種の白衣現象の現れとして評価の対象とする。
＊正常者においても健康管理の観点からたとえ月1回の測定でも家庭血圧の生涯測定が望ましい。
＊臨床薬理学的な一連の研究のなかでは測定頻度は可能なかぎり多いことが望ましいが，その際も測定条件は一連の研究の中では統一されなければならない。

6. 記録

すべての測定値は時刻，心拍数とともに記録されることが望ましい。記録に対象のバイアスを入れてはならない。将来電子メモリーが最も適切な記録法になろう。

7. 集計

記録されたすべての血圧値のうち，朝，晩それぞれ最初の1回目の記録の平均値をある測定期間で算出する。朝と晩の家庭血圧値はそれぞれ別個に集計評価する。

臨床研究では基準として1週間連日測定し，その最後の5日間の平均（朝晩それぞれ，あるいは両者の平均）を用いる。薬効評価時には1週間に少なくとも5日間の記録をとり，その平均を用いる。

日常診療では，1機会に複数回測定された血圧値の評価を行うことも大切である。

＊一般に測定者は，1機会に複数回測定し，最も低い値を医師に報告するという心理的傾向がある。したがって，このようなバイアスを取り除く意味で，1機会における測定値はすべて記録され，報告されることが望ましい。臨床評価にはすべての施設，対象で共通の1機会における最初の1回目の血圧値の長期にわたる血圧値が適当である。家庭血圧測定は，1機会に複数回の測定を求めるよりも，長期間にわたる測定を求めるべきである（各機会の1回目の測定は，あらゆる状況における，あるいはあらゆる施設における共通の測定となる。事実，家庭血圧の世界基準の根拠となったいくつかの臨床疫学研究では朝晩それぞれ1回ずつの測定を行っている。また必ず複数回の測定を求めることは，測定コンプライアンスの低下に連なる）。

8. 評価

家庭血圧は135/80 mmHg以上をもって高血圧と診断し，135/85 mmHg以上なら確実な高血圧として降圧治療の対象とする。一方，家庭血圧は125/80 mmHg未満を正常とし，125/75 mmHg未満を確実な正常血圧と判定する。この正常血圧基準は降圧目標レベルではない。降圧目標レベルに関しては大規模介入試験の成績をまたねばならない。

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検査・診断

10

白衣高血圧と仮面高血圧——家庭血圧による診断と管理

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高血圧管理における家庭血圧測定の意義は大きい

家庭血圧の測定は高血圧の管理において有用であり，外来血圧だけではわからない白衣高血圧，白衣現象や仮面高血圧，逆白衣現象を診断できることの意義は大きい．ここでは，白衣高血圧や仮面高血圧の家庭血圧による診断と管理について，実例を含めてポイントや注意点を示したい．

白衣高血圧と仮面高血圧は家庭血圧か24時間血圧を測らなければ診断できない

高血圧の診断基準は，外来での随時血圧では140/90 mmHg以上であり，家庭血圧では135/85 mmHg以上とされている．ただし，どれも時間をおいての複数回の測定により診断する必要がある．

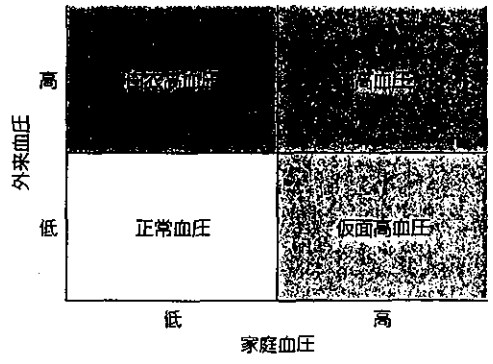
外来血圧と家庭血圧（あるいは24時間血圧）からみれば，血圧の分類は❶のようになる．すなわち，両者とも低い正常血圧，両者とも高い高血圧（真の高血圧），外来では高いが家庭では低い白衣高血圧（診察室高血圧），外来では正常であるが家庭では高い仮面高血圧（逆白衣高血圧）に分けられる．白衣高血圧と仮面高血圧は，家庭血圧（あるいは24時間血圧）を測らなければ診断することができない．

一般に，家庭血圧は外来血圧より低いことが多い（❷）．高血圧患者における両者の差は，平均すると10/5 mmHg程度であるが，50 mmHg以上にもなる場合もあり，個人差が大きいことに留意する必要がある．少数ではあるが家庭血圧が外来血圧より高い例もあり，その頻度は家庭血圧の基準を低くすればより高くなる．

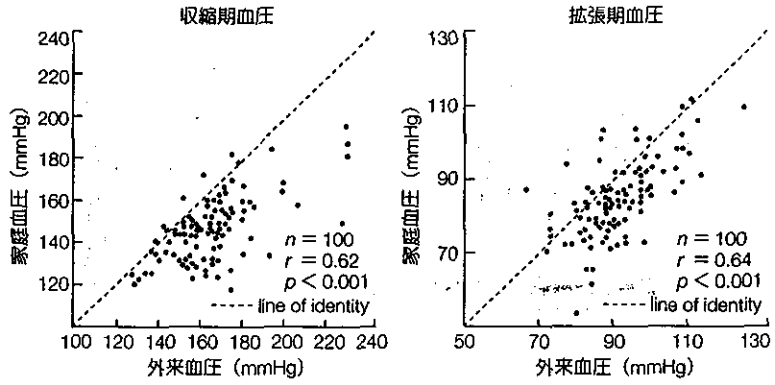
白衣高血圧と白衣現象

白衣高血圧　病院や診察室では高血圧を呈するが家庭血圧や24時間血圧が正常な白衣高血圧は，以前からよく知られている．外来での高血圧は継続して認められ，繰り返しの測定により血圧が低下する慣れの現象とは異なる．また，ほとんどは医療施設や医師の存在に限定された血圧上昇であり，機序として条件づけられた警鐘反応が示唆されている．白衣高血圧が有害か無害かについては議論があるが，予後は真の高血圧よりはるかに良好と考えられる．白衣高血圧の管理については，一般には降圧薬は不要であり，生活習慣指導と経過観察でよいであろう．しかし，臓器障害を伴う場合や真の高血圧に進展した場合は，薬物療法の適応となる．

白衣現象　血圧が受診時や医師の存在下に上昇する白衣現象（白衣効果）は，真の高血圧者においてもよく認められる．❸にその1例を示す．少量の降圧薬内服下での家庭血圧は130/80 mmHg程度であり，外来血圧は約180/110 mmHgと高い．夏にめまいを感じたときの血圧は，110/70 mmHgと低値であった．このような例では，家庭血圧を測ることがなく外来血圧を基準に降圧治療を行えば，不要な降圧薬を大量に用いて日常生活における過剰な降圧をきたす

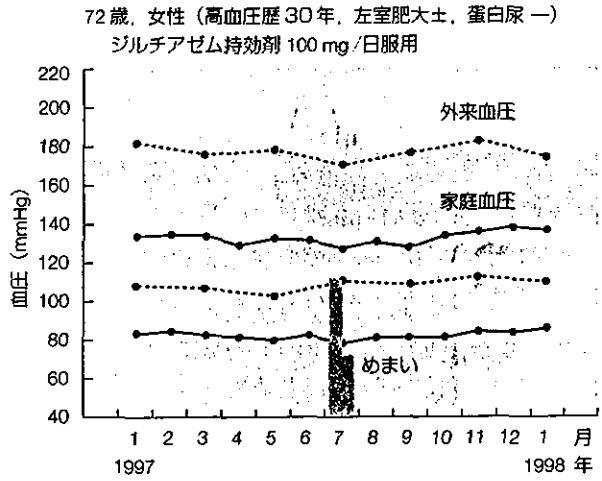


❶外来血圧と家庭血圧による高血圧の分類

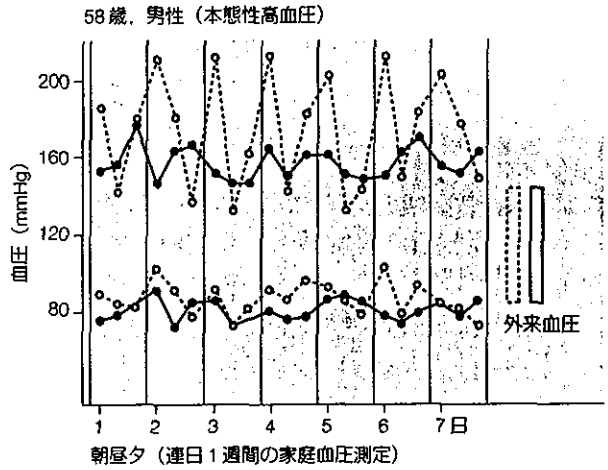


❷未治療の患者100人における外来血圧と家庭血圧の関係

（Abe H, et al：J Clin Hypertens 1987；4：661～669）



❸白衣現象の著明な高血圧症例の1年間の外来血圧と家庭血圧
（河野雄平：今月の治療 1999；7：21-25）



降圧薬変更前
ニカルジピン 80mg 4×
フロセミド 40mg 1×
メトプロロール 120mg 2×
プラゾシン 3mg 3×

降圧薬変更後
ニフェジピンSR錠 80mg 4×
フロセミド 80mg 1×
メトプロロール 120mg 2×

❹短時間作用型の降圧薬により逆白衣現象を示した高血圧症例
（河野雄平：今月の治療 1999；7：21-25）

可能性がある．

仮面高血圧と逆白衣現象

仮面高血圧　検診や外来では正常血圧であるが家庭や24時間（日中）では高血圧を呈する状態で，最近注目されている．頻度は正常血圧と判定された者の10％近いと報告されている．その機序は明らかではないが，ストレスや飲酒，喫煙などの生活習慣が関与していると思われる．仮面高血圧者は，正常血圧者より臓器障害が多く予後も不良であることが明らかになってきた．管理方針としては，生活習慣の改善を指導し，なおも家庭血圧が高ければ薬物治療の適応になると考えられる．

逆白衣現象　日常診療でしばしば経験されるのが，外来血圧に比べて家庭血圧が高い逆白衣現象を示す高血圧者である．これは生活習慣によることもあるが，降圧治療の結果として生じる場合も多く，注意を要する．❹に例を示すが，短時間作用型の降圧薬での治療時には，外来血圧はほぼコントロールされているが，家庭血圧では著しい早朝高血圧を呈している．より長時間作用型の薬剤への変更により，早朝の血圧上昇は改善された．このような例では，降圧薬の作用時間や服薬時刻に考慮すべきであろう．

家庭血圧測定により，よりよい治療と早期発見が可能となる

白衣高血圧と白衣現象，仮面高血圧と逆白衣現象について述べた．これらの診断と管理は家庭血圧や24時間血圧の測定なしではなされえず，また日常診療においては家庭血圧で十分であろう．家庭血圧の測定により，個々の高血圧患者へのよりよい治療とともに，家族を含めての測定により高血圧や仮面高血圧の早期発見が可能となろう．

CLIN. AND EXPER. HYPERTENSION, 24(1&2), 33–39 (2002)

EFFECTS OF ALCOHOL CONSUMPTION AND RESTRICTION ON HOME BLOOD PRESSURE IN HYPERTENSIVE PATIENTS: SERIAL CHANGES IN THE MORNING AND EVENING RECORDS

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ABSTRACT

To study the time course of alcohol effects on blood pressure (BP), we examined morning and late evening home BP for 4 weeks in a regular alcohol consumption period and for 4 weeks in a alcohol restriction period in 30 Japanese men with essential hypertension (52 ± 2 years, $m \pm SE$) in a randomized crossover study. Mean daily intake of alcohol were 66.5 ± 4.7 and 10.2 ± 1.9 ml, respectively. At the end of the regular alcohol period, morning BP had increased by $4.4 \pm 1.1/2.9 \pm 0.8$ mmHg but evening BP had decreased by $7.4 \pm 1.9/5.7 \pm 1.7$ mmHg. The depressor effect of alcohol on the evening BP was evident from day 1 to week 4, while the pressor effect on the morning BP was significant from week 2 regardless of the order of the two periods. These results confirm the biphasic effect of alcohol on BP, and suggest that the status of alcohol intake may markedly influence the morning–evening BP difference.

Key Words: Alcohol; Hypertension; Home blood pressure; Circadian variation

INTRODUCTION

The relationship between alcohol and hypertension is well known, and the restriction of alcohol intake is widely recommended in the management of hypertension (1,2). However, blood pressure (BP) often falls after the ingestion of alcohol. Ethanol has both vasoconstrictive and vasodilative actions, and a

metabolite of ethanol, acetaldehyde, is a vasodilator (3). In our previous study using ambulatory BP monitoring, a single intake of alcohol was found to lower BP for several hours in Japanese men with hypertension (4). This depressor effect of alcohol was more marked in patients with alcohol-induced flush than those without alcohol flush. We have also observed that a repeated intake of alcohol causes biphasic changes in BP without alteration in the mean 24-hour BP in hypertensive patients (5,6). The depressor effect of alcohol may be specific to Asian subjects since it appears to be absent or very small in Caucasians (7,8). These findings suggest that the effects of alcohol on BP depend on several factors such as the amount and duration of alcohol consumption, the time interval since the last drink, and genetic variations of aldehyde dehydrogenase.

To date, the time-related changes in BP after alcohol consumption or restriction have not been clarified well. Self measurements of home BP have been suggested as suitable to investigate serial changes in BP with lifestyle modifications because they can be determined everyday and small changes in BP can be detected (9,10). In the present study, we examined the effects of alcohol consumption and restriction by monitoring home BP in habitual drinkers with hypertension using a randomized crossover method.

SUBJECTS AND METHODS

Subjects

Thirty Japanese male habitual drinkers with essential hypertension aged between 36 and 76 years old (52 ± 2 years, $m \pm SE$) participated in this study. All of the subjects consumed alcohol in the evening, and no subjects drank in the morning or afternoon. Among these 30 subjects, 6 were untreated and 24 were treated with antihypertensive drugs. Pharmacological therapy was continued without changes throughout the study. Informed consent was given by each patient after explanation of the study protocol.

Protocol and Measurements

The subjects were assigned to keep their usual drinking habits for 4 weeks and to abstain or reduce alcohol intake to less than 15 ml/day (one can of beer or equivalent drink) in a randomized crossover manner. Daily alcohol consumption was recorded by each subject throughout the study. Home BP was measured in the sitting position by the patients with electronic devices 3 times in the early morning (before breakfast) and 3 times in the late evening (at least 2 hours after dinner) almost everyday throughout the study period. The average of the 3 measurements was calculated and was listed on the reporting sheet by the patients. Home heart

rate was measured in 15 out of the 30 patients. Office BP and body weight were measured at the end of the regular-alcohol and low-alcohol periods. Office BP was measured twice in the sitting position by physicians with a mercury sphygmomanometer. Fasting blood samples were also collected at the end of both periods. Serum γ-glutamyl transpeptidase and other biochemical variables were determined with an autoanalyzer.

Data Analysis

For the analysis of office BP, the average of the two measurements were used. For the analysis of home BP, the average of the last 3 days were used excluding data from the first day of each period. Data are expressed as means and SEM. Student's paired *t*-test was used for the comparison of data between the two groups. Repeated measures analysis of variance followed by the contrast method was used for the analysis of home BP profiles. A P value of < 0.05 was considered significant. Analyses were performed using Stat View and Super ANOVA software (Abacus Concepts Inc., Berkeley, USA).

RESULTS

The amount of average alcohol intake was reduced to one sixth in the low-alcohol period (Table 1). Serum levels of γ-glutamyl transpeptidase were significantly lower in the low-alcohol period than in the regular-alcohol period, while body weight were not different between the two periods. Office BP was decreased by $3.7 \pm 2.0/2.1 \pm 1.0$ mmHg after alcohol restriction. The change in diastolic BP, but not that in systolic BP, was significant.

Figure 1 shows changes in home BP in the morning and late evening with regular alcohol consumption after the one month of alcohol restriction in 15 hypertensive patients. Morning BP did not change on day 1 and in week 1, but increased significantly in week 2 (systolic BP only) and week 4 (4.6 ± 1.3/

Table 1. Amount of Alcohol Intake, Body Weight, Serum γ-Glutamyl Transpeptidase, and Office Blood Pressure in the High and Low Alcohol Periods in 30 Hypertensive Patients

	High Alcohol Period	Low Alcohol Period
Alcohol intake (ml/day)	66.5 ± 4.7	10.2 ± 1.9***
Body weight (kg)	67.6 ± 1.1	67.2 ± 1.1
Serum γ-GTP (U/l)	85.7 ± 12.7	70.2 ± 13.6**
Office SBP (mmHg)	143.5 ± 2.2	139.8 ± 2.1
Office DBP (mmHg)	95.0 ± 1.3	92.9 ± 1.3*

GTP: glutamyl transpeptidase, SBP: systolic blood pressure, DBP: diastolic blood pressure. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ between the two periods.

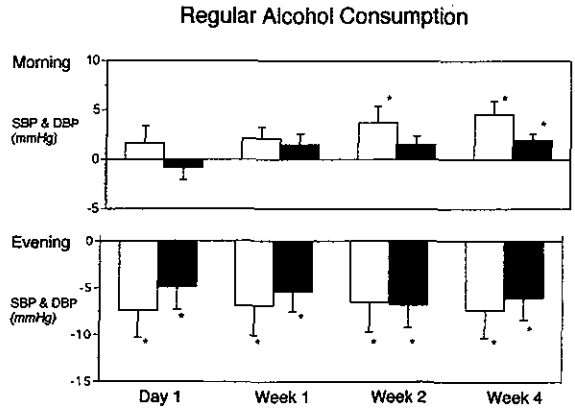

Figure 1. Changes in home blood pressure (BP) in the morning and late evening with regular alcohol consumption after the one month of alcohol restriction in 15 hypertensive patients. White column: systolic BP, black column: distolic BP, *: $P < 0.05$ vs. end of the alcohol restriction period.

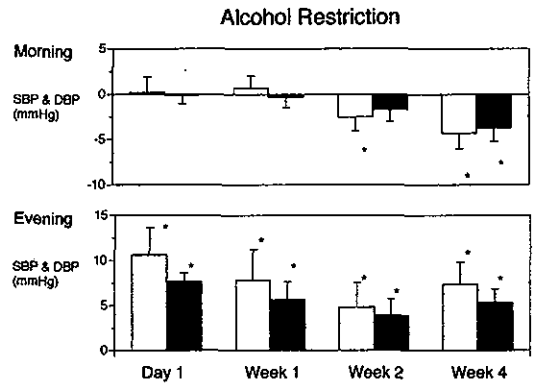

Figure 2. Changes in home BP in the morning and late evening with alcohol restriction after the one month of regular alcohol consumption in 15 hypertensive patients. White column: systolic BP, black column: diastolic BP, *: $P < 0.05$ vs. end of the alcohol consumption period.

2.0 ± 0.6 mmHg). On the other hand, evening BP decreased consistently throughout the regular alcohol period (day 1: $-7.4 \pm 2.9/-4.9 \pm 2.4$ mmHg, week 4: $-7.4 \pm 2.9/-6.1 \pm 2.3$ mmHg).

Changes in home BP in the morning and late evening with alcohol restriction after the one month of regular alcohol consumption in the other 15 patients are shown in Fig. 2. Morning BP did not change until week 1, but fell thereafter (week 4: $-4.3 \pm 1.7/-3.7 \pm 1.5$ mmHg). Evening BP rose significantly from day 1 ($10.6 \pm 3.0/7.6 \pm 1.0$ mmHg) to week 4 ($7.3 \pm 2.5/5.3 \pm 1.5$ mmHg).

Table 2. Home Heart Rate in the Morning and Late Evening with Regular Alcohol Consumption After the One Month of Alcohol Restriction, and Alcohol Restriction After the One Month of Regular Alcohol Consumption

	Baseline	Day 1	Week 1	Week 2	Week 4
Alcohol consumption ($n=7$)					
Morning	61.3 ± 3.0	63.7 ± 3.2	62.4 ± 2.9	63.7 ± 3.0	64.4 ± 2.6
Evening	64.9 ± 2.7	71.6 ± 2.7*	72.4 ± 3.1*	72.0 ± 2.3*	71.7 ± 3.4*
Alcohol restriction ($n=8$)					
Morning	67.0 ± 3.0	66.5 ± 3.2	63.5 ± 3.3	63.0 ± 2.8	64.1 ± 1.9
Evening	74.8 ± 3.1	65.8 ± 3.7*	67.0 ± 1.7*	68.8 ± 2.2*	69.0 ± 2.3*

*$P < 0.05$ vs. the baseline period.

Table 3. Blood Pressure and Heart Rate in the Morning and Late Evening at the End of High and Low Alcohol Periods in 30 Hypertensive Patients

	High Alcohol Period	Low Alcohol Period	H–L Difference
Morning			
SBP (mmHg)	140.5 ± 2.3	136.1 ± 2.5	4.4 ± 1.1***
DBP (mmHg)	91.9 ± 1.5	89.0 ± 1.5	2.9 ± 0.8**
HR (b/min)	65.8 ± 2.0	62.8 ± 1.7	3.0 ± 1.0**
Evening			
SBP (mmHg)	127.9 ± 2.1	135.2 ± 2.4	−7.4 ± 1.9***
DBP (mmHg)	80.8 ± 1.6	86.6 ± 1.3	−5.7 ± 1.3***
HR (b/min)	73.3 ± 2.3	67.1 ± 1.8	6.3 ± 1.4***
M–E difference			
SBP (mmHg)	12.7 ± 2.1***	0.9 ± 1.6	11.8 ± 1.9***
DBP (mmHg)	11.1 ± 1.7***	2.5 ± 1.2	8.6 ± 1.5***
HR (b/min)	−7.5 ± 1.5***	−4.3 ± 1.3**	−3.3 ± 1.5*

H–L: high–low, M–E: morning–evening. **: $P < 0.01$, ***: $P < 0.001$ between the two periods or time of day. $N = 15$ for heart rate.

Home heart rate during the regular alcohol consumption and the alcohol restriction periods was shown in Table 2. Evening heart rate significantly increased with regular alcohol consumption and decreased after alcohol restriction throughout the observation periods. Morning heart rate showed similar but insignificant changes with the alcohol consumption and restriction.

Table 3 shows BP and heart rate in the morning and late evening at the end of high and low alcohol periods in all the patients. Morning BP was significantly higher while evening BP was lower in the regular alcohol period than the alcohol restriction period. In the high alcohol period, morning BP was significantly higher than evening BP. The morning–evening difference in home BP was not observed in the low alcohol period. Morning as well as evening heart rate was significantly higher in the regular alcohol period than the alcohol restriction period, although the change was more profound in the evening.

DISCUSSION

In this study, the regular consumption of alcohol for 4 weeks raised morning BP but lowered evening BP, and the restriction of alcohol intake had opposite effects in Japanese men with hypertension. These results are consistent with our previous studies in which the effects of repeated alcohol intake were investigated using ambulatory BP monitoring (5,6).

Our study confirmed the pressor effect of alcohol in the daytime. However, this effect appears to occur only after repeated intake. Morning BP rose significantly only in weeks 2 and 4 in the present study, although the rise in BP after a shorter duration of alcohol intake has been reported in other studies (5,11). It is known that abstinence in a heavy drinker can cause an increase in both BP and heart rate as a part of the alcohol withdrawal syndrome. In our study, there was a significant increase in evening BP but morning BP did not increase on day 1 in the alcohol restriction period.

In contrast to the pressor effect, the alcohol-induced reduction in evening BP was observed throughout the study period, confirming our previous findings (4–6). The depressor effect might be specific to Oriental subjects since alcohol flush syndrome, which is characterized by peripheral vasodilation and cardiac stimulation, is common in Orientals and rare in Caucasians (12). We observed that the reduction in BP was marked in subjects with alcohol flush, but that a small reduction in BP was also seen in those without flushing (4,5). Criscione et al. reported that norepinephrine-induced vasoconstriction was attenuated by ethanol infusion but that it was potentiated after cessation of the infusion in the rat mesenteric artery (13). This observation is consistent with the biphasic effect of alcohol on BP in our present and previous studies.

The results of the present study also showed that home BP was higher in the morning than in the evening in the regular alcohol period, but that the morning–evening difference disappeared with alcohol restriction. We also previously observed that the restriction of alcohol consumption reduced the day–night BP difference, and resulted in an increase in non-dippers and a decrease in extreme-dippers (6). These findings suggest that the home BP and 24-hour BP profile may vary markedly in the same subject according to alcohol consumption.

In this study, morning as well as evening heart rate was higher in the regular alcohol period than the alcohol restriction period. These results confirmed our previous findings obtained by ambulatory blood pressure monitoring (5,6), and suggest that the mechanisms in the alcohol-induced, time-dependent changes in BP and heart rate are different.

In conclusion, the present study shows that repeated alcohol intake produces a rapid onset of the reduction in BP and a slowly developed BP elevation in Japanese men with hypertension. However, the depressor effect of alcohol was observed throughout the alcohol consumption period. Our study also suggests that the status of alcohol intake may markedly influence the morning–evening BP difference.

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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±14.9/87.0±7.6 mmHg (mean±SD) in 1993 and 146.0±13.7/84.1±7.5 mmHg in 1998. The average home BP was 136.8±10.4/84.3±7.6 mmHg in 1993 and 136.1±9.7/81.2±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 (≥140/90 mmHg in 1993 and <140/90 mmHg in 1998 for clinic BP, ≥135/85 mmHg in 1993 and <135/85 mmHg in 1998 for home BP), worsened control (<140/90 mmHg in 1993 and ≥140/90 mmHg in 1998 for clinic BP, <135/85 mmHg in 1993 and ≥135/85 mmHg in 1998 for home BP), and poor control (≥140/90 mmHg for clinic BP and ≥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 SONOLAYERα 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*):

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

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:

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

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.

Table 2. Status of Target Organ Damage

Variables	*n*	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.

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 antagonists 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. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

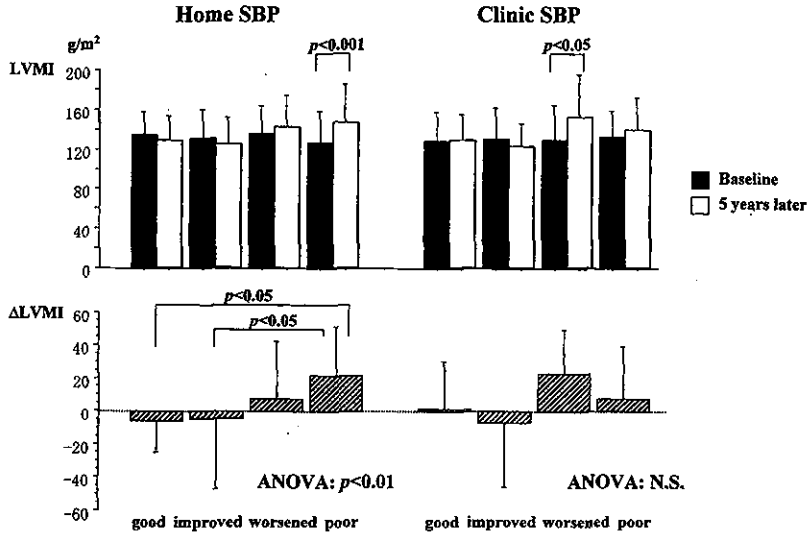

Fig. 1. *Changes in LVMI in subgroups according to SBP control. SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index.*

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	*p*
Clinic SBP control			
n	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			
n	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 (*n*)	Non-use (*n*)	Use (*n*)	Non-use (*n*)
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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Role of blood pressure monitoring in non-pharmacological management of hypertension

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Ambulatory blood pressure monitoring (ABPM) and home blood pressure (BP) measurement appear to be useful in the assessment of the effects of non-pharmacological treatment of hypertension because they can detect small changes in BP without observer bias. We studied the effects of various lifestyle modifications using ABPM and home BP measurement in Japanese patients with hypertension. Weight reduction by a hypocaloric diet (average 4 kg) was associated with decreases in 24-h BP (10/4 mmHg) as well as casual BP (9/6 mmHg). The reductions in daytime and night-time BPs were comparable. The effects of daily walking without weight loss on office, home, and 24-h BPs were 2–3/1–2 mmHg. The changes in home and 24-h BPs were more significant than those in office BP. A low-salt diet (25 mmol/day *versus* 250 mmol/day) decreased 24-h BP by 9/4 mmHg. This hypotensive effect was observed throughout the day. Potassium supplementation (64 mmol/day) decreased office, home and 24-h BPs by 3–4/1–2 mmHg. The changes in home and 24-h BPs were highly significant compared with office BP. Supplementation of magnesium (20 mmol/day) also reduced those BPs significantly. However, the effects of calcium supplementation (25 mmol/day) were small (1–2/1 mmHg) and were significant only for home BP. Alcohol restriction for 4 weeks decreased daytime BP by 3/2 mmHg but increased night-time BP by 4/2 mmHg. Average 24-h BP did not change. Smoking cessation lowered daytime BP without affecting night-time BP. Monitoring of 24-h BP and home BP can detect small changes in BP produced by lifestyle modifications. Ambulatory BP monitoring is particularly suitable in the assessment of changes in lifestyle affecting the circadian pattern of BP such as alcohol consumption and smoking. *Blood Press Monit* **7**: 51–54 © 2002 Lippincott Williams & Wilkins.

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Introduction

Lifestyle modifications, such as weight reduction, restriction of sodium intake, regular exercise and moderation of alcohol intake, are widely recommended in the management of hypertension [1,2]. However, the effects of those non-pharmacological measures on blood pressure (BP) may be different qualitatively and quantitatively [3].

The value of ambulatory BP monitoring (ABPM) and home BP measurements is well established in the pharmacological treatment of hypertension [4]. These methods also appear to be equally or even more useful in the assessment of the effects of non-pharmacological therapy because they can detect small changes in BP without observer bias. However, the application of ABPM and home BP measurement in the non-pharmacological treatment of hypertension has been less extensive compared with the pharmacological therapy.

We have studied the effects of various lifestyle modifications using ABPM and home BP measurement in Japanese patients with hypertension. Presented here are the results of a series of our studies and discussion of the value of BP monitoring in the assessment of non-pharmacological management of hypertension.

Weight reduction

Many clinical studies have demonstrated that weight reduction is effective for lowering BP in hypertensive patients and in subjects with high-normal BP. Based on meta-analysis of intervention studies, it has been estimated that a 1 kg reduction in body weight accounts for a decrease in casual BP by 1.2/1.0 mmHg [5].

We examined the effects of a hypocaloric diet (800 kcal/day for 3 weeks) in 16 obese patients with hypertension [6]. At the end of the study period, loss of body weight (average 4 kg) was associated with significant decreases in 24-h BP (10/4 mmHg) and heart rate (3 b/min) as well as a fall in casual BP (9/6 mmHg). The reductions in daytime and night-time BPs were comparable. On day 1 of the hypocaloric period (without weight reduction), 24-h BP did not change from the control level.

We also compared the effects of a hypocaloric diet and an insulin sensitizer troglitazone (400 mg/day) in 30 obese patients with hypertension [7]. Blood glucose, plasma insulin, and HOMA index decreased similarly in the two treatments. However, a significant reduction in 24-h BP

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