Hemodynamic Effects of Nicardipine-induced Hypotension during Enflurane/Nitrous Oxide Anesthesia in Man

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Hemodynamic effects of nicardipine-induced hypotension during enflurane/nitrous oxide were evaluated in 10 surgical patients. An infusion of nicardipine was titrated to maintain mean arterial pressure at 60 to 70 mmHg under enflurane 1.5 to 2.0 vol% and nitrous oxide 60 vol%. Mean arterial pressure was well controlled with the nicardipine infusion, whereas cardiac index increased with decreased systemic vascular resistance. Heart rate increased concomitantly with decreased blood pressure, which indicated that enflurane 1.5 to 2.0 vol% did not suppress baroreceptor reflex during nicardipine administration. However, rate-pressure-product was not increased by the nicardipine. Right and left ventricular systolic work indices were not increased by the nicardipine. Right ventricular ejection fraction was not also changed by the nicardipine. Although serum norepinephrine level increased during the nicardipine infusion, the values remained within physiological ranges. Our results suggest that nicardipine-induced hypotension may be safely performed during enflurane/nitrous oxide anesthesia because neither ventricular work nor myocardial oxygen demand was increased by nicardipine. (Key words: controlled hypotension, enflurane/nitrous oxide anesthesia, hemodynamics, nicardipine)

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Among various calcium entry blockers, nicardipine decreases arterial blood pressure mainly by action on vascular smooth muscles[1]. Recently, nicardipine has been applied for treatment of hypertension during surgery under general anesthesia[2]. This clinical study was undertaken to evaluate the hemodynamic effects of nicardipine-induced hypotension during enflurane/nitrous oxide anesthesia to evaluate clinical usefulness of nicardipine as a hypotensive drug during anesthesia.

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Methods

Subjects for this study consisted of ten adult patients, average age of 37 years old, 6 females and 4 males, scheduled for elective orthopedic surgery under controlled hypotension. Approval from the Hokkaido University Hospital Ethics Committee was

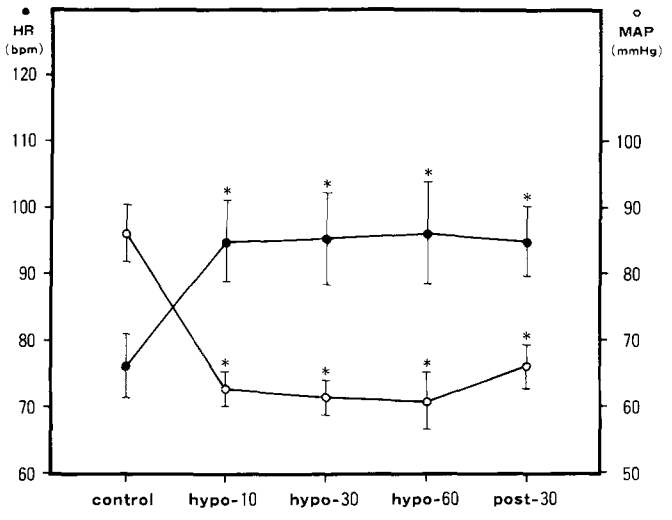

Fig. 1. Changes of mean arterial pressure (MAP) and heart rate (HR) before, during and after nicardipine administration during enflurane/nitrous oxide anesthesia.

*Indicates significant differences vs control.

granted for the study, and informed consent was obtained from each patient.

All patients were premedicated with triazolam 0.25 mg and loxatidine 75 mg P.O. 120 min before induction of anesthesia. Anesthesia was induced by thiamylal (5 $mg \cdot kg^{-1}$ I.V.) and the trachea was intubated by muscle relaxation with vecuronium (0.1 $mg \cdot kg^{-1}$ I.V.). Anesthesia was maintained with enflurane 1.5–2.0 vol% in nitrous oxide ($41 \cdot min^{-1}$) and in oxygen ($21 \cdot min^{-1}$). Their respiration was controlled mechanically to achieve normocapnia monitoring end-tidal carbon dioxide concentration by a capnograph (Novametrics 7000, USA). Arterial blood pressure was continuously monitored at the radial artery using a disposable transducer system (Baxter MP5100 transducer and Uniflow flush system, USA). Electrocardiogram (CM5), Sp_{O_2} by a pulse-oximeter (Novametrics 7000, USA) and bladder temperature (Terumo, Japan) were continuously monitored in all patients. A modified pulmonary artery catheter equipped with a fast-response (100 ms) thermistor (93-A-431H-8.5Fr, American Edwards, USA) was inserted through the right internal jugular vein. A REF-1 Ejection Fraction Cardiac Output Computer (American Edwards, USA) was used for measurements of cardiac output (CO) and right ventricular ejection fraction (RVEF), and other hemodynamic variables were calculated using standard formulae. At the time of skin incision a nicardipine infusion was initiated at the rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and the rate was controlled to maintain mean arterial blood pressure (MAP) among 60 to 70 mmHg. Hemodynamic variables were determined after induction of anesthesia (control), 10, 30 and 60 min after hypotension (hypo-10, hypo-30, hypo-60), and 30 min after cessation of nicardipine administration (post-30). Hemodynamic variables included heart rate (HR), MAP, cardiac index (CI), RVEF, mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), right atrial pressrue (RAP), right ventricular end-diastolic, systolic and end-systolic volume indices (RVEDVI, RVSVI, RVESVI), left and right ventricular stroke work indices (LVSWI, RVSWI), systemic and pulmonary vascular resistance indices (SVRI, PVRI). Pa_{O_2} and Pa_{CO_2} by ABL-3000 (Radiometer, Denmark) and serum epinephrine

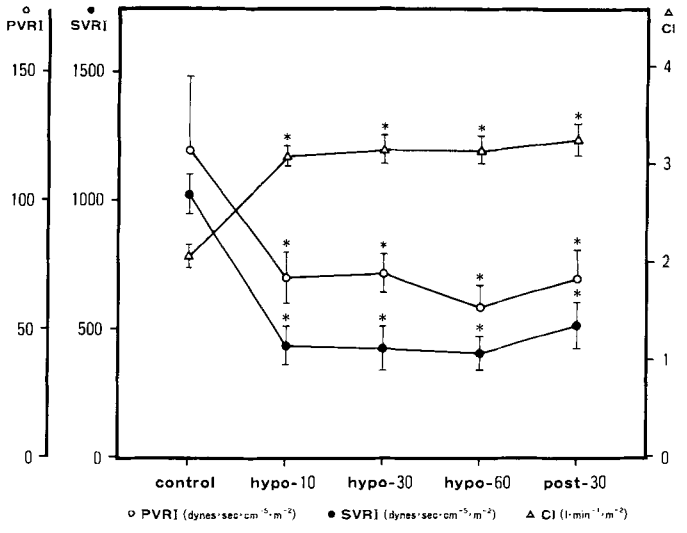

Fig. 2. Changes in cardiac index (CI), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI) before, during and after nicardipine administration during enflurane/nitrous oxide anesthesia.

*indicates significant differences vs control.

and norepinephrine concentrations by high-performance gas chromatography (Shimazu, Japan) were also measured after induction of anesthesia, 30 min after hypotension and 30 min after cessation of nicardipine administration, respectively. Lactate Ringer's solution was administered at a rate of 8 $ml \cdot kg^{-1} \cdot hr^{-1}$ during the study. Blood loss less than 1,000 ml was replaced by its twofold volume of hydroxyethylstarch and more than 1,000 ml of blood loss was replaced by 80% volume of packed red cells. Results were expressed by mean ± SEM and paired Student's t test was used for statistical analysis. A value of P less than 0.05 was deemed statistically significant.

Results

Changes of hemodynamic variables before, during after nicardipine administration were summarized in table 1. Significant decreases in MAP were obtained with concomitant increases in HR by nicardipine administration (fig. 1). CI increased significantly, and SVRI and PVRI decreased significantly as shown in fig. 2. However, there were no significant changes in other hemodynamic variables studied (table 1). Pa_{O_2} and Pa_{CO_2} remained unchanged during the study. Serum norepinephrine level was increased by nicardipine administration, whereas serum epinephrine level remained unchanged (table 2).

Discussion

Nicardipine administration during enflurane/nitrous oxide anesthesia decreased MAP and SVRI, and increased CI. This is due to pharmacological characteristics of nicardipine that acts on vascular smooth muscles selectively rather than myocardium[3]. The negative inotropic effect of nicardipine is less than other calcium entry blockers such as nifedipine, diltiazem and verapamil[4]. HR increased probably because of baroreceptor response to decreased MAP. This indicates that nicardipine-enflurane interaction differs from that with halothane, isoflurane or fentanyl. Tachycardia induced by nicardipine was reported to be less during halothane and isoflurane anesthesia under which the baroreflex pathway would be suppressed[8–11]. Kishi et al. reported that HR was not changed by nicardipine during diazepam/fentanyl anesthesia[2]. In our

Table 1. Hemodynamic variables before, during and after nicardipine administration

		control	Hypo-10	Hypo-30	Hypo-60	Post-30
CI	($l \cdot min^{-1} \cdot m^{-2}$)	2.18 ± 0.20	3.20 ± 0.19*	3.25 ± 0.24*	3.25 ± 0.24*	3.34 ± 0.23*
MAP	(mmHg)	86.0 ± 4.3	62.8 ± 2.1*	62.2 ± 2.1*	60.9 ± 2.8*	66.6 ± 2.6*
HR	(bpm)	77.1 ± 4.4	95.0 ± 5.6*	95.2 ± 6.7*	95.5 ± 6.9*	93.1 ± 6.0*
MPAP	(mmHg)	20.3 ± 0.8	20.3 ± 1.5	19.6 ± 1.4	17.9 ± 1.4	19.0 ± 1.5
PCWP	(mmHg)	11.8 ± 1.1	12.2 ± 1.1	10.9 ± 1.1	10.5 ± 1.3	11.2 ± 0.9
RAP	(mmHg)	9.0 ± 1.2	10.4 ± 1.3	9.8 ± 1.2	8.7 ± 1.2	9.0 ± 1.3
SVRI	($dynes \cdot sec \cdot cm^{-5} \cdot m^{-2}$)	1014 ± 108	461 ± 47*	456 ± 44*	449 ± 37*	508 ± 46*
PVRI	($dynes \cdot sec \cdot cm^{-5} \cdot m^{-2}$)	119 ± 23	71 ± 11*	74 ± 7*	58 ± 8*	71 ± 14*
RVEF		0.45 ± 0.03	0.50 ± 0.02	0.52 ± 0.02	0.50 ± 0.03	0.52 ± 0.02
RVEDVI	($ml \cdot m^{-2}$)	86.5 ± 7.2	98.7 ± 12.3	94.6 ± 9.5	96.8 ± 11.8	96.9 ± 10.5
RVSVI	($ml \cdot m^{-2}$)	38.4 ± 3.5	49.0 ± 5.8	48.2 ± 4.3	46.2 ± 4.1	49.7 ± 5.1
RVESVI	($ml \cdot m^{-2}$)	48.2 ± 5.8	49.9 ± 7.8	46.3 ± 6.1	50.5 ± 9.0	47.3 ± 6.4
RVSWI	($g \cdot m \cdot beat^{-1} \cdot m^{-2}$)	5.97 ± 0.85	6.38 ± 1.2	6.70 ± 0.87	5.98 ± 0.98	6.70 ± 1.03
LVSWI	($g \cdot m \cdot beat^{-1} \cdot m^{-2}$)	37.8 ± 3.6	32.1 ± 3.9	32.1 ± 2.8	32.6 ± 4.5	36.3 ± 4.4
RPP		8853 ± 615	8363 ± 615	8447 ± 641	8229 ± 586	9162 ± 637

(mean ± SEM)

*indicates significant differences vs control.

CI=cardiac index, MAP=mean arterial pressure, HR=heart rate, MPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, RAP=right atrial pressure, SVRI=systemic vascular resistance index, PVRI=pulmonary vascular resistance index, RVEF=right ventricular ejection fraction, RVEDVI=right ventricular end-diastalic volume index, RVSVI=right ventricular systolic volume index, RVESVI=right ventricular end-systolic volume index, RVSWI=right ventricular stroke work index, LVSWI=left ventricular stroke work index, RPP=rate pressure product (systolic blood pressure × heart rate).

Table 2. Changes in Pa_{O_2}, Pa_{CO_2} and catecholamine levels before, during and after nicardipine administration

		control	Hypo-30	Post-30
Pa_{O_2}	(mmHg)	215.7 ± 13.0	199.6 ± 12.4	188.1 ± 14.7
Pa_{CO_2}	(mmHg)	32.9 ± 2.1	35.3 ± 1.8	36.3 ± 2.3
Epinephrine	($ng \cdot ml^{-1}$)	0.022 ± 0.01	0.025 ± 0.01	0.026 ± 0.01
Norepinephrine	($ng \cdot ml^{-1}$)	0.067 ± 0.02	0.25 ± 0.05*	0.24 ± 0.10*

(mean ± SEM)

*indicates significant differences vs control.

study enflurane 1.5–2.0 vol% did not affect nicardipine-induced baroreflex. It was also reported that baroreflex sensitivity to reduction in blood pressure induced by nicardipine has a negative correlation with age[12]. Our

patients' mean age was 37 years, and so baroreflex sensitivity seemed to be normal. Therefore, HR may be increased by nicardipine in young patients during enflurane anesthesia as observed in induced hypotension by nitroglycerin during enflurane anesthesia[13]. This is different in hypotension induced by prostaglandin E_1 and trimethaphan during enflurane anesthesia[13].

Rate-pressure-product, as an index of myocardial oxygen consumption, remained constant. No ischemic patterns on ECG (CM5 lead) were observed, and LVSWI and RVSWI did not change. These results indicate that nicardipine increases neither oxygen demand nor ventricular work. Recently, a modified pulmonary artery catheter equipped with a fast-response thermistor is applied in clinical evaluation of right ventricular function[14]. Ejection fraction (EF), expressed as stroke volume/ventricular end-diatolic volume, is one of the important indices of cardiac function. Stroke volume usually increases when afterload decreases[15]. In this study, PVRI (right ventricular afterload) decreased significantly, whereas RVSVI, RVSWI, RVESVI and RVEDVI did not change. However, RVEF did not increase in this study. Therefore, CI increased mainly due to increses in HR in our study. Takeda et al. reported that RVSWI increased by nicardipine-induced hypotension during halothane anesthesia in dogs[16]. They concluded that increased RVSWI was due to increases in PVR and venous return. These discrepancies between our study and theirs may be related to differences in species (human vs dog) and/or anesthetics (enflurance vs halothane).

No change in Pa_{O_2} during nicardipine administration in this study indicates that nicardipine seems to have little effect on hypoxic pulmonary vasoconstriction. This is not the case with hypotension induced by nitroglycerin. Serum norepinephrine incresed during nicardipine infusion and serum epinephrine did not. Takeda et al. reported that both serum epinephrine and norepinephrine increased by nicardipine in rabbits anesthetized with halothane[17]. The difference may be in part due to species difference. Our results may suggest that enflurane suppresses the adrenal secretion of epinephrine but norepinephrine secretion from sympathetic nerve terminal is not suppressed by enflurane.

In conclusion, nicardipine-induced hypotension during enflurane/nitrous oxide anesthesia easily controlled MAP at the desired level, increased CI without increases in myocardial oxygen consumption, and increased serum norepinephrine levels that were within normal limits. Therefore, controlled hypotension by nicardipine will be safely performed during enflurane/nitrous oxide anesthesia.

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