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Comparison of Effects of Sevoflurane/Nitrous Oxide and Enflurane/Nitrous Oxide on Myocardial Contractility in Humans

Load-independent and Noninvasive Assessment with Transesophageal Echocardiography

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Background: **Few studies have been reported on the direct depressive effects of sevoflurane on myocardial contractility in humans. Direct assessment of contractile state is possible by examining the slope of left ventricular end-systolic wall stress (LVESWS) *versus* velocity of circumferential fiber shortening with heart rate corrected (Vcfc) relationship with echocardiography. Using this contractile index, the effects of sevoflurane/nitrous oxide were compared with that of enflurane/nitrous oxide on myocardial contractility in humans.**

Methods: **Twenty-eight subjects were studied during either sevoflurane/nitrous oxide or enflurane/nitrous oxide anesthesia. Systolic, diastolic, and mean arterial blood pressure, heart rate, and transesophageal echocardiographic data were determined at 0.9 MAC and 1.35 MAC of sevoflurane or enflurane, both with 60% N_2O, and at 1.6 MAC of sevoflurane with 60% N_2O. Furthermore, another 28 awake subjects were studied with transthoracic echocardiography to examine the contractile state at awake state, and echocardiograms, heart rate, and arterial blood pressure were recorded.**

Results: **Heart rate did not changed significantly in either group. Enflurane/nitrous oxide produced significantly greater decrease in arterial blood pressure than did sevoflurane/nitrous oxide. The Vcfc at each anesthetic dose in both anesthetic groups was significantly less than that in the awake subjects group. Sevoflurane/nitrous oxide produced no significant change in Vcfc at 1.5 MAC, whereas enflurane/nitrous oxide caused significant dose-related decrease in Vcfc. Vcfc produced by sevoflurane/nitrous oxide was significantly greater than that produced by enflurane/nitrous oxide. There was no significant difference in LVESWS (index of afterload) between the groups. With respect to the LVESWS-Vcfc relationship, myocardial contractility was significantly depressed in both the sevoflurane and the enflurane groups compared to the awake subjects group. However, myocardial contractility produced by enflurane/nitrous oxide was significantly less than that by sevoflurane/nitrous oxide at equiMAC concentration.**

Conclusions: **The results of the present study suggest that sevoflurane has fewer depressant effects on cardiac function than does enflurane. (Key words: Anesthetic, volatile: enflurane; sevoflurane. Heart: contractility. Measurement technique: transesophageal echocardiography.)**

SEVOFLURANE[1,2] is widely used clinically in Japan and undergoing clinical studies in the United States. Several studies on the cardiovascular effects of sevoflurane in humans[2] and animals[3–5] showed sevoflurane to induce myocardial depression, as do other volatile anesthetics. The negative inotropic action of sevoflurane was shown indirectly by hemodynamic changes or load-dependent contractile indexes influenced by changes in preload and afterload. However, few studies have been conducted to examine the direct effect of sevoflurane on myocardial contractility in humans. With the increasing clinical use of sevoflurane, assessment of its effects on contractility should be made. A new contractile index relationship—with echocardiography—left ventricular end-systolic wall stress (LVESWS) *versus* velocity of circumferential fiber shortening with heart rate corrected (Vcfc) was reported recently by Colan *et al.*[6] In their study, the slope of LVESWS-Vcfc relationship was used as the contractile index, and this relationship was found to be inversely linear. In the assessment of the slope of the LVESWS-Vcfc relationship, Vcfc was higher for any given level of LVESWS in the increased inotropic state and lower for any given level of LVESWS in the

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depressed contractile state. Furthermore, Colan *et al.*[6] found that the LVESWS-Vcfc relationship sensitive to an altered contractile state was independent of preload and incorporated both afterload and heart rate (HR) and that load-independent analysis of contractile state could be ascertained by examining this relationship noninvasively with no change in loading conditions. The present study was conducted to compare the effects of sevoflurane/nitrous oxide and enflurane/nitrous oxide on myocardial contractility as evaluated by this contractile index in humans.

Materials and Methods

Twenty-eight ASA physical status 1 or 2 subjects, 30–58 yr of age, were studied before elective surgery after obtaining informed consent from each subject. This study was approved by the Department Medical Ethical Committee. Patients with clinically significant pulmonary, cardiovascular, hepatic, renal, hematologic, neurologic, or metabolic diseases were excluded from participation in the study. Also excluded were patients who chronically received medications.

The patients were divided randomly into two groups. The sevoflurane group consisted of 14 patients anesthetized with sevoflurane and 60% N_2O, and the enflurane group consisted of 14 patients anesthetized with enflurane and 60% N_2O. A patient age range from 30 to 59 yr was chosen because the 1.71% used as the MAC of sevoflurane[7] in this study was determined in this particular range. All patients received 20 mg famotidine, 0.5 mg atropine, and 50 mg hydroxyzine hydrochloride intramuscularly 45 min before the induction of anesthesia. Anesthesia was induced with 4–5 mg/kg thiopental, 0.15 mg/kg vecuronium bromide intravenously, 6 l/min oxygen, and either 2% sevoflurane or 2% enflurane. After induction of anesthesia, ventilation was manually controlled *via* a face mask for 3–5 min until tracheal intubation. Following tracheal intubation, anesthesia was maintained with oxygen and end-tidal 1.5% sevoflurane with 60% N_2O (total 1.5 MAC) in the sevoflurane group and end-tidal 1.5% enflurane with 60% N_2O (total 1.5 MAC) in the enflurane group. Respiratory rate and tidal volume were controlled so that end-tidal carbon dioxide would be maintained between 35 and 40 mmHg. Inspired and end-tidal anesthetic concentration and end-tidal carbon dioxide were measured and adjusted with a calibrated infrared multigas anesthetic gas analyzer (Capnomac, Datex, Finland) and quadrupole mass spectrometer (MGA-2000SP, Airspec, United Kingdom) frequently to keep end-tidal concentrations at predetermined levels. Body temperature and lead 2 of the electrocardiogram were monitored continuously. Systolic, diastolic, and mean arterial blood pressures (ABP) were measured by automated oscillometry (CBM7000, Colin, Japan) every 2.5 min from before induction of anesthesia to the end of the study. Lactated Ringer's solution was infused intravenously at 2–4 $ml \cdot kg^{-1} \cdot h^{-1}$ throughout the study. After tracheal intubation, a gastroscope tipped with a 5-MHz ultrasonic transducer (Hewlett Packard, Andover, MA) was inserted into the esophagus and positioned behind the left ventricle to obtain a short axis view at the level of the midpapillary muscles. The transducer was connected to an ultrasonograph (77020AC, Hewlett Packard) focused to 12 cm. Two-dimensional echocardiograms were recorded on beta videotapes while ABP and HR measurements were being obtained.

After the end-tidal anesthetic concentration had reached 1.5% sevoflurane or enflurane and was maintained constant for 15 min, data for HR, ABP, and transesophageal echocardiography were obtained. End-tidal concentration of sevoflurane or enflurane was then increased to 2.3% (total 1.95 MAC with 60% N_2O) and held constant for 15 min. The measurements were repeated. Finally, in the sevoflurane group only, end-tidal concentration of sevoflurane was increased to 2.8% (total 2.2 MAC with 60% N_2O) and was held constant for 15 min, and the measurements were repeated. Since potentially dangerous decreases in ABP often were observed at 2.8% enflurane with 60% N_2O (total 2.2 MAC) in a pilot study for the present study, administration of enflurane at that dose has not been done in the present study because of ethical considerations. The anesthetic concentrations were administered, for safety, by increasing the concentration of inhaled anesthetics step by step in both groups. A manipulation of the transesophageal echocardiography (TEE) probe only at the time of recording ends within approximately 60 s to prevent hemodynamic reaction by esophageal stimulation with the TEE probe as much as possible. A left ventricular short axis view at the level of the midpapillary muscles was confirmed at each recording of an echocardiogram. Rate pressure products (RPP) were determined by the following standard formula:

$$RPP\ (beats \cdot mmHg) = heart\ rate \cdot systolic\ ABP.$$

Echocardiographic and hemodynamics data were analyzed after completion of surgery.

The examination with transthoracic echocardiography was made in a different awake subjects group after obtaining informed consent. This additional study was conducted to demonstrate the myocardial depression produced by sevoflurane/nitrous oxide or enflurane/nitrous oxide anesthesia compared to the awake state. This group consisted of 28 ASA 1 or 2 subjects aged 25–66 yr. Subjects with clinically significant systemic diseases or who chronically received medications were excluded. A Hewlett-Packard ultrasound imaging system with a 3.5-MHz transducer was used for transthoracic echocardiography. All subjects were recumbent. The transducer was positioned in the fourth or fifth intercostal space along the left sternal border and was directed posteriorly to obtain left ventricular short axis view at the midpapillary muscle level. Two-dimensional echocardiograms were recorded on videotapes while ABP and HR were measured.

Transesophageal Echocardiographic Analysis

In both transesophageal and transthoracic echocardiography, echocardiographic analysis was performed as follows. We traced the left ventricular short-axis endocardium at end-diastole to obtain end-diastolic area (LVEDA) and end-diastolic circumference (LVEDC) and traced endocardium and epicardium at end-systole to obtain end-systolic area (LVESA) with papillary muscles included, end-systolic circumference of endocardium (LVESC), and the total area (At) enclosed by the left ventricular epicardium and right side of the septum. Leading-leading methods were used to trace the endocardium and epicardium.[8] Left ventricular ejection time (LVET) was determined using the number of frames (one every 33 ms) from end-diastole to end-systole. Ventricular end-diastole was identified by the peak of the R wave and end-systole by the minimal left ventricular dimension. The mean of three consecutive beats at end-expiration was used for analysis. Each echocardiogram was analyzed by 77020AC ultrasonograph system. Systolic fractional area change (FAC) and systolic circumferential fiber shortening (CFS) were determined as follows[9]:

$$\text{FAC (\%)} = (\text{LVEDA} - \text{LVESA})/\text{LVEDA} \cdot 100,$$

$$\text{CFS (\%)} = (\text{LVEDC} - \text{LVESC})/\text{LVEDC} \cdot 100.$$

We determined LVESWS (index of afterload) and Vcfc as follows[6,10]:

$$\text{LVESWS} = (1.35 \cdot \text{Psys} \cdot \text{LVESA})/(\text{At} - \text{LVESA}),$$

where LVESWS is in g/cm^{-2}, systolic ABP and cuff systolic blood pressure are in mmHg, LVEDA and LVESA are in cm^2, and 1.35 is a factor to convert mmHg to g/cm^{-2}.[10]

$$\text{Vcfc} = (\text{LVEDC} - \text{LVESC})/(\text{LVEDC} \cdot \text{LVET}) \cdot (\text{RR})^{1/2}$$

$$= \text{CFS (\%)} \cdot (\text{RR})^{1/2}/(\text{LVET} \cdot 100),$$

where RR is the interval between cardiac cycles, determined as the number of frames from the peak of the R wave to the next peak of the R wave, and LVEDC and LVESC are in cm.[6]

Statistical Analysis

Effects of sevoflurane and enflurane, both with nitrous oxide, on HR, ABP, and echocardiographically analyzed parameters were compared by one- and two-way analysis of variance (ANOVA) followed by the Bonferroni multiple comparison test. We plotted LVESWS on the x-axis and Vcfc on the y-axis and calculated the linear regression equation of LVESWS-Vcfc relationship for each of the anesthetic groups and the awake subjects group. Simple linear regression by the least squares method was used to calculate LVESWS-Vcfc equations. In this relationship, Vcfc is higher for any given level of LVESWS in the increased inotropic state and lower in the depressed contractile state. A change in contractility reflected by a change in the LVESWS-Vcfc relationship was compared by analysis of covariance (covariant ANOVA). Statistical analysis was conducted using the Statistical Analysis System (SAS, Cary, NC). $P < 0.05$ was considered statistically significant. All data were expressed as mean ± SEM.

Results

All data obtained in the awake subjects group were listed in table 1. The sevoflurane and enflurane groups were similar in age, sex, body weight, and height (table 2). Operations included oral, nasal, and ear surgery (43%), laparoscopic cholecystectomy (32%), and gynecologic surgery (25%). There was no statistical difference in HR, ABP, or RPP before induction of anesthesia in either anesthetic group (table 3), nor in HR and ABP between either anesthetic group and the awake subjects group.

Hemodynamic Data

Data for HR, ABP, and RPP in the sevoflurane and enflurane groups are summarized in table 3. There was

Table 1. Data in the Awake Subjects Group

	Awake Subjects Group
Age (yr) (range)	41 ± 3 (25–66)
Sex (M/F)	20/8
Weight (kg)	61 ± 1
Height (kg)	164 ± 1
Heart rate (beats/min)	68 ± 2
Arterial blood pressure (mmHg)	
Systolic	120 ± 17*
Diastolic	75 ± 2*
Mean	90 ± 2*
Echocardiographic parameters	
LVESWS (g/cm^2)	61.9 ± 5.3
Vcfc (circ/s)	1.001 ± 0.045*
FAC (%)	59.9 ± 1.9*
CFS (%)	37.0 ± 1.5*
Ejection time with HR corrected (s)	0.37 ± 0.005*

LVESWS = left ventricular end-systolic wall stress; Vcfc = velocity of circumferential fiber shortening with heart rate corrected; FAC = fractional area change; CFS = circumferential fiber shortening.

* Significantly ($P < 0.05$) different from at any anesthetic concentration in both sevoflurane and enflurane groups.

no significant change in HR under anesthesia in either group. Increasing concentrations of sevoflurane and enflurane caused progressive decrease in systolic, diastolic, and mean ABP. Enflurane produced a decrease in systolic and mean ABP that was significantly greater than for an equiMAC concentration of sevoflurane with nitrous oxide. Rate pressure products decreased significantly from the awake state to that during anesthesia in both groups, but no significant change in RPP could be detected during anesthesia between them.

Transesophageal Echocardiographic Data

A left ventricular short axis view at the level of the midpapillary muscles was satisfactorily obtained in all 28 subjects in the sevoflurane and enflurane groups and in the awake subjects group. No segmental wall motion abnormality, ST-segment change, dysrhythmia, or influence on hemodynamics by probe manipulation was observed in any subject during the study. Transesophageal echocardiographic data are summarized in table 4. Vcfc, FAC, and CFS at each anesthetic dose in both the sevoflurane and the enflurane groups were significantly less than those in the awake subjects group. There was no significant change in Vcfc, FAC, or CFS in the sevoflurane group. In the enflurane group, however, Vcfc, FAC, and CFS decreased significantly from those at 1.5 MAC to those at 1.95 MAC. Vcfc, FAC, and CFS produced by enflurane with nitrous oxide were significantly less than by sevoflurane with nitrous oxide with respect to equiMAC concentration. LVESWS decreased significantly in the sevoflurane group from that at 1.5 MAC to that 2.2 MAC of sevoflurane/nitrous oxide anesthesia. There was no significant change in LVESWS between the sevoflurane and enflurane groups with respect to equiMAC concentration. There was no significant change in ejection time with heart rate corrected, LVEDA, At, or At *minus* LVESA in either group.

Examination was made of the effects of sevoflurane and enflurane, both with nitrous oxide, on the LVESWS-Vcfc relationship. Contractility at the awake state also was assessed with this relationship. In the sevoflurane group, the regression equations are:

$$Vcfc = -0.0038_{LVESWS} + 0.743,$$
$$r = -0.82\ (P < 0.01),\ n = 14 \text{ at } 1.5 \text{ MAC},$$
$$Vcfc = -0.0038_{LVESWS} + 0.668,$$
$$r = -0.78\ (P < 0.01),\ n = 14 \text{ at } 1.95 \text{ MAC},$$
$$Vcfc = -0.0032_{LVESWS} + 0.623,$$
$$r = -0.52\ (P < 0.1),\ n = 14 \text{ at } 2.2 \text{ MAC}.$$

In the enflurane group, the regression equations are:

$$Vcfc = -0.0035_{LVESWS} + 0.653,$$
$$r = -0.79\ (P < 0.01),\ n = 14 \text{ at } 1.5 \text{ MAC},$$
$$Vcfc = -0.0017_{LVESWS} + 0.409,$$
$$r = -0.49\ (P < 0.1),\ n = 14 \text{ at } 1.95 \text{ MAC}$$

In the awake subjects group, the regression equation is:

$$Vcfc = -0.0057_{LVESWS} + 1.356,$$
$$r = -0.67\ (P < 0.01),\ n = 28.$$

Table 2. Demographic Data in Sevoflurane Group and Enflurane Group

	Sevoflurane Group (n = 14)	Enflurane Group (n = 14)
Age (yr) (range)	45 ± 2 (33–56)	42 ± 3 (30–58)
Sex (M/F)	4/10	7/7
Weight (kg)	54 ± 1	53 ± 2
Height (cm)	157 ± 1	158 ± 2

Table 3. Hemodynamic Data and End-tidal Carbon Dioxide in the Sevoflurane and Enflurane Groups

	Sevoflurane Group (n = 14)				Enflurane Group (n = 14)		
	Before Induction	0.9 MAC SEV + 0.6 MAC N_2O	1.35 MAC SEV + 0.6 MAC N_2O	1.6 MAC SEV + 0.6 MAC N_2O	Before Induction	0.9 MAC ENF + 0.6 MAC N_2O	1.35 MAC ENF + 0.6 MAC N_2O
Heart rate (beats/min)	76 ± 4	81 ± 2	83 ± 2	83 ± 2	81 ± 4	85 ± 2	87 ± 3
Arterial blood pressure (mmHg)							
Systolic	141 ± 4	108 ± 3*	97 ± 3*	90 ± 4*†	131 ± 5	94 ± 3*‡	81 ± 4*†‡
Diastolic	81 ± 4	65 ± 3*	60 ± 3*	55 ± 4*	80 ± 4	57 ± 4*	49 ± 3*‡
Mean	102 ± 5	85 ± 3*	75 ± 3*	69 ± 4*†	98 ± 4	71 ± 3*‡	63 ± 3*‡
Rate pressure product (beats · mmHg)	10,588 ± 433	8777 ± 368*	8106 ± 340*	7553 ± 466*	10,729 ± 747	7994 ± 440*	7099 ± 521*
End-tidal carbon dioxide (mmHg)	—	36 ± 1	36 ± 1	35 ± 1	—	36 ± 1	35 ± 1

SEV = sevoflurane; ENF = enflurane.

* Significantly ($P < 0.05$) different from before the anesthetic induction.

† Significantly ($P < 0.05$) different from 1.5 MAC.

‡ Significantly ($P < 0.05$) different from equiMAC concentration of sevoflurane with nitrous oxide.

Correlation between LVESWS and Vcfc was not significant at 2.2 MAC in the sevoflurane group or at 1.95 MAC in the enflurane group. Covariant ANOVA could be performed on those data at the highest concentration in the sevoflurane and enflurane groups, because the data did not violate the assumptions required in this statistical analysis. Those assumptions are that the slopes of regression lines are not significantly different and that they are the same straight lines, not curvature.[11]

The LVESWS-Vcfc relationships in the awake subjects group and the sevoflurane group (fig. 1) or the enflurane group (fig. 2) were shown. In both the sevoflurane and the enflurane groups, contractility produced at each anesthetic concentration was significantly less ($P < 0.01$) than that in the awake subjects group. Comparison with awake subjects indicated that the myocardial contractility was depressed during both sevoflurane/nitrous oxide and enflurane/nitrous oxide anesthesia compared to the awake state. In both the sevoflurane and the enflurane groups, this relationship at 1.5 MAC was inversely linear with a correlation coefficient of -0.82 ($P < 0.01$) in the sevoflurane group and -0.79 ($P < 0.01$) in the enflurane group. In the

Table 4. Transesophageal Echocardiographic Data in the Sevoflurane and Enflurane Groups

	Sevoflurane Group (n = 14)			Enflurane Group (n = 14)	
	0.9 MAC SEV + 0.6 MAC N_2O	1.35 MAC SEV + 0.6 MAC N_2O	1.6 MAC SEV + 0.6 MAC N_2O	0.9 MAC ENF + 0.6 MAC N_2O	1.35 MAC ENF + 0.6 MAC N_2O
LVESWS (g/cm^2)	80.3 ± 6.1	73.2 ± 5.4	66.0 ± 5.3*	89.3 ± 6.3	85.0 ± 7.4
Vcfc (circ/s)	0.434 ± 0.029	0.411 ± 0.027	0.413 ± 0.033	0.340 ± 0.031†	0.261 ± 0.027*†
FAC (%)	37.3 ± 2.0	35.8 ± 2.2	35.9 ± 2.7	28.8 ± 2.5†	23.9 ± 2.2*†
CFS (%)	20.6 ± 1.4	20.0 ± 1.3	20.1 ± 1.6	15.7 ± 1.5†	12.1 ± 1.2*†
Ejection time with HR corrected (s)	0.476 ± 0.010	0.488 ± 0.009	0.488 ± 0.009	0.464 ± 0.012	0.470 ± 0.012
Change in EDA from 1.5 MAC (%)	100	99.7 ± 2.0	99.5 ± 2.8	100	99.6 ± 1.9

SEV = sevoflurane; ENF = enflurane; LVESWS = left ventricular end-systolic wall stress; Vcfc = velocity of circumferential fiber shortening with heart rate corrected; FAC = fractional area change; CFS = circumferential fiber shortening; EDA = end-diastolic area.

* Significantly ($P < 0.05$) different from 1.5 MAC.

† Significantly ($P < 0.05$) different from equiMAC concentration of sevoflurane with nitrous oxide.

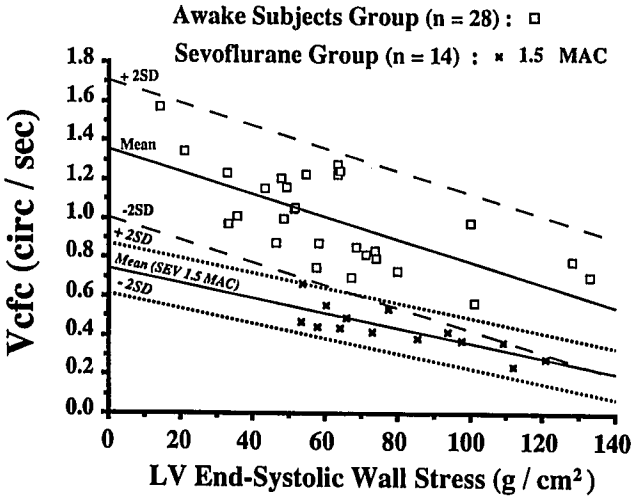

Fig. 1. Left ventricular end-systolic wall stress (LVESWS) *versus* velocity of circumferential fiber shortening with heart rate corrected (Vcfc) relationship obtained in the awake subjects group and at 1.5 MAC in the sevoflurane group. The inverse linear regression (solid lines) with 95% confidence intervals (dashed lines) obtained in the awake subjects and at 1.5 MAC in the sevoflurane group are shown. Data points in both groups are plotted. All data points at 1.5 MAC in the sevoflurane group were below the 95% lower confidence limit obtained in the awake subjects. A change in contractile state was compared by analysis of covariance, and contractility at 1.5 MAC in the sevoflurane group was significantly less than that in the awake subjects. SEV = sevoflurane.

sevoflurane group, there was no significant change in contractility between 1.5 MAC and 1.95 MAC. Contractility at 2.2 MAC sevoflurane with nitrous oxide was significantly less ($P < 0.05$) than that at 1.5 MAC. In the enflurane group, contractility at 1.95 MAC was significantly less ($P < 0.01$) than that at 1.5 MAC. Regression lines between LVESWS and Vcfc were shown at each dose in the sevoflurane group (fig. 3A) and the enflurane group (fig. 3B). In a comparison of volatile anesthetics, myocardial contractility produced by enflurane with nitrous oxide was significantly less ($P < 0.05$) than that caused by sevoflurane with nitrous oxide with respect to equiMAC concentration. In the assessment of LVESWS-Vcfc relationship, sevoflurane was shown to cause depression of myocardial contractility but to a lesser extent than enflurane.

Discussion

In the present study, the assessment with the LVESWS-Vcfc relationship demonstrated that both sevoflurane and enflurane depress myocardial contractility. However, sevoflurane depressed myocardial contractility less than did enflurane at equiMAC concentration with 60% N_2O.

Hemodynamic effects of sevoflurane in this study were essentially the same as those reported previously in humans.[2] Hemodynamic effects of enflurane observed in the present study were similar to those in previous reports on humans.[12,13] In the present study, there was no significant change in HR during enflurane/nitrous oxide anesthesia. In contrast with our results of HR, however, Calverley *et al.*[12] observed the increase in HR with enflurane as the dose was increased from 1.0 to 1.5 MAC.

In previous reports,[2-5] dose-related myocardial depression caused by sevoflurane was indicated by the load-dependent index, dp/dt(max),[3,5] or estimated from a decrease in hemodynamic parameters.[2,4] dp/dt(max) is considered to depend on preload and HR and can be influenced by change in arterial pressure, as when aortic end-diastolic pressure is markedly reduced.[14,15] With increasing clinical use of sevoflurane, pharmacodynamic effects on myocardial contractility should be determined.

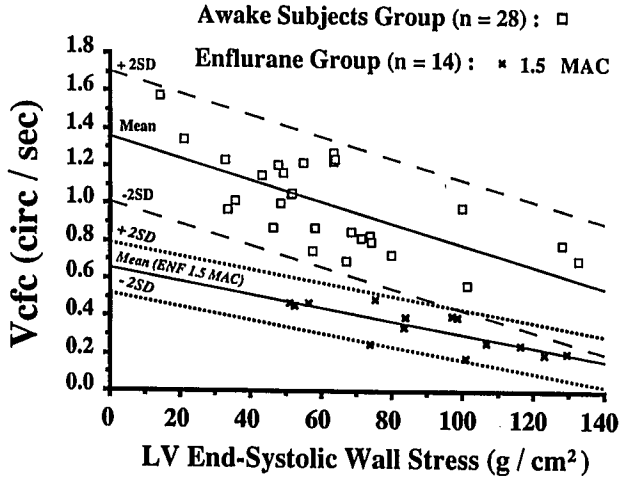

Fig. 2. Left ventricular end-systolic wall stress (LVESWS) *versus* velocity of circumferential fiber shortening with heart rate corrected (Vcfc) relationship obtained in the awake subjects group and at 1.5 MAC in the enflurane group. The inverse linear regression (solid lines) with 95% confidence intervals (dashed lines) obtained in the awake subjects and at 1.5 MAC in the enflurane group are shown. Data points in both groups are plotted. All data points at 1.5 MAC in the enflurane group were below the 95% lower confidence limit obtained in the awake subjects. A change in contractile state was compared by analysis of covariance, and contractility at 1.5 MAC in the enflurane group was significantly less than that in the awake subjects. ENF = enflurane.

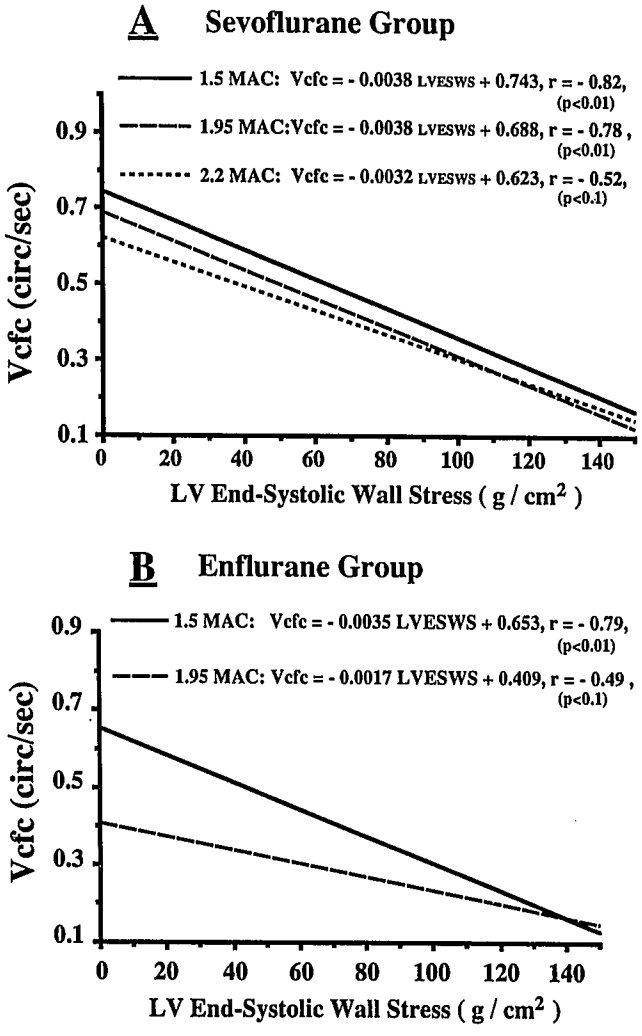

Fig. 3. Regression line between left ventricular end-systolic wall stress (LVESWS) and velocity of circumferential fiber shortening with heart rate corrected (Vcfc) obtained at each anesthetic dose in the sevoflurane group (*A*) and the enflurane group (*B*). Regression equations and correlation coefficients (r) calculated by regression analysis are shown.

The LVESWS-Vcfc relationship as a load-independent index of myocardial contractility was reported by Colan *et al.*[6] in 1984. The LVESWS-Vcfc relationship is inversely linear, and Vcfc is higher for any given level of LVESWS in increased inotropic state and lower for any given level of LVESWS in depressed contractile state. A change in contractility thus was reflected by a change in LVESWS-Vcfc relationship. They found this relationship, which is sensitive to an altered contractile state, to be independent of preload, to incorporate both afterload and HR. Therefore, the direct assessment of contractile state can be available by examining LVESWS-Vcfc relationship, and change of this relationship can be compared using covariant ANOVA.

In the present study, meridional wall stress was used as a measure of LVESWS rather than circumferential wall stress, because the latter depends on the left ventricular major axis, which must be approximated from the short axis. Meridional wall stress, however, is independent of the major axis and requires no such approximation.[10,16] To calculate circumferential wall stress, the major axis is assumed to be twice as long as the short axis based on an ellipsoid model. Circumferential wall stress thus may involve error when the ratio of the major axis to the minor axis changes to less or more than 2 under left ventricle volume changing conditions, as during volatile anesthetic administration. In a study with humans, Reichek *et al.*[17] observed noninvasive cuff systolic arterial pressure to be closely correlated with end-systolic micromanometer left ventricular pressure (r = 0.89), and noninvasive end-systolic left ventricular wall stress with cuff systolic pressure and invasive stress with end-systolic left ventricular pressure correlated even to a greater extent (r = 0.97). Thus, in this study, cuff systolic ABP was considered possibly appropriate for the noninvasive estimation of LVESWS. Calculation of wall stress under abnormally higher or lower blood pressure has a limitation, because blood pressure is underestimated in the abnormally high pressure or overestimated in the abnormally low pressure using the oscillometric method. Vcfc may be an afterload-dependent contractile index, but independent of preload, whereas ejection fraction may be altered significantly by a large change in the preload.[18]

Enflurane with nitrous oxide produced significant decreases in ABP, FAC, and CFS that exceeded those caused by sevoflurane with nitrous oxide. Thus, enflurane is shown to exert a greater cardiac depressant effect than that caused by sevoflurane. Haendchen *et al.*[19] determined FAC and CFS as indexes of contractile function in two-dimensional echocardiography. FAC and CFS clinically facilitate the assessment of cardiac function, as does the ejection fraction, but both are preload- and afterload-dependent and therefore cannot accurately indicate the left ventricular contractile state. Therefore, we used the LVESWS-Vcfc relationship as a contractile index in this study. Furthermore, analysis of preload and afterload can be available by examining the changes of LVEDA and LVESWS, respectively. Examination thus was made of the effects of volatile anesthetics on left ventricular function in more detail

using three parameters; LVEDA (preload), LVESWS (afterload), and the LVESWS-Vcfc relationship (index of myocardial contractility) obtained by TEE.

Changes in LVEDA and LVESA of echocardiography are considered to reflect changes in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), respectively.[20] Thus, the absence of significant change in LVEDA indicated the absence of that in LVEDV or left ventricular preload during sevoflurane or enflurane anesthesia in the present study.

In the sevoflurane group, sevoflurane produced a significant decrease in LVESWS from 1.5 to 2.2 MAC. In previous reports,[3-5] a significant decrease in systemic vascular resistance produced by sevoflurane has been reported. Decrease in LVESWS under sevoflurane anesthesia in the present study primarily may have been due to that in systemic vascular resistance.

With transthoracic echocardiography, we examined a normal contractile state in the 28 awake subjects. The LVESWS-Vcfc relationship obtained in the awake subjects group in the present study was similar to that reported by Colan *et al.*[6] They also reported that neither age (range 3–75 yr) nor sex appeared to influence the LVESWS-Vcfc relationship.[6] In a comparison with the normal LVESWS-Vcfc relationship obtained in the awake subjects group, both sevoflurane/nitrous oxide and enflurane/nitrous oxide were shown to cause depression of myocardial contractility compared to the awake state. However, the negative inotropic effect of sevoflurane was significantly less than that by enflurane at equiMAC concentration with nitrous oxide. Sevoflurane thus may be considered to have fewer detrimental effects conducive to maintaining cardiac function compared to enflurane. In fact, left ventricular function was well maintained without significant decrease in FAC or CFS under sevoflurane anesthesia, whereas significant decrease in FAC and CFS was observed under enflurane anesthesia.

Several limitations exist in the present study. First, we did not obtain echocardiograms during a conscious state in either the sevoflurane or the enflurane group, and we examined myocardial contractility at a conscious state in the different awake subjects group. Furthermore, we used different echocardiographic approaches to the left ventricular short axis view between the awake subjects and anesthetized patients. Therefore, the comparison between the awake subjects and the anesthetized patients may limit the interpretation of the obtained results. However, since the LVESWS-Vcfc relationship in the awake subjects group was similar to that reported by Colan *et al.*,[6] we considered that the relationship obtained in the awake subjects of this study represented a conscious contractile state of normal subjects.

Second, LVESWS and Vcfc did not correlate significantly at 2.2 MAC of the sevoflurane group or at 1.95 MAC of the enflurane group. Thus, lack of a correlation between LVESWS and Vcfc at the highest anesthetic concentration would limit our ability to use the slope of LVESWS-Vcfc relationship as a contractile index. In this study, however, we used covariant ANOVA to compare the LVESWS-Vcfc relationship quantitatively. This statistical analysis requires the assumptions that (1) the slopes of regression lines are not significantly different, and (2) the slopes have the same straight lines, not curvature.[11] If the data do not violate these assumptions, covariant ANOVA can be performed even when the correlation coefficient is not significant.[11] In the present study, we could perform covariant ANOVA because the data did not violate the assumptions of this analysis.

Third, we needed to combine the data from multiple subjects to obtain the LVESWS-Vcfc relationship in the present study. Therefore, we could not get an absolute value that represented a contractile state in each individual patient. In contrast, traditional echocardiographic indexes can be obtained as an absolute value in individual subjects. Thus, the necessity of pooling the data from multiple subjects would be a limitation, when one applied the LVESWS-Vcfc relationship as a contractile index in a clinical setting.

To assess the effects of drugs on cardiac function with TEE, hemodynamic reaction by esophageal stimulation with a TEE probe should be prevented as much as possible. This is because stimulation by probe potentially causes undesirable sympathetic reactions such as increases in HR and blood pressure. Probe manipulation during videotape recording thus was restricted to a period not exceeding 60 s, and the probe was kept flexible except during the recording. Consequently, probe manipulation had no effect on HR or blood pressure in any subject throughout the study.

In summary, the present results demonstrate that both sevoflurane and enflurane depress myocardial contractility. However, depression of contractility by sevoflurane was less than that produced by enflurane at equiMAC concentration with 60% N_2O. Sevoflurane is associated with slight depression of myocardial contractility with no significant changes in HR.

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