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Differential effects of halothane and enflurane on end-systolic pressure-diameter relationship in anesthetized, mechanically ventilated dogs

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Abstract: To clarify the difference of negative inotropic effects, we evaluated the effects of 0, 0.5, and 1 MAC halothane and enflurane on systolic performance in anesthetized, mechanically ventilated, vagotomized dogs. Left ventricular myocardial contractility was assessed by the slope of the end-systolic pressure-diameter relationship (Ees), which have been reported to be independent of alterations in preload and afterload but sensitive to changes in myocardial contractility. Both anesthetics decreased heart rate and dose-dependently decreased left ventricular systolic pressure. Enflurane decreased heart rate and left ventricular systolic pressure more than an equivalent MAC of halothane. Both anesthetics increased left ventricular end-diastolic diameter without any change in %shortening of the left ventricular internal diameter. The Ees was decreased to a similar extent at both 0.5 and 1 MAC halothane. The Ees was decreased with increasing concentrations of enflurane. The Ees was significantly larger ($P < 0.05$) with 1 MAC of halothane than with 1 MAC enflurane. These results suggest that halothane preserves myocardial contractility better than enflurane in the presence of fentanyl.

Key words: Halothane, Enflurane, Myocardial contractility, End-systolic pressure-diameter relationship

Introduction

Halothane and enflurane, which are volatile anesthetics, have myocardial depressant effects. Their negative inotropic effects have been demonstrated in humans [1,2], in experimental animals [3–6], and in isolated atria and ventricles of various mammalian species [7–12]. However, the results of previous studies on the quantification of the inotropic state in vivo are unreliable. The maximum rate of increase in left ventricular pressure (dP/dt_{MAX}) and the maximum unloaded contractile element velocity (V_{MAX}) and influenced not only by intrinsic myocardial contractility but also by altered preload [13]. Ejection fraction may reflect inotropic state, but are inversely related to afterload [13]. Because inhalational anesthetics may alter both afterload and preload by decreasing peripheral vascular tone, it has been difficult to precisely define the negative inotropic effects of anesthetics using conventional hemodynamic determinations of myocardial contractility.

The instantaneous ventricular pressure-volume relationship has been intensively investigated by Sagawa and others [14–17]. They have demonstrated that the myocardial contractile state can be represented by the relation of ventricular blood volume and pressure at end systole. It has been shown that under conditions of constant heart rate and contractile state, extensive changes in preload, afterload, or both do not alter the instantaneous pressure-volume ratio of the canine left ventricle [17]. Changes in heart rate at a given contractile state have no effect on the end-systolic pressure-volume relationship. It has been shown that the end-systolic pressure-diameter relationship is linear over a wide range of preloads in conscious [18] and anesthetized [19] dogs. However, the slope of the end-systolic pressure-diameter relationship (Ees) is dependent on the heart size, and Ees of smaller hearts tends to be greater than that of larger hearts [20]. Therefore, it is impossible to compare the values of Ees among various sizes of hearts.

The purpose of the present study was to reveal the difference in negative inotropic effect on myocardial contractility between halothane and enflurane. We administered halothane and enflurane to each dog anesthetized with continuous infusion of fentanyl, and determined the end-systolic pressure-diameter relationship (ESPDR).

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Materials and methods

Animal preparation

The studies were conducted in accordance with the guidelines of the Animal Care Committee, Chiba University, School of Medicine. Six adult mongrel dogs (12–21 kg) of either sex were anesthetized with intravenous thiopental at 15 $mg \cdot kg^{-1}$ and fentanyl at 0.05 $mg \cdot kg^{-1}$, and their tracheae were intubated. Anesthesia was maintained with a continuous infusion of fentanyl 0.01 $mg \cdot kg^{-1} \cdot hr^{-1}$. $Paco_2$ was maintained in the range of 35–45 mmHg. Each dog was placed in right lateral recumbency and surrounded by warm water heating blankets to keep the body temperature at 37.5°–38.5°C. Each dog received lactated Ringer's solution at 4 $ml \cdot kg^{-1} \cdot min^{-1}$ via a femoral vein throughout the experimental period. Bilateral surgical vagotomy was performed through a midcervical incision.

A fluid-filled catheter was inserted through a femoral artery to the aortic arch and aortic pressure was measured. A left thoracotomy was then performed at the sixth intercostal space and the heart was exposed. To determine a left ventricular anterior-posterior short axis internal diameter, a pair of ultrasonic crystals was implanted on the endocardial surface on opposite sides of the left ventricle, approximately one-third of the distance from the apex to the base. An oscilloscope was used to ensure proper alignment of the crystals. A catheter-tip micromanometer was placed through the left ventricular apex and secured with a purse-string suture. A balloon-tipped aortic occlusion catheter was positioned in the descending aorta through the other femoral artery. The chest was then closed. Arterial pH and blood gases were analyzed, and existing respiratory and metabolic abnormalities were corrected. After these surgical preparations were completed, each dog was allowed to stabilize for about 60 min.

Data acquisition

End-tidal anesthetic gas concentrations were monitored with an anesthetic gas monitor (Normac, Datex, Helsinki, Finland). Total gas flows were maintained constant at 6 $l \cdot min^{-1}$ throughout each experiment. Analogue recordings were made on a 6-channel, forced ink oscillograph. The following measurements were obtained at each anesthetic concentration: heart rate (HR) and electrocardiogram (ECG), left ventricular pressure (LVP), first derivative of LVP with respect to time (dp/dt), left ventricular short axis diameter (LVD), and LVP/LVD. The end-diastolic point was defined by the R wave of ECG. The end-systolic point was defined at the point of maximal LVP/LVD [21–23]. This criterion is in accordance with the definition of end-systole as the instant at which the contractile process reaches its maximum [24–26]. We measured left ventricular end-diastolic pressure (LVEDP), left ventricular end-systolic pressure (LVESP), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD), and calculated the %shortening. ESPDR was computed from data obtained during a transient 10-s aortic occlusion during a ventilatory pause [27]. As afterload progressively increased during successive heart beats, a wide range of values for LVESP and LVESD were obtained. Linear regression analysis was performed on these data pairs to determine the slope and intercept values. Regression analysis of variance was performed to determine the statistical significance of the observed data and any r^2 value < 0.8 was discarded [28].

Experimental protocol

Cardiac contractility was assessed at three levels in each animal, namely 0 (baseline), 0.5, 1 MAC of either halothane or enflurane, each 20 min after a steady state had been reached. The values for MAC used in this study were 0.86% and 2.20% for halothane and enflurane, respectively [29]. After these three measurements, each animal was ventilated with 100% oxygen for 3 h. Then the same measurements were done after changing anesthetic either from halothane to enflurane ($n = 3$) or from enflurane to halothane ($n = 3$). All values are given as mean ± SE.

Statistical analysis

These data were analyzed by two-way analysis of variance, and t-test with the Bonferroni correction when appropriate. A P value < 0.05 was considered significant.

Results

Table 1 shows arterial blood gas data. No significant changes in arterial pH, Pco_2, and Po_2 were observed during the experimental period. There were no significant differences in hemodynamic and dimension data between controls (0 MAC) of halothane and enflurane (Table 2). HR was significantly decreased by both halothane and enflurane. LVESP was significantly reduced with increasing concentrations of either anesthetic. Enflurane significantly decreased HR and LVESP more than an equivalent MAC of halothane. LVEDP was not significantly changed by either halothane or enflurane, but LVEDD was significantly increased by both anesthetics from control values. There was no significant change in %shortening, sug-

Table 1. Arterial blood gas data

	Halothane			Enflurane		
	Control	0.5 MAC	1 MAC	Control	0.5 MAC	1 MAC
pH	7.38 ± 0.02	7.39 ± 0.03	7.41 ± 0.02	7.38 ± 0.02	7.39 ± 0.01	7.40 ± 0.02
P_{CO_2} (mmHg)	38 ± 2	39 ± 1	38 ± 1	39 ± 1	38 ± 1	38 ± 1
P_{O_2} (mmHg)	353 ± 19	321 ± 13	330 ± 12	357 ± 24	333 ± 16	320 ± 11

Values are mean ± SE; n = 6 dogs. There are no significant changes in pH, P_{CO_2}, and P_{O_2}.

Table 2. Left ventricular pressure and dimension data

	Halothane			Enflurane		
	Control	0.5 MAC	1 MAC	Control	0.5 MAC	1 MAC
HR (beats/min)	166 ± 8	131* ± 6	130* ± 5	171 ± 7	114*# ± 4	108*† ± 7
LVESP (mmHg)	162 ± 8	120* ± 5	101* ± 5	159 ± 10	109* ± 7	80*† ± 6
LVEDP (mmHg)	4.8 ± 1.4	5.0 ± 0.8	5.3 ± 0.5	5.5 ± 0.7	5.2 ± 1.2	5.5 ± 0.8
LVEDD (mmHg)	32.6 ± 3.0	34.4* ± 3.2	34.9* ± 3.3	32.7 ± 3.1	34.7* ± 3.0	34.8* ± 3.0
% Shortening (%)	8.5 ± 1.7	8.8 ± 1.2	9.4 ± 1.5	10.0 ± 1.8	10.5 ± 2.2	9.4 ± 2.2
Ees (mmHg/mm)	58.3 ± 24.9	18.9* ± 2.4	17.2* ± 2.4	59.8 ± 21.3	18.2* ± 2.7	12.7*† ± 2.0
Do (mm)	24.1 ± 2.8	23.9 ± 2.6	24.8 ± 3.1	24.8 ± 2.8	24.5 ± 2.6	24.9 ± 2.7

Values are mean ± SE; n = 6 dogs
HR, heart rate; LVESP, left ventricular end-systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEDD, left ventricular end-diastolic diameter; % Shortening, (LVEDD-left ventricular end-systolic diameter)/LVEDD × 100; Ees, slope of ESPDR; Do, diameter intercept of the ESPDR slope line.
* $P < 0.05$ versus control value.
† $P < 0.05$ between anesthetics at 1 MAC.
# $P < 0.05$ between anesthetics at 0.5 MAC.

gesting that neither anesthetics changed the ejection fraction.

The typical effects of halothane and enflurane on left ventricular systolic contractile function are illustrated in Fig. 1. Halothane and enflurane decreased the slope of the Ees. The Ees was better preserved at 1 MAC of halothane than at 1 MAC of enflurane. Figure 2 shows the entire results of the Ees. The Ees was significantly decreased at both 0.5 and 1 MAC of halothane compared with controls, but the Ees for 0.5 and 1 MAC of halothane were not significantly different from each other. The Ees was significantly decreased with increasing enflurane concentration. The Ees was significantly less ($P < 0.05$) at 1 MAC of enflurane (12.7 ± 2.0 mmHg/mm) than at 1 MAC of halothane (17.2 ± 2.4 mmHg/mm).

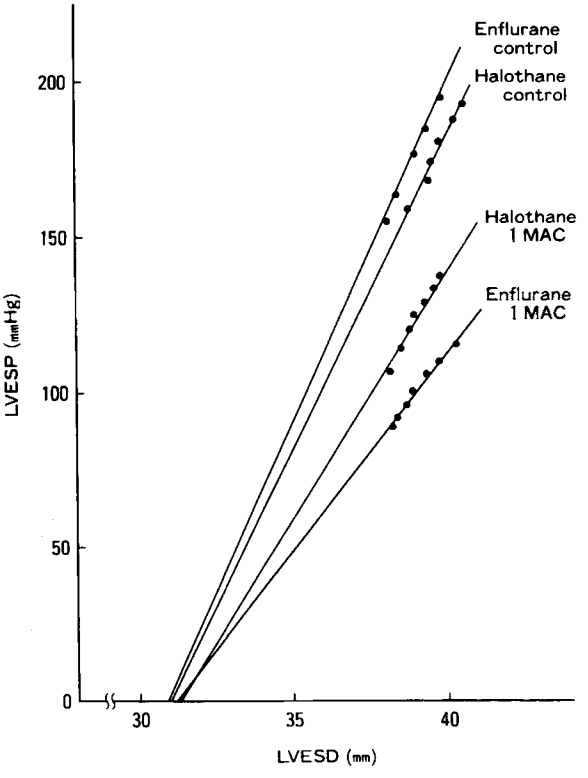

Fig. 1. Effects of halothane and enflurane on the end-systolic pressure-diameter relationship. *LVESP*, left ventricular end-systolic pressure; *LVESD*, left ventricular end-systolic diameter

Discussion

The present in vivo study demonstrated that enflurane is a more potent myocardial depressant than halothane at 1 MAC. The myocardial depression by halothane and enflurane have been investigated in isolated right ventricular cat papillary muscles. Brown and Crout [8] reported that the negative inotropic effect of enflurane is greater than that of halothane at equipotent anesthetic concentrations. By contrast, Shimosato et al. [10] and

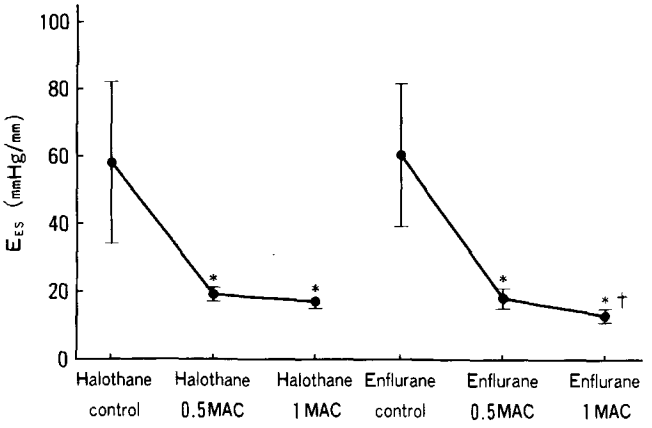

Fig. 2. Effects of halothane and enflurane on the slope of ESPDR (Ees). Both halothane and enflurane significantly decreased Ees, and the Ees was significantly less at 1 MAC of enflurane than at 1 MAC of halothane. Data presented are mean ± SE. * ($P < 0.05$ *vs* control); † $P < 0.05$ between anesthetics at 1 MAC

Kemmotsu et al. [12] found that 1 MAC of halothane has a greater cardiodepressant effect than 1 MAC of enflurane using the same preparation. These conflicting results may be due to the differences in experimental protocols and in methods of assessing myocardial contractility. Furthermore, their conclusions may not be directly applicable to clinical situations, since these experiments were performed in vitro.

We selected thiopental as the induction agent. Coetzee et al. [30] demonstrated that the blood concentration of thiopental 120 min. after induction was less than 12 mg·100 ml^{-1}. A previous study demonstrated that very little, if any, depression of myocardial contractility occurred at thiopental concentrations of 6–12 mg·100 ml^{-1} [31]. Furthermore, no difference could be demonstrated between the baseline values before inhalation of the two anesthetics.

The results of the present study were unavoidably influenced by the concurrent effects of fentanyl anesthesia. However, it is not expected that this dose of fentanyl would cause myocardial depression [32].

Bilateral vagotomy was induced to negate reflex parasympathetic modulation of contractile performance and heart rate during aortic occlusion. The relative contributions of the sympathetic and parasympathetic nervous systems as modulators of cardiovascular homeostasis differ between conscious and anesthetized dogs. Parasympathetic influences may exert primary control in conscious dogs, their influence may be attenuated in anesthetized dogs [33]. Sympathetic reflexes were intact in the present study. Changes in afterload during a transient aortic occlusion may evoke reflex alterations in the inotropic state. However, parasympathetic and sympathetic nervous system responses are characterized by their differing time constants. Vagal responses are typically rapid, having time constants of less than a second. Sympathetic responses are more slowly activated, having time constants of about 8 s [34]. Therefore, sympathetic reflexes were supposed not to contribute to our determinations of Ees.

The present study demonstrates that both halothane and enflurane significantly decreased heart rate at 0.5 and 1 MAC compared with the control (0 MAC). In volunteers who did not undergo surgery, it has been demonstrated that heart rate does not change during anesthesia with halothane [1] but may increase by 20%–40% with enflurane [2]. In the present study, we used fentanyl as a baseline anesthetic so that heart rate was slowed by volatile anesthetics. The steady-state effect of changes in heart rate on the end-systolic pressure-volume relationship of the isolated left ventricle is minimal. In the range 100–180 beats·min^{-1}, there is little change in the end-systolic pressure-volume relationship [35]. Thereby, it is supposed that heart rate does not affect the inotropic state in the present study.

There are two other studies in which the end-systolic pressure-dimension relationship was utilized as a method to compare the effect of halothane and enflurane in dogs. Van Tright et al. [32] demonstrated that at equal MAC, halothane and enflurane similarly suppressed the left ventricular systolic performance. Coetzee et al. [30] showed that enflurane reduced the slope of the end-systolic pressure-length relationship more than halothane, and concluded that the depressant enflurane effect of on the heart was greater.

In conclusion, the present study demonstrates that both halothane and enflurane have load-independent negative inotropic effects, and that enflurane is a more potent myocardial depressant than halothane at 1 MAC. Because this study was performed using a canine model, the results obtained are not directly applicable to the clinical setting. However, we believe the results of this study are relevant to everyday practice.

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