PLASMA RENIN ACTIVITY IN RENOVASCULAR HYPERTENSION*

YUKIO MIURA, TATSUO SATO,
KEISHI ABE, ISAO MIWA,
IWA O ONO AND KAORU YOSHINAGA

Dynamics of plasma renin activity (PRA) in peripheral and renal vein was studied in 22 patients with various types of renovascular hypertension. Significant elevation of resting peripheral vein PRA (PPRA) was observed in 7 out of 8 cases with unilateral main renal artery stenosis (type I). However, PPRA remained normal or slightly elevated in 5 cases with unilateral branch renal artery stenosis (type II), in 5 out of 6 cases with bilateral main renal artery stenosis (type III), and in one with unilateral main renal artery stenosis of the remaining kidney after contralateral nephrectomy. In all cases with type I and II higher renal vein PRA (RPRA) was found on the affected side, while RPRA in type III remained in normal range or slightly elevated on both sides. The ratio of RPRA between higher and lower sides was 1.27 ± 0.10 (SE) in type III. These values were smaller than that of 2.02 ± 0.24 (SE) in type I and II, and were not significantly different from that of 1.20 ± 0.04 (SE) in control group. In statistical analysis of 79 cases including 57 cases reported by other authors, normal PPRA level was found in 69.1% of patients with type III stenosis, while PPRA was normal in only 19.5% of cases with type I stenosis, and in 50.0% of cases with type II. There was significant difference in frequencies of normal PPRA between type I and III ($P < 0.001$), and also between type I and II ($P < 0.05$), respectively. Dynamics of PRA in renovascular hypertension was in close association with the types of renal arterial abnormality. Patients with renovascular hypertension, irrespective of their resting PPRA, responded to i.v. injection of furosemide and upright position with remarkable increase in renin secretion. This procedure was practically useful for the differential diagnosis of renovascular hypertension.

IN 1934 *Goldblatt* and his associates discovered that clamping the renal artery in dog produces hypertension which is mediated through a hormonal factor, namely renin.¹ Recently, there are many studies reporting that increased plasma renin activity (PRA) is found in patients

with renovascular hypertension. However, it has not been always able to demonstrate elevation of PRA in every case with renovascular hypertension. *Brown* and his colleagues showed that PRA was elevated in two-thirds of renovascular hypertension.² Previous data in our laboratory confirmed their observations. Now, it is becoming a popular opinion that estimation of PRA under various conditions provides a most valuable means for evaluating the functional significance of renovascular disorders.³⁻⁸

In the present study, PRA levels in peripheral

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The Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.

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and renal vein from patients with renovascular hypertension were extensively estimated before and after the stimulation of renin secretion, and were evaluated in regard to the correlation between the types of renovascular lesions. The evidence of the different PRA levels in several types of renovascular hypertension will be reported in this paper. The diagnostic values of PRA in renovascular hypertension will also be discussed.

MATERIALS AND METHODS

There were twenty-two cases of renovascular hypertension in this study. The diagnosis was confirmed on the basis of physical findings, intravenous pyelogram, ^{131}I -Hippuran renogram, ^{203}Hg -Neohydrin renoscintigram, split renal function studies (Howard or Rapoport test), abdominal aortogram and selective renal arteriogram. Other types of hypertension were ruled out by renal function studies and endocrinological examinations. These included eight cases with unilateral main renal artery stenosis (type I), five cases with unilateral branch renal artery stenosis (type II) and six cases with bilateral main renal artery stenosis (type III), one of which showed signs and symptoms of malignant hypertension (No.19 in Table I). Unilateral main renal artery stenosis with contralateral branch artery stenosis was found in two cases. The remaining one patient (No.22 in Table I) had main renal artery stenosis of the remaining kidney after the contralateral nephrectomy. All these subjects except one (No.19) showed no clinical evidence of heart or renal failure, and of any complication which might have influence on the dynamics of PRA throughout the study periods. Table I summarizes the clinical data on these patients.

All patients in the present series were hospitalized during the study periods. They were maintained on the general hospital diet without any hypotensive or natriuretic drugs at least 4 weeks prior to PRA assay.

Measurement of PRA was carried out not only in the resting peripheral and renal venous blood, but also after the stimulation of the renin secretion. Resting peripheral vein PRA was measured on specimens obtained in the early morning from fasting recumbent subjects. To stimulate renin secretion, intravenous injection of 60 mg furosemide followed by keeping up and about for two hours was loaded. PRA in peripheral venous blood was estimated before and after this procedure. To collect blood samples from each

renal vein, catheterization was performed by the percutaneous transfemoral retrograde *Seldinger* technique. The catheter tip was introduced in each renal vein under the television fluoroscopic control, aided by small injection of contrast medium.

Plasma renin activity was estimated by our modified method⁹ of *Pickens* and his associates.¹⁰ This procedure consists of prolonged incubation (16 hours) of 2.0–3.0 ml of plasma at 37.5°C, pH 5.5, with small amounts of both ethylenediamine tetraacetic acid and diisopropyl-fluorophosphate, purification of produced angiotensin with Dowex 50W X4 (H^+) column chromatography and bioassay on rat blood pressure. PRA in normal subjects ranged from 3.0 to 17.0 ng angiotensin II equivalents per ml plasma; mean value being 7.9 ± 0.87 (SE) ng/ml.

Statistical analyses in the present study were carried out according to Student's *t* test or Chi-square test.

RESULTS

Plasma renin activities in peripheral and renal venous blood are presented for all twenty-two cases in Table II.

PRA in peripheral venous blood

In eight cases with unilateral main renal artery stenosis (type I), the resting PRA in peripheral venous blood ranged from 16 to 81 ng/ml, averaging 32.3 ± 4.7 (SE). These cases always showed higher than normal values except case 5 who once gave an upper normal range. In five cases with unilateral branch renal artery stenosis (type II), PRA in peripheral venous blood ranged from 8.0 to 26 ng/ml with the mean value of 15.4 ± 1.9 (SE). All these values were in normal range or slightly elevated. In five out of 6 cases with bilateral main renal artery stenosis (type III), the PRA values ranged from 6.0 to 28 ng/ml with the mean value of 14.8 ± 1.8 (SE). Another patient (No.19) of this type had malignant syndrome and showed remarkably increased level of PRA (40 ng/ml). PRA of the benign hypertensive patients with type III stenosis were in normal range or only slightly elevated.

PRA level in type I stenosis was significantly higher than that in type II and III stenosis ($P < 0.01$).

In two cases with unilateral main renal artery stenosis and contralateral branch artery stenosis, PRA ranged from 17 to 39 ng/ml. They showed relatively higher than normal level.

TABLE I CLINICAL FINDINGS FOR TWENTY-TWO PATIENTS WITH RENOVASCULAR HYPERTENSION

Case No.	Age (yr.)	Sex	*Blood pressure (mmHg)	Retino-pathy (KW-grade)	**Intra-venous pyelogram	** ¹³¹ I-Hippuran renogram	**Split renal function	Arterio-gram	Renovascular lesions
A. Unilateral main renal artery stenosis (Type I)									
1.	45	M	190/110	IIb	Right	Right	Right	Rt MAS	Fibromuscular hyperplasia
2.	21	F	170/106	III	Right	Right	Right	Rt MAS	Subadventitial fibroplasia
3.	24	F	248/112	III	Right	...	Left	Lt MAS Rt renal hypoplasia	
4.	12	M	172/ 96	I	Left	Left	Left	Lt MAS Lt cirroid angioma	Neurofibromatosis
5.	36	M	240/140	III	Left	Left	Left	Lt MAS	Aortitis
6.	21	M	210/100	II	Right	Right	Right	Rt MAS	Fibromuscular hyperplasia
7.	21	F	190/ 98	Takayasu's disease	Left	Left	...	Lt MAS	Aortitis
8.	37	M	170/110	0	Left	...	...	Lt MAS	Thrombosis
B. Unilateral branch renal artery stenosis (Type II)									
9.	17	M	160/ 84	0	Normal	Normal	...	Rt BAS	Intrarenal aneurysm
10.	35	M	160/ 96	II	Normal	Left	?	Lt BAS	Intrarenal aneurysm
11.	27	F	240/120	III	Left	?	Left	Lt BAS	Aortitis
12.	14	F	180/120	I	Right	...	?	Rt BAS	Intrarenal aneurysm
13.	16	M	210/120	III	?	?	?	Rt BAS	Thrombosis
C. Bilateral main renal artery stenosis (Type III)									
14.	14	M	260/140	Cyanosis retinae	Normal	?	?	Bil MAS	Fibromuscular hyperplasia
15.	40	F	220/100	I	Normal	?	...	Bil MAS	Aortitis
16.	34	F	190/120	II	Normal	?	?	Bil MAS	Aortitis
17.	49	F	190/120	III	?	?	Left	Bil MAS	Aortitis
18.	48	M	230/120	II	Left	...	...	Bil MAS	Atherosclerosis
19.	17	F	220/130	IV (Malignant syndrome)	...	...	...	Bil MAS	Thrombosis
D. Unilateral main renal artery stenosis and contralateral branch renal artery stenosis									
20.	25	F	240/ 60	III	Right	Right	Right	Rt MAS Lt BAS	Aortitis
21.	22	M	170/110	III	Left	Left	Left	Rt BAS Lt MAS	Lt Fibromuscular hyperplasia Rt Intrarenal aneurysm
E. Unilateral main renal artery stenosis after contralateral nephrectomy									
22.	17	F	204/114	I	...	...	...	Lt MAS Rt Nephrectomy	

Abbreviations: KW-grade; Keith-Wagener classification, MAS; main renal artery stenosis, BAS; branch renal artery stenosis.

* Blood pressure recorded at the time of admission.

** The term 'Right (Rt)', 'Left (Lt)' or 'Bil' indicates the side with abnormal findings, respectively.

The question-mark (?) represents the inconclusive result. No entry indicates that the test was not done.

The split renal function studies were performed and were interpreted according to the criteria of either Howard or Rapoport test.

TABLE II PLASMA RENIN ACTIVITY IN TWENTY-TWO PATIENTS WITH RENOVASCULAR HYPERTENSION

Case* No.	Site of renovascular lesion	Plasma renin activity (ng/ml)			
		Peripheral venous blood	Renal venous blood		
			Right	Left	Ratio**
A. Unilateral main renal artery stenosis (Type I)					
1.	Right	19, 37	20	12	1.67
2.	Right	20, 26, 31	112	48	2.33
3.	Right	37	47	120	2.55
4.	Left	30	10	28	2.80
5.	Left	16, 32	50	55	1.10
6.	Right	81	...	...	...
7.	Left	22, 45	13	22	1.69
8.	Left	23	...	...	...
(Mean $\pm$ SE		32.3 $\pm$ 4.7			2.02 $\pm$ 0.3)
B. Unilateral branch renal artery stenosis (Type II)					
9.	Right	5.5, 11	140	40	3.50
10.	Left	8.0	...	...	...
11.	Left	13, 17	20	23	1.15
12.	Right	19, 20	20	10	2.00
13.	Right	16, 18, 26	29	20	1.45
(Mean $\pm$ SE		15.4 $\pm$ 1.9			2.03 $\pm$ 0.5)
C. Bilateral main renal artery stenosis (Type III)					
14.	Bilateral	15, 15, 18	25	20	1.25
15.	Bilateral	8.8, 14	...	...	...
16.	Bilateral	6.0, 13, 14, 28	...	...	...
17.	Bilateral	11	16	11	1.45
18.	Bilateral	20	18	20	1.11
(Mean $\pm$ SE		14.8 $\pm$ 1.8			1.27 $\pm$ 0.1)
19.	Bilateral	40	...	...	...
(Malignant hypertension)					
D. Unilateral main renal artery stenosis and contralateral branch renal artery stenosis					
20.	Right MAS, Left BAS	39	68	35	1.94
21.	Right BAS, Left MAS	17, 25	16	70	4.38
E. Unilateral main renal artery stenosis after contralateral nephrectomy					
22.	Left MAS Right nephrectomy	10, 12	...	...	...
Control group***		6.7 $\pm$ 0.6	7.6 $\pm$ 2.1	7.9 $\pm$ 2.0	1.20 $\pm$ 0.04
(Essential hypertension)		(76)	(10)	(10)	(10)

Abbreviations: MAS: main renal artery stenosis, BAS: branch renal artery stenosis.

* Case No. is consistent with that of patients presented on Table I.

** Ratio is the ratio of PRA between the right and the left renal vein.

*** The values given refer to means and standard errors. The number of subjects studies is indicated in parenthesis.

TABLE III CHANGES OF MEAN ARTERIAL BLOOD PRESSURE, PULSE RATE, URINE VOLUME AND PRA AFTER THE LOADING OF I.V. FUROSEMIDE AND UPRIGHT POSTURE*

	Mean blood pressure (mmHg)**			Pulse rate (/min)	Urine volume during load (ml/hr)	Hematocrit (%)	PRA (ng/ml)		
	Before (B)	After (A)	$\Delta(A-B)$ ***	$\Delta(A-B)$			Before	After	$\Delta(A-B)$
Essential hypertension (19)	116 ± 8.4	113 ± 7.8	-2.6 ± 3.1	21.7 ± 4.4	490 ± 43.4	8.8 ± 0.7	5.2 ± 0.5	13.0 ± 1.8	4.4 ± 0.9
Renovascular hypertension (15)	139 ± 8.1	134 ± 4.9	-5.9 ± 4.9	18.4 ± 3.2	482 ± 36.5	7.1 ± 1.6	20.8 ± 4.2	45.4 ± 6.6	24.7 ± 3.3
Statistical difference			NS	NS	NS	NS	$P < 0.005$	$P < 0.001$	$P < 0.001$

The number of subjects studied is indicated in parenthesis. NS: not significant.

* The values given refer to means and standard errors.

** The mean arterial blood pressure is calculated from the formula: diastolic BP + pulse pressure/3.

*** The changes, $\Delta(A-B)$, indicate the difference between the values after (A) and before (B) loading.

Fig.1. Plasma renin activity in nineteen cases of essential hypertension and fifteen cases of renovascular hypertension at recumbent (open circles) and at upright position for two hours after i.v. furosemide (closed circles). Case No. on the abscissa is corresponding to that of subjects presented on the Table I.

Abbreviations: BMAS = bilateral main renal artery stenosis, UBAS = unilateral branch renal artery stenosis, UMAS = unilateral main renal artery stenosis.

The remaining one patient (No.22) was 17-years-old female. Her right kidney was extirpated at the age of 12 because of hypertension (180/90) due to right main renal artery stenosis. Normalization of her blood pressure to the level of 120/80 was obtained, but she became hypertensive (204/114) again at the age of 17. Left main renal artery stenosis was developed. This case showed always normal PRA ranging from 10 to 12 ng/ml.

PRA in the renal venous blood

Plasma renin activity was estimated using blood samples taken from the renal vein through the catheter inserted via the femoral vein (Table II).

In ten patients with essential hypertension as controls, PRA in the renal vein showed 3.0–22.5 ng/ml with the mean value of 7.6 ± 2.1 (SE) in the right and 7.9 ± 2.0 (SE) in the left renal vein, respectively. The ratio between higher and lower sides was 1.20 ± 0.04 (SE). There was not significant difference in PRA between both sides.

In all cases with type I stenosis higher PRA was found on the affected side, mean value being about twice as high as unaffected side. Patients with type II stenosis tended to have higher PRA in the affected side than in the unaffected. The ratio between both sides in type I and II cases, 2.02 ± 0.24 (SE), was significantly greater than that of controls ($P < 0.005$). In cases

TABLE IV EFFECT OF SURGICAL CORRECTION ON BLOOD PRESSURE AND PRA IN 11 PATIENTS

Case* No.	Surgical procedure	Blood pressure (mmHg)		Plasma renin activity (ng/ml)			
		Preoperative	Postoperative (3-4 weeks after operation)	Preoperative		Postoperative	
				Recum- bent	Upright & Furosemide	Recum- bent	Upright & Furosemide
A. Unilateral main renal artery stenosis (Type I)							
1.	Angioplasty	190/110	140/ 84** 180/110***	37	80	6.3** 20***	... 34***
2.	Angioplasty	170/106	136/ 80	31	77	7.5	13
4.	Nephrectomy	172/ 96	120/ 76	30	45	4.5	9.5
5.	Angioplasty	240/140	unimproved, died from cardiac failure	16	40	...	...
6.	Nephrectomy	210/100	136/ 80	81	...	...	...
8.	Nephrectomy	170/110	120/ 74	23	...	9.0	...
B. Unilateral branch renal artery stenosis (Type II)							
10.	Nephrectomy	160/ 96	120/ 60	8.0	36	6.0	...
11.	Nephrectomy	240/120	140/ 86	13	34	6.5	7.5
12.	Nephrectomy	180/120	120/ 62	19	27	5.0	...
13.	Nephrectomy	210/120	140/ 80	16 74	20 116	3.0	8.0
C. Unilateral main renal artery stenosis and contralateral branch renal artery stenosis							
21.	Nephrectomy (left)	176/110	170/100	17	27	22	55

* Case No. is corresponding to that of patients presented on Table I.

, * Case 1 had recovered after the angioplasty, and both blood pressure (**) and PRA (**) had become normal. However, soon after postoperative aortography, both blood pressure (***) and PRA (***) elevated again.

with type III stenosis, PRA in the renal vein remained in normal range or slightly elevated on both sides. The ratio between higher and lower sides in these cases was 1.27 ± 0.10 (SE) which was smaller than that of 2.02 in the type I and II patients and was not significantly different from that of 1.20 in control group.

Effect of i.v. furosemide and upright position on PRA

Stimulation of renin secretion by injecting furosemide 60 mg i.v. and keeping the patient up and about for 2 hours was carried out in 15 cases with renovascular hypertension, and in 19 cases with benign essential hypertension as controls.

Fig.1 and Table III illustrate the results of this procedure. Remarkable enhancement in renin secretion after this stimulus was observed in all

patients with renovascular hypertension. The mean values of PRA for renovascular hypertension increased from 20.8 ± 4.2 (SE) ng/ml at rest to 45.4 ± 6.6 (SE) after the stimulation, averaged increments being 24.7 ± 3.3 (SE) ng/ml, while in control group they elevated from 5.2 ± 0.5 (SE) ng/ml at rest to 13.0 ± 1.8 (SE), increments of PRA were significantly greater in renovascular hypertension than in control group ($P < 0.001$).

Between these two groups, there was no substantial difference in the changes of blood pressure, pulse rate, urine volume and hematocrit after the test (Table III). PRA values were not related to the changes in these parameters.

PRA levels and postoperative course

Surgery, either nephrectomy or renal vascular reconstruction, was performed on 11 patients

TABLE V PRA LEVEL AND TYPES OF RENOVASCULAR LESIONS

Types of renovascular lesions	Plasma renin activity level in peripheral venous blood			Total No. of cases
	Increased	Borderline	Normal	
	Cases	Cases	Cases	Cases
Unilateral MAS	29 (2)	5	8	42
Unilateral BAS	5	1	6	12
Bilateral MAS	7 (2)	1	13	21
Unilateral MAS + contralateral BAS	2	1	0	3
Unilateral MAS + contralateral nephrectomy	0	0	1	1
Total No. of cases	43	8	28	79

Abbreviation: MAS; main renal artery stenosis, BAS; branch renal artery stenosis. The number in parenthesis indicates the cases with malignant syndrome. Seventy-nine subjects with renovascular hypertension including 22 cases in the present series and 57 cases reported by other authors^{3,6,7,12,13} are classified according to both the types of renovascular lesions and PRA levels. The term 'increased' signifies PRA level in peripheral venous blood at rest elevated above upper range of normal; 'borderline' ranged from increased level to normal, when determined repeatedly on separate occasions; 'normal' ranged usually within normal level.

out of 22; on 6 cases (No.1, 2, 4, 5, 6, 8) out of 8 with type I stenosis, on 4 cases (No.10, 11, 12, 13) out of 5 with type II stenosis and on a case with both unilateral main renal artery stenosis and contralateral branch artery stenosis (No. 21), respectively. Table IV summarizes the effect of surgical correction on blood pressure and PRA.

Postoperatively, their blood pressure has become normal in 9 cases; in 5 cases with type I stenosis (No.1, 2, 4, 6, 8) and in all operated cases with type II stenosis (No.10, 11, 12, 13).

However, remaining two cases (No.5, 21) were not improved after the surgery. One of them (No.5) died from acute cardiac failure about 2 weeks after the reparative angioplasty without normalization of blood pressure. This case had upper normal or elevated PRA in peripheral vein before the operation and showed an exaggerated response to the renin secreting stimulus. The PRA in the renal vein, however, did not show a substantial difference between two sides. It was hard to evaluate the functional meaning of the renovascular lesion in this case.

Case 21, who has not improved after the left nephrectomy, had preoperatively upper normal or elevated PRA in peripheral vein and showed an exaggerated response in PRA to renin secret-

ing stimulus. Renal vein PRA was found remarkably higher on left side with main artery stenosis than that on right side with branch artery stenosis (Table II). His pyelogram, renogram, renoscintigram and split renal function studies showed clearly the typical ischemic pattern of the left kidney. Other renal function studies were almost normal. Malignant syndrome was not observed. Two weeks after the surgery, peripheral vein PRA was still elevated (22 ng/ml) and responded supernormally to the renin secreting stimulus. From these findings, his unimproved hypertension after the operation may be attributed to the branch artery stenosis in the right kidney.

Another patient (No.1) had recovered smoothly after the vascular repairment, and both blood pressure and PRA in peripheral and renal vein had become normal. Soon after aortography which was done about 4 weeks postoperatively, both the blood pressure and PRA elevated again, probably due to a new obstructive lesion in the manipulated vasculature.

Of the 9 cases in whom blood pressure normalized after the operation, 5 cases (No.4, 10, 11, 12, 13) showed normal or only slightly elevated PRA level preoperatively. However, the

Fig. 2. Frequencies of patients who showed increased, borderline or normal PRA level in various types of renovascular hypertension. The term 'increased', 'borderline' or 'normal' indicates the PRA level classified in the same way on Table V.

procedure stimulating renin secretion elicited supernormal PRA in all 5 cases. Renal vein PRA of these patients was higher on the affected side and the difference between both sides ranged from 3 to 64 ng/ml with the ratio between both sides of 1.85 ± 0.36 (SE). In all these 9 cases, PRA levels in peripheral venous blood before and after the renin secreting stimulus were restored to normal postoperatively (Table IV); the mean values being 5.9 ± 0.7 (SE) ng/ml at recumbent and 9.5 ± 1.5 (SE) at upright posture after i.v. furosemide, respectively.

Of 11 unoperated patients, 3 cases (No. 14, 18, 19) died from cardiac or renal failure before the surgical correction, and they had bilateral renal artery stenosis. The remaining 8 cases (No. 3, 7, 9, 15, 16, 17, 20, 22) are still under palliative treatment.

PRA levels and the types of renovascular lesions

Seventy-nine hypertensive patients with renal artery stenosis including 22 cases in the present series and 57 cases reported by other authors^{3,6,7,11-13} were collected and analyzed in regard to the relationship between the site of stenosis and PRA level (Table V). These subjects consisted of 35 cases with surgically proven renovascular hypertension (20 with type I, 9 with type II, 5

with type III, and one with another type), and 44 cases with presumptive renovascular hypertension. The latter cases possessed the obvious renal artery stenosis without any other cause of hypertension, and showed various clinical evidences of the ischemic process in the renal circulation; namely, 1) apparent ischemic pattern in some renal function studies, 2) the significant pressure gradient across the stenotic lesion, 3) increased PRA level at rest or supernormal response to the secreting stimulus with exaggerated rise in PRA, 4) significant difference in renal vein PRA between affected and unaffected side.

All these subjects were maintained on unrestricted diet without any special medication, and had not any complication which influenced the dynamics of PRA.

Normal PRA in peripheral vein was found in 28 cases of total subjects (35.4%). Frequencies of normal PRA in patients with type I, II and III stenosis were 19.5% (8/42), 50% (6/12) and 61.9% (13/21), respectively. If two cases who showed the malignant syndrome with elevated PRA were excluded, the percentages of normal PRA in the type III cases rose from 61.9% to 68.4% (13/19).

There was statistically significant difference in frequencies of normal PRA between type I and

III ($P < 0.001$), and also between type I and II ($P < 0.05$) (Fig.2).

COMMENTS

The pathogenesis of renovascular hypertension has been considered to be due to the ischemic process in the renal circulation. Although this process is thought to stimulate the renin secretion, there are clinical cases who show normal PRA level at rest. In these cases a question arises whether abnormal pressure gradient across the stenotic lesion exists or does not. If there is no significant pressure gradient, the vascular abnormality does not possess functional meaning and can not be considered to contribute to the cause of hypertension. As described above, patients with renovascular hypertension, irrespective of their resting PRA levels, responded on furosemide injection and upright posture with exaggerated rise in PRA. Their blood pressure was normalized after suitable operation to remove renovascular stenosis. Therefore, it may be assumed that vascular lesion in these cases contributed to the genesis of hypertension. *Koletsky* and associates found that renin secretion from the stenotic side tended to decrease in response to the rise in systemic blood pressure which would compensate the lowering of the perfusion pressure distal to the stenosis.¹⁴ Recently, *Ayers* and his colleagues disclosed in hypertensive dogs due to unilateral renal artery clipping after contralateral nephrectomy that PRA increased initially, then decreased to normal in spite of sustained hypertension. This gradual decrease in PRA is associated with renal vasoconstriction, and this is followed by an increase in renal resistance, a decrease in renal blood flow and an increase in renal artery pressure distal to the stenosis.¹⁵ Also known was the fact that loading sodium and/or DOCA lowered the renin secretion in the animal made hypertensive by renovascular stenosis.¹⁶⁻¹⁸ These experimental results suggest that in clinical renovascular hypertension PRA level might be in normal range, as the results of compensatory rise in perfusion pressure on the stenotic side, restoring equilibrium of the water and electrolyte balance.¹⁹

The present study unveiled that types of renal artery stenosis were in close association with dynamics in PRA level. PRA was elevated in the majority (69%) of unilateral main renal artery stenosis, although it mostly remained in normal range (68.4%) in benign hypertensive cases with bilateral main renal artery stenosis. PRA level

was also normal in a patient who had main renal artery stenosis of the remaining kidney after contralateral nephrectomy.

In making renovascular hypertension in the animal, *Regoli* and associates found that the renin content of the kidney on which arterial stenosis was made rose when the opposite kidney was intact, whereas it did not increase when the contralateral nephrectomy was performed prior to the clipping.²⁰ *Blair-West* and collaborators also reported that after the combination of unilateral renal artery stenosis and contralateral nephrectomy PRA level rose only temporarily for several days and went down to normal level in spite of the persistence of systemic hypertension. When the contralateral kidney was remaining, however, PRA continued to remain on a high level together with a tendency to negative sodium balance.²¹ These results in experimental renovascular hypertension were in good agreement with the findings on the clinical cases in the present study.

In cases of bilateral main renal artery stenosis, there could be some skepticism about the etiological role of renin in the genesis of hypertension. Corrective surgery has not been performed in these cases in the present study, leaving the problem unexplored. However, they were hypertensive for at least several years, and had obvious renal artery stenosis with no other causes of hypertension. We believed, therefore, the vascular abnormality in these patients was playing the etiological role of hypertension. *Carpenter* and collaborators reported that renin content in the kidney tissue was not elevated in the benign hypertensive animal with bilateral renal artery stenosis.²² Our data showed that PRA level in these benign hypertensive cases were usually in normal range, while they responded to i.v. furosemide and upright position with supernormal secretion of renin. Analysis of clinical cases by previous authors revealed also that PRA tended to be in normal range in benign hypertensive patients with bilateral main renal artery stenosis. The degree of renovascular constriction was not always the same on both sides in patients with bilateral main renal artery stenosis. There could be the cases in which only one side had the functional meaning as the cause of ischemia. PRA level in these cases was considered to behave similarly as in those with unilateral stenosis.

PRA level was normal in about half of the cases with unilateral branch renal artery stenosis. Case 9, 10 and 12 had an aneurysm in a branch

of renal artery and localized atrophy of the renal tissue peripheral to it. Case 9 and 10 had hypertension for several years. Their blood pressure became normalized, however, by bed rest in hospital, and PRA was also lowered to normal range; but elevation of PRA was observed after the upright position and/or intravenous furosemide. After the surgery, both of them became normotensive, and remained so even after they had returned to their previous occupations. In these cases the renovascular abnormality seems most likely to have produced or increased localized circulatory insufficiency when the patients were taking a standing position; and this may be the reason why the hypertension observed before hospitalization had become normalized spontaneously thereafter. Case 12 with aneurysm in a branch of renal artery and both case 11 and 13 with branch artery stenosis were all hypertensive before and after the admission, and PRA was always elevated or in upper normal range. The dynamics of PRA in these cases were essentially the same as in cases with unilateral main renal artery stenosis in the sense that the circulatory insufficiency, though localized, had the functional meaning in producing systemic hypertension.

In two cases with unilateral main renal artery stenosis and contralateral branch artery stenosis, PRA level was always elevated.

From these results, it may be concluded that the renovascular hypertension in man has various types of renal arterial lesions, and dynamics of PRA level is in close association with these types of renovascular abnormality. In renovascular hypertension, coexistence of non-ischemic renal tissue may be necessary for continuous renin release to give a high PRA level in peripheral blood.

Provocation of renin secretion by i.v. furosemide and upright position is an useful measure for the diagnosis of this type of hypertension, since all the patients with renovascular hypertension including those who had normal PRA level during recumbent position responded to these stimulus with exaggerated rise in PRA.

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