Original Article

Relationship between Home Blood Pressure and Longitudinal Changes in Target Organ Damage in Treated Hypertensive Patients

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Cross-sectional studies have shown that home blood pressure (BP) correlates with hypertensive target organ damage better than clinic BP. However, there have been few longitudinal studies regarding the predictive value of home BP on the changes in organ damage in treated hypertensive patients. Clinic and home BP over a 12-month period, antihypertensive medication use, echocardiographic and electrocardiographic results, and serum creatinine and urinary protein levels were examined in 209 treated hypertensive patients in 1993. These patients were prospectively followed for 5 years. The patients were divided into 4 subgroups according to hypertension control as follows: good control ($<140/90$ mmHg for clinic BP, $<135/85$ mmHg for home BP), improved, worsened, and poor control. The average clinic BP was $147.0 \pm 14.9/87.0 \pm 7.6$ mmHg (mean $\pm$ SD) in 1993 and $146.0 \pm 13.7/84.1 \pm 7.5$ mmHg in 1998. The average home BP was $136.8 \pm 10.4/84.3 \pm 7.6$ mmHg in 1993 and $136.1 \pm 9.7/81.2 \pm 7.7$ mmHg in 1998. The left ventricular mass index (LVMI) positively correlated with both home systolic BP and clinic systolic BP in 1998 but not in 1993. The correlation tended to be closer for home BP than for clinic BP. LVMI did not change in patients with good or improved home systolic BP, while it increased in those with poor or worsened home systolic BP. The relationship between changes in LVMI and clinic BP was not significant. In conclusion, Home BP was more effective than clinic BP as a predictor of changes in left ventricular hypertrophy in treated hypertensive patients. Home BP should be controlled to below 135/85mmHg to prevent cardiac hypertrophy.

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Key Words: home blood pressure, hypertension, cardiac hypertrophy, proteinuria, antihypertensive therapy

Introduction

Hypertension induces both reversible and irreversible changes in the structure and function of vital organs such as the brain, heart and kidney. It has been shown that left ventricular hypertrophy (LVH) is a powerful predictor for cardiovascular morbidity and mortality (1–4), and that antihypertensive therapy induces regression of LVH (5–9). It has also been shown that the presence of proteinuria or microalbuminuria is associated with an increased risk of cardiovascular complications (10, 11).

Diagnosis and treatment of hypertension has generally been based on casual blood pressure (BP) as measured by physicians or nurses. Along with the increasing availability of electronic devices for home BP measurement, self-measurement of BP at home has become the preferred method in many countries. Home BP measurement appears to be superior to office BP determination because it provides multiple BP records under relatively stable conditions and is not susceptible to a white coat effect (12).

Cross-sectional studies, including our own, have shown that the target-organ damage of hypertension is more closely related to home BP than to clinic BP (12, 13). Similarly,

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population-based prospective studies have also shown that cardiovascular morbidity and mortality are more closely related to baseline home BP than to baseline clinic BP (14–17). However, there have been no longitudinal studies on the predictive value of home BP for assessing changes in target organ damage in treated hypertensive patients.

Accordingly, we here examined the relationship between changes in organ damage in the heart and kidney and home and clinic BP measurements during a 5-year prospective follow-up in treated hypertensive patients. We also studied the effects of the use of different classes of antihypertensive drugs on the course of organ damage in the same cohort.

Methods

Patients

In 1993, a baseline survey was carried out in 282 hypertensive subjects (154 males and 128 females, 31–86 years old) who measured their BP at home almost every day. All of these patients had previously been treated with antihypertensive drugs at the hypertension clinic of our institute, and visited the clinic monthly or bimonthly. Informed consent was obtained from all subjects. The type and doses of antihypertensive agents were determined by the respective attending physicians. Five years later, in 1998, we were able to obtain clinical results for 209 of these patients (110 males and 99 females; mean age, 62.1 ± 8.9 years), who made up the present study group. Movements and referrals to other clinics were the main reason for the loss of patients for follow-up ($n = 67$). There were 6 deaths, including 5 cardiovascular deaths (2 from myocardial infarction, 1 from cerebral hemorrhage, 1 from rupture of aortic aneurysm, and 1 sudden death) during the 5-year period.

Study Design

The present study was carried out with a prospective follow-up design combined with a cross-sectional analysis. We examined home and clinic BP and hypertensive organ damage in 1993 and 1998. The measured parameters of target organ damage were left ventricular mass index (LVMI) as determined by echocardiography, the sum of SV1 + RV5 voltage in the electrocardiogram, and the levels of serum creatinine, urinary protein and 24-h urinary albumin excretion.

The patients were divided into 4 subgroups according to the status of hypertension control: good control ($< 140/90$ mmHg for clinic BP and $< 135/85$ mmHg for home BP (18) in both 1993 and 1998), improved control ($\geq 140/90$ mmHg in 1993 and $< 140/90$ mmHg in 1998 for clinic BP, $\geq 135/85$ mmHg in 1993 and $< 135/85$ mmHg in 1998 for home BP), worsened control ($< 140/90$ mmHg in 1993 and $\geq 140/90$ mmHg in 1998 for clinic BP, $< 135/85$ mmHg in 1993 and $\geq 135/85$ mmHg in 1998 for home BP), and poor control ($\geq 140/90$ mmHg for clinic BP and $\geq 135/85$ mmHg for home

BP in both 1993 and 1998).

Measurement of BP

Clinic BP was measured twice by physicians using a mercury sphygmomanometer with the patient in a seated position at each visit. The first and fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. For all of these parameters, the average of the values over a 12-month period (1993 or 1998) was calculated and used for the subsequent analysis.

Patients measured their own home BP using an automatic oscillometric device. Home BP was measured in the early morning before taking breakfast or morning drugs, and again in the late evening almost every day. The home BP records were presented at each visit and were stored with the patients' medical charts. The morning, evening and the mean values for 7 days in the middle of each month were calculated as the monthly averages. Then the averages for the 12 months in 1993 and 1998 were calculated and used for the analysis.

Estimation of Target Organ Damage

Two-dimensional echocardiography was performed with cardiac ultrasound machines (SONOS5500, Hewlett Packard Inc., Andover, USA and SONOLAYER α SSA-260A, Toshiba Inc., Tokyo, Japan) according to the recommendations of the American Society of Echocardiography (19). End-diastolic interventricular septum thickness (IVSTd), end-diastolic posterior left ventricular wall thickness (PWTd), and end-diastolic and end-systolic left ventricular internal dimensions (LVDd and LVDs) were measured. The left ventricular mass (LVM) was estimated using the following formula from Devereux and Reichek (20):

$$\text{LVM(g)} = 1.04 \times ((\text{IVSTd} + \text{PWTd} + \text{LVDd})^3 - \text{LVDd}^3) - 13.6.$$

The left ventricular mass index (LVMI) was calculated by dividing LVM by body surface area. Relative wall thickness (RWT), a measure of left ventricular geometry, was calculated as:

$$\text{RWT} = (2 \times \text{PWTd})/\text{LVDd}.$$

The images were made and analyzed by a single experienced physician who was unaware of the clinical findings of the subjects. Some cases were excluded from the analysis because the echocardiographic images were technically unsatisfactory.

A twelve-lead electrocardiogram (ECG) at rest was obtained as another estimation of left ventricular hypertrophy. Mean R- and S-wave amplitudes (mm) were measured for 5 beats and used to calculate the Sokolow-Lyon voltage (SV1 + RV5). We divided the patients into 3 groups: a normal group in which the value of SV1 + RV5 was below 35 mm, a left ventricular high voltage group in which SV1 + RV5 was above 35 mm without a strain pattern in repolarization, and a left ventricular hypertrophy group in which SV1 + RV5 was above 35 mm with a strain pattern in repo-

Table 1. Clinic and Home Blood Pressure

		1993	1998
Clinic	SBP (mmHg)	147 ± 15	146 ± 14
	DBP (mmHg)	87 ± 8	84 ± 8***
Morning home	SBP (mmHg)	139 ± 11	138 ± 11
	DBP (mmHg)	86 ± 8	83 ± 8***
Evening home	SBP (mmHg)	135 ± 12	134 ± 11
	DBP (mmHg)	82 ± 8	79 ± 8***
Average home	SBP (mmHg)	137 ± 10	136 ± 10
	DBP (mmHg)	84 ± 8	81 ± 8***

Values are shown as the mean ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure. *** $p < 0.001$ vs. 1993.

larization.

Renal involvement was estimated by the levels of serum creatinine (Cr) and by the presence of proteinuria and microalbuminuria. Serum Cr was determined from fasting blood samples using an autoanalyzer. The presence of proteinuria was examined by the dip stick method from the spot urine samples. Urinary albumin excretion was determined from the 24-h urine samples in a subset of patients. A quantity of 30–300 mg/day was considered to indicate the presence of microalbuminuria.

Data Analysis

Urinary albumin excretion was changed to the logarithmic value to approximate the normal distribution. Continuous variables (LVMI, RWT, SV1 + RV5, serum Cr and urinary albumin excretion) were evaluated by parametric Pearson's correlation coefficients, and categorical parameters (the positive rate of LVH in ECG and the presence of proteinuria) were evaluated by nonparametric Spearman rank correlation coefficients. Differences among continuous variables were tested by Student's *t*-test for paired observations, and by ANOVA with Scheffe's correction for repeated comparisons. The changes in the categorical parameters were analyzed by the Wilcoxon signed rank test. Statistical analysis was performed using StatView Version 4.5 Software (Abacus Concepts Inc., Berkeley, USA). Values were expressed as the mean ± SD. A value of $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline Characteristics

The average age of the 209 patients was 62.1 ± 8.9 years old in 1993, and 52.6% of the patients were male. The percentages of patients with a smoking habit, drinking habit, type 2 diabetes or hyperlipidemia were 18.7, 45.9, 13.4 and 69.4%, respectively.

At both the baseline period and 5 years later, Ca antago-

Table 2. Status of Target Organ Damage

Variables	<i>n</i>	1993	1998
LVMI (g/m ²)	90	131 ± 29	136 ± 32
RWT	93	0.43 ± 0.1	0.47 ± 0.1***
SV1 + RV5 voltage (mm)	170	34 ± 9	32 ± 9***
LVHV	170	40%	37%
Serum Cr (mg/dl)	164	0.75 ± 0.2	0.72 ± 0.2*
u-Alb (mg/g Cr)	67	35 ± 60	38 ± 66
Proteinuria	158	9%	14%

LVMI, left ventricular mass index; RWT, relative wall thickness; LVHV, left ventricular high voltage; Cr, creatinine; u-Alb, urinary albumin. * $p < 0.05$, *** $p < 0.001$ vs. 1993.

nists were the most frequently used antihypertensive medication (74% in 1993 and 79% in 1998), followed by β -blockers (40% and 40%), angiotensin converting enzyme (ACE) inhibitors (24% and 25%), diuretics (18% and 24%) and α -blockers (12% and 17%). The number of patients receiving monotherapy was 93 (44.5%) in 1993 and 77 (36.8%) in 1998.

BP and Target Organ Damage Status in 1993 and 1998

Clinic and home BP values in 1993 and 1998 are shown in Table 1. Home systolic BP (SBP) and diastolic BP (DBP) were higher in the early morning than in the late evening ($p < 0.001$). The changes in clinic and home SBP were not significant, but clinic and home DBP decreased significantly over the 5-year period ($p < 0.001$).

The target organ damage status in 1993 and 1998 is shown in Table 2. The change in LVMI was not significant, but the increase in RWT was significant ($p < 0.001$). Although the rate of electrocardiographical LVH did not change, the average SV1 + RV5 voltage decreased. The level of serum Cr decreased significantly during the 5-year period ($p < 0.05$), while neither urinary albumin nor the rate of proteinuria changed significantly.

Relationship between BP and Target Organ Damage

In 1993, the relationship between the levels of BP and the degree of damage to each target organ was not significant, with the exception of weak correlations between clinic SBP and SV1 + RV5 voltage ($r = 0.18$, $p = 0.02$), and between home SBP and proteinuria ($R_s = 0.18$, $p = 0.03$).

In 1998, LVMI was positively correlated with morning home SBP, average home SBP, and clinic SBP (Table 3). The relationship tended to be closer for home SBP than for clinic SBP. RWT also related with home SBP, but not with home DBP or clinic BP. LVMI and serum Cr were inversely related with evening home DBP and with clinic DBP. The correlations between DBP and LVMI or serum Cr disappeared when they were adjusted by age. Urinary albumin tended to correlate with clinic and home SBP. The rate of proteinuria

Table 3. Relationship between BP and Target Organ Damage in 1998

		LVMI	RWT	SV1 + RV5	LVHV	Serum Cr	log(u-Alb)	Proteinuria
Clinic	SBP	0.27**	0.09	0.18*	0.13	- 0.10	0.23	0.09
	DBP	- 0.29**	- 0.16	0.00	- 0.02	- 0.18**	- 0.05	- 0.09
Morning home	SBP	0.38***	0.34***	0.15	0.19*	0.02	0.23	0.21*
	DBP	- 0.08	- 0.01	0.02	- 0.04	- 0.13	- 0.19	- 0.12
Evening home	SBP	0.18	0.27*	0.10	0.18*	- 0.02	0.23	0.24**
	DBP	- 0.24*	- 0.08	- 0.12	- 0.12	- 0.19*	- 0.20	- 0.04
Average home	SBP	0.32**	0.35***	0.14	0.20**	- 0.02	0.23	0.25**
	DBP	- 0.17	- 0.03	- 0.03	- 0.05	- 0.19*	- 0.19	- 0.07

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index; RWT, relative wall thickness; LVHV, left ventricular high voltage; Cr, creatinine; u-Alb, urinary albumin. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig. 1. Changes in LVMI in subgroups according to SBP control. SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index.

was correlated with home SBP but not with clinic BP.

The left ventricular mass index did not change in patients with good and improved BP, while it increased in the poor and worsened BP groups (Fig. 1). The changes in LVMI between the subgroups were significant in the case of home BP classification but not in the case of clinic BP. The difference in changes in LVMI between the good + improved group and the worsened + poor group was highly significant for home BP, but not for clinic BP (Table 4). The differences in the changes in RWT, SV1 + RV5 voltage, LVH on ECG, serum Cr, urinary albumin excretion, and proteinuria between these groups were not significant for either clinic BP or home BP.

The Influence of Antihypertensive Agents

LVMI tended to decrease in patients who received ACE inhibitors, and to increase in those who did not (Table 5).

There was a significant difference in LVMI between these two groups. Such a difference was not seen in other classes of agents. Urinary albumin excretion tended to decrease in β -blocker users but increased in non-users. A similar difference was observed between users and non-users of ACE inhibitors, but this difference did not reach the level of statistical significance.

Discussion

In the present study, we examined the levels of clinic and home BP, the use of antihypertensive agents, and target organ damage over a 5-year follow-up period in treated hypertensive patients. We found that home BP was more closely related to organ damage, especially LVMI, than clinic BP both cross-sectionally and longitudinally. The present findings confirmed the value of self-measurement of BP at home and the importance of strict control of BP in the management

Table 4. Changes in Target Organ Damage in Subgroups According to the Control of Clinic and Home SBP

	Good + Improved	Worsened + Poor	<i>p</i>
Clinic SBP control			
<i>n</i>	75	134	
Δ LVMI	- 2.7 ± 33	10.6 ± 31 *	0.06
Δ RWT	0.03 ± 0.08	0.04 ± 0.08 ***	0.34
Δ SV1 + RV5 (mm)	- 2.1 ± 5.1 **	- 1.3 ± 6.0 *	0.37
LVHV (%)	42 30	46 39	—
Δ Serum Cr (mg/dl)	- 0.03 ± 0.15	- 0.03 ± 0.15	0.80
Δ log(u-Alb)	0.01 ± 0.66	0.23 ± 0.73 *	0.25
Proteinuria (%)	6 13	12 15	—
Home SBP control			
<i>n</i>	100	109	
Δ LVMI	- 5.7 ± 30	17.2 ± 31 ***	0.0006
Δ RWT	0.03 ± 0.09 *	0.05 ± 0.08 ***	0.29
Δ SV1 + RV5 (mm)	- 2.2 ± 6.1 **	- 1.1 ± 5.3	0.20
LVHV (%)	35 27	45 47	—
Δ Serum Cr (mg/dl)	- 0.03 ± 0.12 *	- 0.02 ± 0.17	0.63
Δ log(u-Alb)	0.07 ± 0.62	0.22 ± 0.77	0.39
Proteinuria (%)	5 8	13 21	—

SBP, systolic blood pressure; LVMI, left ventricular mass index; RWT, relative wall thickness; Cr, creatinine; u-Alb, urinary albumin.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. baseline. p : p value between the two groups.

Table 5. Changes in LVMI and Urinary Albumin Excretion According to the Kind of Antihypertensive Agents

Antihypertensive agents	Changes in LVMI		Changes in log(u-Alb)	
	Use (<i>n</i>)	Non-use (<i>n</i>)	Use (<i>n</i>)	Non-use (<i>n</i>)
Calcium antagonist	8 ± 35 (67)	- 4 ± 23 (23)	0.2 ± 0.8 (53)	0.1 ± 0.5 (14)
ACE-inhibitor	- 8 ± 38 (25)	10 ± 29 (65) *	- 0.1 ± 0.7 (14)	0.2 ± 0.7 (53)
β-Blocker	10 ± 30 (35)	2 ± 34 (55)	- 0.1 ± 0.6 (25)	0.3 ± 0.7 (42) *
α-Blocker	3 ± 33 (17)	6 ± 33 (73)	0.1 ± 0.7 (15)	0.2 ± 0.7 (52)
Diuretics	5 ± 37 (24)	5 ± 31 (66)	- 0.1 ± 0.4 (16)	0.2 ± 0.8 (51)

LVMI, left ventricular mass index; u-Alb, urinary albumin. * $p < 0.05$, vs. use.

of hypertension.

Levels of Clinic and Home BP

In the present study, average clinic SBP was above 140 mmHg although the average clinic DBP was below 90 mmHg. The levels of clinic BP were similar to those observed in treated hypertensive patients in a multicenter study in Japan (21). In a subsequent study, it was found that many treated patients still had higher than normal BP, and that control of SBP to below 140 mmHg was less frequently achieved than control of DBP to below 90 mmHg (22). As in previous studies (12, 23), the level of home BP was lower than that of clinic BP in the present study, and the differences between clinic BP and home BP were about 10/3 mmHg. However, the average levels of home SBP were also higher than 135 mmHg, which is the diagnostic criterion suggested by the Joint National Committee (18).

During the 5-year period, the average levels of clinic and home BP decreased by - 1.0/ - 3.0 mmHg and - 0.7/ - 3.1 mmHg, respectively, indicating better control of hypertension. SBP continued to elevate but DBP decreased with age in the elderly. The relatively greater reduction in DBP may have been partly due to the aging process.

Blood Pressure and Target Organ Damage

In the cross-sectional analysis of the present study, echocardiographically determined LVMI and RWT were more closely related to home BP than clinic BP, confirming previous reports of the value of home BP measurements (12, 13). The present findings also confirmed the importance of SBP over DBP (24), since the cardiac measurements were positively associated with SBP but were inversely related with DBP. However, the correlations between home or clinic BP and the parameters of organ damage were not particularly

good, suggesting that BP measurement alone may have limited value for the prediction of target organ damage in hypertensive patients.

In the longitudinal analysis, average LVMI did not change but RWT increased during the 5-year period. The lack of overall regression of LVMI or RWT may have been related to the finding that the patients in the present study were already being treated with antihypertensive agents in 1993. In addition, the average LVMI was not particularly large and many patients showed normal cardiac mass. However, the changes in LVMI and RWT in treated hypertensive patients depended on the control of BP. These variables remained stable or tended to decrease in the good and improved groups, while they increased in the poor and worsened groups.

The present study also showed the superiority of home BP to clinic BP in the prediction of the changes in cardiac mass during long-term antihypertensive therapy. Strict BP control appears to be necessary in order to achieve LVMI regression in treated hypertensive patients. The present findings indicate that home BP should be reduced to below 135/85 mmHg for the prevention of cardiac hypertrophy.

Previous studies have shown that LVMI reduction is associated with a decrease in cardiovascular events. Koren *et al.* reported that cardiovascular events occurred in 31% of patients whose LVM increased during the follow-up period but only 11% of patients whose LVM decreased (8). Muiesan *et al.* also showed that the cumulative incidence of non-fatal cardiovascular events was significantly higher in the group of patients without regression of LVH (25).

In the present study, the prevalence of electrocardiographically determined LVHV did not change during the 5-year period, although the sum of SV1 + RV5 voltage decreased. However, the prevalence of LVHV tended to decrease in the good and improved groups, supporting the regression of LVH by effective antihypertensive therapy. Neither the prevalence of LVHV nor the sum of SV1 + RV5 decreased in either the poor or the worsened group. The accuracy of ECG in detecting LVH was inferior to that of the echocardiographic method, since many factors such as body weight, lung tissue changes, and amount of subcutaneous fat influence the voltage of the ECG wave. However, Levy *et al.* analyzed the findings of the Framingham Heart Study, and observed that the decrease in electrocardiographic LVH was associated with a reduction in cardiovascular risk (26).

In the present study, the level of serum Cr decreased during the 5-year period, but the change in Cr could not be predicted by the status of BP control. The decrease in serum Cr may have been due to an aging-related loss of muscle mass rather than an improvement of renal function.

The presence of proteinuria and microalbuminuria not only reflects hypertensive renal damage but also indicates high cardiovascular risk (27). The positive rate of proteinuria was more closely associated with home BP than clinic BP in the cross-sectional analysis, although the association of proteinuria with the status of BP control was not significant in the

longitudinal analysis. Urinary albumin excretion did not change during the 5-year period in any of the experimental groups. However, the urinary albumin tended to increase in the patients with poor and worsened home SBP, supporting the importance of strict BP control for the prevention of target organ damage.

Antihypertensive Drugs and Target Organ Damage

Although most antihypertensive agents are clinically useful, their effects on target organ damage appear to be different. It has been shown that ACE inhibitors are more powerful than other classes of drugs in terms of achieving LVH regression (28, 29). It has also been shown that ACE inhibitors effectively reduce urinary albumin excretion in patients with diabetes nephropathy and other forms of renal disease (30, 31).

In the present study, a significant difference in the changes in LVMI was observed between users of ACE inhibitors and nonusers, while such a difference was not seen in other classes of agents. A similar tendency was also observed for the changes in urinary albumin between ACE inhibitor users and nonusers, although this difference was not significant. The present findings may support the advantage of ACE inhibitors over other antihypertensive agents in the prevention of organ damage in hypertensive patients, although the influence of other confounding factors on the observed difference cannot be excluded. Beta-blockers appeared to be effective in the reduction of urinary albumin but not in the regression of LVH in the present study. Although the reason for these different effects was unclear, a previous study reported that β -blockers were as effective as an ACE inhibitor in reducing proteinuria in hypertensive patients with glomerulonephritis (32).

In conclusion, the findings of the present study demonstrated that the levels and changes in left ventricular mass were predicted more closely by home BP than by clinic BP in treated hypertensive patients. To prevent the progression of left ventricular hypertrophy, home BP should be controlled to below 135/85 mmHg. Finally, ACE inhibitors may be more effective than other classes of agents for the prevention of hypertensive heart disease.

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