Effect of Pressor Agents on Blood Pressure, Plasma Renin Activity and Plasma Aldosterone Concentration in Essential Hypertension

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SUMMARY

The responses of blood pressure, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) to infusion of either angiotensin II (10 ng/Kg/min) or norepinephrine (100 ng/Kg/min) were observed in 25 patients with essential hypertension. The difference in modes of response between low renin essential hypertension and normal or high renin essential hypertension was analyzed. For comparison, 5 patients with Conn's syndrome, 4 with renovascular hypertension, and 5 normotensive subjects were also studied.

Following infusion of angiotensin II the changes in diastolic blood pressure (DBP) were $+24 \pm 3.0$ mmHg in low renin essential hypertension and $+25 \pm 3.1$ mmHg in normal or high renin essential hypertension, in PRA -0.28 ± 0.06 ng/ml/h in low renin essential hypertension and -0.69 ± 0.02 mg/ml/h in another and in PAC $+3.7 \pm 1.4$ and $+7.6 \pm 1.8$ ng/100 ml respectively. There was a significant difference in magnitude of response in PRA between the 2 groups of essential hypertension ($p < 0.05$).

Norepinephrine induced rise in DBP with decreases both in PRA and PAC. The mean changes in DBP were $+6 \pm 1.4$ mmHg in low renin essential hypertension and $+16 \pm 2.2$ mmHg in another and the pressor response in the later was significantly greater ($p < 0.01$). The changes in PRA were -0.14 ± 0.07 ng/ml/h in low renin essential hypertension and -0.67 ± 0.26 ng/ml/h in normal or high renin essential hypertension, and in PAC -4.9 ± 1.3 and -3.3 ± 1.9 ng/100 ml respectively. The greater fall in PRA in normal or high renin essential hypertension was observed but the difference between the 2 groups of essential hypertension was not significant. The changes in PAC did not parallel the changes in PRA.

Angiotensin II induced essentially similar effects on blood pressure in both groups but the greater feedback inhibition of PRA was produced by this peptide in normal or high renin essential hypertension than in low renin essential hypertension. Norepinephrine induced significantly greater pressor effect in normal or high renin essential hypertension. The adopted dose of norepinephrine suppressed both PRA and PAC and a

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tendency to the greater fall in PRA was observed in normal or high renin essential hypertension. There was no difference in responses of PAC to both agents between the 2 groups of essential hypertension.

Additional Indexing Words:

Angiotension II   Norepinephrine

UNTIL the assay method of angiotensin became available it was not possible to accumulate enough information to study human hypertension. However, during the last decade with greater availability of assay methods of the peptides, initial bioassay,¹⁾⁻³⁾ and subsequent radioimmunoassay,⁴⁾⁻⁶⁾ extensive investigations in physiology of renin-angiotensin system have made its role clearer. Moreover, in 1960 it was demonstrated by Genest⁷⁾ and Laragh et al⁸⁾ that angiotensin had direct stimulating effect on aldosterone secretion. Thus, renin-angiotensin-aldosterone (R-A) system is now understood to play an important role in regulation of electrolytes and blood pressure. It has been shown that derangement of this hormonal system is in part involved in the pathogenesis of malignant hypertension¹⁰⁾ as well as Conn's syndrome.¹¹⁾ However, these represent rather exceptional hypertensive states in which abnormalities of R-A system are more easily demonstrated and altogether these comprise only a small portion of the large hypertensive population. The participation of the R-A system in the pathogenesis and natural history of so-called "essential hypertension" remains unsettled.

Investigation to date, while not generally in agreement, has often reported normal aldosterone secretion in essential hypertension. However, certain abnormal features of aldosterone secretion¹²⁾ and more apparent abnormalities in plasma renin level have been reported. While in the majority of the patients with essential hypertension plasma renin activity (PRA) is normal but in significant numbers it may be either subnormal or abnormally increased. In fact, PRA in approximately 70% of the patients with uncomplicated essential hypertension does not differ from that in normotensive population.^{13),14)} In 20 to 30% of essential hypertension PRA is lower than normal,¹⁵⁾⁻¹⁸⁾ and it is this group that has attracted the recent research interest in the field of human hypertension.

Although there has been fairly general agreement that responsiveness to vasoactive substances in essential hypertension is increased¹⁹⁾⁻²²⁾ and that 2 most potent pressor agents, angiotensin II and norepinephrine, have opposite effect on renin release in vivo,²³⁾⁻²⁶⁾ the comparative study of effects of these agents on blood pressure and R-A system between low renin essential hypertension and normal or high renin essential hypertension has not fully accomplished.

The present study was designed to examine the effects of pressor agents with different modes of action in low renin essential hypertension and normal or high renin essential hypertension. As pressor substances angiotensin II and norepinephrine were employed. The results were also compared to those obtained from the patients with Conn's syndrome, renovascular hypertension and normotensive subjects.

SUBJECTS AND METHODS

Thirty-four hypertensive patients, 22 males and 12 females, were subjected to the present study. Their ages ranged from 18 to 63, averaging 39.2. In these patients were included 25 patients with essential hypertension (17 males, 8 females), 5 with Conn's syndrome (3 males, 2 females), and 4 with renovascular hypertension (2 males, 2 females) (Table I). In 20 out of 25 patients with essential hypertension angiotensin infusion test and in 14 norepinephrine infusion test were carried out. Nine of these patients received both angiotensin and norepinephrine infusions. The patients with essential hypertension were divided into 2 groups by the level of ambulation PRA determined prior to infusion test. The lower limit of PRA in normal subjects after 1 hour ambulation being 1.45 ng/ml/h in our laboratory, the patients whose ambulation PRA was below this level were classified as low renin essential hypertension (group I) and those with above this level as normal or high renin essential hypertension (group II).

All patients were admitted to the Second Department of Internal Medicine, Kyushu University Hospital and the diagnosis was made on the basis of careful clinical studies. The blood pressure was above 150 mmHg in systole and 90 mmHg in diastole without exception on admission. On all patients with Conn's syndrome and renovascular hypertension were surgical operations performed with success. Five normotensive patients, 3 males and 2 females aged between 26 and 38 averaging 34.0, were also studied as a control group. They were selected from a group of hospital inpatients and were free from disease of the cardiovascular, renal, or endocrine system and no patient was receiving medication known to affect plasma renin level or electrolyte metabolism such as adrenocortical steroids, diuretics, or sodium containing drugs.

All medication was discontinued and the patients were maintained on a fixed sodium and potassium intake, 170–200 mEq and 50–70 mEq per day respectively, for at least 7 days prior to the study. Twenty-four hour urine specimens were collected for urinary electrolytes and catecholamines in 3 consecutive days and

Table I. Number of Patients Studied

Type of Hypertension		Low Renin	Normal or High Renin
Essential hypertension	25	13	12
Conn's syndrome	5	5	
Renovascular hypertension	4		4
Total	34	18	16

peripheral venous blood was obtained for determination of blood urea nitrogen (BUN) and serum electrolytes prior to the infusion test.

At the time between 8 and 9 a.m., following 8 hours or more recumbency and overnight fasting 15 ml of venous blood was drawn and another 15 ml after ambulation for 1 hour for determination of control PRA and PAC. Infusion test of angiotensin II or norepinephrine was carried out in the same period after 8 hours' recumbency and fasting. The pressor agents were dissolved in 5% glucose solution arranging the total infusion volume not to exceed 20 ml and were infused intravenously through antecubital vein with a Sweden constant infusion pump. Angiotensin II supplied as Hypertensin-Ciba, or norepinephrine as dl-noradrenaline was infused for 30 min at the rate of 10 ng/Kg/min and 100 ng/Kg/min respectively and these substances were in general well tolerated. The blood pressure measured indirectly by pressure cuff method and pulse rate were determined before infusion and during infusion at 5 min's interval. Collections of venous blood and 2 hours' urine specimens were performed both before and after infusion, and blood samplings were done at the upper extremity opposite to the side of infusion. Electrolytes were measured by flame photometry and urinary catecholamines were determined by modified von Euler's method.²⁷⁾ Both PRA and PAC were determined by radioimmunoassay. The determination of PRA was done by a modification of method of Haber and associates⁴⁾ using the kits supplied by CEA-IRE-SORIN, and that of PAC by a modified method of Mayes and associates²⁸⁾ using the NIH antialdosterone serum. Normal value of ambulation PRA was 1.45 to 2.60 ng/ml/h and that of supine PAC was 4.4 to 13.5 ng/100 ml in our laboratory.

RESULTS

1. Clinical data (Table II)

(1) The patients with essential hypertension received angiotensin II

The age in 11 patients with low ambulation PRA (group I) ranged from 27 to 63 and in 9 with normal or high ambulation PRA (group II) from 18 to 52 years, averaging 45 and 37 respectively. In group II was included 1 patient of age 18 with no known cause for hypertension. Mean DBP determined on 7th to 10th hospital day was 98 in group I and 97 mmHg in group II. In 3 out of 11 in group I and 2 of 9 in group II, DBP was below 90 mmHg on the day of infusion test. Three patients showed Grade I retinopathy and others Grade II in group I. In group II were included 5 patients with Grade I retinopathy and the rest with Grade II. Cardiothoracic ratio (CTR) was above 50% in 5 patients and in 9 electrocardiographic evidence of left ventricular hypertrophy (LVH) was observed in group I. In group II were included 2 patients with CTR above 50% and 5 with LVH. Serum sodium values ranged from 141 to 146 mEq/L in group I and 140 to 144 mEq/L in group II. Serum potassium values ranged from 3.9 to 4.8 mEq/L in group I and 3.8 to 4.6 mEq/L in group II, averaging 4.3 and 4.1 mEq/L respectively. Urinary catecholamines, 17-KS and 17-OHCS were within normal limits scat-

Table II. Clinical Data of Patients with Essential Hypertension for the Study of Angiotension II and Norepinephrine Infusion

Angiotension II inf.	Group I (n=11)	Group II (n=9)
Age	45 $\pm$ 2.8	37 $\pm$ 4.2
CTR (%)	51 $\pm$ 2.2	47 $\pm$ 2.3
Serum		
Na (mEq/L)	143 $\pm$ 0.6	142 $\pm$ 1.0
K (mEq/L)	4.3 $\pm$ 0.1	4.1 $\pm$ 0.1
Urine		
Na (mEq/24 h)	128 $\pm$ 11	114 $\pm$ 7
K (mEq/24 h)	28 $\pm$ 3.4	26 $\pm$ 4.1
17-KS (mg/24 h)	5.0 $\pm$ 0.8	6.3 $\pm$ 0.8
17-OHCS (mg/24 h)	4.5 $\pm$ 0.4	6.6 $\pm$ 1.2
NE (μ g/24 h)	23 $\pm$ 2.8	22 $\pm$ 7.6
DBP (mmHg)	98 $\pm$ 5.4	97 $\pm$ 5.4
PRA (ng/ml/h)		
supine	0.4 $\pm$ 0.1	1.5 $\pm$ 0.2
ambulation	0.8 $\pm$ 0.1	2.6 $\pm$ 2.7
PAC (ng/100 ml)		
supine	7.4 $\pm$ 2.6	10.7 $\pm$ 2.7

Norepinephrine inf.	(n=6)	(n=8)
Age	47 $\pm$ 4.7	33 $\pm$ 4.6
CTR (%)	50 $\pm$ 1.3	46 $\pm$ 0.8
Serum		
Na (mEq/L)	142 $\pm$ 0.7	143 $\pm$ 0.5
K (mEq/L)	4.3 $\pm$ 0.2	4.0 $\pm$ 0.2
Urine		
Na (mEq/24 h)	108 $\pm$ 6	122 $\pm$ 1.6
K (mEq/24 h)	32 $\pm$ 5.9	27 $\pm$ 3.8
17-KS (mg/24 h)	5.7 $\pm$ 0.9	7.5 $\pm$ 0.8
17-OHCS (mg/24 h)	9.8 $\pm$ 1.1	7.2 $\pm$ 1.0
NE (μ g/24)	21 $\pm$ 5.9	24 $\pm$ 7.4
DBP (mmHg)	98 $\pm$ 5.9	92 $\pm$ 4.5
PRA (ng/ml/h)		
supine	0.3 $\pm$ 0.1	1.3 $\pm$ 0.3
ambulation	0.8 $\pm$ 0.1	3.0 $\pm$ 0.5
PAC (ng/100 ml)		
supine	10 $\pm$ 2.7	8.5 $\pm$ 3.0

The values represent mean $\pm$ S.E.

Group I: Subjects with low PRA. Group II: Subjects with normal or high PRA.

Abbreviations: CTR=cardiothoracic ratio, NE=norepinephrine, DBP=diastolic blood pressure, PRA=plasma renin activity, PAC=plasma aldosterone concentration.

tering in a small range. Supine PRA was low in 7 patients and normal in 4 and ambulation PRA was below normal in all the patients in group I. In group II supine PRA was slightly below normal in 1 patient, normal in 7, and high in 1 and ambulation PRA was normal in 4 and high in 5. Supine PAC varied in group I showing 6 patients with low PAC, 3 with normal, and 2 with high PAC. There were 1 patient with low PAC, 5 with normal, and 3 with low PAC in group II.

(2) The patients with essential hypertension received norepinephrine

The age ranged from 34 to 63 in 6 patients in group I and from 18 to 58 in 8 patients in group II, averaging 47 and 33 years respectively. Mean DBP was 98 in group I and 92 mmHg in group II. In 1 patient in group I and 2 in group II, DBP was below 90 mmHg on the day of infusion test. All patients showed Grade II retinopathy in group I and in group II were included 4 patients with Grade I and 4 with Grade II retinopathy. CTR was above 50% in 3 patients and LVH was evident in 4 in group I. No patient showed CTR above 50% and in 6 patients LVH was found in group II. Supine PRA was low in 3 patients and normal in another 3 and ambulation PRA was below normal without exception in group I. In group II were included 2 patients with low, 6 with normal, and 1 with high supine PRA. Ambulation PRA was normal in 3 patient and high in 5 in group II. Supine PAC was within normal limits in all the patients in group I, while that in group II was low in 2, normal in 5, and high in 1 patient. Serum sodium values ranged from 141 to 145 mEq/L in group I and from 141 to 146 mEq/L in group II, averaging 142 and 143 mEq/L respectively. Serum potassium values were between 3.7 and 4.8 mEq/L, averaging 4.3 in group I and between 3.5 and 4.5 mEq/L, averaging 4.0 in group II. Urinary catecholamines, 17-KS and 17-OHCS were within normal limits in a small range both in group I and group II.

Although mean age and CTR appeared somewhat higher in the group of low renin essential hypertension than in that of normal or high renin essential hypertension, there was no significant difference of control values between the 2 groups of essential hypertension.

2. Infusion test

(1) Effect of angiotensin II

In 5 of normotensive subjects infusion of angiotensin II was associated with rise in DBP, $+19 \pm 2.3$ mmHg (mean $\pm$ S.E.), and decrease in PRA, -0.3 ± 0.1 ng/ml/h. Though determination of PAC in the normotensives was done only in 1 subject, the change in PAC was $+4.7$ ng/100 ml in this case with antiotensin II (Table III).

Table III. Effect of Angiotensin II or Norepinephrine Infusion in Normotensive Subjects

	DBP (mmHg)	PRA (ng/ml/h)	PAC (ng/100 ml)
Angiotensin II inf. (n=5)			
before inf.	71±2.7	1.29±0.28	12.2 (n=1)
change after inf.	+19±2.3	-0.3 ±0.1	+4.7
Norepinephrine inf. (n=5)			
before inf.	62±4.8	1.36±0.19	4.9±0.8
change after inf.	+13±2.1	-0.4 ±0.3	-1.4±0.4

The values represent mean±S.E.

Abbreviations: DBP=diastolic blood pressure, PRA=plasma renin activity, PAC=plasma aldosterone concentration.

Table IV. Effect of Angiotensin II or Norepinephrine Infusion in Conn's Syndrome

	DBP (mmHg)	PRA (ng/ml/h)	PAC (ng/100 ml)
Angiotensin II inf. (n=5)			
before inf.	111±6.3	0.13±0.03	17 ±1.7
change after inf.	+29±6.2	+0.09±0.08	+6.7±0.8
Norepinephrine inf. (n=2)			
before inf.	116, 96	0, 0.17	24, 13
change after inf.	+5, +8	±0, ±0.10	+1.2, +2.2

The values in angiotensin II infusion represent mean±S.E. and those in norepinephrine infusion represent for individuals.

Abbreviations: DBP=diastolic blood pressure, PRA=plasma renin activity, PAC=plasma aldosterone concentration.

In 5 patients with Conn's syndrome, whose control PRA was low, marked pressor effect, $+29\pm6.2$ mmHg, was observed with angiotensin II and this was associated with no remarkable change in PRA, $+0.09\pm0.08$ ng/ml/h, but significant rise in PAC, $+6.7\pm0.8$ ng/100 ml, (Table IV).

In 4 patients with renovascular hypertension with abnormally high control PRA, the change in DBP was $+18\pm1.7$ mmHg, in PRA -2.5 ± 0.5 ng/ml/h, and PAC $+7.6\pm1.9$ ng/100 ml following angiotensin II infusion (Table V).

In group I and group II of essential hypertension, the changes in DBP were $+25\pm3.0$ and $+24\pm3.1$ mmHg, the changes in PRA -0.28 ± 0.06 and -0.69 ± 0.20 ng/ml/h, and in PAC $+3.7\pm1.4$ and $+7.6\pm1.8$ ng/100 ml respectively. There was a greater response of PRA in group II than in group I ($p<0.05$) but no significant difference in magnitude of changes in DBP

Table V. Effect of Angiotensin II or Norepinephrine Infusion in Renovascular Hypertension

	DBP (mmHg)	PRA (ng/ml/h)	PAC (ng/100 ml)
Angiotensin II inf. (n=4)			
before inf.	114±4.2	3.67±0.46	17 ±6.0
change after inf.	+18±1.7	-2.5 ±0.50	+7.6±1.9
Norepinephrine inf. (n=2)			
before inf.	118, 97	4.06, 4.00	8, 10
change after inf.	+4, +4	-3.3, -1.7	-5.7, -8.1

The values in angiotensin II infusion represent mean±S.E. and those in norepinephrine infusion represent for individuals.

Abbreviations: DBP=diastolic blood pressure, PRA=plasma renin activity, PAC=plasma aldosterone concentration.

Table VI. Effect of Angiotensin II or Norepinephrine Infusion in Essential Hypertension

Angiotensin II Inf.	Group I (n=11)	Group II (n=9)
Δ DBP (mmHg)	+25 ± 3.0	+24 ± 3.1
Δ PRA (ng/ml/h)	-0.28± 0.06	-0.69± 0.20*
Δ PAC (ng/100 ml)	+3.7 ± 1.4	+7.6 ± 1.8
Δ SNa (mEq/L)	-0.13± 0.32	+0.33± 0.56
Δ SK (mEq/L)	+0.08± 0.08	+0.02± 0.17
Δ UNa (mEq/h)	-1.5 ± 0.7	-3.8 ± 2.0
Δ UK (mEq/h)	-1.0 ± 0.5	+0.2 ± 0.4
Δ UVol (ml/h)	-6.6 ± 11.2	-2.1 ± 10.1
Norepinephrine Inf.	(n=6)	(n=8)
Δ DBP (mmHg)	+6 ± 1.4	+16 ± 2.2**
Δ PRA (ng/ml/h)	-0.14± 0.07	-0.67± 0.26
Δ PAC (ng/100 ml)	-4.9 ± 1.3	-3.3 ± 2.0
Δ SNa (mEq/L)	+0.17± 0.48	0 ± 0.24
Δ SK (mEq/L)	+0.13± 0.08	+0.08± 0.14
Δ UNa (mEq/h)	+0.9 ± 2.2	+4.7 ± 3.6
Δ UK (mEq/h)	+0.9 ± 0.5	+1.2 ± 1.6
Δ UVol (ml/h)	+2.4 ± 3.5	+16 ± 13.3

The values represent mean±S.E.

* p<0.05, ** p<0.01.

Abbreviations: Δ=change after infusion, DBP=diastolic blood pressure, PRA=plasma renin activity, PAC=plasma aldosterone concentration, SNa=serum sodium, SK=serum potassium, UNa=urinary sodium, UK=urinary potassium, UVol=urine volume.

and PAC existed between the 2 groups of essential hypertension. The changes in serum and urinary sodium and potassium were not remarkable and the effect of angiotensin II on urine volume was variable (Table VI).

When the responses were compared between the normotensive subjects and the patients in group I and group II no significant difference was observed.

(2) Effect of norepinephrine

Norepinephrine induced rise in DBP, $+13 \pm 2.1$ mmHg, falls in PRA and PAC, -0.4 ± 0.3 ng/ml/h and -1.4 ± 0.4 ng/100 ml respectively in 5 normotensive subjects (Table III).

Infusion of norepinephrine for 30 min at the rate of 100 ng/Kg/min produced changes in DBP $+5$ and $+8$ mmHg, in PRA ± 0 and $+0.10$ ng/ml/h, and in PAC $+1.2$ and $+2.2$ ng/100 ml in 2 patients with Conn's syndrome (Table IV).

In 2 patients with renovascular hypertension the changes in DBP were $+4$ and $+4$ mmHg, in PRA -1.70 and -3.30 ng/ml/h, and in PAC -5.7 and -8.1 ng/100 ml following infusion of norepinephrine (Table V).

Pressor effects were thus minimum in patients with Conn's syndrome and renovascular hypertension.

In group I and group II of essential hypertension, mean changes in DBP were $+6 \pm 1.4$ and $+16 \pm 2.2$ mmHg, the changes in PRA -0.14 ± 0.07 and -0.67 ± 0.26 ng/ml/h, and in PAC -4.9 ± 1.3 and -3.3 ± 2.0 ng/100 ml respectively (Table VI). The change in DBP was significantly greater in group II than in group I of essential hypertension following infusion of norepinephrine ($p < 0.01$). Though somewhat greater fall in average PRA in group II was observed, the difference was not significant statistically. No remarkable change in serum and urinary sodium and potassium was observed and urine volume was variable with norepinephrine.

There was a significant difference in pressor effect between the normotensive subjects and the patients in group I essential hypertension ($p < 0.01$).

DISCUSSION

Though the definition of low renin essential hypertension is not strictly established, the term is frequently used for the patient with low PRA not responding to stimuli for renin release such as sodium depletion or upright posture.²⁹⁾⁻³²⁾ Since the function of R-A system is closely related to electrolyte metabolism, determination of renin and aldosterone should be done under the rigid dietary control of salt balance. In the present study, therefore, the determination was performed after the patient had been put on the diet con-

taining a fixed amount of sodium and potassium for at least 7 days to make urinary sodium and potassium excretion stable. The grouping of the patients of essential hypertension presented here was made by the PRA after ambulation for 1 hour, and this was based on our experience that Conn's syndrome could be distinguished in this way from other low renin hypertension with roughly 70% accuracy when the aged patients of 70 years and over were excluded. For more strict separation of low renin hypertension, further stimulation of renin release with administration of furosemide was adopted.

The measurement of PRA was done by a modified method of Haber and associates,⁴⁾ which is the radioimmunoassay of angiotensin I generated during 3 hours' incubation under the condition of preventing a degradation of this peptide and of maximizing the action of renin at pH 5.5 to 6.0. With this method angiotensin I could be determined with a good precision in the range 0.05 to 0.40 ng/ml. In our laboratory the least detectable level is 0.07 ± 0.01 ng/ml/h with the reproducibility of $\pm 11.6\%$ (S.D.). Sampling was performed under close observation of the subjects and blood was collected in the prechilled siliconized glass tube containing appropriate amount of ethylenediaminetetraacetic acid (EDTA) (1 mg/ml of blood). The procedure, therefore, was considered suitable to perform the analytical study.

Though pressor response to angiotensin II in patients with Conn's syndrome was significantly greater than that in those with renovascular hypertension in the present study ($p < 0.02$), there was no significant difference in pressor response to angiotensin II between low renin essential hypertension and normal or high renin essential hypertension. In essential hypertension, pressor response to angiotensin II seemed not to reflect endogenous renin level in blood. Kaplan and Silah³³⁾ suggested that renovascular hypertension could be differentiated from essential hypertension with its smaller pressor response to angiotensin II. However, in several studies,^{34), 35)} no significant difference of pressor effect to this substance could be found between the patients with renovascular hypertension and essential hypertension, suggesting that the pressor response to angiotensin II did not always reflect the circulating angiotensin II level. Even in Conn's syndrome, Weidman³⁶⁾ reported normal pressor response to angiotensin II.

As shown in Tables IV and V, the response of blood pressure to norepinephrine in 2 patients with Conn's syndrome and 2 with renovascular hypertension was minimum. Mendlowitz²⁰⁾ and Distler³⁷⁾ reported similar results in renovascular hypertension. More complicated factors might be involved in pressor response to vasoactive substance in these secondary hypertension. Significantly greater response of blood pressure to norepinephrine infusion was apparent in normal or high renin essential hypertension than in

low renin essential hypertension. Increased pressor response to norepinephrine in essential hypertension was demonstrated by many workers,³⁸⁾⁻⁴⁰⁾ but the comparison was done only between the patients with essential hypertension and normotensive subjects. In the present study, norepinephrine produced a smaller rise in blood pressure in patients with low renin essential hypertension than in normotensive patients ($p < 0.01$) but there was no difference of change in blood pressure between the patients with normal or high renin essential hypertension and the normotensives.

Though the response to vasoactive agent is an integrated function of many factors, there is a possibility that metabolic alteration may in part be responsible for the phenomenon of increased responsiveness in essential hypertension. In regard to catecholamine metabolism, the substance which is released primarily by sympathetic nerve is norepinephrine and when it is infused much is stored in tissues. When norepinephrine stores are depleted in tissues by reserpine, guanethidine, or α -methyldopa, the response to infused norepinephrine is increased.^{41), 42)} In addition, angiotensin II is known to liberate norepinephrine from stores in sympathetic nerve endings in various tissues.^{43), 44)} In this respect, in normal or high renin essential hypertension the relatively higher circulating angiotensin may possibly be related to depleting stored norepinephrine to higher degree and this may be reflected by the greater responsiveness to norepinephrine in this group of essential hypertension. On the other hand, however, Distler³⁷⁾ demonstrated that higher doses of tyramine were required to induce pressor effect in the patients with low plasma renin concentration.

It has also been shown that angiotensin tachyphylaxis was abolished by norepinephrine,⁴⁵⁾ and here may be another possibility in modifying responsiveness in essential hypertension with different levels of endogenous angiotensin.

With these possibilities, interaction of R-A and sympathetic nervous system seems to play some important role in regulating blood pressure, though it still requires more study.

Raising blood pressure, angiotensin II uniformly produced decrease in PRA and increase in PAC as already seen in several previous reports.^{46), 47)} There was a significant difference in magnitude of change in PRA between low renin essential hypertension and normal or high renin essential hypertension. Those with normal or high renin essential hypertension exhibited the greater decrease in PRA following angiotensin II infusion. PRA can be influenced by change in blood pressure per se baroreceptor function but this seems to play a relatively minor role in this situation. Though blood pressure itself is a potent regulator of renin release, a different response of PRA to

angiotensin II between low renin essential hypertension and normal or high renin essential hypertension is not likely to be produced only by similar change in blood pressure. In general, suppression of PRA induced by angiotensin II can be explained by negative feedback mechanism on renin release,^{48), 49)} but the phenomenon of different change in PRA between the 2 groups of essential hypertension still remained unsettled.

Potassium balance can possibly influence renin release with its direct action on the kidney,⁵⁰⁾ but no positive evidence of disorder of electrolyte balance was demonstrated in the result presented here. Therefore, it might be possible to postulate that feedback inhibition of renin release could be augmented when the circulating angiotensin II level is high.

The concept of direct stimulating action of angiotensin II on adrenal cortex may be supported by the data presented here showing the rise in PAC with angiotensin II infusion. Amplifications of PAC were similar in both groups of essential hypertension. In patients with Conn's syndrome, control PAC was high but the magnitude of change in PAC did not differ from those with lower control PAC (Table III). Thus, responsiveness of PAC seemed not to reflect the circulating angiotensin II level.

In sheep studies of sodium depletion, aldosterone secretion was not precisely dependent on proportional rise of blood angiotensin II and there was also a dissociation between aldosterone secretion rate and blood angiotensin II during rapid correction of sodium deficiency.⁵¹⁾⁻⁵⁴⁾ It seems to be that the adrenocortical response to additional angiotensin II is blunted when the basal level of the peptide is already high, in which situation adrenocortical secretory mechanism is stimulated nearly to maximum level. In fact, in patients with cirrhosis of the liver whose endogenous angiotensin level is high exogenous angiotensin II infusion exerted little or no additive effect on aldosterone secretion.¹⁶⁾ Besides, Laragh and associated¹⁶⁾ demonstrated that the patients with low renin essential hypertension were heterogenous as far as aldosterone was concerned. Low renin essential hypertension exhibited a variety of R-A patterns and further included low fixed plasma renin level in association with a normal or high aldosterone secretion to stimuli. This may also explain this renin-aldosterone dissociation. On the other hand, Gagnon⁵⁴⁾ described that long time suppression of PRA was associated with a decrease in reactivity of aldosterone to the stimulation of angiotensin II but the results shown here were not compatible. Potassium loss is accounted for inhibition of aldosterone secretion¹⁶⁾ and the degree of aldosterone stimulation by potassium is of as same order of magnitude as that produced by angiotensin II,¹⁶⁾ but no positive evidence of electrolyte disturbance was demonstrated in the present study.

Infusion of norepinephrine reduced both PRA and PAC and the reduction in PRA tended to be greater in normal or high renin essential hypertension but the difference between the 2 groups was not significant, while PAC was reduced in similar degree in the both groups of essential hypertension. Evidences have been shown by many workers that infusion of norepinephrine was accompanied by distinct increase in both renin release and aldosterone secretion.^{37), 45), 55)–57)} Adrenergic activity has been considered to be one of the major factors regulating renin release and there were reports indicating a direct effect of catecholamines on adrenergic receptor related to renin producing JG cells.²⁴⁾ This view was also supported by studies in the nonfiltering kidney preparation where the renin stimulating effect of norepinephrine persisted after papaverine treatment to prevent a fall in renal blood flow.⁵⁸⁾ Furthermore, the recent work suggests that renin secretion provoked by catecholamine infusion or direct sympathetic stimulation is mediated by β -receptor.^{59)–62)} Thus the direct effect of adrenergic hormones on renin secretion seems likely. In those studies, however, norepinephrine was administered either directly into the renal artery or in larger doses intravenously. Ueda and colleagues⁵⁷⁾ demonstrated that systemic infusion of norepinephrine with doses below 10 $\mu\text{g/Kg/min}$ produced no significant change in renal vein renin activity and at the same time this was associated with slight increase in renal blood flow.

In the present study norepinephrine was infused intravenously for 30 min at the rate of 0.1 $\mu\text{g/Kg/min}$ and this produced moderate rise in DBP with decreases in PRA. It seems to be possible that when this substance is given systemically in small doses, significant amount to stimulate JG cells could not reach the renal circulation and the renin release be suppressed through change in renal circulation under the influence of norepinephrine induced systemic pressor effect. This view could be supported by the results presented here that significantly greater pressor response was associated with larger fall of PRA, though not significant, in normal or high renin essential hypertension. While catecholamines may have significant effect on aldosterone secretion, the effect is not consistent.^{8), 46), 61)} Norepinephrine at times can suppress the increased aldosterone secretion rate, this would happen with sodium depletion. The factors known to influence the adrenal aldosterone secretion are renin-angiotensin system, ACTH, serum Na and K, and possible fifth factor.⁶³⁾ In the present study, however, electrolyte balance was strictly controlled. ACTH may also participate particularly in this acute situation but it stimulates aldosterone secretion. It has been suggested that the influence of catecholamines is indirect⁸⁾ and the observed change could thus be consequent either to decreased PRA or to blood pressure elevation.

If a larger dose of norepinephrine is employed the effect on renal renin release and adrenocortical aldosterone secretion would be different and the different effects on PRA and PAC might be observed.

CONCLUSIONS

To obtain more information about low renin or suppressed renin essential hypertension comparative study was performed of the effects of pressor agents, angiotensin II or norepinephrine, on blood pressure, plasma renin activity and plasma aldosterone concentration between low renin essential hypertension and normal or high renin essential hypertension. Some hypertensive patients with known etiologies were also studied for comparative analysis. The results obtained from the present study were as follows;

1) There was no difference of blood pressure elevation responding to angiotensin II between low renin essential hypertension and normal or high renin essential hypertension.

2) The significantly greater feedback inhibition of plasma renin activity was induced by angiotensin II in normal or high renin essential hypertension than in low renin essential hypertension.

3) Intravenous infusion of norepinephrine at the rate of 100 ng/Kg/min suppressed both plasma renin activity and plasma aldosterone concentration.

4) Norepinephrine induced significantly greater pressor effect in normal or high renin essential hypertension and this was accompanied by somewhat greater fall in plasma renin activity.

5) Angiotensin II produced increase in plasma aldosterone concentration and infusion of norepinephrine at the rate of 100 ng/Kg/min decreased it. There was no difference of mode of responses to both agents between low renin essential hypertension and normal or high renin essential hypertension.

6) In low renin essential hypertension plasma renin activity was little influenced by both angiotensin II and norepinephrine. Despite the poor response of plasma renin activity the response of plasma aldosterone concentration to infusions of both agents varied in low renin essential hypertension.

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