Cardiovascular Interaction between Sevoflurane and Nicardipine in Open Chest Dogs

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Cardiovascular interaction between nicardipine and sevoflurane was examined in dogs and compared with nicardipine-thiopental interaction and nicardipine-halothane interaction. The bolus intravenous injection of nicardipine at dosages of 15 μg/kg and 30 μg/kg under sevoflurane anesthesia produced transient decreases in blood pressure, systemic vascular resistance, left ventricular pressure, left ventricular $\frac{dp}{dt}$ and $-\frac{dp}{dt}$, and a slight increase in cardiac output. The degrees of these changes were almost identical to those under thiopental or halothane anesthesia. Left and right atrial pressure, pulmonary arterial pressure, pulmonary vascular resistance were not changed by nicardipine under any of the three anesthetics. These results suggest that the cardiovascular interaction of nicardipine and sevoflurane is additive and similar to that of nicardipine and halothane and that the cardiovascular changes induced by nicardipine are not modified by the presence of anesthetics. (Key words: sevoflurane, nicardipine, cardiovascular effect)

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Since the clinical importance of calcium channel blockers (CCB) for the treatment of cardiovascular disorders has been widely recognized[1–3], patients treated with such drugs has greatly increased. Studies of the cardiovascular interaction between CCB and inhalational anesthetics, therefore, have become important for the improvement of anesthetic management.

Various combinations of this two classes of drugs have been examined in experimental animals[4–15]. These drugs include CCBs such as verapamil (VR), diltiazem (DL), nifedipine (NF) and nicardipine (NC) and anesthetics such as halothane (HA), enflurane (EN) and isoflurane (IS). In general, the simultaneous use of these two classes of drugs produces additive cardiovascular depression, but such depression is minimal on in situ heart when these drugs are given in clinical doses. Of the inhalational anesthetics, the depression produced by VR appears most strongly under EN anesthesia[10].

Sevoflurane (SE) is a newly developed inhalatinal anesthetic which demonstrates cardiovascular effects similar to those of other potent inhalational anesthetics[16–18]. There have been no reported investigations of the cardiovascular interactions of SE and CCB. NC is the only CCB which can be intravenously administered and presently commercially available in Japan. Thus, we evaluated the cardiovascular interaction of SE and NC by giving NC under SE anesthesia in dogs, and compared to that of NC and HA,

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or NC and thiopental (TH).

Methods

Seven adult mongrel dogs (7–10.5 kg) were anesthetized with intravenous thiopental (25 mg/kg) and intubated. Respiration was controlled by a volume limited animal ventilator (R60, AIKA) with 100% O_2 to maintain Pa_{CO_2} at 35–40 mmHg as monitored continuously with an infra-red gas analyzer (901-MK2, NORGAN). Muscles were paralyzed with intermittent injection of pancuronium throughout the study. After left-sided thoracotomy, a electro-magnetic flow probe was placed on the ascending aorta for cardiac output (CO) measurement using a electromagnetic flow meter (MFV1200, Nihon Kohden). A Swan-Gantz catheter was inserted into the pulmonary artery through the right atrium and one catheter into the left atrium for measurement of pulmonary arterial · pressure (PAP) and right atrial pressure (RAP), and of left atrial pressure (LAP), respectively. Left ventricular pressure (LVP) and its positive and negative derivative, namely, velocity of pressure increase and decrease ($\frac{dp}{dt}$ and $-\frac{dp}{dt}$), were measured by a catheter tip transducer (CAMINO 420) inserted into the left ventricle through the right femoral artery. The left femoral artery was cannulated for measurement of systemic blood pressure (Bp), and the left femoral vein was cannulated for administration of the drugs and fluid (6 ml/kg/hr with lactated Ringers solution in 5% glucose). These catheters were connected to pressure transducers (Statham P23ID) for measurement of Bp, LAP, PAP and RAP. Systemic and pulmonary vascular resistance (SVR and PVR) were calculated by standard formulae; SVR = (mean Bp-mean RAP)/CO, PVR = (mean PAP − mean LAP)/CO. Heart rate (HR) was counted from the ECG (lead 2), continuously monitored on the oscilloscope. These procedures lasted about 30 min, and the dogs were observed for another 30 min for circulatory stability before actual measurement was begun.

After measurement of the control values (pre-injection values), 15 μg/kg of nicardipine (NC) was injected in bolus (less than 10 sec) followed by observation for 20 min for the study of the thiopental group (TH group).

One hour after the completion of the TH study, the same dogs were inhaled with 1 MAC (2.35%) of sevoflurarne (SE) for 30–40 min until circulatory stability was obtained. Under 1 MAC of SE the effect of a bolus injection of 15 μg/kg of NC was observed for 20 min, then that of a slowly injected dosage of 30 μg/kg of 2 min duration was also studied for 20 min (the SE group).

At the end of the SE study, inhalation of SE was replaced with inhalation of 0.5% of halothane (HA). After two hours, HA concentration was increased to 1 MAC (0.78%) for 30 min, and then the effect of 15 μg/kg of NC and that of 30 μg/kg were examined in the same manner as with the SE group (HA group). The order of SE study and HA study was random; 4 dogs received SE followed by HA and 3 first received HA followed by SE.

The data in the table, figures and the text are expressed as mean ± SEM. Statistical analysis of the data was done using two-way analysis of variance. If the F test was significant (less than 0.05), comparisons between individual periods, and between three anesthetic agents were analyzed using paired Student's t test for the actual values and using Wilcox's test for the percent values. A P values of less than 0.05 was assumed to be significant.

Results

The measured absolute values produced by these three anesthetics before administration of NC are listed in the table 1, and the percent values in relation to the values before administration of NC appear in the figures 1, 2 and 3. The absolute values of mean Bp, CO, HR, LVP, maximum $\frac{dp}{dt}$ and $-\frac{dp}{dt}$, and PAP before administration of NC were higher and those of PVR were lower under thiopental (TH) than under sevoflurane (SE) and halothane (HA), but almost the same as those under SE and HA. The other hemodynamic indices of the three groups were almost identical (table 1).

Table 1. Circulatory states produced by anesthetics before the administration of nicardipine

		mBp	CO	SVR	HR	LVP	$\frac{dp}{dt}$	$-\frac{dp}{dt}$	LAP	PAP	RAP	PVR
NC:15 μg/kg group	SE	78.0 ±5.8	0.99 ±0.08	6142 ±549	150.4 ±4.1	93.7 ±3.5	1973 ±171	1721 ±125	3.9 ±0.3	13.2 ±1.8	3.3 ±0.4	778 ±55
	HA	78.9 ±4.5	1.04 ±0.07	6044 ±698	147.3 ±9.8	96.3 ±3.1	1823 ±84	1870 ±77	4.0 ±0.5	13.7 ±1.0	3.3 ±0.5	760 ±79
	TH	124.3* ±8.2	1.70* ±0.24	6130 ±594	197.1* ±13.7	152.1* ±9.3	4254* ±547	3407* ±363	4.6 ±0.6	15.6 ±1.3	2.8 ±0.7	544* ±56
NC:30 μg/kg group	SE	78.6 ±7.2	0.98 ±0.08	6141 ±458	147.7 ±2.9	96.1 ±4.1	1970 ±123	1826 ±151	3.9 ±0.4	13.7 ±0.6	3.6 ±0.3	824 ±73
	HA	78.7 ±4.9	1.04 ±0.08	6162 ±670	146.0 ±7.2	96.1 ±4.0	1760 ±96	1833 ±98	4.0 ±0.5	13.9 ±0.9	3.5 ±0.4	799 ±87

*: $P<0.05$ vs SE (sevoflurane) and HA (halothane). Mean ± SE. mBp = mean blood pressure (mmHg), CO = cardiac output (L/min), SVR = systemic vascular resistance (dyne/sec·cm^5), HR = heart rate (beats/min), LVP = left ventricular pressure (mmHg), $\frac{dp}{dt}$ and $-\frac{dp}{dt}$ = maximum rate of LVP-increase and -decrease (mmHg/sec), LAP = left atrial pressure (mmHg). PAP = pulmonary arterial pressure (mmHg), RAP = right atrial pressure (mmHg), PVR = pulmonary vascular resistance (dyne/sec·cm^5), NC = nicardipine.

Intravenous injection of nicardipine (NC) decreased Bp and SVR, and increased CO immediately after injection (fig. 1). The degree of these changes expressed by percentage of the pre-administration value was similar under SE and HA, but greater under TH. However, the absolute value of Bp was still higher in the TH group than in the SE or the HA group. These changes produced by 15 μg/kg of NC returned to the pre-administration level within 5 min, but those produced by 30 μg/kg lasted longer (10–20 min) (fig. 1). HR was not changed significantly by the administration of NC in the SE and the HA groups, but tended to increase in the TH group (fig. 1). The significant difference, however, appeared only at 10 min after NC injection between TH and SE. The absolute values of HR remained higher in the TH group after the administration of NC.

LVP, $\frac{dp}{dt}$ and $-\frac{dp}{dt}$ decreased immediately after NC injection, but returned to the level of pre-injection 5 min after injection (fig. 2). These changes did not differ among the three groups, thus these absolute values were significantly higher in the TH group than in the other two groups. LAP was not altered by NC in the three groups and there was no significant difference between the groups (fig. 2).

Changes in PAP, PVR and RAP produced by NC were not significant, except in the TH group where PAP increased transiently at 1 min and PVR increased gradually and time-dependently (fig. 3). The absolute values of PVR in the TH group were significantly lower than those of the other groups at any measured time.

Discussion

In the present study, the intravenous administration of nicardipine (NC) in bolus under thiopental (TH) anesthesia transiently decreased Bp, SVR, LVP, $\frac{dp}{dt}$, $-\frac{dp}{dt}$, and increased CO. HR, LAP, PAP, RAP and PVR were unchanged. These findings are comparable to those of previous reports in which NC was administered under urethane-chloralose anesthesia[19,20]. In conscious dogs or in humans without anesthesia, however, HR is increased by NC[14,21,22].

Sevoflurane (SE) is a potent inhalational anesthetic now being widely studied in Japan. The cardiovascular effects of SE

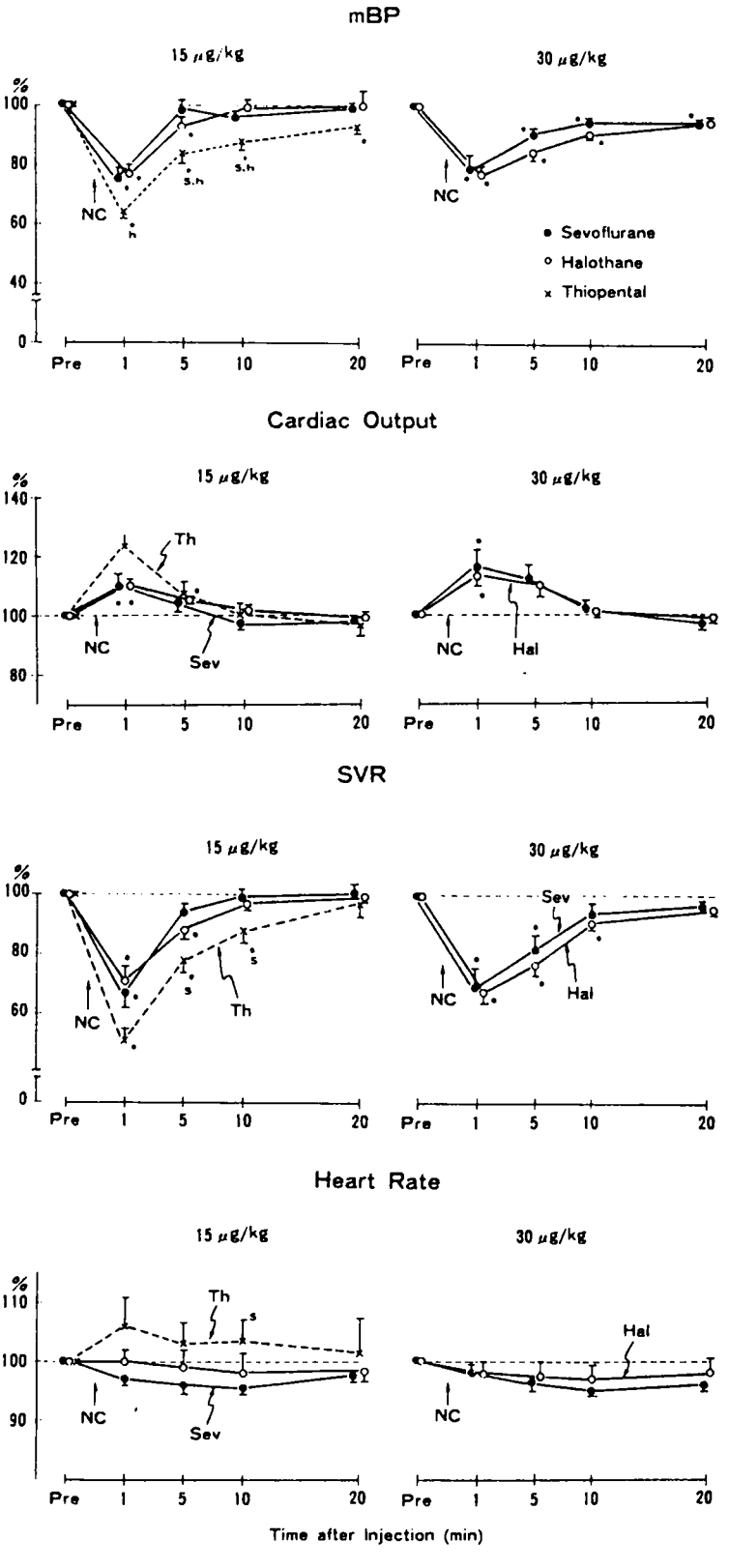

Fig. 1. Percent changes of mean blood pressure (mBp), cardiac output, systemic vascular resistance (SVR) and heart rate produced by nicardipine (NC). The values before NC injection (Pre) are 100% in each groups. *: $P<0.05$ vs Pre, s: $P<0.05$ vs the sevoflurane group, h: $P<0.05$ vs the halothane group. • = sevoflurane, o = halothane and × = thiopental.

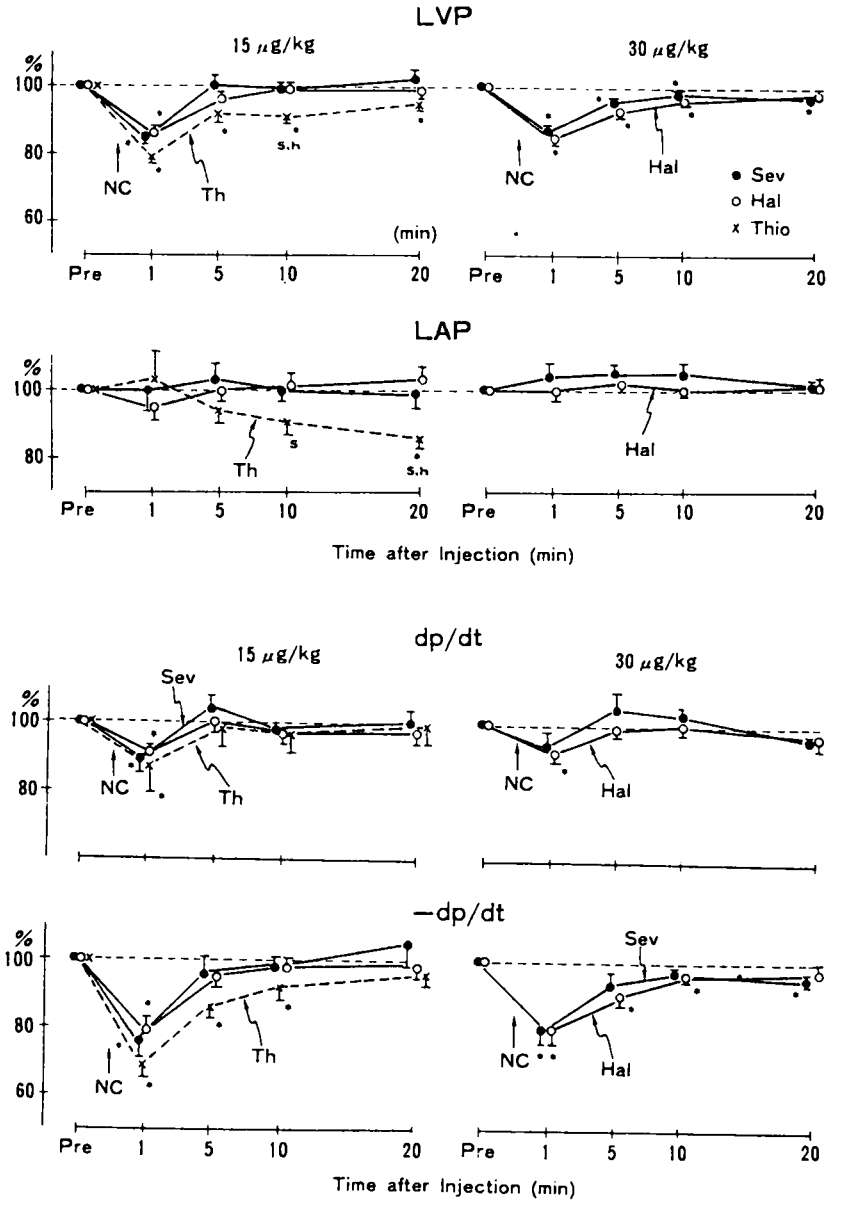

Fig. 2. Percent changes of left ventricular pressure (LVP), left atrial pressure (LAP), maximum rate of LVP increase ($\frac{dp}{dt}$) and decrease ($-\frac{dp}{dt}$) produced by nicardipine. Sev: sevoflurane, Hal: halothane, Thio: thiopental. *, s and h are same as those expressed in fig. 1.

have been reported to be as follows: dose-dependent decreases in Bp, CO and SV, and unaltered HR, LAP, SVR and PVR[16–18]. The same cardiovascular changes were observed in this study when SE was inhaled following TH anesthesia, except that HR significantly decreased. This difference in HR may be attributed to the higher HR resulting from the hyperhemodynamic state under TH anesthesia before SE-inhalation. The decreases in $\frac{dp}{dt}$ and $-\frac{dp}{dt}$ are new findings of this study. The administration of HA in this study was found to mediate cardiovascular changes similar to those with SE inhalation.

The cardiovascular interaction between these two types of drugs, which causes cardiovascular depression is, therefore, of interest. The interactions between various combinations of calcium channel blockers such as diltiazem (DL), verapamil (VR), nifedipine (NF) and NC and inhalational anesthetics such as HA, enflurane (EN), and isoflurane

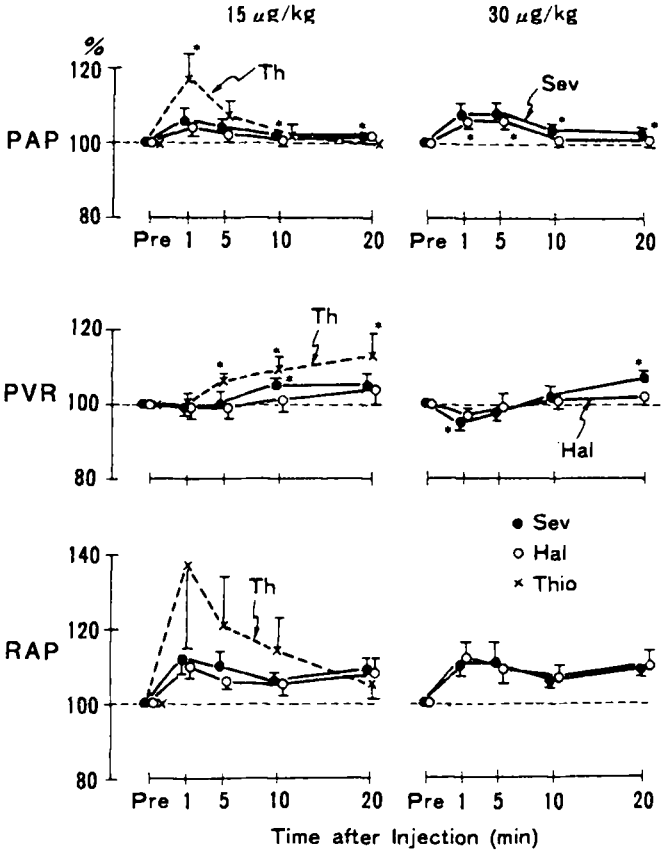

Fig. 3. Percent changes of pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR) and right atrial pressure (RAP) produced by nicardipine. *: $P<0.05$ vs pre-injection values.

(IS) have been examined in experimental animals[4–15]. However, there have been no reports describing the interaction of NC and SE. In general, the cardiovascular interaction of these two types of drugs in vivo is additive and the cardiovascular effects of calcium channel blockers are not modified by the presence of inhalational anesthetics[4–15]. Exceptions are that the depression produced by VR appears to be greater under EN anesthesia[9,10], although it is the same under HA and IS anesthesia, and that the decrease in HR produced by DL lasts longer under HA and IS anesthesia than under intravenous anesthesia[5,15]. The present study has shown that the effect of the NC-SE interaction on cardiovascular function is also additive and that the degree of change is identical to that of the NC-HA or NC-TH interaction. This suggests that the level of cardiovascular change due to NC under SE anesthesia can be estimated from the effect of NC under HA or TH.

The direct depressive effect on myocardial contractility by the combination of these two types of drugs has been reported to be simply additive in all in vitro studies using isolated heart muscle preparation[4,5,7]. The degrees of percent depression mediated by the calcium channel blockers do not alter with the presence of HA, EN and IS, but are greater with NC and NF than with DL and VR at a molar concentration[8]. The in vitro result on the NC-HA interaction supports our findings for in situ heart, in which myocardial contractility was estimated by changes in $\frac{dp}{dt}$, an indirect index of contractility. Although the direct effect of the NC-SE interaction on myocardial contractility has not been reported, from the present results of in vivo study of the NC-SE interaction it may be possible that the direct effect of the NC-SE interaction on contractility is simply additive such as that of as other

combinations.

HR is the only index whose response to NC is influenced by the presence of anesthetics. Namely, HR has been reported to increase by NC in the absence of anesthetic in conscious dogs and in humans[14,21,22], but it is not altered by NC in the presence of intravenous or inhalational anesthetics in this study. The acceleration of the autonomic baro-reflex induced by decreased Bp produced by NC may be depressed under anesthetics to initiate this difference in response of HR to NC. IS has been also reported to inhibit the reflex tachycardia induced by NC[14]. The tendency of HR to increase after NC-administration under TH may be related to the weaker depressive effect of TH on this reflex.

The time-dependent gradual increase in PVR following NC injection during TH anesthesia may not be due to NC, but may rather be due to the lightening of the anesthetic level during TH anesthesia.

A slowly injected 30 μg/kg of NC produced the depression almost similar to that produced by 15 μg/kg in bolus injection. The speed of injection is, therefore, an important factor to modify the degree of cardiovascular depression mediated by NC.

In conclusion, cardiovascular interaction between nicardipine and sevoflurane was additive. The degree of cardiovascular changes produced by nicardipine under thiopental anesthesia did not differe from that under sevoflurane or halothane, suggesting that the cardiovascular effect of nicardipine was not modified by the presence of sevoflurane and halothane.

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