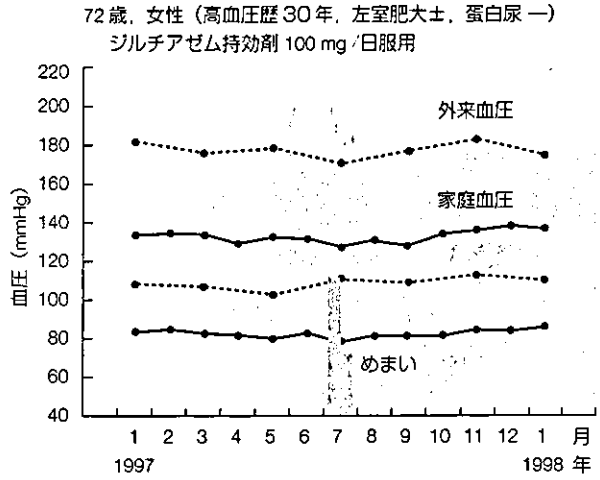
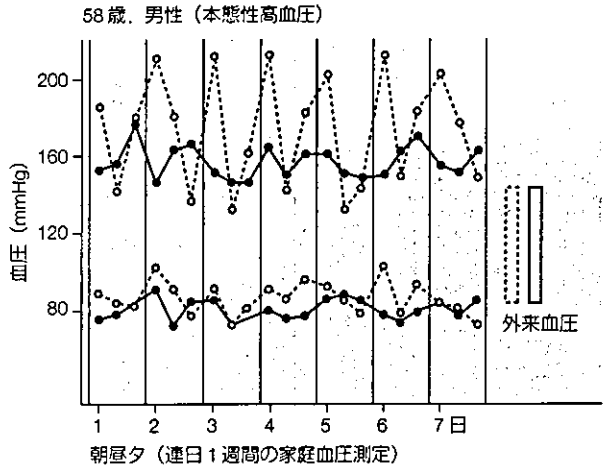


❸白衣現象の著明な高血圧症例の1年間の外来血圧と家庭血圧
（河野雄平：今月の治療 1999；7：21-25）



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．

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ORIGINAL ARTICLE

Diagnostic value of carotid intima–media thickness and plaque score for predicting target organ damage in patients with essential hypertension

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Carotid intima–media thickness (IMT) assessed by ultrasonography is regarded as an early predictor of general arteriosclerosis in patients with essential hypertension. However, the methods of measuring IMT have not been globally standardized, and it remains unclear whether conventional measurement of IMT represents the prevalence of hypertensive target organ damage. In this study, we verified the association between several commonly used carotid ultrasonographical parameters and the severity of hypertensive target organ damage (retinal arteriosclerosis, microalbuminuria, left ventricular hypertrophy (LVH)). Carotid ultrasonography, echocardiography, urinalysis, and funduscopy were performed in 184 patients (64 ± 12 years, 96 males and 88 females) with various stages of essential hypertension. Carotid arteriosclerosis was assessed using four methodologically different methods: conventional-IMT, maximum-IMT (Max-IMT), Mean-IMT, and Plaque Score (the sum of all plaque thicknesses). Age and all carotid ultrasonographical parameters were significantly associated with albuminuria, retinal arteriosclerosis, and left ventricular mass index. High-sensitivity CRP was significantly correlated with retinopathy and LVH. Carotid parameters in patients with histories of cardiovascular events were significantly greater in those without events. Among all carotid parameters, Max-IMT showed the highest correlation coefficient of the severity of target organ damage, and showed significant association with CRP. Stepwise regression analysis revealed that Max-IMT was the independent factor for predicting target organ damage. Max-IMT is suggested to be the most reliable and simplest parameter for predicting hypertensive target organ damage including microangiopathy in patients with essential hypertension.
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Keywords: ultrasonography; arteriosclerosis; intima–media thickness; target organ damage

Introduction

Assessment of subclinical and clinical target organ damage is a key element in the management of patients with hypertension, and practical and applicable examination for predicting the damage has been long-sought. Ultrasonographical measurements of intima–media thickness (IMT) in the carotid arteries are being applied extensively for evaluating the presence and progression of arteriosclerosis in patients with hypertension. The physiopathological importance of wall thickening was suggested to be an adaptive mechanism in the early stages of hypertension to counterbalance the persistent increases in blood pressure, and an abnormal IMT may reflect the consequence of past exposure to risk factors. Thus, thickened carotid IMT is a powerful and independent indicator of the likelihood of not only cerebrovascular diseases but also general arteriosclerosis.[1] These arterial wall modifications have represented an early involvement of the target organs in patients with hypertension.[2–5] Although the usefulness of measuring carotid IMT has been established and several indices for evaluating IMT and plaque have been proposed, the methods of measuring IMT have not been globally standardized, and reliability of the measurements is spatially dependent. In addition, the associations between IMT thickening and the emergence of hypertensive target organ damage in hypertensive patients remain controversial.[2,3,5–7]

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The present examination was a cross-sectional study on carotid intima-media thickening and hypertensive target organ damage in patients with essential hypertension referred to the Hypertensive Division in our hospital. Our aim was to verify the possible association of several commonly used parameters of carotid arteriosclerosis on the severity of hypertensive target organ damage in order to determine the most practical and feasible method of IMT measurement for risk stratification in patients with hypertension.

Materials and methods

Study population

Clinical records of 350 consecutive hypertensive patients who were hospitalized in the National Cardiovascular Center, Division of Hypertension and Nephrology for the purpose of medical examinations for high blood pressure or hypertensive target organ complications during the period April 2001 – February 2003 were analysed. A total of 50 patients were excluded because they were diagnosed or suspected of secondary forms of hypertension, and 71 patients were excluded due to concomitant diabetes mellitus. In all, 45 patients were also excluded because of concomitant proteinuria (more than 0.1 g/day) due to nonhypertensive or hypertensive nephrotic renal disorders. Thus, 184 patients with essential hypertension without diabetes and apparent proteinuria were included in the present study. The diagnosis of hypertension was based upon casual blood pressure values greater than 140/90 mmHg and/or under antihypertensive treatment at the first contact. Patients with other major cardiovascular risk factors, such as dyslipidaemia and smoking habit, were included in the study population. The study was carried out in accordance with the Declaration of Helsinki, and the Guidelines of Epidemiological Research of Ministry of Health, Labour and Welfare and Ministry of Education, Culture, Sports, Science and Technology. All subjects gave informed consent to participate in the study.

Baseline measurements

Medical histories and physical examinations were obtained for each subject at the examination. Systolic and diastolic blood pressure was measured twice in the left arm of seated participants. The body mass index was calculated as the weight in kilograms divided by the square of the height in metres. The total cholesterol and fasting blood glucose (FBG) were measured. High-sensitive C-reactive protein (hs-CRP) was also measured using an automatic immunonephelometer with a sensitivity of 0.02 mg/dl.

Past illnesses of cardiovascular events were defined as coronary artery diseases (angina pectoris and myocardial infarction), stroke, peripheral vascular disease, aortic aneurysm, and congestive heart failure.

Carotid ultrasonography

Ultrasonography of both carotid arteries was performed with a high-resolution Duplex scanner (TOSHIBA SSA-390A) using the probe at a frequency of 7.5 MHz. for the B-scan. The subjects were investigated in the supine position with their head slightly turned from the sonographer. All measurements were performed by six trained sonographers, who were unaware of the subjects' clinical data. The carotid arteries were carefully examined with regard to wall changes from different longitudinal (anterior oblique, lateral, and posterior oblique) and transverse views, and measurements of thickness were performed from the transverse image. The common carotid artery, the carotid bulb, the internal and the external carotid arteries were studied in all subjects. Each ultrasound image was taken in end-diastolic, and was recorded on a personal computer hard-disk with an on-line digital filing system, and IMT and plaque were measured manually by off-line analysis.

We assessed carotid IMT and plaque by measuring generally used parameters, including maximum and mean IMT, and Plaque Score (PS), on the basis of previous studies.[2,3,5,6,8–10] The parameters are schematically depicted in Figure 1. Briefly, conventional-IMT (C-IMT) was defined as an average of five IMTs at approximately 1.5 cm proximal to the carotid bulb in the right and left common carotid arteries avoiding discrete plaques. Maximum-IMT (Max-IMT) was defined as the maximum thickness of intima–media including plaques, and Mean-IMT was defined as the average of Max-IMT and IMTs of its 1 cm proximal and distal region. Max-IMT and Mean-IMT were assessed from the region branching off from brachiocephalic artery (right) or aorta (left) to the bifurcation of common carotid artery. We

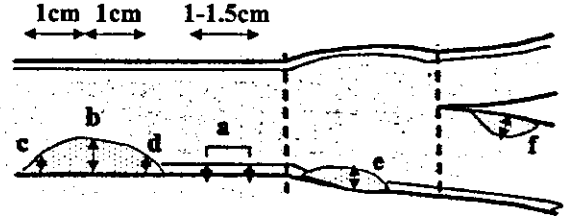

Figure 1 Ultrasonographical parameters of carotid arteriosclerosis. C-IMT: average thickness of intima–media at 1.5 cm proximal from the carotid bifurcation (a) (mm); Max-IMT: maximum IMT in the common carotid artery including plaques (b) (mm): Mean IMT: average thickness of Max-IMT and its 1 cm distal and proximal IMTs ((b+c+d)/3) (mm). PS: sum of plaque thickness (b+e+f) (unitless).

defined a plaque as an area where IMT was >1.10 mm, and calculated PS by summing all plaque thicknesses in the bilateral carotid arteries in the scanning area, following an established manner.[8,9,11] The length of individual plaques was not considered for the calculation of this score.

Assessment of hypertensive target organ damage

Funduscopic diagnosis of hypertensive retinopathy was evaluated bilaterally by an experienced opthalmologist, who had no knowledge of the patient's clinical characteristics. The funduscopic findings considered in this study were arteriolar narrowing and irregular constriction, arteriolar reflex and arterio-venous crossing phenomenon, which were graded using Scheie's arteriosclerotic classification.

Twenty-four-hour urinary excretion of protein and albumin was assessed in all patients during hospitalization. Microalbuminuria was evaluated in patients without evident proteinuria by measuring the albumin-to-creatinine ratio (ACR) in three nonconsecutive, 24-h urine samples.[12,13] The ACR was calculated as follows: urine albumin concentration (milligrams per litre)/urine creatinine concentration (milligrams per litre), and expressed in mg/g creatinine. Creatinine clearance was also evaluated.

Transthoracic echocardiography was performed using an echocardiographic instrument (Phillips, SONOS 5500) with a 3.5 MHz transducer. At the basal examination, regional kinesis of the left ventricle was evaluated by two-dimensional echocardiography, and left ventricular diastolic and systolic diameter (LVDd/Ds); in addition, the diastolic thickness of the left ventricular posterior wall (LVPWT) and interventricular septum (IVST) were assessed in M-mode images of the parasternal long-axis view. The left ventricular mass index (LVMI) (g/m^2) was calculated using the following formula:

$$\text{LVMI}\ (g/m^2) = (1.04 \times ((\text{IVST} + \text{LVPWT} + \text{LVDd})^3 - \text{LVDd}^3) - 13.6)/\text{body height}\ (m)^{2.7}$$

Statistical analysis

For all statistical analyses, we used the computer software application, StatView (Abacus Concepts Inc.). All results were expressed as mean values and s.d. The relation between the severity of the hypertensive target organ damage and continuous variables was evaluated by simple linear regression. Forward stepwise regression analysis was employed to relate the extent of Max-IMT to the hypertensive target organ damage with adjustment for potential confounding variables (age, smoking status, serum cholesterol level, FBG, hs-CRP, and systolic blood pressure). For the stepwise regression model, dummy variables were used to contrast the smoking status (current-smoking = 1; non- or past-smoking = 0). Differences were considered significant at $P<0.05$.

Results

Clinical characteristics of the study patients are given in Tables 1 and 2. The mean age of the participants at entry was 64.4 years and 52.2% were male. In all, 20 patients were not receiving antihypertensive drug therapy, and 61.1% of patients were being treated by combined drug therapy. Calcium antagonists were the most prescribed and angiotensin II type I receptor blockers were the second among the patients. There were 64 episodes of cardiovascular events in 56 patients in their clinical records; 27 strokes, 22 coronary artery diseases, four congestive heart failure, six peripheral vascular diseases, and five aortic aneurysms. Among 74 patients who has been diagnosed dyslipidaemia, 14 patients showed poor control of total serum cholesterol (>240 mg/dl).

Carotid ultrasonography was successfully performed in all study subjects. The values of the carotid ultrasonographical parameters and the extent of target organ damage are summarized in Table 3. In all, 53% of patients had discrete plaques and 75% of patients had increased IMT greater than 1.0 mm. In patients with plaques, 86% plaque lesions were located in the bifurcation of carotid bulbs (distal from the region where C-IMT was

Table 1 Clinical characteristics and prescribed antihypertensive agents of the study patients (n=184)

Age (years)	64.4 ± 12.0
Gender (% males)	52.2
Body mass index (kg/m^2)	24.9 ± 4.1
Systolic blood pressure (mmHg)	147.7 ± 20.7
Diastolic blood pressure (mmHg)	83.6 ± 12.6
Duration of hypertension (years)	17.2 ± 10.2
Calc. creatinine clearance (ml/min)	93.8 ± 41.0
hs-CRP(mg/dl)	0.13 ± 0.15
Calcium antagonist (%)	66.8
ACE inhibitors (%)	20.1
ARB (%)	37.0
Beta blocker (%)	36.4
Alpha blocker (%)	8.2
Diuretics (%)	14.7
HMG CoA inhibitors (%)	27.8

Hs-CRP, high-sensitivity C-reactive protein; ARB, angiotensin II type I receptor blocker. Values are expressed as means ± s.d.

Table 2 Prevalence of cardiovascular risk factors and cardiovascular events

Dyslipidaemia (%)	40.2
Active smoking (%)	15.2
Stroke (%)	14.7
Coronary artery disease (%)	12.0
Congestive heart failure (%)	2.2
Peripheral vascular disease (%)	3.3
Aortic aneurysm	2.7

measured). In all, 42% of patients were diagnosed as having macroalbuminuria (ACR $\geqslant$ 30 mg/g creatinine), 83% met the requirment of LVH (LVMI > 51.0 g/m^2), and 65% of patients had more severe findings of Scheie's arteriosclerotic classification ($\geqslant$2). Figure 2 indicates the ultrasonographical parameters between the patients with and without a clinical history of cardiovascular events. Patients with cardiovascular events showed a greater value of each ultrasonographical parameter than those without events. Max-IMT ($P=0.0007$) and PS ($P=0.0007$) showed a smaller P-value between the subjects with and without cardiovascular events compared with C-IMT ($P=0.046$) and Mean-IMT ($P=0.005$).

Table 4 shows the univariate correlation of clinical parameters and target organ damage. Age showed a significant correlation with all kinds of target organ damage. Hs-CRP and creatinine clearance correlated with retinopathy and LVH, and tended to correlate with microalbuminuria.

Table 4 and Figure 3 show the correlation of carotid ultrasonographical parameters and target

Table 3 Ultrasonographical parameters of carotid arteriosclerosis and the extent of target organ damage in the study patients

C-IMT (mm)	0.81 ± 0.17
Mean-IMT (mm)	1.03 ± 0.31
Max-IMT (mm)	1.64 ± 0.79
Plaque Score	3.35 ± 5.13
Sclerotic changes of fundus (S0:S1:S2:S3)	6:58:107:13
LVMI (g/m^2)	59.6 ± 17.0
ACR (mg/g creatinine)	27.3 ± 24.7

C-IMT, conventional IMT; Max-IMT, maximum IMT; LVMI, left ventricular mass index; ACR, albumin creatinine ratio. Definitions of ultrasonographical parameters are given in the text. Values are expressed as means ± s.d.

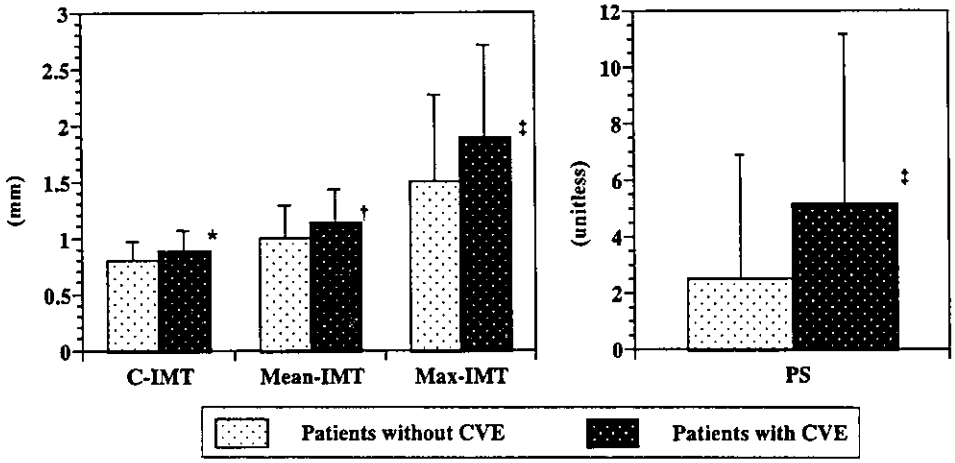

Figure 2 Comparison of ultrasonographical parameters between patients with and without cardiovascular events. Max-IMT ($P=0.0007$) and PS ($P=0.0007$) showed smaller P-value between the subjects with and without cardiovascular events, compared with C-IMT ($P=0.046$) and Mean-IMT ($P=0.005$). CVE, cardiovascular events; C-IMT; conventional IMT, Max-IMT; maximum IMT, PS; plaque score. $^*P<0.05$; $^\dagger P<0.01$; $^\ddagger P<0.001$ *vs* patients without CVE.

Table 4 Correlation coefficients between clinical and ultrasonographical variables and target organ damage

	Retinopathy		*Microalbuminuria*		LVMI	
	r	P	r	P	r	P
Age	0.34	<0.001	0.21	0.004	0.18	0.017
BMI	0.08	0.310	0.02	0.784	0.424	<0.001
CCr	0.22	0.003	0.14	0.062	0.16	0.030
SBP	0.02	0.801	0.10	0.192	0.08	0.283
DBP	0.07	0.329	0.01	0.866	0.10	0.172
T. Chol.	0.05	0.501	0.01	0.900	0.05	0.473
FBG	0.16	0.03	0.08	0.276	0.09	0.242
hs-CRP	0.20	0.006	0.12	0.100	0.17	0.023
C-IMT	0.27	0.002	0.28	0.0001	0.06	0.432
Mean-IMT	0.49	<0.0001	0.39	<0.0001	0.27	0.0003
Max-IMT	0.54	<0.0001	0.42	<0.0001	0.52	<0.0001
PS	0.44	<0.0001	0.24	0.001	0.26	0.0003

LVMI, left ventricular mass index; BMI, body mass index; CCr, creatinine clearance; T. Chol, total serum cholesterol; FBG, fasting blood glucose; hs-CRP, high-sensitivity C-reactive protein; C-IMT, conventional IMT; Max-IMT, maximum IMT; PS, plaque score.

organ damage. All parameters of intima-medial arteriosclerotic alterations showed a significant correlation with target organ damage, except C-IMT and LVH. Max-IMT showed the highest correlation coefficient among all parameters. Hs-CRP was significantly associated with Max-IMT among all ultrasonographical parameters.

A multivariate logistic regression model including age, systolic blood pressure, total serum cholesterol, FBG, smoking habbits, hs-CRP, and Max-IMT as the confounding parameters of hypertensive target organ damage was used. Max-IMT was shown to be the best relation with each hypertensive target organ damage (Table 5).

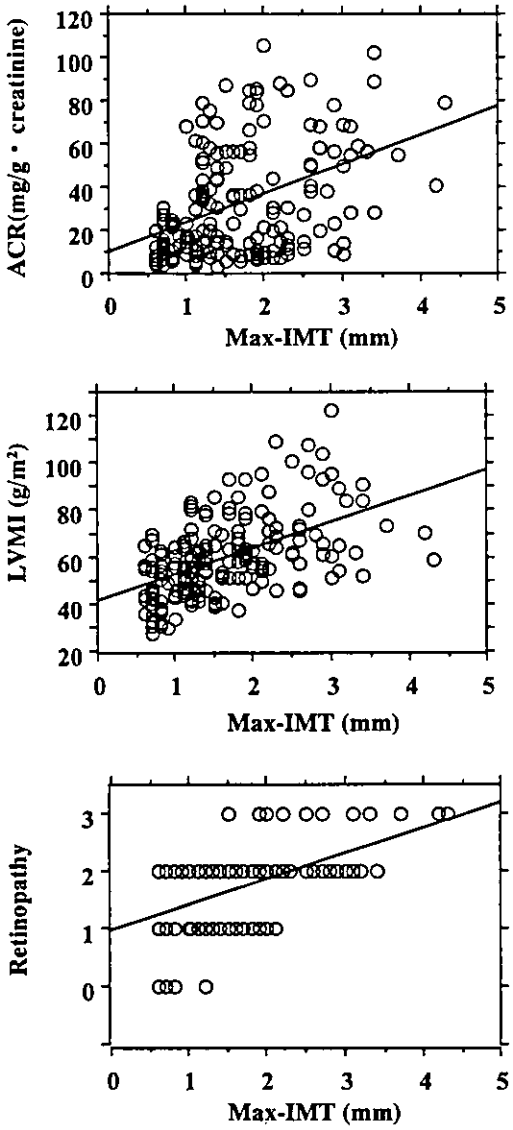

Figure 3 Correlation between target organ damage and Max-IMT. ACR: albumin–creatinine ratio ($r=0.42$, $P<0.0001$), LVMI: left ventricular mass index ($r=0.52$, $P<0.0001$). Retinal arteriosclerosis defined using Scheie's classification (for details, see text) ($r=0.54$, $P<0.0001$).

Discussion

Carotid ultrasonography was proposed as a useful and noninvasive tool with proven ability to show cross-sectional associations with cardiovascular risk factors, prevalence of vascular disease, and predictive power in the general population.[4,5,14] The method appears highly suited to the goal of detecting asymptomatic vascular target organ damage, which also may greatly assist with the assessment of risk and selection of appropriate, preventive strategies for the management of hypertension. Furthermore, assessment of carotid IMT is increasingly used as a surrogate end point for determining the efficacy of pharmacological interventions in large cardiovascular clinical trials, and used as an important phenotype of cardiovascular complications in the field of epidemiology and genetics in patients with hypertension.

However, the markers of carotid IMT have not been standardized, and the reliability of measurements is spatially dependent. Carotid IMT measurement is easily managed among the healthy general population, because the thickness is relatively invariable in overall carotid arteries. In contrast, it is difficult to evaluate carotid IMT of hypertensive patients objectively, because the wall is so erratic due to the development of carotid arteriosclerosis. According to the baseline data of 2300 patients in the cohort study provided by Zanchetti *et al*,[15] greater than 80% of the patients had 'plaques' (defined as 1.3 mm). Less than 1% of the cohort had carotid results showing no plaques and IMT values less than 1.0 mm. In the present findings, only 28% of study patients showed no ultrasonographically defined plaques or IMT thickening, and most of the plaques were located around the bifurcation of the common carotid artery. Thus, the conventional method for measuring IMT avoiding discrete plaques at 1–2 cm proximal to the carotid bifurcation tended to underestimate the severity of arteriosclerosis, although a relatively good correlation with hypertensive target organ damage was shown. As Max-IMT or PS could estimate the arteriosclerosis comprehensively, they showed

Table 5 Stepwise regression analysis of determinants of target organ damage

	Variables	β	F
Microalbuminuria	Max-IMT	13.6	39.6
	$R^2=0.180$, $P<0.0001$		
Retinopathy	Age	0.01	6.7
	Max-IMT	0.39	50.8
	$R^2=0.312$, $P<0.0001$		
LVMI	Max-IMT	9.7	58.5
	BMI	1.4	33.6
	$R^2=0.384$, $P<0.0001$		

LVMI, left ventricular mass index; BMI, body mass index; Max-IMT, maximum IMT.

stronger correlation with arteriosclerotic hypertensive target organ damages.

According to the ELSA trial, the mean of the maximum IMT of the four far walls of the carotid bifurcations and the common carotid arteries (CBM_{max}) showed the highest reproducibility of ultrasound measurements (coefficient of reliability: 0.872), and the overall single maximum IMT ('Max-IMT' in the present study) also showed high reproducibility (coefficient of reliability: 0.794).[16] Although PS and Mean-IMT also showed significant association with target organ damage, the procedures of measuring them are relatively complicated and the reliability of the measurements is spatially dependent. Max-IMT measurement is quite simple and straightforward, because it is performed by only measuring the maximum thickness of intima-media including plaques.

IMT of the common carotid arteries is a general measure of the severity of atherosclerosis, and increased IMT is related to generalized atherosclerosis. In addition to the association between carotid IMT and cerebrovascular disease, a number of studies have demonstrated that carotid IMT significantly correlated with the status of coronary atherosclerosis.[17] However, some reports suggested that the relationship between mean IMT of 10 mm distal of the carotid artery and severity of the coronary artery disease was significant but weak.[18] C-IMT in the present study also showed significantly greater values in subjects with former cardiovascular events compared with those without events, but the difference was relatively small. On the other hand, differences in Max-IMT or PS between the two groups were greater. As 53% of patients had discrete plaques and 75% of patients had increased IMT in our hypertensive patients, we assumed that Max-IMT and PS reflect the genuine severity of the arteriosclerosis, especially in patients with high risk. Since our study was a cross-sectional investigation, we could not conclude that Max-IMT or PS were the best parameters to predict future cardiovascular events. Thus, further prospective study should be helpful to clarify the association.

There have been several studies that compared the associations between carotid IMT and hypertensive target organ damage. Some studies demonstrated that carotid IMT was highly associated with microalbuminuria,[2] LVH[3,5] and cardiovascular events. On the other hand, some studies showed no association with microalbuminuria.[6,7] In the present study, carotid IMT, especially Max-IMT, was highly associated with a history of cardiovascular events and target organ damage. Interestingly, the present findings demonstrated that retinal arterial stenosis and microalbuminuria, which were suggested to relate to microangiopathy due to hypertension, were also correlated with the severity of changes in large conduit arteries. The mechanism that links macro- and microangiopathy closely is unknown. One possible mechanism might be the participation of low-grade chronic inflammation.[19] Arteriosclerosis in both macro- and microvasculature was recently suggested to be due in part to an inflammatory response.[20] According to our present findings, hs-CRP was significantly associated with the severity of retinopathy, and tended to associate with microalbuminuria. We could also find a significant association between Max-IMT and hs-CRP. Further study is be needed to investigate the association between inflammation, arteriosclerosis, and target organ damages among patients with 'active' arteriosclerosis, because most of our study subjects had a long history of hypertension, or other metabolic disorders (dyslipidaemia, smoking). Insulin resistance, which is latent in those conditions, might exist in the case of accumulating risk, and it may accelerate the carotid arteriosclerosis.[21] Insulin resistance is also one of the augmentative factors of microalbuminuria[22] and diabetic retinopathy.[23]

In the present study, we verified several commonly used ultrasonographical parameters of carotid arteriosclerosis. Max-IMT is suggested to be the best and simplest and the most reliable parameter for predicting hypertensive target organ damage including microangiopathy, especially in high-risk hypertensive patients. Although longitudinal investigations will be needed to clarify the association between carotid parameters and future cardiovascular events, we recommend that Max-IMT is the essential parameter for risk stratification in hypertensive patients.

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降圧薬療法の進歩—これからの治療法 1

降圧薬の多剤併用療法

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● はじめに

高血圧の治療においては，単独の降圧薬では血圧のコントロールが不十分で，多剤併用療法を要する場合が少なくない。また従来は，薬物療法は特殊な場合を除き，単剤から始めることが基本と考えられていた。しかし，最近では初めから併用療法を行うことも提唱されており，欧米のガイドラインもこの考えを取り入れている。本稿では，降圧薬の多剤併用療法について，その必要性と利点，適応や望ましい組合せなどについて概説する。

● 降圧薬の単剤療法と併用療法

1 単剤療法の限界

高血圧の薬物治療においては，従来は特殊な場合を除いて，単剤で低用量から始めることが基本と考えられていた[1]。しかし，多くの高血圧患者は単剤では血圧コントロールが不十分であり，複数の降圧薬を要する。国立循環器病センターの高血圧腎臓外来においては，単剤は約1/3であり，2/3は併用である。われわれの施設を含む共同調査でも，単剤治療の高血圧者は中年者では約1/3，老年者では約1/2であり，また治療中の平均収縮期血圧は140 mmHgを超えていた[2]。

単剤治療の限界は，多くの降圧治療の臨床試験においても示されている。われわれの家庭血圧に基づいた高血圧治療共同研究であるHOSP (Hypertension Control Based on Home Systolic Pressure) 研究では，Ca拮抗薬アムロジピン，あるいはAII受容体拮抗薬ロサルタンによる家庭収縮期血圧の目標達成率は，140 mmHg未満群では約60%であったが，130 mmHg未満群は30%にすぎなかった[3]。ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) 研究においては，収縮期血圧は140 mmHg未満にコントロールされているが，60%以上の例は併用治療を要している。また，糖尿病や腎障害を伴う高血圧の治療試験においては平均して3〜4剤の降圧薬が用いられており（図1），多剤併用療法の必要性がさらに明らかとなっている[4]。

2 併用療法の必要性と利点

降圧薬の併用療法の利点としては，まず降圧効果が大きくなり血圧コントロールが容易になることがあげられる。クラスの異なる降圧薬の併用は，相加的あるいは相乗的にはたらく場合が多い。すなわち，少量の併用でも比較的大きな降圧が得られるであろう（表1）。Lawらによれば，60歳代で脳血管障害を有する血圧150/90 mmHgの患者を標準用量の半量の3剤で治療すると，血圧は20/11 mmHg低下し，脳卒中は63%，虚血性心疾患は46%予防できることになる[5]。

一方，薬剤の副作用は用量依存性で，大量投与時に起こりやすい（表2）。したがって，単剤

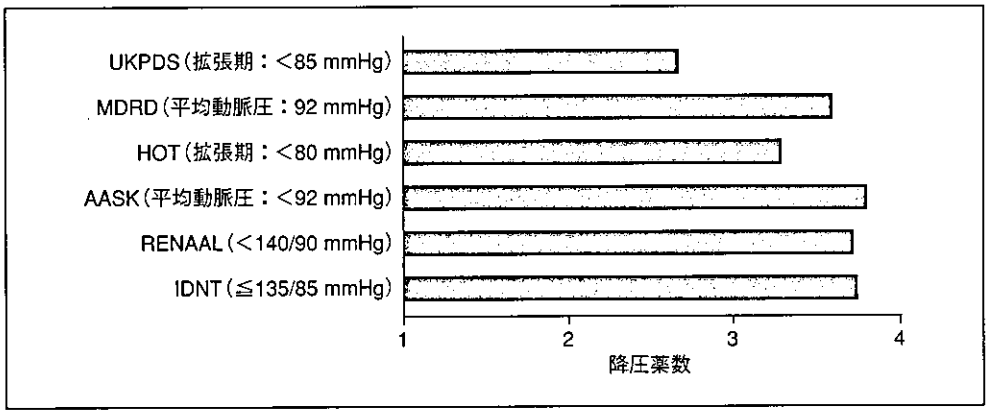

図 1　大規模臨床試験において目標血圧を達成するために用いられた降圧薬の数（文献 4 より）
UKPDS：UK Prospective Diabetes Study, MDRD：Modification of Diet in Renal Disease, HOT：Hypertension Optimal Treatment, AASK：African American Study of Kidney Disease and Hypertension, RENAAL：Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan, IDNT：Irbesartan Diabetic Nephropathy Trial

表 1　無作為臨床試験における降圧薬の少量投与（標準用量の半量）による降圧効果
（文献 5 改変）

	1 剤	2 剤	3 剤
収縮期血圧（mmHg）	6.7	13.3	19.9
拡張期血圧（mmHg）	3.7	7.3	10.7

表 2　無作為臨床試験における降圧薬の種類と用量によるプラセボと比較した副作用頻度（文献 5 改変）

	半量（%）	標準用量（%）	倍量（%）
利尿薬	2.0	9.9	17.8
β遮断薬	5.5	7.5	9.4
ACE 阻害薬	3.9	3.9	3.9
AII 受容体拮抗薬	−1.8	0	1.9
Ca 拮抗薬	1.6	8.3	14.9

の大量投与より多剤の少量投与のほうが，降圧効果は同等あるいはそれ以上で副作用は少ないと考えられる。また，降圧薬の組合せによっては副作用を相殺するようにはたらく。利尿薬とACE 阻害薬あるいは AII 受容体拮抗薬の併用は，血圧には相乗的にはたらき，低カリウム血症をきたしにくい。Ca 拮抗薬による心拍数増加や皮膚血管拡張は，β遮断薬の併用で抑制される。

● 多剤併用療法の原則

1　併用療法の適応

降圧薬の併用療法のよい適応，また最も多い理由となるのは，単剤治療では血圧コントロールが不十分な場合である。単剤でコントロールできる患者より併用を要する者のほうが多く，これは降圧目標を低くする場合には特に著しい。また，いくつもの合併症を有する患者では，各々の合併症に対する積極的適応として複数の降圧薬を用いる必要があるかもしれない。

最近は，併用療法は高血圧治療の開始時点においてもよい適応であるとの考えが強まっている[6~8]。低用量の併用は高用量の単剤治療に比べて降圧効果は大きく副作用は少ないことが期待でき，実際にアムロジピンとベナゼプリルの併用などにより示されている[7]。欧米では ACE 阻害薬や AII 受容体拮抗薬と利尿薬，Ca 拮抗薬と ACE 阻害薬，サイアザイド系とカリウム保持性の利尿薬といった合剤が多数市販されており，それも併用療法を行いやすい理由であろう。わが国でも合剤の認可が待たれる。

新しいガイドラインは，高血圧の初期治療からの併用療法を認めている。米国の JNC 7 は，ステージ 2（中等症および重症）の高血圧患者については 2 剤での治療を考慮し，うち 1 剤は利尿薬を用いることを勧めている[9]（**図 2**）。また，ESH と ESC のガイドラインは，患者の血

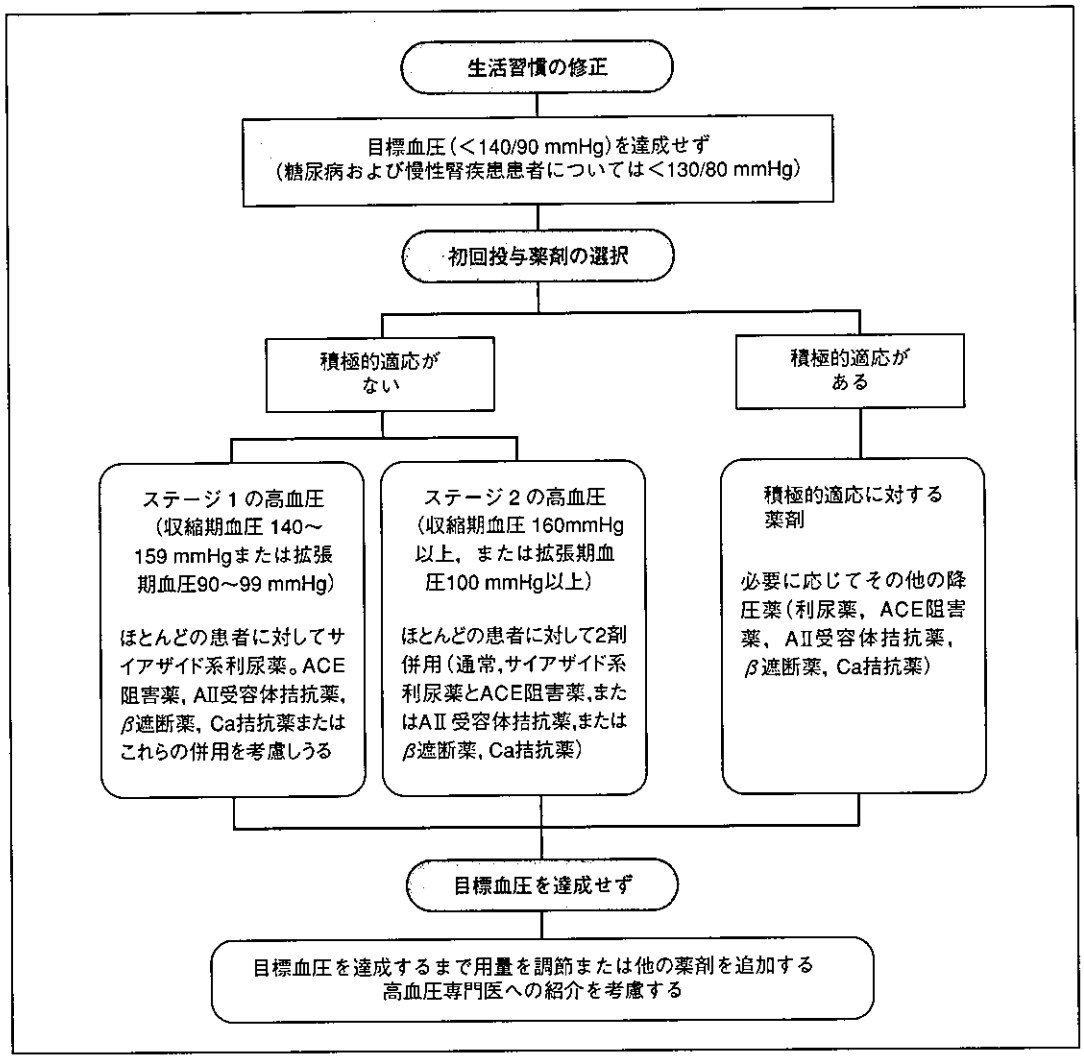

図 2　JNC 7 による高血圧治療手順（文献 9 より）

圧レベルや臓器障害，危険因子を考慮して，低用量の単剤か低用量の 2 剤併用を選択するのが妥当であるとしている[10](図 3)。したがって，かなり多くの高血圧患者においては初回からの併用療法もよい適応になると考えられる。

2　望ましい組合せ

降圧薬の併用においては，各症例の病態を考慮したうえで，降圧効果を高め副作用を軽減するような組合せが望ましい。このためには，血行動態，電解質代謝，神経内分泌系などについて作用機序の異なる降圧薬の併用が原則となる。

併用療法として JNC 7 は，利尿薬と他剤の組合せを推奨している[9]。ESH/ESC のガイドラインは効果的で忍容性の高い組合せとして，利尿薬とβ遮断薬，ACE 阻害薬または AII 受容体拮抗薬の併用，Ca 拮抗薬とβ遮断薬，ACE 阻害薬，AII 受容体拮抗薬または利尿薬の併用，α遮断薬とβ遮断薬，をあげている[10]。

筆者は降圧薬を 3 つのグループに分けて考えている。すなわち，Ca 拮抗薬と利尿薬，ACE 阻害薬と AII 受容体拮抗薬とβ遮断薬，α遮断薬とそれ以外に分ける (図 4)。初めは I 群または II 群の単剤使用，あるいは I 群と II 群の併用を行う。単剤で不十分な場合には，他のグルー

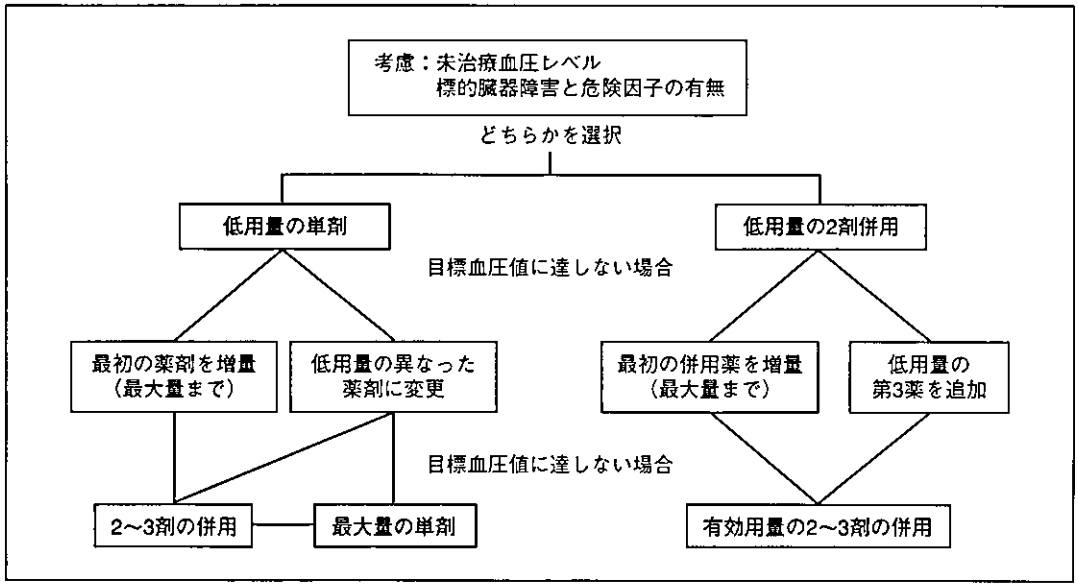

図 3　ESH/ESC ガイドラインによる単剤療法と併用療法の選択（文献 10 より）

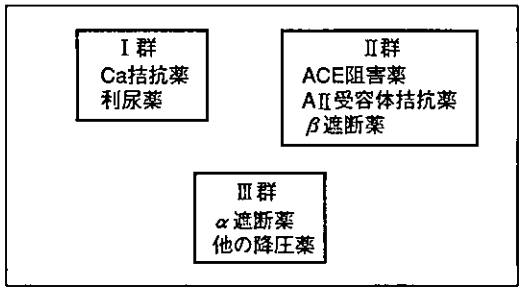

図 4　併用療法における降圧薬のグループ分け

プの薬剤を加える。2 剤併用でも不十分な場合には，さらに I～III の群の薬剤を追加して多剤併用を行う。ただし，多剤併用の場合には利尿薬を含むことが望ましい。また，合併症を有する場合には，それに対する積極的適応の薬剤を用いるべきである。

● おわりに

降圧薬の併用療法について述べた。適切な併用により降圧効果は高まり，副作用はむしろ少なくなることが期待できる。血圧の厳格なコントロールのためには，大部分の高血圧患者は併用療法を要することになろう。また，低用量の併用は，高血圧の初期治療においても多くの例でよい適応になると考えられる。

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Pulse Pressure Is an Independent Predictor for the Progression of Aortic Wall Calcification in Patients With Controlled Hyperlipidemia

Yoshikazu Miwa, Motoo Tsushima, Hisatomi Arima, Yuhei Kawano, Toshiyuki Sasaguri

Abstract—Recent epidemiological studies suggested that calcifications of the aorta and the coronary arteries are important predictors for cardiovascular morbidity and mortality. However, the relation between blood pressure components and the progression of vascular wall calcification has remained unclear. We quantified calcium deposits in the abdominal aorta as the percentage of aortic calcification volume (%ACV) using computed tomography in patients with hyperlipidemia. Those who had aortic calcification were treated with lipid-lowering agents and followed-up for >2 years (6.3±3.2 years). The relationship between the components of blood pressure and the increase in %ACV per year (Δ%ACV/year) was assessed in subjects in whom serum lipid levels were well controlled during the follow-up periods. An age- and sex-adjusted correlation analysis showed that Δ%ACV/year was significantly correlated to body mass index (r=0.229, P=0.015), systolic blood pressure (r=0.244, P=0.009), and pulse pressure (r=0.359, P<0.001). A multivariate regression analysis revealed that pulse pressure is an independent and the most sensitive predictor for Δ%ACV/year (β=0.389, P<0.001) among the blood pressure components. These results suggested that increase in pulse pressure promotes the progression of vascular calcification. (***Hypertension.* 2004;43:536-540.**)

Key Words: hypertension ■ calcium ■ aorta ■ pulse ■ imaging ■ risk factors

Calcification in the aorta and coronary arteries is a strong predictor for cardiovascular morbidity and mortality.[1,2] Previous studies have shown the close relationships between arterial wall calcification and abnormal serum lipid levels. Arterial wall calcification is common in patients with familial hypercholesterolemia, a genetic disorder of cholesterol metabolism.[3–5] Several studies have identified the relationship between the serum level of low-density lipoprotein cholesterol (LDL-C) and arterial wall calcification; moreover, lipid-lowering therapy using 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has been reported to inhibit the progression of arterial wall calcification.[6,7] In patients receiving long-term hemodialysis, elevated serum triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels are risk factors for coronary artery calcification.[8] These studies suggested that abnormal serum lipid levels promote calcium deposition in the arterial wall.

Several studies have examined the influence of hypertension on the progression of arterial wall calcification. In these studies, antihypertensive therapy has been shown to inhibit the formation of calcified lesions, suggesting that hypertension promotes calcium deposition in the arterial wall.[9–11] However, it remains undetermined which blood pressure (BP) component, ie, systolic BP (SBP), diastolic BP (DBP), mean BP (MBP), or pulse pressure (PP) is responsible for the accelerated formation of calcification, probably because the abnormal serum lipid levels may have made it difficult to assess the effect of BP alone on the formation of calcified lesions.

Computed tomography (CT) is a useful tool to evaluate the level of arterial wall calcification. Most of the previous studies used the "calcium score" determined by CT as a semiquantitative index of calcification of the aorta or coronary arteries.[3–7] However, the calcium score may not accurately reflect subtle changes in calcium deposit levels. To accurately quantify the degree of calcium deposition, we developed an image color analysis software program that can automatically determine the percentages of calcified volume against whole vascular volume (%ACV) using plain CT.[9] We previously reported a strong correlation between %ACV and aortic calcification dimension in aortas of autopsy specimens, the latter of which was determined using soft X-ray photographs.[12]

In the present study, using our method, we studied the relationship between the BP components and the progression of aortic wall calcification. To exclude interference by serum lipid levels, only subjects whose lipid levels were well controlled during the follow-up periods were analyzed.

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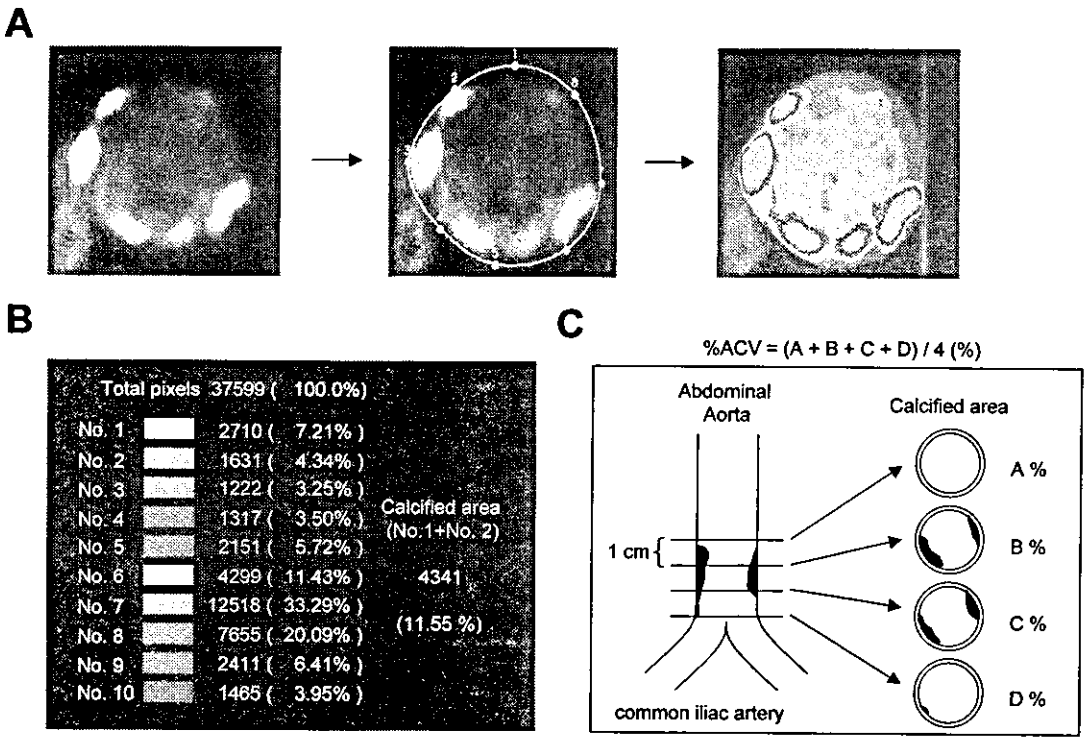

Figure 1. The method to determine %ACV. A, When an observer circles the abdominal aorta, the software program (TES-100 image color analysis software program) transforms the monochrome contrast image into a color image. B, The software automatically calculates the percentage of calcified area from pixel numbers. C, %ACV was calculated as an average value of 4 slices just above the bifurcation.

Methods

Subjects

This prospective cohort study was started in April 1988 at the National Cardiovascular Center (Suita, Japan). Recruitment of the subjects was closed in March 1999 and the follow-up ended in April 2001. We obtained informed consent to join this study from asymptomatic patients with untreated hyperlipidemia (serum total cholesterol [TC] levels >5.72 mmol/L or serum TG levels >1.70 mmol/L). Patients with severe hyperlipidemia (TC >9.10 mmol/L or TG >5.65 mmol/L), genetic disorders in lipid metabolism such as familial hypercholesterolemia, severe diabetes mellitus (HbA1c >7.0%), secondary hypertension, renal insufficiency, and abdominal aortic aneurysm were excluded from the analysis. Those using warfarin were also excluded. They were subjected to lipid-lowering therapy and followed until 2001. Simultaneously, we started antihypertensive therapy in all subjects with untreated hypertension. To subjects already using antihypertensive agents, we re-administered the drugs after a washout period of at least 1 month.

Four hundred eight patients agreed to join the study. They were subjected to a plain CT examination, and aortic wall calcification was found in 204 subjects. During the study, 2 subjects died of cerebral infarction, 16 subjects chose to discontinue their participation in the study, and serum lipid levels could not be well controlled in 70 subjects. Finally, 116 subjects (74 men and 42 women) who achieved optimal serum lipid levels (whose average TC and TG concentrations through the follow-up periods were <5.72 and 1.70 mmol/L, respectively) entered into the present study.

Calculation of %ACV and Δ%ACV/Year

We conducted plain CT at the first examination and every 6 months thereafter during follow-up periods for >2 years. The lower abdominal aortas of subjects in the supine position were scanned for 9.6 seconds at 120 kV and 200 to 250 mA at 10-mm intervals using a CT/T 2-8800 (GE Company, Milwaukee, Wisc). The percentages of calcified areas against the whole vascular area were calculated from images of 4 consecutive slices just above the bifurcation of common iliac arteries using the TES-100 image color analysis software program as described.

As shown in Figure 1A, when an observer traced the edge of the aorta after placing CT images into the computer system, this software transformed the monochrome CT image into a color image indicating the levels of density with 10 different colors. We considered the areas with 2 yellow colors (Figure 1B, No.1 and No. 2) to be calcified. The percentage of the sum of these areas against the whole area was automatically calculated by the software program; %ACV was determined by averaging the values of the 4 slices (Figure 1C).

To assess the reproducibility of %ACV measurements, paired examinations were performed by a single observer on 2 different occasions (intraobserver reproducibility) and by two observers on the same occasion (interobserver reproducibility) in a group of 50 subjects. The intraobserver and interobserver coefficients of variation were 4.4% and 5.1%, respectively.

Two independent masked observers determined the level of %ACV. The rate of progression of %ACV was represented by Δ%ACV/year calculated with the following formula: (%ACV at the end of follow-up−%ACV at the baseline)/follow-up period (year).

Clinical Parameters

We evaluated several clinical parameters at the first examination and every 6 months thereafter during follow-up periods for more than 2 years. In each examination, we measured BP, fasting serum lipid levels (TC, LDL-C, HDL-C, and TG), fasting plasma glucose (FPG), and %ACV. The measurements were performed in the morning after an overnight fast. BP was measured after 15 minutes of quiet rest in the supported right arm of the seated subjects with a mercury sphygmomanometer cuff-size adjusted for arm circumferences. Phases I and V of the Korotkoff sounds were considered SBP and DBP, respectively. PP and MBP were calculated with the following formula: PP=SBP−DBP and MBP=DBP+PP/3. Three measure-

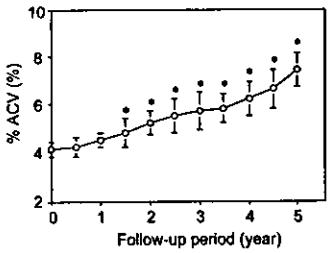

Figure 2. In 50 randomly selected subjects, %ACV values determined every 6 months were plotted. Error bars indicate the standard deviations. *$P<0.05$ against the baseline (time 0).

ments performed with intervals for more than 2 minutes were averaged. Hypertension was defined as: (1) current use of antihypertensive agents and/or a history of hypertension; (2) SBP≥140 mm Hg; or (3) DBP≥90 mm Hg. During follow-up periods for more than 2 years, we examined BP, lipid levels, and FPG every 6 months. TC, HDL-C, and TG levels were enzymatically determined using an autoanalyzer. The levels of LDL-C were calculated using Friedewald equation. The concentration of FPG was measured by the glucose oxidase method.

Statistical Analyses

In the present study, we used the values of clinical parameters obtained at the first examination after starting treatment as baseline values. To compare the mean values of %ACV, analysis of covariance was used. When a significant difference was obtained by analysis of variance, the differences among groups were assessed by Scheffe test. In a simple regression analysis, Pearson correlation coefficients were used for continuous variables and Spearman correlation coefficients were used for categorical variables. Age- and, sex-adjusted, and multivariate-adjusted correlations were analyzed by multiple regression models. In a multivariate-adjusted analysis, age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking (yes=1, no= 0), antihypertensive treatment (yes=1, no=0), and follow-up period were entered into the model. Values were represented as means±SD; $P<0.05$ was considered statistically significant. Statistical analyses were performed with Stat View Version 5.0 (SAS Institute Inc, Cary, NC).

Results

First, to confirm that our method is able to evaluate the progression of aortic calcification, we analyzed the change of %ACV during follow-up for 5 years in 50 randomly selected subjects. As shown in Figure 2, %ACV significantly increased at 1.5 or more years after the baseline examination. The increase in %ACV was almost linear. Therefore, we considered Δ%ACV/year as a marker of the progression of calcification in subjects whom we could follow-up for >2 years in the present study.

Table 1 shows the characteristics of the subjects at the baseline (first examination after the beginning of the treatment). Their ages ranged from 43 to 75 years. The mean value of basal %ACV was 5.0%. The mean follow-up period was 6.3 years. %ACV decreased in 12 subjects and increased in 103 subjects when the study was completed.

To determine clinical parameters that influence the progression of aortic wall calcification, we analyzed the relationships between the conventional risk factors for atherosclerosis and Δ%ACV/year. In a simple correlation analysis, Δ%ACV/year was significantly correlated with age, BMI, SBP, and PP (Table 2). The lipid levels, FPG, habitual smoking, and the use of HMG-CoA reductase inhibitors showed no significant relationships with Δ%ACV/year. In an age- and sex-adjusted correlation analysis, BMI, SBP, and PP showed significant correlations with Δ%ACV/year. When the subjects were divided into 3 groups according to the levels of PP, age-adjusted and sex-adjusted Δ%ACV/year was significantly elevated in the high PP (≥60 mm Hg) group compared with the moderate PP (50≤PP<60 mm Hg) and low PP (<50 mm Hg) groups (Figure 3). Furthermore, by a multivariate regression analysis including age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking, antihypertensive treatment, and follow-up period, PP was revealed to be the strongest risk factor for the progression of aortic wall calcification, whereas DBP and MBP were not detected as a predictive factor (Table 3).

TABLE 1. Baseline Characteristics of the Subjects

N (men/women)	116 (74/42)
Age (years)	57.4±8.3
BMI (kg/m^2)	24.0±2.2
SBP (mm Hg)	132.1±14.4
DBP (mm Hg)	77.4±9.1
MBP (mm Hg)	95.6±10.3
PP (mm Hg)	54.8±9.3
TC (mmol/L)	5.44±0.28
HDL-C (mmol/L)	1.26±0.36
LDL-C (mmol/L)	3.52±0.47
TG (mmol/L)	1.41±0.40
FPG (mmol/L)	5.48±0.74
%ACV (%)	5.0±4.4
Habitual smoking (%)	44.8
Hypertension (%)	62.9
Lipid-lowering drug	
HMG-CoA reductase inhibitors (%)	79.3
Probucol (%)	31.9
Fibrates (%)	21.6
Antihypertensive drug	
ACEIs (%)	14.7
CCBs (%)	35.3
BBs (%)	17.2
Others (%)	5.2
N of antihypertensive drug	
0 (%)	37.1
1 (%)	55.2
2 (%)	6.0
≥3 (%)	1.7

Values are the mean±SD or frequencies.

Discussion

To our knowledge, this is the first prospective study revealing that PP is an independent risk factor for the progression of arterial wall calcification in patients with controlled hyperlipidemia to exclude the influence of abnormal lipid levels.

In general, SBP progressively increases while DBP decreases in humans older than 50 years, resulting in the

TABLE 2. Correlation Coefficients Relating to Δ%ACV/year

	Simple Correlation		Age- and Sex-Adjusted Correlation	
Risk Factors	*r*	*P* Value	β	*P* Value
Age	0.206	0.026	...	...
Sex	0.117	0.209	...	...
BMI	0.196	0.035	0.229	0.015
SBP	0.274	0.003	0.244	0.009
DBP	0.032	0.736	0.044	0.640
MBP	0.147	0.116	0.136	0.144
PP	0.392	<0.001	0.359	<0.001
TC	0.040	0.673	0.004	0.969
HDL-C	−0.022	0.812	−0.084	0.387
LDL-C	0.010	0.913	0.031	0.737
TG	0.080	0.394	0.103	0.303
FPG	0.024	0.803	0.047	0.619
Smoking habit (yes/no)	−0.075	0.425	−0.024	0.806
HMG-CoA reductase inhibitor (yes/no)	−0.045	0.633	−0.042	0.648

increase in PP. This change is thought to be caused by the remodeling of arterial walls resulting from the decrease in wall elasticity, for which vascular calcification is one of the major factors. In the present follow-up study, the multivariate regression analysis showed that PP was the strongest risk factor for the increase in %ACV/year. To take into account the interim measures every 6 months during the follow-up periods, we also assessed predictors for the increase in %ACV by the pooling of repeated observation method.[13,14] By using this method, PP was again detected as the strongest predictor for %ACV increase (data not shown). These results suggest that the increase in PP on its own promotes arterial calcification.

Previous studies reported a difference between genders in the frequency of vascular calcification. In a cohort study in a large population of >100 000, the prevalence of aortic calcification detected with a chest x-ray examination did not

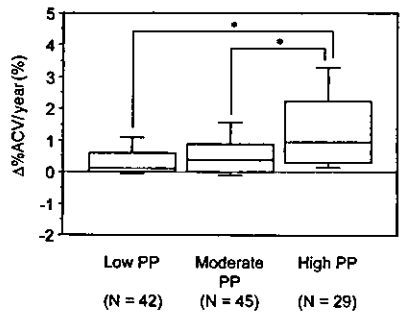

Figure 3. The levels of Δ%ACV/year in the 3 groups divided by PP. Low PP group indicates PP<50 mm Hg; moderate PP group, 50 mm Hg≤PP<60 mm Hg; high PP, PP≥60 mm Hg. The central line represents the distribution median, and the boxes span from the 25th to 75th percentile. Error bars indicate the 95% confidence interval. Statistical significances between the groups were evaluated by age-adjusted and sex-adjusted analysis of variance. *$P<0.01$.

TABLE 3. Multivariate Regression Coefficients Relating to Δ%ACV/year

	r	β	*P* Value
SBP	0.381	0.293	0.008
DBP	0.295	0.059	0.577
MBP	0.324	0.166	0.124
PP	0.436	0.389	<0.001

Multivariate regression analysis including age, sex, BMI, HDL-C, LDL-C, TG, FPG, habitual smoking, antihypertensive treatment, and follow-up period.

differ between men and women before middle age. However, in subjects older than 65 years, the frequency was significantly larger in women than in men.[15] One of the reasons for this difference was considered to be the change in hormone levels after menopause in women. The decrease in estrogen concentrations is associated with the increase in LDL-C levels and induces vascular calcification; furthermore, hormone replacement therapy suppresses the progression of aortic calcification in women after menopause.[16–18] However, in our population, there was no significant gender difference in Δ%ACV/year (Table 2), probably because most of our subjects were middle-aged and the lipid profiles were controlled.

The calcified lesions we analyzed in the present study were only atherosclerosis-related. There are 2 distinct forms of arterial wall calcification.[19] One is an intimal calcification that develops as part of an atherosclerotic plaque, and the other is a medial calcification formed with aging and in patients with diabetes, end-stage renal disease, neuropathy, and a number of rare genetic disorders. Most previous studies did not discriminate between them, although the volume of vascular calcification has been reported to be proportional to that of whole atheromatous plaques including calcification.[20,21] However, we excluded patients who had diseases that would promote the medial calcification, and almost all of the calcium deposits found with CT were located in the intima in our subjects. Therefore, our results may be inapplicable to the medial calcification.

Our study has several limitations. First, although ≈80% of the subjects were administered HMG-CoA reductase inhibitors, the other classes of lipid-lowering drugs such as probucol and fibrates were also used. HMG-CoA reductase inhibitors[22] and probucol[23,24] have been reported to have pleiotropic effects besides cholesterol-lowering effects in recent studies. In our subjects, however, this lack of uniformity may not have affected the analysis because there was no significant difference in Δ%ACV/year among lipid-lowering agents in a simple correlation analysis (Table 2). Second, BP was measured only in the office. Therefore, other factors such as the white-coat effect may have influenced the BP.

In conclusion, we demonstrated that PP is an independent predictor for the progression of atherosclerotic calcification in lipid-controlled subjects. Our results suggested that an increase in PP is not only a result of vascular wall stiffening but also an accelerator of vascular calcification. These results support, in part, the strong correlation between PP and cardiovascular morbidity and mortality.

Acknowledgments

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Original Article

Effects of Repeated Alcohol Intake on Blood Pressure and Sodium Balance in Japanese Males with Hypertension

Yuhei KAWANO, Hitoshi ABE, Shunichi KOJIMA, Shuichi TAKISHITA, and Hiroaki MATSUOKA

Alcohol consumption causes biphasic changes in blood pressure (BP) in Asians. The aim of the present study was to investigate the effects of repeated alcohol intake on BP and sodium metabolism. Fourteen Japanese males with hypertension (37–67 years old) were examined under standardized conditions (Na intake 120 mmol/day). After 1 week of alcohol restriction, the patients consumed a control drink with dinner for 3 days, 1 ml/kg of alcohol for the next 7 days, then the control drink for 3 days. Supine BP and heart rate were measured 5 times daily, and urinary excretion of water and sodium was determined throughout the study period. Average BP decreased initially, then returned to the baseline level during the alcohol period. Evening BP decreased significantly throughout the alcohol period, although the reduction was attenuated during the late phase. Morning and afternoon BP did not change significantly, but tended to be elevated during the late phase. Heart rate increased both in the morning and evening during the alcohol period. Urine volume did not change during the early phase, but increased significantly during the late phase. Urinary sodium excretion decreased initially, but increased during the middle phase of the alcohol period. In conclusion, BP decreases initially with sodium retention, then returns to the baseline level with restoration of sodium balance during repeated alcohol intake in Japanese males with hypertension. Sodium retention during the early phase appears to be the consequence of BP reduction and may contribute to the subsequent changes in BP. (*Hypertens Res* 2004; 27: 167–172)

***Key Words*: alcohol, hypertension, blood pressure, sodium, natriuresis**

Introduction

The relation between alcohol consumption and hypertension is well known (*1*, *2*), and restriction of alcohol intake is recommended in the management of hypertension (*3*). Although the pressor effect of alcohol has been well documented (*1*, *2*, *4–6*), ethanol has both vasoconstrictive and vasodilatory actions, and a metabolite of ethanol acetaldehyde dilates blood vessels (*7*). We reported previously that a single intake of alcohol lowers blood pressure (BP) for several hours, while repeated alcohol consumption causes biphasic changes in the BP of Japanese males with hypertension (*8–10*). It is also known that cessation of drinking sometimes causes alcohol withdrawal syndrome, which includes transient BP elevation and tachycardia (*11*). These effects of alcohol appear to be dependent on the duration and amount of consumption, the time from the last drinking, and the presence or absence of alcohol flush, which is common in Asians (*12*, *13*). However, the time-related changes in BP caused by alcohol consumption and its withdrawal have not been clarified precisely.

It has been reported that alcohol has effects on water and electrolyte metabolism, such as diuresis due to the suppres-

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sion of vasopressin release and increases in urinary excretion of magnesium and calcium (*14–16*). We observed previously that ingestion of alcohol decreased the serum potassium level and intracellular sodium concentration in hypertensive subjects (*17*). It has also been reported that alcohol acutely reduces urinary sodium excretion (*14*, *18*, *19*). This effect of alcohol may be involved in alcohol-induced hypertension, since sodium balance plays an important role in BP regulation and hypertension. However, there have been no studies investigating the effects of repeated alcohol consumption on sodium balance with reference to changes in BP.

In the present study, we examined the effects of repeated intake of alcohol and its withdrawal on BP and sodium and water metabolism in Japanese males with essential hypertension. To investigate the effects of alcohol on BP in detail, BP was measured 5 times per day from early morning to late evening throughout the study period under standardized conditions.

Methods

Subjects

Fourteen Japanese males with essential hypertension and drinking habits were studied. Their ages were 37–68 years old (54±2 years, mean±SEM), and average height and weight were 168±1 cm and 67±1 kg, respectively. The amount of their usual alcohol intake ranged from 30–105 ml/day (67±5 ml/day). All patients were diagnosed as having mild to moderate essential hypertension and none of them had serious cardiovascular, hepatic, or renal disorders. Two patients were never treated, and the other 12 patients were treated with antihypertensive drugs before the present study.

Protocol

The study protocol was approved by the Ethics Committee of the National Cardiovascular Center, and informed consent was obtained from each subject. All subjects abstained from alcoholic drinks and stopped antihypertensive medications for at least 1 week before the study. Subjects were hospitalized in a ward of the National Cardiovascular Center where they ate a regular hospital diet (Na 120 mmol/day, 1,600 kcal/day). Before entering the protocol, subjects stayed in the ward for several days to minimize the effect of hospitalization on BP during the study protocol.

The study was divided into three consecutive phases: Control phase—a 3-day period during which nonalcoholic drinks having the same number of calories as the alcoholic drinks were added to the dinners (17:00–18:00); Alcohol phase—a 7-day period during which 1 ml/kg of ethanol was administered with dinner, in the form of vodka, lime juice and water; Recovery phase—a 3-day period during which the nonalcoholic drinks were added to dinners. Additional water intake was not restricted throughout the study protocol.

Supine BP was measured using mercury sphygmomanometers at 6:00, 10:00, 14:00, 18:00 and 21:00 by trained nurses throughout the study period. Heart rate was measured manually immediately before the BP measurements. Urine collections for 24 h and measurements of fasting body weight were also carried out each day. Venous blood samplings were performed before dinner (17:00), 60–90 min after dinner (19:00), and before breakfast (8:00) on the morning following the last day of the control period and on Days 1 and 7 of the alcohol period.

Biochemical Measurements

Serum electrolytes and urinary excretion of sodium, potassium and creatinine were determined using a biochemical analysis system (TBA-80S; Toshiba, Tokyo, Japan).

Statistical Analysis

Values are expressed as the mean±1 SEM. Comparisons were made by repeated measures analysis of variance followed by the contrast method. Analyses were performed using Stat View (ver. 5) and Super ANOVA software (Abacus Concept Inc., Berkeley, USA). A p value of less than 0.05

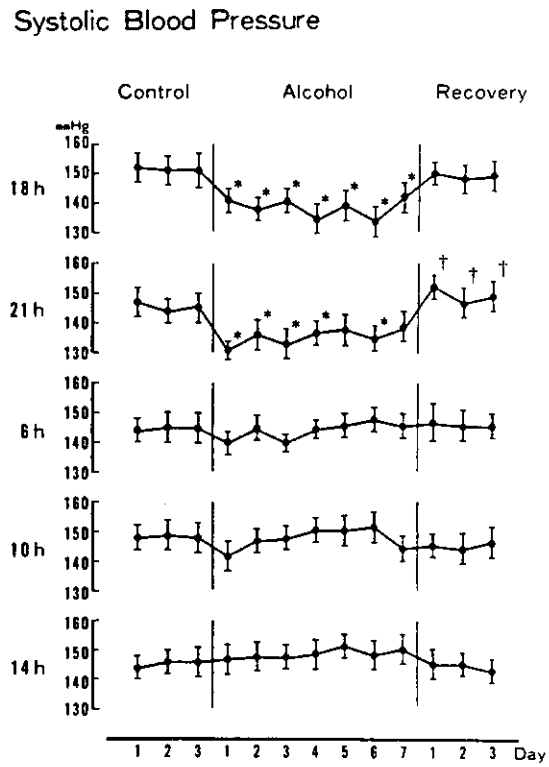

Fig. 1. *Systolic blood pressure at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

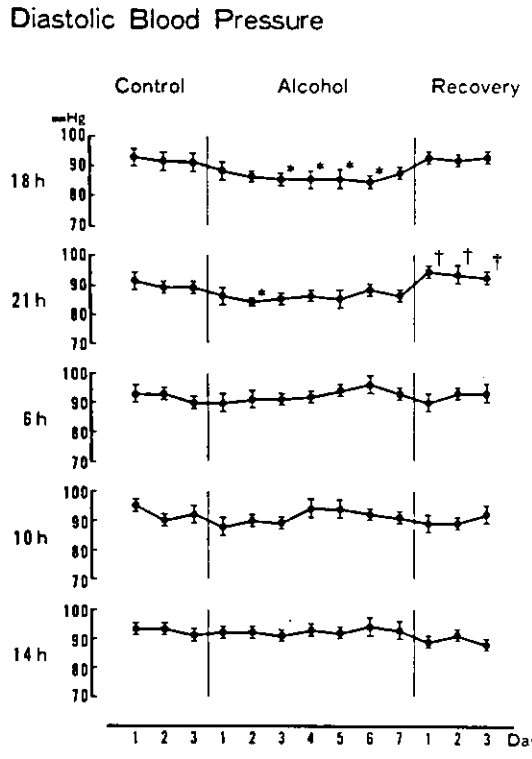

Fig. 2. *Diastolic blood pressure at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

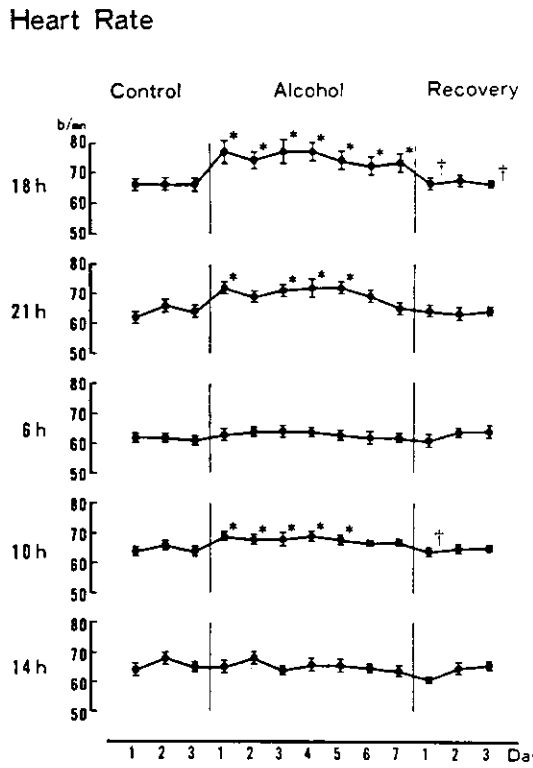

Fig. 3. *Heart rate at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

was considered statistically significant.

Results

Blood pressure and heart rate at different times of the day during the control, alcohol and recovery periods are shown in Figs. 1–3. Evening BP during the alcohol period was consistently lower than that during the control period (systolic BP at 21:00 was 145.4±4.9 mmHg on the last day of the control period, and 130.7±3.2 mmHg on Day 1 of the alcohol period). Morning and afternoon BPs did not change during the alcohol period, although they tended to increase during the late phase (systolic BP at 14:00 was 146.1±6.2 mmHg on the last day of the control period, and 151.8±4.9 mmHg on Day 7 of the alcohol period). These changes in BP returned to the control level during the recovery period. Heart rate increased significantly both in the morning and evening during the alcohol period, although these changes were attenuated during the late phase. The increases in heart rate returned to baseline during the recovery period.

Daily average BP and heart rate are shown in Fig. 4. Systolic BP decreased significantly during the early phase of the alcohol period (Day 1: 140.2±3.2 mmHg) compared with the control period (147.2±4.7 mmHg); however, the reduction was blunted during the late phase (Day 7: 144.7±

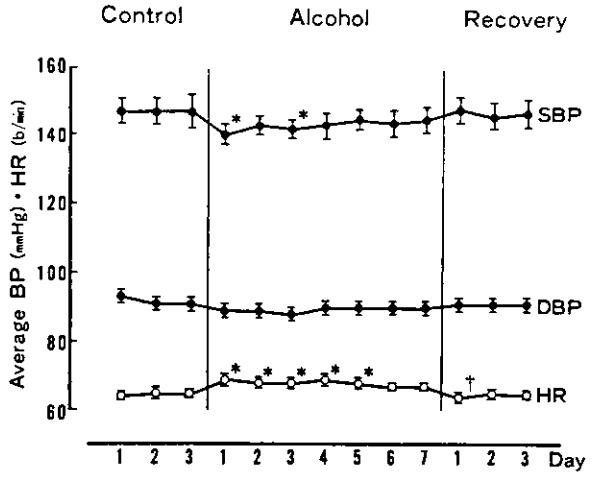

Fig. 4. *Average systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

3.6 mmHg). Diastolic BP showed a similar tendency, although its change was not significant. Average heart rate increased during the alcohol period (Control: 64.0±1.0; Day