J Anesth (1995) 9:247–251

Journal of
Anesthesia

The effects of isoflurane and sevoflurane on the left ventricular end-systolic pressure-volume relation in dogs

SUMIO HOKA, MICHIKO SATO, and SHOSUKE TAKAHASHI

The Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812 Japan

Abstract: The influence of two inhalational anesthetics, isoflurane and sevoflurane, on the end-systolic pressure-volume relations (ESPVR) of the left ventricle (LV) in situ was investigated in open-chest dogs anesthetized with α-chloralose. The LV volume was measured by a conductance catheter while the LV pressure was measured by a tip-micromanometer. The end-systolic elastance (Ees) of the LV was calculated as the slope of ESPVR which was elicited when the inferior vena cava was transiently occluded. The dogs were randomly assigned to two groups, receiving either 1.3% and 2.6% isoflurane ($n = 6$) or 2.3% and 4.6% sevoflurane ($n = 6$), which are equivalent to 1 and 2 MAC of isoflurane or sevoflurane, respectively. Both isoflurane and sevoflurane produced dose-dependent decreases in the cardiac output to a similar degree. Isoflurane and sevoflurane caused equivalent decreases in Ees of 23% and 16% at 1 MAC, and 48% and 41% at 2 MAC, respectively. Dobutamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced a simultaneous restoration of Ees and recovery of the cardiac output at 1 and 2 MAC of both isoflurane and sevoflurane. We thus conclude that the depressant effect of sevoflurane on cardiac contractility is almost identical to that of isoflurane in the dog, and they are both reversed by the use of a low dose of dobutamine.

Key words: Cardiac contractility, Inhalational anesthetic, Conductance catheter, Dobutamine, Ees

Introduction

The currently used volatile anesthetics such as isoflurane and sevoflurane have been shown to exert cardiac depression in a dose-related manner [1–4]. The cardiac depressant effects have been demonstrated in the isolated myocardium, isolated whole hearts, and in situ hearts from animals and humans [1,4,5] based on several indices of cardiac contractility. The slope of the left ventricular (LV) end-systolic pressure-volume relations (ESPVR), often referred to as end-systolic elastance (Ees), has been considered useful for understanding cardiac performance under various loading and contractile conditions, since Ees has been found to be sensitive to inotropic interventions and also to be practically independent of loading conditions [6,7].

The Ees is obtained by combining intraventricular pressure with volume. Most of the studies on Ees have been performed in the isolated canine ventricle because of the difficulty in accurately measuring volume. Otherwise, they have employed volume estimation by means of a crystal sonomicrometer, echocardiography, or ventriculography in the heart in situ. The development of a conductance catheter, however, has now made it possible to measure the LV volume in the heart in situ, allowing the study of pressure-volume relations in the intact or open-chest animal and in humans [8,9]. The accuracy of this method has been shown to be comparable to that of balloon-mediated volume measurement in the isolated heart [10].

The purpose of this study was to examine the effects of isoflurane and sevoflurane on Ees using an in situ conductance catheter in the canine heart, and also to investigate the effects of dobutamine on these anesthetic-induced changes in Ees.

Methods

General preparation

Experiments were performed on 12 mongrel dogs with body weights ranging from 15 to 19 kg. This study was approved by our institutional animal investigation committee. Anesthesia was induced with thiopental (20 $mg \cdot kg^{-1}$) and maintained with an infusion of α-chloralose (10 $mg \cdot kg^{-1} \cdot h^{-1}$). The trachea was intubated, and a constant-volume intermittent positive-pressure ventilation at a rate of 14 breaths·min^{-1} with a mixture of oxygen and nitrogen was instituted to produce

Address correspondence to: S. Hoka
Received for publication on July 18, 1994; accepted on January 28, 1995

normocapnia and to keep the arterial oxygen tension at approximately 150 mmHg. The electrocardiogram (lead II) was monitored continuously. Body temperature was maintained between 37°C and 38°C by external warming. The arterial blood pressure was measured by means of a catheter placed in the aorta through the right axillary artery. A catheter was placed in the inferior vena cava through the femoral vein for the administration of fluids and drugs. A transit time flow probe (Transonic Systems, New York, NY, USA) was placed on the ascending aorta to measure the aortic blood flow. A catheter-tip manometer (Millar Instruments, Houston, TX, USA) was placed in the left ventricular (LV) cavity by retrograde insertion through the right carotid artery via the aortic valve to measure the LV pressure. A vascular ligature was placed around the intrathoracic inferior vena cava (IVC) to rapidly alter left ventricular preload by occluding the blood flow.

A conductance catheter was introduced into the LV through the apex to measure the LV volume. A full description of the principles and technique of the Baan volume catheter method has appeared elsewhere [8,9]. Briefly, the method is based on the measurement of the time-varying electrical conductance of five segments of blood in the LV, from which the total LV volume is calculated. The conductance catheter has eight platinum electrodes and generates an electrical field (20 kHz, 0.07 mA) in the LV from electrodes at the apex and at the aortic valve. The sensing electrodes, which are evenly distributed along the catheter, measure the conductance between the electrode pairs located within the LV. The conductances are summed and converted to the volume using a signal coordinator, Sigma 5 (Leycom, Oegstgeest, The Netherlands). The volume of the LV, V(t), is computed as

$$V(t) = (1/\alpha)\,[L^2 \varrho G(t) - \alpha Vc]$$

where G(t) is the sum of the five segmental conductances, α is a unitless constant, L is the distance between the sensing electrodes, ϱ is the blood resistivity, and αVc is the volume correction due to parallel conductance outside the LV blood pool.

In practice, L and ϱ are set on the Sigma 5 unit. To determine αVc, 3 ml of hypertonic saline (5% NaCl) was injected as a bolus into the main pulmonary artery through a previously placed catheter causing a transient increase in the measured volume, G(t), without significantly altering the cavity volume. The calculation of parallel conductance by the saline method assumes that V(t) remains constant and that the ejection fraction does not change.

Assessment of Ees

To rule out the influence of respiration and variations in lung volume on LV volume and conductance, all data were collected during periods of suspended respiration. Ventilation was stopped at end-expiration. Each set of isochronic points of the LV volume, V(t), and LV pressure, P(t), was digitized and displayed on a microcomputer (PC 9801 RX, NEC, Tokyo, Japan) at a sample frequency of 333 Hz.

Ees was determined during a quick decrease in the venous return produced by a transient occlusion of IVC. The duration of the occlusion was about 10 s, and the pressure-volume relation was obtained during the initial 5 – 7 s. This occlusion was considered not to affect the level of sympathetic tone because the determination of the pressure-volume relation was completed at an early stage of the occlusion and the heart rate remained unchanged during this procedure. This procedure was repeated at least twice to obtain the pressure-volume relation. The end-systole was defined as the instantaneous peak of the ratio of the LV pressure to volume. The pressure-volume data points at the end-systole during caval occlusion were fitted by a linear regression using the least-squares method.

Experimental protocol

After the control measurements, the animals received either isoflurane or sevoflurane. Six dogs received isoflurane and the other six dogs received sevoflurane at equivalent concentrations of 1 and 2 MAC for each agent. For each anesthetic agent evaluated, the order of concentration was randomized during each experimental procedure. The anesthetic concentrations evaluated in each animal were 1.3% and 2.6% for isoflurane and 2.3% and 4.6% for sevoflurane, which are equal to 1 and 2 MAC for each anesthetic, respectively [2,11].

Twenty minutes were allowed for a steady cardiovascular state to be achieved after each change in the inspired concentration. Thereafter, dobutamine was infused at three doses of 3, 6, and 9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at each anesthetic concentration. Vaporizers were calibrated over the appropriate range of concentrations using an anesthesia/respiratory gas monitor (Raman Scattering Gas Monitor, Rascal, Albion Instruments, Salt Lake City, UT, USA). The ability of the vaporizer to maintain these concentrations over the time-course for the study was also established.

Statistical analysis

All the data are shown as the mean ± SD, but in figures they are shown as the mean ± SE for simplicity. The differences in the hemodynamic variables were tested by a repeated-measures analysis of variance. If a significant effect was present, inter-group comparisons were performed using Scheffe's test. The percent changes from the baseline values were tested by the paired *t*-test. $P < 0.05$ was considered to be statistically significant.

Results

The cardiac output; Ees; mean arterial pressure (MAP); and heart rate in the absence of sevoflurane or isoflurane (0 MAC), at 1 MAC (1.3% for isoflurane and 2.3% for sevoflurane), and 2 MAC (2.6% for isoflurane and 4.6% for sevoflurane) for the two anesthetics are all summarized in Table 1. Isoflurane and sevoflurane produced dose-related decreases in the Ees and cardiac output. The Ees decreased by 23% ($P < 0.05$) and 48% ($P < 0.05$) at 1 and 2 MAC of isoflurane and by 16% (n.s.: not significantly) and 41% ($P < 0.05$) at 1 and 2 MAC of sevoflurane, respectively (Table 1 and Figs. 1 and 2). The cardiac output decreased by 29% ($P < 0.05$) and 35% ($P < 0.05$) at 1 and 2 MAC of isoflurane and by 20% ($P < 0.05$) and 42% ($P < 0.05$) at 1 and 2 MAC of sevoflurane, respectively. The MAP decreased by 25% (n.s.) and 54% ($P < 0.05$) and 1 and 2 MAC of isoflurane and by 10% (n.s.) and 28% ($P < 0.05$) at 1 and 2 MAC of sevoflurane, respectively. The heart rate tended to decrease, but not significantly, at each MAC of isoflurane and sevoflurane. The systemic vascular resistance did not significantly change at each MAC of both anesthetics. The decreases in these variables were not significantly different between the two anesthetics at comparable MAC values.

Figures 1 and 2 show the effects of dobutamine on the Ees, cardiac output, MAP, and heart rate during isoflurane and sevoflurane administration, respectively. Dobutamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced a restoration of Ees simultaneously with a recovery of the cardiac output at 1 and 2 MAC of both the isoflurane (Fig. 1) and sevoflurane (Fig. 2) groups. Dobutamine 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced a significant increase in the MAP at 1 and 2 MAC of isoflurane and 1 MAC of sevoflurane, as compared with those in the absence of dobutamine. The heart rate significantly increased during dobutamine 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 1 and 2 MAC of both isoflurane and sevoflurane, as compared with those in the absence of dobutamine. The systemic vascular resistance was not significantly altered by dobutamine at each MAC of both anesthetics.

Discussion

The major findings in this study are that isoflurane and sevoflurane produced a dose-related depression of Ees to a similar degree, and that a low dose of dobutamine effectively reversed the depressed Ees with a simultaneous recovery of cardiac output.

The depressant effects of isoflurane and sevoflurane on cardiac performance have been previously shown in a study by Bernard et al. [1]. They demonstrated in chronically instrumented dogs dose-dependent decrease in the left ventricular dP/dt by approximately 40% and 60% at 1.2 MAC and 2 MAC of both anesthetics, respectively, which were compatible with out data which indicated that isoflurane and sevoflurane at 2 MAC decreased Ees by 50% and 60%, respectively. Conzen et al. [3] also reported that equipotent hemodynamic concentrations of sevoflurane and isoflurane, which produced a mean arterial pressure of 70 mmHg, had similar effects on the depression of the cardiac output and stroke volume in rats.

We used Ees as an index of cardiac contractility. Since the preload and afterload are likely to change during isoflurane and sevoflurane anesthesia, the indices which are easily influenced by loading conditions, such as stroke volume, maximum dP/dt, or ejection fraction, cannot accurately reflect the contractile state during anesthesia [12]. Ees is considered to be relatively insensitive to changes in the preload and afterload [6,7]. Therefore, we chose to use the Ees as an indicator of contractility.

To obtain the Ees, it is necessary to combine the measurements of the left ventricular pressure and volume simultaneously. We used a conductance catheter

Table 1. The changes in cardiac output (CO), end-systolic elastance (Ees), the mean arterial poressure (MAP), heart rate (HR), and systemic vascular resistance (SVR) for the control, 1 MAC, and 2 MAC of isoflurane (ISO) and sevoflurane (SEVO)

		Control	1 MAC	2 MAC
CO	ISO	138 ± 41	96 ± 29*	78 ± 27*#
($ml \cdot kg^{-1} \cdot min^{-1}$)	SEVO	118 ± 25	93 ± 17*	65 ± 12*#
Ees	ISO	5.1 ± 1.7	4.0 ± 1.7*	2.5 ± 1.7*#
($ml \cdot mmHg^{-1}$)	SEVO	4.7 ± 2.0	4.1 ± 1.5	2.4 ± 0.7*#
MAP	ISO	79 ± 10	59 ± 15	36 ± 10*#
(mmHg)	SEVO	95 ± 25	80 ± 20	55 ± 20*
HR	ISO	119 ± 17	113 ± 12	99 ± 12
($beats \cdot min^{-1}$)	SEVO	126 ± 29	119 ± 24	107 ± 25
SVR	ISO	0.61 ± 0.17	0.67 ± 0.25	0.47 ± 0.34
($mmHg \cdot kg \cdot min \cdot ml^{-1}$)	SEVO	0.80 ± 0.17	0.86 ± 0.20	0.85 ± 0.29

$n = 6$ for ISO and $n = 6$ for SEVO. Values are the means ±SD.
* $P < 0.05$ vs. control; # $P < 0.05$ vs. 1 MAC.

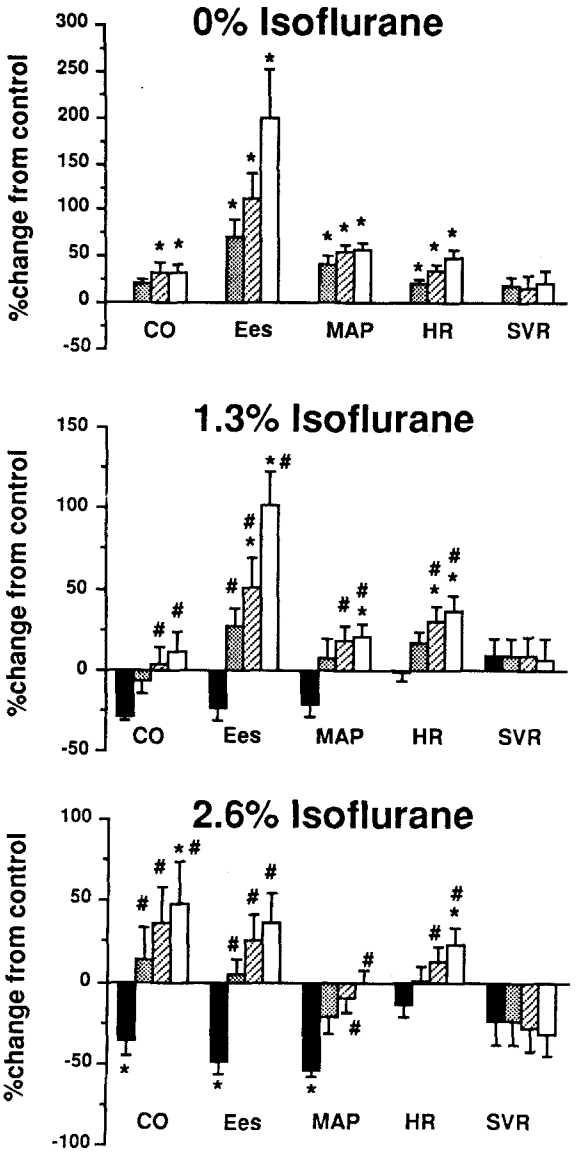

Fig. 1. Effects of dobutamine infusion on hemodynamics in the absence of isoflurane (0% isoflurane) and during the administration of 1.3% (1 MAC) and 2.6% (2 MAC) of isoflurane. The CO and Ees decreased by 29% and 23%, and 35% and 48% at 1 and 2 MAC of isoflurane, respectively. Dobutamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced a restoration of Ees simultaneously with a recovery of the cardiac output at both 1 and 2 MAC of isoflurane. *CO*, cardiac output; *Ees*, end-systolic elastance; *MAP*, mean arterial pressure; *HR*, heart rate; *SVR*, systemic vascular resistance. Data are shown as mean ± SE. *Closed bars*, without dobutamine; *shaded bars*, dobutamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *hatched bars*, dobutamine 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *open bars*, dobutamine 9 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $^{*}P < 0.05$ *vs* no dobutamine at 0% isoflurane; $^{\#}P < 0.05$ *vs* no dobutamine at each % isoflurane

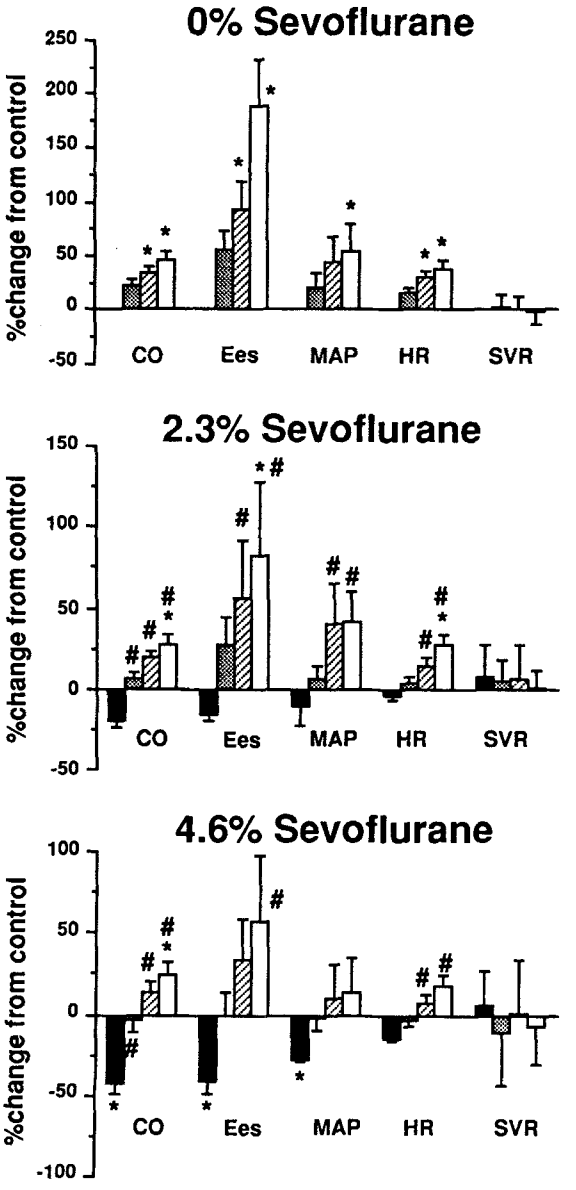

Fig. 2. Effects of dobutamine infusion on hemodynamics in the absence of sevoflurane (0% sevoflurane) and during the administration of 2.3% (1 MAC) and 4.6% (2 MAC) of sevoflurane. The CO and Ees decreased by 20% and 16%, and 42% and 41% at 1 and 2 MAC of isoflurane, respectively. Dobutamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced a restoration of Ees simultaneously with a recovery of the cardiac output at both 1 and 2 MAC of isoflurane. Data are shown as means ± SE. *Closed bars*, without dobutamine; *shaded bars*, dobutamine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *hatched bars*, dobutamine 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$; *open bars*, dobutamine 9 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $^{*}P < 0.05$ *vs* no dobutamine at 0% sevoflurane; $^{\#}P < 0.05$ *vs* no dobutamine at each % sevoflurane

introduced by Baan et al. [8] to assess the Ees. The conductance catheter can measure LV volume continuously by measuring intraventricular conductance and provide real-time pressure-volume loops. Although there are potential sources of error in the measurement of volume by the conductance catheter such as a mismatch between the length of the catheter and the ventricular long axis, as well as a possible bending of the

catheter during contraction, this method has been validated in both experimental [8,13,14] and clinical studies [8,9].

Using a conductance catheter, we found that isoflurane and sevoflurane could decrease Ees to a similar degree, indicating a comparable decrease in cardiac contractility. Our results also show that dobutamine $3\,\mu g \cdot kg^{-1} \cdot min^{-1}$ could reverse the depressed cardiac contractility simultaneously with the recovery of the cardiac output (Figs. 1 and 2). The major mechanisms by which volatile anesthetics depress the myocardial contractility include a depression of the slow-channel-mediated Ca^{2+} entry and alteration of the Ca^{2+} uptake and release by the sarcoplasmic reticulum, which resulted in a reduction of the Ca^{2+} available to the contractile elements [15,16]. The fact that dobutamine can reverse the isoflurane- and sevoflurane-induced depression of cardiac contractility may suggest that the stimulation of the β-receptor-mediated Ca^{2+} channel can thus overcome the reduction in the Ca^{2+} availability produced either directly or indirectly by both agents.

Our results also show that several other cardiovascular effects of sevoflurane, including a slight but not significant decrease in the heart rate, closely paralleled that of isoflurane. In contrast, Bernard et al. [1], using chronically instrumented dogs, reported a greater increase in the heart rate during sevoflurane than isoflurane. However, previous studies have shown various results on the heart rate [3,4,17] during the administration of isoflurane and/or sevoflurane anesthesia. Therefore, the effects of these anesthetics on the heart rate may thus depend on the experimental conditions.

Our experiments were performed in the presence of an α-chloralose-based anesthetic. We do not assume that α-chloralose-based anesthesia had any particular pronounced effect on the canine cardiovascular system since α-chloralose has only a minor effect on hemodynamics [18]. Our results of the hemodynamic variables including Ees under α-chloralose-based anesthesia were also in good agreement with those obtained in conscious dogs [9].

In summary, our study in which Ees was used as an index of cardiac contractility by means of a conductance catheter, indicates that isoflurane and sevoflurane are cardiodepressive agents in vivo and that have almost identical negative inotropic effects at the given concentrations. Our findings also indicate that the circulatory depression observed during isoflurane and sevoflurane anesthesia may be counteracted by increasing the myocardial contractility.

Acknowledgments. We are indebted to Taisho Biomed Instruments, Osaka, Japan, for the instrumental services. This study was supported by a Grant-in-Aid for Scientific Research (05671269), from The Ministry of Education, Science and Culture, Japan.

References

1. Bernard J-M, Wouters PF, Doursout M-F, Florence B, Chelly JE, Merin RG (1990) Effects of sevoflurane and isoflurane on cardiac and coronary dynamics in chronically instrumented dogs. Anesthesiology 72:659–662
2. Kazama T, Ikeda K (1988) Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. Anesthesiology 68:435–437
3. Conzen PF, Vollmar B, Habazettl H, Frink EJ, Peter K, Messmer K (1992) Systemic and regional hemodynamics of isoflurane and sevoflurane in rats. Anesth Analg 74:79–88
4. Kasuda H, Akazawa S, Shimizu R (1990) The echocardiographic assessment of left ventricular performance during and after halothane anesthesia. J Anesth 4:295–302
5. Hatakeyama N, Ito Y, Momose Y (1993) Effects of sevoflurane, isoflurane, and halothane on mechanical and electrophysiologic properties of canine myocardium. Anesth Analg 76:1327–1332
6. Sagawa K, Suga H, Shoukas AA, Bakalar KM (1977) End-systolic pressure/volume ratio: a new index of ventricular contractility. Am J Cardiol 40:748–753
7. Carabello BA, Spann JF (1984) The uses and limitations of end-systolic indexes of left ventricular function. Circulation 69:1058–1064
8. Baan J, Van Der Velde ET, De Bruin HG, Smeenk GJ, Koops J, Van Duk AD, Temmerman D, Senden J, Buis B (1984) Continuous measurement of left ventricular volume in animals and humans by conductance catheter. Circulation 70:812–823
9. Asanoi H, Ishizaka S, Kaneyama T, Sasayama S (1994) Neural modulation of ventriculoarterial coupling in conscious dogs. Am J Physiol 266:H741–H748
10. Burkhoff D, Van Der Velde ET, Kass D, Baan J, Maughan L, Sagawa K (1985) Accuracy of volume measurement by conductance catheter in isolated, ejecting canine hearts. Circulation 72:440–447
11. Steffy EP, Howland D (1977) Isoflurane potency in the dog and cat. Am J Vet Res 38:1833–1836
12. Mahler F, Ross J, O'Rourke RA, Covell JW (1975) Effects of changes in preload, afterload and inotropic state on ejection and isovolumic phase measures of contractility in the conscious dog. Am J Cardiol 35:626–634
13. Burkhoff D, Van der Velde D, Kass D, Baan J, Maughan WL, Sagawa K (1985) Accuracy of volume measurement by conductance catheter in isolated, ejecting canine hearts. Circulation 72:440–447
14. Kass DA, Yamazaki T, Burkoff D, Maughan WL, Sagawa K (1986) Determination of left ventricular end-systolic pressure-volume relationships by the conductance (volume) catheter technique. Circulation 73:586–595
15. Housmans PR. (1990) Negative inotropy of halogenated anesthetics in ferret ventricular myocardium. Am J Physiol 259:H827–H834
16. Price HL, Ohnishi ST (1980) Effects of anesthetics on the heart. Fed Proc 39:1575–1579
17. Frink EJ Jr, Morgan S, Coetzee A, Conzen P, Brown BR Jr (1992) The effects of sevoflurane, halothane, enflurane, and isoflurane on hepatic blood flow and oxygenation in chronically intrumented greyhound dogs. Anesthesiology 76:85–90
18. Greisheimer EM (1965) The circulatory effects of anesthetics. In: Hamilton WF, Dow P (eds) Handbook of Physiology. Circulation. Section 2, Vol. III. American Physiological Society, Washington, DC, pp 2477–2510