Studies on Plasma Renin Activity in Patients with Renovascular Hypertension*

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ALTHOUGH various concepts concerning the blood pressure elevation in renovascular hypertension (RVH) have been proposed previously, it is not yet clearly elucidated what principles are playing a main role in its pathogenesis. Previous reporters confirmed that in animals with RVH renin secretion was elevated only in the initial stage and then decreased to normal after establishment of their hypertension. On the other hand, Brown and his colleagues showed increased renin activity (RA) in the majority (two-thirds) of clinical RVH. Clinically, measurement of RA under various conditions provides a most valuable means for making diagnosis of this type of hypertension. It seems likely that there are some differences in the behavior of RA between experimental and clinical RVH. We reported in previous paper that there were different renin levels in different types of RVH.

In the present study, an evaluation was made in regard to the dynamics of renin secretion. We also discussed possible role of it in the pathogenesis of RVH.

MATERIALS AND METHODS

There were 34 patients with RVH in which the diagnosis was confirmed on the basis of physical findings, pyelogram, renoscntigram, split renal function studies and renal angiography. These included 15 cases of unilateral main renal artery stenosis (type I), 8 cases of unilateral branch artery stenosis (segmental renal ischemia, type II) and 7 cases of bilateral main artery stenosis (type III). Unilateral main artery stenosis with contralateral branch artery stenosis was found in two cases, and one case showed bilateral branch artery stenosis. The remaining one patient had main renal artery stenosis of the remaining kidney which was found after the contralateral nephrectomy. All these subjects except one showed no clinical evidence of heart or renal failure, and of any other complication which might have influence on the dynamics of renin secretion throughout the study periods. Of these 34 subjects 20 cases were proven surgically to have RVH and 14 cases were diagnosed clinically. The latter cases possessed the obvious renal artery disorders without any other cause of hypertension and showed various clinical evidences of the ischemic process in the renal circulation: 1) apparent ischemic pattern in some renal function studies, 2) increased RA level at rest or supernormal responses to the renin secreting stimulus with exaggerated rise in RA, 3) significant increase in RA in the venous blood of the affected kidney. There were also 36 cases with benign essential hypertension (EH) as a control.

Experimental Design: 1) Peripheral venous RA (PVRA) in basal condition; All these subjects were maintained on unrestricted diet, without any special medication. Blood samples were drawn into heparinized syringe from antecubital vein at resting-recumbent position in the morning. To evaluate the daily variations of PVRA, serial determinations were carried out at least 3–6 times in the same subjects before surgery. Diurnal variations were also evaluated by the serial determinations during the day-time from

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PERIPHERAL VENOUS PRA IN RENOVASCULAR HYPERTENSION

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<th>Unilateral main artery stenosis</th>
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Normal range

Fig. 1. Peripheral venous PRA in renovascular hypertension.

AM 8:00 to PM 8:00 on the hospitalized patients who were kept recumbent all the day long except when they had meals or went to the toilet.

2) Salt loading or salt deprivation; To examine the effect of salt intake on the renin secretion, salt was loaded (630–750 mEq) or restricted (30–40 mEq) for 7 or 3 days, respectively. PVRA was estimated before and after these treatments.

3) I.v. furosemide and upright position; Stimulation of renin secretion by i.v. furosemide 60 mg and then keeping the patients upright for 2 hours was carried out in 15 cases of RVH, and also in 19 cases of EH.

4) Renal and inferior caval venous RA; Renal and inferior caval venous blood samples were obtained through the transfemoral retrograde Seldinger technique. The catheter tip was introduced in each proper position under the television fluoroscopic control.

5) Assay of RA; Plasma RA was estimated by the method previously reported. By this method, RA in normal subjects in recumbent position ranged 3.0–17.0 ng/ml plasma; mean value being 7.9 ± 4.7 (SD). Renin content of the kidney tissue was measured by the indirect method; briefly, the kidney tissue was extracted with saline, and then an aliquot of extract was incubated with Cohn's fraction IV as substrate at pH 5.5 in the presence of EDTA and DFP. After the incubation, angiotensin produced was partially purified with Dowex 50W-X4 (H+) column chromatography and bioassayed on rat blood pressure.

RESULTS

Peripheral venous renin activity (PVRA); The resting PVRA of RVH ranged 5.0–120 ng/ml, with average of 24.8 ± 17.0 (SD). These values were significantly higher than normal (P<0.01). PVRA was highest in patients with type I stenosis. PVRA levels were in normal range or only slightly elevated in type III patients. In two cases who had main renal artery stenosis on one side and branch artery stenosis on the other, PVRAs were higher than normal, ranging 17–39 ng/ml. In one case with multiple intrarenal aneurysms in both kidneys, PVRA ranged 50–90 ng/ml. The remaining one case was 17-years-old female. Her right kidney was extirpated at the age of 12, because of hypertension due to right main renal artery stenosis. After operation, normal blood pressure was obtained, but she became hypertensive (204/114) again at the age of 17. Left main renal artery stenosis was found. This case showed always normal PVRA ranging 10–12 ng/ml (Fig. 1).

From these results, it was obvious that there were statistical difference in PVRA levels among these various types of renovascular disorders. In analysis of 78 subjects with RVH, including 22 cases in the present series and 56 cases reported by others, normal PVRA was found in 28 cases (36%). Frequencies of normal PVRA in patients with type I, II and III stenosis were 19.5%, 50% and 61.9%, respectively. If two cases who showed the malignant syndrome were excluded, the percentage of normal PVRA in type III increased to

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DAILY VARIATION OF PRA

![Graph showing daily variation of PRA](image)

Fig. 2. Daily variation of PRA.

68.4%. There was statistically significant difference in frequencies of normal PVRA between type I and III (P<0.001) and also between type I and II (P<0.05).

Daily Variations: Daily variations of PVRA in each subjects were tested with the index of 'mean deviation, calculation formula being

\[ \frac{\sum |X - \bar{X}|}{N} \]

These values in 19 patients with RVH ranged 0.86–30.0, averaging 8.8 ± 7.4 (SD), while in 22 cases of EH, they ranged 0.23–9.4 (2.6 ± 2.4 (SD)). The mean deviation of PVRA in RVH was significantly greater than that in EH (P<0.01) (Fig.2).

Diurnal Variations: In 6 cases of benign EH, diurnal variations of PVRA were 7.3 ± 4.9, 8.4 ± 6.6, 5.8 ± 1.4 and 6.4 ± 2.1 (SD) ng/ml, at AM 8:00, 12:00, PM 4:00 and 8:00, respectively. However, greater and irregular variations of PVRA were observed in RVH as compared with that in EH.

Renal venous renin activity (RVRA); In 10 subjects with benign EH, the ratio between both sides was 1.23 ± 0.39 (SD). There was not significant difference in RVRA between them. On the other hand, almost all cases of unilateral renal artery stenosis showed higher RVRA on the affected side, about twice as high as on unaffected side. Only two cases of type I stenosis had normal RVRA in affected side, whose RVRA was also within normal range. RVRA in cases with type III stenosis was normal or slightly elevated on both sides. The ratio between them was 1.27 ± 0.85 (SD) and was not significantly different from that of EH. But one patient with type III stenosis, in whom the degree of vascular constriction was obviously different between two sides, showed a significantly higher PVRA on the more severe side. One case of bilateral branch artery stenosis showed remarkably elevated, RVRA on both sides.

Effect of furosemide and upright position on PVRA; Enhancement in renin secretion after the stimulus was observed in RVH, even if resting PVRA was remained in normal range. The mean values of PVRA increased from resting values of 20.8 ± 4.2 (SD) ng/ml to 45.4 ± 26.4 (SD) after it, while in EH they elevated from 5.2 ± 2.2 (SD) ng/ml to 13.0 ± 7.7 (SD). The increments of PVRA were significantly greater in RVH (24.7 ± 13.3 (SD) ng/ml) than in EH (4.4 ± 4.1 (SD) ng/ml) (P<0.001).

Effect of salt intake on renin secretion; Significant decrease or increase of PVRA was ob-
served on the high or low Na intake, respectively. Diurnal variations of PVRA on high Na intake also became less marked than in control period.

**Renin content in the kidney tissue:** The kidney was obtained from 12-years-old boy, who had hypertension due to segmental renal ischemia. Preoperatively, his PVRA and RVRA on the affected side were remarkably increased. The upper segment of the extirpated kidney was found to have sharply localized ischemic area on inspection and histology, other portion being completely normal. Renin content in the ischemic segment was from 9.9 to 11.2 ng/mg tissue, while non-ischemic segment contained only from 3.4 to 4.9 ng/mg. Remarkable renin release from the ischemic segment of the kidney was suggested.

**Postoperative course of arterial blood pressure:** Progressive lowering of blood pressure was obtained in 19 of 20 surgically treated cases, which began in the first postoperative day. In an average, systolic arterial pressure was decreased to 95%, 91%, 81% and 76% of the preoperative level, on the fifth, tenth, 20th and 30th day after the surgery. Normalization of arterial blood pressure was found at the 20–30th day. PVRA and its response to the stimulus also return to normal.

**Comments and Conclusion**

In the present study, significant elevation of the renin-angiotensin system was proven in the majority of patients with RVH.

The results obtained can be summarized as follows: 1) increased PVRA in 65% of the cases with RVH, 2) statistical differences in PVRA levels among various types of renovascular disorders, 3) increased RVRA level on the affected side, 4) high renin content in the ischemic kidney tissue compared with the non-ischemic tissue, 5) greater and irregular variations of the diurnal PVRA in RVH than those in EH, 6) higher and greater variations in the daily PVRA levels in RVH compared with those in EH, 7) supernormal PVRA responses to the diuretics and/or upright position, even when the resting PVRA was normal, 8) abnormal response to sodium loading (suppression was less marked) and to sodium restriction (increase in PVRA was exaggerated).

The dynamics of renin secretion in RVH was considered essentially to be due to the ischemic process in the renal circulation. The types and severity of renovascular abnormality could be closely associated with the dynamics of renin secretion. The water-salt balances and systemic circulation might be related to the renal circulation and to the kidney functions, influencing the renin secretion. In addition, these variables would also be interrelated to each other, and maintain a homeostatic equilibrium. As suggested previous authors, sympathetic nervous system, circulating catecholamines or yet unidentified hormonal factors might be concerned in these situations. Although dynamics of renin secretion in clinical RVH might be responsible for the balance or equilibrium of renal circulatory conditions, in the present study the evidence of elevated function in renin-angiotensin system could be essentially proven.

The precise role of renin-angiotensin system for the pathogenesis of RVH is not yet definitely elucidated up to date. Now, most intensive arguments against the causative role of renin for this type of hypertension are based on several experimental results in which increased renin secretion could be observed in the initial stage of the experimental animals, but not during the established stage of hypertension. Moreover, the active or passive immunization to angiotensin II could not influence the development or maintenance of the experimental RVH. On the contrary, there are several experimental and clinical evidences enough to support a pathogenetic role of renin for this type of hypertension. It has been well established that the primary disorders of the renin-angiotensin-aldosterone system can cause some types of clinical hypertension such as primary aldosteronism and renin-producing tumor. Segmental renal ischemia localized in only from 5 to 15% or less of the whole kidney tissue in the present series was the cause of sustained arterial hypertension with high renin secretion. It seems, therefore, this pathophysiological situation is similar to that of renin-producing tumor. However, postoperative restoration of clinical RVH took rather prolonged course. Complete normalization of arterial pressure was eventually obtained on the 20–30th postoperative day. These results might indicate that the some mechanism operating outside the affected kidney was necessary to maintain systemic arterial hypertension.

**Acknowledgement**

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REFERENCES

DISCUSSION:
Chairman: TATSUO ODA, Nihon Univ.

CHAIRMAN: Thank you, Dr. Miura for your excellent lecture about studies on plasma renin activity in patients with renovascular hypertension. Dr. Miura divided three major groups of patients with renovascular hypertension and observed the plasma renin activity (or level) and responses to the various stimulating factors respectively. Any comments or discussions?

Dr. TAGAWA (Tokyo Univ.): I have some comments on these problems. Generally it is said that the plasma renin activity (PRA) is normal in the chronic stage of renovascular hypertension in animals and even renal artery stenosis in humans. However, I think that the problem is pointed to the fact whether the stenosis is functionally significant to secret renin, or not. I suppose that a perfusion pressure of renal artery may be less than 70-80 mmHg for necessity of secreting renin.

Namely I have data that when a renal artery, which was formally by a catheter in order to measure the renal perfusion pressure ahead of the inflatable cuff that is surrounded around a renal artery, was constricted, a renin secretion was promoted during several days only when the perfusion pressure became less than 70-80 mmHg. When blood pressure rose and perfusion pressure became over than the above mentioned level, renin secretion was decreased and promoted again by the increase of grade of constriction and lowering the perfusion pressure.

Therefore, I think that we had better discuss a renin secretion under the consideration of a renal perfusion pressure.

Dr. TAKEDA (Tokyo Univ.): I have many patients strongly responding to various stimuli of renin release in cases with normal peripheral PRA in recumbent position. The other authors also reported rather frequently a normal PRA under recumbent position in the cases with bilateral renal artery stenosis. However by our experience a renin release of such cases responded strongly by stimuli for renin release. Even in the cases showing a slight difference of grade of constriction by renal arteriography, an augmentation of the difference seems to be reflected by measuring separately bilateral renal venous PRA.

Dr. MIURA (Tohoku Univ.): I have recognized that a much increasing response occurred by the stimuli, such as standing position and intravenous injection of furosemide in cases with bilateral renal artery stenosis. Therefore, I believe that the renovascular anomaly mentioned above had a functional significance. In most of such cases a postoperative blood pressure became normal by bilateral renovascular reconstruction.

Dr. YAMAMOTO (Osaka Municipal Univ.): (1) I believe that a distribution of renin in renal cortex is not homogenous and shows a steep slope of renin content from outer cortex to inner one of kidney. Therefore, we must take care of a site of sampling a piece of renal cortical tissue. (2) I think that the critical point of renin release due to lowering of renal artery pressure is 75-80 mmHg. When we lower a perfusion pressure, a variation of distribution pattern of intrarenal blood flow or regional GFR may become a trigger of renin release without a variation of total renal blood flow.

Dr. MIURA: As a result of measuring a renin content of various parts of excised segmental renal ischemia, I recognized an increased PRA localized an ischemic part of kidney.

CHAIRMAN: I have read a paper with much interest before, which showed a slight to moderate increase and disappearance of diurnal variation of plasma cortisol. Please tell me about such information, if possible.

Dr. MIURA: I am studying now on your presentation and going to report soon.

CHAIRMAN: I think it seems to be the time to end this session. Thank you to all.