Release of Renal Renin in Patients under Long-Term Dialysis Treatment

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KANEDA, H., TASHIRO, M., MATSUMOTO, J., HARUYAMA, T., MURATA, T. and ABE, K. *Release of Renal Renin in Patients under Long-Term Dialysis Treatment.* Tohoku J. exp. Med., 1979, 127 (1), 25-33 — Plasma renin activity (PRA) was studied in 61 patients under long-term dialysis treatment. They were divided into three groups, low (0.1-5.0 ng/ml), normal (5.1-30.0 ng/ml), and high renin groups (more than 30.1 ng/ml) according to the levels of PRA. The difference in clinical features in the three groups and the factors influencing the secretion of renin were investigated. 1) With regard to the pre-dialysis PRA (resting PRA), low renin levels were found in 13.1 per cent of patients, normal in 65.5 per cent, and high in 21.4 per cent. 2) The pre-dialysis PRA (resting PRA) was significantly correlated with the Δ PRA/removed-sodium, but not with the removed sodium or removed water by the preceding dialysis. 3) Severe retinal changes were observed in patients with high resting PRA values. In contrast, fundoscopic findings were mild in patients with low resting PRA values. 4) Elevated resting PRA values were obtained in younger subjects under 29 years of age, while the PRA levels were very low in patients of advanced ages (over 60 years). The latter showed low levels of Δ PRA/removed-sodium. 5) Though the ratios of Δ PRA/removed-sodium were very low in patients under hemodialysis for over 3 years, the resting PRA levels did not decrease with the duration of dialysis treatment, because renin secretion was stimulated strongly by the excessive removal of sodium and water in these later periods of hemodialysis. 6) With regard to the post-dialysis PRA, low renin levels were found in 6.8 per cent of patients, normal in 55.9 per cent, and high in 37.3 per cent. Post-dialysis PRAs were significantly correlated with the pre-dialysis PRAs and the Δ PRA/removed-sodium. From these results, it may be concluded that high PRA is a risk factor producing the hypertensive complications and Δ PRA/removed-sodium is a most important factor controlling the levels of PRAs (pre-dialysis PRA and post-dialysis PRA). Furthermore, age, removed sodium, removed water and the duration of dialysis also might be concerned with the secretion of renin. ——— renin subgroup in chronic dialysis patients; sensitivity index of renin secretion vs. sodium status; high incidence of vascular complications in high renin group

Recently, Laragh et al. (1972) and other investigators (Kem et al. 1972; Spark 1972; Amery et al. 1973; Doyle et al. 1973; Kono et al. 1973; Mroczek et al. 1973; Shimizu et al. 1973; Case et al. 1976) had classified the resting PRA in

essential hypertension into three groups; low, normal, and high renin groups. Laragh et al. reported that characteristic features of high renin group were high incidence of cardiovascular complications, high diastolic blood pressure, and high blood urea nitrogen levels compared with the other two groups.

In Japan, Abe and coworkers (1975) also reported that marked impairment of renal function and severe retinal changes were observed in patients with essential hypertension having high resting PRA values. On the contrary, hypertensive complications of the kidney and ocular fundi were mild in patients with low resting PRA values. However, such investigations have never been done in chronic dialysis patients, though many studies (Stokes et al. 1970; Brown et al. 1971; Craswell et al. 1972; Schalekamp et al. 1973; Lazarus et al. 1974) about the relationship between renin and hypertension in patients under chronic dialysis treatment have been made. So, we tried to classify the resting PRA into three groups according to the mean levels of serial determinations along a course of three months and clarify the clinical significance of those subgroups in chronic dialysis patients. Furthermore, we also studied the factors influencing the secretion of renin in these patients.

PATIENTS AND METHODS

Sixty-one patients (36 males and 25 females) under chronic dialysis treatment were studied. Their age ranged from 15 to 69 years (mean 42.8), and their duration of dialysis ranged from 3 to 83 months (mean 19.8 months); 26 patients, less than 1 year; 20 patients, 1 to 2 years; 4 patients, 2 to 3 years; 6 patients, 3 to 4 years; and 5 patients, more than 5 years. Their underlying diseases were chronic glomerulonephritis (60 patients) and Alport's syndrome (1 patient).

All patients had stopped hypotensive medications at least 1 month before the test. All patients were treated by hemodialysis alone, through arterio-venous fistula, two or three times per week, total dialysis time being 14 to 18 hr per week. The dialysate supply system was composed of a 50 liters tank and a recirculation system, so that the fluid and electrolytes dialysed out of the body were easily calculated at the end of dialysis. Removed sodium, removed water, and other removed substances were routinely checked and recorded in each dialysis. Plasma renin activity (PRA) was measured before and after the dialysis once a month. It was analysed by radioimmunoassay of angiotensin I (Abe et al. 1972; normal range, 5 to 30 ng/ml). We usually calculated Δ PRA (post-dialysis PRA minus pre-dialysis PRA)/removed-sodium and evaluated it as a sensitivity index of PRA to the sodium status of the body. All patients were on a restricted salt intake (approximately 100 mEq or less of daily sodium intake). Furthermore, clinical and laboratory data, such as blood pressure, serum sodium concentration, and eye ground changes were also checked and evaluated.

RESULTS

Table 1 shows the results of renin subgroups which are divided into three according to the level of resting PRA. In 61 patients, low renin group (0.1–5.0 ng/ml) was found in 13.1 per cent, normal (5.1–30.0 ng/ml) in 65.5 per cent, and high (more than 30.1 ng/ml) in 21.4 per cent.

Each PRA level represents the mean value of serial determinations of PRA for three months. Mean age was 44.7 years in low, 45.5 years in normal, and 34.8 years in high PRA group. Mean duration of dialysis was 17.2 months in low, 19.6

TABLE 1. *Results of three renin subgroups divided according to the level of resting PRA*

	Group		
	Low PRA (0.1-5.0 ng/ml)	Normal PRA (5.1-30.0 ng/ml)	High PRA (more than 30.1 ng/ml)
Number of patients	8	40	13
Per cent	13.1	65.5	21.4
Age (years)	44.7 $\pm$ 5.9	45.5 $\pm$ 2.1	34.8 $\pm$ 2.5
Duration of dialysis (Months)	17.2 $\pm$ 5.5	19.6 $\pm$ 3.0	21.9 $\pm$ 5.8
Pre-dialysis PRA (ng/ml)	3.87 $\pm$ 0.34	14.48 $\pm$ 1.13	49.95 $\pm$ 3.62
Post-dialysis PRA (ng/ml)	4.80 $\pm$ 0.56	22.67 $\pm$ 2.31	60.15 $\pm$ 5.94
Δ PRA/removed-sodium	0.0024 $\pm$ 0.0017	0.0215 $\pm$ 0.0053	0.0387 $\pm$ 0.0132
Removed sodium by the preceding dialysis (mEq)	442.8 $\pm$ 64.6	468.4 $\pm$ 22.0	499.2 $\pm$ 45.2
Removed water by the preceding dialysis (liters)	2.16 $\pm$ 0.24	2.45 $\pm$ 0.10	2.76 $\pm$ 0.16

months in normal, and 21.9 months in high PRA group. Average Δ PRA/removed-sodium was 0.0024 in low, 0.0215 in normal, and 0.0387 in high PRA group. The correlation coefficient (r) between resting PRA and Δ PRA/removed-sodium was 0.405 ($n=60$, $p<0.01$). Removed sodium by the preceding dialysis was 442.8 mEq in low, 468.4 mEq in normal, and 499.2 mEq in high PRA group. Removed water by the preceding dialysis was 2.16 liters in low, 2.45 liters in normal, and 2.76 liters in high PRA group. The relationship between resting PRA and the removed sodium or removed water by the preceding dialysis was not statistically significant in any of the three groups.

Fig. 1 illustrates the blood pressure, serum sodium concentration and retinal change in each group. Mean systolic blood pressure was 142.8 mmHg in low, 140.1 mmHg in normal, and 145.4 mmHg in high PRA group. Average diastolic blood pressure was 86.8 mmHg in low, 89.8 mmHg in normal, and 94.6 mmHg in high PRA group. There were no statistically significant correlation between resting PRA and systolic or diastolic blood pressure. Mean serum sodium concentration was 141.9 mEq/liter in low, 140.8 mEq/liter in normal, and 139.7 mEq/liter in high PRA group. There was statistically significant correlation ($n=61$, $r=-0.270$, $p<0.05$) between resting PRA and serum sodium concentration.

As for the retinal changes, per cent of patients who had KW III or IV was zero in low (KW I, 4; KW II, 0; KW III, 0; and KW IV, 0), 7.7 per cent in normal (KW I, 10; KW II, 14; KW III, 2; and KW IV, 0), and 50 per cent in high PRA group (KW I, 3; KW II, 3; KW III, 5; and KW IV, 1).

Fig. 2 shows pre-dialysis PRA, Δ PRA/removed-sodium, removed sodium or removed water by the preceding dialysis at different ages. The level of resting PRA in younger persons under 29 years of age was slightly higher than in the older age groups. On the contrary, the level of resting PRA in advanced age over 60 years was very low compared with other age groups. The level of Δ PRA/removed-sodium in younger subjects under 29 years of age was highest, whereas the levels in the individuals from 40 to 49 years of age and in advanced ages over 60 years were

Fig. 1. Blood pressure, serum sodium concentration, and retinal change in the three groups at rest.

Fig. 2. Pre-dialysis PRA, Δ PRA/removed-sodium, removed sodium and removed water by the preceding dialysis in different ages.

very low. On the other hand, the levels of removed sodium or removed water by the preceding dialysis were not significantly different between the age groups.

Fig. 3 demonstrates pre-dialysis PRA, Δ PRA/removed-sodium, removed sodium and removed water by the preceding dialysis at different dialysis-period. The level of resting PRA in the individuals from 2 to 3 years of dialysis-period was the highest, whereas the levels of Δ PRA/removed-sodium in the patients more than 3 years of dialysis-period was very low. The levels of removed sodium or removed water by the preceding dialysis were highest in the group of patients dialysed for 2 to 3 years, and the values were lowest in the group of patients dialysed for less than 1 year.

Fig. 3. Pre-dialysis PRA, Δ PRA/removed-sodium, removed sodium and removed water by the preceding dialysis at different dialysis-period.

Table 2 presents the results in the three groups divided according to the levels of post-dialysis PRA. Of the 59 patients, 6.8 per cent had low, 55.9 per cent normal, and 37.3 per cent high post-dialysis PRA values. As compared to the groups according to resting PRA, per cent of low PRA group had decreased and

TABLE 2. Results of three renin subgroups divided according to the level of post-dialysis PRA

	Group		
	Low PRA (0.1–5.0 ng/ml)	Normal PRA (5.1–30.0 ng/ml)	High PRA (more than 30.1 ng/ml)
Number of patients	4	33	22
Per cent	6.8	55.9	37.3
Age (years)	53.0±8.4	43.2±2.3	39.1±2.8
Duration of dialysis (months)	18.5±8.6	21.6±3.5	18.5±3.9
Post-dialysis PRA (ng/ml)	4.12±0.54	15.55±1.44	52.56±4.44
Pre-dialysis PRA (ng/ml)	4.70±0.54	11.72±1.19	35.88±3.43
Δ PRA/removed-sodium	-0.0027±0.0028	0.0088±0.0018	0.0489±0.0108
Removed sodium (mEq)	380.1±103.0	526.7±25.5	433.4±31.5
Removed water (liters)	2.10±0.50	2.71±0.12	2.61±0.18

high PRA group increased. Mean age was 53.0 years in low, 43.2 years in normal, and 39.1 years in high post-dialysis PRA group. There was no statistically significant correlation between post-dialysis PRA and age. Mean duration of dialysis was 18.5 months in low, 21.6 months in normal, and 18.5 months in high post-dialysis PRA group. Mean post-dialysis PRA was 4.12 ng/ml in low, 15.55 ng/ml in normal, and 52.56 ng/ml in high post-dialysis PRA group. Mean pre-dialysis PRA was 4.70 ng/ml in low, 11.72 ng/ml in normal, and 35.88 ng/ml in high post-dialysis PRA group. There was highly significant correlation ($n=58$, $r=0.884$, $p<0.01$) between pre- and post-dialysis PRA. Mean Δ PRA/removed-sodium in each group was -0.0027 in low, 0.0088 in normal, and 0.0489 in high post-dialysis PRA group. There was also a statistically significant correlation ($n=58$, $r=0.738$, $p<0.01$) between post-dialysis PRA and Δ PRA/removed-sodium. Mean removed sodium was 380.1 mEq in low, 526.7 mEq in normal, and 433.4 mEq in high post-dialysis PRA group. On the other hand, mean removed water was 2.10 liters in low, 2.71 liters in normal, and 2.61 liters in high post-dialysis PRA group. There was no significant correlation between post-dialysis PRA and removed sodium or removed water.

DISCUSSION

The present study revealed that 13.1 per cent of patients under chronic dialysis treatment had low, 65.5 per cent had normal, and 21.4 per cent had high PRA levels at rest. These results are slightly different from those of Laragh et al. (1972) and Abe et al. (1975) in essential hypertension in which PRA values were subnormal in 27–23.5 per cent, within normal range in 57–64.5 per cent, and increased in 12 per cent. In dialysis patients, per cent of high PRA group was about twice that in essential hypertension. On the contrary, hypertensive complications of ocular fundi were almost the same in the two groups. Furthermore, it is clear that Δ PRA/removed-sodium is one of the important factors influencing the secretion of renin in chronic dialysis treatment.

From these data, the following discussions seem to be warranted.

Pre-dialysis PRA (resting PRA)

As mentioned above, per cent of high renin group in patients under hemodialysis was clearly high, whereas per cent of low renin group was lower compared with that of the essential hypertension. These differences in resting PRA values between patients with essential hypertension and chronic dialysis patients might result from the fact that in dialysis patients, a great deal of sodium (400–600 mEq) and water (2–4 liters) were usually removed at one dialysis, which was repeated 2 or 3 times per week, thus the sodium balance, as a whole, was more negative in dialysis patients than in patients with essential hypertension. It was interesting that the resting PRA was correlated significantly with $\Delta\text{PRA}/\text{removed-sodium}$, but not with the removed sodium or the removed water by the preceding dialysis. The $\Delta\text{PRA}/\text{removed-sodium}$ can be regarded as a sensitivity index of the renin secretion in a given sodium status in chronic dialysis patients. The removed sodium and removed water by the preceding dialysis were not statistically correlated with the resting PRA, but they might influence the level of resting PRA to some extent.

From these results, we speculated that the most important factor influencing the resting PRA was $\Delta\text{PRA}/\text{removed-sodium}$, and the second was removed sodium or removed water by the preceding dialysis. As for the hypertensive complications, per cent of patients who had KW III or IV was prominently high in high resting PRA group, though the levels of blood pressure (systolic and diastolic) and ages were not so different in the three groups. These results coincide with the reports of Laragh et al. (1972), Abe et al. (1975), and Brunner et al. (1973) in essential hypertension, but not with Doyle and coworkers (1973). The high incidence of vascular complication in high renin group might suggest the possibility that high renin itself has vasculotoxic effects in the human body.

Concerning the resting PRA and age, old patients over 60 years had significantly low values as well as low $\Delta\text{PRA}/\text{removed-sodium}$, a finding already confirmed in essential hypertension (Abe et al. 1975; Brunner et al. 1973; Laragh et al. 1972).

Thirteen patients aged 40 to 49 had an average resting PRA level almost the same as other age groups except subjects over 60 years of age, though $\Delta\text{PRA}/\text{removed-sodium}$ was very low. This phenomenon perhaps meant that resting PRA in these patients was in a state of stimulation by the excessive removal of sodium and water by the preceding dialysis. Similarly, as for the resting PRA and the duration of dialysis, patients dialysed for more than 3 years had low $\Delta\text{PRA}/\text{removed-sodium}$, but their resting PRAs were not so suppressed as compared with other groups in disagreement with that of Craswell et al. (1972). This result also might indicate that the excessive removal of sodium and water by the preceding dialysis stimulates the secretion of renin. On the other hand, subjects dialysed for less than 1 year had normal resting PRA, though only small amounts of sodium and water were removed by the preceding dialysis, because of a high index of $\Delta\text{PRA}/\text{removed-sodium}$.

Post-dialysis PRA

Per cent of high post-dialysis PRA in chronic dialysis patients was clearly increased compared with those of pre-dialysis PRA. Furthermore, patients with normal and high post-dialysis PRA values were younger in age compared with the subjects with low values. It was very interesting that the post-dialysis PRA was strongly correlated with pre-dialysis PRA and Δ PRA/removed-sodium, but not with the removed sodium or removed water.

From these results, it is likely that the post-dialysis PRA was controlled mainly by the pre-dialysis PRA and Δ PRA/removed sodium. However, age, removed sodium, and removed water might also influence the levels of post-dialysis PRA to some extent.

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