Anesthesiology
76:775–780, 1992

Direct Comparative Effects of Isoflurane and Desflurane in Isolated Guinea Pig Hearts

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The aim of this study was to test if myocardial and coronary vascular effects of desflurane and isoflurane were similar in the isolated heart. The cardiac effects of these anesthetics were examined in 12 guinea pig hearts perfused in a retrograde manner. Spontaneous heart rate, atrioventricular (AV) conduction time, systolic left ventricular pressure, and coronary flow were measured. To differentiate direct vasodilatory effects of these anesthetics from an indirect metabolic effect due to autoregulation of coronary flow, O_2 delivery ($\dot{D}_{O_2}$), myocardial O_2 consumption ($M\dot{V}_{O_2}$) and percent O_2 extraction were also monitored. Isoflurane and desflurane were injected directly into sealed bottles containing oxygenated perfusate solution. Each heart was perfused randomly with these anesthetics. Anesthetic concentrations in the perfusate were 0.28 ± 0.02 and 0.52 ± 0.02 mM for isoflurane and 0.59 ± 0.01 and 1.02 ± 0.09 mM for desflurane (mean ± standard error of the mean). Calculated vapor concentrations were 1.3 and 2.5 vol % for isoflurane and 6.8 and 11.8 vol % for desflurane which correspond to approximately 1 and 2 MAC *in vivo*. Each anesthetic similarly decreased heart rate and prolonged AV conduction time in a concentration-dependent manner. Left ventricular pressure (control 93 ± 4 mmHg) decreased by 11 ± 1% and 24 ± 2% with isoflurane and by 15 ± 1% and 30 ± 2% with desflurane. The decreases in heart rate and pressure were accompanied by decreases in $M\dot{V}_{O_2}$ of 12 ± 2% and 30 ± 3% with isoflurane and of 19 ± 3% and 40 ± 4% with desflurane from a control of 57 ± 2 $\mu l \cdot g^{-1} \cdot min^{-1}$. Although $M\dot{V}_{O_2}$ decreased, coronary flow (control 5.7 ± 0.2 $ml \cdot g^{-1} \cdot min^{-1}$) increased submaximally by 16 ± 2% and 30 ± 4% with isoflurane and by 10 ± 2% and 19 ± 3% with desflurane. These changes in left ventricular pressure, $M\dot{V}_{O_2}$, and coronary flow were significantly different between isoflurane and desflurane at both anesthetic levels. $\dot{D}_{O_2}$ increased proportionally with coronary flow. The differences in $\dot{D}_{O_2}$ and $M\dot{V}_{O_2}$ were proportional so that the $\dot{D}_{O_2}/M\dot{V}_{O_2}$ ratios, as well as percent O_2 extraction, were not different between isoflurane and desflurane. This study shows that desflurane, like isoflurane, is a direct myocardial depressant in the isolated heart. Although desflurane produced a slightly greater negative inotropic effect than isoflurane, both anesthetics had similar coronary vasodilatory effects on the basis of similar increases in the ratio of $\dot{D}_{O_2}$ to $M\dot{V}_{O_2}$. (Key words: Anesthetics, volatile: desflurane; isoflurane. Animal: guinea pig. Heart: coronary flow; electrophysiology; isolated; left ventricular pressure; oxygen consumption; perfused.)

THE NEW VOLATILE ANESTHETIC desflurane, which is an analog of isoflurane, differs only in the substitution of fluorine for chlorine on the α-ethyl carbon. Several potentially advantageous properties of desflurane that make it attractive for further clinical and laboratory investigation are its low blood solubility,[1] its stability in soda lime,[2] and its resistance to biodegradation.[3,4]

The cardiovascular effects of desflurane have been tested in several *in vivo* animal[5–9] and human[10] studies. Generally, these studies have shown that desflurane and isoflurane have very similar cardiovascular effects. Desflurane/nitrous oxide anesthesia has also been shown to produce hemodynamic changes similar to those produced by isoflurane/nitrous oxide anesthesia in human volunteers.[11]

The direct myocardial and coronary vascular effects of desflurane have not been previously reported *in vitro*. The isolated heart preparation may be a good model to compare direct cardiac effects of desflurane and isoflurane because its mechanical function is unaffected by preload, afterload, extrinsic, autonomic, and humoral influences. Additionally, this model is well suited for measuring O_2 supply and O_2 demand, which are essential variables for assessing whether an agent is a direct coronary vasodilator.[12]

In this study, we used the isolated perfused guinea pig heart model to examine the direct effects of isoflurane and desflurane on heart rate, atrioventricular (AV) conduction time, left ventricular function, coronary flow, and myocardial O_2 supply relative to O_2 demand. These effects were measured in the same heart during administration of two approximately equianesthetic concentrations of isoflurane and desflurane.

Materials and Methods

Following Animal Studies Committee approval, 12 albino English short-haired guinea pigs (250–350 g) were decapitated and the hearts excised. A detailed description of our isolated heart model has been published previously.[13] Briefly, the hearts were perfused in a retrograde

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Received from the Departments of Anesthesiology and Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin. Accepted for publication December 27, 1991. Supported in part by grants from the National Institutes of Health HL 01901 and HL 34708 and Anesthesiology Research Training Grant GM 08377. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 1991.

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manner by the Langendorff technique at a control perfusion pressure of 55 mmHg. The perfusate, a modified Krebs-Ringer solution, 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, ethylene-diaminetetraacetic acid (EDTA) 0.05, and insulin 5 units/l. Perfusate and bath temperatures were maintained at 36.4 ± 0.1° C using a thermostatically controlled water circulator. Perfusate solutions were equilibrated with a gas mixture of 97% O_2 and 3% CO_2.

Left ventricular pressure was measured isovolumetrically with a transducer connected to a thin, saline-filled latex balloon (Hugo Sachs Electronic, KG, Germany) inserted into the left ventricle through the mitral valve from a cut in the left atrium. Balloon volume was adjusted to maintain an end-diastolic pressure of 0 mmHg during the initial control period. Two pairs of bipolar electrodes (Teflon®-coated silver, diameter 125 μM) were placed in each heart to monitor intracardiac electrograms, from which spontaneous sinoatrial rate and AV conduction time were measured. Atrial rate was determined from the right atrial beat-to-beat interval. AV conduction time was determined as the interval between the superior right atrial beat and the right ventricular pulmonary conus beat. Coronary flow was measured at constant temperature using an electromagnetic flow probe (Biotronix® BL610-2A with Series 2000C extracorporeal transducer, 1.5 mm ID, Biotronix Laboratories, Inc., Kensington, MD) placed into the aortic inflow line. Coronary sinus effluent was collected by placing a cannula into the right ventricle through the pulmonic artery after ligating the venae cavae.

Coronary inflow and outflow (coronary sinus) O_2 tensions (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-1, Metron Chicago, Inc., Des Plains, IL). Because these hearts depend solely on the crystalloid solution from which to extract dissolved O_2, O_2 delivery ($\dot{D}_{O_2}$) was calculated from the inflow O_2 tension multiplied by O_2 solubility (24 μl · ml saline^{-1} · 760 mmHg^{-1}) multiplied by coronary flow per gram wet heart tissue. Percent O_2 extraction was calculated as 100 multiplied by the difference between inflow and outflow O_2 tensions divided by inflow O_2 tension. Myocardial O_2 consumption ($M\dot{V}_{O_2}$) was calculated as O_2 solubility multiplied by coronary flow per gram wet heart tissue multiplied by the difference between inflow O_2 and outflow O_2 tension. Electrograms, heart rate, AV conduction time, outflow O_2 tension, coronary flow, left ventricular pressure, and perfusion pressure were tape-recorded for later detailed analysis. All measured variables were displayed on a high resolution, eight-channel recorder (Astro-Med® MT9500, Astro-Med Inc., West Warwick, RI).

Anesthetic Delivery and Determination of Concentrations

The anesthetics were not administered by vaporizers but were injected directly through a specially designed cannula and stopcock system into hermetically sealed 4-l glass bottles each containing 1 l of preoxygenated perfusate solution (average *p*H 7.37 ± 0.01, P_{CO_2} 28 ± 1 mmHg, and P_{O_2} 617 ± 9 mmHg). Gas-tight syringes with a lock-up valve were used for aspiration and injection of the anesthetics (Pressure Lok® Series A2 syringe, Precision Sampling Co., Baton Rouge, LA). Specific volumes of liquid desflurane (−10° C) or isoflurane (+22° C) were aspirated anaerobically and injected immediately into the designated sealed bottle using a double stopcock system to avoid leakage and volatilization of the anesthetics before and during injection. A 120-ml volume of 3% CO_2/97% O_2 was also injected into each sealed bottle to account for displacement of approximately 120 ml of solution during a 10-min period of cardiac perfusion. The sealed perfusate was stirred continuously to facilitate equilibration of the anesthetics between the gas and liquid phases.

Isoflurane MAC for guinea pigs was estimated as 1.2 vol %[14] and the Krebs' solution/gas partition coefficient as 0.55 at 37° C and 1 atm.[15] To obtain a perfusate concentration of isoflurane equivalent to about 1 MAC, 150 μl of liquid isoflurane was injected into the sealed bottle. The guinea pig MAC for desflurane has not been determined, but we calculated it to be about five times that for isoflurane,[16–19] or approximately 6 vol %. The saline/gas partition coefficient for desflurane is 0.225 at 37° C and 1 atm.[1] To approach a perfusate concentration of desflurane equivalent to 1 MAC, 700 μl of liquid desflurane was injected into the sealed bottle. In the figures, the low concentrations of each anesthetic represent about 1 MAC. To obtain the high concentrations (approximately 2 MAC), the volumes injected into a sealed bottle were doubled.

At each experimental interval, 1 ml of perfusate solution was collected at the aortic inflow port into sealed, 2-ml vials for a head-space analysis of anesthetic concentration by gas chromatography. Concentrations were 0.28 ± 0.02 (low) and 0.53 ± 0.02 mM (high) for isoflurane and 0.59 ± 0.01 (low) and 1.02 ± 0.09 mM (high) for desflurane. Effective vapor concentrations were calculated as 1.3 and 2.5 vol % for isoflurane and 6.8 and 11.8 vol % for desflurane, which gave the following effective calculated MAC values: 1.08 and 2.08 for isoflurane and 1.13 and 1.96 for desflurane. Analysis of anesthetic concentrations sampled at the aortic root by gas chromatography showed that the concentration of each anesthetic

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TABLE 1. Depressant Effects of Isoflurane and Desflurane on Spontaneous Heart Rate and Atrioventricular Conduction Time during Exposure to Two Equianesthetic Concentrations of Isoflurane and Desflurane in 12 Isolated Hearts

		Control 1	Low	Control 2	High	Control 3
Heart rate (beats/min)	Isoflurane	218 ± 4	205 ± 4*	218 ± 5	198 ± 4†	217 ± 5
	Desflurane	219 ± 4	204 ± 4*	219 ± 4	198 ± 5†	218 ± 5
Atrioventricular time (ms)	Isoflurane	64 ± 1	67 ± 2*	65 ± 2	75 ± 2†	65 ± 2
	Desflurane	65 ± 2	67 ± 2*	65 ± 2	76 ± 2†	64 ± 1

Control 1, 2, 3 = control values (initial and after washout periods); low = 1.3% isoflurane and 6.8% desflurane; high = 2.5% isoflurane and 11.8% desflurane. All data are means ± standard error of means.

* $P < 0.05$ *versus* control 1.
† $P < 0.05$ *versus* low and control 2.

did not change during the 10-min period of cardiac perfusion. Anesthetic was not measurable in the perfusate at the end of the washout periods.

PROTOCOL AND STATISTICAL ANALYSIS

Following a 30-min stabilization period, each of the 12 hearts was exposed to isoflurane and to desflurane. Each heart was first given either isoflurane or desflurane in a randomized fashion for 10 min with 15-min anesthetic-free control periods between anesthetics. Adenosine (0.2 ml of 200 μM stock) was injected into the aortic (coronary perfusion) cannula during the initial and final control period so that maximal coronary flow could be assessed. Measurements were made during the last minute of each control (washout) period and during the last minute of exposure to each anesthetic at each concentration.

All data are expressed as means ± standard error of the means. The following statistical comparisons were made by two-way analysis of variance (repeated measures) using software noted previously[13]: values obtained during the low and high anesthetic concentrations and the secondary controls *versus* the initial control values; low *versus* high concentrations of each anesthetic; and isoflurane *versus* desflurane at each concentration. Fisher's least significant difference test was used to compare means. Data from the initial control, low, and high levels for each anesthetic as a function of approximate MAC were also subjected to linear regression analysis. Mean values were considered significant at $P \leq 0.05$.

Results

The effects of isoflurane and desflurane on heart rate and AV conduction time were similar (table 1). Heart rate was significantly decreased at each anesthetic level, and AV conduction time was prolonged in a concentration-dependent fashion. Upon washout, after exposure to either anesthetic, heart rate and AV conduction time approached their initial control values of 218 ± 4 beats/min and 64 ± 1 ms, respectively.

Systolic left ventricular pressure also decreased significantly in a concentration-dependent manner at each level of isoflurane and desflurane, from the initial control values (93 ± 4 mmHg) (fig.1). However, desflurane produced a slightly, but significantly, greater depression of left ventricular pressure at both concentrations than did isoflurane. The depressant effects of isoflurane and desflurane were readily reversible during the control anesthetic-free periods. Assuming equivalent MACs for isoflurane and desflurane, best-fit linear analysis for isoflurane reduced left ventricular pressure by 11.5%/MAC and for desflurane by 15.2%/MAC. Diastolic left ventricular pressure was not altered with administration of either anesthetic.

Isoflurane and desflurane increased coronary flow from the control levels in a dose-dependent fashion (fig. 2). However, isoflurane induced a significantly greater increase in coronary flow than did desflurane at both anesthetic levels. This increase in flow was smaller than the maximal coronary flow elicited with adenosine injection, which indicates that coronary flow reserve was not abolished. Coronary responsiveness to adenosine (data not shown) decreased significantly from the initial control

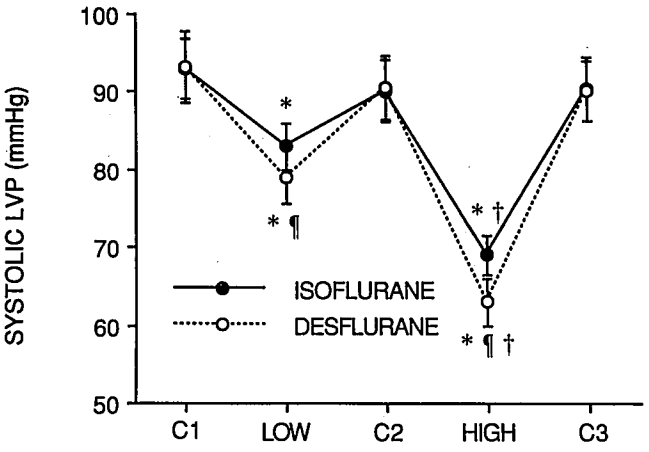

FIG. 1. Effects of isoflurane and desflurane on systolic left ventricular pressure (LVP) during exposure to two equivalent MAC concentrations of isoflurane and desflurane in 12 isolated hearts. C1, C2, C3 = control values (initial or after wash out periods); LOW = 1.3% isoflurane and 6.8% desflurane; HIGH = 2.5% isoflurane and 11.8% desflurane *$P < 0.05$ *versus* C1; †$P < 0.05$ *versus* LOW; ¶$P < 0.05$ *versus* isoflurane.

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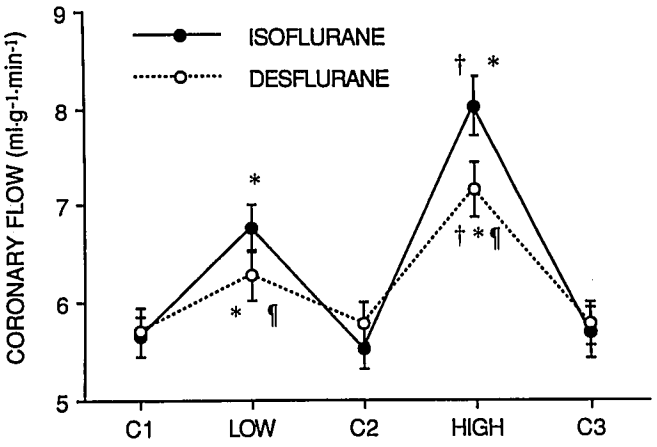

FIG. 2. Effects of isoflurane and desflurane on coronary flow. *P < 0.05 *versus* C1; †P < 0.05 *versus* LOW; ¶P < 0.05 *versus* isoflurane. See figure 1 for details.

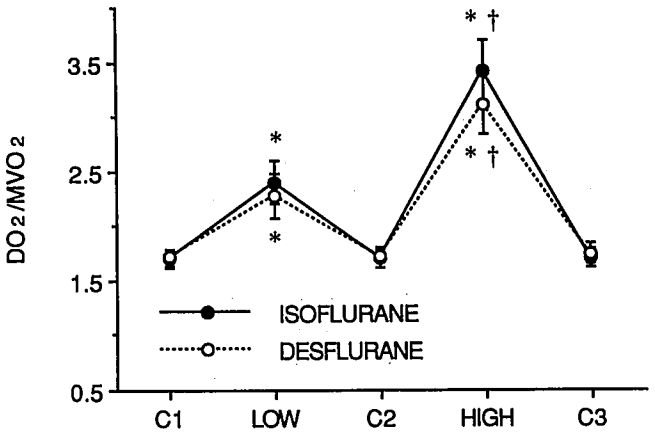

FIG. 4. Effects of isoflurane and desflurane on the ratio of oxygen supply to demand ($\dot{D}_{O_2}/M\dot{V}_{O_2}$). *$P$ < 0.05 *versus* C1; †P < 0.05 *versus* LOW. See figure 1 for details.

mean of 11.7 ± 0.5 ml·g^{-1}·min^{-1} to the final control mean of 10.0 ± 0.4 ml·g^{-1}·min^{-1}.

$M\dot{V}_{O_2}$ (fig. 3), in parallel with the decreases in heart rate and left ventricular pressure, decreased in a concentration-dependent manner with each anesthetic. However, desflurane decreased $M\dot{V}_{O_2}$ significantly more than isoflurane at both anesthetic levels.

$\dot{D}_{O_2}$, like coronary flow, increased in a dose-dependent manner with both anesthetics. However, the increases with isoflurane were greater than the increases with desflurane. The ratio between myocardial $\dot{D}_{O_2}$ and O_2 demand increased similarly, in a concentration-dependent manner, for isoflurane and desflurane (fig. 4). The decreases in percent O_2 extraction were also concentration-dependent with both agents (fig. 5). There were no significant differences in percent O_2 extraction between the two anesthetics at each concentration.

Discussion

This is the first *in vitro* cardiac study examining the direct comparative effects of desflurane and isoflurane on the isolated heart. Several *in vivo* studies in instrumented domestic swine[5] and dogs[6–8] have shown that isoflurane and desflurane have similar cardiac effects. One group examined contractile function in terms of the maximum rate of change in left ventricular pressure ($dLVP/dt_{max}$)[7]. The other group studied contractile function in terms of an end-systolic pressure–length relationship, a measure of contractility that is relatively heart rate- and load-in-

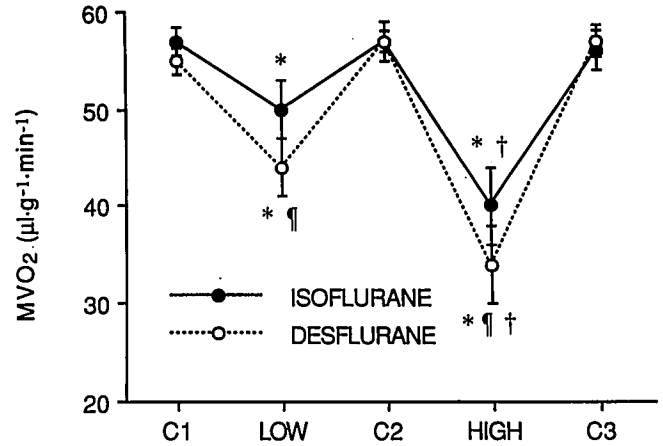

FIG. 3. Effects of isoflurane and desflurane on myocardial oxygen consumption ($M\dot{V}_{O_2}$). *P < 0.05 *versus* C1; †P < 0.05 *versus* LOW; ¶P < 0.05 *versus* isoflurane. See figure 1 for details.

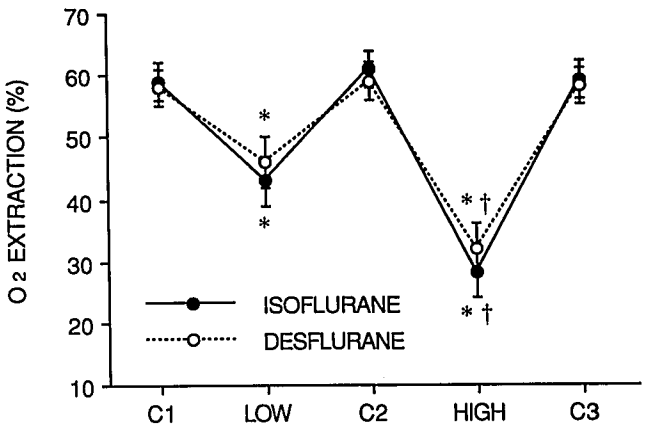

FIG. 5. Effects of isoflurane and desflurane on percent oxygen extraction. *P < 0.05 *versus* C1; †P < 0.05 *versus* LOW. See figure 1 for details.

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dependent,[6,8] but is also useful to compare the direct mechanical effects of these anesthetics using a model in which various cardiac variables can be measured independently of the peripheral circulation.

Merin *et al.*[7] and Pagel *et al.*[8] found that both of these anesthetic agents increased coronary blood flow to a similar degree in autonomically intact dogs. However, after autonomic nervous system blockade, isoflurane increased coronary blood flow, but desflurane did not.[8] Although these studies suggested that desflurane has a vasodilatory effect, this could not be documented because myocardial $\dot{D}_{O_2}$ and $M\dot{V}_{O_2}$ were not measured. Additionally, the direct anesthetic effects on the coronary vasculature may be obscured *in vivo* by other determinants of coronary vascular resistance such as coronary perfusion pressure, myocardial wall tension, heart rate, circulating vasoactive factors or autonomic nervous control.

We determined the direct chronotropic, dromotropic, inotropic and coronary vasodilatory effects of isoflurane and desflurane, free of autonomic influence and alterations in preload volume or afterload impedance. Measurements of arterial and coronary sinus O_2 tension allowed us to examine the effects of isoflurane and desflurane on $\dot{D}_{O_2}$ and O_2 utilization and their relative effects on attenuating coronary flow autoregulation. In our recent reports in which the effects of isoflurane were investigated in isolated hearts alone or with other anesthetics, we found quantitatively similar results for isoflurane at 1 MAC.[13,20]

Exposure to approximately equivalent MAC concentrations of isoflurane and desflurane resulted in almost identical decreases in spontaneous heart rate and prolongation of AV conduction time. This indicates that desflurane has no apparent advantage over isoflurane on decreasing automaticity and conduction in the isolated heart.

Although *in vivo* animal studies have indicated that equianesthetic concentrations of desflurane and isoflurane produce similar decreases in contractility,[5–8] Pagel *et al.*[6] suggested that desflurane might have produced a greater negative contractile effect than isoflurane because desflurane also increased left ventricular end-diastolic pressure more than did isoflurane. In our *in vitro* study, contractile function was also depressed with both anesthetics, and diastolic pressure was unchanged. However, desflurane produced a slightly greater depression of isovolumetric left ventricular pressure than did isoflurane. Because the major determinants of $M\dot{V}_{O_2}$ are contractility and heart rate, $M\dot{V}_{O_2}$ in the presence of both agents decreased appropriately with decreases in these variables.

A reduction in coronary flow would be expected to occur with a decrease in $M\dot{V}_{O_2}$ if autoregulatory mechanisms were intact. However, both isoflurane and desflurane increased coronary flow and $\dot{D}_{O_2}$. This indicates that autoregulation of coronary flow was blunted by these two agents, and therefore, that they are direct vasodilators. Moreover, isoflurane and desflurane inherently differed in their myocardial effects. At both anesthetic levels, isoflurane caused a greater increase in coronary flow and $\dot{D}_{O_2}$ than did desflurane. However, desflurane produced a greater decrease in contractility and $M\dot{V}_{O_2}$ than did isoflurane. Consequently, the ratio $\dot{D}_{O_2}/M\dot{V}_{O_2}$ was not statistically different between isoflurane and desflurane. Along with the similar increases in the $\dot{D}_{O_2}/M\dot{V}_{O_2}$ ratios with isoflurane and desflurane, percent O_2 extraction was equally decreased with both anesthetics. These changes seem to indicate that isoflurane and desflurane are vasodilators with similar potency. Although both anesthetics significantly increased coronary flow, coronary reserve was not abolished because adenosine produced a much larger increase in coronary flow.

A potential disadvantage in comparing the guinea pig MAC for isoflurane against desflurane is that the guinea pig MAC for desflurane has not been determined and our calculations were based on ratios of MAC for isoflurane and desflurane determined in other species. Therefore, a slight alteration in the MAC ratio of isoflurane and desflurane from that used in this study might make the effects of these anesthetics on contractility and coronary vasodilation more or less similar. Moreover, the concentration of an anesthetic that produces anesthesia on the basis of MAC may not be proportional to its direct cardiac effects.

In summary, our study indicates that isoflurane and desflurane, at the given concentrations, are cardiodepressive agents *in vitro* and that they have almost identical negative chronotropic and dromotropic effects. Desflurane, however, appears to produce a slightly greater depression of contractility than does isoflurane. Both isoflurane and desflurane are direct-acting coronary vasodilators with similar potencies on the basis of similar alterations in vascular autoregulation. Overall, our direct findings in the isolated heart are in good agreement with the cardiac effects of isoflurane and desflurane that have been described *in vivo*.

The authors thank Ms. Miriam Mick for secretarial assistance in the preparation of the manuscript and Mr. James Heisner and Ms. Mary Ziebell for technical assistance. The authors are indebted to Dr. Ron Ferrone of Anaquest (Murray Hill, NJ) for generously supplying desflurane.

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