Changes in Circulating Blood Volume following Isoflurane or Sevoflurane Anesthesia

Hiroshi HAMADA, Masuhiko TAKAORI, Ken'ichi KIMURA, Akira FUKUI and Yoshihisa FUJITA

Changes of circulating blood volume (CB volume) measured by the dual indicator dilution method were observed in 33 chronically instrumented mongrel dogs following either alpha-chloralose-urethane (C group), additive isoflurane (I group) or sevoflurane anesthesia (S group). These anesthetic groups were each divided into two subgroups with regard to respiratory care, namely Cp, Ip and Sp for those with intermittent positive pressure ventilation (six animals per subgroups), and Cs, Is and Ss for those with spontaneous breathing (five animals per subgroups).

The CB volume under positive pressure ventilation remained unchanged in the Ip and Sp groups at both 0.5 and 1.0 MAC, and in the Cp group. The CB volume remained essentially unchanged in the Cs and Is groups at both 0.5 or 1.0 MAC, but the plasma volume tended to increase slightly in the Is group at 1.0 MAC.

In the Ss group under spontaneous breathing, however, the CB volume increased from 84.4 ± 7.0 to 91.4 ± 7.7 at 0.5 MAC, and to 91.4 ± 10.2 $ml \cdot kg^{-1}$ at 1.0 MAC ($0.01 < P < 0.05$). These increases were caused by an increase in the plasma volume.

The above data suggests that a concomitant increase in the venous pressure associated with an increase in the intrathoracic pressure produced by positive pressure ventilation would attenuate changes in the CB volume during sevoflurane anesthesia. (Key words: circulating blood volume, RBC volume, plasma volume, isoflurane, sevoflurane)

(Hamada H, Takaori M, Kimura K, et al.: Changes in circulating Blood volume following isoflurane or sevoflurane anesthesia. J Anesth 7: 316–324, 1993)

Many studies concerning changes in circulating blood volume (CB volume) during surgery and/or general anesthesia have previously been performed. Previous studies have demonstrated that reduction in the CB volume was always greater under ether anesthesia than that which could be assumed to be caused by surgical blood loss[1–3]. On the other hand, Nakajo et al.[4] noted a significant increase in the CB volume accompanied by an increase in red blood cell (RBC) volume during ether anesthesia. Grable et al.[5] reported that the CB volume usually increased by 10% in surgical patients anesthetized with halothane but re-

Department of Anesthesiology, Kawasaki Medical School, Kurashiki, Japan

Address reprint requests to Dr. Hamada: Department of Anesthesia, Onomichi General Hospital, 7-19 Kohama-cho, Onomichi, 722 Japan

mained unchanged under cyclopropane anesthesia.

Recently new inhalation anesthetics have been introduced in practice, but little study has been done regarding the influence of these agents on the CB volume. It is important for the anesthesiologists to be aware of the specific effects of these anesthetics on the CB volume for intraoperative circulatory management and fluid therapy. We attempted to study the influence of isoflurane and sevoflurane on the CB volume in dogs.

Materials and Methods

Animal preparations:

The protocol for this study was approved by the Animal Care and Use Committee of Kawasaki Medical School. The experiments were carried out in 33 mongrel dogs with a body weight of 7-13 kg. All animals were anesthetized with pentobarbital 20 $mg \cdot kg^{-1}$ iv and intubated with a cuffed endotracheal tube on the day before the experiment. They were ventilated by an animal respirator (Aika R-50S) with 66% N_2O and 34% oxygen delivered from an anesthetic machine. The left jugular vein and carotid artery were exposed surgically and cannulated with an 8F and a 5F vinyl catheters. The wound was sutured and a vinyl bandage was rolled around the neck for protection of the catheters. The animals were allowed to wake, and then were subsequently extubated, and left in a cage until the next morning.

Measurements:

On the experiment day, 10 ml of arterial blood was withdrawn into a heparinized syringe from the catheter under an awake state. Red blood cells were labeled *in vitro* with Na_2CrO_4 containing 50 μC of ^{51}Cr. These red blood cells and radioactive iodine human albumin containing 20 μC of ^{125}I were injected into each animal through the implanted venous catheter. At 5, 10, 30 and 40 min after the injection, respectively, 1 ml of the arterial blood was sampled in a counting vial. Radioactivity in each blood sample was measured three times by a gamma counter (Aloca Auto-Well Gamma System ARC-361). The zero time concentration of the indicator (either ^{51}Cr-RBC or ^{125}I-albumin) in the CB was calculated mathematically from concentrations in the sample obtained at the serial periods. Then the RBC volume and plasma volume were determined by comparison with the external standard, which was prepared in a volumetric flask. The CB volume was calculated as the sum of the RBC volume and plasma volume.

Study 1

After the above measurement of the CB volume, 18 mongrel dogs were anesthetized with intravenous alpha-chloralose (60 $mg \cdot kg^{-1}$) and urethane (600 $mg \cdot kg^{-1}$) and intubated with a cuffed endotracheal tube. The animals were ventilated with 100% oxygen by the animal respirator and their tidal volume was adjusted to maintain Pa_{CO_2} at 35–40 mmHg while the respiratory rate was fixed at 20 $times \cdot min^{-1}$. The right jugular vein was exposed surgically and a 5F thermodilution catheter (Spectramed, SP5105, USA) was introduced into the pulmonary artery. The animal's body temperature was kept at 37°C with a cooling-warming blanket.

After the animals were left in place for circulatory stabilization for 30 min, they were divided randomly into three groups. In the Ip group (n=6) isoflurane 0.5 MAC (0.64%[6]) was added to the inspiratory gas and in the Sp group (n=6) sevoflurane 0.5 MAC (1.18%[7]) was added. The remaining animals (Cp group, n=6) were left under basal anesthesia and were ven-

tilated with 100% oxygen alone. The end-tidal concentration of the anesthetics were monitored in the lumen of the endotracheal tube by an anesthetic gas analyzer (Normac^{TM}, Datex). After stabilization of the end-tidal concentration of the anesthetics, which usually required 30 min, measurement of the CB volume was started in the same fashion as done in the awake state. Mean arterial blood pressure (mBP), mean pulmonary arterial blood pressure (mPAP), pulmonary capillary wedge pressure (PCWP) and the ECG pattern on lead II were recorded continuously on a polygraph (Nihon Kohden, RM-6200, Japan). The heart rate was counted by the number of R waves recorded on the ECG. Simultaneously, cardiac output was measured twice by the thermodilution method using a cardiac output computer (KMA, Goodman, USA), and the subsequent cardiac index was calculated. The arterial blood pH and gases were measured by a blood gas analyzer (ABL2^{TM}, Radiometer, Denmark). The hematocrit value (H) was measured by the microcapillary method (12,000 rpm for five min, KH-120 M^{TM}, Kubota, Japan) and was corrected by the plasma trapping factor of 0.96. The mean corporeal hematocrit value (H_0) was calculated by the measured RBC volume and plasma volume expressed as follows:

$$H_0 = \text{RBC volume}/(\text{RBC volume} + \text{plasma volume})$$

Subsequently the F cell ratio was calculated by H_0/H.

After the completion of all measurements at 0.5 MAC, the inspiratory anesthetic concentration was increased to 1.0 MAC. The end-tidal concentration was monitored for about 30 min until it stabilized, and then the same physiological measurements were carried out. In the Cp group, the physiological measurements were done in the same fashion at periods corresponding to those in the Ip and Sp groups.

Study 2

Fifteen animals were anesthetized with alpha-chloralose and urethane in the same manner as in Study 1 and were left to breathe 100% oxygen spontaneously. Blood gases and pH were analysed to maintain Pa_{CO_2} at 35–40 mmHg at 15 min after the initiation of basal anesthesia. The insertion of a thermodilution catheter was carried out in the same fashion as in Study 1.

The animals were divided into three groups; a Cs group (n=5), an Is group (n=5) and an Ss group (n=5). Via a Y adaptor tube with one way valve, they breathed 100% oxygen, oxygen with isoflurane and oxygen with sevoflurane, respectively. The end-tidal concentration of the anesthetic was monitored continuously in the lumen of endotracheal tube. The interval for inhalation of the anesthetic and the physiological measurements were performed in the same fashion as that in Study 1.

Statistical analysis:

All data obtained were expressed as the mean ± standard deviations (SD). Comparisons of the data in the three groups under either positive pressure ventilation or spontaneous breathing and of the data within groups anesthetized with the same anesthetic were made using repeated-measures analysis of variance (ANOVA). Comparison of the data obtained in the two different MAC periods in each group were assessed by the Wilcoxon's rank sum test. Values of $P < 0.05$ were considered significant.

Results

Study 1

The CB volume changed from 86.3 ± 13.8 at 0 MAC to 94.0 ± 18.5 ml·kg^{-1} at 0.5 MAC in the Cp group, but

Table 1. Changes in blood volumes during control ventilation

Group	MAC	CB	RBC	Plasma
C	0	86.3 ± 13.8	37.3 ± 10.3	49.0 ± 8.9
	0.5	94.0 ± 18.5	41.3 ± 9.7	52.8 ± 15.5
	1.0	93.1 ± 18.7	41.8 ± 19.1	51.4 ± 6.0
I	0	90.1 ± 18.7	35.5 ± 14.8	54.6 ± 12.5
	0.5	87.5 ± 17.2	29.9 ± 10.7	57.6 ± 10.4
	1.0	94.1 ± 23.6	32.9 ± 7.0	61.2 ± 18.3
S	0	91.6 ± 12.5	29.8 ± 5.7	61.8 ± 10.4
	0.5	96.5 ± 15.0	31.2 ± 7.4	65.3 ± 11.5
	1.0	94.1 ± 8.5	29.8 ± 6.4	64.3 ± 8.6

All values are mean ± SD ($ml \cdot kg^{-1}$, n=6 in each group)

Table 2. Circulatory variables during IPPV and spontaneous breathing

Group	MAC	mBP (mmHg)	HR (bpm)	mPAP (mmHg)	PCWP (mmHg)	CI ($l \cdot min \cdot BSA$)
Cp	0	118.0 ± 13.4	158.4 ± 41.9	17.8 ± 7.3	8.2 ± 4.0	3.2 ± 0.9
	0.5	120.6 ± 14.9	166.0 ± 29.8	19.0 ± 5.9	7.3 ± 3.6	3.8 ± 1.5
	1.0	114.4 ± 10.2	162.0 ± 24.9	17.2 ± 4.8	6.5 ± 4.0	2.4 ± 0.7
Ip	0	110.0 ± 11.5	116.0 ± 22.3	13.8 ± 9.4	3.8 ± 3.5	2.6 ± 0.4
	0.5	97.3 ± 26.6	126.0 ± 21.1	12.7 ± 4.4	4.0 ± 3.0	3.1 ± 1.0
	1.0	74.5 ± 27.9*	114.0 ± 16.5	9.2 ± 4.8*	2.7 ± 2.8*	3.2 ± 0.9
Sp	0	121.5 ± 20.4	127.7 ± 43.3	14.5 ± 8.6	4.0 ± 1.1	5.2 ± 1.4
	0.5	112.7 ± 20.2	131.0 ± 37.6	11.7 ± 7.0†	3.3 ± 1.9	4.3 ± 1.2
	1.0	94.8 ± 23.9*	115.7 ± 24.5	11.2 ± 5.9†	3.2 ± 2.3	4.1 ± 0.9
Cs	0	111.7 ± 7.6	132.0 ± 12.0	13.3 ± 2.0	6.0 ± 1.2	3.3 ± 0.2
	0.5	126.7 ± 5.8	152.0 ± 13.9	13.7 ± 1.2	6.7 ± 1.2	3.5 ± 0.2
	1.0	125.0 ± 5.0	152.0 ± 13.9	14.0 ± 1.2	6.7 ± 2.0	3.5 ± 0.1
Is	0	122.0 ± 13.5	124.8 ± 42.1	14.9 ± 2.7	6.4 ± 2.4	3.2 ± 0.2
	0.5	135.0 ± 26.5	158.4 ± 28.7	15.8 ± 5.9	6.8 ± 3.4	3.4 ± 0.2
	1.0	131.0 ± 13.9	146.4 ± 36.4	15.2 ± 3.6	6.8 ± 2.6	3.4 ± 0.6
Ss	0	117.0 ± 17.7	119.8 ± 30.8	13.0 ± 2.1	6.2 ± 3.8	2.9 ± 0.3
	0.5	116.0 ± 14.7	122.4 ± 29.9	12.8 ± 2.3	5.6 ± 3.8	3.1 ± 0.1
	1.0	110.0 ± 10.4	132.0 ± 36.0	12.4 ± 4.7	5.6 ± 3.9	3.3 ± 0.4

All values are mean ± SD (n=6 in Cp, Ip, Sp-group and n=5 in Cs, Is, Ss-group)
* $0.01 < P < 0.05$, vs 0 & 0.5 MAC value
† $0.01 < P < 0.05$, vs 0 MAC value
Abbreviations: mBP=mean blood pressure, HR=heart rate
mPAP=mean pulmonary pressure
PCWP=pulmonary capillary wedge pressure
CI=cardiac index

Table 3. F cell ratio during IPPV and spontaneous breathing

MAC	Cp-group	Ip-group	Sp-group
0	0.95 ± 0.15	0.92 ± 0.24	0.94 ± 0.21
0.5	0.95 ± 0.14	1.16 ± 0.22*	0.94 ± 0.14
1.0	0.97 ± 0.11	1.25 ± 0.32*	1.02 ± 0.12
MAC	Cs-group	Is-group	Ss-group
0	0.93 ± 0.03	0.98 ± 0.04	0.92 ± 0.02
0.5	0.95 ± 0.07	0.97 ± 0.04	0.99 ± 0.07*
1.0	0.95 ± 0.05	0.98 ± 0.02	1.01 ± 0.06*

All values are mean ± SD (n=6 in Cp, Ip, Sp-group and n=5 in Cs, Is, Ss-group)
*$0.01 < P < 0.05$, vs 0 MAC value

the difference was not significant. Subsequently, the CB volume remained unchanged until the end of the experiment. RBC volume and plasma volume also remained unchanged (table 1).

In the Ip group, the CB and RBC volumes remained unchanged throughout the experiment. The plasma volume increased from 54.6 ± 12.5 at 0 MAC to 61.2 ± 18.3 $ml \cdot kg^{-1}$ at 1.0 MAC, but the difference was not significant (table 1).

The CB, plasma and RBC volumes in the SP group remained unchanged (table 1).

In the Cp group, HR, CI, mPAP and PCWP remained unchanged throughout the experiment. In the Ip group, however, mBP, mPAP and PCWP decreased significantly at 0.5 MAC, while HR and CI were unchanged. In the Sp group, mBP decreased significantly at 0.5 and 1.0 MAC, while the other circulatory variables remained unchanged (table 2). Both HR and PCWP were significantly lower in the Ip and Sp groups at each MAC than those in the Cp group.

Arterial blood gases and pH were maintained within the physiological ranges and remained unchanged in all groups. F cell ratio values were similar in all groups ranging from 0.92 to 0.95 at 0 MAC (table 3). The values remained unchanged in the Cp and Sp groups at 0.5 and 1.0 MAC. In the Ip group, on the other hand, they increased from 0.92 ± 0.24 to 1.16 ± 0.22 at 0.5 MAC and to 1.25 ± 0.32 at 1.0 MAC.

Study 2

The CB volume of 79.5 ± 2.3 $ml \cdot kg^{-1}$ at 0 MAC remained essentially unchanged in the Cs group as shown in table 4. The RBC and plasma volumes also remained unchanged throughout the experiment. Similarly the CB volume remained unchanged in the Is group (table 4). Significant increases in the CB and plasma volumes were observed in the Ss group at both 0.5 and 1.0 MAC, but the RBC volume remained unchanged (table 4).

The circulatory variables remained essentially unchanged in all groups throughout the experiment (table 2).

Pa_{CO_2} remained within physiological ranges in all groups during the first period. It remained unchanged in the Cs group, and increased significantly in both the Is and Ss groups during the later period. Nevertheless these values still remained below 46 mmHg (table 5).

The F cell ratio increased significantly at 0.5 and 1.0 MAC in the Ss group. In the Cs and Is groups, however, it remained unchanged throughout the experiment (table 3).

Table 4. Changes in blood volumes during spontaneous breathing

Group	MAC	CB	RBC	Plasma
C	0	79.5 ± 2.3	28.6 ± 2.7	50.9 ± 1.5
	0.5	80.9 ± 1.3	28.3 ± 2.6	52.6 ± 1.7
	1.0	83.1 ± 2.2	29.4 ± 2.5	53.7 ± 1.4
I	0	87.7 ± 8.2	34.7 ± 8.0	53.0 ± 6.0
	0.5	88.7 ± 5.0	34.4 ± 6.2	54.3 ± 6.9
	1.0	91.0 ± 5.9	34.3 ± 6.8	56.7 ± 9.8
S	0	84.4 ± 7.0	31.2 ± 6.8	53.2 ± 3.6
	0.5	91.4 ± 7.7*	33.4 ± 8.6	58.0 ± 4.2*
	1.0	91.4 ± 10.2*	32.6 ± 8.9	58.8 ± 5.7*

All values are mean ± SD ($ml \cdot kg^{-1}$, n=5 in each group)
*$0.01 < P < 0.05$, vs 0 MAC value

Table 5. Pa_{CO_2} during spontaneous breathing

	Cs-group	Is-group	Ss-group
0 MAC	39.0 ± 5.8	38.1 ± 1.3	39.2 ± 3.5
0.5 MAC	44.4 ± 4.5	43.7 ± 0.7*	45.1 ± 1.1*
1.0 MAC	45.6 ± 4.1	44.0 ± 0.3*	45.4 ± 1.5*

All values are mean ± SD (mmHg, n=5 in each group)
*$0.01 < P < 0.05$, vs 0 MAC value

Discussion

The CB volume is defined as an amount of blood existing in the blood vessels and actually circulating through the heart, lungs and peripheral vascular network. A part of the CB volume, however, exists in some vessels isolated from the actual circulation but occasionally communicating with it. Also new red cells are synthesized continuously in the bone marrow and released into the circulation. Therefore, it is not surprising that unexplained changes in the CB volume are observed during surgery and anesthesia when changes in the CB volume are estimated by the balance in surgical blood loss, fluid infusion and blood transfusion.

It has been documented that anesthesia per se influences the CB volume. Price et al.[3] observed that cyclopropane and diethyl-ether decreased the CB volume accompanied by a reduction in the plasma volume. The reduction was probably due to a concomitant increase in catecholamines in blood which constricts minute vessels and, consequently, elevates the venous pressure. Grable et al.[5] reported, however, that halothane increased the plasma volume and, consequently, the CB volume.

Presently it is considered that general anesthesia is more likely to increase the CB volume. The mechanisms of this increase are considered to be as follows:

1) Most of general anesthetics dilate the minute vessels, particularly at the capillary and venular sites, and recruit the pooled blood into the circulation; and
2) The dilatation of the minute vessel decreases the intraluminal pressure and induces influx of the interstitial fluid into the intravascular space.

It has been reported that both isoflurane[9] and sevoflurane[10] produce vasodilation at the clinical depth of anesthesia. Therefore, we anticipated that both anesthetic agents would increase the CB volume as similarly observed during halothane anesthesia[5]. No significant change, however, was observed in the CB volume following either isoflurane or sevoflurane anesthesia in Study 1.

Price et al.[3] noted that the plasma volume decreased markedly in association with increases in the arterial and/or venous pressure. The increase in the intrathoracic pressure caused by intermittent positive pressure ventilation might have suppressed the decrease of venous pressure and might have attenuated the increase in the CB volume produced by isoflurane or sevoflurane anesthesia in Study 1. In fact, Grable's study[5] was done in the patients under spontaneous breathing and a 10% increase in the CB volume was observed. Therefore, our second experiment was carried out under spontaneous breathing. The results indicated that the CB volume increased following sevoflurane anesthesia but not after isoflurane anesthesia.

The release of red cells from depot organs, such as the spleen, liver and skeletal muscles, should be considered as one of the sources of an increase in CB volume. The hematocrit value is quite different in various organs and is relatively high in the depot organs. Therefore, a moderate increase may be observed not only in the CB volume but also in the hematocrit value when those organs constrict. Hausner et al.[12] observed that constriction of the spleen resulted in an increase in the RBC count in the blood. Nakajo et al.[4] reported that halothane released blood from the depot organs and resulted in an increase in the CB volume. Physiological and pharmacological studies in which changes in the CB volume or RBC volume were observed have been done mostly in splenectomized animals. Our studies, however, were performed in intact dogs. We attempted to observe changes in the CB volume under conditions much more closely simulating a clinical situation. Nevertheless the RBC volume remained unchanged and, furthermore, the F cell ratio did not decrease throughout the experiment. These results seem to indicate that the anesthetics tested in this study had no effect on the spleen.

The whole body hematocrit value, which is calculated by dividing the RBC volume by the CB volume, is usually less than the hematocrit value in the blood obtained from the large vessels. The ratio of these two hematocrit values is called the F cell ratio, and this is usually 0.91 in normal subjects[13]. Heath et al.[14] observed that the F cell ratio decreased in patients into whom stored blood was transfused but did not decrease in those into whom dextran solution was infused. They found that the decrease in the F cell ratio was closely related to concomitant vasoconstriction. Nakanishi[15] observed that the F cell ratio decreased following hemorrhagic shock and recovered to its initial level following treatment with hydroxyethyl starch solution. Nakajo et al.[16] also observed that the F cell ratio decreased during hemorrhagic shock, and that it was restored by administration of phenoxybenzamine. These studies noted that the restoration of F cell ratio was accompanied by a concomitant improvement in microcirculation. In this study, F cell ratio increased significantly following isoflurane anesthesia under positive pressure ventilation and following sevoflurane anesthesia under spontaneous breathing. It was concluded that considerable vasodilation, particularly in minute vessels, might occur under the above conditions.

Hypercapnia caused by respiratory depression during general anesthesia should be considered as one of the factors which might cause vasodilatation. Doi et al.[17] reported that a compensatory increase in the respiratory rate during sevoflurane anesthesia was not enough to prevent a decrease in minute volume with increasing depth of anesthesia. In this study, Pa_{CO_2} increased significantly in correspondence with the depth of anesthesia in both Is and Ss groups. Nevertheless Pa_{CO_2} did not exceed 46 mmHg in any of the groups throughout the experiment. Therefore, it was concluded that the CB volume was increased by the sevoflurane anesthesia per se and not by hypercapnia. Present results in comparison between study 1 and 2 indicates that the different respiratory conditions during either basal anesthesia or additional isoflurane anesthesia caused little change in the CB volume. During sevoflurane anesthesia, however, positive pressure ventilation markedly suppressed the increase in CB volume noted under spontaneous breathing.

In conclusion, the plasma volume did not changed significantly following isoflurane or sevoflurane anesthesia under intermittent positive pressure ventilation and increased definitely following the sevoflurane anesthesia under the spontaneous breathing. It is strongly suggested, therefore, that intermittent positive pressure ventilation, which might increase the intrathoracic pressure and concomitantly the venous pressure, might suppress the increase in the CB volume, particularly during sevoflurane anesthesia.

Acknowledgments: The authors greatly appreciate Takayuki Sakai, Associate Professor of Anesthesiology, and the other medical staff for their appropriate advice. The authors also thank Miss Masumi Miyake, Research Assistant, for her assistance in this study.

(Received Apr. 27, 1992, accepted for publication Jan. 28, 1993)

References

1. Gibson JG, Branch CD: Blood volume changes during surgical procedures. Surg, Gynec & Obst 65:741–747, 1937
2. Stewart JD, Rourke GM: Changes in blood and interstitial fluid resulting from surgical operation and ether anesthesia. J Clin Invest 17:413–416, 1938
3. Price HL, Helrich M, Conner EH: A relation between hemodynamic and plasma volume alterations during general anesthesia in man. J Clin Invest 35:125–131, 1956
4. Nakajo N, Matsumoto H, Takaori M: The effect of anesthetics (halothane and diethylether) on blood volume and flow of various organs in the dog. Masui 29:641–647, 1980
5. Grable E, Finck AJ, Abrams AL, et al: The effect of cyclopropane and halothane on the blood volume in man. Anesthesiology 23:828–831, 1962
6. Steffey EP, Howland D Jr: Isoflurane potency in the dog and cat. Am J Vet Res 38:1833–1836, 1977
7. Kazama T, Ikeda K: Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. Anesthesiology 68:435–437, 1988
8. Guyton AC, Jones CE, Coleman TG: Cardiac output and its regulation, Circulatory physiology 2nd. edition. Philadelphia, WB Saunders, 1973, pp. 11
9. Stevens WO, Cromwell TH, Halsey MJ, et al: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 35:8–16, 1971
10. Akazawa S, Shimizu R, Kasuda H, et al: Effects of sevoflurane on cardiovascular dynamics, coronary circulation and myocardial metabolism in dogs. J Anesth 2:227–241, 1988
11. Gibson JG, Seligman AM, Peacock WC, et al: The distribution of red cells and plasma in large and minute

vessels of the normal dog, determined by radioactive isotopes of iron and iodine. J Clin Invest 25:848–857, 1946
12. Hausner E, Essex HE, Mann FC: Roentgenologic observations of the spleen of the dog under ether, sodium amytal, pentobarbital sodium and pentothal sodium anesthesia. Am J Physiol 121:387–391, 1938
13. Gregersen MI, Rawson RA: Blood volume Physiol Rev 30:307–342, 1959
14. Heath ML, Vickers MD, Dunlap D: A comparison of macrodex and stored blood as replacement for blood loss during planned surgery. II: Changes in peripheral haematocrit and whole body/large vessel haematocrit ratio. Br J Anaesth 41:816–820, 1969
15. Nakanishi Y: Changes of distribution of circulating red cells following administration of hydroxyethyl starch and crystalloid solution in hemorrhagic shock. Masui 21:771–780, 1972
16. Nakajo N, Takaori M: Changes in F cell ratio following hemorrhagic shock – Treatment with phenoxybenzamine-Clin Physiol 6:65–72, 1976 (Japanese)
17. Doi M, Ikeda K: Respiratory effects of sevoflurane. Anesth Analg 66:241–244, 1987