The geometry of LV was stratified into four different patterns according to the values of LVMI (< or ⩾125/110 g/m², men/women) and RWT (< or ⩾0.44). Patients with increased LVMI and increased RWT were considered to have concentric hypertrophy, and those with increased LVMI and normal RWT were considered to have eccentric hypertrophy. Those with normal LVMI and increased or normal RWT were considered to have concentric remodelling or normal geometry, respectively.

Biochemical measurement

Blood samples were obtained in the morning after an overnight fast. Total cholesterol, triglycerides, fasting plasma glucose, haemoglobin A1c and serum creatinine levels were determined by standard laboratory measurements. Creatinine clearance was calculated from the Cockcroft-Gault formula.[22]

Statistical analysis

Statistical analysis was performed using StatView Version 5 Software (Abacus Concepts Inc., Berkeley, CA, USA). Values are expressed as the mean ± s.d. Simple correlations between variables were assessed using univariate linear regression analyses and Pearson's correlation coefficient. An unpaired Student's *t*-test was used for comparison between the two groups. The significance of differences among the three groups was evaluated by an unpaired ANOVA with subsequent Fisher's multiple comparison test. A multiple logistic regression analysis was performed to identify independent determinants of LV mass increase and concentric hypertrophy. A value of $P<0.05$ was accepted as statistically significant.

Results

Simple correlations of office and ambulatory BP levels with two indices of LV structural changes, LVMI and RWT, in all subjects are shown in Table 1. Office systolic or diastolic BP had no correlation with either LVMI or RWT. In contrast, LVMI and RWT were positively correlated with daytime and 24-h systolic BPs, and LVMI was also correlated with night time systolic BP. In addition, these two indices were significantly correlated with the difference between office BP and daytime BP. As shown in Figure 1, LVMI had a close negative correlation with office–daytime systolic BP difference ($r=-0.377$, $P<0.001$). RWT were also inversely correlated with office–daytime systolic BP difference ($r=-0.170$, $P=0.005$). These results suggested that reverse white-coat effect was significantly associated with increases in LVMI and RWT.

Clinical characteristics of the two subject groups classified according to the difference between office and daytime ambulatory systolic BP levels are summarized in Table 2. One hundred and twenty-three (45%) patients were identified as having reverse white-coat effect (Group 2), and the other 149 (55%) patients belonged to Group 1. The proportion of men and the rate of habitual drinkers

Table 1 Correlation of office and ambulatory blood pressure with left ventricular structure in all subjects

	LVMI		*RWT*	
	r	P	r	P
Office systolic BP	0.039	0.526	0.014	0.816
Office diastolic BP	−0.124	0.053	−0.040	0.508
Daytime systolic BP	0.290	<0.001	0.173	0.004
Daytime diastolic BP	0.020	0.742	0.100	0.099
Night time systolic BP	0.318	<0.001	0.113	0.062
Night time diastolic BP	0.099	0.104	0.078	0.198
24-h systolic BP	0.325	<0.001	0.158	0.009
24-h diastolic BP	0.051	0.398	0.096	0.113
(Office − daytime) systolic BP	−0.377	<0.001	−0.170	0.005
(Office − daytime) diastolic BP	−0.211	<0.001	−0.147	0.015

Abbreviations: BP, blood pressure; LVMI, left ventricular mass index; RWT, relative wall thickness.

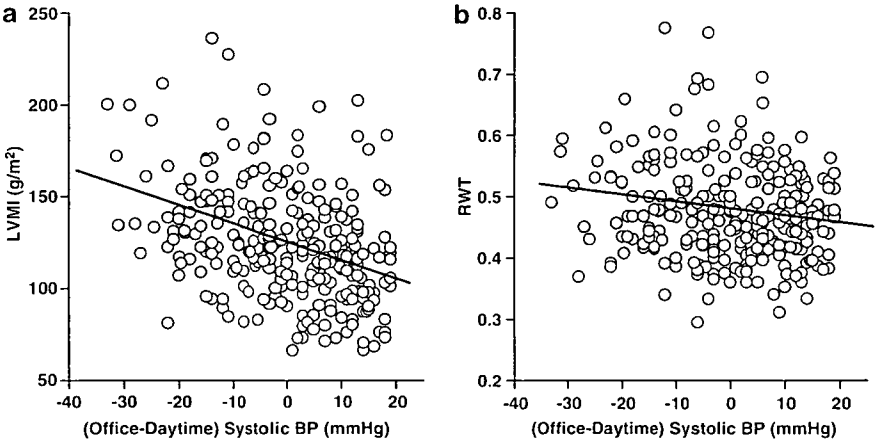

Figure 1 Correlation of the difference between office and daytime systolic BP levels with LVMI (a, $r=-0.377$, $P<0.001$) and RWT (b, $r=-0.170$, $P=0.005$) in all subjects.

Table 2 Clinical characteristics of two study groups

	Group 1 (n = 149)	*Group 2 (n = 123)*	P
Age (years)	65.8±9.1	65.1±11.0	0.593
Sex (male) (%)	41.6	65.0	<0.001
Body mass index (kg/m²)	24.2±2.9	24.7±4.0	0.182
Duration of hypertension (years)	17.6±10.8	17.8±11.0	0.850
Diabetes mellitus (%)	19.5	23.6	0.412
Hyperlipidemia (%)	64.9	66.1	0.831
Current smoking (%)	15.6	21.1	0.235
Habitual drinking (%)	50.7	63.6	0.033
Creatinine clearance (ml/min)	81.5±24.8	85.1±32.8	0.297
Fasting plasma glucose (mmol/l)	5.7±1.2	5.8±1.1	0.486
Hemoglobin A1c (%)	5.6±0.8	5.7±0.7	0.257
Total cholesterol (mmol/l)	5.3±0.8	5.2±0.7	0.576
Triglycerides (mmol/l)	1.4±0.7	1.5±0.8	0.126
Antihypertensive treatment			
Period of medication (years)	12.4±9.3	11.7±9.1	0.497
Ca channel blockers (%)	71.8	71.5	0.961
RAS inhibitors (%)	49.7	53.7	0.514
β-Blockers (%)	28.2	32.5	0.440
Diuretics (%)	16.8	22.8	0.216
Others (%)	9.4	12.2	0.458
Total number of classes	1.8±0.9	1.9±0.9	0.141
Office systolic BP (mm Hg)	145.6±12.7	133.8±11.6	<0.001
Office diastolic BP (mm Hg)	83.4±9.9	78.8±10.0	<0.001
Daytime systolic BP (mm Hg)	136.5±12.6	145.1±11.9	<0.001
Daytime diastolic BP (mm Hg)	80.1±9.3	84.8±11.5	<0.001
Night time systolic BP (mm Hg)	126.8±14.9	134.1±15.8	<0.001
Night time diastolic BP (mm Hg)	73.1±9.5	76.9±11.1	0.002
24-h systolic BP (mm Hg)	134.0±12.3	141.6±12.2	<0.001
24-h diastolic BP (mm Hg)	78.2±9.0	82.3±10.5	<0.001
Nocturnal systolic BP dipping (%)	7.1±8.0	7.6±8.0	0.572
Nocturnal diastolic BP dipping (%)	8.5±8.4	9.0±8.5	0.671

Abbreviations: BP, blood pressure; RAS, renin angiotensin system.
RAS inhibitors represent angiotensin II receptor blockers and angiotensin converting enzyme inhibitors. Values are mean±s.d. or percentage.

were significantly higher in Group 2 than in Group 1. Age, body mass index, hypertension duration, the prevalence of diabetes mellitus and hyperlipidemia, the rate of current smokers, renal function and glucose and lipid parameters did not differ between the two groups. In addition, there were no inter-group differences in the period of medication, the use of any class of antihypertensive agent and the total number of classes of antihypertensive drugs.

Office and ambulatory BP levels had clear differences between the two groups. That is, Group 2 had significantly lower office systolic and diastolic BPs than Group 1, but daytime, night time, and average 24-h ambulatory BPs in Group 2 were significantly elevated compared with those in Group 1. The degree of nocturnal BP dipping, an index of circadian BP variation, did not differ between the two groups.

The comparison of echocardiographic parameters between the two groups is shown in Table 3. Group 2 had a significantly greater LVMI than Group 1, resulting from more increased LV wall thickness and internal dimension. RWT was also significantly increased in Group 2 compared with Group 1. In addition, the prevalence of LVH, defined as an increased LVMI by sex, was significantly higher in Group 2. There was no difference in fractional shortening between the two groups.

Table 3 Comparison of ecchocardiographic parameters between the two groups

	Group 1 (n = 149)	*Group 2 (n = 123)*	P
IVSTd (mm)	10.3±1.5	11.4±1.9	<0.001
PWTd (mm)	10.3±1.4	11.1±1.5	<0.001
LVDd (mm)	44.8±4.5	46.8±4.2	<0.001
LVDs (mm)	26.5±4.9	27.7±4.6	0.037
Fractional shortening (%)	41.1±7.4	41.0±6.8	0.920
LVMI (g/m²)	115.3±28.3	136.4±30.8	<0.001
RWT	0.46±0.07	0.49±0.09	0.010
Prevalence of LVH (%)	41.6	65.9	<0.001

Abbreviations: IVSTd, interventricular septal thickness at end-diastole; LVDd, left ventricular diameter at end-diastole; LVDs, left ventricular diameter at end-systole; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; PWTd, posterior wall thickness at end-diastole; RWT, relative wall thickness.
LVH is defined as LVMI of ⩾125 g/m² in men and 110 g/m² in women.
Values are mean±s.d. or percentage.

To assess the impact of reverse white-coat effect on LVH, Group 2 was divided into two sub-groups by the extent of its phenomenon. As shown in Figure 2, both LVMI and prevalence of LVH were

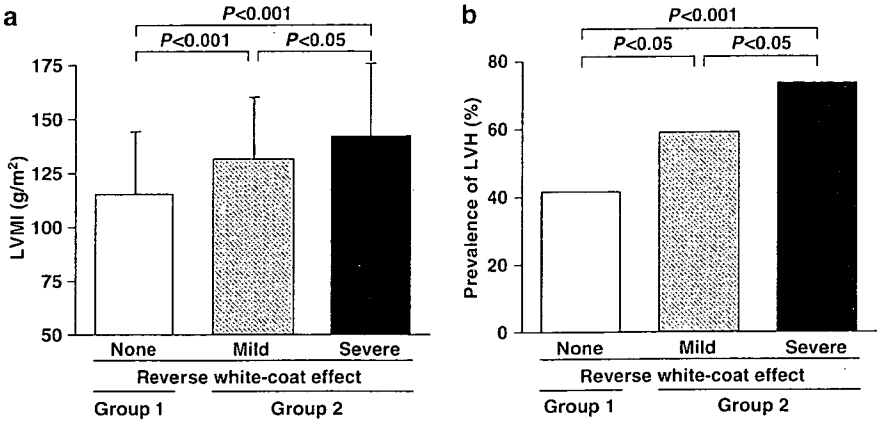

Figure 2 Comparison of LVMI (a) and prevalence of LVH (b) among the three groups classified by the extent of reverse white-coat effect. None, office systolic BP ≥ daytime systolic BP (i.e., Group 1, $n=149$); Mild, office systolic BP < daytime systolic BP, but daytime systolic BP−office systolic BP < 10 mm Hg ($n=63$); Severe, daytime systolic BP−office systolic BP ≥ 10 mm Hg ($n=60$). LVH is defined as LVMI of ≥125 g/m² in men and 110 g/m² in women. Values are given as the mean ± s.d. (a) or percentage (b).

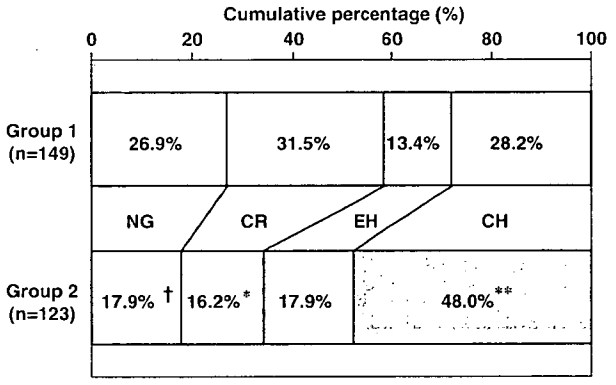

Figure 3 Comparison of LV geometric patterns between the two groups. NG, normal geometry (normal LVMI and RWT); CR, concentric remodelling (normal LVMI and increased RWT); EH, eccentric hypertrophy (increased LVMI and normal RWT); CH, concentric hypertrophy (increased LVMI and RWT). †$P<0.05$, *$P<0.01$, and **$P<0.001$ vs Group 1.

significantly greater in subjects with mild reverse white-coat effect (office systolic BP < daytime systolic BP, but daytime systolic BP−office systolic BP < 10 mm Hg) than in those without reverse white-coat effect (i.e., Group 1), and these values were further increased significantly in the sub-group with severe reverse white-coat effect (daytime systolic BP−office systolic BP ≥ 10 mm Hg).

Figure 3 shows the comparison of LV geometric patterns between the two groups. Group 2 had a significantly higher rate of concentric hypertrophy compared with Group 1 (48 vs 28%, $P<0.001$). In contrast, the rates of patients with normal geometry and concentric remodelling were significantly lower in Group 2 than in Group 1.

To confirm whether the influence of reverse white-coat phenomenon on LV mass increase and specific geometric change was independent of various clinical parameters, we investigated possible predictive factors using a multiple logistic regression analysis in all subjects (Table 4). Although average 24-h systolic BP was the strongest predictor for both LVH and concentric hypertrophy, the presence of reverse white-coat effect (i.e., Group 2) was found to be a significant determinant for these LV structural changes, independent of age, sex, body mass index, hypertension duration, the use of any class of antihypertensive agent and 24-h systolic and diastolic BP levels (for LVH: odds ratio 2.42 vs Group 1, $P=0.005$; for concentric hypertrophy: odds ratio 1.89, $P=0.039$). The significant predictive value of reverse white-coat effect remained even when daytime systolic and diastolic BPs, instead of 24-h BPs, were adopted as independent predictors (data not shown).

Discussion

This study has demonstrated that the presence of reverse white-coat effect is one of the independent predictors for LVH, especially for LV concentric hypertrophy, in patients with treated essential hypertension. The new findings suggest that reverse white-coat phenomenon, independent of average ambulatory blood pressure levels, may have an unfavourable influence on left ventricular geometry in essential hypertension.

The present subjects with reverse white-coat effect (Group 2) had a controlled office BP in spite of elevated ambulatory BP, indicating that the group took on an aspect of masked hypertension. There have been a few studies reporting the possible association between masked hypertension and cardiac and carotid arterial structural changes in the general population. Liu *et al.*[23] found that LV mass and carotid wall thickness in patients with masked hypertension were significantly greater than those in true normotensive subjects and similar to those in patients with sustained hypertension. The data from the PAMELA Study also showed that LVMI was

Table 4 Independent predictors for left ventricular mass increase and concentric hypertrophy by multiple logistic regression analysis

	LVH		*Concentric hypertrophy*	
	OR (95% CI)	P	*OR (95% CI)*	P
Age (10 years)	0.88 (0.58–1.34)	0.544	0.70 (0.46–1.05)	0.087
Sex (male)	0.60 (0.30–1.16)	0.128	0.82 (0.42–1.60)	0.557
Body mass index (1 kg/m^2)	1.10 (1.00–1.23)	0.046	1.10 (1.00–1.22)	0.053
Hypertension duration (1 year)	1.02 (0.99–1.05)	0.123	1.03 (1.00–1.06)	0.028
Diabetes mellitus (yes)	1.04 (0.48–2.22)	0.929	1.02 (0.49–2.13)	0.959
Hyperlipidemia (yes)	1.49 (0.82–2.71)	0.186	1.35 (0.73–2.47)	0.339
Current smoking (yes)	0.99 (0.46–2.13)	0.978	1.25 (0.60–2.58)	0.553
Habitual drinking (yes)	1.09 (0.58–2.06)	0.783	1.22 (0.64–2.32)	0.541
Creatinine clearance (10 ml/min)	0.91 (0.77–1.06)	0.231	0.87 (0.74–1.02)	0.095
Ca channel blocker (yes)	1.36 (0.67–2.77)	0.402	1.09 (0.53–2.24)	0.808
RAS inhibitor (yes)	1.15 (0.60–2.21)	0.678	1.57 (0.82–2.99)	0.170
β-Blocker (yes)	1.89 (0.99–3.59)	0.052	1.36 (0.73–2.55)	0.337
Diuretic (yes)	1.04 (0.49–2.22)	0.921	0.72 (0.34–1.56)	0.407
24-h systolic BP (10 mm Hg)	2.35 (1.66–3.33)	<0.001	1.97 (1.45–2.68)	<0.001
24-h diastolic BP (10 mm Hg)	0.60 (0.40–0.90)	0.014	0.67 (0.45–0.98)	0.041
Reverse white-coat effect				
Absence (Group 1)	1 (reference)		1 (reference)	
Presence (Group 2)	2.42 (1.31–4.48)	0.005	1.89 (1.03–3.44)	0.039

Abbreviations: BP, blood pressure; CI, confidence interval; LVH, left ventricular hypertrophy; OR, odds ratio; RAS, renin angiotensin system. RAS inhibitor represents angiotensin II receptor blocker or angiotensin converting enzyme inhibitor. LVH is defined as LVMI of $\geqslant$125 g/m^2 in men and 110 g/m^2 in women. Concentric hypertrophy is defined as LVH combined with increased RWT ($\geqslant$0.44).

increased in untreated subjects with masked hypertension and sustained hypertension than in those with true normotension.[24] In addition, our recent study showed that masked hypertension was associated with advanced target organ damage in treated hypertensive patients, comparable to that in cases of sustained hypertension.[25] Furthermore, prospective studies have revealed that a high ambulatory or home BP is a powerful predictor for cardiovascular morbidity and mortality in the general population and treated hypertensive patients even when their office BP is normal or well controlled.[10,11,26–28] As for the association between LV geometry and cardiovascular prognosis, it was reported that hypertensive patients with concentric hypertrophy among four LV geometric patterns had the highest incidence of cardiovascular events and death.[13] Taken together, it is likely that advanced target organ changes including LV concentric hypertrophy in patients with masked hypertension or reverse white-coat condition are linked to poor cardiovascular prognosis in such patients.

A higher level of ambulatory BP is a major determinant of target organ damage in hypertensive patients.[1,2] In the present study, however, the presence of reverse white-coat effect was a significant predictor for LVH and concentric hypertrophy, independent of average 24-h ambulatory BP levels. Other factors than a higher ambulatory BP could contribute to target organ damage in reverse white-coat hypertension. Our study has not provided the specific mechanism by which reverse white-coat effect could promote LV concentric hypertrophy in patients with treated hypertension. Therefore, further investigations are required to clarify how reverse white-coat or masked hypertension has a specific unfavourable effect on the hypertensive target organ.

There were some limitations in our study. The present findings were derived from cross-sectional data on the basis of one-time examination of ambulatory BP monitoring and echocardiography. Our subjects were divided into subgroups based on office–daytime difference only in systolic BP, not considering diastolic BP difference. In addition, cardiac magnetic resonance imaging might be more adequate than echocardiography in evaluating LV mass exactly.

All patients in the present study had received antihypertensive medication. As another limitation of this study, therefore, we must consider the possibility that different classes of antihypertensive drugs may have differently affected the development of LVH, partly independently of their BP-lowering effects. Renin angiotensin system inhibitors, particularly, are known to have BP fall-independent protective effects on hypertensive target organ. However, the percentage of patients treated with angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors did not differ between the two study groups. Our multivariate analysis also showed that the association of reverse white-coat effect with LVH and concentric hypertrophy was independent of the use of any class of antihypertensive agent.

In conclusion, the present study indicates that reverse white-coat effect is a significant determinant of LVH, especially concentric hypertrophy, in patients with treated essential hypertension, independent of average ambulatory BP levels and

various other clinical risk factors. Our findings suggest that the presence of this phenomenon may be an independent risk for the adverse LV geometric change in treated hypertensive patients and ambulatory BP monitoring seems to be necessary to unmask this latent risk that is not detectable by routine BP measuring in the office.

What is known about this topic

- Ambulatory blood pressure is an important determinant of target organ damage and a predictor for cardiovascular morbidity and mortality in hypertensive patients.
- The converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension' is associated with poor cardiovascular prognosis.
- Left ventricular hypertrophy, especially concentric hypertrophy, is a significant risk factor for cardiovascular complications and death.

What this study adds

- Reverse white-coat effect was an independent predictor for left ventricular hypertrophy, especially for concentric hypertrophy, in treated hypertensive patients.
- The presence of reverse white-coat phenomenon, independent of average ambulatory blood pressure levels, may have an unfavourable influence on left ventricular geometry.

Acknowledgements

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Brief Report

Reverse white-coat effect as an independent risk for microalbuminuria in treated hypertensive patients

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Abstract

Background. The influence of the converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension' on hypertensive target organ damage has not been fully elucidated. The present study assessed the hypothesis that this phenomenon may specifically associate with microalbuminuria, a marker of early renal damage, in treated hypertension.

Methods. A total of 267 treated essential hypertensive patients (133 men and 134 women; mean age, 66 years) without renal insufficiency or macroalbuminuria were enroled in this study. Patients were classified into three groups by the difference between office and day-time ambulatory systolic blood pressure (BP) levels; i.e. subjects with white-coat effect (W group: office − day-time systolic BP $\geq$20 mmHg, $n=48$), with reverse white-coat effect (R group: office − day-time systolic BP <-10 mmHg, $n=43$) and without white-coat or reverse white-coat effect (N group: -10 mmHg $\leq$ office − day-time systolic BP $<$20 mmHg, $n=176$). The urinary albumin (U-Alb) level was measured as the albumin to creatinine excretion ratio in the urine. Microalbuminuria was defined as U-Alb of $\geq$30 and $<$300 mg/g Cr.

Results. R group had a well-controlled office BP (130/77 mmHg), but their day-time BP (148/87 mmHg) was elevated compared with the other two groups. The levels of U-Alb excretion in N group, W group and R group were 12.3 (8.4, 25.6), 16.0 (10.5, 31.7) and 24.3 (10.2, 79.7) mg/g Cr [median (interquartile range)], respectively. Both U-Alb level and prevalence of microalbuminuria were significantly greater in R group than in N group. Multivariate analyses revealed that the presence of reverse white-coat effect, but not white-coat effect, was a significant predictor for microalbuminuria, independent of various clinical variables including ambulatory BP levels (odds ratio 2.63 *vs* N group, $P=0.02$).

Conclusion. These findings suggest that the presence of reverse white-coat effect may be an independent risk for early renal damage in treated hypertensive patients.

Keywords: ambulatory blood pressure monitoring; hypertension; microalbuminuria

Introduction

Ambulatory blood pressure (BP) is an important determinant of target organ damage and a significant predictor for cardiovascular morbidity and mortality in hypertensive patients [1–6]. There is often a discrepancy between office and ambulatory BPs, and many studies have investigated the association between white-coat hypertension, a normal ambulatory but elevated office BP, and cardiovascular risk [7,8]. On the other hand, the converse phenomenon of white-coat hypertension called 'reverse white-coat hypertension' or 'masked hypertension', i.e. a high ambulatory but normal (or well-controlled) office BP, has received little attention [9]. Whereas, some studies have revealed that the proportion of subjects with reverse white-coat effect evaluated by the difference between office and ambulatory BPs is 20–40% in the general population and hypertensives [10,11]. In treated hypertensive patients with this phenomenon, particularly, the chance of active and sufficient antihypertensive treatment may be lost by an apparent well-controlled BP in the office. Recent studies suggested that an elevated ambulatory or home BP despite a well-controlled office BP, is associated with poor cardiovascular prognosis in treated hypertensive patients [12,13]. However, the influence of reverse white-coat effect on target organ damage in treated hypertension has remained to be elucidated.

Microalbuminuria, which is one of the early end-organ changes observed in hypertensives, has been shown to be a significant risk for not only renal

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insufficiency but also cardiovascular events [14,15]. Thus, the present study was aimed to investigate the association of reverse white-coat effect with microalbuminuria as a sensitive marker of target organ damage in treated hypertensive patients.

Methods

Subjects

From 314 consecutive patients with essential hypertension who were chronically treated and underwent a 24-h ambulatory BP monitoring at an outpatient clinic of our hospital between May 2000 and December 2003, 267 subjects [133 men and 134 women; age, 30–90 years (mean, 66 years)] in whom urinary albumin (U-Alb) data were simultaneously obtained were enroled in our retrospective study. Patients with secondary hypertension, stroke, ischaemic heart disease including myocardial infarction, congestive heart failure or insulin-treated diabetes mellitus were excluded from this study. Individuals with chronic glomerulonephritis, nephrotic syndrome, renal insufficiency (serum creatinine $\geq$1.5 mg/dl), or macroalbuminuria (described later) were also excluded. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria, such as a fasting plasma glucose of $\geq$126 mg/dl and/or a plasma glucose level at 2 h after a 75 g oral glucose load of $\geq$200 mg/dl, or when medication was taken for treatment of hyperglycaemia. A diagnosis of hyperlipidaemia required a serum total cholesterol level of $\geq$220 mg/dl and/or a serum triglyceride level of $\geq$150 mg/dl or the use of lipid-lowering drugs.

All patients had taken antihypertensive drugs for at least 1 year (average, 12 years). A total of 185 (69%) were treated with Ca channel blockers, 86 (32%) with angiotensin II receptor blockers, 41 (15%) with angiotensin-converting enzyme inhibitors, 83 (31%) with β-blockers, 51 (19%) with diuretics and 27 (10%) with other classes of agents. All subjects gave their informed consent to participate in the present study. All procedures of the present study were carried out in accordance with institutional and national ethical guidelines for human studies.

Measurement of BP

In each visit, office BP was measured twice by a physician in a hospital outpatient clinic with the patient in a sitting position after over 20 min of rest, using an appropriate-size arm cuff and mercury sphygmomanometer. The first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Office BP was determined by averaging six measurements taken on three separate occasions during a 3-month period.

In the same study period, all subjects underwent 24-h ambulatory BP monitoring. BP was measured every 30 min during the day and night by the oscillometric method using an automatic monitoring device (TM-2421, A&D Co Ltd, Tokyo, Japan) [16]. The accuracy and performance of this device have been demonstrated previously [17]. The patients were instructed to carry on with their normal daily activities during measurements and note their activity and location in a diary. According to the diary, day-time and night-time were determined as the waking and sleeping periods of the patient, respectively, and mean values of 24-h, day-time and night-time BPs (systolic and diastolic) were calculated. Nocturnal BP dipping was determined as 100 × (day-time BP–night-time BP)/day-time BP.

In the present study, all subjects were classified into three groups by the difference between office and day-time ambulatory systolic BP levels according to some previous studies [10,11,18], with minor modifications; that is, subjects with overt white-coat effect (W group: office systolic BP − day-time systolic BP $\geq$20 mmHg), with overt reverse white-coat effect (R group: office systolic BP − day-time systolic BP <-10 mmHg) and with neither white-coat nor reverse white-coat effect (N group: -10 mmHg $\leq$ office systolic BP − day-time systolic BP $<$20 mmHg).

Biochemical measurement

Blood samples were obtained in the morning after an overnight fast. Fasting plasma glucose, haemoglobin A_{1c}, total cholesterol, triglycerides and serum creatinine levels were determined by standard laboratory measurements. Creatinine clearance was calculated from the Cockcroft and Gault formula [19]. The U-Alb level was measured as the albumin to creatinine excretion ratio (mg/g Cr) in the urine. Mircoalbuminuria was defined as U-Alb of $\geq$30 and $<$300 mg/g Cr. Patients with macroalbuminuria (U-Alb $\geq$300 mg/g Cr) were excluded from the study.

Statistical analysis

Statistical analysis was performed using StatView Version 5.0 Software (Abacus Concepts Inc., Berkeley, CA, USA). Values are expressed as mean ± SE, except for U-Alb, and frequencies are expressed as percentages. Levels of U-Alb are given as median and interquartile range (25–75th percentiles). The significance of differences among the three groups (N group, W group and R group) was evaluated by an unpaired ANOVA with subsequent Scheffe's multiple comparison test. Due to skewed distribution, U-Alb levels were analysed by a non-parametric Kruskal–Wallis test. In addition, log-transformed U-Alb levels were used for comparison between groups or for correlation analysis. Simple correlations between log-transformed U-Alb and BP parameters were assessed using univariate linear regression analyses and Pearson's correlation coefficient. A multiple logistic regression analysis was used to identify independent determinants of microalbuminuria. A value of $P < 0.05$ was accepted as statistically significant.

Results

Clinical characteristics of the three subject groups classified according to the difference between office and day-time ambulatory systolic BP levels are summarized in Table 1. Forty-eight (18.0%) and 43 (16.1%) patients were identified as having overt white-coat effect (W group) and reverse white-coat effect (R group), respectively, and the other 176 (65.9%) patients belonged to N group. The proportion of men was higher and body mass index was greater in R group compared with W group.

Table 1. Clinical characteristics of study subjects

Variable	N group ($n=176$)	W group ($n=48$)	R group ($n=43$)
Age, years	65.3 ± 0.8	68.1 ± 1.2	64.2 ± 1.7
Sex (men),%	50.6	33.3	65.1†
Body mass index, kg/m^2	24.3 ± 0.3	23.5 ± 0.4	25.5 ± 0.7†
Duration of hypertension, years	18.2 ± 0.8	21.4 ± 1.4	14.4 ± 1.4†
Diabetes mellitus,%	19.9	16.7	14.0
Hyperlipidaemia,%	64.6	75.0	74.4
Current smoking,%	14.9	18.8	23.3
Serum creatinine, mg/dl	0.75 ± 0.02	0.69 ± 0.03	0.78 ± 0.03
Creatinine clearance, ml/min	84.4 ± 2.0	81.7 ± 3.9	92.3 ± 5.8
Fasting plasma glucose, mg/dl	102 ± 2	105 ± 3	101 ± 3
Haemoglobin A_{1c},%	5.5 ± 0.1	5.7 ± 0.1	5.6 ± 0.1
Total cholesterol, mg/dl	203 ± 2	204 ± 3	200 ± 3
Triglycerides, mg/dl	121 ± 5	126 ± 15	140 ± 9
Antihypertensive treatment			
Period of medication, years	12.4 ± 0.7	15.1 ± 1.4	9.3 ± 1.1†
AII receptor blockers,%	33.5	27.1	32.6
ACE inhibitors,%	17.0	10.4	14.0
Ca channel blockers,%	67.6	68.8	76.7
β-Blockers,%	29.0	41.7	27.9
α-Blockers,%	10.8	8.3	9.3
Diuretics,%	18.8	20.8	18.6
Total number of classes	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.1
Office systolic BP, mmHg	142.0 ± 0.8	165.4 ± 2.0*	129.7 ± 1.5*,†
Office diastolic BP, mmHg	82.5 ± 0.7	91.0 ± 1.7*	76.9 ± 1.3*,†
Day-time systolic BP, mmHg	137.1 ± 0.8	132.4 ± 1.7*	148.0 ± 1.5*,†
Day-time diastolic BP, mmHg	80.9 ± 0.7	78.6 ± 1.5	87.0 ± 1.5*,†
Night-time systolic BP, mmHg	127.6 ± 1.1	124.4 ± 2.2	136.0 ± 2.4*,†
Night-time diastolic BP, mmHg	74.0 ± 0.8	72.6 ± 1.7	78.0 ± 1.5†
24-h systolic BP, mmHg	134.7 ± 0.9	130.9 ± 1.7	143.9 ± 1.6*,†
24-h diastolic BP, mmHg	78.9 ± 0.7	76.6 ± 1.6	84.1 ± 1.3*,†
Nocturnal systolic BP dipping,%	6.9 ± 0.6	6.1 ± 1.1	8.2 ± 1.1
Nocturnal diastolic BP dipping,%	8.3 ± 0.7	7.6 ± 1.1	10.0 ± 1.2

Values are mean ± SE or percentage. *$P < 0.05$ *vs* N group; †$P < 0.05$ *vs* W group.
AII, angiotensin II; ACE, angiotensin-converting enzyme; BP, blood pressure.

Duration of hypertension and period of medication were significantly shorter in R group than in W group. The prevalence of diabetes mellitus and hyperlipidaemia, the rate of current smokers, renal function and glucose and lipid parameters did not differ among the three groups. In addition, no intergroup differences were found in the use of any class of antihypertensive agent including angiotensin II receptor blocker and angiotensin-converting enzyme inhibitor and total number of classes of antihypertensive drugs.

Office systolic and diastolic BPs were significantly higher in W group and lower in R group compared with N group. Day-time, night-time and average 24-h ambulatory BPs were significantly elevated in R group than in the other two groups. There were no significant differences in ambulatory BPs between N group and W group, except that day-time systolic BP was somewhat lower in W group than in N group. The degree of nocturnal BP dipping, an index of circadian BP variation, did not differ among the three groups.

The U-Alb levels in N group, W group and R group were 12.3 (8.4, 25.6), 16.0 (10.5, 31.7) and 24.3 (10.2, 79.7) mg/g Cr, respectively, indicating that R group had a significantly higher level of U-Alb compared with N group (Figure 1A). The percentage of patients with microalbuminuria was also significantly higher in R group than in N group (Figure 1B). U-Alb level and prevalence of microalbuminuria in W group did not differ from those in N group.

To avoid the influence of diabetes mellitus or the specific effect of renin–angiotensin system (RAS) inhibitors (i.e. angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors) on U-Alb excretion, we re-examined the U-Alb level after excluding some subjects. Even after excluding patients with diabetes mellitus ($n=218$), U-Alb level was significantly increased in R group than in N group [24.3 (10.5, 73.8) and 11.5 (7.6, 24.2) mg/g Cr, $P=0.0024$]. Likewise, even after excluding patients receiving RAS inhibitors ($n=141$), U-Alb level in R group was still higher compared with that in N group [36.5 (19.0, 101.3) and 12.1 (8.7, 26.2) mg/g Cr, $P=0.0004$].

Simple correlations of office and ambulatory BPs with U-Alb levels were examined in all 267 subjects. Although office systolic or diastolic BP had no correlation with log-transformed U-Alb level (data not shown), log U-Alb was positively correlated with ambulatory systolic BP during day-time ($r=0.272$, $P<0.0001$), night-time ($r=0.230$, $P=0.0001$),

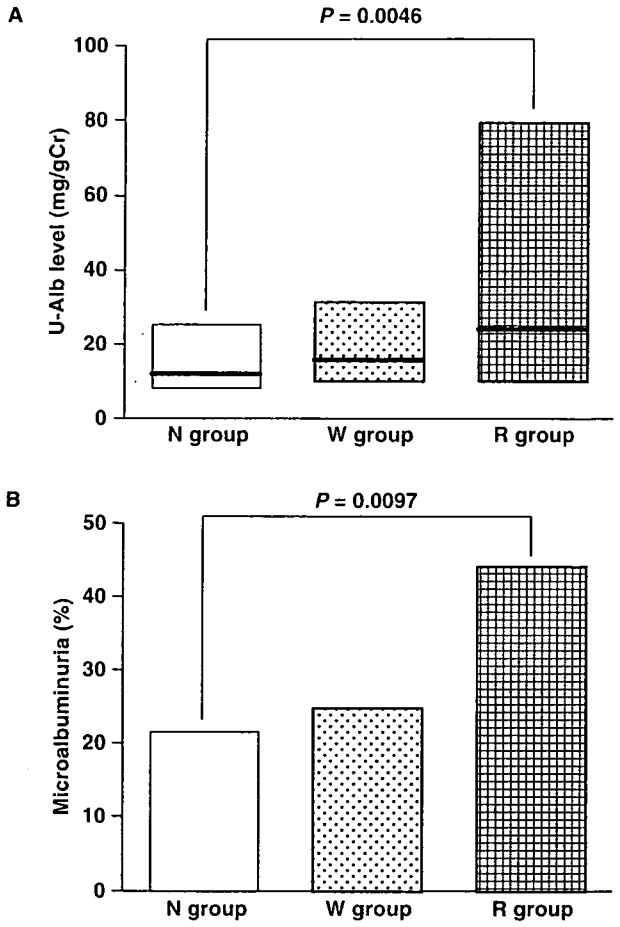

Fig. 1. U-Alb levels (A) and prevalence of microalbuminuria (B) in the three groups classified by the difference between office and day-time systolic BP levels. Values are given as median and interquartile range (25th–75th percentiles) (A) or percentage (B). Due to skewed distribution, U-Alb levels were analysed by a non-parametric Kruskal–Wallis test ($P=0.0095$). Log-transformed U-Alb levels were used for comparison between groups.

and 24 h ($r=0.246$, $P<0.0001$). The difference between office and day-time systolic BP tended to correlate inversely with log U-Alb, but it was not statistically significant ($r=-0.114$, $P=0.0628$).

To confirm whether the influence of reverse white-coat phenomenon on U-Alb excretion was independent of various clinical parameters including ambulatory BP levels, we investigated possible predictive factors using a multiple logistic regression analysis in all subjects. As shown in Table 2, the presence of reverse white-coat effect (i.e. R group) was found to be a significant predictor for microalbuminuria, independent of age, sex, hypertension duration, use of RAS inhibitor, complication of diabetes mellitus, renal function (creatinine clearance) and day-time average systolic and diastolic BP levels [odds ratio (OR) 2.627 *vs* N group, $P=0.0197$]. The presence of white-coat effect (i.e. W group) was not an independent determinant of microalbuminuria (OR 1.163 *vs* N group, $P=0.7125$). The significant predictive value of reverse white-coat effect remained even though average 24-h systolic and diastolic BPs, instead of day-time BPs, were adopted as independent predictors (data not shown).

Table 2. Independent predictors for microalbuminuria by multiple logistic regression analysis

Variable	OR (95% CI)	*P*-value
Age, 10 years	1.014 (0.675–1.523)	0.9473
Sex, men	0.962 (0.513–1.803)	0.9029
Duration of hypertension, 1 year	1.037 (1.007–1.068)	0.0167
Use of RAS inhibitor, yes	0.509 (0.276–0.937)	0.0301
Diabetes mellitus, yes	1.473 (0.679–3.193)	0.3268
Creatinine clearance, 10 ml/min	0.939 (0.821–1.074)	0.3552
Day-time systolic BP, 10 mmHg	1.491 (1.098–2.023)	0.0105
Day-time diastolic BP, 10 mmHg	0.947 (0.653–1.374)	0.7749
BP pattern		
N group (normal type)	1 (reference)	
W group (white-coat effect)	1.163 (0.521–2.596)	0.7125
R group (reverse white-coat effect)	2.627 (1.167–5.916)	0.0197

RAS inhibitor represents angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor.
CI, confidence interval; RAS, renin–angiotensin system; BP, blood pressure.

Discussion

This study has demonstrated that the presence of reverse white-coat effect is one of the independent predictors for microalbuminuria in patients with treated essential hypertension. Our study provided the novel findings to prove the significant association of reverse white-coat phenomenon with U-Alb excretion in essential hypertension, because the relation between reverse white-coat hypertension (or masked hypertension) and early renal damage such as microalbuminuria in hypertensive subjects has not been elucidated.

In the present study, subjects with reverse white-coat effect (R group) had a well-controlled office BP (<130/80 mmHg) in spite of elevated ambulatory BP, suggesting that R group took on an aspect of masked hypertension. There have been a few studies reporting the possible association between masked hypertension and cardiac and carotid arterial structural changes. Liu *et al.* [20] originally found that left ventricular mass and carotid wall thickness in subjects with masked hypertension were significantly greater than those in true normotensive subjects and similar to those in patients with sustained hypertension. Another study also showed that left ventricular mass index and prevalence of left ventricular hypertrophy were increased in untreated subjects with masked hypertension and sustained hypertension than in those with true normotension [21]. Therefore, the present findings

were broadly consistent with these previous observations concerning the association between masked hypertension and target organ damage. Recent prospective studies revealed that a high ambulatory or home BP is a powerful predictor for cardiovascular morbidity and mortality in the general population and treated hypertensive patients even when their office BP is normal or well controlled [12,13,22–24]. Taken together, it is likely that advanced target organ changes in patients with masked hypertension or reverse white-coat condition are linked to poor cardiovascular prognosis in such patients.

A higher level of ambulatory BP is a major determinant of target organ damage in hypertensive patients [1,2]. In the present study, average levels of day-time, night-time and 24-h ambulatory BPs were the highest in R group. Whereas, since the association of reverse white-coat effect with microalbuminuria was still significant after adjusted for average day-time (or 24-h) BP levels, our results suggest that other factors than a higher ambulatory BP could contribute to target organ damage in reverse white-coat hypertension. A shorter period of antihypertensive medication might partially explain the advanced end-organ change in the present subjects with reverse white-coat effect. However, our study has not provided the specific mechanism by which reverse white-coat effect could promote renal damage in patients with treated hypertension. Further investigations are required to clarify how reverse white-coat or masked hypertension has a specific unfavourable effect on the hypertensive target organ.

There were some limitations in our study. Considering the intra-individual variability of U-Alb level, the evaluation of albuminuria using a single urine collection might underestimate the prevalence of microalbuminuria and weaken the relationship between U-Alb and patterns of BP variation. In addition, our subjects were divided into subgroups on the basis of office–day-time systolic BP difference obtained from one-time examination of ambulatory BP monitoring. A reverse white-coat phenomenon is usually identified as an office BP lower than day-time (or 24-h) ambulatory BP [10,11]. In the present study, however, it was defined as office–day-time systolic BP of <-10 mmHg to detect only overt reverse white-coat effect from one-time monitoring of ambulatory BP.

All patients in the present study had received antihypertensive medication. As another limitation of this study, therefore, we must consider the possibility that different classes of antihypertensive drugs may have differently affected U-Alb excretion. RAS inhibitors, particularly, are known to have BP fall-independent protective effects against renal damage. However, the percentage of patients treated with angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors did not differ among the three study groups. Our multivariate analysis also showed that the relation of reverse white-coat effect to microalbuminuria was independent of the use of RAS inhibitors. Nonetheless, since BP reduction *per se*, regardless of classes of antihypertensive drugs, decreases U-Alb excretion, the determination of U-Alb level under drug-free period might be more desirable to evaluate the basal renal damage.

In conclusion, the present study indicates that reverse white-coat effect is a significant predictor for microalbuminuria in patients with treated essential hypertension, independent of average ambulatory BP levels and various other clinical risk factors. Our findings suggest that the presence of this phenomenon may be an independent risk for early renal damage in treated hypertensive patients and ambulatory BP monitoring (or home BP measurement) seems to be necessary to unmask this latent risk that is not detectable by routine BP measuring in the office.

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Conflict of interest statement. None declared.

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Report

Report of the Working Group for Dietary Salt Reduction of the Japanese Society of Hypertension: (1) Rationale for Salt Restriction and Salt-Restriction Target Level for the Management of Hypertension

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Salt excess is well known to be involved in the pathophysiology of hypertension, and thus restriction of salt intake is widely recommended for management of the disease. Excessive salt intake induces blood pressure (BP)–dependent as well as –independent progression of cardiovascular disease. Although the human body is considered to be adapted to very low salt intake (0.5–3 g/day), restriction to such a low level of salt intake is extremely difficult to accomplish in developed countries. Significant BP reduction has been reported in large-scale clinical studies in which salt intake was decreased to less than 6 g/day, and the results of a meta-analysis have shown that systolic BP was reduced about 1 mmHg with every decrease in salt intake of 1 g/day in hypertensive subjects. Current guidelines for the treatment of hypertension, including Japanese guidelines, recommend dietary salt reduction to 6 g/day or less in hypertensive patients. However, it appears to be fairly difficult to attain this target of salt intake, especially in Japan. There is thus a need for feasible and effective measures to attain this salt restriction target. (*Hypertens Res* 2007; 30: 879–886)

***Key Words*: dietary salt, hypertension, cardiovascular disease, guidelines, large-scale clinical study**

Introduction

Salt excess is well known to be involved in the pathophysiology of hypertension, and thus restriction of salt intake is widely recommended for management of the disease. Treatment guidelines for hypertension in Western countries recommend salt restriction to 6 g/day (sodium [Na] 100 mmol/day) or less for hypertensives (*1*, *2*). Because salt intake is higher in Japan than in Western countries, the 2000 version of the Guidelines for the Management of Hypertension (JSH 2000) from the Japanese Society of Hypertension (JSH) set the target of salt intake at 7 g/day or less (*3*). However, the target was revised to less than 6 g/day in the new Japanese guidelines (2004 version: JSH 2004) (*4*). To promote salt restriction for the management of hypertension, the JSH organized the Working Group for Dietary Salt Reduction in 2005. In this report, we summarize the rationale for restricting salt intake for the management of hypertension. The Japanese version of the working group report has been published previously (*5*).

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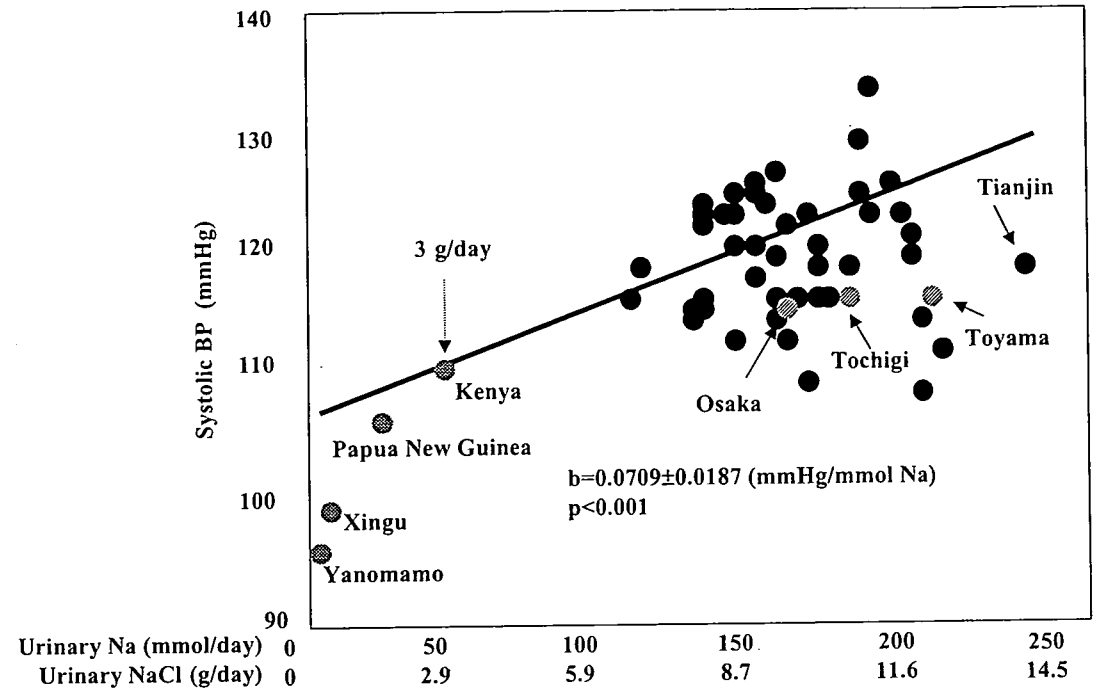

Fig. 1. *Relationship between salt intake and systolic blood pressure (BP) (from Intersalt Cooperative Research Group (8) with modification).*

Historical Background and Current Status of Salt Intake

Many land-dwelling animal species have difficulty gaining free access to salt and an innate salt appetite. In humans, low availability of salt has been a problem for millennia, and the period in which they could consume a large amount of salt has been very short in the history of mankind. It is estimated that humans in the Stone Age consumed salt at only 0.5–3 g/day (*6*), and the human body is considered to be adapted to such low salt intake. Physiologic studies have also suggested that the minimum salt requirement for human survival is about 0.5 g/day (*7*).

The amount of salt intake in humans shows wide regional and individual variations. The international cooperative Intersalt study, which investigated salt intake and blood pressure (BP) in various parts of the world, reported that salt intake ranged from less than 0.1 g/day in Yanomano, South America to about 15 g/day in Tianjin, China (*8*) (Fig. 1). Generally, salt intake is low in undeveloped regions and high in developed countries.

In Japan, the salt intake was traditionally high, especially in the Tohoku District (about 25 g/day in the 1950s) (*3*). Although the amount of salt consumption in Japanese has considerably decreased, the intake remains high, at about 11 g/day (*9*) (Fig. 2). Therefore, even today, most Japanese are consuming about 10 times the required amount of salt. In hypertensive patients treated on an outpatient basis, the mean salt intake estimated from the urinary Na excretion has also been reported to be high, at about 11 g/day (*10*) or 10 g/day (*11*). Salt intake is slightly higher in males than in females (*9*, *11*). Since this gender difference disappears when the values are corrected for body weight, it is considered to be ascribable to gender-related differences in physique (*11*).

Effects of Excessive Salt Intake

Hypertension

Many epidemiological, experimental, and clinical studies have clearly indicated that excessive salt intake is related to increases in BP and the progression of hypertension (*12*). For example, the Intersalt study found that salt intake was significantly correlated with BP; BP was extremely low particularly in groups with very low (less than 3 g/day) salt intake (*8*, *13*) (Fig. 1, Table 1). Moreover, little age-associated increase in BP was noted in these groups. Therefore, salt intake of less than 3 g/day is considered to be ideal for the prevention or treatment of hypertension.

Experimentally, the intake of excessive salt has been shown to induce or exacerbate hypertension in many models, including Dahl salt-sensitive rats and deoxycorticosterone acetate (DOCA)–salt hypertensive rats. Although the mechanism by which salt increases BP has not been completely elucidated, the kidney is considered to play an important role. The central

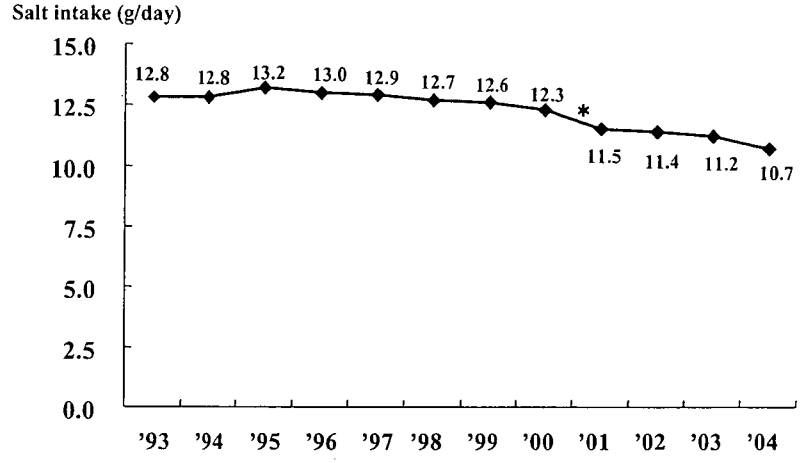

Fig. 2. *Trend of daily salt intake in Japan (based on data of Lifestyle-Related Disease Control Section, General Affairs Division, Health Bureau, Ministry of Health, Labor and Welfare (9)). *Calculated on the basis of the 4th edition of the Standard Tables of Food Composition in Japan until 2000 and 5th edition after 2001.*

Table 1. Comparison of Low Salt Intake Groups with Other Groups—Intersalt Study*

	Yanomamo	Xingu	Papua New Guinea	Kenya	Others (n=48)
Lifestyle					
Salt intake (g/day)	<0.06	0.35	1.6	3.0	9.4
Na/K ratio	<0.01	0.08	0.48	1.8	3.4
BMI (kg/m^2)	21.2	23.4	21.7	20.8	25.2
Regular drinkers (%)	0	0	8.7	30.7	53.0
Bood pressure					
Systolic BP (mmHg)	95.4	98.9	107.7	109.9	118.7
Diastolic BP (mmHg)	61.4	61.7	62.9	67.9	74.0
Hypertensives (%)	0	1.0	0.8	5.0	17.4
Age-associated increases in BP (mmHg/10 years)	−1.1	+0.6	−1.4	+2.4	+5.0

*From Stamler *et al.* (*13*) with permission. Na/K ratio, sodium/potassium ratio; BMI, body mass index; BP, blood pressure.

nervous system, various neurohumoral factors, and vasoactive substances may also be involved (*12*).

Many clinical reports have suggested that BP is increased by excessive salt intake. However, the increase in BP due to excessive salt intake varies widely among individuals, and many people remain normotensive even on a high-salt diet. In fact, hypertensives can be classified into salt-sensitive and non–salt-sensitive groups, because the responses of BP to a high-salt or low-salt diet are not uniform (*14*, *15*). Many factors, including genetic interference, renal function, and neurohumoral elements, are involved in the salt sensitivity of BP.

Cardiovascular Diseases

Salt excess is related to the occurrence and progression of cardiovascular diseases through its BP-increasing effects, but it has also been shown that salt exerts adverse effects on the cardiovascular system by different mechanisms in addition to rise in BP (*16*) (Table 2). Excessive salt intake causes left ventricular hypertrophy and thickening of the vascular wall independently of its effects on BP. According to a report from Finland, mortality from ischemic heart disease, stroke and all causes increased significantly with increases in salt intake even after correction for BP or other factors (*17*) (Table 3). Furthermore, salt intake has been shown to be an independent risk factor of stroke and heart failure (*18*, *19*). Dietary salt may also relate to impairment of platelet aggregation and renal function (*15*), so that salt excess is considered to confer a greater risk of cardiovascular diseases than would be expected by a mere increase in BP.

Other Disorders

Excessive salt intake is also related to several other disorders (*16*) (Table 2). An increase in salt intake elevates the urinary calcium (Ca) excretion and the incidence of urolithiasis. This loss of Ca through the kidney also decreases Ca in the bone and increases the risk of osteoporosis. Moreover, a relation-

Table 2. Adverse Effects of Salt Independent of BP

Cardiovascular system
Left ventricular hypertrophy
Thickening/hardening of vascular wall
Platelet aggregation
Cardiovascular disorders
Stroke
Ischemic heart disease, Heart failure
Impairment of renal function
Other disorders
Urolithiasis
Osteoporosis
Stomach cancer
Asthma

ship between salt intake and stomach cancer has been suggested by epidemiological studies. A high-salt environment has recently been reported to promote the propagation of *Helicobacter pyroli*. A relationship between salt intake and asthma has also been suspected. Thus, excessive salt intake is considered to exert various adverse effects.

Antihypertensive Effect of Salt Restriction

There is much evidence based on clinical studies that restriction of salt intake reduces BP in hypertensives. In Japan, Ito *et al.* reported the results of moderate restriction of salt intake in a small number of subjects. Blood pressure decreased slightly but not significantly when salt intake was reduced from 13 g/day to 7 g/day but significantly when it was rigorously restricted to 3 g/day (*20*). All large-scale clinical studies to date have been performed in Europe or America. Significant decreases in BP were observed in the Trials of Hypertension Prevention (TOHP)-Phase I (TOHP-I) (*21*), the Trial of Nonpharmacologic Interventions in the Elderly (TONE) (*22*), a report from He *et al.* (*23*), and the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial (*24*), in all of which salt intake was reduced to less than 6 g/day (Table 4). But the decreases were not significant in the TOHP-II study (*25*), in which restriction of salt intake was milder. In the Hypertension Prevention Trial (HPT), salt intake was reduced to less than 6 g/day, but no significant decrease in BP was observed, probably because salt intake was also decreased in the control group (*26*). In the TONE, evaluations were also performed at various levels of salt restriction achieved, and salt intake to 5.64 g/day or less was effective for the maintenance of a normal BP after discontinuation of antihypertensive medication (*22*). On the basis of these results, many guidelines for the management of hypertension in Western countries recommend less than 6 g/day as a target for salt restriction (*1*, *2*).

According to a meta-analysis of randomized studies on the effect of moderate salt restriction, BP decreased by a mean of 5.0/2.7 mmHg in hypertensive subjects (*27*) (Fig. 3). The

Table 3. Hazard Ratios and 95% CI of Deaths Due to Ischemic Heart Disease, Stroke, and All Causes Associated with Increases in the Urinary Na Excretion (100 mmol/day) after Adjustment*

Cause of death	Hazard ratio (95% CI)
Ischemic heart disease	1.56 (1.15–2.12)
Stroke	1.36 (1.05–1.76)
All causes	1.22 (1.02–1.47)

*From Tumilehto *et al.* (*17*) with modification. CI, confidence interval; BP, blood pressure.

median urinary Na excretion was 161 mmol/day (conversion to salt: 9.5 g/day) on an unrestricted diet and 87 mmol/day (5.1 g/day) on a low-salt diet, with a median decrease in the urinary Na excretion of 78 mmol/day (4.6 g/day). In normotensive subjects, the mean decrease in BP was 2.0/1.0 mmHg, and the decrease in the urinary Na excretion was 74 mmol/day (4.4 g/day). A recent analysis showed a clear quantitative relationship between the degree of decrease in salt intake and BP in a salt intake range of 3–12 g/day (*27*). In hypertensives, the systolic BP is considered to decrease by about 1 mmHg with each decrease in salt intake of 1 g/day. If a person who has consumed salt at 12 g/day restricts salt intake to 6 g/day, a considerable decrease in BP is expected with a consequent decrease in the dose of antihypertensive medication and prevention of cardiovascular diseases.

There have been no large-scale clinical studies about the effects of salt reduction on BP in Japan. However, many short-term clinical studies have shown that the restriction of salt intake effectively lowers BP in hypertensive Japanese (*20*, *28–31*). The average reduction in mean BP with a low-salt diet in those studies was 5–10 mmHg, which was comparable to the results of a meta-analysis. It has been shown that there is a racial difference in the salt sensitivity of BP, with the sensitivity in blacks being greater than that in whites (*32*). Although there are no studies directly comparing the salt sensitivity among Japanese and other races, the salt sensitivity of BP in Japanese may be intermediate between those of blacks and whites.

However, the responses of BP to a decrease in salt intake show marked individual variation. The depressor effect of reduction in salt intake has been shown to be large in the elderly, patients with renal dysfunction, those with severe hypertension, and those with low-renin hypertension (*28*, *32*). However, because hypertension arises through the intricate interplay of many factors, it is not easy to predict the salt sensitivity of BP in individual patients, and evidence is not sufficient to warrant individualized recommendations of salt restriction.

Decreases in BP due to salt restriction are observed 24 h a day (*29*). Also, it has been reported that many salt-sensitive hypertensives are non-dippers, who show only small nocturnal decreases in BP, on a high-salt diet, but become dippers

Table 4. Antihypertensive Effects of Reductions in Salt Intake in Large-Scale Clinical Studies

Study (year of publication)	Subjects	Observation period	Group	Number of subjects	Intake or urinary excretion of salt (g/day)			Systolic BP (mmHg)			Diastolic BP (mmHg)		
					Before	After	Difference	Before	After	Difference	Before	After	Difference
HPT (1990) (*26*)	Healthy adults	6 months	Control	196	7.66	6.97	−0.69	123.9	121.8	−1.7±0.9	83.0	80.0	−0.4±0.7
			Salt reduction	196	7.55	5.89	−1.66	124.0	120.2	p=0.126	82.6	79.2	p=0.664
		3 years	Control	196	7.66	7.66	0	123.9	121.0	0.1±1.0	83.0	80.0	0.2±0.8
			Salt reduction	196	7.55	6.81	−0.74	124.0	121.2	p=0.885	82.6	79.8	p=0.8
TOHP-I (1992) (*21*)	Healthy adults*	6 months	Control**	417	9.20			125.1	121.9	−1.69	83.9	80.6	−0.85
			Salt reduction**	327	9.09	6.50	−2.59	124.8	119.9	p<0.01	83.7	79.6	p<0.05
TOHP-II (1997) (*25*)	Healthy adults	36 months	Control	596	11.95	11.33	−0.62	127.3	127.0	−0.4±0.4	85.8	83.4	−0.1±0.3
			Salt reduction	594	11.98	8.99	−2.99	127.7	127.0	p=0.24	86.1	83.2	p=0.68
TONE (1998) (*22*)	Healthy adults***	30 months	Control	147	8.53	8.51	−0.02		24.4%†	RR 0.69			
			Salt reduction	144	8.53	6.19	−2.34		37.8%†	p<0.001			
He *et al.* (2000) (*23*)	Healthy adults (from TOHP-I)	7 years	Control	70	8.69	7.5	−1.19	122.6	120.2	p=0.01	84.2	78.6	p=0.08
			Salt reduction	58	8.71	5.56	−3.15	122.7	117.0		83.8	76.6	
DASH-Sodium†† (2001) (*24*)	Healthy adults (including hypertensives)†††	30 days	DASH diet/Salt reduction	204	8.47	6.29	−2.18	128.1	126.8	p<0.001	83.1	82.5	n.s.
			Control/Salt reduction	208	8.29	6.24	−2.05	135.0	132.9	p<0.05	86.0	84.9	p<0.01

*Diastolic BP: 80–89 mmHg. **Frequency of hypertensives: 11.3% in the control group, 8.6% in the salt reduction group (RR 0.84, 95% CI 0.62–1.13). ***BP < 145/85 mmHg at ages 60–80 years. †Percentage of subjects not having reached the endpoint (diagnosis of hypertension, beginning of antihypertensive medication, cardiovascular event). ††Only the results of moderate salt reduction. †††BP > 120/80 mmHg, including mildly hypertensive (140–159/90–99 mmHg). BP, blood pressure; RR, relative risk; CI, confidence interval.

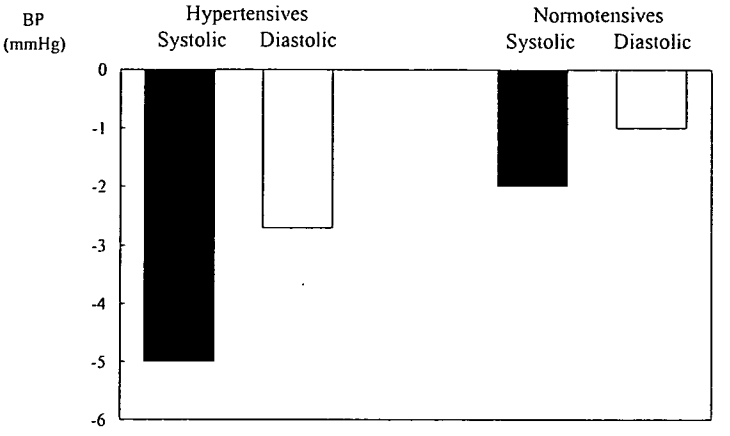

Fig. 3. *Effects of moderate salt reduction on BP according to a meta-analysis of randomized clinical trials (based on data of He et al. (27)).*

Table 5. Salt Reduction Accomplishment Rate in the TONE Study*

Salt reduction level	<5.6 g/day	>7.1 g/day
Control group	15.3%	67.7%
Salt reduction group	51.2%	29.7%
Weight control group	6.1%	79.6%
Salt reduction + weight control group	23.8%	49.0%

*From Espeland *et al.* (*36*) with modification.

with salt restriction (*31*).

Dietary intakes of potassium and sodium interact in the regulation of BP (*33*). Increasing potassium intake decreases BP mainly *via* natriuresis, and increasing sodium intake stimulates potassium excretion. A high potassium diet accomplished by means of fruit and vegetable intake is now widely recommended in the management of hypertension (*1*, *2*, *4*). The DASH-Sodium study has shown that a DASH (high potassium) diet and sodium restriction additively lower BP, but the effect of sodium restriction was greater under a normal diet than under the DASH diet (*24*). Thus a low sodium, high potassium diet is suitable for hypertensive subjects, but the BP-lowering effect of salt reduction appears to be attenuated by increasing potassium intake.

Restriction of salt intake also enhances the effects of some antihypertensive agents. This effect is particularly evident in inhibitors of the renin-angiotensin system. Sympatholytic agents are also expected to have similar effects.

An improvement of cardiovascular disease outcome can be expected with long-term restriction of sodium intake. The follow-up study of the TOHP-I and -II has shown that risk of a cardiovascular event is 30% lower among participants in the intervention (sodium restriction) group compared to those in the control group after adjustment for confounding factors (*34*). Therefore, sodium restriction not only lowers BP but may also reduce long-term risk of cardiovascular events.

Attainment and Maintenance of the Salt-Reduction

Lifestyle modifications, including salt restriction, are extremely important for the management of hypertension, but the difficulty of attaining and maintaining such changes is a problem (*35*). There have been few reports on the attainment rate of salt reduction in hypertensives, but in the TONE, a trial with elderly hypertensive subjects, the target of less than 5.6 g/day was attained by about half of the patients in the salt reduction guidance group and about 1/4 of the patients in the salt reduction plus weight control group (*36*) (Table 5). In Japan, in a trial in which physicians provided salt reduction guidance to hypertensives with a target of less than 6 g/day, mean salt intake decreased from 11.2 to 9.9 g/day, but the target was attained in only 12% of subjects (*10*, *35*). Also, while salt intake was lower in hypertensives intending to reduce salt intake than in those not intending, it was 9.4 and 10.6 g/day, respectively, with a minor difference (*11*). According to a report of the International Population Study on Macronutrients and Blood Pressure (INTERMAP), in Japanese subjects, among those practicing salt reduction, only 41.6% attained a target of less than 10 g/day, and the average salt intake estimated from the urinary Na excretion was 10.5 g/day (*37*). Therefore, attainment of the target of less than 6 g/day appears to be fairly difficult.

Limitations of long-term compliance to salt restriction and its effects have also been demonstrated. In the Treatment of Mild Hypertension Study (TOMHS), which provided 4-year lifestyle guidance to mildly hypertensive subjects, salt intake decreased by 2–3 g/day during the first year, but the decrease regressed to less than 1 g/day after 4 years (*38*). Moreover, a meta-analysis of long-term randomized interventional studies of 6 months or longer duration in normotensive and hyperten-

sive subjects showed that the mean decrease in salt intake was 2.1 g/day, and the mean decrease in BP was only 1.1/0.6 mmHg (*39*).

Salt-Reduction Target for the Management of Hypertension

Dietary salt appears to be related to hypertension, and excessive salt intake exerts adverse effects on the cardiovascular system independently of BP. While the antihypertensive effect of salt restriction is dependent on the degree of salt reduction, significant depressor effects have been confirmed at restriction levels of 6 g/day or less in large-scale clinical trials. Therefore, for the management of hypertension, the target of salt reduction should ideally be less than 6 g/day as in Western guidelines. In Japan, the target of salt reduction was set at 7 g/day or less in JSH 2000 (*3*) because of the traditionally high salt intake, but salt intake of Japanese has since decreased by about 1 g/day, so that it was considered reasonable to reset the target to less than 6 g/day in the subsequent JSH 2004 guidelines (*4*).

Presently, it appears to be difficult to attain the target of less than 6 g/day, but promotion of nationwide educational activities about the importance of the prevention and treatment of hypertension by salt restriction and its considerable preventive effect against cardiovascular and other diseases is considered to be a socially, economically, and medically important task. The establishment of feasible and effective measures by multi-faceted approaches is desirable for the attainment of the target of salt reduction.

Conclusions

Excessive salt intake is closely related to the occurrence and progression of hypertension, and it also exerts adverse effects on the cardiovascular system independently of BP. The depressor effect of salt restriction is dose-dependent, and despite marked individual variation, BP has been shown to decrease about 1 mmHg on average with each decrease in salt intake of 1 g/day. Salt reduction is important for the prevention and treatment of hypertension, and there is reasonable evidence in support of the current salt-restriction target of less than 6 g/day (Na < 100 mmol/day). Salt reduction is particularly important in Japan, a country with high salt intake, but attaining the new target has proven difficult in Japanese hypertensives. There is thus a need to establish new effective measures for attaining the target.

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