Hiroshima Journal of Medical Sciences
Vol. 32, No. 2, June, 1983
HIJM 32-29

Sympathetic Nerve and Hormonal Responses to a Single Dose of Nifedipine in Patients with Essential Hypertension and Normal Subjects: Comparison Among Renin-Subgroups*)

Hamed OEMAR, Shigeko KUBO, Satoko MASAOKA,
Ikuo KANAZAWA, Akira YUASA, Yukiko TSUCHIOKA,
Hideo MATSUURA, Hiroyuki KUROGANE and Goro KAJIYAMA

The First Department of Internal Medicine, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan.

(Received March 22, 1983)

Key words: *Essential hypertension, Nifedipine, Catecholamines, Renin-angiotensin-aldosterone system, Renin subgroup*

ABSTRACT

Behaviors of sympathetic and renin-angiotensin-aldosterone systems to an acute sublingual administration of nifedipine (10 mg) were studied in essential hypertensive (EHT) and normotensive (NT) groups. Basal values of plasma norepinephrine (NE) and plasma renin activity (PRA) were not consistent with mean blood pressure (BP), indicating no important role of NE and PRA values for determining BP level.

Nifedipine reduced BP, and increased NE and PRA in both groups. Simultaneously, nifedipine produced a significant decrease of plasma aldosterone concentration (PAC) and plasma cortisol. High-renin EHT subgroup showed greater responses of BP, NE and PRA than normal- or low-renin subgroup but not in NT group. In high-, normal- and low-renin subgroups of both groups, the correlations between mean BP and △mean BP ($r=-0.85$, $p<0.001$; $r=-0.89$, $p<0.001$ and $r=-0.77$, $p<0.001$, respectively), △mean BP and △NE ($r=-0.76$, $p<0.01$; $r=-0.71$, $p<0.05$ and $r=-0.57$, NS, respectively) and △mean BP and △PRA ($r=-0.87$, $p<0.001$; $r=0.59$, NS and $r=-0.05$, NS, respectively) were observed. A significant relationship between basal PRA and △PRA was demonstrated in EHT group ($r=0.77$, $p<0.001$) but not in NT group ($r=0.37$, NS).

These data indicate the presence of high vascular tone in high-renin EHT subgroup which is probably produced by an increased vascular responsiveness to sympathetic and/or to angiotensin II or by some other factors. It is suspected that juxtaglomerular cell response to vasodilator may be altered in patients with low-renin essential hypertension. The present study also suggests that nifedipine blocked aldosterone and cortisol secretion through Ca^{++} influx inhibition into the adrenal cortex.

INTRODUCTION

Calcium-entry blocker nifedipine, one of the potent depressor substances due to the vasodilatation, is clinically interesting in the treatment of hypertension and ischemic heart disease[23]. It has been reported that nifedipine caused greater depressor response in essential hypertensive patients[15], than in normotensive subjects, because of a functional abnormality in essential hypertension with increased dependency of arteriolar tone on calcium influx[8]. Arteriolar vasodilatation is generally known as the cause of sympathetic drive[2] and further, in

*) Hamed Oemar, 久保慈子, 正岡智子, 金沢郁夫, 湯浅 明, 土岡由紀子, 松浦秀夫, 鍈 寛之, 梶山梧朗：本態性高血圧症患者および正常血圧者の Nifedipine 1回経口投与に対する交感神経ならびに内分泌応答のレニン群間比較

part, stimulates for renin secretion [10,26]. However, the relationships between the grade of vascular relaxation by nifedipine and the plasma renin activity and sympathetic activity have not been clarified fully.

Calcium plays an important role as a mediator in stimulus-secretion coupling in a variety of neural and glandular cells[16], though available information about the effect of nifedipine on hormone release is scanty.

The purpose of the present study is to investigate the responses of sympathetic nerve and renin-angiotensin-aldosterone systems according to the renin subgroup to nifedipine in essential hypertensive patients and normotensive subjects.

SUBJECTS AND METHODS

The single-blind protocol of the investigation procedure was designed in hypertensive out- and in-patients and normal volunteers, with free diet. Those patients were selected who had blood pressure (BP) equal to or higher than 160/95 mmHg, and they were classified as WHO stage I-II. Thirty patients (21 males and 9 females), aged 25-66 (46.6 ± 12.3 years), were diagnosed as having essential hypertension (EHT) after exclusion of secondary hypertension. Twenty eight normal subjects (NT) (21 males and 7 females), aged 24-53 (33.7 ± 9.6 years), were included in this study. All antihypertensive drugs or other medications were withdrawn at least one week prior to the study.

After 30 min in the supine position comfortably, BP was measured three times with a standard cuff sphigmomanometer. Mean BP was defined as diastolic BP+1/3 pulse pressure. Heart rate (HR) was obtained from electrocardiogram. The examination was carried out in the morning period, 9 : 00-11 : 00 a. m. All subjects crunched a capsule containing 10 mg of nifedipine and kept the content in the mouth for one to two min before swallowing. The BP and HR were recorded before, 30 and 60 min after nifedipine administration. The venous blood specimens were taken before, 30 and 60 min after nifedipine administration. Plasma renin activity (PRA), plasma aldosterone concentration (PAC) and plasma cortisol (Cortisol) were analysed by radioimmunoassay kit (CIS) based on antibody-coated tubes methods. Plasma norepinephrine (NE) and epinephrine (E) were measured electrochemically by using a high power liquid chromatography.

Correlations were calculated by linear and multiple regression analyses. Student's t test was used for statistical evaluation of paired data. Statistical differences in the mean ($\pm$SD) of values between groups and among different subgroups were determined by the Mann-Whitney U test and the Kruskal-Wallis test, respectively. The level of significance was set at $p<0.05$.

RESULTS

Under the basal condition, BP, HR and hormonal characteristics in NT and EHT patients are presented in Table 1. Systolic and diatolic BP in EHT group was significantly higher than in NT group ($p<0.001$), but HR showed an equal level in both groups. NE was significantly higher in EHT than in NT group ($p<0.05$) and there was a weak but statistically significant correlation between basal mean BP and NE in both groups ($r=0.43$, $p<0.05$). No significant difference in PRA between groups nor significant correlation between mean BP and PRA in both groups were observed ($r=0.12$, NS). Moreover, both group did not show any correlation between basal NE and PRA ($r=0.18$, NS). Since there was a significant difference in the mean age between EHT and NT groups, NE, PRA and PAC of each group were compared among three age subgroups (Table 2). Basal mean BP was not correlated with age in both groups ($r=0.40$, NS). In the subgroup above 51 years, NE showed a tendency of an increase, but PRA and PAC marked decrease ($p<0.05$ and NS, respectively) in both groups. NE was higher in EHT than in NT group in every subgroup, but a significant difference was recognized only in younger subgroup ($p<0.05$).

The BP, HR and hormonal responses to nifedipine in NT and EHT groups are summarized in Table 3. Mean BP significantly decreased until 60 min after nifedipine in NT and EHT groups($p<0.01$ and $p<0.001$, respectively). HR significantly increased in EHT group at 30 and 60 min after nifedipine ($p<0.01$ and $p<0.05$, respectively), whereas in NT group HR showed a minor but significant increase at 30 min after ($p<0.05$) and returned to the basal value at 60 min after nifedipine

Table 1. Blood pressure, heart rate, plasma norepinephrine, plasma epinephrine, plasma renin activity, plasma aldosterone concentration and plasma cortisol under basal condition in normotensive subjects and essential hypertensive patients.

Subject	Age (year)	Blood pressure (mmHg) systolic	Blood pressure (mmHg) diastolic	Heart rate (bpm)	NE (ng/ml)	E (ng/ml)	PRA (ngAI/ml/h)	PAC (pg/ml)	CORTISOL (ng/ml)
NT	33.7± 9.6	116.0±11.5 (n=28)	74.0±7.8 (n=28)	64.1±7.3 (n=28)	0.130±0.057 (n=17)	0.021±0.016 (n=16)	2.04±2.03 (n=28)	58.67±24.34 (n=28)	67.29±28.73 (n=25)
EHT	46.6±12.3	166.0±17.7 (n=30)	102.6±12.1 (n=30)	66.9±8.0 (n=30)	0.188±0.083 (n=18)	0.015±0.011 (n=16)	2.25±2.18 (n=30)	65.12±23.53 (n=30)	78.79±44.51 (n=27)
p	<0.05	<0.001	<0.001	NS	<0.05	NS	NS	NS	NS

Values are means±SD. NT=normotensive subject; EHT=essential hypertensive patient; NE=plasma norepinephrine; E=plasma epinephrine; PRA=plasma renin activity; PAC=plasma aldosterone concentration; NS=not significant.

Table 2. Distribution of norepinephrine, plasma renin activity and plasma aldosterone concentration in normotensive subjects and essential hypertensive patients by age subgroup.

Age (years)	mean BP (mmHg) NT	mean BP (mmHg) EHT	NE (ng/ml) NT	NE (ng/ml) EHT	PRA (ngAI/ml/h) NT	PRA (ngAI/ml/h) EHT	PAC (pg/ml) NT	PAC (pg/ml) EHT
-30	87.23± 8.30 (n=13)	128.40±11.10** (n=5)	0.107±0.047 (n=9)	0.176±0.067* (n=5)	2.59±2.03 (n=13)	2.45±1.56 (n=5)	74.48±48.01 (n=13)	74.09±42.60 (n=5)
31-50	87.21± 6.74 (n=11)	122.25± 7.59** (n=12)	0.133±0.022 (n=5)	0.193±0.084 (n=4)	1.34±1.06 (n=11)	2.94±2.06 (n=12)	82.44±28.85 (n=11)	84.90±21.78 (n=12)
51-	91.60±10.61 (n=4)	123.60± 8.54** (n=13)	0.139±0.041 (n=3)	0.190±0.071 (n=9)	0.73±0.41† (n=4)	1.21±1.01† (n=13)	54.48±12.21 (n=4)	53.36±28.84 (n=13)

Values are means±SD. BP=blood pressure; other abbriviations are the same as in Table 1
* $p<0.05$ compared to NT group in the same age subgroup
** $p<0.001$ compared to NT group in the same age subgroup
† $p<0.05$ compared to the first or second age subgroup in the same group

Table 3. Effects of nifedipine on mean blood pressure, heart rate and plasma hormone levels in normotensive subjects and essential hypertensive patients.

	NT				EHT			
	n	before	30 min	60 min	n	before	30 min	60 min
mean BP (mmHg)	28	88.00 ± 8.15	78.40 ± 7.5**	81.66 ± 9.2**	30	123.86 ± 8.58	97.90 ±10.2***	102.45 ± 9.41***
HR (bpm)	28	64.1 ± 7.3	67.5 ± 7.0*	66.2 ± 6.9	30	66.9 ± 8.0	72.1 ± 7.4**	70.5 ± 8.1*
PRA (ngAI/ml/h)	28	2.04 ± 2.03	2.22 ± 1.61**	2.41 ± 2.27**	30	2.25 ± 2.18	5.11 ± 1.92***	3.34 ± 2.24***
PAC (pg/ml)	28	58.67 ±31.34	48.23 ±19.01*	42.19 ±21.32**	30	65.12 ±23.53	56.24 ±39.44**	47.43 ±27.50***
CORTISOL (ng/ml)	25	67.29 ±28.73	56.62 ±34.23	40.22 ±20.00**	27	78.79 ±44.51	64.32 ±22.15	55.44 ±27.88**
NE (ng/ml)	17	0.130± 0.057	0.144± 0.060*	0.15 ± 0.064**	18	0.188± 0.083	0.294± 0.104***	0.267± 0.105***
E (ng/ml)	16	0.021± 0.016	0.024± 0.010	0.020± 0.011	16	0.015± 0.011	0.025± 0.013**	0.023± 0.010**

Values are means±SD. BP=blood pressure; HR=heart rate; n=number of cases; other abbreviations are the same as in Table 1.
Significances vs before levels; *$p<0.05$, **$p<0.01$, ***$p<0.001$

administration. PRA rose significantly at 30 and 60 min after administration of nifedipine in EHT group (both $p<0.001$) and in NT group (both $p<0.01$). However, PAC decreased significantly at 30 and 60 min after nifedipine administration both in EHT group ($p<0.01$ and $p<0.001$, respectively) and in NT group ($p<0.05$ and $p<0.01$, respectively). Simultaneously, cortisol concentration decreased significantly at 60 min after nifedipine administration in both groups (both $p<0.01$). In EHT group, NE increased significantly at 30 and 60 min after nifedipine (both $p<0.001$), while in NT group NE showed a minor increase at the same period ($p<0.05$ and $p<0.01$, respectively). The mean value of E also rose significantly at 30 and 60 min after nifedipine in EHT group (both $p<0.01$), but it did not show any marked change in NT group.

The distribution of NE, changes in NE (△NE) and mean BP (△mean BP) at 60 min after nifedipine administration in both groups could be clasified in terms of the individual level of PRA: the level of basal PRA less than 1 ng Angiotensin I (AI)/ml/h was regarded as low-renin, between 1 to 3 ng AI/ml/h as normal-renin, and above 3 ng AI/ml/h as high-renin subject (Table 4). In every renin subgroup, basal NE showed a tendency higher in EHT than in NT group, but a significant difference in NE was observed only in high-renin subgroup ($p<0.05$). The △NE was greater in EHT than in NT group in low-, normal- and high-renin subgroups (NS, $p<0.05$ and $p<0.01$, respectively). Both groups showed that △NE was greater by increasing basal PRA value. In EHT group, △NE was significantly higher in high-renin than in low-renin subgroup ($p<0.05$). However, no significant difference in △NE with respect to the renin level was recognized in NT group. The △PRA was found to be higher in high-renin EHT than in high-renin NT subgroup ($p<0.001$), but not in normal- or low-renin subgroup. High-renin EHT subgroup proved significantly higher in PRA response than in normal- or low-renin subgroup ($p<0.01$). The △mean BP was higher in EHT than in NT group in every subgroup (all $p<0.001$). Intersubgroup differences in △mean BP were observed in EHT group ($p<0.01$) but not in NT group.

In both groups, significant correlations were

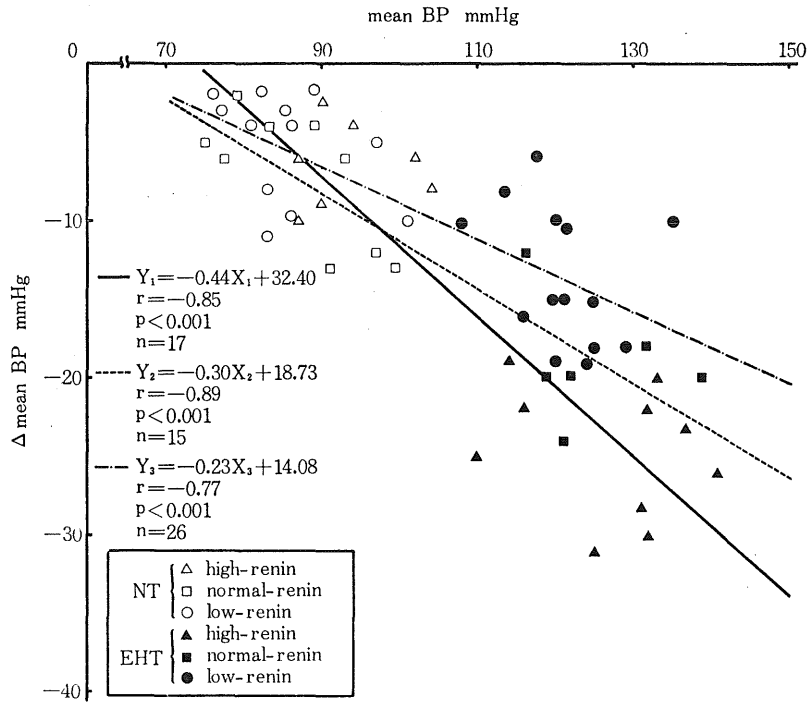

Fig. 1. Relationship between basal mean BP and change in mean BP (△mean BP) after nifedipine 10 mg in normotensive subjects (NT) and essential hypertensive patients (EHT) (regression line Y_1=high-renin subgroup; Y_2=normal-renin subgroup; Y_3=low-renin subgroup).

observed between the basal mean BP and △mean BP at 60 min after nifedipine in high-, normal- and low-renin subgroups ($r=-0.85$, $p<0.001$; $r=-0.89$, $p<0.001$ and $r=-0.77$, $p<0.001$, respectively) (Fig. 1). In this relationship, analysis of variance showed a highly significant difference among renin-subgroups. In EHT group, depressor response to nifedipine became greater as renin level became higher; in NT group, it did not show any difference between three renin subgroups. Fig. 2 shows significant correlations between △mean BP and △NE at 60 min after nifedipine in high- and normal-renin subgroups of both groups ($r=0.76$, $p<0.01$ and $r=-0.71$, $p<0.05$, respestively), but not in low-renin subgroup ($r=-0.57$, NS). In the range of △mean BP observed in NT group, △NE was similar in EHT and NT groups.

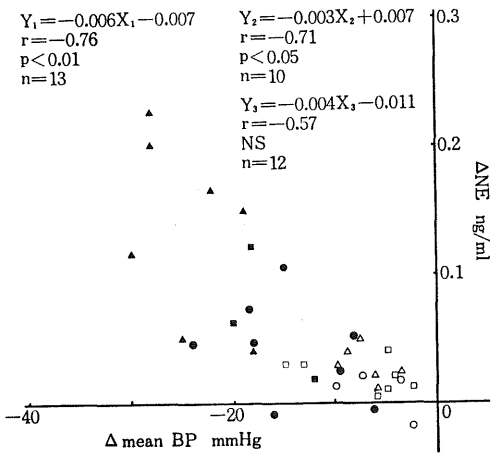

Fig. 2. Relationship between changes in mean BP (△mean BP) and plasma norepinephrine (△NE) after nifedipine 10 mg in normotensive subjects and essential hypertensive patients. Symbols and abbreviations are the same as in Fig. 1.

As demonstrated in Fig. 3, both groups showed a good correlation between △mean BP and change in PRA (△PRA) in high-renin subgroup ($r=-0.87$, $p<0.001$), but this correlation was not found in normal-renin ($r=-0.59$, NS) nor in low-renin subgroup ($r=-0.05$, NS).

A significant relationship was observed between △NE and △PRA at 60 min after

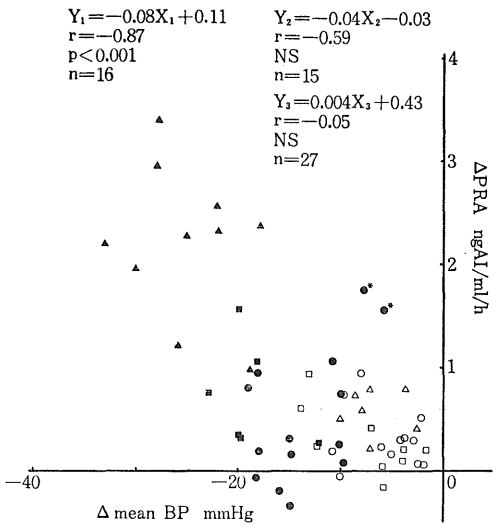

Fig. 3. Relationship between changes in mean BP (△mean BP) and plasma renin activity (△PRA) after nifedipine 10 mg in normotensive subjects and essential hypertensive patients. Symbols and abbreviations are the same as in Fig. 1.

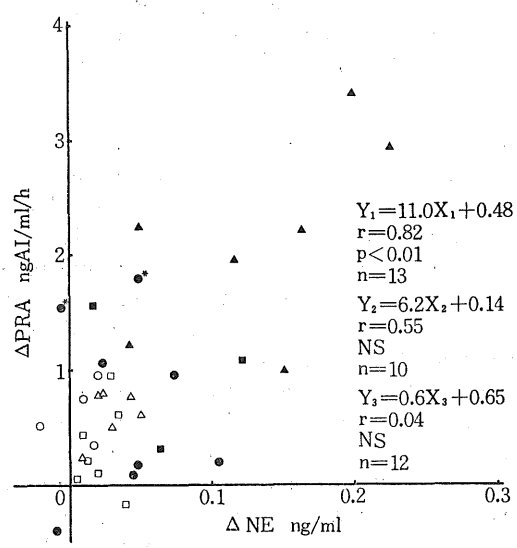

Fig. 4. Relationship between changes in plasma norepinephrine (△NE) and plasma renin activity (△PRA) after nifedipine 10 mg in normotensive subjects and essential hypertensive patients. Symbols and abbreviations are the same as in Fig. 1.

nefidipine in high-renin subgroup of both groups ($r=0.82$, $p<0.01$) but not in normal- and low-renin subgroups ($r=0.55$, NS; $r=0.04$, NS, respectively) (Fig. 4). In EHT group, a positive correlation was observed between △NE and △PRA only in high-renin subgroup ($r=0.60$, $p<0.05$), whereas in NT group this correlation was not found in each renin subgroup.

The basal PRA was significantly correlated with △PRA in EHT group ($r=0.77$, $p<0.001$), but not in NT group ($r=0.37$, NS) (Fig. 5). Relationships between the basal value of PRA and PAC in EHT group ($r=0.75$, $p<0.001$) and in NT group ($r=0.76$, $p<0.001$) were not different in renin-subgroup distributions (NS) (Fig. 6). Linear correlations were observed between △PRA and changes in PAC (△PAC) at 60 min after nifedipine administration in EHT group ($r=0.65$, $p<0.01$) and in NT group ($r=0.60$, $p<0.05$) (Fig. 7). In both groups, when a subject showed a greater rise in PRA, a smaller fall in PAC was observed after nifedipine administration.

DISCUSSION

The fact that nifedipine decreases the tone of resistance vessels, leading to lower arterial blood pressure, has been widely known[14]. In this study, nifedipine induced a greater reduction of mean BP in EHT patients than in NT subjects. The responses of sympathetic activity and PRA were also greater in EHT group. These responses may reasonably be attributed to the difference of depressor responses between EHT and NT subjects. However, they can not explain the reasons why EHT patients revealed greater depressor response to nifedipine than NT subjects.

Since the basal PRA was not correlated with mean BP nor with NE and only a weak correlation between mean BP and NE was observed in this study, these findings can not explain the role of the higher activity of sympathetic nerve and renin-angiotensin-aldosterone system for maintaining higher blood pressure and vascular tone.

The important role of the sympathetic nervous system to control BP is well documented[1,6], but the evidences that the circulating level of NE increased in EHT patients still remain controversial. Some investigators reported a high level of plasma catecholamines in EHT patients as compared with NT subjects[6], but other did not find any significant difference between those groups[9]. In this study, the mean

Table 4. Distribution of plasma norepinephrine and changes in plasma norepinephrine and mean blood pressure after nifedipine in normal subjects and essential hypertensive patients by plasma renin subgroup.

Renin Subgroup	NE (ng/ml)			△NE (ng/ml)			△PRA (ngAI/ml/h)			△mean BP (mmHg)		
	NT	EHT	p	NT	EHT	p	NT	EHT	p	NT	EHT	p
Low-renin	0.097±0.053	0.176±0.084		0.007±0.018	0.042±0.039		0.31±0.29	0.51±0.64		5.33±3.44	13.57±4.32	
(<1 ngAI/ml/h)	(n=4)	(n=8)	N S	(n=4)	(n=8)	N S	(n=12)	(n=14)	N S	(n=12)	(n=14)	<0.001
Normal-renin	0.142±0.061	0.217±0.067		0.022±0.012	0.080±0.037		0.28±0.33	0.71±0.54		7.32±4.26	18.83±3.71*	
(1-3 ngAI/ml/h)	(n=7)	(n=3)	N S	(n=7)	(n=3)	<0.05	(n=9)	(n=6)	N S	(n=9)	(n=6)	<0.001
High-renin	0.140±0.056	0.250±0.129		0.029±0.014	0.136±0.072†		0.58±0.22	2.24±0.68**		6.50±2.69	24.70±4.29**	
(>3 ngAI/ml/h)	(n=6)	(n=7)	<0.05	(n=6)	(n=7)	<0.01	(n=7)	(n=10)	<0.001	(n=7)	(n=10)	<0.001

Values are means±SD. △NE=change in plasma norepinephrine; △PRA=change in plasma renin activity; △mean BP=change in mean blood pressure.
Other abbreviations are the same as in Table 1.
† $p<0.05$ compared to the low-renin subgroup in the same group
* $p<0.01$ compared to the low-renin subgroup in the same group
** $p<0.01$ compared to the normal-or low-renin subgroup in the same group

NE level was significantly higher in EHT than in NT group (Table 1). Plasma NE level in normal subjects[9] and in patients with essential hypertension[13] was reported to become higher by aging; this phenomenon was explained on a hypothesis that the NE plasma clearance become lower in older subjects[7].

The comparison of plasma of NE level of the same age subgroup in both groups indicated that plasma NE value was higher in EHT than in NT group in every age subgroup (Table 2). As relationship between basal mean BP and depressor respons to nifedipine was significantly different among three renin subgroups (Fig. 1), plasma NE tended to be higher in increasing PRA value, especially in EHT group which provided a larger NE level in each renin subgroup (Table 4). These data reveal that EHT group have a higher value of NE as compared with NT group. It should be carefully considered that some abnormalities in automatic nervous system might be present in EHT patients: first, EHT patients might have a reduction in the number of prejunctional α_2-receptors that causes a lack of inhibition in NE relase upon nerve stimulation[1], second, the decrease of parasympathetic inhibition of NE release[5], and third, the enhanced vascular activity to adrenergic stimuli might be caused by an increase in the number of α_1-postjunctional receptors[1].

It had been well reported that catecholamines concentration increased after arterial vasodilator[1]. As nifedipine acts predominatly on arteriolar system[23], this study confirmed that the accelerated sympathetic response after nifedipine-induced arteriolar dilatation was reflected on a compensatory raise in plasma NE and E as well as an elevated HR in both study groups (Table 3). In this regard our results are in agreement with a previous study by Tarazi et al. who reported that vasodiators which lower blood pressure by a relating effect on the resistance vessels increase HR, but those that cause a vascular dilatation of the capacitance vessels do not raise HR[19].

As noted in Table 3, NT group showed a slight increase in HR because of the minor decrease in BP. However, in EHT patients, a significant rapid elevation in HR was observed, but it tended to diminish 60 min after nifedipine administration even catecholamines were still

markedly higher than its basal state and depressor effect has been remained. This may be explained as due to a property known as "tachyphylaxis phenomenon".

In view of the changes in the sympathetic activity toward the arterial vasodilation, it may be suggested that the sympathetic response in EHT and NT group were similar for a given magnitude of BP reduction (Fig. 2). Although high renin-subgroup showed a greater response in NE as compared with normal- and/or low-renin subgroups, it does not mean that high-renin subjects enhanced a sympathetic drive after vasodilator. These results may be regarded as the evidence of a large reduction in mean BP in high-renin EHT patients (Fig. 1) that can lead to augment sympathetic activity. It may also be suggested that low-renin EHT patients, who were regarded as possessing a low vascular tone, have a low response to arterial vasodilator, including nifedipine, reflecting a low sympathetic drive. In NT subjects, however, renin level failed to differentiate the grade of depressor response, though the PRA level was similar between to groups. This means that the grade of vacular tone depend not only on PRA level but also, probably, on the grade of vascular responsiveness to angiotensin II.

Since high-renin subgroup in EHT patients produced a greater vascular relaxation after nifedipine, it suggests that the basal PRA level may be useful as a valuable indicator of the effectiveness of nifedipine in the treatment of patients with essential hypertension.

The present study showed a lower PRA level in the elderly subjects in both groups, indicating that aging may cause a decrease in circulating renin[24]. Several factors could theoretically lower renin release in the elderly subjects. Nephrosclerosis or morphological and functional alternations normally occurring in the aging kidney, which may disturb the function of the juxtaglomerular (JG) apparatus, lead to a reduction in renin release[18]. Other explanations were proposed by Crane et al.[3], who postulated that the differences in β-adrenergic activity, pituitary-adrenal function and physical activity between the various age subgroups were possible causes.

The tendency of increased PRA following the administration of nifedipine (Table 3) is consistent with previous observations[2,14]. Davis and Freeman[4] have classified the control of renin release into a) two intrarenal receptors, the renal vascular receptors in the afferent arteriole and the macula densa; b) a group of humoral agent (including vasopressin, angiotensin II, and prostaglandins).

The rise in PRA is associated with baroreflex-stimulate sympathetic nervous system[26] as noted in this study (Fig. 3 and Fig. 4). Sympathetic innervation of the JG cells can exert a direct stimulation on renin release[10]; and more recently, Ueda et al.[20] have suggested that the catecholamine-induced renin secretion may be mediated either via β-adrenergic receptors or indirect action through some other unknown mechanism.

The role of calcium in the control of renin secretion has recently been reported. Van Dongen et al.[22] have suggested that an inhibition of renin secretion was related with smooth muscle activity by the involvement of calcium-dependent process similar to that involved in contration, and activation of renin release would be expected by blocking calcium inward current. This hypothesis is further supported by the findings of Park and Malvin[12] that the control of renin secretion is mediated, in part, by changes in the intracellular concentration of Ca^{++}, most likely in the JG cells. Probably, this hypothesis is useful for explaining the renin reactivity in EHT patients (*) shown in Figs. 3, 4 and 5, who had low depressor and sympathetic responses after nifedipine administration and revealed higher increase in PRA. These findings indicate that renin release was modulated by nifedipine at the JG cells level through Ca^{++} influx inhibition, in addition to being stimulated by the decrement of renal perfusion pressure and/or by sympathetic activity[4,26]. However, it is interesting to note that other calcium-entry blocker like verapamil does not stimulate renin release[10,26], though it reduced arterial blood pressure markedly. This observation may reveal the presence of different mechanism for activation of renin secretion and the presence of different groups of calcium channels activated by different stimuli, as documented by van Breeman et al.[21].

A good correlation between the basal PRA and $\triangle$PRA after nifedipine in EHT group (Fig. 5) is in agreement with the observations by Pedersen et al.[14]. In this study, however,

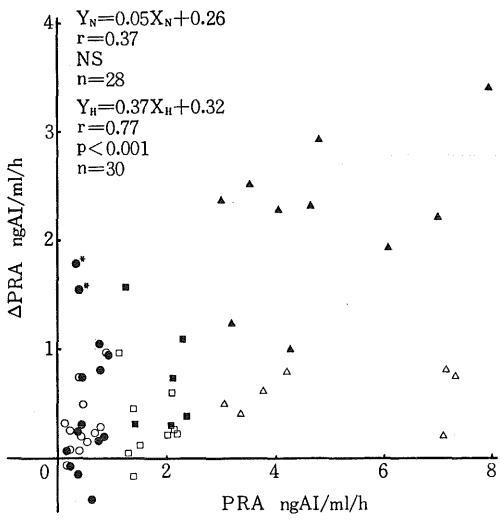

Fig. 5. Correlation between basal plasma renin activity (PRA) and its change (△PRA) after nifedipine 10 mg in normotensive subjects and essential hypertensive patients (regression line Y_N=normotensive subjects; Y_H=essential hypertensive patients). Symbols are the same as in Fig. 1.

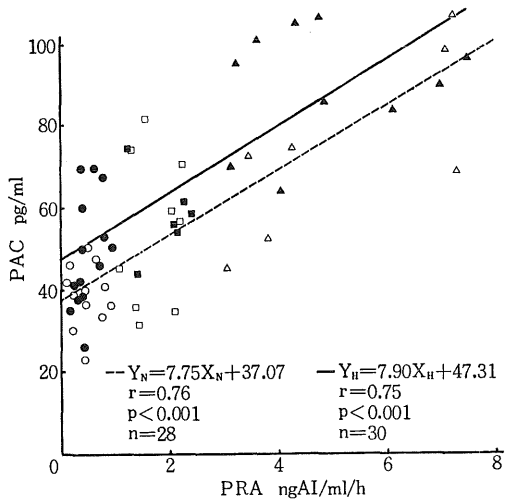

Fig. 6. Correlation between basal plasma renin activity (PRA) and plasma aldosterone concentration (PAC) in normotensive subjects and essential hypertensive patients. Symbols and abbreviations are the same as in Fig. 1 and Fig. 5, respectively.

this correlation was not observed in NT group. The difference in renin response between groups was found only in high-renin subgroup; this may be explained by the lower depressor response, observed in NT group, the lower responses of sympathetic nerve and renin secretion (Fig. 1 and Table 4). Interestingly, in low-renin subgroup, the renin response appeared to be similar between groups. Since depressor and sympathetic nerve responses were markedly higher in low-renin EHT than in low-renin NT subgroup, the unelevation in renin response is probably due to the presence of functional disturbances of JG cell in patients with low-renin essential hypertension.

It is well known that renin-angiotensin system, potasium, and adrenocortocotropic hormone (ACTH)[17,25] as well as catecholamines[4] regulate aldosterone secretion in man. By plotting an individual level of basal PRA and PAC (Fig. 6), a general view has been confirmed that aldosterone release is well controlled by the renin-angiotensin system[25]. After nifedipine administration, in this study, the elevated plasma catecholamines coupled with the raised PRA was assumed to contribute to activate aldosterone secretion. Since nifedipine augmented hepatic blood flow[11,14], the decreased PAC in both groups (Table 3) might be caused mainly by enhanced metabolic rate of aldosterone in the liver, where a majority of circulating aldosterone was metabolized, coupled with the raised aldosterone excretion through the kidney[25].

According to the current concept of stimulus-

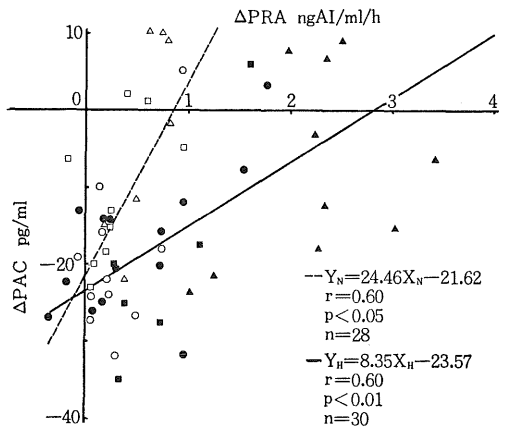

Fig. 7. Correlation between changes in plasma renin activity (△PRA) and plasma aldosterone concentration (△PAC) after nifedipine 10 mg in normotensive subjects and essential hypertensive patients. Symbols and abbreviations are the same as in Fig. 1 and Fig. 5, respectively.

secretion coupling in a variety of neural and glandular cells, Ca^{++} plays a role of the mediator of agents that stimulate aldosterone biosythesis by adrenal glomerulosa cells[16]. It has been suggested that calcium-entry blocker such as verapamil and lanthanum, mersalyl acid and tetracaine may block the effect of aldosterone secretagogues[17]. Judging from the correlation between △PRA and △PAC after nifedipine (Fig. 7), it appears that nifedipine may prodominantly suppress aldosterone secretion in subjects with small PRA response.

Our findings confirm that nifedipine administration significantly lowers the circulating level of cortisol both in normotensive and hypertensive patients (Table 3). Since calcium is essential for the potentiation of cortisol secretion[27], there may be some direct effect of nifedipine to prevent cortisol secretion though the inhibition of Ca^{++} influx into the zona fasciculate cells. However, very little information is available about direct effects of calcium-entry blocker on cortisol release.

Since the value of NE and/or PRA was not consistent with the basal mean BP in EHT and NT groups, these results indicate that NE and PRA do not play an important role for determining the level of BP. The evidence of greater depressor response to vasodilitor nifedipine, which was closely related with an augmented sympathetic activity and excessive renin release and was observed in patients with high-renin essential hypertension, indicates the presence of high vascular tone in high-renin EHT subgroup. In fact, however, this phenomenon was not observed in NT group. The difference in depressor response between high-renin in EHT and in NT group may indicate that a high vascular tone in patients with essential hypertension is produced either by a possible presence of an increased vascular responsiveness to sympathetic activity and/or to angiotensin II or by some other factors. In low-renin EHT subgroup, the greater depressor and sympathetic responses to vasodilator nifedipine were assumed to contribute to heighten renin response as compared to that in low-renin NT subgroup (Table 4). This indicates that there may be disturbances of JG response in patients with low-renin essential hypertension.

The present study also suggests that nifedipine may act directly on JG apparatus to increase renin release. Since calcium is required to secrete adrenal hormone, the decreased aldosterone and cortisol secretion observed in this study are caused, in part, by a direct effect of nifedipine-inhibited Ca^{++} inward current into the adrenal cortex.

ACKNOWLEDGEMENT

The authors wish to express their thanks to Dr. Masahiro Kawanishi for his advice on the statistical analysis of the data, to Makoto Onodera for his technical assistance and to Naoko Shimizu for her secretarial help. Nifedipine (Adalat) was supplied by Bayer AG, Leverkusen, West Germany.

REFERENCES

1. **Abbout, F. M.** 1982. The sympathetic system in hypertension. State-of-the-art review. Hypertension **4** (suppl 2) : 208-222.
2. **Corea, L., Miele, N., Bentivoglio, M., Boschetti, E., Agabitirosei, E. and Muiesan, G.** 1979. Acute and chronic effects of nifedipine on plasma renin activity and plasma adrenaline and noradrenaline in controls and hypertensive patients. Clin. Sci. **57** (suppl) : 115-117.
3. **Crane, M. G. and Harris, J. J.** 1976. Effect of aging on renin activity and aldosterone excretion. J. Lab. Clin. Med. **87(6)** : 947-959.
4. **Davis, J. O. and Freeman, R. H.** 1976. Mechanism regulating renin release. Physiol. Rev. **56** : 1-16.
5. **De Champlain, J., Nadeau, R. A., Lavallee, M. and Denis, G.** 1981. Autonomic dysfunctions in human hypertension. Hypertension **3** (suppl 2) : 124-128.
6. **De Quatro, V. and Chan, S.** 1972. Raised plasma catecholamines in some patients with primary hypertension. Lancet **1** : 806-809.
7. **Esler, M., Skews, H., Leonard, P., Jackman, G., Bobik, A. and Korner, P.** 1981. Age-dependence of noradrenaline kinetics in normal subjects. Clin. Scien. **60** : 217-219.
8. **Hulthen, U. L., Bolli, P., Amann, F. W., Kiowski, W. and Buhler, F. R.** 1982. Enhanced vasodilatation in essential hypertension by calcium channel blockade with verapamil. Hypertension **40(3)** (suppl 2) : 26-30.
9. **Lake, C. R., Ziegler, M. G., Coleman, M. D. and Kipin, I. J.** 1977. Age adjusted plasma norepinephrine levels are similar in normotensive and hypertensive subjects. N. Engl. J. Med. **296** : 208-209.
10. **Logan, A. G. and Chatzilias, A.** 1981. Humoral mechanisms of renin release, p. 228-231. *In* J. H. Laragh, F. R. Buhler and D. W. Seldin (ed.), Fron-

tiers in Hypertension Research. Springer-Verlag, New York.

11. **Mostbeck, A., Partsch, H. and Peschl, L.** 1975. Extracardial effects of nifedipine (Adalat): Measurements of liver blood flow in animals and humans and of peripheral circulation in the lower limbs, p. 303-310. *In* W. Lochner, W. Baasch and G. Kroneberg (ed.), 2nd International Adalat Symposium. Springer-Verlag, Berlin.
12. **Park, C. S. and Malvin, R. L.** 1978. Calcium in the control of renin release. Am. J. Physiol. **251** : F22-F25.
13. **Pedersen, F. B. and Christensen, N. J.** 1975. Catecholamines in plasma and urine in patients with essential hypertension determined by double-isotope derivate techniques. Acta Med. Scand. **198** : 373-377.
14. **Pedersen, O. L., Mikkelsen, E., Christensen, N. J., Kornerup, H. J. and Pedersen, E. B.** 1979. Effect of nifedipine on plasma renin, aldosterone and catecholamines in arterial hypertension. Europ. J. Clin. Pharmacol. **15** : 235-240.
15. **Robinson, B. F., Dobbs, R. J. and Kelsey, C. R.** 1980. Effects of nifedipine on resistance vessels, arteries and veins in man. Br. J. Clin. Pharmacol. **10** : 433-438.
16. **Rubin, R. P.** 1970. The role of calcium in the release of neurotransmitter substances and hormones. Pharmacol. Rev. **22** : 389-428.
17. **Schiffrin, E. L., Gutkowska, J., Lis, M. and Genest, J.** 1982. Relative role of sodium and calcium ions in the steroidogenic response of isolated rat adrenal glomerulosa cells. Hypertension. **4** (Suppl 2) : 36-42.
18. **Swales, J. D.** 1975. Low-renin hyptertension: nephrosclerosis? Lancet **1** : 75-77.
19. **Tarazi, R. C., Dustan, H. P., Bravo, E. L. and Niarchos, A. P.** 1976. Vasodilating drugs: contrasting hemodynamic effects. Clin. Sci. Mol. Med. **51** (Suppl) : 575-578.
20. **Ueda, H., Yasuda, H., Takabatake, Y., Iizuka, M., Iizuka, T., Ihori, M. and Sakamoto, Y.** 1970. Observations on the mechanism of renin release by catecholamines. Circ. Res. **26, 27** (Suppl 2) : 195-200.
21. **Van Breemen, C., Mangel, A., Fahim, M. and Meisheri, K.** 1982. Selestivity of calcium antagonistic action in vascular smooth muscle. Am. J. Cardiol. **49** : 507-510.
22. **Vandongen, R. and Peart, W. S.** 1974. Calcium dependence of the inhibitory effect of angiotensin on renin secretion in the isolated perfused kidney of the rat. Br. J. Pharmacol. **50** : 125-129.
23. **Vanhoutte, P. M.** 1982. Calcium-entry blockers and vascular smooth muscle. Circulation **65** (Suppl 1) : 11-19.
24. **Weidmann, P., De Myttenaere-Bursztein, S., Maxwell, M. H. and De Lima, J.** 1975. Effect of aging on plasma renin and aldosterone in normal man. Kidney Int. **8** : 325-333.
25. **Williams, G. H. and Dluhy, R. G.** 1972. Aldosterone Biosynthesis: Interrelationship of regulatory factors. Am. J. Med. **53** : 595-605.
26. **Zanchetti, A., Stella, A., Leonetti, G. and Mancia, G.** 1981. The control of renin release, p. 219-231. *In* J. H. Laragh, F. R. Buhler, and D. W. Seldin (ed.), Frontier in Hypertension Research. Springer-Verlag, New York.
27. **Zofkova, I., Blahos, J. and Starka, L.** 1981. Effect of calcium on adrenocortical secretion. Endokrinologie **77**(1) : 65-69.