HYPERTENSION IN PATIENTS ON CHRONIC HEMODIALYSIS: THE ROLE OF THE RENIN-ANGIOTENSIN SYSTEM

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The effects of volume-loading and removal on mean blood pressure were evaluated in patients with high blood pressure and on chronic hemodialysis. Simultaneous measurements of plasma renin activity, plasma angiotensin II and plasma norepinephrine were made. The patients were divided into two groups according to their levels of plasma renin activity. Group 1 ($n = 10$) had a basal plasma renin activity below 2.5 ng/ml/hr while the level in group 2 ($n = 5$) exceeded 2.5 ng/ml/hr. The mean blood pressure of the two groups was 105 ± 5 mmHg and 107 ± 4 mmHg, respectively. On the day of hemodialysis, saline loading (0.5 ml/kg/min for 20 min) was followed by routine hemodialysis. The mean blood pressure rose to 113 ± 6 mmHg in group 1. However, the patients in group 2 did not respond to volume loading and hemodialysis. The plasma renin activity, plasma angiotensin II and plasma norepinephrine were not changed by volume loading in both group 1 and 2. Volume removal by hemodialysis caused a reduction in mean blood pressure in group 2 without alteration of vasoactive hormones. In group 1, the mean blood pressure was not reduced by hemodialysis, accompanied by increases in plasma renin activity, plasma angiotensin II, and plasma norepinephrine. In the high renin group, elevated circulating angiotensin II maintained a high blood pressure and in the low renin group, the renin-angiotensin system influenced the prevention of fall in blood pressure after hemodialysis.

These results suggest that the renin-angiotensin system plays an important role in the regulation of blood pressure in relation to volume status regardless of whether the plasma renin activity is high or low.

ALTHOUGH volume and/or sodium and the renin-angiotensin system have been considered to be two major contributory factors to high blood pressure,¹⁻³ inappropriate volume-renin homeostasis occurs in patients with chronic renal failure.⁴⁻⁶ Several investigators^{2,3,5,6} have therefore attempted to establish the interrelation between volume and the renin-angiotensin sys-

tem in hypertensive patients with chronic renal failure. However, the results are contradictory. In addition to these two factors, it is suggested that the sympathetic nervous system may play a role in the regulation of blood pressure in chronic renal failure as well as that in essential hypertension.⁷⁻⁹

The present study was designed to examine the relationship among three components- volume, the renin-angiotensin system and the sympathetic nervous system- in conditions of volume load and its removal by hemodialysis in patients on chronic hemodialysis.

Key words:

Renin-Angiotensin system
Volume load
Hemodialysis
Norepinephrine

(Received June 11, 1986; accepted November 26, 1986)

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TABLE I CLINICAL AND BIOCHEMICAL DATA: PRE-AND POST-HEMODIALYSIS FOR INDIVIDUAL SUBJECTS

Patient No.	Age (y.o.)	Duration (month)	Body Weight Change (kg)		Total Protein (g/dl)		Creatinine (mg/dl)		Na (mEq/l)		K (mEq/l)	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Group 1												
1.	31	12	+0.8	−1.0	6.6	6.8	17.4	6.2	141.7	142.6	5.9	3.3
2.	39	15	+2.3	−1.8	7.0	7.7	19.7	7.0	138.4	137.3	5.2	3.2
3.	39	12	0.0	−0.1	7.4	6.4	11.7	5.2	140.7	140.1	4.4	3.2
4.	42	14	+0.5	−1.0	6.7	7.1	12.5	4.4	136.6	140.4	4.4	3.5
5.	42	12	+0.7	−1.4	6.9	7.8	13.1	4.9	138.4	139.0	5.0	3.4
6.	40	14	+1.8	−2.0	6.8	7.8	12.9	5.5	137.3	141.0	4.2	3.2
7.	47	14	+0.4	−0.8	6.6	6.9	9.9	2.9	139.2	139.9	5.6	3.7
8.	45	16	+1.2	−1.1	7.1	8.0	11.5	3.2	137.4	139.0	5.1	3.2
9.	42	24	+0.1	−0.1	6.2	5.7	11.9	4.9	141.0	139.1	3.5	2.8
10.	40	40	+2.2	−3.0	5.4	6.1	8.3	3.1	142.9	142.7	3.8	2.8
Mean	41	17	+1.0	−1.2	6.7	7.0	12.9	4.7	139.4	140.0	4.7	3.2
± SEM	±4	±9	±0.3	±0.3	±0.2	±0.3	±1.1	±0.4	±0.7	±0.5	±0.2	±0.1
Group 2												
1.	35	15	+1.3	−1.5	6.7	7.3	14.8	4.8	138.6	136.6	5.3	3.6
2.	45	21	+2.9	−2.5	6.9	8.0	20.9	8.3	136.7	135.1	4.9	3.6
3.	35	14	+2.3	−2.0	6.6	7.1	12.3	4.8	137.5	139.8	5.4	3.7
4.	24	12	+1.5	−1.3	6.3	6.9	21.7	8.6	137.4	139.5	5.8	3.6
5.	47	14	+3.2	−2.6	6.7	8.3	12.9	4.6	138.6	138.1	6.2	4.2
Mean	37	15	+2.2	−2.0	6.6	7.5	16.5	6.2	137.7	137.8	5.8	3.7
± SEM	±9	±3	±0.4	±0.3	±0.1	±0.3	±2.0	±0.9	±0.4	±0.9	±0.5	±0.1

Fig.1. Responses of mean arterial pressure to volume loading and volume removal in two groups. *p < 0.05 compared to presaline loading value.

MATERIALS AND METHODS

Fifteen hospitalized patients maintained on chronic hemodialysis were studied. They comprised 10 men and 5 women, aged 24 to 45 years. The duration of treatment ranged from 3 to 7 years. The underlying renal disease in all cases was chronic glomerulonephritis. The subjects were maintained on their usual daily diets of

60 mEq NaCl and were dialyzed for 4 to 5 hrs per dialysis, 2 or 3 times a week. All patients were judged to be at or near their previously assessed 'dry weight'. A hollow fiber artificial dialyzer (Asahi AM-series, Tokyo, Japan) was used with a 0.8 to 1.5 m² surface area on hemodialysis. The dialyzate contained 135 mEq Na/L, 2.2 mEq K/L, 3.5 mEq Ca/L, 1.0 mEq Mg/L, 106 mEq Cl/L, and 34 mEq HCO₃⁻/L. Four patients had been administered Ca antagonists to control blood pressure but these were discontinued 7 days prior to the study. The study was performed on a day of routine dialysis. After a 12 hour fast, the patients were kept supine and resting for at least 30 min before the initiation of the study. The indwelling catheters for routine dialysis were inserted and intravenous infusion of saline was carried out at a speed of 0.5 ml/kg/min for 20 min. Before and during the infusion the mean blood pressure (MAP) and pulse rate were monitored with an automatic device (BP-103, PT-50, Nippon Koden Tokyo, Japan) every 5 min. After completion of the saline infusion, routine hemodialysis was performed. Before and after the saline infusion and after the hemodialysis, blood samples were collected to determine the plasma concentration of total protein (TP), blood urea nitrogen (BUN), creatinine (CR), Na, K, Cl, hematocrit (Ht) and as hormonal factors, the plasma renin activity (PRA), angiotensin II (Ang II) and norepinephrine (NE). Samples for hormone measurement were drawn into glass tubes containing EDTA, placed on ice, and the plasma was separated and frozen immediately until assay. The plasma concentrations of Na, K, Cl, total protein, BUN and creatinine were measured with a multichannel autoanalyzer (Aloka, Tokyo, Japan). PRA and Ang II were estimated by radioimmunoassay as described elsewhere.¹⁰ The plasma NE was determined by high-performance liquid chromatography.¹¹ The normal range was 50-400 pg/ml. The data expressed as averages-SEM were evaluated statistically by Student's t-test for paired values or Wilcoxon's test for unpaired values or by one-way analysis of variance. Associated correlation coefficients were computed by the least-square formula. Statistical significance was considered to be at $p < 0.05$.

Fig. 2. Changes in plasma renin activity (column) and angiotensin II (line) by saline loading and hemodialysis in group 1 (upper) and group 2 (lower).

RESULTS

For the purposes of analysis, two groups were defined. Group 1 ($n = 10$) had a pre-saline load-

Fig.3. Correlation between change in mean arterial pressure by saline loading and pre-saline loading value of plasma renin activity.

Fig.4. Effects of saline loading and hemodialysis on % change in plasma norepinephrine in group 1 and group 2.

ing PRA below 2.5 ng/ml/hr while group 2 ($n = 5$) had a pre-saline loading PRA in excess of 2.5 ng/ml/hr. The mean values of PRA were 0.7 ± 0.3 ng/ml/hr and 4.9 ± 0.5 ng/ml/hr, respectively and the difference was significant ($p < 0.001$).

Table I summarizes the basal characteristics of patients in both groups. There were no significant differences in any values between the two groups.

The predialysis MAP was 105 ± 5 mmHg for group 1 and 107 ± 4 mmHg for group 2 (Fig. 1).

Effects of volume-loading and -removal on MAP (Fig. 1)

MAP in group 2 was significantly elevated ($p < 0.05$) from 107 ± 4 mmHg to 113 ± 6 mmHg within 5 min after initiation of saline loading. It reached its highest level (117 ± 7 mmHg) within 10 min and became stabilized around at 115 ± 7 mmHg. After dialysis, MAP fell 10.7% of the predialysis level. Also, this value was significantly lower ($p < 0.05$) than the pre-saline loading level. In contrast to these responses to alterations in volume in group 2, MAP in group 1 showed no significant changes after the same manipulations.

Effects of both volume loading and removal on PRA and Ang II (Fig. 2)

Figure 2 shows the PRA and Ang II levels before and after saline loading and after dialysis. The pre-saline loading value of PRA was significantly correlated with the basal value of MAP in group 2 ($r = 0.97$, $p < 0.01$) but not in group 1 ($r = 0.35$, $p > 0.05$). The simultaneously measured Ang II levels were correlated with PRA ($r = 0.72$, $p < 0.01$) in both groups 1 and 2. PRA and Ang II in both groups did not respond to saline loading. However, the volume removal by dialysis significantly increased PRA and Ang II in group 1 but not in group 2. The basal values of PRA were significantly correlated with the changes in MAP induced by saline loading in both groups ($r = 0.76$, $p < 0.01$) (Fig. 3).

Effects of volume-loading and -removal on plasma norepinephrine

The pre-saline loading plasma NE values for groups 1 and 2 were 125 ± 23.6 pg/ml and 97.5 ± 34.9 pg/ml respectively. Saline loading did not induce any changes in NE in either group (Fig. 4). After dialysis, the plasma NE values in group 1 rose 2-fold (from 97.5 ± 34.0 to 186.7 ± 48.6 pg/ml, $p < 0.05$) accompanied by increases in PRA and Ang II and showed no changes in MAP. In group 2, the plasma NE did not change significantly during saline loading and dialysis.

Changes of hematocrit with volume alterations

The pre-saline loading hematocrit in groups 1 and 2 were $19.1 \pm 1.1\%$ and $25.0 \pm 1.6\%$ respectively ($p < 0.05$). The changes in hematocrit corresponded significantly with volume-load and -removal in both groups. Saline loading reduced the hematocrit by 4% and 6% in group 1 and 2 respectively while the hematocrit was increased by 7% and 14%, respectively, after dialysis.

DISCUSSION

The present results demonstrate that chronic hemodialysis patients with high blood pressure can be divided into higher and normal or lower PRA groups. Also, the blood pressure with a high PRA was further elevated by predialysis volume loading without changes in PRA, whereas patients with a low or normal PRA did not respond to such volume-loading. Furthermore, the changes in blood pressure induced by volume-loading correlated significantly with the basal values of PRA. Similar to these changes observed on volume-loading, volume-removal by hemodialysis caused a significant reduction of the elevated blood pressure in high PRA patients accompanied by mild increases in PRA and Ang II. Compared to these changes in blood pressure in high PRA patients, the blood pressure of low PRA patients was maintained after volume-removal with a significant elevation of PRA. Significant alterations of plasma NE were found only in patients with a high PRA after hemodialysis.

It is suggested that measurements of PRA do not represent an accurate method for evaluating the contribution of the renin-angiotensin system to blood pressure regulation.^{5,6} Brunner et al⁶ proposed that the major cause of hypertension in chronic renal failure may be attributable to inappropriate renin secretion in relation to a subtle

degree of sodium retention. In order to evaluate interaction, many investigators have employed blockade of the renin-angiotensin system with such agents as angiotensin II analogue and angiotensin I converting enzyme inhibitor.¹²⁻¹⁴

In the present study, evaluations of the renin-angiotensin system and the sympathetic nervous system in chronic renal failure were performed by inducing volume alterations. In the high renin group, a very subtle volume load of 70 ml raised the blood pressure. However, the blood pressure fell after more than 500 ml of volume-removal. In spite of these changes, PRA was unchanged. Since volume expansion in the high renin condition easily increases blood pressure, these findings indicate that elevated circulating angiotensin II contributes to the high blood pressure and that subtle volume changes may induce further elevations of blood pressure through the potent vasoconstrictive effects of angiotensin II. In patients with normal renal function, volume expansion counteracts the renin angiotensin system and PRA is suppressed.¹⁵ However, in patients with chronic renal failure, no sufficient urine volume excretion occurs and the blood pressure is elevated without suppression of PRA. In contrast to volume load, mild to moderate volume reduction did not lower the blood pressure. These data may also be attributable to high circulating angiotensin II, which was sufficient to sustain the blood pressure, even after volume reduction, since several investigators have reported that in patients with chronic renal failure renin is inappropriately secreted in relation to its volume status.^{5,6} In the low or normal renin group, volume-load did not cause any changes in blood pressure. Combining these findings with the elevation of blood pressure observed in the high PRA group, it seems probable that circulating angiotensin II represents a critical factor in the regulation of blood pressure in hemodialysis patients. Furthermore, compared to the lack of change in PRA in the high renin group on volume-removal, volume reduction resulted in a marked elevation of norepinephrine in the low renin group. These findings suggest that, even in the low or normal renin group, renin secretion is stimulated by volume reduction. Volume reduction, such as dehydration and hemorrhage, is known to stimulate the renin-angiotensin system and the sympathetic nervous system.^{15,16} These stimulated systems support the maintenance of blood pressure by raising the levels of circulating vasoconstrictive hormones, such as angiotensin II,

norepinephrine and vasopressin.¹⁷ It is suggested therefore that the blood pressure of dialysis patients with low or normal renin may be maintained by increased angiotensin II and norepinephrine after volume removal. The increases in norepinephrine are probably due to activation of the baroreceptor reflex, since the baroreceptor reflexes are activated by volume reduction and stimulate the sympathetic outflow via central mechanisms.¹⁸ In the high renin group, it is possible that the high circulating angiotensin II hinders activation of the baroreceptor reflexes in spite of volume reduction, since angiotensin II is known impair these reflexes.^{19,20} A study on volume challenges in dialysis patients has been conducted previously by Leeman et al.²¹ Their data indicated that long-term volume load elevated blood pressure and reduced PRA. In the present study, there was no suppression of PRA in any patients examined after short term volume-load. It cannot be excluded therefore that the relation between volume and the renin angiotensin system may differ between short- and long-term regulation.

In conclusion, the renin-angiotensin system is important in the regulation of blood pressure in relation to volume status whether PRA is high or low. In the high renin group, the elevated circulating angiotensin II maintained a high blood pressure and in the low renin group, the renin angiotensin system influenced the prevention of fall in blood pressure after hemodialysis.

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