

## Associations between Sympathetic Activity, Plasma Concentrations of Renin, Aldosterone, and Parathyroid Hormone, and the Degree of Intractability of Blood Pressure Control in Hemodialysis Patients

This study was designed to examine how such factors as hemodialysis parameters, body mass index, renin and aldosterone concentrations, sympathetic nervous activity, and parathyroid hormone concentrations are associated with the control of hypertension in hemodialysis patients. Hemodialysis patients (n=114) were grouped into four categories. Group 1 had normal BP without antihypertensive medication. Group 2 needed one antihypertensive drug, Group 3 needed combination of two or three categories of antihypertensive drugs without minoxidil. Group 4 needed more than three categories of antihypertensive drugs including minoxidil. Parathyroid hormone,  $\beta$ 2-microglobulin, renin and aldosterone, epinephrine, norepinephrine, and hemodialysis parameters were measured. The fractional clearance of urea as Kt/V urea was significantly lower in Group 3 and Group 4 than in Group 2 ( $p<0.01$ ). Concentrations of parathyroid hormone were significantly higher in Group 4 than the other groups ( $p<0.01$ ). Pre-hemodialysis norepinephrine concentrations were significantly higher in Group 4 than the other groups ( $p<0.05$ ). Traditional factors associated with hypertension did not seem to be relevant to the degree of hypertension in hemodialysis patients in the present study. In conclusion, poor Kt/V urea, elevated parathyroid hormone concentrations, and elevated concentrations of plasma norepinephrine seemed to be the factors that might be associated with control of hypertension in hemodialysis patients.

Key Words : Hypertension; Hemodialysis; Hyperparathyroidism

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## INTRODUCTION

Hypertension (HT), either as a primary cause or consequence of renal failure, is a major risk factor for high cardiovascular morbidity in uremic patients (1). HT in patients with end stage renal disease (ESRD) who are on hemodialysis (HD) is defined by either a systolic blood pressure (SBP) >150 mmHg or a diastolic blood pressure (DBP) >85 mmHg (2). HT occurs in 70-90% of HD patients, which is a substantially higher incidence than that in the general population (2-4). Several factors have been reported to be involved in the pathogenesis of HT in HD patients, most of which have been categorized according to whether they are volume-dependent or volume-independent based on the response to ultrafiltration, i.e., in terms of the response to volume removal and/or dietary sodium restriction. Volume-independent factors are characterized by increased activity of the rennin-angiotensin aldosterone system (RAAS) and a limited rate of blood pressure (BP) reduction by volume reduction.

Theoretically, it should be relatively easy to control BP in

most of HD patients by ensuring that patients maintain a target body weight during the HD treatment process, which is estimated by the dry weight. However, contrary to the aforementioned theory, most HD patients (~75%) require antihypertensive drugs to control BP (5). Many reasons have been proposed to explain this discrepancy between the theory and practice of regulating BP in HD patients. The reasons could be explained by the activation of volume-independent factors such as the RAAS, an overactive sympathetic nervous system, impaired vasodilatation, elevated erythropoietin (EPO), and secondary hyperparathyroidism.

The best way to avoid HT in HD patients would be to identify and remove those factors that play a dominant role. However, in clinical practice, it is difficult to determine which factors are responsible for HT, especially when the control of BP is intractable even in the face of substantial weight loss during HD. In addition, the responses of HD patients to antihypertensive therapy are highly variable.

Several causes seem to be involved in its difficulty to determine which single factor might cause HT in ESRD patients.

First, the multiple physiological factors that can cause HT may be distinct from the factors that maintain normal BP. Second, factors may interact with one another. For example, in some HT patients, there is a direct correlation between plasma renin activity and plasma concentrations of norepinephrine (NEP) (6). Third, hormones that directly regulate BP, such as angiotensin, also have stimulatory effects on the sympathetic nervous system, including enhancing sympathetic outflow and/or acting on stimulatory presynaptic receptors (7-12).

Collectively, the observations of associations among hyperparathyroidism, impairment of vitamin D metabolism, and overactivity of the sympathetic nervous system in ESRD patients suggest that the RAAS, the parathyroid hormone (PTH)-vitamin D-calcium axis, and sympathetic activity interact to make it difficult for ESRD patients to regulate their BP. We guess that the difficulty in the regulation of hypertension was affected by multiple factors, so we investigated which factors have effects on HT control according to the need of hypertensive drug.

The present study was carried out to analyze the associations between the degree of HT and various factors in ESRD patients who underwent HD.

## MATERIALS AND METHODS

ESRD patients ( $n=114$ ; 61 males, 53 females; age= $53.1 \pm 13.0$  yr, mean body mass= $56.5 \pm 10.9$  kg; mean height= $163.6 \pm 9.1$  cm) who had undergone HD periodically for at least 6 months (mean duration of HD= $117 \pm 58.4$  months) were enrolled in this study. All patients provided informed consent, and the study protocol was approved by the Ethics Committee of Soonchunhyang University Cheonan Hospital, Korea. All patients underwent HD for 12-15 hr per week using a dialyzer (polyamide membrane; Polyflux 6L, Gambro, Gambro Dialysatoren, Hechingen, Germany). The flow rate of the dialysate was fixed at 500 mL/min during each HD session. The blood flow rate was 250-300 mL/min. The variable-volume, single-pool urea kinetic model was used to for dialysis prescriptions and to monitor dietary protein intake (quantified as the normalized protein catabolic rate; nPCR). The dose of HD was described as the fractional clearance of urea as a function of its distribution volume ( $Kt/V$  urea).

Among the 114 patients, there were 35 cases of diabetes mellitus (30.7%), 37 cases of HT (32.5%), 28 cases of chronic glomerulonephritis (24.6%), 4 cases of polycystic kidney disease (3.5%), 3 cases of renal tuberculosis (2.6%), and 7 cases with an unknown cause of ESRD (6.1%). There was no difference in the distribution of underlying disease among Group 1-4.

The blood pressure and heart rate were measured on the opposite arm of vascular access before and after HD, and the means of the results of last two weeks were used as data.

The target SBP and DBP was 150 and 85 mmHg, respec-

tively. All patients were placed on a low-sodium diet and interdialytic weight gain was required to be less than 3.0 kg. The target weight for each patient was established according to the maximum endurance of volume depletion by ultrafiltration.

In terms of the definition of dry weight as a point from which BP goes down, a large number of patients had not reached the point. In cases where the BP could not be regulated by employing a low-sodium diet to control body weight, antihypertensive drugs were prescribed as follows. The categories of antihypertensive drugs included  $\beta$ -blockers (atenolone, 50 mg/tablet), calcium channel blockers (splendil [felodipine], 5 mg/tablet; Norvasc [amlodipine camsylate], 5 mg/tablet), angiotensin-converting enzyme (ACE) inhibitors (enalapril, 10 mg/tablet), and angiotensin II receptor blockers (ARB) (Aprovel [irbesartan], 150 mg/tablet; Coz-zar [losartan], 100 mg/tablet). Only one drug from each category was prescribed. The ACE inhibitor and the ARB were regarded as belonging to the same category. When BP could not be controlled even when the dose of the initially prescribed drug was doubled, an additional drug from another category was prescribed rather than increasing the dose of the drug prescribed initially. For patients who were prescribed with antihypertensive drugs from more than two categories, the drugs were prescribed without the vasodilator, minoxidil (5 mg/tablet). Minoxidil was prescribed only for cases in which BP remained elevated despite treatment with antihypertensive drugs from three categories. The first class of antihypertensive drug prescribed was either ARB (16 cases), calcium channel blockers (8 cases), the  $\beta$ -blocker (7 cases), or the ACE inhibitor (1 case). The number of the patients who used an antihypertensive drug (regardless of whether they used other category of antihypertensive drugs) was 61 for ARB, 58 for calcium channel blockers, 40 for the  $\beta$ -blocker, 12 for the vasodilator, and 7 for the ACE inhibitor.

Patients were classified into four groups according to the aforementioned drug treatment regimen to reflect the difficulty in the control of HT as follows: In Group 1, BP was within the normal range and no antihypertensive drugs were prescribed; in Group 2, control of BP required antihypertensive drugs from only one category; in Group 3, two or three categories of antihypertensive drug were required to control BP, but not minoxidil; and in Group 4, antihypertensive drugs from more than three categories were required to control BP, including minoxidil. The application of these criteria resulted in 22 cases (10 male and 12 female) in Group 1, 32 (14 male and 18 female) in Group 2, 46 (25 male and 21 female) in Group 3, and 14 (14 male and 2 female) in Group 4.

Blood samples were collected prior to HD (pre-HD) to measure CBC, blood chemistry, electrolytes, and concentrations of PTH,  $\beta_2$ -microglobulin, renin, and aldosterone. Blood samples were collected from the antecubital vein contralateral to the site at which the vascular access was gained for HD. Samples were collected immediately prior to the initiation of HD and 10 min after the end of the HD ses-

sion to measure pre- and post-HD concentrations of renin, aldosterone, epinephrine (EP), and NEP, respectively. All samples were stored at  $-70^{\circ}\text{C}$  until analysis. Commercially available radioimmunoassay kits were used to measure plasma concentrations of renin (Renin Riabead; Dainabot, Tokyo, Japan), aldosterone (Immunotech SA, Marseille, France), EP and NEP (IBL, Hamburg, Germany), intact PTH (iPTH) (PTH-120 MIN IRMA; BioSource Europe SA, Belgium), and  $\beta 2$ -microglobulin ( $\beta 2$ -microglobulin radioimmunoassay kit; Abbott Laboratories, Chicago, IL, U.S.A.).

Statistical analyses were performed with SPSS for Windows (version 12.0; SPSS, Chicago, IL, U.S.A.). The duration of HD, and plasma concentrations of EPO,  $\beta 2$ -microglobulin, iPTH, aldosterone, renin, EP, and NEP were presented as means  $\pm$  SEM. The values of the remaining parameters were presented as means  $\pm$  SD. To examine associations between these parameters and the severity of HT, we analyzed differences in the concentrations of iPTH, aldosterone, renin, EP, and NEP as well as the aldosterone/renin ratio among the groups of patients (Groups 1-4) using chi-squared tests (for categorical variables) and Kruskal-Wallis tests or ANOVA (analysis of variance). If the results were significant by ANOVA, we analyzed the difference among the groups based on Turkey's multiple comparison test.

## RESULTS

There were no significant associations between the following parameters and the degree of HT: age, duration of HD, dry weight, height, BMI, pre- and post-HD body weight, interdialytic weight gain, blood flow during HD, ultrafiltration during HD, nPCR, and the concentrations of Hb, Hct, EPO doses, albumin, calcium, phosphorus, total cholesterol, triglycerides,  $\beta 2$ -microglobulin, and  $\text{HCO}_3$ . However, the

Kt/V urea was significantly lower ( $p < 0.01$ ) in Groups 3 ( $1.49 \pm 0.29$ ) and 4 ( $1.40 \pm 0.23$ ) compared to Group 2 ( $1.75 \pm 0.40$ ) (Table 1, Fig. 1). Pre- and post-HD SBP was significantly higher in Groups 3 and 4 compared to Groups 1 and 2 ( $p < 0.01$ ), but there was no such difference in DBP. The pre-HD ( $p < 0.01$ ) and post-HD ( $p < 0.02$ ) heart rate was significantly higher in Groups 3 and 4 than in Group 1 (Table 2). Changes in the concentrations of iPTH, aldosterone, renin, aldosterone, EP, and NEP were not associated with the degree of HT (data not shown). The concentration of iPTH was significantly higher in Group 4 than in Groups 1-3 ( $p < 0.01$ ; Table 3, Fig. 2). The pre-HD ( $p < 0.01$ ) and post-HD ( $p < 0.01$ ) aldosterone concentrations were significantly lower in Groups 3 and 4 compared to Groups 1 and 2. Neither pre- and post-HD renin concentrations nor pre- and post-HD aldosterone/

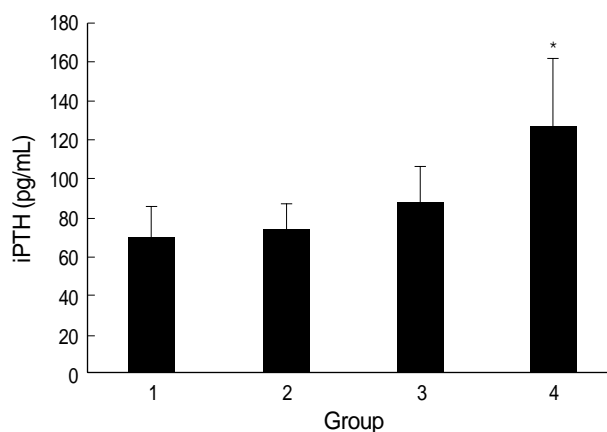


Fig. 1. Comparison of the fractional clearance of urea as a function of its distribution volume (Kt/V urea) among groups. The value of Kt/V urea was significantly lower in Groups 3 and 4 (\*) than in Group 2 tested by one-way analysis of variances ( $p < 0.01$ ) and Turkey's multiple comparison test. iPTH, intact parathyroid hormone.

Table 1. Comparison of dialysis-related data among groups

	Group 1	Group 2	Group 3	Group 4	$p^*$
Age (yr)	53.2 $\pm$ 13.8	56.8 $\pm$ 10.6	52.9 $\pm$ 12.8	45.2 $\pm$ 15.3	0.52
HD duration	64.4 $\pm$ 7.4	61.4 $\pm$ 7.9	52.4 $\pm$ 6.6	62.0 $\pm$ 10.1	0.65
Dry weight (kg)	53.8 $\pm$ 9.4	57.5 $\pm$ 11.4	56.6 $\pm$ 12.1	58.1 $\pm$ 6.9	0.61
Height (cm)	163.2 $\pm$ 9.1	162.2 $\pm$ 8.6	163.8 $\pm$ 9.7	167.4 $\pm$ 8.4	0.37
BMI (kg/m <sup>2</sup> )	20.2 $\pm$ 3.0	21.6 $\pm$ 3.0	21.0 $\pm$ 3.3	20.8 $\pm$ 2.6	0.46
Body weight (kg)					
Pre-HD	56.9 $\pm$ 10.0	60.2 $\pm$ 12.1	60.4 $\pm$ 13.0	62.1 $\pm$ 6.5	0.57
Post-HD	54.4 $\pm$ 9.5	57.6 $\pm$ 11.6	57.7 $\pm$ 12.7	58.6 $\pm$ 6.3	0.63
Weight gain (kg)	2.8 $\pm$ 1.1	2.7 $\pm$ 1.0	2.8 $\pm$ 0.8	3.3 $\pm$ 1.0	0.32
Blood flow	281.7 $\pm$ 34.8	291.8 $\pm$ 18.1	288.2 $\pm$ 25.1	289.6 $\pm$ 21.2	0.54
Ultrafiltration	3.3 $\pm$ 0.8	3.2 $\pm$ 0.9	3.3 $\pm$ 0.9	3.6 $\pm$ 1.0	0.40
Kt/V urea	1.60 $\pm$ 0.26	1.75 $\pm$ 0.40	1.49 $\pm$ 0.29	1.40 $\pm$ 0.23	<0.01
T <sup>†</sup>	a, b	a	b	b	
Npcr	0.86 $\pm$ 0.26	0.82 $\pm$ 0.24	0.84 $\pm$ 0.26	0.75 $\pm$ 0.14	0.62

\*Statistical significance was tested by one-way analysis of variances among groups; <sup>†</sup>The same letters indicate a difference not significant between groups based on Turkey's multiple comparison test.

HD, hemodialysis; BMI, body mass index; Kt/V urea, the fractional clearance of urea as a function of its distribution volume.

**Table 2.** Comparison of blood pressure and heart rate among groups

	Group 1	Group 2	Group 3	Group 4	<i>p</i> *
Systolic blood pressure (mmHg)					
Pre-HD	126.8±22.8	136.6±17.0	143.1±19.5	149.3±18.2	<0.01
T <sup>†</sup>	a	a	b	b	
Post-HD	124.5±19.2	129.1±16.3	140.9±19.4	140.7±18.6	<0.01
T <sup>†</sup>	a	a	b	b	
Diastolic blood pressure (mmHg)					
Pre-HD	76.8±9.4	78.1±8.2	80.2±7.5	80.7±10.7	0.36
Post-HD	75.0±8.6	77.8±6.6	80.6±10.3	79.3±8.3	0.10
Heart rate (beats/min)					
Pre-HD	50.5±16.3	60.0±15.0	64.2±16.7	68.6±14.6	<0.01
T <sup>†</sup>	a	a, b	b	b	
Post-HD	50.3±13.9	55.5±15.2	61.9±15.0	61.4±14.1	<0.02
T <sup>†</sup>	a	a, b	b	b	

\*Statistical significance was tested by one-way analysis of variances among groups; <sup>†</sup>The same letters indicate a difference not significant between groups based on Turkey's multiple comparison test.

**Table 3.** Comparison of concentrations of intact parathyroid hormone (PTH), renin, aldosterone, epinephrine, and norepinephrine among groups

	Group 1	Group 2	Group 3	Group 4	<i>p</i> *
PTH					
Pre-HD	69.9±16.3	74.3±12.6	88.5±16.9	126.8±34.9	<0.01
T <sup>†</sup>	a	a	a	b	
Aldosterone					
Pre-HD	418.0±130.6	272.6±84.9	67.1±7.4	91.6±18.5	<0.01
T <sup>†</sup>	a	a	a	b	
Post-HD	333.5±115.6	289.5±89.6	62.9±9.0	92.9±23.8	<0.01
T <sup>†</sup>	a	a	b	b	
Renin					
Pre-HD	2.40±0.50	5.52±1.12	4.00±0.78	3.31±1.25	0.15
Post-HD	4.34±0.83	8.51±1.64	5.56±1.09	4.44±2.20	0.15
Aldosterone/renin ratio					
Pre-HD	209.5±46.7	93.4±28.7	120.9±44.7	96.8±32.8	0.29
Post-HD	96.7±28.2	39.5±7.1	50.2±14.6	61.3±16.8	0.13
Epinephrine					
Pre-HD	39.9±4.9	41.5±2.6	43.0±3.4	44.5±4.5	0.91
Post-HD	43.5±4.6	32.9±1.9	34.5±3.2	33.7±2.4	0.16
Norepinephrine					
Pre-HD*	188.6±32.8	281.4±35.5	225.3±28.9	366.4±56.7	<0.05
T <sup>†</sup>	a	a, b	a	b	
Post-HD	161.5±32.5	149.8±26.1	136.9±19.5	226.9±60.8	0.31

\*Statistical significance was tested by one-way analysis of variances among groups; <sup>†</sup>The same letters indicate a difference not significant between groups based on Turkey's multiple comparison test.

renin ratio were significantly different among groups (Table 3). The pre- and post-HD EP concentration was 39.9±4.9 vs. 43.5±4.6 in Group 1, 41.5±2.6 vs. 32.9±1.9 in Group 2, 43.0±3.4 vs. 34.5±3.2 in Group 3, and 44.5±4.5 vs. 33.7±2.4 in Group 4, (*p*=0.91 for comparison of pre-HD EPO concentration among Groups 1-4; *p*=0.16 for post-HD EPO concentration). The pre-HD NEP concentration was significantly higher in Group 4 than in Groups 1 and 3 (*p*<0.05), but was not significantly different in Group 2 (Table 3, Fig. 3). There was a significant correlation between pre- and post-HD NEP concentrations (*p*<0.01), but there was no correlation between pre-HD NEP concentrations and any

of renin, aldosterone, and PTH concentrations.

Neither the pre- nor post-HD renin activity was significantly different between patients who did and those who did not use the ACE inhibitors, ARB, the  $\beta$ -blocker, calcium channel blockers, and minoxidil. However, both pre- and post-HD aldosterone concentrations were significantly lower in patients who used ARB compared to those who did not (*p*<0.01). Similarly, pre-HD aldosterone concentrations were significantly lower in patients who used the calcium channel blockers compared to those who did not (*p*<0.01; Table 4). Post-HD EP concentrations were significantly higher in patients who did not use minoxidil compared to those who did use this drug

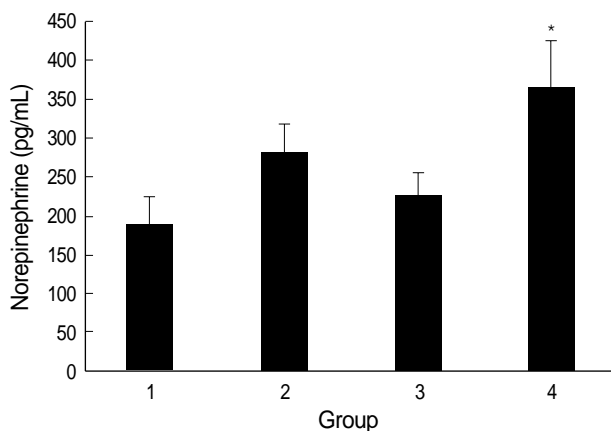


Fig. 2. Comparison of the concentration of intact parathyroid hormone (PTH) among groups. Intact PTH concentrations were significantly higher in Group 4 (\*) compared to the other groups tested by oneway analysis of variances ( $p < 0.01$ ) and Turkey's multiple comparison test.

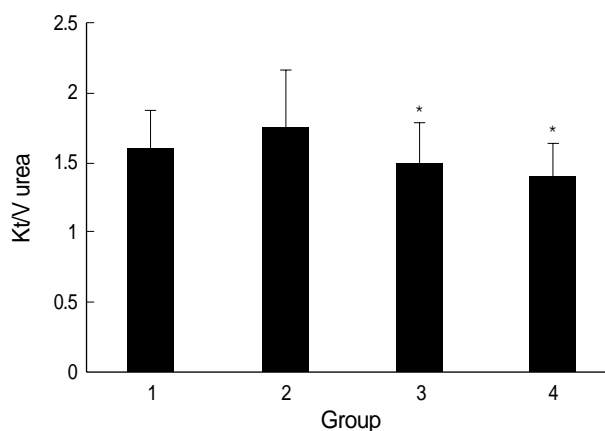


Fig. 3. Comparison of norepinephrine concentrations among groups. Norepinephrine concentrations prior to hemodialysis (pre-HD) were significantly higher in Group 4 (\*) than in Groups 1 and 3 tested by one-way analysis of variances ( $p < 0.05$ ) and Turkey's multiple comparison test.

Table 4. Effects of antihypertensive drugs on the concentrations of renin, aldosterone, epinephrine, and norepinephrine

Drug		ACEI	ARB	Beta-blocker	CCB	Minoxidil
Renin						
Pre-HD	Absence	3.7±0.5	3.0±0.7	4.3±0.7	3.6±0.7	4.0±0.5
	Presence	5.3±1.6	4.5±0.6	3.5±0.7	4.2±0.6	3.8±1.0
Post-HD	Absence	5.9±0.8	5.2±1.1	6.4±0.9	6.1±1.0	6.1±0.8
	Presence	6.5±2.1	6.4±0.9	5.3±1.1	5.9±1.0	5.3±1.6
Aldosterone						
Pre-HD	Absence	197.9±39.0	347.8±91.0 <sup>†</sup>	246.2±54.8	307.4±78.7 <sup>†</sup>	205.5±42.6
	Presence	206.4±129.1	128.9±33.0	130.1±46.3	130.9±34.8	176.4±84
Post-HD	Absence	185.2±38.5	316.4±91.7 <sup>†</sup>	229.8±54.3	262.3±69.0	194.4±42.0
	Presence	181.7±104.5	122.6±28.4	118.8±38.1	135.8±38.7	150.1±69.0
Epinephrine						
Pre-HD	Absence	43.0±2.1	43.9±3.7	39.7±2.3	41.6±3.1	41.8±2.3
	Presence	36.5±4.5	41.3±2.2	45.8±21.0	42.5±2.4	43.4±2.9
Post-HD	Absence	36.8±1.9	40.1±3.6	36.9±19.4	39.2±2.9	36.6±2.1 <sup>†</sup>
	Presence	29.7±2.8	33.8±1.8	34.3±15.2	33.7±2.1	32.9±1.5
Norepinephrine						
Pre-HD	Absence	255.3±19.9	239.3±33.4	216.6±21.9*	236.3±28.4	224.2±19.3
	Presence	209.7±47.9	254.0±22.1	298.1±30.9	257.5±24.1	343.8±44.4
Post-HD	Absence	154.9±15.1	144.7±20.6	142.2±16.2*	143.9±22.1	140.1±13.9 <sup>†</sup>
	Presence	162.9±45.8	161.2±18.9	176.3±26.4	163.9±19.0	215.2±42.6
Aldosterone/renin ratio						
Pre-HD	Absence	139.3±25.4	176.0±33.0	143.8±31.1	161.3±32.6	137.3±27.3
	Presence	69.7±25.9	106.5±28.6	107.7±30.2	109.2±29.7	99.2±25.5
Post-HD	Absence	59.0±9.9	87.0±20.3*	57.4±11.2	69.3±16.1	55.9±9.5
	Presence	54.4±17.2	44.7±8.3	59.8±14.4	51.3±10.1	67.6±22.4

Because drugs were prescribed after the commencement of HD, the pre- and post-HD values correspond to the values of the parameters in the absence and presence of each drug. \* $p < 0.05$ ; <sup>†</sup> $p < 0.01$ .

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

( $p = 0.003$ ; Table 4). NEP concentrations were significantly lower in the patients who used the  $\beta$ -blocker compared to those who did not ( $p < 0.05$ ). Pre- and post-HD NEP concentrations were significantly higher in patients who used minoxidil compared to those who did not ( $p < 0.05$ ; Table 4).

## DISCUSSION

In the present study, the degree of intractability of BP control in HD patients was associated with pre- and post-HD SBP, heart rate, Kt/V urea, pre- and post-HD aldosterone concentrations, and pre-HD NEP concentrations. Of course,

the associations between the aforementioned parameters and the intractability of BP control do not necessarily mean these factors were the cause of HT in these patients. SBP was higher in those patients who required a greater number of different antihypertensive drugs to control BP; this finding implies that abnormally elevated BP was not controlled completely in the HT patients in the present study.

There was no association between the degree of HT and parameters such as body weight, interdialytic weight gain, BMI, or amount of ultrafiltration during HD. To control the HT of HD, first the patients should reach the target weight, and if HT is not well controlled, the other factors should be searched.

The value of Kt/V urea was significantly lower in Group 3 and 4 than Group 2 (Fig. 1). It suggests that the adequacy of HD is an important factor to control HT. Interestingly, aldosterone concentrations were lower in Groups 3 and 4 than in Groups 1 and 2, and aldosterone concentrations were lower in patients who were treated with ARB and/or calcium channel blockers. This result suggests that aldosterone could be suppressed by hypertensive drugs in uncontrolled hypertensive HD patients. HD, itself, seemed to have no effect on the variation of renin and aldosterone because there was no difference before and after HD. In the present study, NEP concentrations were significantly higher in Group 4 than in Groups 1 and 3 (Fig. 3), but there was no significant difference in the post-HD concentrations of NEP among the groups. By contrast, there was a substantial individual variation in the changes in NEP concentrations before and after HD, and there was no correlation between changes in NEP concentrations and the degree of intractability of BP control. This suggests that NEP may be involved partly in HT in HD patients.

We cannot explain why the apparent association between plasma NEP concentrations and the degree of HT that was observed prior to HD was no longer apparent after HD. However, it is worth noting that the process of HD can either stimulate or suppress sympathetic activity. Some reports showed that the plasma volume decreases during HD, which can lead to an increase in plasma catecholamine concentrations and in contrast, catecholamines are small molecules that might be dialyzed and removed during HD (13-15). The role of sympathetic activity on HT in hemodialysis was controversial, but it seems to be that sympathetic activity is individually involved in HT of HD patients. Minoxidil is direct vasodilator. It induces a more marked activation of adrenergic drive. However, our data (Table 4) showed that the patients prescribed with minoxidil had a the higher concentration of EP and a lower concentration of NEP at post-HD. The reasons might be that the patients on minoxidil had other drugs including  $\beta$ -blocker.

Interaction between renin and the hormones that regulate calcium metabolism has been proposed to explain calcium-induced vasoconstriction and sodium-sensitivity in HT pa-

tients (16). Raine and co-workers (17) reported higher intracellular calcium concentrations within the platelets of ESRD patients with elevated plasma concentrations of PTH compared to patients with normal plasma concentrations of PTH; moreover, they reported significant correlations between PTH concentrations, platelet calcium concentrations, and mean arterial BP. Similarly, hypercalcemia induced a greater increase in BP in rats with ESRD than in normal rats (18). Such vascular hyperresponsiveness can be reversed by parathyroidectomy, which suggests that PTH plays an important role in hypercalcemia-induced HT. In agreement with a previous report, the intact PTH concentration in the present study was significantly higher in Group 4 than in Groups 1-3, which suggests that PTH is one of the factors that is involved in the inability of ESRD patients to regulate BP effectively.

Previous reports indicated that the incidence of HT in EPO-treated HD patients was 10-12% (19, 20). An increase in total peripheral resistance is the primary cause of the increase in BP in ESRD patients, while increased blood viscosity and reversal of hypoxic vasodilation (21) have often been cited as the main causes of the effects of EPO on total peripheral resistance and BP (22-24). In the present study, we found no significant difference in either the EPO dose or Hct and/or Hb concentrations among the various groups. We thought that EPO-induced hypertension could be controlled by hypertensive drug, but further investigations are needed to prove this.

Our study design had several limitations. First, we did not examine all of the factors that have been implicated in the development of HT in ESRD patients, such as arginine vasopressin (25, 26), endothelial factors (27, 28), and natriuretic peptides (29, 30). However, the aim of this study was not to evaluate all the factors that are involved in HT, but rather to elucidate which factor (s) may be responsible for HT in ESRD patients. Second, antihypertensive drugs may stimulate the RAAS, sympathetic activity, and PTH. To reduce such nonspecific effects, we evaluated parameters in patients who were grouped based on their use of antihypertensive drugs. Both pre- and post-HD aldosterone concentrations were significantly lower in patients who used ARB, and pre-HD aldosterone concentrations were significantly lower in the patients who used calcium channel blockers. Because aldosterone concentrations appeared to be influenced by the antihypertensive drugs, this was not considered as a factor that might be involved in HT. Third, our classification of patients according to their use of antihypertensive drugs does not mean that those factors that appeared to be associated with the degree of HT are necessarily the cause of HT. Nevertheless, in practice, these factors should be addressed as the first step in controlling HT in ESRD patients who are undergoing HD.

In conclusion, we found that a low Kt/V urea, hyperparathyroidism, and increased plasma NEP concentrations, rather than traditional causes of HT, could be associated with the

intractability of BP control in ESRD patients who underwent HD.

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