The Effects of an Intravenous Nicardipine Injection on Baroreflex Control of Heart Rate in Man

Zen'ichiro WAJIMA, Tetsuo INOUE and Ryo OGAWA

The effects of nicardipine injection on baroreflex control of heart rate were investigated by both pressor and depressor tests in 17 adult patients. Baroreflex sensitivity was attenuated after nicardipine injection by the pressor test using phenylephrine, whereas it was not changed by the depressor test using nitroglycerine. No resetting of the baroreflex occurred after nicardipine injection. By the pressor test, the plasma norepinephrine level was decreased, indicating that parasympathetic activity increased, and by the depressor test, the plasma norepinephrine concentration was increased, indicating that sympathetic activity increased. These results suggest that it is safe to use nicardipine clinically even when reduction in blood pressure for hypovolemia or unclamping the main artery is expected, and it is disadvantageous to administer the drug when an increase in blood pressure due to cross-clamping of the main artery is forecasted. (Key words: nicardipine, baroreflex, pressor test, depressor test, resetting, norepinephrine)

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Arterial baroreflex is a very potent cardiovascular reflex which occurs with a rapid blood pressure change: an increase in arterial pressure ordinarily produces an immediate decrease in heart rate (pressor response), whereas a decrease in arterial pressure is usually followed by an increased heart rate (depressor response)[1]. It is considered that parasympathetic activity increases in the pressor response, whereas sympathetic activity increases in the depressor response[2,3].

Recently, injectable nicardipine, a calcium channel blocker, was introduced into the clinical field. In this study we evaluated the effects of intravenously administered nicardipine on arterial baroreflex control of heart rate in man because there are no reports of nicardipine on this subject.

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Patients and Methods

Seventeen adult patients undergoing elective surgery with an ASA physical status of I or II who had no history of neural, respiratory or cardiovascular disease were selected as subjects. Their ages ranged from 19 to 46 yr. Institutional approval and informed consent from all of the patients were obtained. The patients were randomly divided into two groups. One group comprised 9 patients and the pressor tests were

performed for them (the pressor test group), and other one comprised 8 patients and the depressor tests were carried out for them (the depressor test group).

These procedures have been published once elsewhere[4].

Teflon catheters (18 and 20 G) were inserted into a forearm vein and a radial artery under local anesthesia (1% lidocaine). Blood pressure and ECG were displayed on a polygraph (model CBM-3000, Nippon Colin, Japan), using a Gould P-50 transducer.

No patient was premedicated. After hemodynamic stabilization, the pressor baroreceptor response was assessed by the pressor test, originally described by Smyth et al.[5]; phenylephrine, 2–3 $\mu g \cdot kg^{-1}$ was injected to increase arterial blood pressure by 20–30 mmHg. Fifteen minutes later, when arterial blood pressure had returned to the preinjection level, nicardipine, 20 $\mu g \cdot kg^{-1}$ was injected. After 10 min, another pressor test was carried out. Nitroglycerine, 8–10 $\mu g \cdot kg^{-1}$ was used for the depressor test. The relationship between systolic blood pressure and the succeeding R-R interval was quantitatively evaluated during the phase of increase (in the pressor test) or the phase of decrease (in the depressor test) in arterial pressure. Systolic pressure and R-R intervals were plotted in a beat-to-beat analysis. Data were assessed using the least-square linear regression analysis of the linear part of the relationship between blood pressure and R-R interval. Only patients whose regression slopes had a correlation coefficient greater than 0.8 were included in the group mean. The slope of this linear regression expressed in msec per mmHg was used as an index of baroreflex function. These data were analyzed using a package software called "autonomic nerve system package"[6] processed with a computer (PC-9801VX21, NEC, Japan) connected with CBM-3000 through an RS-232C interface.

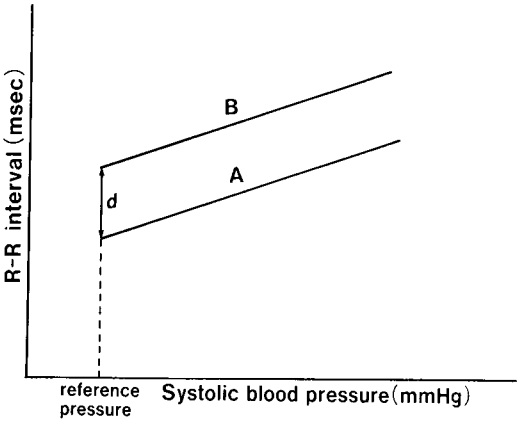

Fig. 1. The control line A and the line B obtained during a different experimental period are baroreflex slope. The resetting of the reflex is shown by the arrow, *d*.

Blood gas analysis was conducted before the first pressor or depressor test as control and 10 min after nicardipine injection. Plasma epinephrine and norepinephrine concentrations also were measured by high performance liquid chromatography at the following points: before the first pressor or depressor test as the control, just after the first pressor or depressor test, just before nicardipine injection (15 min after the first test), 10 min after nicardipine injection, and just after the second pressor or depressor test.

Resetting of baroreflex was determined by calculation of the pulse interval at the reference pressure, as described by Bristow et al.[7]: to determine reflex resetting, a vertical line was constructed at the level of the control systolic blood pressure. The resetting of the reflex is shown by the arrow, *d* (fig. 1).

The data were presented as mathematical means and central tendencies were expressed by standard deviations. ANOVA and Student's t-test

Table 1. Physical and clinical characteristics of patients in the two groups

Group	Age (year)	Body Weight (kg)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	R-R interval (msec)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pHa
Pressor test group	32.3 ± 7.2	60.7 ± 8.1	135.6 ± 16.6	71.3 ± 7.6	841.3 ± 148.8	98.0 ± 9.1	37.7 ± 3.3	7.428 ± 0.016
Depressor test group	35.4 ± 10.8	54.1 ± 13.6	127.0 ± 11.6	64.4 ± 8.1	918.3 ± 133.7	95.1 ± 10.3	40.1 ± 4.1	7.422 ± 0.008

Values are expressed as mean ± SD

Table 2. Blood gas analysis before and after nicardipine

Group			pre-injection	post-injection	significance
Pressor test group	Pa_{O_2}	(mmHg)	98.0 ± 9.1	87.5 ± 10.3	$P < 0.005$
	Pa_{CO_2}	(mmHg)	37.7 ± 3.3	39.8 ± 3.3	$P < 0.05$
	pHa		7.428 ± 0.016	7.415 ± 0.010	$P < 0.05$
Depressor test group	Pa_{O_2}	(mmHg)	95.1 ± 10.3	92.1 ± 9.2	NS
	Pa_{CO_2}	(mmHg)	40.1 ± 4.1	40.0 ± 3.9	NS
	pHa		7.422 ± 0.008	7.415 ± 0.010	NS

Values are expressed as mean ± SD
NS: not significant

Table 3. Systolic blood pressure, diastolic blood pressure, R-R interval and R-R interval at reference blood pressure before and after nicardipine

Group			pre-injection	post-injection	significance
Pressor test group	Systolic blood pressure	(mmHg)	135.6 ± 16.6	132.0 ± 15.1	NS
	Diastolic blood pressure	(mmHg)	71.3 ± 7.6	64.3 ± 6.9	$P < 0.01$
	R-R interval	(msec)	841.3 ± 148.8	777.3 ± 152.0	$P < 0.01$
	R-R interval at reference blood pressure	(msec)	822.1 ± 205.3	806.4 ± 245.3	NS
Depressor test group	Systolic blood pressure	(mmHg)	127.0 ± 11.6	126.5 ± 16.7	NS
	Diastolic blood pressure	(mmHg)	64.4 ± 8.1	60.1 ± 7.7	$P < 0.001$
	R-R interval	(msec)	918.3 ± 133.7	842.1 ± 126.6	$P < 0.01$
	R-R interval at reference blood pressure	(msec)	959.8 ± 149.1	899.5 ± 166.3	NS

Values are expressed as mean ± SD
NS: not significant

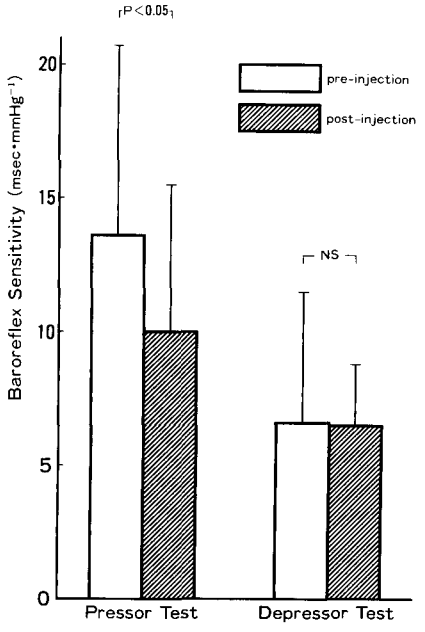

Fig. 2. Changes in baroreflex sensitivity induced by nicardipine injection, 20 $\mu g \cdot kg^{-1}$. Baroreflex sensitivity was attenuated 10 min after nicardipine injection by the pressor test, whereas it was not changed by the depressor test.

were used to analyze the values obtained. A *P*-value less than 0.05 was used to accept or reject statistical hypotheses.

Results

There were no significant differences in age, body weight, systolic blood pressure, diastolic blood pressure, R-R interval, Pa_{O_2}, Pa_{CO_2}, or pHa between the two groups before the study (table 1).

Pa_{O_2} and pHa were significantly decreased 10 min after nicardipine injection in the pressor test group but were not altered in the depressor test group (table 2). Pa_{CO_2} was significantly increased 10 min after nicardipine injection in the pressor test group but was not changed in the depressor test group (table 2).

In the pressor test group, systolic blood pressure was not changed significantly 10 min after nicardipine injection, whereas diastolic blood pressure and the R-R interval had decreased significantly. The pulse interval at reference pressure was not significantly altered (table 3). Baroreflex sensitivity was attenuated significantly after nicardipine injection (fig. 2).

In the depressor test group, systolic blood pressure was not altered significantly 10 min after nicardipine injection, whereas diastolic blood pressure and the R-R interval had decreased significantly. The pulse interval at reference pressure was not significantly changed (table 3). Baroreflex sensitivity remained unchanged after nicardipine injection (fig. 2).

In the pressor test group, the plasma norepinephrine level was significantly decreased just after the first pressor test, just before nicardipine injection and just after the second pressor test compared with the control. It was significantly higher 10 min after nicardipine injection than just before nicardipine injection, and was significantly lower just after the second pressor test than 10 min after nicardipine injection. The plasma epinephrine level remained unchanged throughout the study (fig. 3).

In the depressor test group, the plasma norepinephrine level was significantly higher than the control at each point. It was significantly higher just after the second depressor test than 10 min after nicardipine injection. The plasma epinephrine level remained stable throughout the study, as in the pressor test group (fig. 4).

Discussion

In this study, nicardipine injection attenuated baroreflex control of heart rate by the pressor test, whereas it did not by the depressor test.

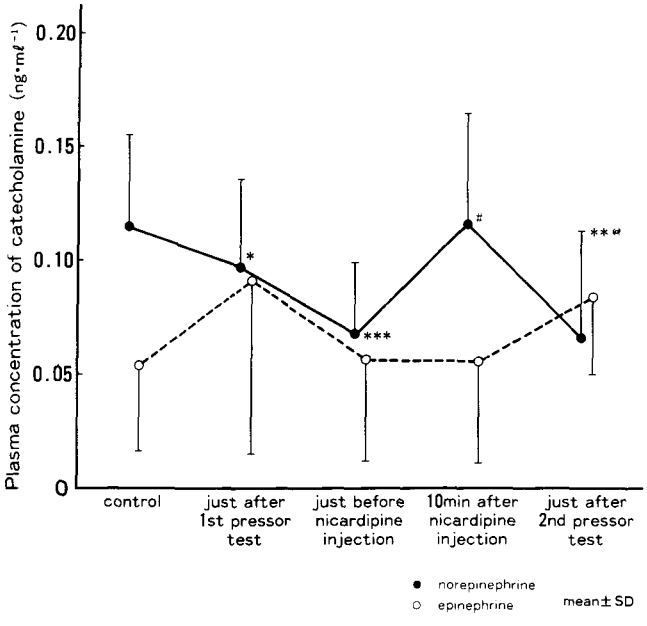

Fig. 3. Changes in plasma epinephrine and norepinephrine level in the pressor test group.

Values represent the mean ± SD.

*significant difference vs. control ($P < 0.05$).

**significant difference vs. control ($P < 0.005$).

***significant difference vs. control ($P < 0.0001$).

#significant difference vs. just before nicardipine injection ($P < 0.0001$).

@significant difference vs. 10 min after nicardipine injection ($P < 0.05$).

The plasma norepinephrine level was significantly decreased just after the first pressor test, just before nicardipine injection and just after the second pressor test compared with the control. It was significantly higher 10 min after nicardipine injection than just before nicardipine injection, and was significantly lower just after the second pressor test than 10 min after nicardipine injection. The plasma epinephrine level remained unchanged throughout the study.

Pa_{CO_2} increased significantly after nicardipine injection in the pressor test group. Cunningham et al.[8] reported that hypercapnia was associated with a significant fall of baroreflex sensitivity. In the present study, Pa_{CO_2} increased but remained within normal range, suggesting a negative influence on baroreflex.

Taylor et al.[9] compared the actions of the calcium channel inhibitors nimodipine, nifedipine, verapamil and diltiazem on baroreceptor reflex-induced bradycardia elicited by the pressor response induced by norepinephrine and on reflex-induced tachycardia elicited by the hypotensive response to acetylcholin in α-chloralose-anesthetized dogs. The results were as follows: the reflex vagal bradycardic ratio elicited by the norepinephrine-induced pressor response was reduced dose-dependently by nimodipine, diltiazem and verapamil. In contrast, nifedipine did not inhibit the bradycardic ratio. The reflex tachycardia ratio evoked by acetylcholine-induced hypotensive responses was reduced in a dose-related fashion by all of the agents. Moreover they studied the site of action, finding that nimodipine attenuated the reflex vagal bradycardia evoked by pressure elevations in the isolated carotid sinus and concluded that the site of action of nimodipine was confined to a peripheral baroreceptor locus. They proposed that the mechanism of action could possibly involve blockade of alpha-1 adrenoceptors, calcium or sodium ion channels, or the membrane sodium pump. Heesch et al.[10] isolated the carotid sinus region in a dog and investigated the effects of nifedipine and verapamil on the carotid sinus nerve activity and concluded that these drugs have direct effects on the carotid sinus baroreceptors.

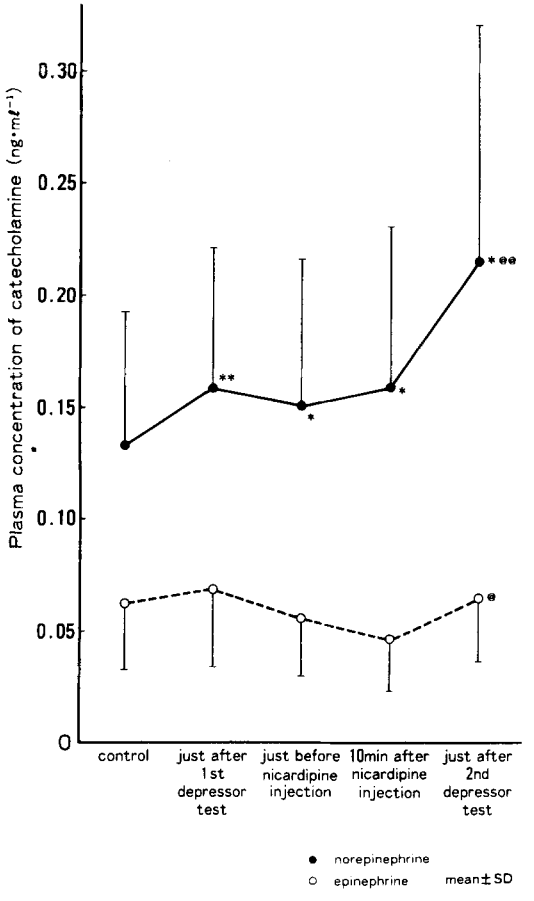

Fig. 4. Changes in plasma epinephrine and norepinephrine level in the depressor test group.

Values represent the mean ± SD.

*significant difference vs. control ($P < 0.005$).

**significant difference vs. control ($P < 0.00005$).

@significant difference vs. 10 min after nicardipine injection ($P < 0.005$).

@@significant difference vs. 10 min after nicardipine injection ($P < 0.01$).

In the depressor test group, the plasma norepinephrine level was significantly higher than the control at each point. It was significantly higher just after the second depressor test than 10 min after nicardipine injection. The plasma epinephrine level remained stable throughout the study, as in the pressor test group.

Although the present study did not investigate which components of the baroreflex arc nicardipine depressed by the pressor test, we believe that the drug nicardipine is also applied locally to the baroreceptors.

Ferguson[11] studied the effect of 20 mg of sublingually administered nifedipine, which is a dihydropyridine derivative like nicardipine, on baroreflex modulation of heart rate control by the pressor test in man, and concluded that this treatment with nifedipine increased baroreflex sensitivity. Giudicelli et al.[12] investigated the effect of 120 mg of diltiazem administered orally on the response to baroreflex activation and deactivation by the pressor and depressor tests in man and concluded that baroreflex sensitivity was not altered by the pressor test, whereas it was depressed by the depressor test. Moreover, Littler et al.[13] investigated the effect of 30 mg of nicardipine administered orally to patients with essential hypertension on the baroreflex response. There was no change in baroreflex sensitivity 1 hour after administration in the pressor test. It is interesting to note that the effect on baroreflex control of heart rate varies with the calcium channel blocker.

As present it is not known why there is a discrepancy between the results of Litter et al.'s orally administered nicardipine and these of our intravenous injection. The difference in results is probably due to the difference in subjects and methods, or to the concentration of nicardipine in the blood. This needs further investigation.

No resetting of the baroreflex occurred after nicardipine injection, since the pulse interval at reference pressure was not significantly altered.

By the pressor test, plasma norepinephrine tended to decrease, indicating that parasympathetic activity increased, and the decrease lasted over

15 min. Conversely, by the depressor test, plasma norepinephrine tended to increase, indicating that sympathetic activity increased, and it remained increased over 15 min. During and after hypotension induced by nicardipine, plasma norepinephrine increases in rabbits[14] and mongrel dogs[15]. In this study, systolic blood pressure had not decrease significantly 10 min after nicardipine injection, but transient hypotension was seen in every patient (data are not shown). The plasma norepinephrine level was significantly higher 10 min after nicardipine injection than just before nicardipine injection in the pressor test group, but not in the depressor test group. This phenomenon is apparently caused by the effect of the depressor test, which causes the plasma norepinephrine level to remain increased over 15 min.

In our study, plasma norepinephrine tended to decrease and the decrease lasted over 15 min by the pressor test because the increase of parasympathetic activity once occurred. Balagny et al.[16] studied the effects of intravenous droperidol on baroreflex control of heart rate using the pressor test and on plasma catecholamine levels. Their results was that values of plasma norepinephrine concentration was significantly increased only at 5 min after droperidol injection, while no significant change was observed at 10 and 15 min. Marty et al.[17] investigated the effects of induction of anesthesia with diazepam and midazolam on baroreflex control of heart rate and on plasma levels of catecholamines. Their results was that plasma norepinephrine concentrations decreased at 5, 10 and 15 min after intravenous drug administration with both drugs. Our results mean that it is very possible to misinterpret plasma catecholamine levels after administration of some drugs when the pressor test was conducted.

The results obtained in the present study suggest that it is safe to use nicardipine when reduction of blood pressure for hypovolemia or unclamping the main artery is expected and that it is disadvantageous clinically to administer the drug when an increase in blood pressure due to cross-clamping of the main artery is forecasted.

In conclusion, intravenous administration of nicardipine was found to depress the baroreflex response by the pressor test, whereas no change was found by the depressor test, and no resetting of the baroreflex occurred.

A part of this study was presented at "The 37th Annual Meeting of the Japan Society of Anesthesiology, 1990" and "The 8th Asian-Australasian Congress of Anaesthesiologists, 1990".

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References

1. Murat I, Lapeyre G, Saint-Maurice C: Isoflurane attenuates baroreflex control of heart rate in human neonates. Anesthesiology 70:395–400, 1989
2. Levy MN: Cardiac sympathetic-parasympathetic interactions. Fed Proc 43:2598–2602, 1984
3. Takeshima R, Dohi S: Circulatory response to baroreflex, Valsalva maneuver, coughing, swallowing, and nasal stimulation during acute cardiac sympathectomy by epidural blockade in awake humans. Anesthesiology 63:500–508, 1985
4. Wajima Z: Large dose of flunitrazepam attenuates baroreflex control of heart rate in man. J Anesth 5:10–16, 1991
5. Smyth HS, Sleight P, Pickering GW: Reflex regulation of arterial pressure during sleep in man: A quantitative method of assessing baroreflex sensitivity. Circ Res 24:109–121, 1969
6. Wajima Z, Ogawa R: Measurement of baroreflex sensitivity by arterial tonometry (A comparison with the invasive method) (abstract in English). Junkanseigyo (Circ Cont) 10:607–612, 1989

7. Bristow JD, Prys-Roberts C, Fisher A, et al: Effects of anesthesia on baroreflex control of heart rate in man. Anesthesiology 31:422–428, 1969
8. Cunningham DJC, Petersen ES, Pickering TG, et al: The effects of hypoxia, hypercapnia, and asphyxia on the baroreceptor-cardiac reflex at rest and during exercise in man. Acta Physiol Scand 86:456–465, 1972
9. Taylor DG, Kowalski TE: Comparison of calcium channel inhibitors on vagal heart rate response elicited by arterial baroreceptor reflexes in anesthetized dogs. J Pharmacol Exp Ther 228:491–499, 1984
10. Heesch CM, Miller BM, Thames MD, et al: Effects of calcium channel blockers on isolated carotid baroreceptors and baroreflex. Am J Physiol 245:H653–H661, 1983
11. Ferguson DW: Influence of nifedipine on arterial baroreflex modulation of heart rate control during dynamic increases in arterial pressure: Studies in normall man. Am Heart J 114:773–781, 1987
12. Giudicelli JF, Berdeaux A, Edouard A, et al: Attenuation by diltiazem of arterial baroreflex sensitivity in man. Eur J Clin Pharmacol 26:675–679, 1984
13. Littler WA, Young MA: The effect of nicardipine on blood pressure, its variability and reflex cardiac control. Br J Clin Pharmac 20:115S–119S, 1985
14. Takeda S, Inada Y, Tashiro N, et al: Endocrine effects of hypotension induced by nicardipine in rabbits (abstract in English). Masui (Jpn J Anesthesiol) 39:971–977, 1990
15. Takeda S, Inada Y, Nakamizo N, et al: A comparison of the endocrine effects of hypotension induced by nicardipine with those by sodium nitroprusside in dogs (abstract in English). Masui (Jpn J Anesthesiol) 40:1063–1069, 1991
16. Balagny D, Gauzit R, Marty J, et al: Effects of droperidol on sympathetic activity and baroreflex control of heart rate in humans. Anesthesiology 67:473–476, 1987
17. Marty J, Gauzit R, Lefevre P, et al: Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. Anesth Analg 65:113–119, 1986