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Direct Comparative Effects of Halothane, Enflurane, and Isoflurane on Oxygen Supply and Demand in Isolated Hearts

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The authors examined the direct myocardial and coronary vascular responses to isoflurane, enflurane, and halothane and compared their effects on attenuating autoregulation of coronary flow (CF) as assessed by changes in the O_2 supply–demand relationship. The effects of these anesthetics on left ventricular pressure (LVP), CF, percentage of O_2 extraction, O_2 delivery (D_{O_2}), and myocardial O_2 consumption ($M\dot{V}_{O_2}$) were examined in 47 isolated guinea pig hearts perfused at constant pressure. An increase in D_{O_2} from control relative to $M\dot{V}_{O_2}$ was used to indicate attenuation of autoregulation, and a decrease in $M\dot{V}_{O_2}$ relative to D_{O_2} to indicate a reduction of myocardial work and O_2 utilization. Each heart was exposed to 0.51, 0.70, and 1.20 vol% halothane (n = 16); 0.91, 1.41, and 2.04 vol% enflurane (n = 16); or 0.45, 0.87, and 1.22 vol% isoflurane (n = 15). Adenosine (2 mM) was given to test maximal CF in arrested and in paced hearts. Mean results for increasing concentrations of each agent were as follows: LVP (average control 92 ± 5 mmHg) (standard error of mean [SEM]) decreased by 15%,* 25%,* and 34%* with halothane; 13%,* 24%,* and 34%* with enflurane; and only 3%, 7%, and 13%* with isoflurane (*$P < 0.05$ *vs.* controls). CF (control 6.1 ± 0.3 $ml \cdot min^{-1} \cdot g^{-1}$) was not altered significantly with halothane or enflurane but increased by 6%, 9%, and 16%* with isoflurane and maximally by 86 ± 7%* with adenosine. The percentage of O_2 extraction (control 69.2 ± 1.8%) decreased by 9%,* 16%,* and 22%* with halothane; 7%,* 15%,* and 22%* with enflurane; and only 1%, 4%, and 7%* with isoflurane. $M\dot{V}_{O_2}$ (control 59 ± 3 $\mu l \cdot min^{-1} \cdot g^{-1}$) decreased by 0%, 7%, and 14% with halothane and 4%, 9%,* and 17%* with enflurane, but was unchanged with isoflurane. The ratio of D_{O_2} to $M\dot{V}_{O_2}$ increased by 9%,* 17%,* and 22%* with halothane; 8%,* 16%,* and 23%* with enflurane; and only 1%, 3%, and 8%* with isoflurane. In this model, the findings show that isoflurane only slightly increases CF and D_{O_2}, with no change in $M\dot{V}_{O_2}$, whereas halothane and enflurane do not increase CF or D_{O_2} but moderately decrease $M\dot{V}_{O_2}$ so that the ratio of D_{O_2} to $M\dot{V}_{O_2}$ increase is significantly larger with halothane and enflurane than with isoflurane. This indicates that the greater direct negative inotropic effects of halothane and enflurane, compared with isoflurane, are associated with a lesser attenuation of coronary autoregulation, but with a larger reduction in O_2 utilization. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: atrial rate; atrial–ventricular conduction time; autoregulation; coronary flow; coronary reserve; left ventricular pressure; myocardial oxygen consumption; oxygen delivery; oxygen extraction.)

THE THREE VOLATILE ANESTHETICS currently used in clinical practice—halothane, enflurane, and isoflurane—are negative chronotropic, dromotropic, and inotropic agents. They each directly decrease heart rate,[1–3] increase atrioventricular (AV) conduction time,[2,3] and decrease contractile function.[2–11] However, it appears that there are quantitative differences in the degree to which these agents depress electrical[3] and mechanical[3,6–11] function and alter coronary flow (CF).[12–18] Because the concentration of an anesthetic that produces anesthesia on the basis of the minimal alveolar concentration (MAC) may not be proportional to its depressant effects on the myocardium, it is difficult to compare quantitatively the cardiac effects of the various volatile anesthetic agents.

To determine differential depressant effects of these agents, it is best to use a model in which mechanical function is unaffected by preload, afterload, and extrinsic, autonomic, and humoral influences. To adequately assess vasodilatory responses, maximal coronary reserve and autoregulatory effects resulting from metabolic activity and O_2 supply and demand should be measured.[19] Several equivalent vapor concentrations of each anesthetic should be tested for comparison with one another because equivalent MAC comparisons may be meaningless for the myocardium.

Several suitable mechanical models (*i.e.*, papillary and ventricular muscle of various species[4–11,20]) have been used to study mechanics and, indirectly, the mechanism of action of anesthetics; however, few studies have examined, in a well-controlled and randomized fashion, the simultaneous effects of anesthetics on mechanical function, CF, and myocardial O_2 extraction. Measurements of CF and O_2 extraction are necessary to elucidate directly the anesthetic effect on coronary vascular resistance. This assumes that myocardial O_2 utilization reflects the contribution of autoregulatory factors—such as local metabolites, nutrients, and O_2—to coronary blood flow. Recent studies in an acute dog model[21] and isolated perfused rat heart models[15,17] have compared the effects of volatile anesthetics on CF and myocardial O_2 consumption ($M\dot{V}_{O_2}$). In two of these studies,[15,21] it was demonstrated that halothane and isoflurane equivalently reduce O_2 consumption and that CF is increased more by isoflurane

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than by halothane. In the other study,[17] isoflurane and halothane were found to be equipotent for inducing direct dilatation of coronary resistance vessels and reducing O_2 extraction when hearts were arrested by tetrodotoxin.

The current study furnishes additional findings on the relationships among mechanical function, CF, and myocardial O_2 supply relative to O_2 demand in isolated guinea pig hearts. The aims of these experiments were as follows: 1) to compare direct cardiac effects of three concentrations of halothane, enflurane, and isoflurane on electrical and mechanical function and CF; 2) to examine CF responses as a function of maximal coronary reserve, as indicated by administration of adenosine; and 3) to determine the relative effectiveness of each of these agents in altering O_2 supply and myocardial O_2 demand. The results demonstrate that there are indeed important quantitative differences in the effects of halothane and enflurane *versus* those of isoflurane on myocardial contractility, CF, and the O_2 supply–demand ratio when comparisons of either equivalent MAC levels or equivalent effective vapor concentrations are considered.

Materials and Methods

After approval was obtained from the Animal Studies Committee, 10 mg ketamine and 1,000 units heparin were injected intraperitoneally into 47 albino English short-haired guinea pigs (400–600 g). The animals were decapitated when unresponsive to noxious stimulation. After thoracotomy, the inferior and superior venae cavae were cut and the aorta cannulated distal to the aortic valve. Each heart immediately was perfused retrogradely through the aorta with cold perfusate solution and was excised. All hearts were perfused at an aortic root perfusion pressure of 55 mmHg. The perfusate, a modified Krebs–Ringer's salt solution, was filtered (5-μm pore size) in-line (Astrodisc®; Gelman Scientific, Ann Arbor, MI) and had the following composition (millimolar): Na^+ 137, K^+ 4.5, Mg^{2+} 1.2, Ca^{2+} 2.5, Cl^- 134, HCO_3^- 15.5, $H_2PO_4^-$ 1.2, glucose 11.5, pyruvate 2, mannitol 16, EDTA (ethylenediaminetetraacetic acid) 0.05, and insulin 5 units/l. Perfusate and bath temperatures were maintained at 36 ± 0.3° C with the use of a thermostatically controlled water circulator (Haake E 52®; Haake Buchlar, Inc., Saddle Brook, NJ). The solution was equilibrated with a gas mixture of 96% O_2 plus 4% CO_2 at a flow rate of 3 l/min.

Systolic left ventricular pressure (LVP) was measured isovolumetrically with a transducer (Gould-Statham P23; Gould Electronics, Inc., Elk Grove, IL) connected to a thin, saline-filled latex balloon (Hugo Sachs Electronic AG, March, Germany) inserted into the left ventricle through the mitral valve by a cut in the left atrium. Balloon volume was adjusted to maintain a diastolic LVP of 0 mmHg during the initial control period. Positive dP/dt_{max} and negative $dPdt/_{max}$ are the peak time derivatives of LVP and were obtained electronically. Two pairs of bipolar electrodes (Teflon®-coated silver electrodes; 125-μm diameter) were placed in each heart to monitor intracardiac electrographs from which spontaneous sinoatrial rate and AV conduction time were measured. The two electrode signals were amplified and displayed continuously on an image-storing oscilloscope (model 5A26N, 5B12N; Tetronix, Beaverton, OR). Atrial rate was determined from the right atrial beat-to-beat interval, and AV conduction time was determined from the superior right atrial to right ventricular pulmonary conus beat-to-beat interval. Electrograph intervals were measured automatically on-line by digital timer systems that allowed instantaneous interval and rate analyses.

Coronary sinus effluent was collected by placing a cannula into the right ventricle through the pulmonic artery after ligation of the venae cavae. Coronary (aortic) inflow was measured at a constant temperature by an electromagnetic flow meter (Biotronex BL610-2A with Series 2000C extracorporeal transducer, 1.5 mm ID; Biotronex Laboratories, Inc., Kensington, MD) that was calibrated daily by four-point, timed collections into a volumetric cylinder over the flow range of 0–24 ml/min. Calibration curves were best fitted by nonlinear regression analysis ($R^2 > 0.98$). Zero inflow was established periodically by temporarily bypassing the flow transducer. Adenosine (0.2 ml of a 2 mM solution) was injected into the aortic (coronary perfusion) cannula during the initial control period and during the final O_2 control period so that maximal CF could be assessed. Because this dose temporarily arrests the heart, each heart also paced at 240 beats per min during injection to allow maximal flow to be assessed in the contracting heart so that the mechanical compressive effect of myocardial contraction on CF could be established.

Coronary inflow and outflow (coronary sinus) O_2 tensions (in mmHg) were measured continuously on-line (Instech 203B; Instech Laboratories, Plymouth Meeting, PA) and verified off-line with an intermittently self-calibrating analyzer system (Radiometer ABL-2®; Metron Chicago, Inc., Des Plaines, IL). The in-line, temperature-controlled, miniature Clark electrodes were calibrated periodically with a bypass circuit in which perfusate was gassed with 100% nitrogen, 21% O_2, and 96% O_2 to adjust O_2 tension to 20, 150, and 650 mmHg, respectively. These hearts depend solely on the crystalloid solution from which to extract dissolved O_2. O_2 delivery (D_{O_2}) was calculated from the inflow O_2 tension multiplied by O_2 solubility (24 μl/ml saline at 760 mmHg and 37° C) multiplied by $CF \cdot g^{-1}$ wet heart tissue (average 1.84 ± 0.05 g SEM). The percentage of O_2 extraction was calculated as 100 times the difference between inflow and outflow O_2 ten-

sions divided by inflow O_2 tension. $M\dot{V}_{O_2}$ was calculated as O_2 solubility multiplied by $CF \cdot g^{-1}$ multiplied by the difference between inflow and outflow O_2 tensions. Electrograms, heart rate, AV conduction time, outflow O_2 tension, CF, LVP, and perfusion pressure were recorded on tape (Model D1; Vetter Company, Rebersburg, PA) for later detailed analysis of these data and for measurement of LV dP/dt. All measured variables were displayed on a fast-writing (3 kHz), thermal array, eight-channel recorder (model MT9500; Astro-Med, Inc., West Warwick, RI). Derived variables were computed with the use of a software program (Microsoft Excel®; Microsoft Corporation, Redmond, WA).

Protocol and Statistical Analysis

Hearts prepared for study were assigned randomly to one of three groups treated with the following: halothane (n = 16), enflurane (n = 16), or isoflurane (n = 15). Coronary arterial (inflow) *p*H, P_{CO_2} (in mmHg), and P_{O_2} (in mmHg), respectively, were 7.49 ± 0.01 (SEM), 37 ± 1, and 513 ± 5 for halothane; 7.47 ± 0.01, 35 ± 1, and 515 ± 7 for enflurane; and 7.45 ± 0.01, 36 ± 1, and 500 ± 9 for isoflurane. Each heart was exposed to only one anesthetic. After a 30-min period of stabilization, each heart was exposed, in random order, to three concentrations of the assigned anesthetic delivered by agent-specific vaporizers (Ohio Medical Products, Madison, WI). Hearts were exposed to each concentration for 10 min, with 15-min anesthetic-free control periods between each level—designated low, medium, and high. Measurements were made during the last minute of the 30-min initial control period (control 1), the last minute of exposure to an anesthetic level, and the last minute of the final 20-min postcontrol period (control 2).

Designated levels (low, medium, high), the delivered (vaporizer) concentrations (vol%), and the inflow perfusate concentrations (micromolar), which were measured in duplicate or triplicate (n = 356 samples) by gas chromatography,[2,3] were as follows: low, 0.375%, 159 ± 7 μM; medium, 0.75%, 218 ± 18 μM; high, 1.12%, 374 ± 12 μM for halothane; low, 0.75%; 282 ± 20 μM; medium, 1.5%, 435 ± 24 μM; high, 2.25%, 633 ± 37 μM for enflurane; low, 0.5%, 103 ± 7 μM; medium, 1.0%, 200 ± 9 μM; high, 1.5%, 282 ± 12 μM for isoflurane. Anesthetic was not measurable in the solution at the end of the control periods. In guinea pigs, MAC is estimated to be approximately 1.0% for halothane, 2.2% for enflurane, and 1.2% for isoflurane.[22] Based on calculated concentrations of 310 μM per vol% for halothane and enflurane and 230 μM per vol% for isoflurane in perfusate solution at 37° C at 1 atm,[23] and on our measured bath concentrations given above, the effective fractional MACs were as follows: low 0.51, medium 0.70, high 1.20 for halothane; low 0.41, medium 0.64, high 0.93 for enflurane; and low 0.38, medium 0.73, high 1.03 for isoflurane. The calculated effective vapor concentrations (vol%) and guinea pig fractional MACs are given in table 1.

All data are expressed as means ± SEM. Statistical differences were determined for values obtained at control; low, medium, high, and postcontrol periods among the three anesthetic groups (intergroup comparisons) and within each group for differences between controls and anesthetic levels. Differences among variables were determined by two-way analysis of variance (Statview®; Abacus Concepts, Calabasas, CA; and CLR anova®; Clear Lake Research, Houston, TX) software programs on a computer (Macintosh® SE30 computer; Apple Computers, Inc., Cupertino, CA); if F tests were significant, Fisher's least-significant difference tests were used to compare means. Mean values were considered significant at $P < 0.05$. In figures 1–4, the following notations for significance are used: [a] = halothane, enflurane, and isoflurane and final control *versus* initial control; [b] = medium *versus* low MAC level for each anesthetic; [c] = high *versus* low MAC level for each anesthetic; [d] = halothane *versus* isoflurane at corresponding MAC levels; [e] = enflurane *versus* isoflurane at corresponding MAC levels; and [f] = enflurane *versus* halothane at corresponding MAC levels. Because "d, e, and f" refer to comparisons among the three anesthetic groups, statistical comparisons were made on the change from the initial O_2 controls. If a given variable showed significance for "a" as well as "b" or "c," the response was considered MAC dependent. For this study, MAC dependency refers to equivalent fractional guinea pig MACs (*i.e.*, at low, medium, and high levels). Comparisons (Student's paired *t* tests) also were made for each variable between these approximately equivalent effective vapor concentrations: low enflurane (0.91 vol%, 0.41 MAC) *versus* medium halothane (0.70 vol%, 0.70 MAC) and low enflurane *versus* medium isoflurane (0.87 vol%, 0.73 MAC). Statistical comparisons of equivalent MAC fractions (levels) appear in table 1 and figures 1–4, whereas those of approximately equivalent vapor concentrations are mentioned only in the text.

Results

Our findings are presented in table 1 and figures 1–4. Heart rate decreased significantly from control with each increasing fractional MAC level of halothane (−6 ± 1%, −8 ± 1%, −10 ± 1%) and enflurane (−18 ± 2, −25 ± 2, −29 ± 3%), and with the two highest levels of isoflurane (−5 ± 1%, −8 ± 1%, −12 ± 2%); this effect was dependent on MAC for the three levels of enflurane and for the low and high levels of halothane (table 1). At each MAC level, both halothane and enflurane decreased heart rate more than isoflurane; the decreases in heart rate with enflurane

TABLE 1. Comparative Effects of Three Levels of Three Anesthetics on Several Cardiac Variables

ANES	Level	MAC fraction	Vol (%)	Heart Rate (beats per min)	AV Time (ms)	LV-dP/dt ($mmHg/s \cdot 10^{-3}$)	$\dot{D}_{O_2}$ ($\mu l \cdot min^{-1} \cdot g^{-1}$)	$M\dot{V}_{O_2}$ ($\mu l \cdot min^{-1} \cdot g^{-1}$)	O_2 Extraction (%)
ISO	C	0	0	222 ± 3	59.4 ± 1.3	2.2 ± .06	94 ± 5	66 ± 4	71.6 ± 1.3
HAL	C	0	0	215 ± 5	57.3 ± 1.6	2.0 ± .08§	82 ± 7	56 ± 4§	70.5 ± 2.1
ENF	C	0	0	218 ± 4	58.7 ± 1.0	2.1 ± .06	86 ± 5	54 ± 3¶	64.1 ± 1.8¶
ISO	Low	0.38	0.45	217 ± 3	59.8 ± 1.5	2.1 ± .06	97 ± 6	67 ± 4	70.1 ± 1.7
HAL	Low	0.51	0.51	203 ± 5*§	58.3 ± 1.5	1.8 ± .09*§	91 ± 6	57 ± 3§	64.2 ± 2.4*§
ENF	Low	0.41	0.91	200 ± 4*¶	59.0 ± 1.1	1.9 ± .07*¶	89 ± 6	52 ± 3*¶	59.7 ± 2.2*¶
ISO	Med.	0.73	0.87	214 ± 2*	61.1 ± 1.3	2.0 ± .08	100 ± 6	69 ± 4	68.9 ± 1.9
HAL	Med.	0.70	0.70	199 ± 5*§	58.8 ± 1.4	1.6 ± .10*§	90 ± 6	52 ± 3¶	59.2 ± 2.7*†§
ENF	Med.	0.64	1.41	193 ± 4*†¶	60.6 ± 1.1	1.7 ± .07*†¶	91 ± 6	49 ± 3*¶	55.2 ± 2.5*†¶
ISO	High	1.03	1.22	210 ± 2*‡	62.1 ± 1.2*‡	2.0 ± .06*‡	106 ± 6*‡	71 ± 4	66.7 ± 2.2*‡
HAL	High	1.20	1.20	193 ± 5*‡§	62.1 ± 1.6*‡§	1.5 ± .11*‡§	90 ± 7§	48 ± 3*‡§	55.3 ± 3.3*‡§
ENF	High	0.93	2.04	189 ± 4*‡¶	64.8 ± 1.6*‡¶	1.5 ± .07*‡¶	91 ± 6¶	45 ± 3*‡¶	50.6 ± 2.7*‡¶
ISO	PC	0	0	221 ± 2	58.9 ± 1.4	2.1 ± .05	91 ± 5	65 ± 4	71.7 ± 2.6
HAL	PC	0	0	210 ± 5§	57.4 ± 1.5	1.9 ± .08§	86 ± 5	58 ± 2§	70.0 ± 2.5
ENF	PC	0	0	208 ± 4*¶	58.4 ± 1.1	2.0 ± .07	85 ± 5	53 ± 3¶	64.0 ± 1.9¶

Fractional MAC was determined from the effective vapor concentration (vol %) and the estimated MAC for the guinea pig.[22] Effective vapor concentration was calculated from the measured inflow perfusate concentration (micromolar) by gas chromatography, as described in Materials and Methods. The order of the level of each anesthetic was randomized.

ANES = anesthetic; ISO = isoflurane; HAL = halothane; ENF = enflurane; C = initial control; PC = postcontrol; Med. = medium; AV = atrioventricular; LV-dP/dt = peak negative derivative of isovolumetric left ventricular pressure; $\dot{D}_{O_2}$ = oxygen delivery; and $M\dot{V}_{O_2}$ = myocardial oxygen consumption.

For $P < 0.05$: *HAL, ENF, ISO *versus* C; †Med. *versus* low (each anesthetic); ‡high *versus* low; §HAL *versus* ISO (each level); ¶ENF *versus* ISO (each level); **ENF *versus* HAL (each level). ISO n = 15; HAL n = 16; ENF n = 16 hearts.

and halothane were similar. Along with the decreases in heart rate, AV conduction time increased. This was significant only at the high level for each anesthetic; the increases in AV time at the high level of halothane (9 ± 2%) and enflurane (10 ± 2%) were greater than at the high level of isoflurane (5 ± 1%).

Left ventricular pressure decreased with each increasing level of halothane and enflurane (fig. 1). These values were −15.2 ± 1.9%, −25.1 ± 2.3%, and −33.8 ± 2.7% of the initial control for halothane, and −13.5 ± 1.85, −23.7 ± 2.1%, and −34.3 ± 2.4% of the initial control for enflurane. Only the high level of isoflurane decreased LVP (−12.8% of control). The decreases in LVP with halothane and enflurane were statistically similar, and they were significantly larger than the decrease with isoflurane.

Figure 2 shows that LV + dP/dt_{max} similarly was decreased by these three anesthetics. The decreases with the three increasing levels of halothane were −15.2 ± 1.6%, −23.7 ± 2.5%, and −32.4 ± 3%; for enflurane the decreases were −11.5 ± 1.6%, −18.7 ± 1.5%, and −28.5 ± 2.3%; only the high level of isoflurane significantly decreased peak LV plus dP/dt (−10.4 ± 0.8%). The responses with halothane and enflurane were statistically similar, except that at the medium level halothane decreased LV plus dP/dt_{max} more than did enflurane. As with LVP, the decreases in LV plus dP/dt_{max} with each level of halothane were greater than those with isoflurane.

Table 1 shows that LV $-dP/dt_{max}$ similarly was depressed by the three anesthetics. Only the high level of isoflurane decreased this variable (−9.3 ± 1.0%); but LV $-dp/dt_{max}$ was decreased at each level of halothane (−10.4 ± 2.2%, −16.9 ± 3.0%, and −25.0 ± 3.7%) and enflurane (−9.0 ± 1.9%, −16.6 ± 2.3%, and −26.4 ± 2.8%). Middle and high MAC levels of halothane and enflurane caused significantly greater depression of contractile function than did low MAC levels; this demonstrates that cardiac depression was dependent on the effective MAC level.

Figure 3 indicates that adenosine maximally increased CF 94 ± 9% for halothane, 77 ± 6% for enflurane, and 86 ± 6% for isoflurane above the initial control; as shown, these responses were statistically similar after exposure to the anesthetics (postcontrol). Not shown in figure 3 is the increase in CF with adenosine during atrial pacing at 240 beats per min; these increases were as follows: 54 ± 5% for halothane, 46 ± 6% for enflurane, and 39 ± 8% for isoflurane. Compared with their controls, halothane and enflurane caused no change in CF at any effective anesthetic MAC level. Only the high level of isoflurane significantly increased CF; this increase was 15.6 ± 3.1%; the increase in flow with isoflurane was much smaller than the increase in flow with adenosine in arrested and in paced hearts. Table 1 shows that D_{O_2}, like CF, was not altered significantly by halothane and enflurane, and was

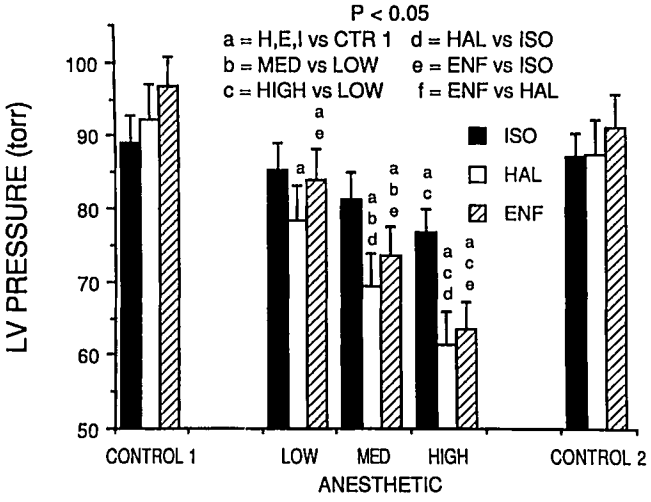

FIG. 1. Effects of low, medium (MED), and high levels of isoflurane (ISO), halothane (HAL), and enflurane (ENF) on isovolumetric left ventricular (LV) pressure. Low, medium, and high levels correspond to effective vapor concentrations of: 0.45, 0.87, and 1.22 vol % for isoflurane, 0.51, 0.70, and 1.20 vol % for halothane, and 0.91, 1.41, and 2.04 vol % for enflurane. Minimum alveolar concentration (MAC) as a fraction of MAC for the guinea pig,[22] was determined from the effective vapor concentrations calculated from molar concentrations measured in the perfusate solution. For $P < 0.05$: [a] = isoflurane, halothane, or enflurane *versus* control 1; [b] = medium *versus* low for a given agent,; [c] = high *versus* low for a given agent; [d] = halothane *versus* isoflurane for a given MAC level (change from control 1); [e] = enflurane *versus* isoflurane for a given MAC level (change from control 1); and [f] = enflurane *versus* halothane for a given MAC level (change from control 1). N = 15 hearts for isoflurane and 16 hearts each for enflurane and halothane. (Torr = mmHg.)

significantly increased (17 ± 5%) only with the high level of isoflurane.

Myocardial oxygen consumption, as shown in table 1, was slightly lower in the halothane and enflurane groups

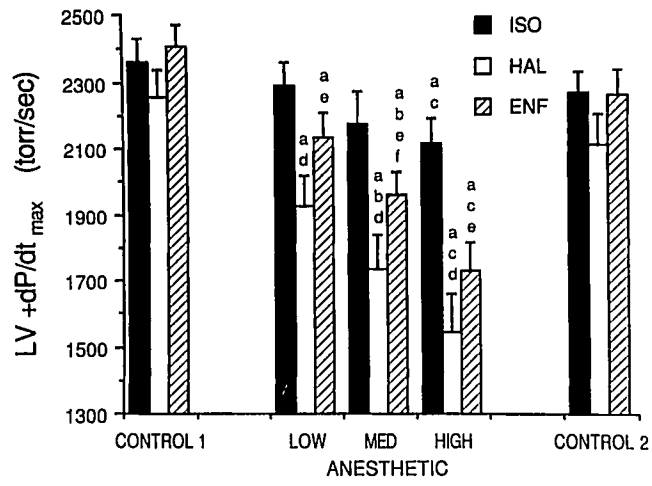

FIG. 2. Effects of three levels of isoflurane, halothane and enflurane on peak positive LV pressure derivative (LV $+dP/dt_{max}$). See figure 1 for explanations.

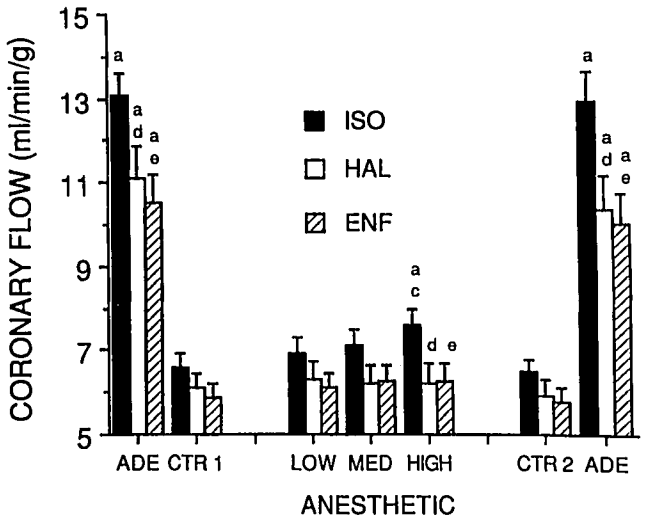

FIG. 3. Effects of three levels of isoflurane, halothane, and enflurane on coronary flow. ADE = the maximal flow response in arrested hearts to adenosine before the initial control (CTR 1) and after the final control (CTR 2). See figure 1 for explanations.

than in the isoflurane group during the initial and final controls. Isoflurane caused no significant change in $M\dot{V}_{O_2}$, whereas halothane decreased $M\dot{V}_{O_2}$ at the high level (−14 ± 2%) and enflurane decreased $M\dot{V}_{O_2}$ at medium (−9 ± 2%) and high MAC levels (−17 ± 3%). The decreases in $M\dot{V}_{O_2}$ with halothane and enflurane at medium and high levels were significantly greater than the decreases with isoflurane; this held true if the changes in $M\dot{V}_{O_2}$, rather than $M\dot{V}_{O_2}$, among the three anesthetics were compared (significance not shown).

Table 1 shows that the percentage of O_2 extraction in

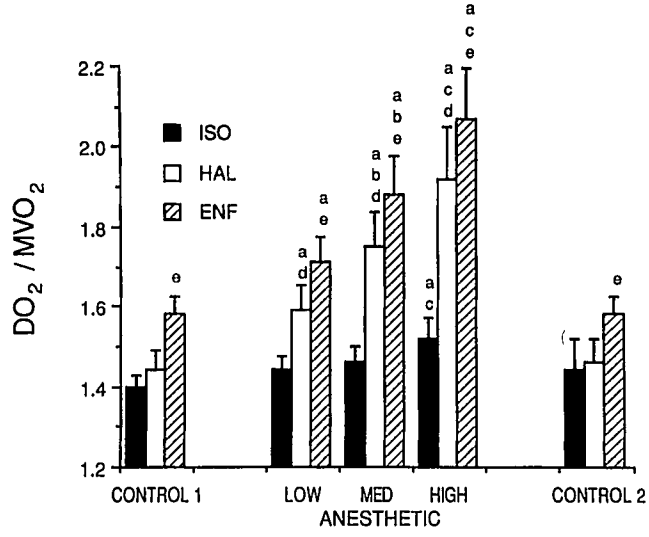

FIG. 4. Effects of three levels of isoflurane, halothane, and enflurane on the oxygen delivery ($\dot{D}_{O_2}$) to myocardial oxygen consumption ($M\dot{V}_{O_2}$) ratio. See figure 1 for explanations.

the enflurane group was lower than that of the halothane and isoflurane groups during control. Control outflow (coronary sinus) P_{O_2} values (in mmHg) (*i.e.*, before exposure to anesthetics) for the three groups were as follows: 154 ± 11 for halothane; 168 ± 11 for enflurane; and 156 ± 13 for isoflurane. The percentage of O_2 extraction decreased for each of the three levels of halothane (−9 ± 2%, −16 ± 2%, −22 ± 3%) and enflurane (−7 ± 1%, −15 ± 2%, −22 ± 3%). This decrease was dependent on the effective low and medium MAC levels for halothane and enflurane and the effective low and high MAC levels for halothane and enflurane. For isoflurane, only the high MAC level decreased the percentage of O_2 extraction (−7 ± 3%). At each MAC level, the decrease in the percentage of O_2 extraction for halothane was statistically similar to that of enflurane and at each level was significantly larger ($P < 0.01$) than that for isoflurane.

Figure 4 shows the relationship between O_2 supply (D_{O_2}) and myocardial O_2 demand ($M\dot{V}_{O_2}$). During the initial control period, the calculated ratio of D_{O_2} to $M\dot{V}_{O_2}$ was significantly greater for the enflurane group than for the isoflurane or halothane groups. This ratio increased significantly at each increasing level of halothane (9 ± 3%, 17 ± 4%, 22 ± 3%) and enflurane (8 ± 3%, 16 ± 4%, 23 ± 3%) but increased only at the high level (8 ± 4%) of isoflurane. The increases at medium and high levels of halothane and enflurane were significantly larger than the responses at the low levels. The increases in the ratio for halothane and enflurane were statistically similar and were significantly larger ($P < 0.05$) than the increase found with isoflurane.

Not shown statistically in table 1 and figures 1–4 are comparisons between calculated effective vapor concentrations (vol%) that were found to be approximately equivalent at different effective MAC levels. Analysis of these data indicates that 0.70 vol% halothane (medium level, 0.70 MAC) produced significantly ($P < 0.05$) lower values for LVP, LV $+dP/dt_{max}$, and LV $-dP/dt_{max}$ compared with 0.91 vol% enflurane (low level, 0.41 MAC); for all other variables, there were no statistical differences. The same vapor concentration of enflurane (0.91 vol%) produced significantly ($P < 0.05$) lower values for heart rate, $M\dot{V}_{O_2}$, and percentage of O_2 extraction; an increased value for $D_{O_2}/M\dot{V}_{O_2}$; and no change in the other variables measured, compared with 0.87 vol% isoflurane (medium level, 0.73 MAC).

Discussion

We used the isolated, perfused guinea pig heart to compare the direct chronotropic, dromotropic, inotropic, and coronary vasodilatory effects of isoflurane, enflurane, and halothane unencumbered by autonomic influence and alterations in preload volume or afterload impedance. Measurement of arterial and coronary sinus O_2 tension allowed us to also examine for differential effects of these volatile agents on delivery and utilization of O_2 and on their relative attenuation of CF autoregulation. At roughly equivalent MAC fractions (*i.e.*, low, medium, and high levels), the results indicate the following: 1) isoflurane produces smaller decreases in atrial rate, LVP, and its positive and negative peak derivatives that are not accompanied by a reduction in O_2 consumption; 2) halothane and enflurane produce larger MAC-dependent decreases in atrial rate, LVP and its positive and negative peak derivatives that are accompanied by reductions in O_2 consumption at the higher levels; 3) isoflurane is a mild, direct coronary vasodilating agent as demonstrated by the smaller increase in CF compared with adenosine and by the absence of a decrease in O_2 consumption; 4) halothane and enflurane are even weaker coronary vasodilating agents, as demonstrated by the maintained CF during exposure to these anesthetics despite large reductions of O_2 consumption that would be expected to reduce CF through autoregulatory mechanisms; and 5) isoflurane produces a smaller increase in the O_2 supply–demand ratio; this results more from the moderate increases in CF and D_{O_2} than from a decrease in $M\dot{V}_{O_2}$. In contrast, the larger increase in this ratio produced by enflurane and halothane results more from a decrease in $M\dot{V}_{O_2}$ than from an increase in CF and D_{O_2}. Overall, this study demonstrates that these agents have differential direct effects on myocardial function, CF, and the O_2 supply–demand ratio in the isolated heart perfused at constant pressure. Because of the relatively greater myocardial depressant effects of halothane and enflurane, and the relatively smaller effect of isoflurane on increasing CF, effective myocardial tissue oxygenation is greater with halothane and enflurane than with isoflurane.

Differential Effects on Heart Rate, AV Conduction, and Left Ventricular Pressure

The decreases in spontaneous atrial rate and the increases in AV conduction time produced by exposure to increasing concentrations of isoflurane, halothane, and enflurane are qualitatively similar to our previous findings.[1–3] At equivalent MAC levels, enflurane and halothane had similar depressant effects that were greater than those of isoflurane. At those effective vapor concentrations that were approximately equivalent at different MAC levels (*i.e.*, 0.70 vol% halothane and 0.91 vol% enflurane, 0.91 vol% enflurane and 0.87 vol% isoflurane), halothane and enflurane had similar negative chronotropic and dromotropic effects and enflurane had a greater negative chronotropic effect than isoflurane. The mechanism of the negative chronotropic and dromotropic

effects of these agents is not well understood, but nonspecific depression of the pacemaker currents, particularly those carried by sodium and calcium, as demonstrated in ventricular cells,[4,5,24] probably are involved.

Contractile function was assessed by measuring isovolumetric LVP, LV $+dP/dt_{max}$, and LV $-dP/dt_{max}$. Preload and afterload factors are constants, and the observed changes in heart rate (185–225 beats per min) do not alter these indices of contractile function significantly, compared with those of hearts paced at 225 beats per min (unpublished observations). At equivalent MAC levels, the depressant effects of enflurane and halothane on LVP, LV $+dP/dt_{max}$, and LV $-dP/dt_{max}$ were similar and were greater than those of isoflurane. At approximately equivalent vapor concentrations, the middle MAC level of halothane (0.70 vol%) produced a greater negative inotropic effect than did the low MAC level of enflurane (0.91 vol%), and the same level of enflurane (low) produced a negative inotropic effect that was similar to that of the middle MAC level of isoflurane (0.87 vol%). Each of the three indices of contractile function was decreased comparably; this demonstrates that in this model the maximal rates of LVP development and relaxation are correlated closely to the peak systolic pressure generated by the heart. With comparison of either equivalent fractional MACs or equivalent vapor concentrations, it appears that isoflurane is a less negative inotropic anesthetic than is halothane or enflurane. This study verifies the many recent *in vitro* reports indicating that isoflurane is less of a cardiac inotropic depressant than is halothane or enflurane.[3,4,6–11,14,15] Compared with our previous study,[25] in which we reported the cardiac effects of approximately 0.5 MAC N_2O (48% N_2O), 0.51 vol% halothane (0.51 MAC) and 0.91 vol% enflurane (0.41 MAC) cause greater cardiac depression than 48% N_2O, whereas 0.45 vol% isoflurane (0.38 MAC) produces cardiac depression that is approximately equivalent to that of 48% N_2O. Many mechanisms for the differential effects of the volatile agents have been proposed. Likely sites of action are the sarcolemma,[4,5,7,20,24,26] sarcoplasmic reticulum,[6,8–10,27,28] and myofibrillar apparatus.[9,11,29,30]

Effects on Coronary Flow, and Oxygen Consumption, Percentage of Oxygen Extraction, and the Oxygen Supply–Demand Ratio

A reduction in CF would be expected with the induced decreases in O_2 consumption if autoregulation is intact. However, halothane and enflurane did not decrease CF and D_{O_2} at any delivered concentration. This indicates that they indeed are weak vasodilators. Isoflurane increased CF and D_{O_2}, but only at the highest concentration. The lack of a flow increase with enflurane and halothane and the small increase in flow with isoflurane, compared with the large increase produced by adenosine in arrested as well as in paced hearts, demonstrate that CF reserve was unchanged with enflurane and halothane and only slightly reduced by isoflurane. We reported previously that higher measured perfusate molar concentrations of enflurane and isoflurane increased CF and caused larger decreases in LVP.[3]

The extent to which these agents alter coronary vascular resistance along with decreases in cardiac work has been controversial. Coronary angiography, when used to examine changes in vessel dimensions,[31] indicates a minimal effect of isoflurane on large coronary vessels. Halothane and enflurane have been reported to decrease,[15,21,32] increase,[12] or cause no change[12,32] in CF at the arteriolar level (*i.e.*, at flow resistance vessels). Isoflurane generally has been found to produce no change[21,33] or to increase CF.[1,14–16,31,32,34,35] In many of these studies, however, it is difficult to determine the direct coronary vascular effects of these agents because other anesthetics and adjuvant drugs were used, and because compensatory changes in flow caused by altered coronary perfusion pressure and ventricular compressive forces on the coronary vascular bed were not controlled. Moreover, few studies have compared all three anesthetics with the use of similar methods at equivalent effective vapor concentrations and MAC fractions for the species examined.

To assess whether an agent has direct coronary vasoactive effects, the autoregulatory effect of altered cardiac metabolic demand as a determinant of CF must be examined and maximal coronary reserve should be measured.[19] One useful way to assess steady-state metabolic demand is to measure changes in the percentage of O_2 extraction. In human and *in vivo* animal studies in which myocardial O_2 extraction has been measured, the reductions in the percentage of O_2 extraction with halothane,[21,32] enflurane,[12] and isoflurane[12,21,32,35,36] generally exceeded the reductions in coronary vascular resistance. Most of these studies indicate that anesthetics cause a relative overperfusion of the myocardium (*i.e.*, attenuation of coronary autoregulation), but it is not always clear whether there were differential effects. Hickey *et al.*[21] used chronically instrumented dogs exposed to 1 MAC of halothane, enflurane, and isoflurane to assess changes in regional coronary autoregulation by altering left common coronary artery perfusion pressure while measuring distal left common coronary artery blood flow. Based on the changes in autoregulatory slopes and the equivalent decreases in O_2 consumption, they found that all three anesthetics disturbed coronary autoregulation, but that isoflurane caused the greatest blunting of autoregulation and the highest increase in flow when compared with values for the awake state. However, the blunting of autoregulation was much less than that caused by adenosine. Sill

et al.[31] observed in acute dog preparations that isoflurane increased CF (measured by a radiolabeled technique) above control for any measured rate of O_2 consumption.

Myocardial O_2 extraction has been measured in only a few studies in humans with ischemic heart disease,[12,32] and in healthy patients.[37] Sonntag *et al.*[37] observed that 0.7–1.5 vol% halothane increased coronary vascular resistance 14% and decreased the percentage of O_2 extraction 14%, suggesting no attenuation of autoregulation. Reiz and Lowenstein[12] found that coronary vascular resistance decreased approximately 30% with 1 vol% isoflurane and 18% with 1.4 vol% enflurane, and did not change with 1 vol% halothane; however, the percentage of O_2 extraction decreased approximately 35% with isoflurane and 20% with enflurane, and did not change with halothane. Their study suggests that isoflurane and, to a lesser extent, enflurane attenuate CF autoregulation in patients with severe coronary artery disease. Moffitt and Sethna[32] observed that coronary sinus blood flow was reduced approximately 33%, 11%, and 17%, whereas $M\dot{V}_{O_2}$ was reduced approximately 55%, 35%, and 45% with 1–3 vol% enflurane, 1–3 vol% halothane, and 0.8–3.8 vol% isoflurane, respectively. Their numbers from patients with moderate coronary artery disease suggest that halothane, isoflurane, and, to a lesser degree, enflurane decrease O_2 demand more than they decrease O_2 supply. However, a major problem of the above studies, in determining the direct effects of volatile anesthetics on CF autoregulation and O_2 utilization, stems from the uncorrected 20–50% decrease in mean arterial pressure (*i.e.*, coronary perfusion pressure), the principal determinant of coronary blood flow.

It is useful to compare our *in vitro* results with those of several other recent *in vitro* studies in which CF and O_2 extraction also were measured at constant coronary perfusion pressure during exposure to volatile anesthetics.

Larach *et al.*[17] exposed isolated rat hearts to 0.5–2.0 vol% halothane and to 0.7–2.8 vol% isoflurane after causing electromechanical arrest of the myocardium using tetrodotoxin at a concentration not believed to have direct coronary vascular smooth muscle effects. They observed that the highest doses increased CF as much as a maximally dilating dose of adenosine and concluded that these anesthetics are equally potent in depressing coronary vascular resistance under their study conditions. The percentage of O_2 extraction decreased greatly with exposure to tetrodotoxin but did not decrease further with exposure to the highest administered concentrations of halothane or isoflurane. Although their data demonstrate that halothane and isoflurane are potent coronary vasodilators in tetrodotoxin-treated hearts, flow was increased submaximally to approximately 33% above the baseline during cardiac standstill with 1.0 vol% halothane and 1.4 vol% isoflurane. These concentrations, which are similar to those used in our study in the nonarrested guinea pig heart, nevertheless produced a greater dilatation in their study, and the effects of halothane and isoflurane were equivalent.

Our study furnishes results more similar to those of Sahlman *et al.*,[15] who used the isolated working rat heart as a model to compare isoflurane, enflurane, and halothane. They found that 1.1 vol% halothane decreased flow approximately 24%, that 2.3 vol% enflurane did not alter flow, and that 1.5 vol% isoflurane increased flow approximately 16% when systemic (aortic) pressure was kept at 100 mmHg. Myocardial O_2 extraction was reduced approximately 25% by both halothane and enflurane and approximately 15% by isoflurane. Thus, the reductions in O_2 extraction by each of these anesthetics were observed to be greater than their effects on CF. Interpretation of their data suggests that halothane and enflurane increased the myocardial O_2 supply–demand ratio more than did isoflurane. However, we did not observe halothane to decrease flow or isoflurane to reduce the percentage of O_2 extraction as reported from their experimental preparation. In our preparation, halothane and enflurane increased the O_2 supply–demand ratio much more than did isoflurane at equivalent MAC levels by producing greater decreases in the percentage of O_2 extraction without changing CF; isoflurane increased CF only slightly and decreased the percentage of O_2 extraction at the high MAC level.

In summary, halothane, enflurane, and isoflurane were found to have several differential effects on cardiac mechanics, CF, and the supply of O_2 relative to demand in the isolated heart perfused at a constant coronary perfusion pressure. Concomitant to the greater decreases in cardiac mechanical function with halothane and enflurane, these agents decrease O_2 consumption, which causes a relative improvement in tissue O_2 perfusion. Isoflurane—which has a lesser effect on reducing heart rate, contractility, and O_2 consumption—mildly increases CF and D_{O_2}, to cause a relatively smaller improvement in tissue O_2 perfusion. Our study suggests that, if the anesthetic goal is to improve myocardial tissue O_2 perfusion, it is more beneficial to reduce O_2 demand with halothane or enflurane than to increase D_{O_2} with isoflurane. *In vivo*, the direct anesthetic effects on the coronary vasculature may be obscured by other determinants of coronary vascular resistance (*i.e.*, coronary perfusion pressure, myocardial wall tension, heart rate, circulating vasoactive factors, and neural control).

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