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Comparative Coronary Vascular Reactivity and Hemodynamics during Halothane and Isoflurane Anesthesia in Swine

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To assess the dose-response effects of isoflurane and halothane anesthesia on hemodynamics and coronary artery reactivity, the authors studied myocardial hyperemic responses following brief single artery flow arrests in 21 open chest, isocapnic swine in which arterial blood pressures and cardiac outputs were recorded. A specially designed Doppler probe was used to measure the peak and time course of coronary blood flow velocity in the left anterior descending coronary artery (LAD) after 15-s LAD occlusions. The ratio of peak velocity of blood flow to resting velocity (coronary reserve), relative repayment of flow debt, and duration of hyperemic responses were studied. Surgery was performed at MAC end-tidal concentrations ($[Et]_{isoflurane}$ = 1.45%. $[Et]_{halothane}$ = 1.25%) of isoflurane (n = 7) or halothane (n = 7), and recordings were made after 15-min steady state $[Et]_{agent}$ at 0.5, 1, 1.25, 1.5, 1.75, 2 MAC, and further 0.5 MAC increments until the demise of each animal. To compare coronary reactivity at similar coronary pressures, an aortic snare was used to elevate arterial pressures in a third group of halothane anesthesized pigs (n = 7) to those in the previously studied isoflurane group at each MAC level. There were three major differences between halothane and isoflurane. First, cardiac depression (reduction in arterial pressure, cardiac output, and stroke volume) was less with isoflurane compared with halothane anesthesia. Second, with halothane anesthesia, there was a marked decrease in coronary reactivity independent of coronary perfusion pressures with marked, dose-dependent reductions in both coronary reserve and relative flow repayment. During isoflurane anesthesia, coronary reactivity and coronary reserve was well preserved within physiologic limits up to 1.75 MAC [Et]. Third, halothane anesthesized pigs died in cardiac collapse at much lower agent concentrations than with isoflurane (no animals survived 1.75 MAC halothane, whereas all animals survived 2.5 MAC isoflurane). Therefore, pigs anesthesized with isoflurane had greater coronary reserve, better preserved cardiac function, and greater tolerance to increasing agent concentration than pigs anesthesized with halothane. (Key words: Anesthesia: cardiovascular. Anesthetics, volatile: halothane; isoflurane. Arteries: reactivity. Heart: blood flow, myocardial; coronary occlusion; coronary reactive hyperemia; myocardial function; reactive hyperemia. Potency: anesthetics; MAC.)

EFFECTS OF POTENT inhalation anesthetics on systemic and coronary circulation remain controversial. Isoflurane has been variously contended to have beneficial or deleterious effects on myocardial ischemia in human and animal studies.[1-7] Halothane has similarly been reported to cause or inhibit myocardial ischemia and to increase, decrease, or not influence coronary vascular resistance (CVR).[8-16] Also, both coronary vasodilation[1,17] and unchanged CVR[18-20] have been attributed to isoflurane. Interpretation of systemic and coronary hemodynamic changes during anesthesia in humans is often difficult due to multiple drug administration and/or poorly controlled hemodynamic conditions.[21] Relevant animal studies have been done in the canine model, which has abundant coronary artery collaterals in the disease-free state, unlike the normal human end-arterial coronary circulation. The aim of this study was to obtain quantitative information on changes in coronary vascular reactivity and general hemodynamics during increasing concentrations of halothane or isoflurane in oxygen in domestic swine. The coronary anatomy in this species is closer to that in the non-diseased human heart than other animal models in which coronary hemodynamics have been studied.[22-24] Measurement of myocardial blood flow under conditions of maximal coronary vasodilation is a very sensitive indicator of the quality of myocardial perfusion, and coronary reserve is considered a good physiological index of myocardial vasodilator responsiveness, both in animals (dogs) and in man.[25,26] Since there is no known physiologic stimulus to coronary vasodilation greater than that produced by ischemia, estimating peak reactive hyperemic flow following a 15–30-s coronary artery occlusion is a valid way to measure maximum vasodilator capacity of this vascular system.[27] We postulated that this estimate of coronary reserve, namely, quantified coronary reactive hyperemia, would be a useful way to compare isoflurane and halothane with respect to their absolute and relative effects on coronary reactivity and vasodilator capacity in nondiseased porcine heart *in vivo*. Since coronary artery pressure has major influence on characteristics of myocardial reactive hyperemia following brief arterial flow arrests,[28] we not only wanted to compare coronary reactivity with the two agents at similar MAC increments, but also with similar coronary pressures.

Our specific hypothesis was that preservation of coronary vascular reactivity, despite increased agent levels, would provide evidence against that agent causing di-

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rect, indiscriminate coronary vasodilation. We found that isoflurane preserved coronary reserve at and beyond concentrations at which halothane was associated with markedly depleted coronary reserve.

Material and Methods

Instrumentation

Twenty-one male mongrel pigs weighing 26–37 kg were deprived of food, but not water, for 12 h before the experiments. Anesthesia was induced without premedication with the agent under test in oxygen *via* animal anesthesia mask. A catheter was placed in an ear vein for administration of muscle relaxant and maintenance fluids.

Following paralysis with succinylcholine and endotracheal intubation *via* tracheotomy, the animals were kept normothermic with warming blankets and were normoventilated. Arterial pressure (AP) was transduced *via* the right common carotid artery. Pulmonary artery pressures (PAP) and thermodilution cardiac outputs (CO) were measured *via* a 7F thermodilution PA catheter inserted *via* the femoral vein. AP, PAP, and ECG were continuously displayed and recorded. Cardiac output was measured in triplicate at each data point using iced 5% dextrose-water. Arterial blood-gases and *p*H values were monitored frequently during each experiment. End-tidal concentrations of isoflurane ($[Et]_{iso}$) and halothane ($[Et]_{halo}$) were continuously sampled from the endotracheal tube and measured with a calibrated mass spectrometer (Perkin-Elmer).

All surgery was performed at 1 MAC [Et] agent. The pericardium was exposed through a median sternotomy and a cradle was formed. The shortest possible segment (1.5–2 mm) of the proximal part of the left anterior descending coronary artery (LAD) was dissected proximal to the first major bifurcation to allow passage of an oiled 3-0 silk ligature placed loosely around the vessel and rigged *via* 0.5 mm ID tubing so that rapid on/off occlusion of the vessel could be accomplished later to elicit coronary reactive hyperemia.

LAD coronary blood flow velocity was measured *via* a 20 mHz piezoelectric ultrasonic Doppler probe embedded in a silicone suction cup placed on the LAD distal to the snare as per Marcus *et al.*[29] The probe weight was less than 0.5 g, and the crystal was set at 45° with respect to the surface of the myocardium when the probe was attached with vacuum.[29] The position of the Doppler probe was adjusted to obtain a maximum phasic signal, which was then electronically meaned and recorded.

In an additional group of halothane-anesthesized pigs, we passed a snare around the aorta distal to the left subclavian to allow mechanical control of coronary pressure. By snaring the aortic band gradually, we could accurately elevate mean aortic pressure (MAP) without pharmacologic intervention.

Coronary Reactive Hyperemia

Coronary reactive hyperemia was defined as the vascular response to a brief period of arterial flow arrest, elicited by carefully occluding the LAD with the snare for 15 s. This time period has been sufficient to produce maximal physiologic distal coronary dilation in humans and dogs without deranging left ventricular function.[26–29] Following release of the snare and restoration of pre-occlusion driving pressure, LAD blood flow velocity typically increased markedly, then returned to baseline within 1–2 min. Three such hyperemic responses were recorded at each anesthetic concentration. Following each response, we waited until flow velocity had returned to baseline (or at least 3 min) before a new response was elicited.

Measurement of Hyperemic Responses

Each hyperemic response was analyzed as described by Coffman and Gregg.[30] We calculated the ratio of peak velocity of coronary blood flow after a 15-s occlusion to resting velocity, and defined the resultant value as coronary reserve.[27,29] Also, the ratio between areas representing flow repayment to flow debt areas was calculated based on integrals of the flow curves during reactive hyperemia and occlusion, respectively. The duration of reactive hyperemia was measured from release of occlusion to the time hyperemic flow decreased to 95% of its peak value.[28] Areas of flow debt and flow repayment were measured by with computerized planimetry (Irex Cardio 80 Graphic analyzer, Kontron, Munich, W. Germany) (fig. 1). The investigator performing the analyses of the hyperemic responses at each datapoint was blinded as to agent and concentration before analysis. We found no significant variance between the three hyperemic responses at each MAC level.

Drugs

We used 1.45% $[Et]_{isoflurane}$ and 1.25% $[Et]_{halothane}$ as MAC for pigs.[19,31,32] No other drugs were given as premedicants or anesthetics during the study except succinylcholine, as needed, to maintain muscle paralysis.

Experimental Protocol

Our goal during each experiment was to obtain dose-response curves for both general hemodynamics and coronary reserve in each animal over the widest possible

range of anesthetic concentrations. Only one volatile agent was tested in each pig, which, therefore, served as its own control. We recorded hemodynamic variables and elicited hyperemic responses in triplicate following graded increments in concentrations of either halothane or isoflurane until each animal died. Because equi-MAC levels of the two agents did not result in equal coronary driving pressures, and because we wished to test the possibility that this might account for the differences thus far observed between halothane and isoflurane, in the third group of halothane anesthetized pigs, we mechanically raised arterial pressures to those seen previously at equi-MAC levels of isoflurane (see below) using the aortic snare.

Pigs were thus divided into three groups. The first fourteen received isoflurane (group 1, n = 7) or halothane (group 2, n = 7); all 14 of these were studied in random order. In a third group of halothane-anesthesized pigs (group 3, n = 7), we elevated the coronary driving pressure as above. Arterial pressure at each anesthetic increment was adjusted prior to testing the hyperemic responses and remained elevated with the snare until three hyperemic responses were performed, *i.e.*, at least 10–12 min at each MAC level. Otherwise the aortic snare was not tightened. The mean arterial pressure was elevated to the group average MAP from the previously studied isoflurane group at that MAC level in order to test coronary vascular reactivity at equal coronary driving pressures between isoflurane and halothane.

Surgery was performed at MAC of the anesthetic under test. When surgery was completed, hemodynamic variables and reactive hyperemic responses were recorded at end-tidal concentrations of 0.5, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5 and 4 MAC agent or until the pig died. At least 15 min was allowed for blood-brain equilibration at constant end-expiratory concentration at each MAC level before recording values for any variable or testing coronary reactive hyperemia.

Statistics

Values are presented as mean ± SD. Each pig served as its own control. Values were tested for normality by constructing normal probability plots. If the variances did not appear constant across different dose levels, variance stabilizing transformations were tentatively selected and applied using the Box-Cox transformation method.** If such transformations stabilized the variances, the variables were transformed accordingly. The dependent variables were various measures of hemodynamics and coronary functions, and the independent variables were anesthetic agents and concentrations (MAC multiples). Each dependent variable was analyzed separately.

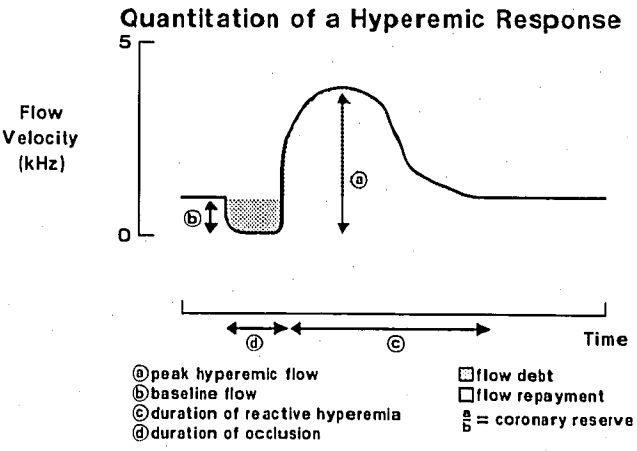

FIG. 1. Schematic illustration of one coronary artery flow velocity recording during occlusion and hyperemia following release of LAD-snare.

Repeated measures analysis of variance (ANOVA) was performed in order to evaluate the effects of dose and anesthetic agents. Since complete information on all groups was only available up to 1.5 MAC due to a number of deaths at lower concentrations in the halothane groups than in the isoflurane group, four concentration levels (0.5, 1.0, 1.25, and 1.5 MAC) were included in the analysis. First the interaction between agents and concentration levels was tested. Interaction can be viewed as differences in the rates of change in responses across the concentration levels of the two anesthetic agents. If the interaction was not significant, *i.e.*, the rate of change was the same for both agents, the effects of the dose and anesthetic agents were evaluated. If the interaction was significant, *i.e.*, the rate of change is significantly different between the two agents, the dose effects were evaluated for each agent, and the agent effects were evaluated at each dose level. The dose effects are tested by comparing variables at 0.5 MAC with those at the higher MACs. These comparisons were made with Bonferroni adjustments (drug comparisons evaluated at $\alpha = 0.0042$ and MAC comparisons at $\alpha = 0.0056$) in order to protect the overall error rate of 0.05.[33]†† A $P < 0.05$ was considered statistically significant. All analyses were performed using general linear model (GLM) procedures in Statistical Analysis System Computer Software (version 82.4 SAS Inc.).

** Box GEP, Cox DR: An analysis of transformation. Journal of the Royal Statistical Society, Series B. 26:211–252, 1964.

†† Dunn OJ: Multiple comparisons among means. Journal of The American Statistical Association 56:52–64, 1951.

TABLE 1. End-tidal Agent Concentrations and Number of Animals (Mean ± SD)

MAC	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.0	3.5
[ET]%									
Group 1	.69 ± .04	1.45 ± .02	1.84 ± .05	2.16 ± .06	2.54 ± .03	2.88 ± .03	3.6 ± .06	4.26 ± .07	5.04 ± .08
Group 2	.62 ± .02	1.26 ± .04	1.57 ± .02	1.86 ± .03	2.21 ± .05	—	—	—	—
Group 3	.61 ± .01	1.26 ± .03	1.56 ± .02	1.89 ± .04	2.16 ± .02	—	—	—	—
n									
Group 1	7	7	7	7	7	7	7	4	1
Group 2	7	7	7	6	3	0	0	0	0
Group 3	7	7	6	5	1	0	0	0	0

[Et]% = end-tidal agent concentrations; n = number of animals surviving 15 min steady state $[Et]_{agent}$ at each level; MAC = multiple of 1 MAC_{agent} ($[Et]_{halothane}$ = 1.25%, $[Et]_{isoflurane}$ = 1.45%); group 1 = isoflurane anesthesia; groups 2 and 3 = halothane anesthesia; group 3 = aortic snare (see text).

Results

Overview

We present results from 21 consecutive animal experiments. Table 1 shows anesthetic concentrations at each MAC multiple and the number of animals surviving at least a 15-min stabilization period at each MAC level. Because of the very small number of animals in both halothane groups which survived to 1.75 MAC, statistical comparisons between groups were not possible from 1.75 MAC and higher concentrations.

Effects on Coronary Reserve, Repayment, and Duration

Data are presented in table 2. Increasing MAC multiples of halothane and isoflurane had significant and markedly different effects on coronary reserve, repayment percent, and duration of each hyperemic response. At 0.5 MAC of agent, peak divided by baseline LAD flow velocity ratio (coronary reserve) was 5.53 ± 1.87 for isoflurane and 4.45 ± 1.15 with halothane (NS). Increasing the [Et] of isoflurane did not cause any decrements in this ratio. In contrast, halothane caused a significant reduction from 4.45 ± 1.15 at 0.5 MAC to 2.03 ± .63 at 1.5 MAC. At halothane concentrations of 1.25 and 1.5 MAC, coronary reserve was significantly below control (0.5 MAC of halothane), and also significantly lower than corresponding values for the isoflurane group. Mechanically increasing the coronary driving pressure (MAP) in group 3 during each hyperemic response to the average of that previously observed in the isoflurane group did not increase coronary reserve. Despite coronary perfusion pressure similar to group 1 (isoflurane), coronary vascular reserve remained significantly below the 0.5 MAC value, and also much lower at 1.25 and 1.5 MAC halothane than in the isoflurane group. With isoflurane, coronary reserve remained at or above 3 up to 2.5 MAC isoflurane (fig. 2).

Repayment was not significantly different between

TABLE 2. Coronary Reactivity Variables (Mean ± SD)

MAC	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.0	3.5	ANOVA
Coronary reserve										
Group 1	5.5 ± 1.9	5.5 ± 2.3	5.8 ± 2.4¶	5.5 ± 2.6¶	4.5 ± .8	4 ± 1.3	3.4 ± 1.2	2.8	—	‡
Group 2	4.5 ± 1.2	3.6 ± 1.5	3 ± 1§	2 ± .6§	1.0	—	—	—	—	
Group 3	3.9 ± 1.1	3.4 ± 1	2.9 ± 1.1§	2.2 ± .9§	2.7	—	—	—	—	
Repay (%)										
Group 1	1092 ± 452	926 ± 291**	1101 ± 454¶	888 ± 303¶	796 ± 310	532 ± 220	586 ± 332	448	—	‡
Group 2	640 ± 214	379 ± 275§	286 ± 133§	233 ± 129§	61	—	—	—	—	
Group 3	716 ± 314	570 ± 269	500 ± 372§	312 ± 164§	382	—	—	—	—	
Duration										
Group 1**	89 ± 38	81 ± 15	87 ± 23	71 ± 27	76 ± 33	58 ± 31	72 ± 6	71	—	*
Group 2	65 ± 28	34 ± 12	36 ± 15	55 ± 28	38	—	—	—	—	
Group 3	78 ± 29	71 ± 36	62 ± 28	46 ± 33	63	—	—	—	—	

Coronary reserve = peak hyperemic divided by baseline LAD-flow velocity; repay = hyperemic flow area relative to flow debt area in percent (fig. 1); duration = duration of hyperemic response (seconds); MAC = multiple of 1 MAC_{agent} ($[Et]_{halothane}$ = 1.25%, $[Et]_{isoflurane}$ = 1.45%); group 1 = isoflurane anesthesia; groups 2 and 3 = halothane anesthesia; group 3 = aortic snare (see text).

ANOVA: NS = not significant; *$P < .05$ *vs.* groups; †$P < .05$ *vs.* concentration (MAC multiples); ‡$P < .05$ *vs.* group × concentration.

Follow-up tests: §sign. different from .5 MAC; ¶sign. different from group 2 and group 3; **sign. different from group 2.

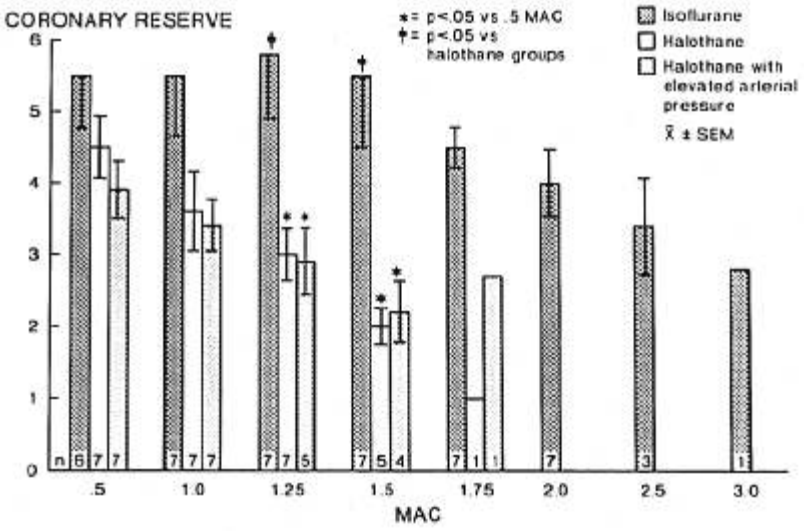

FIG. 2. Calculated coronary reserve in pigs during step increments of either halothane or isoflurane. MAC_{agent} is 1.25% end-tidal halothane and 1.45% end-tidal isoflurane.

groups at the 0.5 MAC concentration, and was not affected by increasing isoflurane concentrations (fig. 3). Again, in contrast, halothane caused a significant reduction in repayment from 640 ± 214% at 0.5 MAC to 233 ± 129% at 1.5 MAC, whereas, with isoflurane, repayment was not significantly reduced below 0.5 MAC until 2 MAC. Repayment was much lower with halothane compared to isoflurane at 1.0, 1.25, and 1.5 MAC. The dose-response reduction (*i.e.*, slope) in repayment was significantly greater (worse) with halothane than isoflurane whether MAP was below (group 2) or at the same level (group 3) as with isoflurane. The only effect of increasing MAP in group 3 was that repayment remained unchanged when halothane was increased from 0.5 to 1 MAC. Isoflurane gradually reduced repayment percent above 1.5 MAC, but, even at the 3 MAC level, repayment was still numerically higher than seen with halothane at 1.5 MAC halothane. With isoflurane, the hyperemic responses lasted longer than with halothane (group 1 *vs.* 2). Raising MAP in group 3 did abolish this difference, *i.e.*, it increased the duration of the response toward that seen with isoflurane.

HEMODYNAMIC EFFECTS

Hemodynamic variables are presented in tables 3, 4, and 5. We found no significant difference in any hemodynamic variable between the two halothane groups (2 and 3) except in MAP when arterial pressure was elevated mechanically *via* the aortic snare in group 3 as per the protocol.

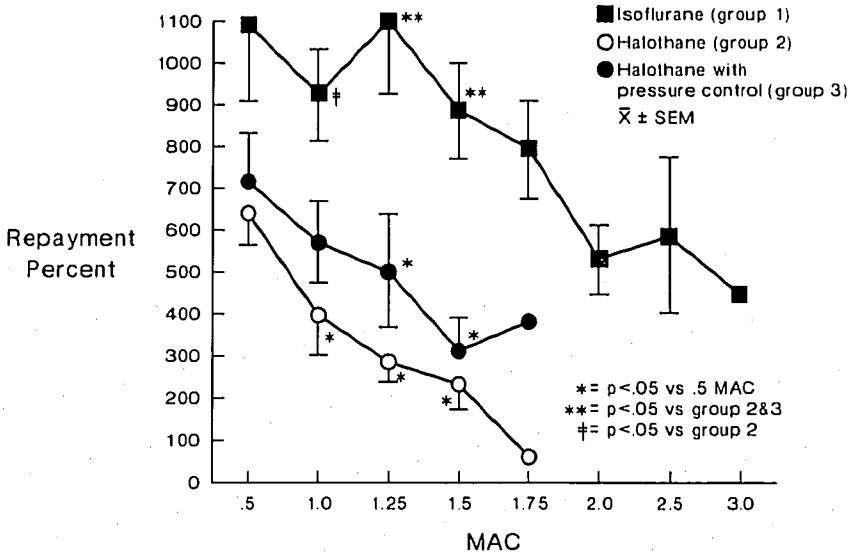

FIG. 3. Coronary artery flow repayment following 15 s LAD occlusion in pigs during step increases in concentrations of halothane or isoflurane. MAC_{agent} is 1.25% end-tidal halothane and 1.45% end-tidal isoflurane.

TABLE 3. Hemodynamic Data (Mean ± SD)

MAC	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.0	3.5	ANOVA
HR (beats · min^{-1})										
Group 1	108 ± 30	100 ± 19	94 ± 16	87 ± 5	86 ± 11	93 ± 13	95 ± 15	105 ± 24	80	NS
Group 2	100 ± 19	86 ± 18	98 ± 22	96 ± 21	113 ± 13	—	—	—	—	
Group 3	104 ± 27	100 ± 21	104 ± 19	110 ± 7	152	—	—	—	—	
SAP (mmHg)										
Group 1	111 ± 15	91 ± 15§¶	87 ± 11§¶	80 ± 10§¶	77 ± 8	73 ± 8	55 ± 23	44 ± 24	35 ± 13	‡
Group 2	93 ± 7	63 ± 10§	58 ± 10§	50 ± 14§	40 ± 18	—	—	—	—	
Group 3	92 ± 14	60 ± 14§	54 ± 18§	42 ± 12§	44	—	—	—	—	
Snared	107 ± 6	87 ± 8	72 ± 15	74 ± 11	46					
DAP (mmHg)										
Group 1¶	67 ± 17	51 ± 9§	50 ± 6§	45 ± 5§	42 ± 8	39 ± 7	34 ± 6	32 ± 7	17 ± 4	*†
Group 2	53 ± 7	29 ± 7§	27 ± 4§	22 ± 6§	16 ± 10	—	—	—	—	
Group 3	60 ± 14	36 ± 8§	32 ± 12§	22 ± 9§	24	—	—	—	—	
Snared	69 ± 8	51 ± 7	43 ± 13	44 ± 8	46					
MAP (mmHg)										
Group 1	82 ± 15**	65 ± 9§¶	62 ± 6§¶	56 ± 5§¶	54 ± 5	50 ± 5	36 ± 16	28 ± 19	23 ± 6	‡
Group 2	67 ± 6	41 ± 7§	37 ± 5§	31 ± 8§	25 ± 14	—	—	—	—	
Group 3	71 ± 13	44 ± 10§	44 ± 9§	29 ± 10§	31	—	—	—	—	
Snared††	85 ± 5	65 ± 7	53 ± 12	50 ± 9	55					

HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; MAC = multiple of 1 MAC_{agent} ($[Et]_{halothane}$ = 1.25%, $[Et]_{isoflurane}$ = 1.45%); group 1 = isoflurane anesthesia; groups 2 and 3 = halothane anesthesia; group 3 = aortic snare (see text).

ANOVA: NS = not significant; *$P < .05$ *vs.* groups; †$P < .05$ *vs.* concentration (MAC multiple); ‡$P < .05$ *vs.* group × concentration.

Follow-up tests: §sign. different from .5 MAC; ¶sign. different from group 2 and group 3; **sign. different from group 2; ††not different from group 1.

Heart rates, pulmonary artery pressures (systolic, diastolic, and mean), pulmonary capillary wedge pressures (PCWP), and calculated systemic vascular resistances (SVR) were not significantly affected by either type or concentration of agent to 1.5 MAC. Diastolic arterial pressure (DAP) and calculated coronary perfusion pressure (CPP = DAP − PCWP) were significantly higher with isoflurane compared to halothane. At all MAC levels where statistical analysis was possible between the two agents, there were significant and similar dose-response effects; namely, decreasing DAP and CPP with increasing agent concentrations. Systolic (SAP) and mean (MAP) arterial pressures, cardiac outputs (CO), and stroke volumes (SV) were considerably and significantly more reduced with increasing concentrations of halothane than with isoflurane. SAP was not different between groups at 0.5 MAC, but significantly lower at each subsequent [Et] of halothane compared with isoflu-

TABLE 4. Hemodynamic Data (Mean ± SD)

MAC	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.0	3.5	ANOVA
MPAP (mmHg)										
Group 1	14 ± 3	17 ± 7	18 ± 7	15 ± 6	14 ± 8	13 ± 7	13 ± 6	13 ± 3	11 ± 0.0	NS
Group 2	15 ± 2	13 ± 5	13 ± 5	15 ± 2	16 ± 6	—	—	—	—	
Group 3	17 ± 3	16 ± 5	17 ± 5	17 ± 6	19	—	—	—	—	
Snared	18 ± 4	18 ± 2	17 ± 5	19 ± 3	22	—	—	—	—	
CPP (mmHg)										
Group 1‡	56 ± 19	43 ± 8	39 ± 7	35 ± 7	32 ± 11	28 ± 9	19 ± 2	3	3	*†
Group 2	42 ± 7	19 ± 8	15 ± 5	11 ± 5	2 ± 8	—	—	—	—	
Group 3	49 ± 13	26 ± 10	22 ± 13	11 ± 10	—	—	—	—	—	
PCWP (mmHg)										
Group 1	10 ± 2	10 ± 3	11 ± 4	9 ± 5	8 ± 6	9 ± 6	8 ± 6	16 ± 1	11	NS
Group 2	12 ± 2	10 ± 5	12 ± 2	12 ± 2	14 ± 5	—	—	—	—	
Group 3	12 ± 3	9 ± 3	10 ± 3	10 ± 4	—	—	—	—	—	
Snared	12 ± 4	12 ± 3	13 ± 3	11 ± 1	—	—	—	—	—	

MPAP = mean pulmonary artery pressure; CPP = coronary perfusion pressure; PCWP = pulmonary capillary wedge pressure; MAC = multiple of 1 MAC_{agent} ($[Et]_{halothane}$ = 1.25%, $[Et]_{isoflurane}$ = 1.45%); group 1 = isoflurane anesthesia; groups 2 and 3 = halothane anesthesia; group 3 = aortic snare (see text).

ANOVA: NS = not significant; *$P < .05$ *vs.* groups; †$P < .05$ *vs.* concentration (MAC multiples).

Follow-up tests: ‡sign. different from group 2 and group 3.

TABLE 5. Hemodynamic Data (Mean ± SD)

MAC	0.5	1.0	1.25	1.5	1.75	2.0	2.5	3.0	3.5	ANOVA
CO ($l \cdot min^{-1}$)										
Group 1	4.07 ± 1.27	3.58 ± 1.5	3.05 ± .9†	2.74 ± .96†	2.55 ± .92	2.36 ± .87	2.07 ± 1.07	1.96 ± 1.3	—	*
Group 2	4.84 ± 1.52	2.88 ± 1.2†	2.67 ± 1.1†	1.74 ± .98†	1.70 ± .87	—	—	—	—	
Group 3	3.51 ± .64	2.17 ± .81†	2.18 ± .68†	1.28 ± .21†	1.57	—	—	—	—	
SV ($ml \cdot beat^{-1}$)										
Group 1	38.6 ± 12.4	36.5 ± 15.4	33.1 ± 10.6	31.4 ± 10.7*‡	30.2 ± 11	25.9 ± 10	21.8 ± 10.6	18.3 ± 12	—	*
Group 2	47.9 ± 11.4	33.2 ± 13.9†	27.4 ± 10.6†	18.2 ± 9.5†	15.4 ± 8	—	—	—	—	
Group 3	34.4 ± 4.2	21.8 ± 7.3†	20.5 ± 3.8†	11.7 ± 1.7†	10.3	—	—	—	—	
SVR ($dyn \cdot sec^{-1} \cdot cm^{-5}$)										
Group 1	1698 ± 558	1656 ± 596	1745 ± 535	1804 ± 559	1906 ± 738	1899 ± 696	1422 ± 303	1209 ± 736	—	NS
Group 2	1297 ± 762	1671 ± 1703	1321 ± 745	1584 ± 762	1288 ± 829	—	—	—	—	
Group 3	1639 ± 247	1771 ± 521	1644 ± 212	1736 ± 298	1578	—	—	—	—	
PVR ($dyn \cdot sec^{-1} \cdot cm^{-5}$)										
Group 1	311 ± 126	462 ± 301	531 ± 291†	496 ± 292	490 ± 405	458 ± 340	563 ± 455	976 ± 1082	—	*
Group 2	292 ± 170	573 ± 670	496 ± 335	932 ± 496†	900 ± 577	—	—	—	—	
Group 3	383 ± 76	773 ± 739†	592 ± 192†	1025 ± 319†	221	—	—	—	—	

CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; MAC = multiple of 1 $MAC_{agent}([Et]_{halothane} = 1.25\%, [Et]_{isoflurane} = 1.45\%)$; group 1 = isoflurane anesthesia; groups 2 and 3 = halothane anesthesia; group 3 = aortic snare (see text).

ANOVA: NS = not significant; *$P < .05$ *vs.* group × concentration.

Follow-up tests: †sign. different from .5 MAC; ‡sign. different from group 3.

rane. SAP fell from 93 ± 7 to 50 ± 14 mmHg when halothane was increased from 0.5 to 1.5 MAC *versus* from 111 ± 15 to 80 ± 10 mmHg with equi MAC increases in isoflurane concentration. With both agents, SAP and MAP was significantly reduced below 0.5 MAC with every MAC increment. CO and SV were also similar at 0.5 MAC, but the dose-response decrement was significantly less pronounced with isoflurane than halothane. When halothane was increased from 0.5 to 1.5 MAC, CO decreased from 4.84 ± 1.52 to 1.74 ± .98 l/min, whereas, with isoflurane, the decrease was significantly less; namely, from 4.07 ± 1.27 to 2.74 ± .96 l/min. Similarly, the decrease in SV with halothane from 47.9 ± 11.4 to 18.2 ± 9.5 ml/beat was significantly worse than that seen with isoflurane; namely, from 38.6 ± 12.4 to 31.4 ± 10.7 ml/beat. Therefore, dose-dependent depression of overall left ventricular performance was less with isoflurane based on the significantly smaller decreases in SAP, MAP, CO, and SV when similar MAC multiples were compared. Pulmonary artery pressure and PCWP did not change when aorta was snared in group 3.

Discussion

CRITIQUE OF METHODS

We chose a well-established method of assessing coronary artery reactivity or vasodilator reserve by analyzing reactive hyperemic responses.[25,30,34] Measurements of blood flow velocity rather than volume flow were chosen because this method better conserves vessel integrity, since no vascular dissection is needed. Our methodology depends on two assumptions: a) that it is valid to describe coronary hyperemic responses using measurements of flow velocity rather than actual flow measurements; and b) that the vacuum used to apply the Doppler probe caused no significant time-related tissue damage or vessel distortion.

Blood flow velocity measurements with ultrasonic Doppler crystals are influenced by the angle between the crystal and blood column, which must be relatively constant. Extrapolation to volume flow requires continual information about cross-sectional vessel area under the crystal. Cross-sectional coronary artery area increases during elevated coronary flow, and large coronary arteries undergo substantial active vasodilation (reactive dilation) following brief periods of coronary artery occlusion and myocardial ischemia.[35] The reactive dilation has, however, a distinctly delayed onset, and follows 50–60 s after the reactive hyperemia.[36] Since the peak flow velocity is reached in the course of 3–5 beats following release of the occlusion, and we quantified the coronary reserve from this peak, we do not consider reactive dilation of LAD an important source of error for this measurement of coronary reserve. Marcus *et al.*[29] performed validation studies with the epicardial Doppler probe we used, and have shown close correlations between blood flow measured by venous timed collection, electromagnetic flow probes, and mean flow velocities measured with epicardial Doppler probes during both *in vivo* and *in vitro* tests. Also, similar hyperemia curves were produced during

paired recordings obtained with electromagnetic *versus* Doppler probes adjacently placed on coronary arteries. Although the correlation coefficients were high, velocity was actually higher than volume flow, peak to resting velocity was found 9 ± 5% greater, and the repayment percent 27 ± 6% greater with Doppler than electromagnetic probes.[29] These results are essentially the opposite of the results reported by Gould *et al.*, who reported that velocity recordings during coronary flow elevation after vasodilation underestimated true increases in volume flow by 30–40%.[35] It is not clear if the discrepancy is due to different degree or rapidity of changes in vessel diameter or other methodology. Our purpose was to obtain dose-response relationships in each animal to compare the two agents between animals. During each experiment, changes in Doppler probe position were avoided. We consider the method acceptable as a measure of flow variation with the limitations mentioned.

With respect to damage caused by the application of vacuum, the wall of the Doppler probe is extremely thin; thus, the probe flattened on the epicardium when the vacuum was applied rather than the vessel being distorted into the probe. Marcus *et al.*[29] have studied this question in detail using histology and repeated measures of flow over time with microspheres, and were satisfied that application of vacuum does not affect the flow velocity measurement importantly.

Hemodynamic Effects

In this study, halothane and isoflurane caused different dose-dependent reductions in arterial pressures, cardiac output, and stroke volume with increasing concentrations. Depression of these variables during halothane was significantly greater than during isoflurane, suggesting greater cardiac depression with halothane than isoflurane, in agreement with previous animal and human studies.[3,16,18,37,38] We found dose-dependent reductions in stroke volume with both agents. With isoflurane, this was not offset by an increased heart rate (unlike human findings[39]), and cardiac output consequently fell, but less than that with halothane. Peripheral vasodilation has been reported with isoflurane in animals and humans.[1,3] Our finding of unchanged peripheral resistance during isoflurane is consistent with findings in swine exposed to 1 and 1.5 MAC[19] and horses exposed to 1–2 MAC.[40] A well-controlled, although not dose-response, human study showed no systemic dilation with 0.5% isoflurane and N_2O anesthesia.[4] Most experimental studies with higher than MAC concentrations have shown isoflurane to be a systemic dilator. Experimental design and species differences are most likely explanations for different vascular effects reported. Coronary perfusion pressure was significantly lower with halothane due to lower DAP with halothane at similar PCWP.

Coronary Vascular Reactivity

Coronary vascular reserve estimated by quantitated hyperemic responses (peak to resting flow velocity) was unaffected by increasing concentrations of isoflurane up to 1.5 MAC. In striking contrast, halothane exhausted coronary reserve at lower agent concentrations. Correcting low coronary driving pressure during halothane by mechanically increasing afterload did not improve coronary reserve, but did slightly improve repayment. Coronary reserve (peak/baseline flow ratio) of 5–7 have been reported in unanesthesized pigs,[41] dogs,[26] and humans.[25] We are unaware of any study comparing effects of isoflurane and halothane on coronary reserve in dose-response fashion. Verrier *et al.* found greater coronary reserve in dogs during a single low concentration of halothane anesthesia supplemented with thiopental compared with a single dose of nitrous oxide anesthesia.[42] They reported coronary vascular reserve of approximately 3.5 during 0.8% $[Et]_{halothane}$, which compares well with our finding of 4.4 ± 1.2 at 0.62% $[Et]_{halothane}$. Fedor *et al.* studied coronary and regional myocardial flow responses of porcine coronary circulations to transient coronary occlusions in chronically instrumented awake pigs, and found coronary reserve (calculated from their data) of 5.5 following occlusions of approximately 10 s and 6.2 following 14 s occlusions.[42] Coronary reserve in awake greyhounds was 4–5 following 15 s occlusions.[26] In healthy human hearts, coronary reserve is approximately 5.[25] Our findings suggest that coronary reserve was maintained within normal, physiologic limits during clinically relevant levels of isoflurane anesthesia. With halothane, coronary reserve was rapidly reduced to 2 at 1.5 MAC. Functionally significant coronary heart disease in humans reduces coronary reserve from 5 to 2.5 or even less.[25] When coronary reserve is less than 2, severe coronary heart disease appears always to be the cause.[25]

What, then, could explain the different effects of halothane and isoflurane on coronary artery reactivity? Mechanisms of coronary reactive hyperemic dilation remains unclear. Metabolic factors and myogenic reflexes have been suggested.[27,43] Modulators of coronary reactive hyperemic responses include coronary driving pressure, vasomotor tone, myocardial metabolism, calcium blockers, and disease states.[44]

We corrected differences in perfusion pressure without ameliorating the large differences between halothane and isoflurane with respect to coronary reserve. There were no changes in pulmonary artery pressures or PCWP during the periods of aortic snaring, and acute increases in ventricular filling pressures are un-

likely to be the cause of reduced hyperemic flow velocity. We cannot dismiss low perfusion pressure and development of ischemia as part of the explanation for the observed differences, since the control group also had low perfusion pressures between the periods when we elevated arterial pressure with the aortic snare.

Coronary vascular resistance is mainly located distal to large epicardial arteries. Peak hyperemic flow implies minimal distal coronary resistance. Our results suggest that isoflurane decreased baseline resistance to a lesser degree than halothane, since the peak (during minimal resistance) to baseline (autoregulated) flow velocity ratios remained significantly higher with isoflurane, regardless of driving pressure. Our finding of relatively unaffected vascular reactivity over a relatively wide range of isoflurane concentrations does not preclude pharmacologic vasodilation distally in arterioles. Nonetheless, severe indiscriminate distal vasodilation was not likely present with isoflurane in this model, since alterations in coronary vasomotor tone unrelated to myocardial metabolism would affect coronary reactive hyperemic responses.[44]

One possible explanation for the decreased coronary reserve with halothane is that it changed myocardial metabolism significantly. Although we did not measure myocardial oxygen supply and demand directly, arterial pressures, heart rates, and coronary driving pressures were similar in the halothane control group[3] and the isoflurane group during testing of reactive hyperemia. Similar coronary driving pressures and rate pressure products suggest similar oxygen supply/demand relations in these two groups during reactive hyperemia.

Volatile inhalation anesthetics directly affect coronary vasomotor tone by mechanism(s) that remain obscure. Domenech *et al.*[15] found a 23% reduction in diastolic coronary resistance in working canine hearts exposed to 2–3% halothane, and suggested a direct vasodilatory action. Halothane exerts differential effects on regional vascular resistances, dilates some peripheral vessels directly, and may dilate the coronary vascular bed directly, opposing the constriction due to reduced myocardial oxygen demand.[14] Halothane has a direct, three to four times stronger relaxant action *versus* isoflurane on aortic strips contracted with phenylephrine, an effect which may be mediated *via* the ATP/cAMP system.[45] Sustained hyporesponsiveness of vascular smooth muscle in rabbits occurs following termination of 2 h of 1.6% inspired halothane anesthesia.[46] In studies on potassium- or prostaglandin-constricted, isolated porcine epicardial coronary artery rings, halothane caused more relaxation than did isoflurane.[47] The mechanism for halothane's depletion of coronary reserve may thus be moderate direct dilation coupled with inhibition of coronary autoregulation, the latter mediated through complex subcellular effects on vascular smooth muscle and myocardial metabolism. Sivarajan *et al.* demonstrated severe intolerance to tachycardia in dogs with collateral-dependent myocardium, and suggested depletion of collateral function by halothane.[48] Tachycardia in the presence of depleted coronary reserve would combine to severely limit the potential to provide increased oxygen supply.

In contrast, Tarnow *et al.* studied tolerance to pacing-induced myocardial ischemia in patients with stable angina pectoris awake and during 0.5% $[Et]_{isoflurane}$ anesthesia plus 50% nitrous oxide, and found improved tolerance to pacing-induced tachycardia despite reduced coronary perfusion pressure.[4] At increasing halothane concentrations, we found coronary reserve decreased to 2.0 ± 0.18 at 1.5 MAC prior to collapse. Between 1.75 and 2.0 MAC, all 14 pigs (both groups) anesthesized with halothane died, while all seven pigs in the isoflurane group were alive with coronary reserves still between 4 and 4.5 (fig. 2). We speculate that the reduction of coronary reactivity contributed to the much earlier cardiac collapse. We have reported significant differences between the safety margins of halothane and isoflurane with a fatal/anesthetic ratio for isoflurane almost twice that of halothanes in this species.[49]

The response of the coronary bed to isoflurane remains controversial. Some human studies have suggested that isoflurane causes indiscriminant coronary dilation with coronary steal.[1,17,21] Other studies utilizing different techniques have demonstrated the opposite, *i.e.*, maintained myocardial oxygen supply/demand ratio.[18,20,50] We have demonstrated for the first time a marked dose-related difference in coronary vascular reactivity between halothane and isoflurane, using a different experimental approach; namely, *in vivo* studies of coronary blood flow velocity during reactive hyperemia. We think that the implications of our data are twofold. First, it is unlikely that isoflurane caused important direct dilation of the vascular bed distal to our measurement site, because this would have blunted hyperemic responses and reduced the coronary reserve. Halothane was a much more potent reducer of coronary reactivity. Second, we have demonstrated that inhalation anesthetics are significant factors during experiments on coronary vessels. Recent studies assessing coronary reserve in patients with aortic stenosis were performed with a variety of anesthetic techniques, including halothane, without control for specific effects of anesthetics on vascular responsiveness.[34] Similarly, in a study of myocardial reactive hyperemia and collateral function in patients with left ventricular hypertrophy, the primary anesthetic was halothane.[51] Studies of coronary vascular reactivity must take the anesthetic into account.

In conclusion, we have demonstrated marked differences between dose-response effects of isoflurane *versus* halothane on coronary vascular reserve and general hemodynamics in swine. Isoflurane preserved coronary reserve measured by quantitated hyperemic responses at least up to 1.5 MAC. In contrast, from 1.25 MAC and upward, halothane depleted coronary reserve, by a mechanism unrelated to driving pressure. Our data are in agreement with previous and recent studies in humans and animals reporting greater cardiac and circulatory depression and narrower safety margins with halothane compared with isoflurane. Our results in the pig are not compatible with the contention that isoflurane, *per se*, is a potent direct pharmacologic coronary vasodilator in clinically relevant concentrations.

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