). Segment shortening in the area of no stenosis (LVSL$_n$) decreased. LVP = left ventricular pressure. B. When (in the same animal as in A) isoflurane was reintroduced at constant AoP, marked systolic bulging developed in the area of stenosis (LVSL$_s$). At the same time, CBF$_{LAD}$ decreased, and CBF$_{Cfx}$ increased. See A for further abbreviations.

tolic SL in the area of stenosis were significantly greater than in the area of no stenosis. (No such difference existed during the control state or following induction of coronary artery stenosis.) Following the substitutions of ISO for HAL, systolic SL in the area of no stenosis became significantly smaller (they decreased in seven animals, and remained unchanged in one animal), and in the area of stenosis, systolic SL became significantly greater (they increased in seven animals, and remained unchanged in one animal).

Due to the differences in systolic SL, systolic segment shortening (ΔSL) was similarly affected. First, ΔSL was significantly greater in the area of no stenosis than in the area of stenosis. (No such difference existed during the control state or following induction of coronary artery stenosis.) Second, following the substitutions of ISO for HAL, ΔSL in the area of no stenosis became significantly greater (ΔSL increased in six animals, re-

mained unchanged in one, and decreased in another), and in the area of stenosis, ΔSL became significantly smaller (ΔSL decreased in seven animals, and remained unchanged in one).

Substitution of ISO for HAL resulted in qualitatively more deleterious effects on regional myocardial performance in the area supplied by the stenosed LAD. Paradoxical systolic lengthening or akinesis were observed 12 times in a total of six animals during ISO, but never during HAL ($P < 0.05$). Post-systolic shortening was observed ten times in a total of five animals during ISO, and only six times (and less severe) in a total of three animals during HAL. Following substitution of HAL for ISO, systolic lengthening and akinesis always disappeared.

Representative recordings of substitutions are shown in figures 6A and B, and 7A and B, representing two animals. When HAL was substituted for ISO (fig. 6A),
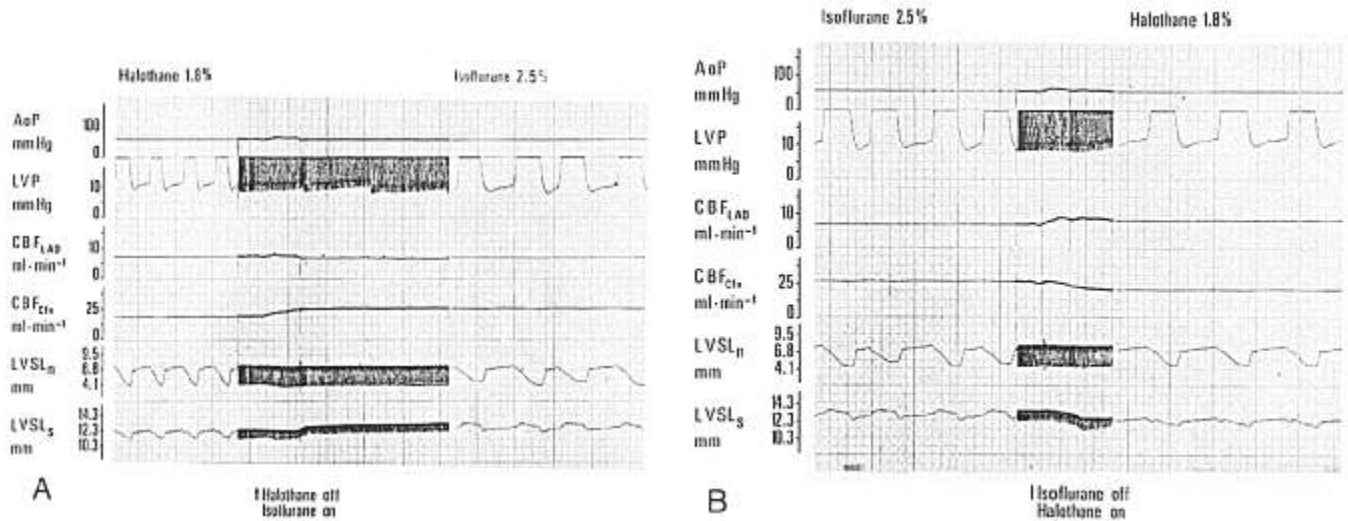
FIG. 7. *A.* During halothane 1.8% (left hand side), contraction amplitude in the area of stenosis (LVSL$_s$) is reduced when compared to the area of no stenosis (LVSL$_n$). However, net contraction during systole is perserved. When halothane was discontinued and isoflurane substituted at constant AoP, marked systolic bulging with no net contraction during systole developed in the area of stenosis (LVSL$_s$). This marked deterioration in regional myocardial performance was accompanied by only little change in the flow through the stenosed LAD (CBF$_{LAD}$). In contrast, CBF$_{Cfx}$ clearly increased. *B.* When (in the same animal as in *A*) halothane was reinstituted at constant AoP, systolic bulging disappeared, and CBF$_{LAD}$ increased despite increased left ventricular end-diastolic pressure (LVP) and end-diastolic segment length in the area of no stenosis (LVSL$_n$).

LAD flow increased, Cfx flow decreased, and systolic lengthening in the area of stenosis (LVSL$_s$) disappeared. Some degree of post-systolic shortening remained. When ISO was subsequently reinstituted (fig. 7B), LAD flow fell, Cfx flow increased, and marked systolic lengthening developed (see figure legends for further details).

In the other animal, when ISO was substituted for HAL (fig. 7A), LAD flow changed little, Cfx flow increased, and marked systolic lengthening developed in the area of stenosis (LVSL$_s$). When HAL was subsequently reinstituted (fig. 7B), the reverse was seen (see figure legends for further details).

EFFECTS OF SUBSTITUTIONS ON CORONARY HEMODYNAMICS

Following the 12 substitutions of HAL for ISO, LAD flow increased ten times (in seven animals) and remained unchanged twice (in one animal) (fig. 8). In contrast, Cfx flow decreased all 12 times in all eight animals. As a result, LAD flow was significantly higher (~20%) and Cfx flow was significantly lower (~20%) during HAL than during ISO. This was associated with a higher CVR$_{Cfx}$ during HAL.

Discussion

The principal findings of this study are: in the presence of a critical coronary artery stenosis, 1) HAL- and ISO-induced hypotension are associated with comparable decreases in global cardiac function, but with dissim-

ilar effects on regional myocardial function (better preserved during HAL) and coronary hemodynamics (less coronary vasodilation during HAL); and 2) substitution of HAL for ISO at equally low coronary perfusion pressure and comparable global cardiac function, resulted in amelioration of regional myocardial dysfunction in the underperfused area, associated with increased coronary vasomotor tone.

CRITIQUE OF METHODS

Limitations of the experimental model employed have been discussed previously in detail.[10,15] Such limitations relate to the use of an acute open-chest animal,[21,22] and the concomitant administration of droperidol[23] (for premedication), and of fentanyl[24] and pentobarbital[25] (for baseline anesthesia). It has, therefore, to be taken into consideration that the effects elicited by HAL and ISO occurred in the presence of, and may thus have been modified by, the acute surgical preparation and the baseline anesthesia. Nevertheless, this is what is to be expected in the clinical situation in which patients with CAD are premedicated and receive a baseline anesthetic during ongoing surgery, to which HAL or ISO are subsequently added to either deepen the anesthetic state or to reduce systemic arterial pressure.

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, since the results obtained from the first and third substitution were comparable, since HAL and

ISO were administered in a random fashion, and since indicators of general homeostasis (pH, Pa_{O_2}, Pa_{CO_2}, Hct, temperature) remained unchanged, it is unlikely that significant deterioration of the preparation had occurred.

Although end-tidal concentration of the preceding anesthetic agent had declined to less than 0.1% at the time repeat measurements were taken, some residual effect may have influenced subsequent results. However, since the order of the first administration was randomized, and three substitutions were performed in all but one animal, and since there were no significant differences between results based on the very first, the last, and the means of identical substitutions, it is unlikely that residual concentrations of the preceding anesthetic could have significantly affected subsequent results.

The degree of critical coronary artery stenosis at which I aimed,[26,27] and its induction and maintenance, have previously been described in detail.[10] Following induction of the LAD stenosis, resting CBF in this study remained well within the range reported by other investigators.[26,27]

Regional myocardial function was evaluated by the ultrasonic dimension technique[16,17] with which an excellent correlation between reduction in CBF and regional mechanical function has been demonstrated in dogs.[18] Paradoxical systolic bulging is the most intense form of regional myocardial dysfunction developing at reductions in regional CBF of 95%. This[18] and other work[28-30] indicates that regional myocardial dysfunction and systolic paradox are changes characteristic of myocardial ischemia.

INITIAL EFFECTS OF HAL AND ISO

Induction of the LAD coronary artery stenosis *per se* did not result in any kind of myocardial dysfunction in the area supplied by the stenosed LAD. This was to be expected because resting LAD flow decreased very little. 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.

SV, AoF, and SVR were reduced similarly by HAL and ISO. It has been stated that ISO is less of a myocardial depressant than HAL, and that cardiac output is better maintained during ISO.[31] This has been attributed to ISO's potent systemic vasodilatory property.[32] Although systemic vasodilation may not necessarily occur during HAL,[32] several studies[13,34-36] have shown that SVR may also decline following HAL. Experimental animals[34,36] and patients with CAD[13,35] may well react differently from healthy patients,[33] possibly related to differences in baseline sympathetic tone.
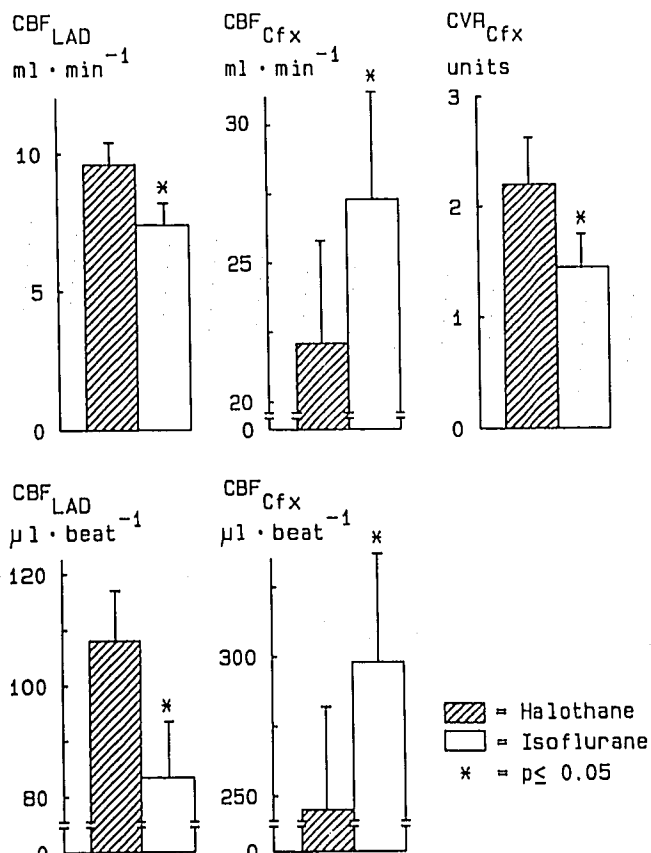

FIG. 8. Bars represent mean values and SE following the substitutions of halothane and isoflurane for each other. See figure 5 and table 1 for further abbreviations.

ISO- and HAL-induced hypotension caused decreases in segment shortening (ΔSL) in all animals in both the area supplied by the stenosed LAD and in the area supplied by a presumably unobstructed coronary circulation. However, there were quantitative, as well as qualitative, differences 1) between the area of stenosis and the area of no stenosis, and 2) between ISO and HAL. Following both HAL and ISO, ΔSL decreased more in the area supplied by the stenosed LAD because the increases in systolic segment lengths (SL) were significantly greater in that area. In addition, changes in regional contraction patterns indicative of ischemia (akinesis, paradoxical systolic lengthening, post-systolic shortening) occurred only in the area of stenosis. Since no such changes developed in the area of no stenosis, it is unlikely that ISO- and HAL-induced hypotension *per se* caused regional myocardial dysfunction.

Although the quantitative differences in regional myocardial performance between HAL and ISO barely reached statistical significance, there were qualitative differences. Contraction patterns indicative of regional ischemia developed more frequently during ISO than during HAL, and the most severe manifestations of

myocardial ischemia (systolic lengthening and akinesis[18]) developed only during ISO.

In contrast to the effect on systolic SL, neither HAL nor ISO significantly increased end-diastolic SL in either area of the LV. This supports the contention that an increase in systolic SL may be a more sensitive index of ischemia.[18] However, the end-diastolic SL might have been slightly underestimated because increases in HR tend to reduce cardiac size.[37]

There were differences also in the effects on coronary hemodynamics 1) between ISO and HAL, and 2) between LAD and Cfx. Following ISO, CVR_{Cfx} fell markedly, and mean Cfx flow did not decrease significantly. In contrast, following HAL CVR_{Cfx} did not fall significantly, and Cfx flow decreased. These findings are in agreement with previous studies demonstrating marked coronary vasodilation following ISO,[15,32,38] but little effect of HAL on coronary vasomotor tone.[38-40]

Both anesthetic agents caused greater decreases in LAD than in Cfx flow. However, following ISO, the reduction in Cfx flow was significantly less, but the reduction in LAD flow significantly greater than following HAL. These differences cannot be explained on the basis of differences in systemic hemodynamics or $M\dot{V}O_2$, because both are likely to have been affected very similarly. These differences in coronary hemodynamics are, therefore, likely to be due to different effects on coronary vasomotor tone.

EFFECTS OF SUBSTITUTIONS

Except for a smaller SVR during ISO, there were no significant differences following the substitutions of ISO and HAL for each other. Thus, major determinants of coronary perfusion and $M\dot{V}O_2$ were comparable, and subsequent differences between ISO and HAL cannot be explained on this basis alone.

Substitution of ISO for HAL resulted reproducibly in worsening of regional function in the area of stenosis, but in less depression of ΔSL in the area of no stenosis. Since end-diastolic dimensions were affected in neither area and by neither anesthetic agent, less depression of ΔSL in the area of no stenosis was due to reduced systolic SL (indicating improved systolic shortening), and worsening of ΔSL in the area of stenosis was due to elevated systolic SL (indicating impaired systolic shortening). Such different behavior in regional myocardial performance may, in part, be based on the mechanism of a compensatory increase in systolic shortening in non-ischemic areas in response to acute ischemia elsewhere.[41-43]

When compared to the control segment in the normally perfused area, there was exaggerated depression of regional function in the area of stenosis during HAL as well, indicating inadequate coronary perfusion. However, ΔSL improved in the vast majority of substitutions for ISO, and, perhaps most importantly, akinesis and paradoxical systolic bulging always disappeared upon discontinuation of ISO.

Whereas improved ΔSL during HAL in the area of the stenosed LAD can be explained on the basis of improvement in regional function, it is somewhat more difficult to find an explanation for the reduced ΔSL in the normally perfused area. Two explanations are conceivable: 1) the compensatory hyperfunction in the non-ischemic area became less pronounced because function in the ischemic area improved; and 2) the concentration of HAL (mean 1.8%) necessary to maintain AoP_m at 55 mmHg was more myocardial depressant than the corresponding concentration of ISO (mean 1.8%). In fact, when expressed as multiples of minimum alveolar concentration (MAC), in the dog, 1.8% ISO is equivalent to 1.4 MAC,[44] whereas 1.8% HAL is equivalent to 2.1 MAC.[45] Usually, at equi-anesthetic concentrations there is more depression of LV performance during HAL than during ISO.[32,46,47] The reduction in ΔSL in the normally perfused area of the LV during HAL could be evidence of greater myocardial depression.

ISO and HAL affected regional distribution of CBF very differently. Following the substitutions of ISO for HAL, CBF to the unobstructed Cfx increased on average 20%, whereas CBF to the (already) ischemic area decreased, on average, another 20%. Since proximal coronary perfusion pressure (i.e., aortic pressure) and indices of $M\dot{V}O_2$ (i.e., end-diastolic dimensions and pressure, systolic and mean aortic pressures, HR, ΔSL) remained comparable, differences in the distribution of CBF must have occurred on the basis of different effects on coronary vasomotor tone.

Why did LAD flow fall following substitution of ISO for HAL? There are two possible explanations. One, there may have been dynamic changes in the severity of the stenosis itself. There is unequivocal experimental evidence that coronary stenoses induced by external constrictors of normal coronary arteries may become hydraulically worse after distal coronary bed vasodilation when associated with a reduction in distal coronary artery pressure.[48-51] With a decrease in distal pressure, intraluminal distending pressure at the site of the stenosis will decrease, and flow turbulance in the stenotic segment itself will increase. As a result, there can be a passive mechanical collapse of the wall of the stenotic segment which, in turn, may cause a paradoxical decrease in CBF in response to coronary vasodilation.[52] Thus, distal coronary arteriolar vasodilators should worsen, and proximal arterial large vessel dilators should lessen the severity of stenoses. The decrease in LAD flow could, in part, be explained on this basis. ISO

has been shown to be an arteriolar-type dilator,[53] whereas HAL is more potent than ISO as a direct relaxant of large preconstricted epicardial arterial segments.[54]

It is important to recall that the majority of human coronary stenoses are compliant.[55,56] Thus, transient dynamic variations in the severity of a stenosis in response to coronary vasodilation must not be limited to the healthy experimental animal with externally compressed flexible coronary arteries, but they may also develop in eccentric lesions of human coronary arteries.[48]

A second explanation for the decrease in LAD flow following the introduction of ISO may be a reduction in the pressure gradient across the stenosis. As resistance in the Cfx decreased, the pressure gradient across the left main coronary artery and the Cfx must have increased. It is, thus, conceivable that, despite constant aortic pressure, pressure at the origin of the LAD was somewhat lower during ISO than during HAL.

As an arteriolar-type coronary vasodilator, ISO has clearly the potential for inducing coronary "steal."[57,58] Whether coronary steal developed in this model cannot be answered, because distal coronary perfusion pressure, retrograde LAD flow, and transmural blood flow distribution were not determined. However, the changes in mean CBF and the associated changes in regional myocardial performance are compatible with development of transmural steal[59–61] during ISO. Considering the subendocardial placement of the piezoelectric crystals and the close correlation between regional blood flow and regional function,[18] it is quite possible that, following ISO subendocardial flow decreased in the area supplied by the stenosed LAD. This would explain why regional myocardial performance worsened even in those cases in which mean CBF did not decrease by very much.

The results are consistent with recent human[5–8] and experimental[9] data. In a canine model of chronic coronary artery occlusion, ISO caused both intercoronary and transmural redistribution of CBF, associated with a decrease in systolic contraction in the collateral-dependent zone.[9] In contrast, under identical conditions, HAL did not significantly affect CBF distribution, coronary pressure, CVR, and systolic contraction.

ISO may elicit myocardial ischemia in patients with CAD, despite concomitant decreases in $M\dot{V}O_2$ by 40–50%.[5–8] This might have been, in part, due to simultaneous decreases in systemic arterial pressure by 25–45%. However, in a similar population with similar decreases in arterial pressure, HAL did not elicit myocardial ischemia.[13] On the other hand, ISO has been used successfully to treat a hyperdynamic circulation in patients with CAD.[11,12]

A recent experimental study supports the contention that HAL-induced hypotension in the presence of a critical stenosis may have less adverse effects on myocardial function than ISO.[14] In a very similar canine preparation, the combination of a critical stenosis of similar severity (decrease in resting CBF by 9%) and HAL-induced hypotension to an AoP_m of 50 mmHg reduced total transmural myocardial blood flow by 40% and distal coronary perfusion pressure by almost 60% without evidence of regional myocardial ischemia. These data are seemingly in contradiction to those of another study in which HAL-induced hypotension to an AoP_m of 50 mmHg in the presence of coronary artery stenosis resulted in marked regional myocardial ischemia.[62] However, the data are not entirely comparable because, in this study, the degree of stenosis was not quantitated by flow or distal pressure measurements. It is very likely that the stenoses were more severe, because induction of the stenoses during baseline conditions already produced changes in regional function suggestive of ischemia. Individual differences in the severity of the stenoses may also explain why three (i.e., 27%) of the 11 animals studied did not become ischemic.

CLINICAL IMPLICATIONS

Extrapolation of these results in open-chest anesthetized dogs to the clinical situation must be undertaken with extreme caution. How ISO and HAL 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. multi-vessel lesions), status of the collateral system (immature vs. well developed), and concomitant $M\dot{V}O_2$ (reduced vs. increased by elevated pre- or afterload and heart rate). Such a multitude of diverse factors makes it very unlikely that HAL- and ISO-associated hypotension in the presence of coronary artery stenosis will necessarily lead to myocardial ischemia in each patient.

However, the combined experimental[9,14,62] and clinical evidence,[13] and these data suggest that HAL-associated pronounced hypotension in the presence of a critical stenosis may be less likely to result in regional myocardial ischemia, or that at least regional dysfunction may be less pronounced than during ISO. It is very likely that the direct effect or the lack of such an effect on coronary vasomotor tone is the major factor responsible for the difference between HAL and ISO. Thus, in the presence of a critical coronary artery stenosis, it is not necessarily the net effect of the anesthetic agent on the myocardial O_2 supply/demand ratio that determines regional myocardial function, but, at times, more importantly, it is its effect on coronary vasomotor tone.

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