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Alteration of vascular capacitance and blood flow distribution during halothane anesthesia

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Abstract: We examined the effect of halothane on systemic vascular capacitance as well as on systemic vascular resistance using cardiopulmonary bypass in dogs. Venous outflows from two different vascular beds, the splanchnic and extrasplanchnic beds, were also measured. Under constant perfusion flow and constant central venous pressure, a change in reservoir blood volume inversely represented a change in systemic blood volume and then in systemic vascular capacitance, and a change in mean arterial pressure directly reflected a change in systemic vascular resistance. Administration of 1% and 2% halothane produced the blood concentrations of 0.58 ± 0.14 mM and 1.34 ± 0.06 mM, respectively. Systemic vascular resistance decreased by 12 ± 6% and 40 ± 4% during 1% and 2% halothane, respecitively. Systemic blood volume increased by 7 ± 2 ml·kg^{-1} and 15 ± 4 ml·kg^{-1} during 1% and 2% halothane, respectively. Halothane did not cause significant blood flow redistribution between the splanchnic and extrasplanchnic vascular beds. These results suggest that halothane causes an increase in systemic vascular capacitance as well as a decrease in systemic vascular resistance. This increase in vascular capacitance may contribute in part to a decrease in cardiac output during halothane anesthesia.

Key words: Halothane—Vein—Splanchnic—Vascular capacitance—Blood volume—Blood flow distribution

Introduction

Cardiac output is determined by four principal factors such as myocardial contractility, heart rate, preload, and afterload. Halothane has been shown to decrease cardiac output due primarily to depression of myocardial contractility [1,2]. However, the effect of halothane on preload has not yet been clearly determined. Preload is defined as ventricular end-diastolic volume or pressure, and it is influenced by circulating blood volume, ventricular filling time, ventricular diastolic compliance, and vascular capacitance. The purpose of this study was to examine the changes in vascular capacitance during halothane anesthesia. Vascular capacitance is defined as the blood volume contained in the systemic circulation, especially in the venous system at a given venous pressure [3]. An increase in vascular capacitance can be derived largely from venous dilatation, leading to a contained blood volume in the venous system and thus a decrease in venous return.

To elucidate the effect of halothane on vascular capacitance, we used cardiopulmonary bypass in dogs, where a change in vascular capacitance can be evaluated as an inverse change in reservoir blood volume under constant venous pressure and constant perfusion flow. Venous outflow from the systemic circulation was divided into two compartments; the splanchnic and extrasplanchnic vascular beds, which are considered to have different time constants for venous drainage, as described by Caldini et al. [4] and others [5,6].

Methods

Five mongrel dogs weighing 20–30 kg were anesthetized with 30 mg/kg of pentobarbital sodium. Supplemental doses of the anesthetic were given as necessary to maintain the basal anesthetized state of the experimental animals. The trachea was intubated with a cuffed endotracheal tube and connected to Bird Mark 7 respirator for mechanical ventilation with 100% oxygen until cardiopulmonary bypass was instituted. $Paco_2$ was maintained between 30 and 40 mmHg and kept constant during mechanical ventialtion. Catheters were

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placed in the thoracic aorta via the left axillary artery to measure arterial pressure and the superior vena cava via the left axillary vein and the inferior vena cava via the femoral vein to measure central venous pressure. The catheters were connected to Statham pressure transducers (Statham Instruments, Los Angeles, CA, USA). Body temperature was maintained by external warming with a heating pad, and also by a heat exchanger during cardiopulmonary bypass.

The surgical preparation and experimental apparatus for measurements of regional venous outflow and blood volume changes are described previously in detail [7,8]. Briefly, the chest was opened through a meadian sternotomy, and animals were placed on cardiopulmonary bypass using a Sarns roller pump (Sarns 3M Health Care, Model 3500, Annarbor, MI, USA) and Shiley reservoir oxygenator (Sorin Biomedical, Irvine, CA, USA) The reservoir was primed with a mixture of lactated Ringer's (2000 ml) and Dextran 40 (1000 ml) containing 10000 units of sodium heparin. An oxygenator was bubbled with 5-6 $L \cdot min^{-1}$ of oxygen and 250-300 $ml \cdot min^{-1}$ of CO_2 to maintain $Paco_2$ at 35–40 mmHg. Systemic perfusion was performed through cannulas placed in both femoral arteries. Venous outflow was divided into two compartments; splanchnic and extraaplanchnic. The splanchnic venous outflow was collected through a cannula placed in the inferior vena cava at the level of the diaphragm, and this region was isolated by a ligation on the inferior vena cava below the renal veins. The splanchnic outflow, therefore, includes renal outflow in the present experiments. The extrasplanchnic venous outflow was collected through four cannulas placed in the superior vena cava, the right ventricle, the left ventricle, and the femoral vein. The azygos vein was ligated. The cardiopulmonary bypass pump was adjusted so that arterial blood pressure was approximately equal to the level before bypass and maintained constant throughout the experiment. Venous pressures in the extrasplanchnic and splanchnic vascular beds were measured via the catheters placed into the superior and inferior vena cava above the renal veins, respectively. The height of the opening of the tube draining venous return into the reservoir was adjusted so that the mean central venous pressure measured 5-6 mmHg. The splanchnic and extrasplanchnic venous outflows were measured using a multichannel Biotronex electromagnetic flowmeter and in-line flow probe (Biotronex Laboratory, Chester, MD, USA).

The arterial pressure, splanchnic and extrasplanchnic venous pressure, and splanchnic and extrasplanchnic venous outflows were recorded simultaneously on a Grass Model 7 polygraph (Grass Instrument, Braintree, MA, USA).

Changes in blood volume within the animal were assessed by changes in the reservoir volume. The reservoir volume was measured by reading the blood level on the reservoir scale to the nearest 10 ml. After each experiment, the relationship between real blood volume change and the volume change measured by graduation on the reservoir was examined by adding blood of known volume to the reservoir. Subsequently, the real blood volume change was obtained by correction of the measured volume change. Average correlation was as follows: real blood volume change = 0.75 × blood volume change measured by the reservoir scale.

Measurements were done under three conditions in series: control, 1% halothane, and 2% halothane. Under each condition, 20 min were allowed for hemodynamics to stabilize before measurements were done. Halothane was provided using a Fluotec 2 vaporizer (Cyprane, Keighley, England) installed in-line with a gas mixture supply to the oxygenator. Halothane concentrations in blood were measured on a Perkins-Elmer Cetus (Norwalk, CT, USA) Sigma 3B gas chromatography at 5, 10, and 15 min after the application of halothane. Sodium bicarbonate was added to the reservoir to maintain optimal pH and base excess if necessary.

All data are expressed as the mean ± standard deviation (SD) of the mean. Statistical analysis was performed using analysis of variance (ANOVA), and if the F value was significant, a paired *t*-test was done. A *P* value of less than 0.05 was considered significant.

Table 1. Arterial blood gas analysis and hemoglobin concentration

	Before CPB	20 min after CPB	End of CPB
Hgb ($g \cdot L^{-1}$)	157 ± 58	88 ± 10*	85 ± 8*
pH	7.42 ± 0.06	7.36 ± 0.06	7.40 ± 0.06
Pao_2 (mmHg)	261 ± 200	393 ± 88	375 ± 110
$Paco_2$ (mmHg)	34 ± 14	38 ± 2	36 ± 4
HCO_3^- ($mmol \cdot L^{-1}$)	21 ± 4	21 ± 4	22 ± 2
BE ($mmol \cdot L^{-1}$)	22.2 ± 1.6	23.4 ± 4.0	22.6 ± 2.2

CPB, cardiopulmonary bypass; Hgb, hemoglobin; BE, base excess.
Mean ± SD, * $P < 0.05$ *vs* before CPB.

Table 2. Halothane concentration in the blood (*HAL*), mean arterial pressure (*MAP*), splanchnic (*SPL*), and extrasplanchnic (*EX*) outflow at control, 1% halothane, and 2% halothane administration

	Control	1% halothane	2% halothane
HAL (mM)	0	0.58 ± 0.14*	1.34 ± 0.06*#
MAP (mmHg)	107 ± 16	82 ± 10*	63 ± 6*#
SPL flow (ml·min^{-1})	61 ± 10	65 ± 10*	68 ± 12*
EX flow (ml·min^{-1})	57 ± 8	53 ± 8*	50 ± 6*

Mean ± SD, * $P < 0.05$ *vs* control, # $P < 0.05$ *vs* 1% halothane.

Results

Table 1 shows the blood gas analysis and hemoglobin concentrations. Hemoglobin decreased from 157 ± 58 to 88 ± 10 g·L^{-1} after the institution of cardiopulmonary bypass and 85 ± 8 g·L^{-1} at the end of the experiment. Blood gas values showed no significant changes throughout the experiment. The halothane concentration in the blood became stable 15 min after the administration, and the values were 0.58 ± 0.14 mM for 1% halothane and 1.34 ± 0.06 mM for 2% halothane.

The arterial pressure, venous outflow, and reservoir volume were measured approximately 20 min after the initiation of cardiopulmonary bypass in controls. The data at 1% and 2% halothane were obtained when all these variables became stable following changes of the inspired halothane concentration. The average times were 15.3 ± 3.2 and 15.6 ± 2.8 min for 1% and 2% halothane, respectively. Table 2 shows the changes in the arterial pressure and venous outflow from each vascular bed. The mean arterial pressure showed dose-related decreases of 23 ± 6% and 40 ± 2% during 1% and 2% halothane, respectively. Halothane did not cause significant blood flow redistribution between the splanchnic and extrasplanchnic vascular beds. If anything, halothane tended to increase splanchnic outflow by 6 ± 4% and 10 ± 10% at 1% and 2% halothane, respectively. On the other hand, the extrasplanchnic outflow showed a tendency to decrease by 5 ± 2% and 11 ± 2% during 1% and 2% halothane, respectively. Figure 1 shows the changes in vascular resistance of the total and each vascular bed, calculated by dividing the perfusion pressure by each outflow obtained under a steady state. The total, splanchnic and extrasplanchnic

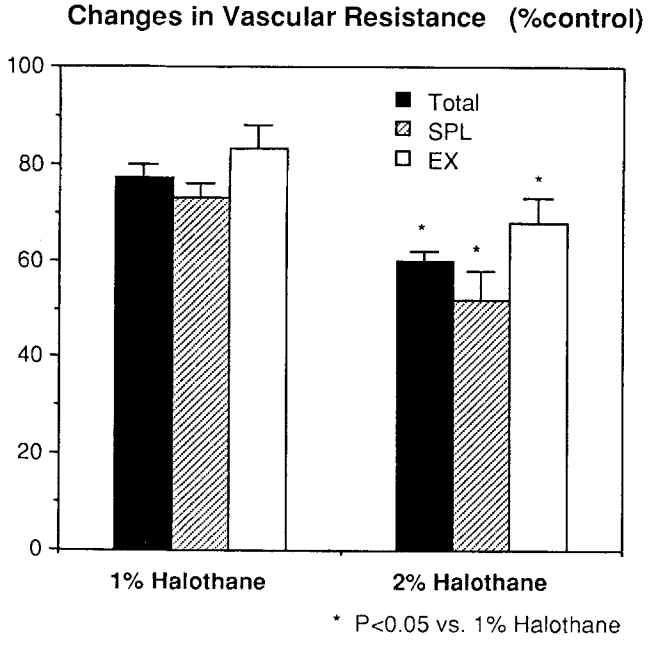

Fig. 1. Percent changes in vascular resistance in total vasculature (*Total*), the splanchnic vascular bed (*SPL*) and the extrasplanchnic vascular bed (*EX*) during 1% and 2% halothane anesthesia. Halothane caused significant decreases in vascular resistance in all three in a dose-related fashion. *$P < 0.05$ vs. 1% halothane.

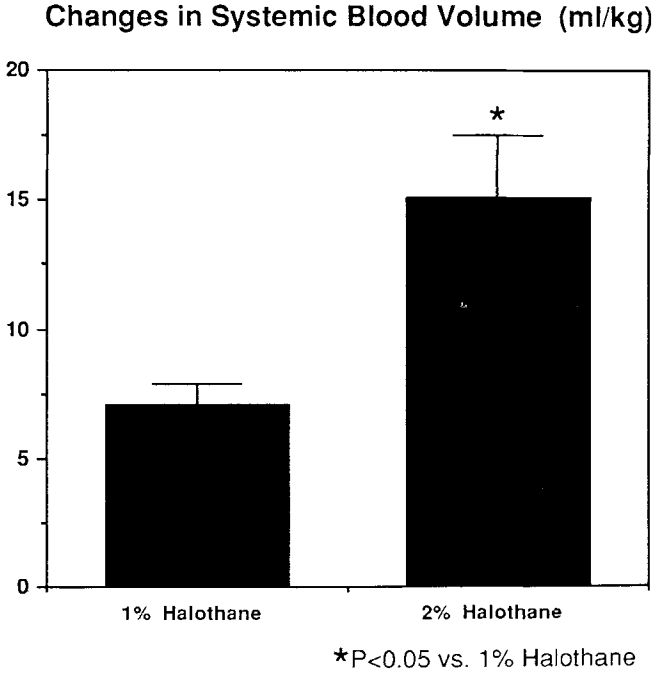

Fig. 2. Changes in systemic blood volume during 1% and 2% halothane anesthesia. Halothane caused significant increases in systemic blood volume in a dose-related fashion. *$P < 0.05$ vs. 1% halothane

resistance decreased in a dose-dependent manner. There were no significant differences in the extent of the decreases of vascular resistance among three vascular beds.

Figure 2 shows changes in systemic blood volume in response to 1% and 2% halothane. Halothane at 1% and 2% caused decreases in reservoir blood volume by 7.1 ± 1.6 and 15.1 ± 4.8 ml·kg^{-1}, respectively.

Discussion

This study was conducted to examine whether halothane alters vascular capacitance and blood flow distribution. Vascular capacitance is defined as the total contained volume of the vasculature at a given transmural pressure [3]. The observed decreases in the reservoir blood volume at constant central venous pressure inversely represented increases in the systemic blood volume. Therefore, the decreases in reservoir blood volume of 7 and 15 ml·kg^{-1} caused by respective 1% and 2% halothane represent the increases in systemic blood volume and hence the increases in systemic vascular capacitance. This increase in systemic vascular capacitance may cause a decrease in venous return and therefore contribute in part to a decrease in cardiac output during halothane anesthesia.

An increase in systemic blood volume can arise from both active and passive mechanisms [3]. The active change is that produced by a direct decrease in vascular tone in capacitance vessels, which are primarily veins and venules. The passive change in blood volume is that produced by a change in blood flow [3]. An increase in blood flow can cause a passive increase in the contained blood volume. Since systemic blood volume is stored mainly in the splanchnic vascular beds [9], an increase in the splanchnic blood flow can result in a passive increase in systemic blood volume. The redistribution of blood flow from the splanchnic to extrasplanchnic vascular beds can interfere with an increase in systemic blood volume. Halothane, in this study, did not cause a significant blood flow change between the splanchnic and extrasplanchnic vascular beds. Therefore, it is suggested that an increase in systemic blood volume may be derived from active dilatation of capacitance vessels.

Blood volume contained in the arterial vascular bed can also contribute to the observed change in systemic blood volume. Assuming that the compliance of the arterial bed is about 0.067 ml·mmHg^{-1}·kg^{-1} in dogs [10], decreases in arterial pressure of about 25 to 44 mmHg produced by 1% and 2% halothane in this study are equivalent to decreases in the contained blood volume of 1.7 and 2.9 ml·kg^{-1}, respectively. This suspected decrease in arterial blood volume may slightly counteract the increase in systemic blood volume produced by dilatation of the capacitance vessels.

An increase in systemic vascular capacitance can lead to a decrease in venous return, filling pressure and ultimately cardiac output. Our experiments were performed using a cardiopulmonary bypass and under constant cardiac output. In an intact condition, a reduction in cardiac output will lead to a decrease in blood flow in the venous vasculature and then cause a decrease in the distending transmural pressure with a passive release of contained blood to systemic circulation. This passive change in blood volume will also counteract the direct venodiating effect of halothane and must have played a compensatory role in maintaining cardiac output.

Our results show that halothane did not cause a significant blood flow change in the splanchnic circulation provided that the cardiac output is constant. A number of investigators have demonstrated a decrease in splanchnic blood flow during halothane anesthesia in animals [11–13] and humans [14,15]. The magnitude of the decrease in splanchnic or hepatic blood flow was approximately 20–50% under 1–2% halothane anesthesia [11–15]. However, these decrease in splanchnic blood flow occurred concurrently with decreases in cardiac output. Therefore, our results are not necessarily inconsistent with those of previous studies.

This study was done in dogs in which pentobarbital was used as a basal anesthesia. Pentobarbital may have some influence on the observed effects of halothane [16]. It should be noted that, in dogs, especially in those anesthetized with pentobarbital, the spleen plays a larger role in changes of vascular capacitance than in humans [17]. In addition, a time-control experiment was not performed here. In a preliminary study, the reservoir volume gradually decreased as a function of time by approximately 0.02–0.1 ml·kg^{-1}·min^{-1}. Therefore, it should be considered that the magnitude (7 and 15 ml·kg^{-1}) of the changes in systemic blood volume during halothane anesthesia may be larger (approximately 10–20%) than the actual volume change.

In conclusion, halothane caused an increase in systemic vascular capacitance in association with a decrease in systemic vascular resistance in a dose-dependent manner in dogs. The increase in vascular capacitance may play an important role in circulatory depression during halothane anesthesia.

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