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Effects of Halothane, Enflurane, and Isoflurane on Coronary Vascular Tone, Myocardial Performance, and Oxygen Consumption during Controlled Changes in Aortic and Left Atrial Pressure

Studies on Isolated Working Rat Hearts In Vitro

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The effects of equi-anesthetic concentrations of halothane (HAL, $n = 11$), enflurane (ENF, $n = 11$), and isoflurane (ISO, $n = 10$) on cardiac function were studied and compared with a control group ($n = 12$) in isolated paced rat hearts by means of an antegrade heart perfusion technique. Left atrial pressure (LAP) and mean aortic pressure (MAP) could be altered independently of each other, and aortic flow, coronary flow (CF), and p_{O_2} in venous coronary effluent were continuously recorded. Stroke volume (SV), myocardial oxygen consumption (MVO_2), and myocardial oxygen extraction were calculated: 1) MAP was altered from 60 to 120 mmHg at a constant LAP (7.5 mmHg), and 2) LAP was varied from 4 to 12.5 mmHg at a constant MAP (80 mmHg). Left ventricular function curves (LVFC) were constructed and the maximal SV (SV_{max}) was obtained. The LAP needed to perform 75% of the maximal SV ($LAP_{0.75}$) was estimated to assess the effect of the anesthetics on diastolic function. HAL, ENF and ISO decreased SV_{max} significantly compared to control. This decrease was more pronounced for HAL (41%) compared to both ENF (26%) and ISO (26%). Accordingly, SV, at various levels of MAP, at a constant LAP, was significantly lower for HAL

than for both ENF and ISO, while there was no significant difference between the latter two. None of the anesthetics shifted the LVFC to the right, *i.e.*, did not affect diastolic properties. HAL induced the most pronounced decrease in MVO_2 , while there was no significant difference between ENF and ISO in this respect. Coronary flow (CF), at controlled perfusion pressures, decreased significantly with HAL but not with ENF or ISO compared to control. CF was significantly higher with ISO compared to both ENF and HAL. HAL and ISO, but not ENF, decreased myocardial oxygen extraction significantly compared to control and, thus, increased the myocardial oxygen supply-to-demand ratio. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart, isolated: coronary flow; oxygen consumption; oxygen extraction.)

SEVERAL STUDIES HAVE described the depressant action of halothane,¹⁻¹⁰ enflurane,^{5,8,11} and isoflurane^{8,9,11} on the contractile performance of isolated preparations of heart muscle *in vitro*. Some of these reports, specifically designed to compare the relative effect of these anesthetics on myocardial contractile force at equivalent anesthetic concentrations, have yielded conflicting results. Brown and Crout⁵ showed that enflurane was more depressant than halothane, but did not study the effects of isoflurane on myocardial contractility. Kemmotsu *et al.*¹² concluded from pooled results of separately undertaken but similarly conducted studies^{8,11,12} that the hierarchy of severity of myocardial depression was halothane > isoflurane > enflurane. This conclusion was supported by a recent, although preliminary,

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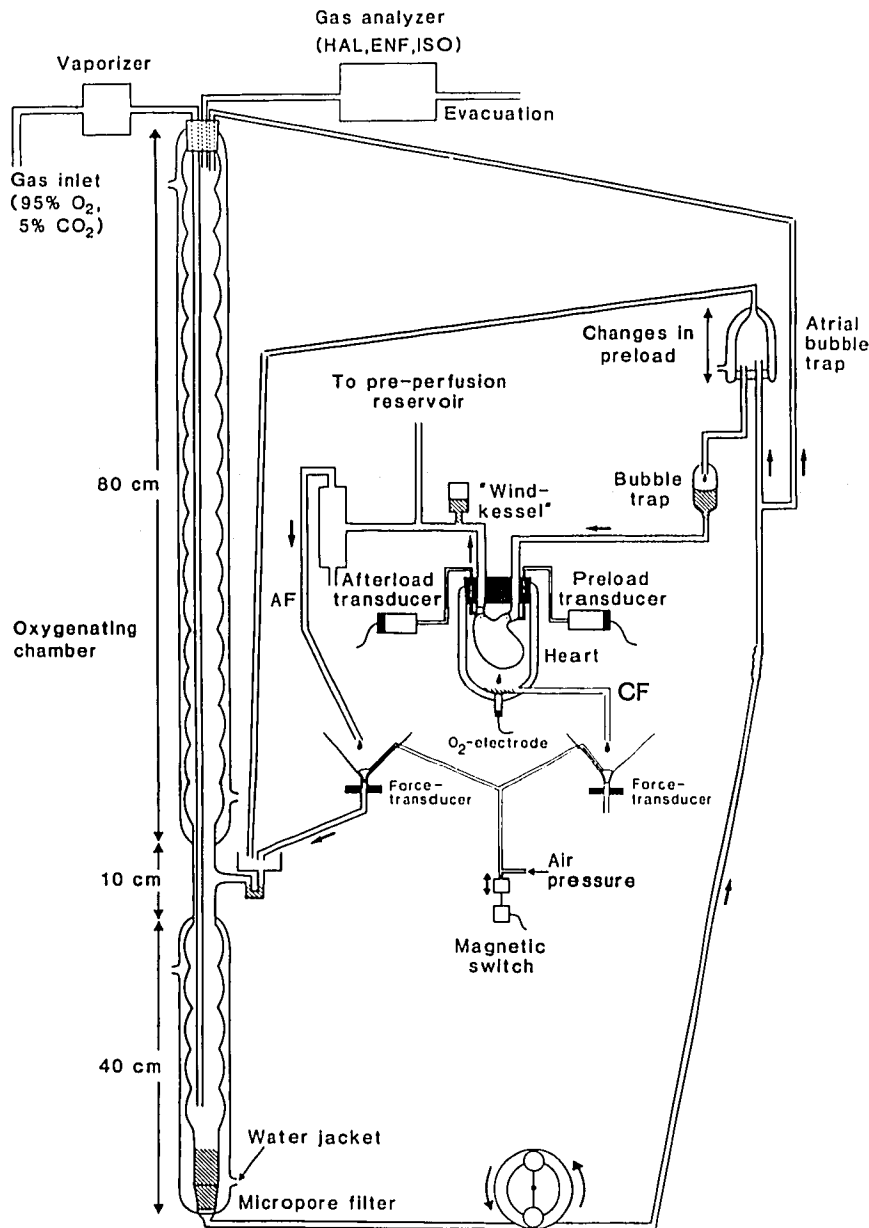


FIG. 1. Schematic illustration of the experimental setup for antegradely perfused hearts. Left atrial pressure and aortic pressure could be altered independently. The hearts were electrically paced. Aortic flow (AF) and coronary flow (CF) were collected and intermittently weighed in separate funnels by means of a force transducer and balloons in the funnels driven by a magnetic switch and an air pressure system. Oxygen tension was continuously measured in the coronary venous effluent.

report on the effect of these volatile anesthetics on contractile force in isolated guinea pig atria.⁸ Furthermore, Lynch recently demonstrated⁹ that isoflurane depressed myocardial contractility less than halothane, especially at physiologic stimulation frequencies.

The aim of the present investigation was to study the relative effects of halothane, enflurane, and isoflurane on left ventricular performance and oxygen consumption and on coronary vascular tone at equivalent anesthetic concentrations. Experiments were performed on isolated, paced rat hearts using an antegrade perfusion system, in which stroke volume, coronary flow, and coronary venous P_{O_2} were continuously recorded and in which left atrial and aortic pressure could be varied independently from each other.

Materials and Methods

These experiments were approved by the Animal Ethical Committee of the University of Göteborg. Forty-four 3–4-month-old male Wistar rats weighing 300–500 g were used. The animals were anesthetized with methohexital (Brietal®) 75–100 mg/kg b.w. which was administered intraperitoneally together with heparin 1000 IU/kg b.w. The hearts were then rapidly excised and put into ice-cold saline, which stopped the heart activity within seconds. The aorta, which was transected approximately 4–5 mm above the aortic valves, was mounted on a steel aortic cannula and a retrograde perfusion of the coronary arteries was started (fig. 1). Non-recirculating Krebs-Henseleit bi-

carbonate buffer (see below) was used as preperfusate. The time from excision of the heart to the start of preperfusion was about 30 s. During the retrograde perfusion, the left atrium was connected *via* a pulmonary vein to an angled steel cannula. The remaining pulmonary veins were ligated to avoid leakage. Antegrade perfusion was started by clamping the tube from the preperfusion reservoir and unclamping the tube connected to the left atrium.

PERFUSION APPARATUS

A slight modification of an earlier described¹³⁻¹⁶ antegrade perfusion apparatus was used as shown in figure 1. It consisted of a 130 cm long oxygenating chamber with a micropore filter at the bottom. The perfusate was pumped to the heart *via* an atrial bubble trap, placed above the heart, or to the top of the chamber. To strictly prevent air bubbles from entering the heart, another bubble trap was placed in series with the atrial bubble trap closer to the left atrium. Left atrial pressure (preload) could be varied by changing the height of the main atrial bubble trap over the heart level, and was recorded at the atrial level *via* a side-tube to the atrial steel cannula connected with a Satham 23 DC transducer recording on a Grass polygraph (model 7D).

The pressure against which the heart pumped could be altered and set to any desired level by means of a Starling resistor.¹⁵ Aortic pressure was measured just above the aortic valves *via* a thin steel tube connected to a Satham 23 DC transducer *via* a PE-10 tube and recorded as described above. A windkessel function on the aortic outflow was established by connecting the steel aortic cannula to a 8 mm wide and 40 mm long Penrose drain rubber tube and by connecting a side tube to a 2-ml syringe containing 1 ml of air. The coronary flow flowed freely from the heart onto a Clark P_O₂ electrode (Radiometer, Copenhagen, Denmark) located at the bottom of the water-jacketed heart glass-chamber (fig. 1). Coronary flow was then collected in a funnel placed on top of a Grass FT 10 transducer and weighed intermittently. An automatic time-controlled magnetic switch regulated outflow from the funnel, so that coronary effluent was collected and weighed for 6 s and then the funnel was emptied for 4 s. Thus, both the coronary outflow and its P_O₂ were continuously measured. P_O₂ in the perfusate entering the left atrium was measured immediately before and after the experiment, using the O₂ electrode described above, and the mean value of these measurements was used when calculating myocardial oxygen consumption, MVO₂ (mmoles/min × gram), according to the formula:

$$MVO_2 = (P_{O_{2LA}} - P_{O_{2V}}) \times CF \times b/22.4,$$

where: P_{O_{2LA}} = P_{O₂} in the perfusate entering left atrium; P_{O_{2V}} = P_{O₂} in the venous coronary effluent; CF = coro-

nary flow/gram heart wet weight; b = Bunsen coefficient, 0.0239 ml O₂/ml H₂O × 760 mmHg, which is the solubility of O₂ at 37°; and 22.4 = conversion factor from ml O₂ to mmoles O₂.

Aortic flow was collected in a separate funnel and also measured continuously as described above (fig. 1). Cardiac output was considered as the sum of the aortic and coronary flows. The hearts were paced in all experiments at 325 beats/min by a square wave stimulator, at a pulse duration of 4 msec and at 2-4 V. Stroke volume was expressed as μl/100 g body weight. A non-recirculation Krebs-Henseleit bicarbonate buffer was used also during the antegrade perfusion. The perfusate was maintained at 37° C and contained (mM): NaCl 118, KCl 4.7, CaCl₂ 2.5, MgSO₄ 1.2, KH₂PO₄ 1.2, NaHCO₃ 25, di-NaEDTA 0.5, and glucose 14. Halothane, enflurane, and isoflurane was equilibrated with the perfusate in the oxygenating chamber by passing 95% O₂/5% CO₂ (2 l/min) through the appropriate vaporizer for at least 30 min before mounting the heart. The concentration of the anesthetic was measured continuously in the gas phase of the oxygenating chamber by a Servo Gas Monitor 120 (Siemens-Elma, Sweden) (fig. 1). The concentrations of halothane, enflurane, and isoflurane used were 1.1%, 2.3%, and 1.5%, respectively, which are considered as the MAC values in male rats.¹⁷

EXPERIMENTAL PROCEDURES

Initially, the hearts were exposed for at least 10 min to the perfusate without (control group n = 12) or with halothane (n = 11), enflurane (n = 11), or isoflurane (n = 10) at a mean aortic pressure (MAP) of 80 mmHg and a left atrial pressure (LAP) of 7.5 mmHg. This was sufficient time to get stable values of stroke volume (SV), coronary flow (CF), and P_O₂ in the venous coronary effluent. These variables were then recorded continuously at various levels of MAP (60, 80, 100, and 120 mmHg). During these MAP variations, LAP was kept constant at 7.5 mmHg. After these MAP variations at a constant preload, MAP was again set to 80 mmHg and LAP to 7.5 mmHg to receive stable control values of SV, CF, and coronary venous P_O₂. LAP was now varied (4.5, 7.5, 10, and 12.5 mmHg) at a constant MAP (80 mmHg) continuously recording SV, CF, and coronary venous P_O₂. For each experiment, the relationships between MAP and SV (μl/100 g b.w.), CF (ml/min × g heart weight), myocardial oxygen extraction (%), and MVO₂ (mmoles/min × g heart weight) were plotted. A left ventricular function curve (LVFC), relating LAP to SV at a constant level of MAP (80 mmHg), were also constructed for each experiment to obtain the SV at a LAP of 12.5 mmHg (SV_{max}). Furthermore, from the LVFC, the LAP needed to perform 75% of the maximal SV (LAP_{0.75}) was estimated. This was done to assess

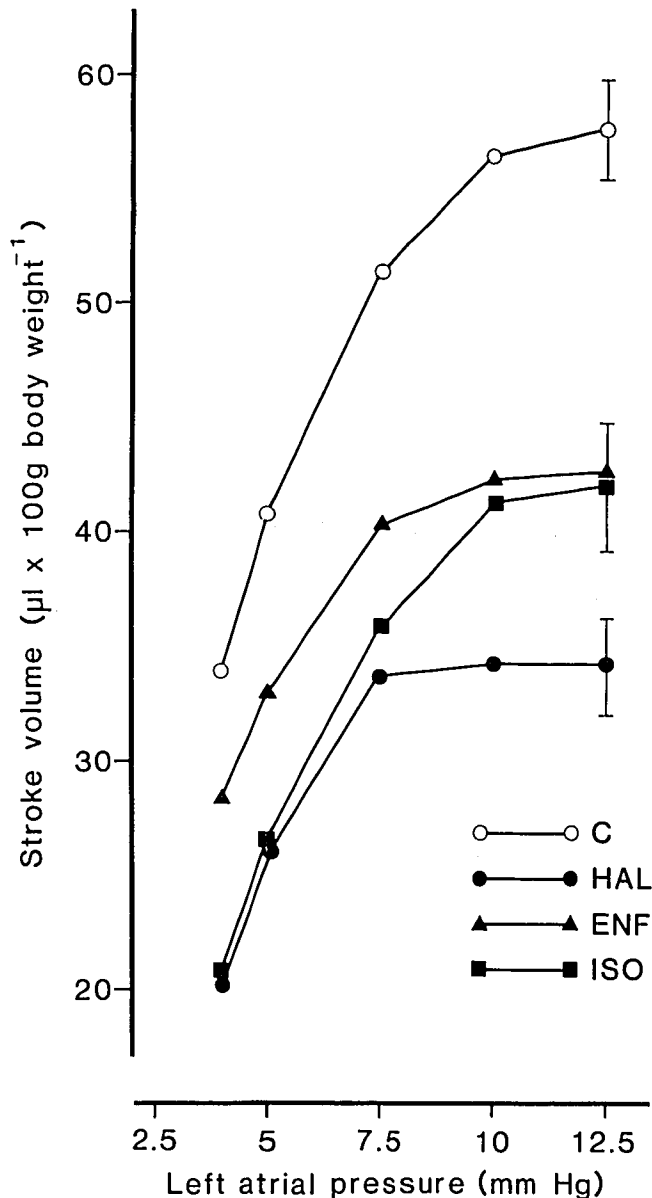


FIG. 2. Left ventricular function curves for the control group, halothane (HAL), enflurane (ENF), and isoflurane (ISO) groups. At an optimal prestretch of the myocardium (LAP = 12.5 mmHg) and at a MAP of 80 mmHg, the volatile anesthetics induced a significant decrease in stroke volume, which was most pronounced for HAL, compared to control. For clarity, standard error is provided only for the last measurement. Symbols of significance are given in figure 3.

whether any of the anesthetics affected diastolic properties, *i.e.*, displaced the left ventricular function curve compared to the control group.

Testing for significant differences ($P < 0.05$) among the different anesthetics and the control group was accomplished by a one-way analysis of variance performed on the SV_{\max} and the $LAP_{0.75}$, followed by Duncan's multiple range test. A two-way analysis of variance for

repeated measurements was performed on the relationships between MAP and SV, CF, MVO_2 , and myocardial oxygen extraction. This was followed by Duncan's multiple range test on the main effects, *i.e.*, on the overall mean values of the mentioned variables for each group, where MAP was the repeated factor.

Results

EFFECTS OF HALOTHANE, ENFLURANE, AND ISOFLURANE ON LEFT VENTRICULAR PERFORMANCE

The mean LVFC for the control group and the different anesthetics are seen in figure 2. In all experiments, the highest value of SV was seen at a LAP of 12.5 mmHg. The mean values for SV at this filling pressure (SV_{\max}) were 57.6 ± 2.2 , 34.1 ± 2.1 , 42.7 ± 2.1 , and 42.6 ± 3.5 $\mu\text{l}/100$ g body weight for the control group, halothane (HAL)-, enflurane (ENF)-, and isoflurane (ISO) groups, respectively. Significant differences between the groups are outlined in figure 3A. SV_{\max} was significantly ($P < 0.01$) depressed by the three anesthetics compared to control. Furthermore, HAL induced a more pronounced decrease in SV_{\max} compared to both ENF ($P < 0.05$) and ISO ($P < 0.05$), while there was no significant difference between ENF and ISO.

When mean aortic pressure (MAP) was increased from 60 to 120 mmHg at a constant LAP (7.5 mmHg) SV decreased in all experiments. The mean values of SV for the groups at the different levels of MAP are seen in figure 4. The overall mean values of SV were 51.4, 29.1, 44.0, and 38.2 $\mu\text{l}/100$ g b.w. for the control group, HAL, ENF, and ISO, respectively. Significant differences between groups are outlined in figure 3B. Overall mean values of SV were significantly lower for HAL ($P < 0.01$) and ISO ($P < 0.01$), but not for ENF, compared to control. The overall mean value for HAL was significantly lower than both ENF ($P < 0.01$) and ISO ($P < 0.05$), while there was no significant difference between ENF and ISO.

The filling pressure that was necessary for the left ventricle to perform 75% of the maximally obtained SV ($LAP_{0.75}$) was 5.2 ± 0.4 ; 5.1 ± 0.2 ; 5.8 ± 1.1 , and 6.1 ± 0.6 mmHg for the control group, HAL, ENF, and ISO, respectively, values not being significantly different.

EFFECTS OF HALOTHANE, ENFLURANE, AND ISOFLURANE ON MYOCARDIAL OXYGEN CONSUMPTION (MVO_2), CORONARY FLOW (CF) AND OXYGEN EXTRACTION AT VARYING LEVELS OF MAP

When MAP was increased, MVO_2 and CF increased in all experiments. The mean values of MVO_2 at the

different levels of MAP for the groups are seen in figure 5. The overall mean values of MVO_2 were 8.9, 4.3, 6.9, and 8.0 $\text{mmoles O}_2/\text{min} \times \text{g heart weight}$ for the control group, HAL, ENF, and ISO, respectively. Significant differences between groups are seen in figure 3C. The overall mean values of MVO_2 were significantly lower for HAL ($P < 0.01$) and ENF ($P < 0.01$), but not for ISO, compared to the control group. The overall mean value for HAL was significantly lower compared to both ENF ($P < 0.01$) and ISO ($P < 0.01$), while there was no significant difference between ENF and ISO.

The mean values of CF at the different levels of MAP:s are seen in figure 6. The overall mean values of CF were 16.7, 12.1, 15.5, and 18.9 $\text{ml}/\text{min} \times \text{g heart weight}$ for the control group, HAL, ENF, and ISO, respectively. Significant differences between groups are seen in figure 3D. The overall mean value was significantly lower for HAL ($P < 0.01$), but not for ENF or ISO, when compared with the control group. The overall mean value for HAL was significantly lower compared to both ENF ($P < 0.01$) and ISO ($P < 0.01$), and the overall mean value for ENF was significantly lower compared to ISO ($P < 0.01$).

3A					3B				
SV _{max}					MAP vs. SV				
	C	HAL	ENF	ISO	C	HAL	ENF	ISO	
C	—	**	**	**	C	—	**	n.s.	**
HAL		—	*	*	HAL		—	**	*
ENF			—	n.s.	ENF			—	n.s.
ISO				—	ISO				—

3C					3D				
MAP vs. MVO ₂					MAP vs. CF				
	C	HAL	ENF	ISO	C	HAL	ENF	ISO	
C	—	**	**	n.s.	C	—	**	n.s.	n.s.
HAL		—	**	**	HAL		—	**	**
ENF			—	n.s.	ENF			—	**
ISO				—	ISO				—

3E				
MAP vs. O ₂ -extr				
	C	HAL	ENF	ISO
C	—	**	n.s.	**
HAL		—	**	**
ENF			—	*
ISO				—

FIG. 3. Results of Duncan's multiple range test on the main effects where the control (C), halothane (HAL), enflurane (ENF), and isoflurane (ISO) groups were compared against each other. SV_{max} = stroke volume (μl), at a left atrial pressure

of 12.5 mmHg; MAP = mean aortic pressure (mmHg); SV = stroke volume (μl); MVO_2 = myocardial oxygen consumption ($\text{mmoles O}_2/\text{min} \times \text{g heart weight}$); CF = coronary flow ($\text{ml}/\text{min} \times \text{g heart weight}$); $O_2\text{-extr}$ = myocardial oxygen extraction (%). * $P < 0.05$, ** $P < 0.01$.

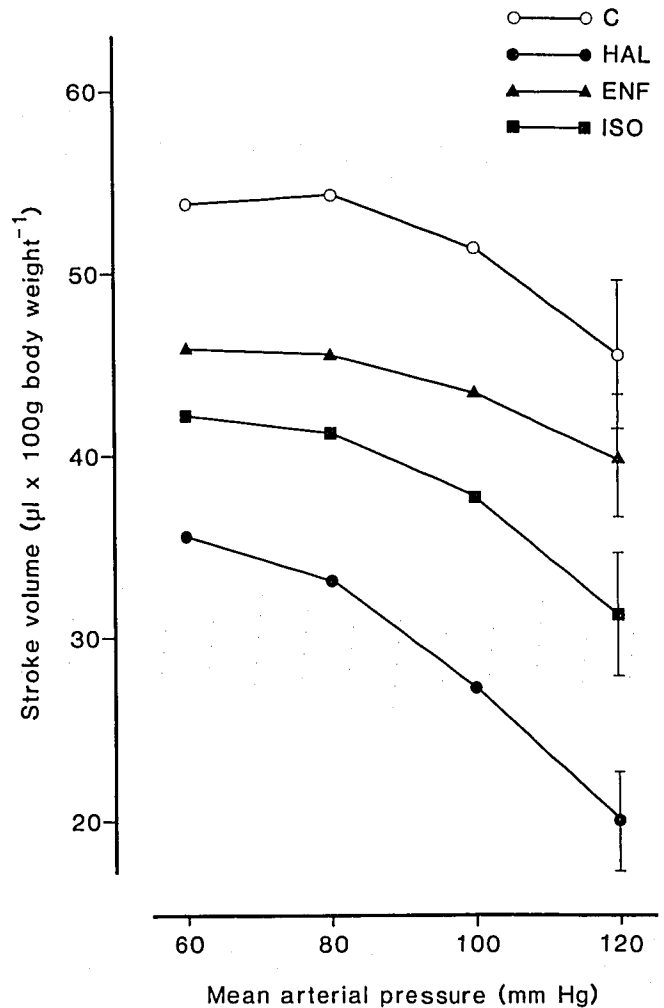


FIG. 4. Stroke volumes at various levels of mean arterial pressure and at a preload of 7.5 mmHg in the control, halothane (HAL), enflurane (ENF), and isoflurane (ISO) groups. Overall mean values were significantly lower for HAL and ISO, but not for ENF, compared to control. The overall mean value for HAL was significantly lower than for both ENF and ISO, while the latter two did not differ significantly. For clarity, standard error is provided only for the last measurement. Symbols of significance are given in figure 3.

In all experiments, oxygen extraction decreased slightly when MAP was increased from 60 to 120 mmHg. Mean values of oxygen extraction for the groups at the different levels of MAP are seen in figure 7. The overall mean values of oxygen extraction were 71.1, 54.5, 67.5, and 61.1% for the control group, HAL, ENF, and ISO, respectively. The overall mean values were significantly lower for HAL ($P < 0.01$) and ISO ($P < 0.01$), but not for ENF, compared to the control group. The overall mean value for HAL was significantly lower compared to both ENF ($P < 0.01$) and ISO ($P < 0.01$), and the overall mean value for ISO was significantly lower than ENF ($P < 0.05$).

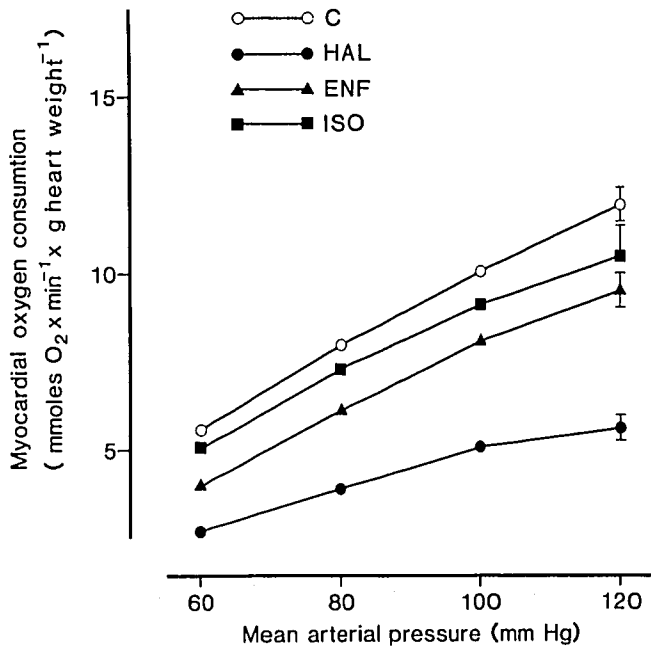


FIG. 5. Myocardial oxygen consumption at various levels of mean aortic pressure and at a constant preload (7.5 mmHg) for the control, halothane (HAL), enflurane (ENF), and isoflurane (ISO) groups. Overall mean values were significantly lower for HAL and ENF, but not for ISO, compared to control. The overall mean value for HAL was significantly lower compared to both ENF and ISO, while the latter two did not differ significantly. For clarity, standard error is provided only for the last measurement. Symbols of significance are given in figure 3.

Discussion

Studies in humans and animals have demonstrated that myocardial function is depressed less by isoflurane than it is by halothane or enflurane.¹⁸⁻²¹ However, it is difficult to assess the direct effects on myocardial contractility *in vivo*, as extracardiac actions of volatile anesthetics will modify the direct cardiodepressant effects. We, therefore, studied the relative effects of halothane, enflurane, and isoflurane on cardiac performance on a working, isolated heart model, where the major extracardiac determinants of myocardial performance, aortic pressure left ventricular filling pressure and heart rate, could be kept constant or varied independently from each other. Furthermore, we could relate the effects of the volatile anesthetics on cardiac performance to the effects on myocardial oxygen consumption, oxygen extraction and perfusion at physiological levels of heart rate, filling pressure, and mean aortic pressure.

The isolated working rat heart *in vitro* is a slowly deteriorating preparation. Attempts at reducing the duration of the experiments were, therefore, utilized *e.g.*, by the use of a separate control group not being exposed to anesthetics. In spite of this, one can see, from figure 2

and figure 4, that there is a small decrease in myocardial performance during the experiments which, however, has not influenced interpretation of the results. At equi-potent concentrations (MAC) and at a constant MAP and HR, halothane, enflurane, and isoflurane depressed the LVFC, compared to control. At an optimal myocardial filling pressure (12.5 mmHg), halothane exerted the most pronounced negative inotropic action, while there was no significant difference between enflurane and isoflurane. In a recent preliminary report, the cardiac effects of halothane, enflurane, and isoflurane were compared in a dog heart/lung preparation.²² LVFC were constructed at corresponding MAC levels and, in striking contrast to our findings, no significant differences in the depression of contractility were observed for halothane and isoflurane, while enflurane shifted the LVFC curve markedly to the right. Furthermore, and strangely enough, at 1 MAC, halothane and isoflurane decreased dP/dt, while enflurane had no significant effect on this variable of myocardial contractility. The results of this study are, thus, difficult to interpret, especially as it is not clear whether HR and MAP were kept constant during the experimental procedures.

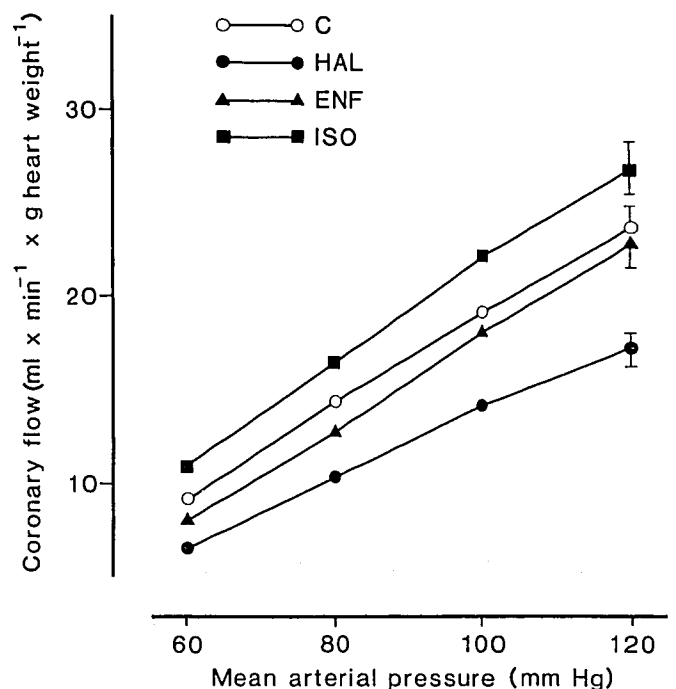


FIG. 6. Coronary flow (CF) at various levels of mean arterial pressure and at a constant preload (7.5 mmHg) for the control, halothane (HAL), enflurane (ENF), and isoflurane (ISO) groups. When comparing the overall mean values, HAL, but not ENF or ISO, induced a significant decrease in CF compared to control. HAL induced the most pronounced coronary vasoconstriction, followed by ENF. For clarity, standard error is provided only for the last measurement. Symbols of significance are given in figure 3.

Another way to assess myocardial performance is to expose the heart to increasing levels of MAP, keeping HR and filling pressure constant.²³ When MAP was increased from 60 to 120 mmHg at a constant LAP of 7.5 mmHg, halothane induced the most pronounced reduction in stroke volume, while there was no significant difference between enflurane and isoflurane. The more pronounced negative inotropic action during the after-load stress by halothane was also reflected by a lower MVO₂ compared to both enflurane and isoflurane. Thus, at equivalent anesthetic concentrations and at completely controlled and comparable level of MAP and LAP, halothane seemed to exert the most depressant action on cardiac performance. We could not demonstrate any significant difference between enflurane and isoflurane in this respect. The present findings support the data from Lynch,⁹ who demonstrated that isoflurane depressed peak developed tension in a guinea pig papillary muscle significantly less at physiologic stimulation frequencies than did equivalent doses of halothane. Isoflurane became less depressant as the stimulation rate increased to physiological frequencies, whereas halothane depressed peak tension at all frequencies. This finding may explain why Kemmotsu *et al.*¹² found that 1 MAC isoflurane or halothane depressed the peak force of a cat papillary muscle almost to the same extent at a low stimulation frequency (0.2 Hz). In a recent preliminary report on isolated working rat hearts, Cronau *et al.*²⁴ demonstrated that halothane decreased MVO₂ considerably more than isoflurane at equipotent concentrations. These data possibly reflect the greater negative inotropic effect induced by halothane, although neither data on myocardial performance nor on the loading conditions of the left ventricle were presented. Brown and Crout⁵ demonstrated that enflurane depressed isolated cat papillary muscles significantly more compared to halothane at a stimulation rate of 0.2 Hz, while Kemmotsu *et al.*¹² found the opposite using the same species and the same stimulation frequencies. These contradictory results are difficult to evaluate, as an unphysiologic stimulation frequency was used in both studies.

In the present study, isoflurane and enflurane exerted comparable effects on myocardial inotropism and oxygen consumption that was significantly less pronounced compared to halothane. To our knowledge, there is no available report designed to compare the relative inotropic effects of equi-potent concentrations of enflurane and isoflurane on *in vitro* preparations of cardiac muscle performing normal contractions at physiological stimulation frequencies.

There are conflicting reports on the effect of halothane on diastolic function. It has been suggested that halothane may decrease diastolic compliance,²⁵⁻²⁷ while

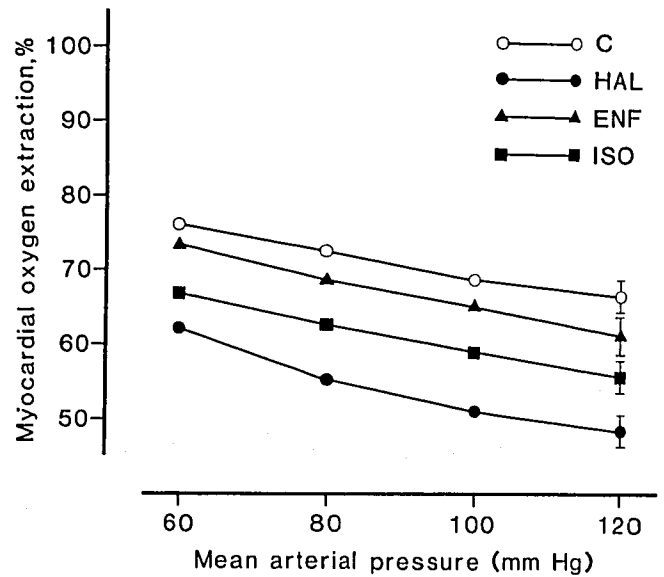


FIG. 7. Myocardial oxygen extraction at various levels of mean aortic pressure and at a constant preload (7.5 mmHg) for the control, halothane (HAL), enflurane (ENF), and isoflurane (ISO) groups. When comparing overall mean values, HAL and ISO, but not ENF, induced a significant decrease in oxygen extraction compared to control. This increase in myocardial oxygen supply-to-demand ratio was most pronounced for HAL. For clarity, standard error is provided only for the last measurement. Symbols of significance are given in figure 3.

others have shown that halothane does not alter diastolic mechanical properties of the myocardium.²⁸⁻³⁰ Data on the effect of isoflurane on diastolic stiffness have been presented in preliminary reports, and are also controversial.^{30,31} Shimosato *et al.*³⁰ demonstrated no effect of isoflurane on dynamic stiffness, while Tamura³¹ showed that isoflurane depressed diastolic filling. To our knowledge, there is no report on the effect of enflurane on diastolic properties of the heart. In the present investigation, we have estimated from the LVFC the filling pressure needed to perform 75% of the maximal SV (LAP_{0.75}). If the volatile anesthetics only impaired systolic performance without altering diastolic mechanics, the LVFC would only be depressed downwards. This means that LAP_{0.75} would not be affected compared to control, *i.e.*, there would be no shift of the LVFC rightwards or leftwards. We could not detect any significant differences in LAP_{0.75} between the volatile anesthetics and the control group. Thus, our data do not support the hypothesis that any of the volatile anesthetics induces a parallel shift of the LVFC to the right, *i.e.*, increases diastolic dynamic stiffness compared to control.

There is controversy in the literature on how volatile anesthetics affect coronary vascular resistance. Thus, it has been shown that halothane increases,³²⁻³⁶ de-

creases,³⁷⁻³⁹ or does not change^{20,40-43} coronary vascular resistance. In the majority of reports on the effects of isoflurane on coronary vascular tone, it has been shown that isoflurane is a coronary vasodilator both in animals^{20,44-47} and humans.⁴⁸⁻⁵⁰ However, a few conflicting reports could not demonstrate any effect of isoflurane on coronary vascular resistance.^{21,43,51,52} There are only a few studies on the effects of enflurane on coronary vascular resistance. In dogs, enflurane decreases coronary vascular resistance.^{20,53} In humans, enflurane has been shown to induce both a decrease⁵⁴ and no change⁵⁵ in coronary vascular resistance. However, it is difficult to evaluate the direct actions of volatile anesthetics *in vivo* on coronary vessels, as these agents, to a great extent, and probably in different ways, also alter the major determinants of coronary vascular tone:⁵⁶ aortic pressure, heart rate, inotropism, intramyocardial tissue pressure, and cardiac sympathetic and parasympathetic nerve activity. It was, therefore, of interest to compare the direct effects of equi-anesthetic concentrations of halothane, enflurane, and isoflurane on coronary vascular tone, as measured by coronary flow, at a constant filling pressure and at identical levels of left ventricular afterloads and coronary perfusion pressures in paced working hearts devoid of neural influences. Under these conditions, we found that halothane induced a coronary vasoconstriction, coronary flow being significantly lower than the enflurane, the isoflurane, and the control group, while a significant effect of enflurane or isoflurane on coronary vascular tone could not be demonstrated compared to control. When comparing enflurane and isoflurane, coronary flow was significantly higher with isoflurane.

Myocardial oxygen extraction was calculated in the present study to assess the effects of halothane, enflurane, and isoflurane on coronary perfusion in relation to myocardial oxygen consumption, *i.e.*, the oxygen supply-to-demand ratio. Halothane induced the most pronounced decrease in myocardial oxygen extraction followed by isoflurane, while enflurane had no significant effect compared to control. Thus, halothane exerted the most favorable effect on the oxygen supply-to-demand ratio due to the combination of a pronounced decrease in myocardial oxygen consumption and an inappropriate autoregulatory response of the coronary vascular bed. Thus, for a certain level of myocardial oxygen consumption, coronary flow was highest for halothane. Isoflurane, on the other hand, increased the oxygen supply-to-demand ratio, probably due to the combination of an insignificant increase in coronary flow and a insignificant decrease in myocardial oxygen consumption compared to control. Although isoflurane increased myocardial oxygen supply-to-demand ratio,

which has been demonstrated in several previous *in vivo* studies,^{20,47-50,55} coronary vasodilatation induced by isoflurane may be dangerous for the patient with coronary artery disease,⁵⁷ as it may induce coronary steal and myocardial ischemia.^{47-50,55}

In conclusion, we have found on isolated, paced working rat hearts that halothane exerts the most pronounced decrease in myocardial inotropism and oxygen consumption, while enflurane and isoflurane did not differ significantly in these respects. None of the volatile anesthetics seem to affect myocardial distensibility. Halothane, but not enflurane or isoflurane, increased coronary vascular tone compared to control. Coronary flow was significantly higher for isoflurane compared to both enflurane and halothane. Halothane and isoflurane, but not enflurane, increased the myocardial oxygen supply-to-demand ratio. This effect was most pronounced for halothane, which increased this ratio mainly by lowering myocardial oxygen demand.

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