Effects of Sevoflurane on Cardiovascular Dynamics, Coronary Circulation and Myocardial Metabolism in Dogs

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The effects of 2.5% and 5% of sevoflurane anesthesia on hemodynamics and myocardial metabolism were studied in pentobarbital-pancuronium anesthetized dogs. The interaction between nicardipine and 2.5% sevoflurane was also examined. Sevoflurane produced dose-dependent ($P<0.05$ to $P<0.01$) decreases in systolic arterial pressure (SAP), heart rate (HR), cardiac index (CI), left ventricular minute work index (LVMWI), maximum rate of rise of left ventricular pressure (LV dP/dt), the time constant of fall in isovolumic left ventricular pressure (T) and systemic vascular resistance (SVR), whereas stroke volume index (SVI) and left ventricular end-diastolic pressure (LVEDP) remained unchanged. Central venous pressure (CVP) was significantly ($P<0.05$) increased at 5%. Myocardial oxygen consumption ($M\dot{V}o_2$), and myocardial lactate extraction ratio (ML ext) were decreased in a dose-dependent manner ($P<0.05$). Myocardial oxygen extraction ratio (Mo_2 ext) was significantly ($P<0.01$) decreased at 5%. The ratio of the left ventricular minute work index to myocardial oxygen consumption ($LVMWI/M\dot{V}o_2$), i.e., left ventricular efficiency was significantly decreased only at 5% ($P<0.05$). Coronary sinus blood flow (CSBF) was significantly ($P<0.05$) decreased only at 2.5% sevoflurane and coronary vascular resistance (CVR) was significantly ($P<0.01$) decreased only at 5% sevoflurane. The ratio of CSBF to CO (CSBF/CO) showed a tendency to increase as sevoflurane concentrations were increased. Nicardipine (0.01 $mg \cdot kg^{-1}$) administered intravenously under 2.5% sevoflurane caused significant ($P<0.05$ to $P<0.01$) decreases in SAP, HR, LV dP/dt, SVR, and CVR, and increases in CVP, SVI, CI, and CSBF ($P<0.05$ to $P<0.01$). CSBF/CO remained unchanged. $M\dot{V}o_2$, Mo_2 ext, and ML ext were significantly ($P<0.05$ to $P<0.01$) decreased. $LVMWI/M\dot{V}o_2$ showed a tendency to increase. It is concluded that sevoflurane causes a rapidly and easily controlled cardiovascular depression and may not have unfavorable effects on coronary circulation and myocardial metabolism. Nicardipine exerts a synergistic myocardial depressant effect on sevoflurane, in terms of both cardiovascular dynamics and myocardial metabolism. (Key words: sevoflurane, hemodynamics, myocardial metabolism, nicardipine)

(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)

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J Anesth 2: 227–241, 1988

Sevoflurane (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether) is a new, potent inhaled anesthetic agent[1,2]. While sevoflurane has been shown to have some favorable characteristics, such as low blood/gas partition coefficient of 0.60[1], much

higher arrhythminogenic dose of epinephrine than with isoflurane[3] and the lower incidence of hepatic injury than with halothane[4], the effects of sevoflurane on the cardiovascular system have not been studied throughly. In addition, there is no information available about the interaction of the widely used calcium channel blocking agent, nicardipine hydrochloride, with this anesthetic.

This study was performed to assess the cardiovascular and myocardial metabolic effects of sevoflurane and the interaction between nicardipine and sevoflurane in an open-chest dog preparation.

Material and Methods

Thirteen mongrel dogs (mean weight 17.4 kg, range 12-23 kg) were anesthetized with intravenous sodium pentobarbital (30 $mg \cdot kg^{-1}$). After tracheal intubation, ventilation was controlled using an animal ventilator (R-60, Aika, Co., Ltd.) at tidal volumes of 25–30 $ml \cdot kg^{-1}$ with the rate adjusted to maintain a Pa_{CO_2} of 30–35 mmHg at an $F_{I_{O_2}}$ of 1.0. All the animals were paralyzed with pancuronium 0.2 $mg \cdot kg^{-1}$ and supplementary small doses of sodium pentobarbital were administered as needed to perform the surgical procedure.

Monitoring electrocardiogram (ECG, lead II) and heart rate (HR), a micromanometer-tipped catheter (7F 45326, TOYODA Instr., Ltd.) was placed in the abdominal aorta via the left femoral artery for measurements of systolic, diastolic, and mean arterial pressure (SAP, DAP, and MAP). A polyethylene catheter was placed in the superior vena cava via the right external jugular vein for measurements of central venous pressure (CVP). Another catheter was placed in the abdominal aorta via the right femoral artery for arterial blood sampling. Catheter pressure were transduced through Stantham® transducers (Stantham P23 ID).

Following median sternotomy, an electromagnetic flow probe (FB-140T, NIHON KOHDEN Co., Ltd.) was placed around the ascending aorta and connected to a flowmeter (MFV2100, NIHON KOHDEN Co., Ltd.) for measurement of aortic flow regarded as cardiac output (CO). Left ventricular pressure (LVP) and left ventricular end-diastolic presure (LVEDP) were measured with a micromanometer-tipped catheter (8F PC380, Millar Instr., Inc.) inserted into the left ventricular cavity via the cardiac apex. The rate of rise of left ventricular pressure (LV dP/dt) was obtained with an analog differentiating circuit (Contractility Unit 1323, NEC Sanei Instr., Ltd.). Coronary sinus blood flow was determined by the retrograde thermodilution technique with a catehter (Thermoflow® CCS-7U-90A, Webster Labs., Inc.) inserted into the coronary sinus via the right auricle[5]. Cold normal saline as the indicator was infused by a constant rate infusion pump (SW-367, Sage Instr., Inc.). The infusion rate of the indicator was kept at 20 $ml \cdot min^{-1}$ for a period of about 20 sec for each measurement.

Blood was sampled simultaneously from the arterial and coronary sinus catheters for determination of oxygen content and lactate concentration (UV method). The pH, Pa_{CO_2}, and Pa_{O_2} were measured by an automated analyzer (IL 813, Instr., Labs.) and corrected for temperature. Hemoglobin levels were determined by the cyanmethemoglobin method. Oxygen saturations were calculated from the nomogram of Kelman & Nunn[6]. These values were used to calculate oxygen contents using 1.39 $ml \cdot O_2 \cdot g^{-1}$ of hemoglobin at 100 per cent saturation.

During the surgical procedure, lactated Ringer's solution was infused at 15–20 $ml \cdot kg^{-1} \cdot h^{-1}$ via an intravenous catheter placed in the right femoral vein. At the end of the surgical procedure, the infusion was discontinued. Temperature was measured from an esophageal thermister and was maintained at 35–37°C by means of an external heating pad.

A period of about 20 min after the end of the surgical procedure was allowed for stabilization of hemodynamic variables, and control values were obtained. In seven dogs, 2.5% (1.1MAC) and 5% (2.2MAC) of inspired concentrations of sevoflurane were administered at 10 min intervals in this order. Hemodynamic measurements and blood sam-

Table 1. Derived parameters

CI	cardiac index = CO/BW	$(l \cdot min^{-1} \cdot kg^{-1})$
SV	stroke volume = $[CO/HR] \times 10^3$	(ml)
SVI	stroke volume index = SV/BW	$(ml \cdot kg^{-1})$
LVMWI	left ventricular minute work index = $(MAP - LVEDP) \times SVI \times HR \times 0.0136$	$(g \cdot m \cdot kg^{-1} \cdot min^{-1})$
SVR	systemic vascular resistance = $(MAP - CVP)/CI$	$(mmHg \cdot l^{-1} \cdot min \cdot kg)$
CPP	coronary perfusion pressure = DAP - LVEDP	(mmHg)
CVR	coronary vascular resistance = $(DAP - LVEDP)/(CSBF \times 10^{-3})$	$(mmHg \cdot l^{-1} \cdot min)$
$M\dot{V}o_2$	myocardial oxygen consumption = $(a - cs)\ Do_2 \times CSBF \times 10^{-2}$	$(ml \cdot min^{-1})$
Mo_2 ext. (%)	myocardial oxygen extraction ratio = $[(a - cs)\ Do_2/CaO_2] \times 10^2$	(%)
ML ext. (%)	myocardial lactate extraction ratio = $[(a - cs)\ DL/La] \times 10^2$	(%)

Abbreviations

BW = body weight (kg); CO = cardiac output $(l \cdot min^{-1})$; HR = heart rate (bpm); MAP = mean arterial pessure (mmHg); LVEDP = left ventricular end-diastolic pressure (mmHg); CVP = central venous pressure (mmHg); DAP = diastolic arterial pressure (mmHg); CSBF = coronary sinus blood flow $(mil \cdot min^{-1})$; (a–cs) Do_2 = arterio-coronary sinus oxygen content difference $(ml \cdot dl^{-1})$; Ca_{O_2} = arterial oxygen content $(ml \cdot dl^{-1})$; (a–cs) DL = arterio-coronary sinus lactate content difference $(mg \cdot dl^{-1})$; La = arterial lactate concentration $(mg \cdot dl^{-1})$

pling were performed at the end of each concentration of sevoflurane anesthesia.

In six dogs, the interaction between sevoflurane and nicardipine was studied 10 min after 2.5% sevoflurane (1.1MAC), and hemodynamic measurements were performed prior to and 2 min after intravenous administration of nicardipine $(0.01\ mg \cdot kg^{-1})$. Hemodynamic variables measured directly were continuously recorded on a polygraph (RECTI-HORIZ-8K23, NEC San-ei, Instr., Ltd.).

Derived parameters of all variables and their abbreviations are shown in table 1.

LV dP/dt and the time constant (T) were used as the indices of the contractile and the relaxing function of the left ventricle, respectively.

The signals of left ventricular pressure (LVP), LV dP/dt, LVEDP, and ECG were also fed to another recorder (Visigraph® 5L37, NEC San-ei Instr., Ltd.) and these four parameters were recorded on a multi-channel photographic oscillograph at paper speed of $50\ cm \cdot s^{-1}$ for measurement of the time constant (T). T is the inverse negative of the slope of the line which is obtained by plotting the natural logarithm of left ventricular pressure fall beginning at maximum negative dP/dt to the level of LVEDP against time[7].

Student's t test for paired samples was used to evaluate statistical significance. A P value less than 0.05 was considered statistically significant. All results are presented as means ± SE.

Results

Effects of 2.5% and 5% sevoflurane on hemodynamics, coronary circulation and myocardial metabolism are shown in table 2.

In seven dogs, 2.5% (1.1MAC) and 5% (2.2MAC) of sevoflurane produced a small decrease in arterial oxygen tension, but there were no physiologically significant changes in the controlled parameters (table 2, section

Table 2. Effects of 2.5% and 5% sevoflurane concentrations on hemodynamics, coronary circulatin and myocardial metabolism

measured variables and calculated parameters		control value		Sevoflurane 2.5%	Sevoflurane 5%
A) Controlled Parameters					
pH		7.39±0.03	(7)	7.39±0.03	7.39±0.03
Pa_{CO_2}	(mmHg)	32.1±2.1	(7)	31.9±1.9	31.5±2.0
Pa_{O_2}	(mmHg)	290.3±16.5	(7)	260.4±21.0	262.6±15.6
Base excess	($mEq \cdot l^{-1}$)	−4.8±0.8	(7)	−4.9±0.7	−4.8±0.9
B) Hemodynamics					
SAP	(mmHg)	158±9	(7)	118±9**	87±7**††
DAP	(mmHg)	105±8	(7)	76±8**	57±6**††
MAP	(mmHg)	122±8	(7)	90±8**	67±6**††
HR	($beats \cdot min^{-1}$)	132±7	(7)	113±8**	101±6**††
CI	($l \cdot min^{-1} \cdot kg^{-1}$)	0.13±0.01	(7)	0.11±0.01*	0.09±0.01*††
CVP	(mmHg)	5.9±0.6	(7)	6.0±0.6	6.2±0.6*†
LVEDP	(mmHg)	8.1±1.2	(7)	8.1±1.0	8.7±0.8
SVI	($ml \cdot kg^{-1}$)	1.02±0.09	(7)	0.98±0.10	0.92±0.11
LVMWI	($g \cdot m \cdot kg^{-1} \cdot min^{-1}$)	185.2±21.7	(7)	114.6±19.4**	69.4±10.5**††
SVR	($mmHg \cdot l^{-1} \cdot min \cdot kg$)	847±102	(7)	673±44*	562±27*†
LV dP/dt	($mmHg \cdot sec^{-1}$)	3624±503	(7)	2603±433**	1874±427**††
T	(msec)	32.7±4.9	(7)	38.1±4.4**	43.8±5.1**††
C) Coronary Circulation and Myocardial Metabolism					
CPP	(mmHg)	103±5	(7)	72±6**	50±5**††
CSBF	($ml \cdot min^{-1}$)	81.4±5.0	(7)	68.0±6.7**	71.6±6.6
CSBF/CO	(%)	4.3±0.8	(7)	4.4±1.0	5.5±1.7
CVR	($mmHg \cdot l^{-1} \cdot min$)	1279±74	(7)	1136±134	751±110**††
(a–cs) Do_2	($ml \cdot dl^{-1}$)	7.9±0.7	(7)	7.1±0.7	6.2±0.5**††
(a–cs) DL	($mg \cdot dl^{-1}$)	10.2±2.1	(7)	7.8±1.7**	7.8±2.2*
$M\dot{V}o_2$	($ml \cdot min^{-1}$)	6.8±0.6	(7)	5.1±0.8*	4.4±0.7*††
M_{O_2} ext. ratio	(%)	50.7±5.3	(7)	45.7±5.8	40.4±4.6**
ML ext. ratio	(%)	50.7±6.8	(7)	42.0±6.2*	34.3±5.3*†
LVMWI/$M\dot{V}o_2$	($g \cdot m \cdot kg^{-1} \cdot ml^{-1}$)	29.7±4.4	(7)	22.3±3.2	15.6±2.2*††

Values are means ± SE.

SAP=systolic arterial pressure; DAP=diastolic arterial pressure; MAP=mean arterial pressure; HR=heart rate; CI=cardiac index; CVP=central venous pressure; LVEDP=left ventricular end-diastolic pressure; SVI=stroke volume index; LVMWI=left ventricular minute work index; SVR=systemic vascular resistance; LV dP/dt= maximum rate of rise of left ventricular pressure; T=time constant; CPP=coronary perfusion pressure; CSBF=coronary sinus blood flow; CSBF/CO=the ratio of CSBF to cardiac output; CVR=coronary vascular resistance; (a–cs) Do_2=arterio-coronary sinus oxygen content difference; (a–cs)DL=arterio-coronary sinus lactate content difference; $M\dot{V}o_2$=myocardial oxygen consumption; M_{O_2} ext. ratio (%)=myocardial oxygen extraction ratio; ML ext. ratio (%)= myocardial lactate extraction ratio; LVMWI/ $M\dot{V}o_2$=the ratio of the left ventricular minute work index to myocardial oxygen consumption.

* $P<0.05$ vs. control value
** $P<0.01$ vs. control value
† $P<0.05$ vs. 2.5% sevoflurane
†† $P<0.01$ vs. 2.5% sevoflurane

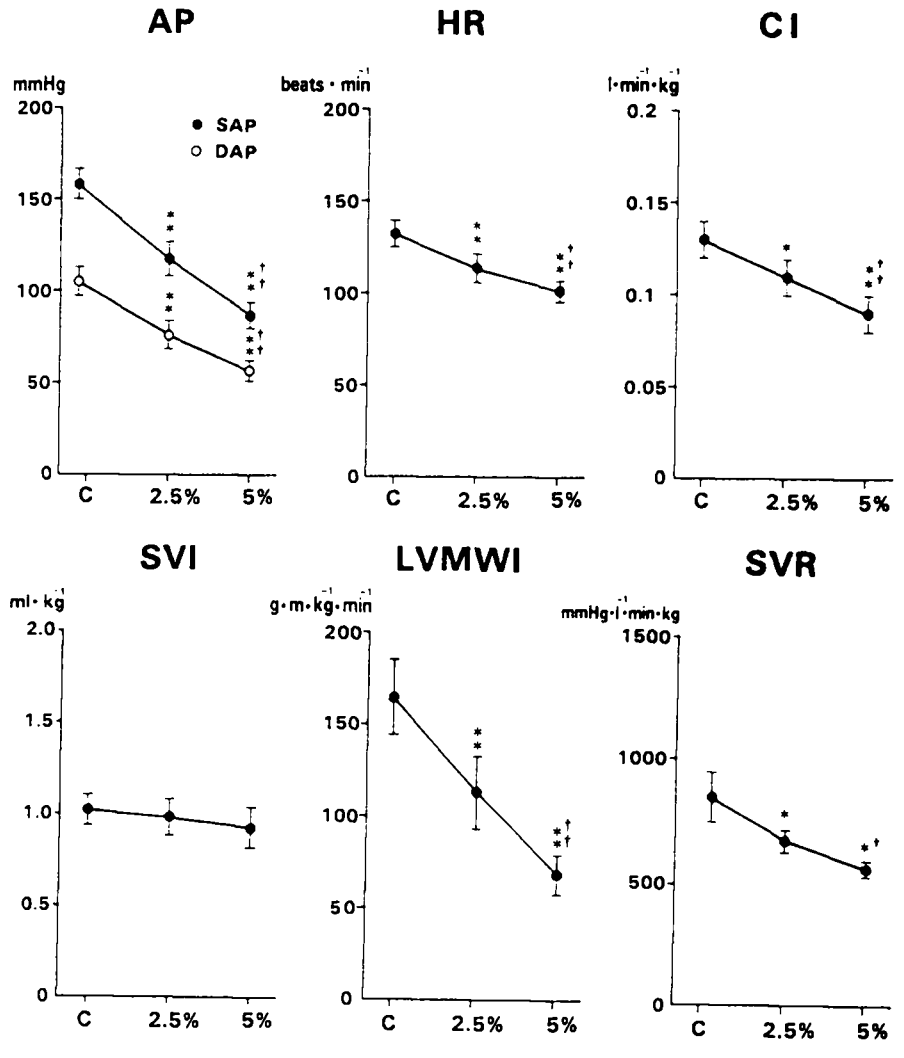

Fig. 1. Effects of 2.5% and 5% sevoflurane on hemodynamics. The hemodynamic variables were decreased in a dose-dependent manner except for SVI.

Values are means ± SE.

C = control; AP = systolic and diastolic arterial pressure (SAP and DAP, respectively); HR = heart rate; CI = cardiac index; SVI = stroke volume index; LVMWI = left ventricular minute work index; SVR = systemic vascular resistance

* $P<0.05$ vs. control value † $P<0.05$ vs. 2.5% sevoflurane
** $P<0.01$ vs. control value †† $P<0.01$ vs. 2.5% sevoflurane

A).

Sevoflurane (2.5% and 5% inspired) produced dose-dependent decreases in arterial pressure (AP), heart rate (HR), cardiac index (CI), left ventricular minute work index (LVMWI), and systemic vascular resistance (SVR). Stroke volume index (SVI) remained unchanged. Although central venous pressure (CVP) rose significantly during 5% sevoflurane, there was no significant increase in left ventricular end-diastolic pressure (LVEDP) (table 2, section B and fig.1). Left ventricular

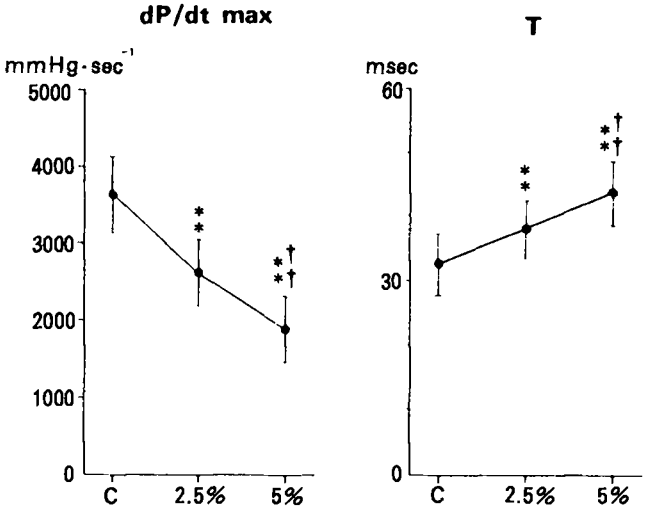

Fig. 2. Effects of 2.5% and 5% sevoflurane on LV dP/dt and T. Sevoflurane produced dose-dependent depression of both LV dP/dt and T.

Values are means ± SE.

C = control; dP/dt max = maximum rate of rise of left ventricular pressure; T = time constant of fall in isovolumic left ventricular pressure

* $P<0.05$ vs. control value
** $P<0.01$ vs. control value
† $P<0.05$ vs. 2.5% sevoflurane
†† $P<0.01$ vs. 2.5% sevoflurane

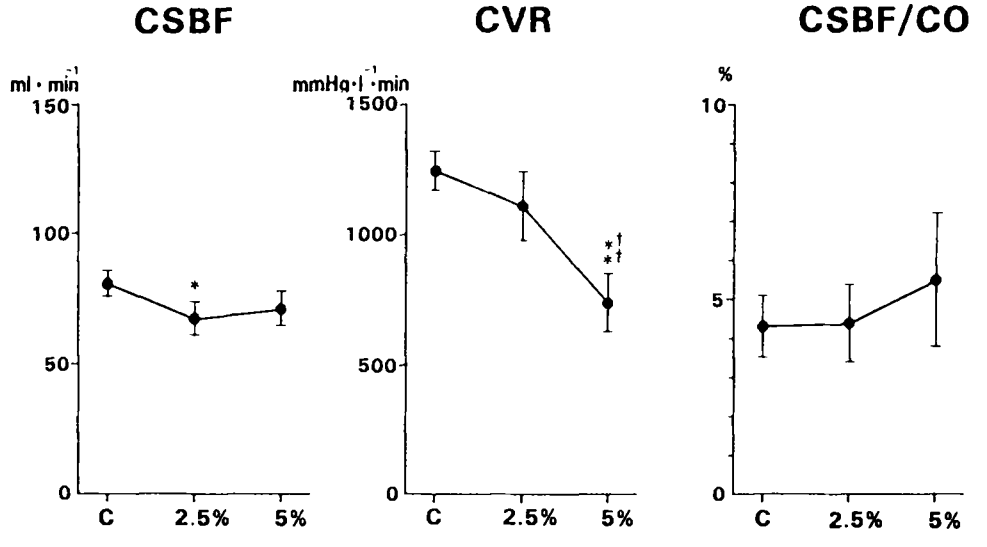

Fig. 3. Effects of 2.5% and 5% sevoflurane on coronary circulation. CSBF decreased by 16% at 2.5% sevoflurane showed a small degree of increase at 5% sevoflurane, in spite of a significant decrease in coronary perfusion pressure (–51% vs. control value). As a result, CVR was significantly decreased at 5% sevoflurane. CSBF/CO tended to increase at low and high concentrations.

Values are means ± SE.

C = control; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; CSBF/CO = the ratio of CSBF to cardiac output (CO)

* $P<0.05$ vs. control value † $P<0.05$ vs. 2.5% sevoflurane
** $P<0.01$ vs. control value †† $P<0.01$ vs. 2.5% sevoflurane

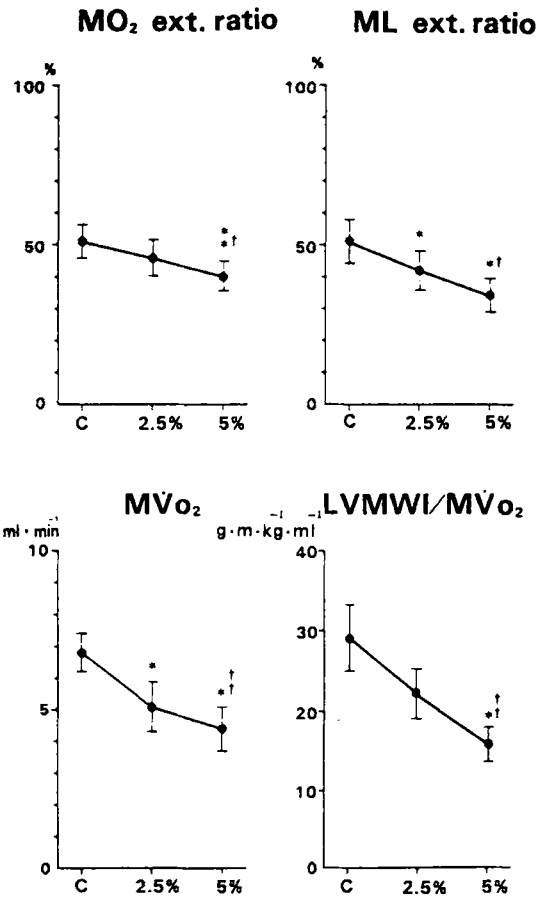

Fig. 4. Effects of 2.5% and 5% sevoflurane on myocardial metabolism and efficiency.

Myocardial metabolism was decreased with higher concentrations.

LVMWI/$M\dot{V}o_2$ was well maintained at 2.5% and decreased at 5%.

Values are means ± SE.

C = control; MO_2 ext. ratio = myocardial oxygen extraction ratio; ML ext. ratio = myocardial lactate extraction ratio; $M\dot{V}o_2$ = myocardial oxygen consumption; LVMWI/$M\dot{V}o_2$ = the ratio of the left ventricular external work to myocardial oxygen consumption

* $P<0.05$ vs. control value
** $P<0.01$ vs. control value
† $P<0.05$ vs. 2.5% sevoflurane
†† $P<0.01$ vs. 2.5% sevoflurane

dP/dt (LV dP/dt) and the time constant (T) were depressed in a dose-related manner (fig. 2).

Sevoflurane produced a dose-dependent decrease in coronary perfusion pressure (CPP) to 70% and 49% of control value (2.5% and 5%, respectively). Despite this effects, coronary sinus blood flow (CSBF) was significantly decreased only at 2.5% sevoflurane and remained unchanged at 5% sevoflurane. Coronary vascular resistance (CVR) was significantly decreased at 5% sevoflurane. The ratio of CSBF to cardiac output (CSBF/CO) showed a tendency to increase at both low and high concentrations of sevoflurane (table 2, section C and fig. 3).

Myocardial oxygen consumption ($M\dot{V}o_2$) was decreased in a dose-dependent manner. Myocardial oxygen and lactate extraction ratio (Mo_2 ext and ML ext) were also significantly decreased at 5% and 2.5%, respectively. The ratio of left ventricular minute work index to $M\dot{V}o_2$ (LVMWI/$M\dot{V}o_2$) was significantly decreased at 5% (table 2, section C and fig. 4).

The hemodynamic changes in phasic AP, LVP, dP/dt, LVEDP, ECG. AoF, CO, and HR to each concentration of sevoflurane is shown in figure 5. The hemodynamic variables depressed to 50–80% of control values at 5% were restored to 70–90% of control 10 min after discontinuation of sevoflulane.

Combined effects of 2.5% sevoflurane and nicardipine (0.01 $mg \cdot kg^{-1}$) on hemodynamics, coronary circulation and myocardial metabolism are shown in table 3, figure 6 and 7.

Under 2.5% sevoflurane, nicardipine produced a significant decrease in arterial pressure (SAP, DAP and MAP), heart rate (HR) and systemic vascular resistance (SVR), and a significant increase in cardiac index (CI)

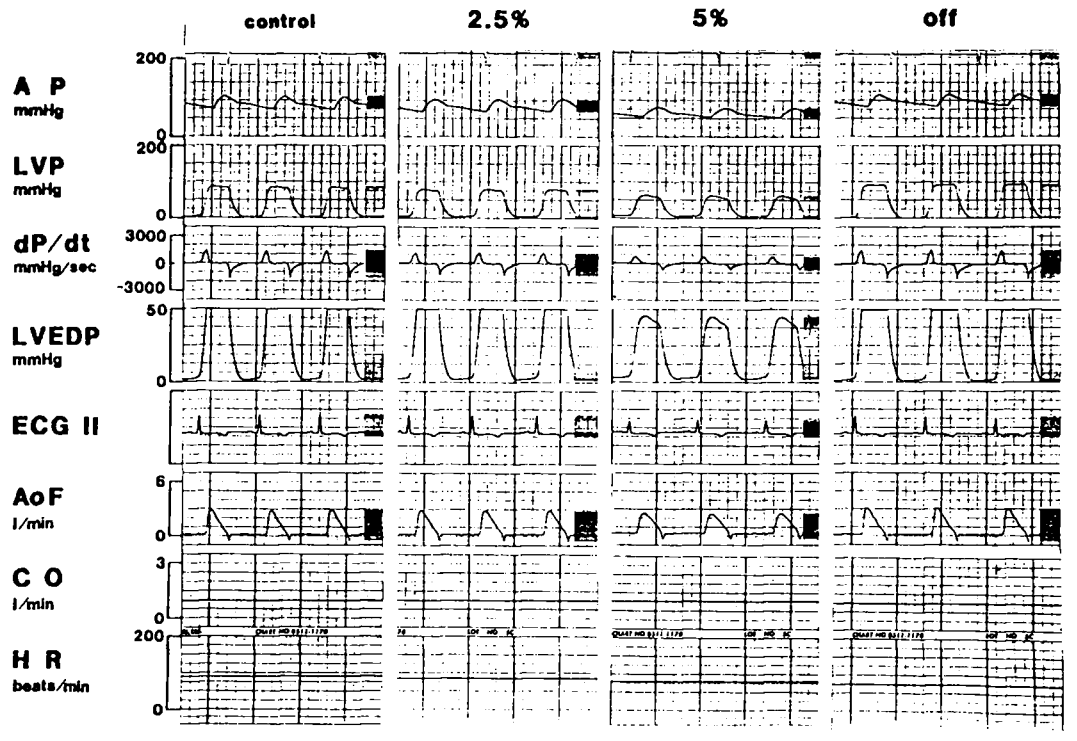

Fig. 5. Time course of changes in hemodynamic variables after administration of each concentration of sevoflurane at 10 min intervals in this order. When 5% sevoflurane was discontinued (off), the variables depressed to 50 ~ 80% of control values during 5% sevoflurane were restored to 70 ~ 90% of control values within 10 min.

and stroke volume index (SVI). LV dP/dt was significantly decreased, whereas the time constant (T) shortened slightly. Nicardipine produced a significant decrease in coronary perfusion pressure (CPP), an increase in coronary sinus blood flow (CSBF), and a significant decrease in coronary vascular resistance (CVR). CSBF/CO showed a tendency to decrease. Myocardial oxygen and lactate extraction ratio (Mo_2 ext and ML ext), and myocardial oxygen consumption ($M\dot{V}o_2$) were significantly decreased. LVMWI/$M\dot{V}o_2$ was slightly increased.

Discussion

As with other inhalation anesthetics[8-10], sevoflurane is certainly a myocardial depressant in the dog. The administration of 2.5% and 5% sevoflurane was followed by significant decreases in cardiac index (CI) and LV dP/dt.

However, the depression of myocardial function appears to be not so intense, because this depression was not accompanied by a significant increase in left ventricular end-diastolic pressure. Of more significance is the fact that stroke volume index (SVI) was well maintained to about 90% of control value even at 5% sevoflurane in spite of a marked decrease (48%) in LV dP/dt. This finding may be contributed to sevoflurane-induced-afterload reduction as evidenced by the dose-dependent reduction in systemic arterial pressure (AP).

Sevoflurane produced a dose-dependent decrease in heart rate (HR) as with isoflurane in our previous study[11]. Isoflurane has been clearly demonstrated to inhibit the baroreflex pathway both peripherally and centrally[12]. It can be thought that a decrease in HR produced by sevoflurane may be brought about through the inhibition of the baroreflex pathway in the same manner with isoflurane. A decrease in cardiac output

Table 3. Combined effects of 2.5% sevoflurane and nicardipine (0.01mg·kg^{-1}) on hemodynamics, coronary circulation and myocardial metabolism

measured variables and calculated parameters		2.5% Sevoflurane control value		after Nicardipine administration (0.01 mg·kg^{-1})
A) Hemodynamics				
SAP	(mmHg)	108±11	(6)	79±6**
DAP	(mmHg)	70±11	(6)	44±4**
MAP	(mmHg)	83±11	(6)	55±5**
HR	(beats·min^{-1})	100±6	(6)	90±6**
CI	(l·min^{-1}·kg^{-1})	0.09±0.01	(6)	0.10±0.01*
CVP	(mmHg)	5.8±0.7	(6)	6.4±0.7*
LVEDP	(mmHg)	5.0±0.6	(3)	5.7±0.9
SVI	(ml·kg^{-1})	0.87±0.09	(6)	1.14±0.09**
LVMWI	(g·m·kg^{-1}·min^{-1})	85.6±14.1	(3)	71.6±9.5
SVR	(mmHg·l^{-1}·min·kg)	1022±294	(6)	493±53*
LV dP/dt	(mmHg·sec^{-1})	1943±540	(3)	1783±552*
T	(msec)	47.0±10.4	(3)	43.7±8.4
B) Coronary Circulation and Myocardial Metabolism				
CPP	(mmHg)	70±11	(6)	44±4*
CSBF	(ml·min^{-1})	84.6±11.8	(6)	98.5±14.8*
CSBF/CO	(%)	6.0±0.9	(6)	5.6±0.7
CVR	(mmHg·l^{-1}·min)	904±213	(6)	455±74*
(a-cs) Do_2	(ml·dl^{-1})	5.9±0.8	(6)	3.5±0.5**
(a-cs) DL	(mg·dl^{-1})	7.8±1.7	(5)	5.3±1.8*
$M\dot{V}o_2$	(ml·min^{-1})	5.0±0.8	(6)	3.5±0.8*
M_{O_2} ext. ratio	(%)	36.4±4.2	(6)	23.0±4.1**
ML ext. ratio	(%)	42.8±5.7	(5)	29.2±3.5*
LVMWI/$M\dot{V}o_2$	(g·m·kg^{-1}·ml^{-1})	12.6±1.8	(3)	15.0±3.1

Values are means ± SE.
SAP=systolic arterial pressure; DAP=diastolic arterial pressure; MAP=mean arterial pressure; HR=heart rate; CI=cardiac index; CVP=central venous pressure; LVEDP=left ventricular end-diastolic pressure; SVI=stroke volume index; LVMWI=left ventricular minute work index; SVR=systemic vascular resistance; LV dP/dt= maximum rate of rise of left ventricular pressure; T=time constant; CPP=coronary perfusion pressure (diastolic arterial pressure); CSBF=coronary sinus blood flow; CSBF/CO=the ratio of CSBF to cardiac output; CVR=coronary vascular resistance; (a-cs) Do_2=arterio-coronary sinus oxygen content difference; (a-cs)DL=arterio-coronary sinus lactate content difference; $M\dot{V}o_2$=myocardial oxygen consumption; M_{O_2} ext. ratio (%)=myocardial oxygen extraction ratio; ML ext. ratio (%)= myocardial lactate extraction ratio; LVMWI/$M\dot{V}o_2$=the ratio of the left ventricular minute work index to myocardial oxygen consumption.
* $P<0.05$ vs. control value
** $P<0.01$ vs. control value

caused by sevoflurane may be due mainly to a decrease in HR.

Sevoflurane significantly increased time constant (T). The shorter the T, the better the relaxing function of the left ventricle, and vice versa. Therefore, sevoflurane may depress the left ventricular relaxing function. Because T also tends to increase with a decrease in HR, the decrease in T observed here appears to be related not only to a

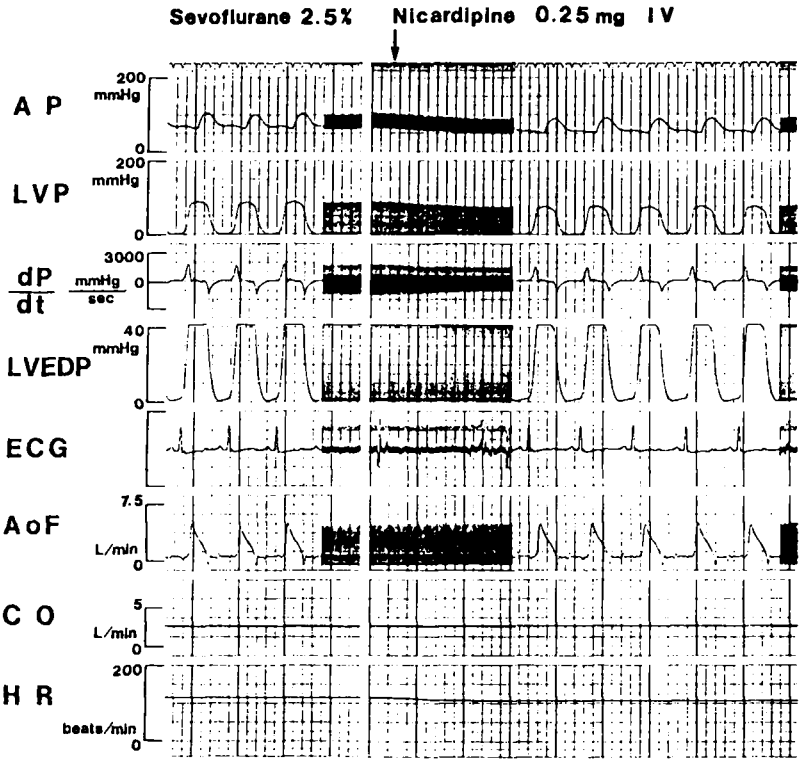

Fig. 6. Typical hemodynamic changes after intravenous administration of nicardipine (0.01 mg·kg^{-1}).

When nicardipine was administered (0.25 mg IV), the maximum hemodynamic changes occurred within the first minute after its administration.

Note the immediate decreases in AP, LVP, dP/dt, and HR, and the increase in CO. (See text for abbreviations.)

depressed systolic fiber shortening but also to a decreased HR[7].

Decreased myocardial metabolism appears to follow the decreased functional demands of the heart as evidenced by marked decreases in AP, HR, and myocardial contactility. It is of particular note that a significant decrease in cardiac efficiency (LVMWI/$M\dot{V}o_2$) occurred only at 5% sevoflurane. This suggests that cardiac efficiency can be well maintained, if high concentration of sevoflurane is not employed.

Afterall, the reduction in afterload produced by sevoflurane may partially compensate for the direct myocardial depressant effects of sevoflurane. Although our data showed a decrease in SVR, it is unknown whether sevoflurane may possess a vasodilatory property or not, because a decrease in SVR calculated using AP, CVP, and CO does not necessarily indicate a systemic vasodilatory action of sevoflurane.

At 5% sevoflurane, a decrease in CSBF was less than that in myocardial oxygen consumption, so there was a marked decrease in oxygen extraction (fig. 4). Coronary vascular resistance (CVR) was also significantly decreased. The decreases in CVR and myocardial oxygen demand were simultaneously observed. However, the latter is a condition that tends to induce an increase in CVR via metabolic autoregulation of the coronary vessels. Therefore, there appears to be some degree of coronary vasodilation i.e., "luxury perfusion" in this circumstance.

There are several possible mechanisms to explain this finding. First, the decrease in CVR produced by 5% sevoflurane may be

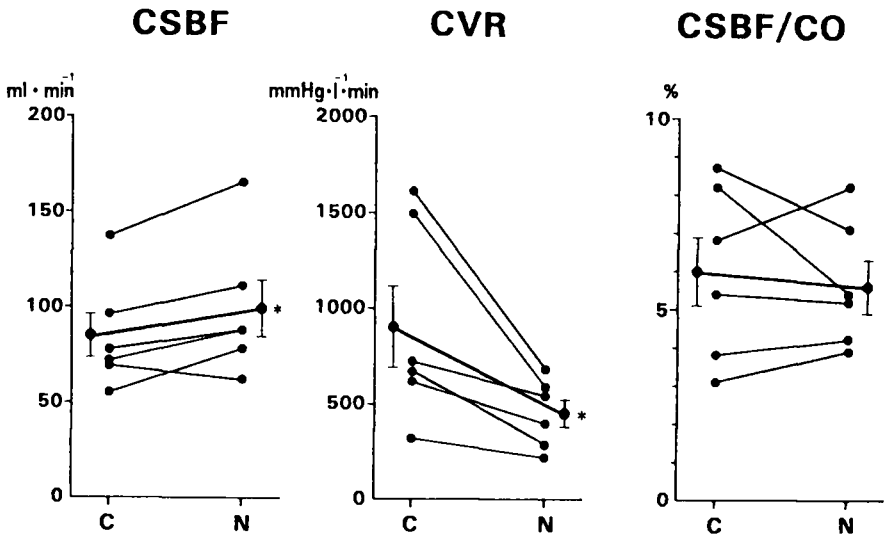

Fig. 7. Effects of nicardipine on coronary circulation under 2.5% sevoflurane anesthesia.

Nicardipine produced an increase in coronary sinus blood flow (CSBF) and a decrease in coronary vascular resistance (CVR). The ratio of CSBF to cardiac output (CSBF/CO) showed a tendency to decrease.

Values are means ± SE. N: after nicardipine injection

C: control (2.5% sevoflurane value) * $P<0.05$ vs. control value

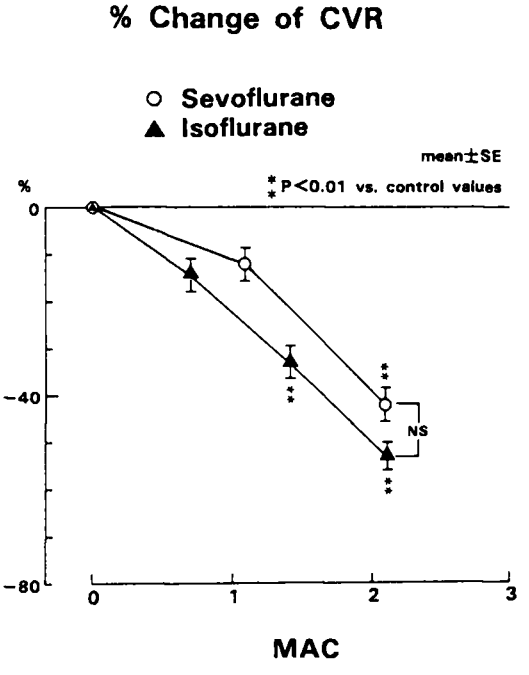

Fig. 8. Comparison of the effects of sevoflurane and isoflurane on coronary vascular resistance (CVR). The effects of 2.5% (1.1 MAC) and 5% (2.2 MAC) concentrations of sevoflurane compared with the control value (per cent change) reported in this study are graphically compared with those of isoflurane previously studied in eight dogs[11]

the result of a direct vasodilatory action of sevoflurane itself on the coronary vessels. The direct vasodilatory action of sevoflurane on the coronary vessels may be counteracted by a tendency to vasoconstriction due to the decrease in the metabolic rate

of the heart at 2.5% sevoflurane. In other words, coronary blood flow autoregulation may be still preserved at low concentration of sevoflurane. When 5% sevoflurane was administered, however, the direct vasodilatory action predominated, causing a loss of autoregulation. The facts that coronary sinus blood flow (CSBF) tended to decrease in proportion to a decrease in myocardial oxygen demand at 2.5% sevoflurane, and that CSBF showed a small degree of increase in spite of a further decrease in myocardial oxygen demand at 5% sevoflurane may support this hypothesis. Furthermore, the possibility that vasodilation of small magnitude during diastole might be overlooked in this study using mean instead of diastolic CSBF values for calculation of coronary resistance must be considered. This view is supported by the data reported by Domenech et al.[13], who observed a 12% decrease in diastolic coronary vascular resistance calculated using diastolic flow values at 2% halothane anesthesia in the dog. This suggest that a vasodilatory action may have been present even at 2.5% sevoflurane and that a greater degree of decrease in CVR than that in this study may have been observed, when diastolic flow instead of mean flow values is used for calculation for CVR.

Second, the possibility that the decrease in CVR was due to a decrease in the extravascular resistance (EVR) of the coronary vessels could be raised, because sevoflurane produced significant decreases in myocardial contractility and afterload of the heart. The EVR, which is found to be as much as one third of the total coronary resistance at normal ventricular and perfusion pressures, is mainly determined by the following two components; 1) the magnitude of the intramyocardial pressure which in turn is a function of the passive parietal stress in equilibrium with the intraventricular pressure; 2) myocardial contractility[14]. In this study, significant decreases in myocardial contractility and intraventricular pressure were actually found in a dose-dependent manner, indicating that a marked decrease in the EVR may have occurred indeed. In addition, the EVR have been demonstrated to become the major determinant of coronary blood flow under the conditions that coronary artery tends to dilate to a greater extent as a result of a loss of autoregulation as we discussed above[14]. Therefore, it seems possible that this decrease in the EVR may also play an important role in the decrease in CVR under sevoflurane anesthesia.

Thirdly, acute withdrawal of increased sympathetic activity produced by the depressant effect of sevoflurane on the central nervous regulatory system may partially explain the decrease in CVR. It has been demonstrated that α-adrenergic vasoconstriction could effectively compete with increases in metabolic vasodilation during exercise, and that coronary reserve is not exhausted even at peak exercise in the dog[15]. Conversely, α-adrenergic blockade may increase coronary flow to a greater extent than could be expected during maximal exercise[15].

In our experimental conditions, there appeared to be some degree of an increase in sympathetic activity in response to surgical stimulation in the control state. The administration of sevoflurane resulted in a marked depression of the increased sympathetic activity as evidenced by dose-dependent reductions in many hemodynamic variables. The baroreceptor reflex was also found to be abolished. Although, sevoflurane's action on the cardiovascular system may be a complex synthesis of its direct depressant effects on the heart, peripheral resistance vessels and the cardiovascular regulatory system, our data suggest that the depressant effect of sevoflurane especially on the central regulatory system may result in a decrease in sympathetic vasoconstrictive tone and subsequent decreases in SVR and CVR.

These mechanisms described above are expected to explain a significant decrease in CVR at 5% sevoflurane; i.e., no single mechanism seems to be useful for explanation of this finding. CSBF was well maintained in spite of a marked decrease in coronary perfusion pressure at any concentration of sevoflurane. We previously found a significant decrease in CVR at 2% and 3% isoflu-

rane in the same acute dog preparation[11], which is consistent with the other published reports, indicating that isoflurane is a potent coronary vasodilator[16–19].

Comparison of the effects of sevoflurane and isoflurane on coronary vascular resistance is presented in figure 8. No significant per cent change was found between sevoflurane and isoflurane at near 1MAC and 2MAC.

Judging from these findings, we conclude that sevoflurane may have a coronary vasodilatory action as seen with isoflurane. Sevoflurane's coronary vasodilatory effect itself may be beneficial to clinical practice. However, these data should alert us to the possibility that "coronary steal", i.e., redistribution of blood flow from the ischemic region to the normal areas with dilated vessels would be likely to occur in patients with coronary artery disease during high concentrations of sevoflurane anesthesia as is the case with isoflurane[20–23]. Therefore, careful ECG monitoring should be instituted for detection of a deterioration of myocardial ischemia in this situation.

In the presence of sevoflurane, the most striking effects of nicardipine on hemodynamics were its marked depression of heart rate and myocardial contractility as evidenced by a further decrease in LV dP/dt. The decrease in heart rate may be partially responsible for the decrease in LV dP/dt. Hysing et al.[24] reported that the tachycardic properties of nicardipine which were related to both baroreflex-mediated response initiated by the peripheral vasodilation and direct baroreflex stimulation were blunted during isoflurane anesthesia. They also found a significant decrease in LV dP/dt after nicardipine (10 $\mu g/kg^{-1}$) administration during 1.6% and 3.0% isoflurane anesthesia.

Nicardipine has been demonstrated to have both negative chronotropic and inotropic properties in vitro[25]. Although there were differences in the inhalation anesthetics used and in the depth of anesthesia at the time nicardipine was administered between their experiments and ours, our result was in agreement with those of Hysing et al. in terms of synergistic depressive effects of nicardipine with inhalation anesthetics on HR and LV dP/dt in such conditions that baroreflex function was blunted or almost abolished.

The sevoflurane-induced-inhibition of the reflex tachycardia elicited by nicardipine may be considered to be beneficial, especially in patients with decreased coronary reserve. It must be emphasized, however, that smaller dose of nicardipine should be given, especially when deep sevoflurane anesthesia is employed, because synergistic effects of sevoflurane and nicardipine may lead to a profound depression in cardiac function.

Despite these depressant effects described above, significant increases in stroke volume index (SVI) and cardiac index (CI) occurred after nicardipine administration. This increase in SVI suggests that the afterload reduction produced by nicardipine as evidenced by a significant decrease in systemic arterial pressure may counteract the synergistic cardiac depressant effects of sevoflurane with nicardipine. Thus, an increase in CI may be related to a potent peripheral vasodilatory action of nicardipine[26].

In our study, nicardipine showed a decrease of 50% in CVR and an increase of 16% in coronary sinus blood flow (CSBF) at 2.5% sevoflurane. The magnitude of vasodilator properties of nicardipine has been demonstrated to be dependent on the degree of vasomotor tone prior to its administration[27,28]. Therefore, this finding also suggests that 2.5% sevoflurane may slightly affect a baseline coronary vasomotor tone. It is interesting that the time constant (T) showed a slight decrease after nicardipine administration. This indicates an improvement of the relaxing function of the left ventricle, in spite of the decrease in myocardial contractility and heart rate. This may be due to an increase in the extent of systolic fiber shortening resulted from a reduction in afterload and an increase in preload of the left ventricle[7].

Marked decreases in myocardial oxygen consumption ($M\dot{V}o_2$) and lactate extraction appears to follow the decreased functional

demands of the heart due to the reductions in heart rate, myocardial contractility and afterload induced by nicardipine. On the other hand, the decrease in $M\dot{V}o_2$ was accompanied by a decrease in LVMWI resulted from a reduction in afterload. The decrease in LVMWI was slightly smaller than that in $M\dot{V}o_2$, therby causing a small degree of increase in cardiac efficiency ($LVMWI/M\dot{V}o_2$).

In summary, our results suggest that sevoflurane might possess a great margin of hemodynamic safety in this animal preparation, and possibly also in patients with decreased cardiovascular reserve. The decrease in the pumping of the heart at both low and high concentrations of sevoflurane was due mainly to a decrease in heart rate. Despite this depression, cardiac efficiency still remained unchanged, when low concentration of sevoflurane was employed.

Although our results suggest that sevoflurane may bring about coronary vasodilation, the effects of sevoflurane on extracardial neurohumoral factors through which the change in coronary resistance is mediated and those of the extravascular components on the coronary vessels should be eliminated to determine the direct vasodilatory effect of sevoflurane on the coronary vessels.

In the presence of 2.5% sevoflurane, nicardipine exerted a synergistic depressant effects on heart rate and myocardial contractility. This depression was counteracted by the nicardipine-induced-afterload reduction. This brought about a slight increase in cardiac output. If these results can be extrapolated to humans, however, smaller dose of nicardipine should be given during sevoflurane anesthesia. Nicardipine also exerted a potent coronary vasodilatory action at 2.5% sevoflurane, which suggests that 2.5% sevoflurane may only slightly affect a coronary vasomotor tone.

(Received Jul. 11, 1988, accepted for publication Jul. 13, 1988)

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