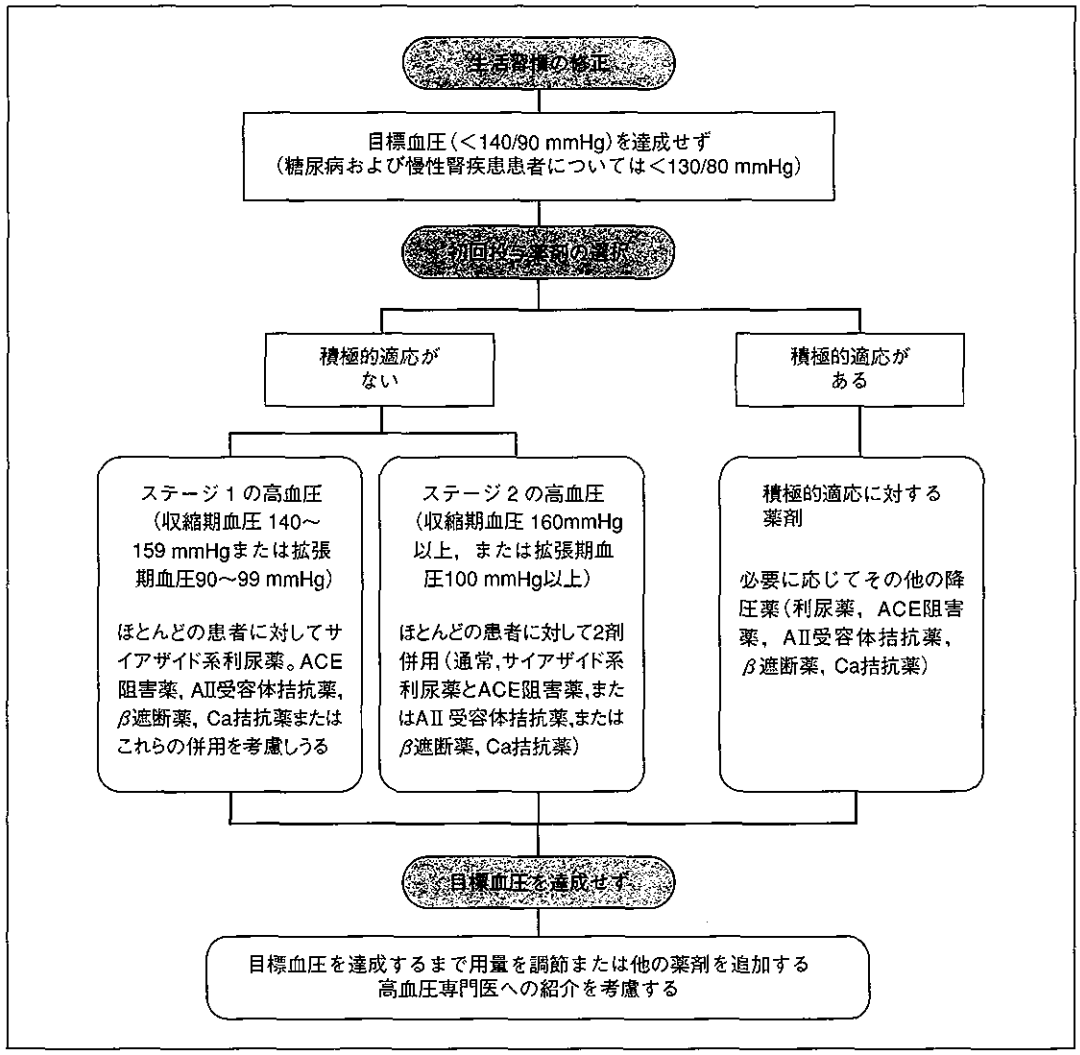

図 2　JNC 7 による高血圧治療手順（文献 9 より）

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

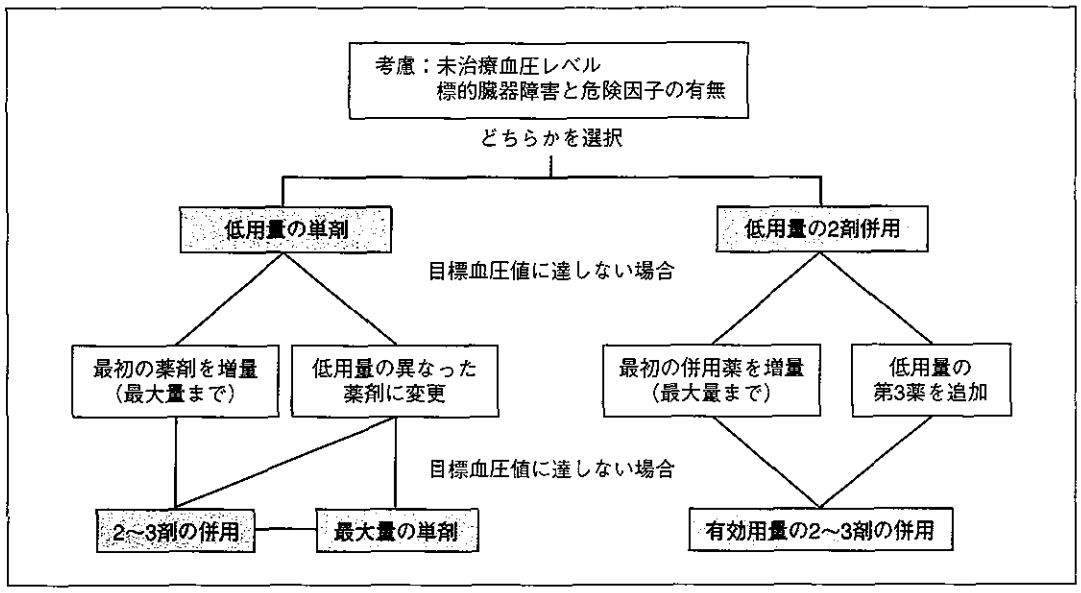

図 3　ESH/ESC ガイドラインによる単剤療法と併用療法の選択（文献 10 より）

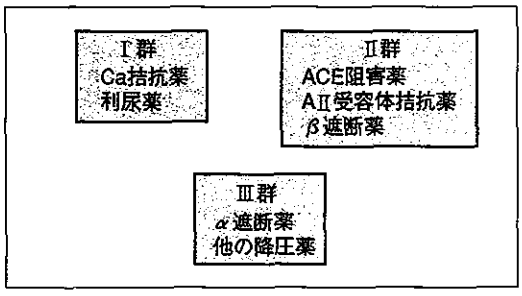

図 4　併用療法における降圧薬のグループ分け

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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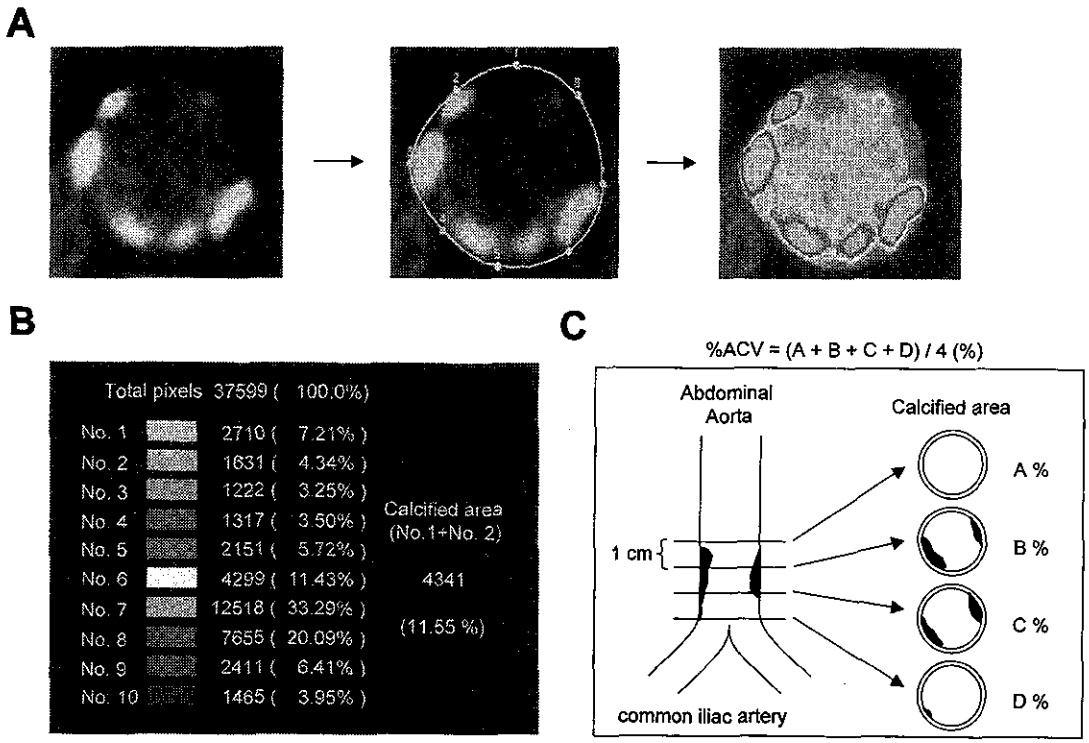

Figure 1. The method to determine %ACV. A, When an observer circles the abdominal aorta, the software program (TES-100 image color analysis software program) transforms the monochrome contrast image into a color image. B, The software automatically calculates the percentage of calcified area from pixel 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-

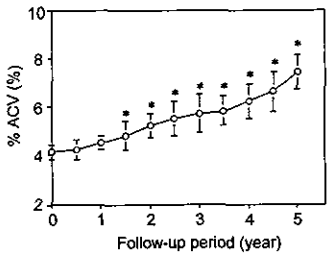

Figure 2. In 50 randomly selected subjects, %ACV values determined every 6 months were plotted. Error bars indicate the standard deviations. *$P<0.05$ against the baseline (time 0).

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

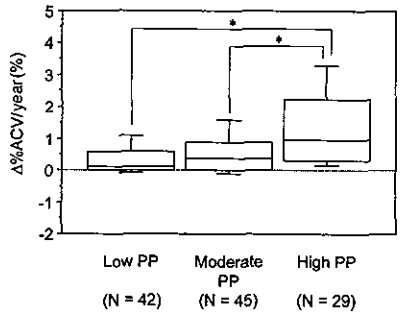

Figure 3. The levels of Δ%ACV/year in the 3 groups divided by PP. Low PP group indicates PP<50 mm Hg; moderate PP group, 50 mm Hg≤PP<60 mm Hg; high PP, PP≥60 mm Hg. The central line represents the distribution median, and the boxes span from the 25th to 75th percentile. Error bars indicate the 95% confidence 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

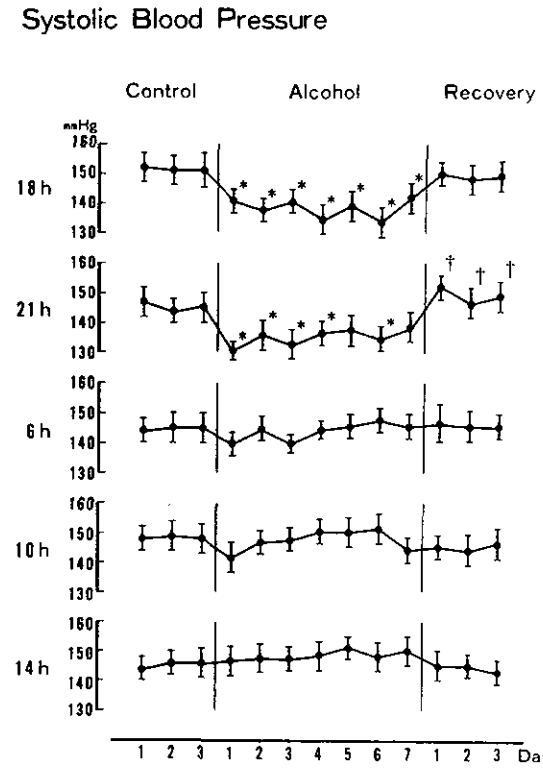

Fig. 1. *Systolic blood pressure at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

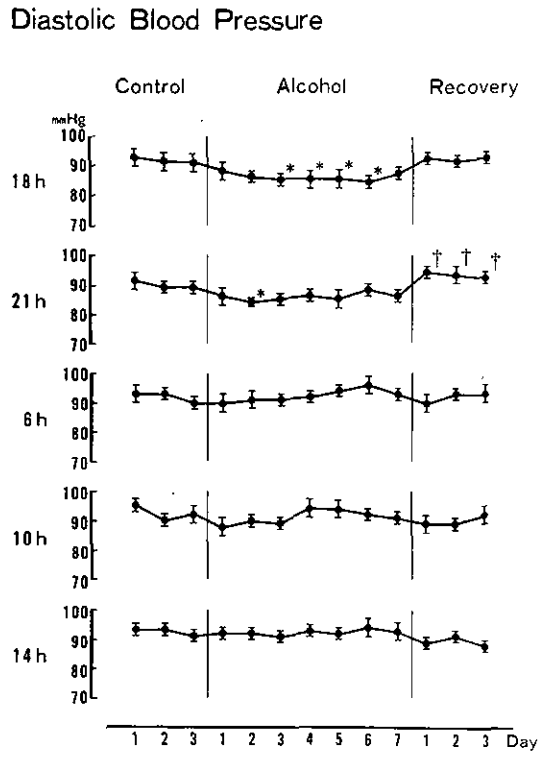

Fig. 2. *Diastolic blood pressure at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

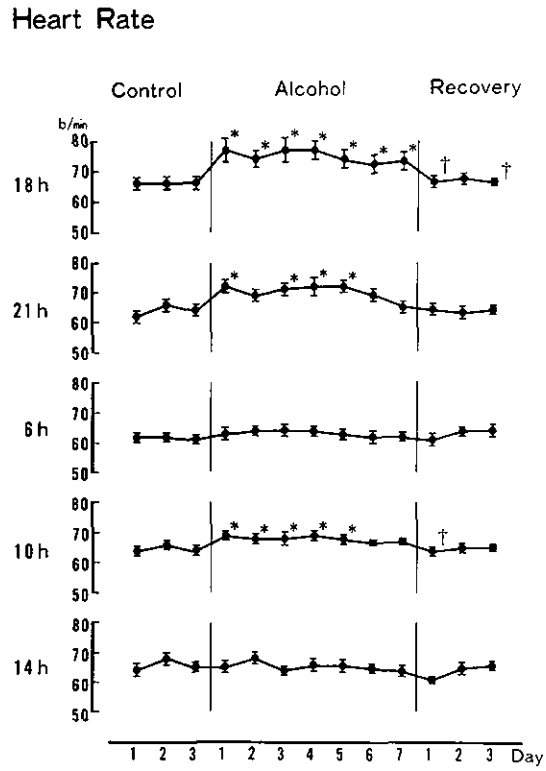

Fig. 3. *Heart rate at 5 different time points during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

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±

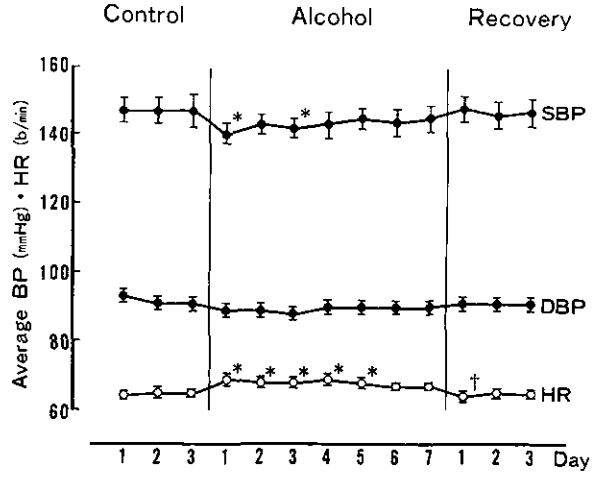

Fig. 4. *Average systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.* † $p<0.05$ vs. *the last day of the alcohol period.*

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

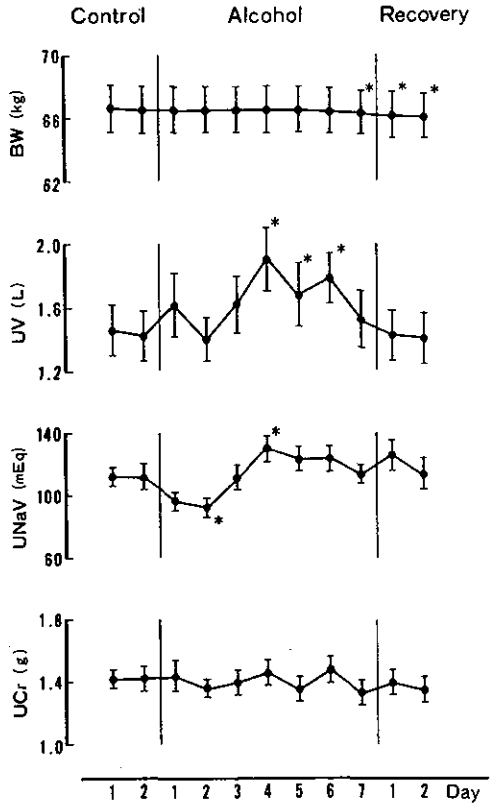

Fig. 5. *Body weight (BW), urine volume (UV), urinary sodium excretion (UNaV), and urinary creatinine excretion (UCr) during the control, alcohol, and recovery periods.* * $p<0.05$ vs. *the last day of the control period.*

1: 68.7±1.4; Day 7: 66.5±1.1 beats/min), and returned to baseline during the recovery period.

Body weight decreased slightly but significantly during the late phase of the alcohol period and the recovery period (Fig. 5). Urine volume did not change during the early phase of the alcohol period, but increased significantly on Days 4–6. Biphasic changes in urinary Na excretion were observed during the alcohol period. It decreased from 112± 8 mmol/day during the control period to 97±6 mmol/day on Day 2, then increased to 130±8 mmol/day on Day 4. There were no significant changes in urinary excretion of creatinine or K.

Serum Na and K concentrations at 17:00, 19:00 and 8:00 during the control and alcohol periods are shown in Table 1. There were no significant changes in serum Na concentration. Serum K decreased after meals both during the control and alcohol periods; however, the level of serum K after ingestion of alcohol was significantly lower than that during the control period.

The alcohol-induced reductions in BP and urinary sodium excretion were more obvious in two patients who showed marked facial flush after alcohol ingestion than in the rest of subjects. The amount of usual alcohol intake did not relate to the changes in BP or sodium excretion.

Table 1. Serum Concentrations of Sodium and Potassium during the Control and Alcohol Periods

	Control	Alcohol Day 1	Alcohol Day 7
Serum Na (mmol/l)			
17:00	140.1±0.7	140.0±0.5	139.5±0.5
19:00	139.7±0.7	140.0±0.6	139.6±0.6
8:00	140.3±0.7	140.1±0.6	139.6±0.5
Serum K (mmol/l)			
17:00	4.09±0.06	4.06±0.07	3.97±0.05
19:00	3.84±0.05†	3.65±0.05†,*	3.61±0.04†,*
8:00	4.18±0.06	4.16±0.07	4.14±0.06

† $p<0.05$ *vs.* 17:00, * $p<0.05$ *vs.* control period.

Discussion

In the present study, repeated intake of alcohol for 7 days caused significant changes in BP and Na balance in Japanese males with hypertension. The alcohol-induced reduction in evening BP was consistently observed throughout the alcohol intake days, while the decrease in average BP was observed in the early but not the late phase of alcohol consumption. These changes in BP were associated with early sodium retention followed by natriuresis during the alcohol period. The present study demonstrates that repeated alcohol intake causes biphasic changes in BP and sodium metabolism, and suggests these changes may interact with each other.

The changes in BP after repeated alcohol consumption confirm previous observations (*8–10*). The reduction in evening BP was observed throughout the alcohol period in this and our previous studies. This depressor response may be specific to Asian subjects, since alcohol flush syndrome characterized by facial flush and tachycardia is common in Asians but rare in Caucasians and Africans (*8, 20*). The alcohol-induced BP elevation was not apparent in the present study, but morning and afternoon BPs tended to increase in the late phase (*9, 10*). The mechanisms of the hypertensive effect of alcohol have not been completely clarified, although neurohumoral substances, vascular smooth muscle, and endothelium may be involved (*13, 16*). Our studies suggest that the alcohol withdrawal rather than any straightforward action of alcohol itself may play an important role in the BP elevation because BP fell at the time of high blood alcohol level. The average BP measured at 5 different hours decreased during the early phase of the alcohol period, then returned to the baseline level in the present study. These findings suggest that some slow pressor mechanisms may operate in the changes in BP after repeated alcohol intake.

Heart rate increased during the alcohol period in the present study, confirming previous observations (*8–10, 16*). The change in heart rate was most apparent in the evening but was also seen in the morning. The evening tachycardia appears to be due to the direct action of alcohol and to the re-

flex response to BP reduction. Mechanisms related to alcohol withdrawal, such as activation of the sympathetic nervous system, may be involved in the morning rise in heart rate.

Urinary sodium excretion decreased during the early phase but increased during the middle phase of the 7-day alcohol period in the present study. The early reduction in sodium excretion appears to be related to the initial decrease in BP, since BP is a powerful regulator of renal sodium handling and *vise versa* (*21*). This sodium retention may contribute to the subsequent BP change, including the rise in daytime BP. The late natriuresis also appears to follow the change in average BP, which returned to the baseline level after repeated alcohol consumption. The acute reduction in urinary sodium excretion after alcohol consumption was also observed in some earlier studies (*14*, *18*, *19*). In addition to the hemodynamic mechanism, neurohormonal factors might contribute to the alcohol-induced sodium retention, since activation of the sympathetic nervous system and the renin-angiotensin system acts on the kidney to reduce sodium excretion (*22*). In the related previous studies, we observed that both plasma norepinephrine concentration and plasma renin activity increased after a single alcohol ingestion (*8*, *23*). However, those changes were attenuated after repeated intake of alcohol (*9*).

The alcohol-induced changes in BP, heart rate and sodium metabolism may not be restricted to hypertensive patients, but may also be seen in normotensive subjects. Acute reductions in BP and sodium excretion (*19*, *20*) and a chronic increase in BP (*24*) have also been observed in normotensive individuals. However, these effects of alcohol may be more clinically relevant in hypertensives than in normotensives. The effects of alcohol on BP appear to be dose-dependent, since a linear relationship has been observed between the amount of alcohol consumption and the level of BP (*1*, *2*). A similar dose-related effect would be expected regarding sodium metabolism, although have been no studies examining the dose-response relationship in humans.

In the present study, urine volume did not change during the early phase but increased during the middle phase of the alcohol period. It is known that alcohol temporally stimulates water excretion from the kidney. This alcohol-induced diuresis is mediated by the suppression of vasopressin secretion (*18*, *23*). The lack of initial diuresis in our study may be related to the decrease in BP, which acts to reduce renal water excretion. The increase in urine volume was observed in parallel with natriuresis when BP returned to the baseline level. However, a precise assessment of water balance was not possible in the present study, since the amount of daily water intake was not measured.

Several studies have shown that serum sodium concentration increases after alcohol ingestion (*25*, *26*). This change in sodium concentration may be related to the alcohol-induced diuresis. In the present study, the level of serum sodium did not change during the alcohol period. The lack of marked diuresis and the free access to water may explain the stable level of serum sodium. On the other hand, the serum potassium concentration decreased acutely after alcohol intake, confirming earlier observations (*8*, *26*, *27*). This alcohol-induced hypokalemia was not due to kaliuresis, but was mediated by activation of the sympathetic nervous system, since propranolol attenuated the change in serum potassium in our previous study (*27*).

Alcohol consumption may also influence BP through its effects on magnesium and calcium metabolism (*13*). It has been shown that urinary excretion of these minerals increases after ingestion of alcohol (*14*, *15*), although we did not measure urinary magnesium and calcium in the present study. The alcohol-induced deficiency of these minerals may play a role in BP elevation. An experimental study has shown that magnesium supplementation prevents the development of alcohol-induced hypertension in rats (*28*). However, the depressor effect of magnesium and calcium supplementation was not significantly different between drinkers and nondrinkers in our previous studies (*29*, *30*).

In conclusion, the findings of the present study show that average BP decreases during the early phase but returns to the baseline level during the late phase during repeated alcohol intake in Japanese males with hypertension. Urinary sodium excretion decreased initially, then increased during the alcohol period. The early sodium retention appears to be the consequence of alcohol-induced BP reduction and may participate in the subsequent BP elevation.

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総　説

高血圧の個別管理と集団管理

河野雄平*

要　約　高血圧は種々の循環器病の危険因子であるとともに普遍的な疾患であり、とくに老年者における有病率は高い。これらのことは、高血圧の循環器病の予後への絶対リスクが非常に大きく、その管理が極めて重要であることを意味している。高血圧の個別管理はhigh risk strategyであり、個々の患者に対する生活習慣改善（非薬物療法）の指導および薬物療法が主となる。降圧治療により高血圧患者の心血管予後、生命予後が改善することは明らかである。しかし、正常高値血圧者はより低い血圧の者に比べて高リスクであるが、個別管理の対象にならないことが多い。また、治療中であってもコントロールされていない者は少なくない。治療中の高血圧患者の予後は正常血圧者より不良であり、不十分な降圧や他の危険因子、臓器障害が問題と考えられる。将来は遺伝子研究が進めば、生活習慣や薬物治療についてのより的確な個別管理が可能になるであろう。高血圧の集団管理はpopulation strategyであり、血圧測定の普及と高血圧についての啓蒙、生活習慣改善の教育と指導が中心となる。人口集団の血圧が全体として数mmHg低下すれば、循環器疾患の予防にかなりの効果が期待できる。しかし、これのみでは重症高血圧者の心血管リスクはなおも非常に高いことになる。日本ではすでに職場や学校、自治体などによる種々の検診がなされているが、全国民における定期的な血圧測定が望まれる。また、高血圧の予防と治療のためには学会や国をあげての啓蒙が重要であろうが、現在の状況で十分とは言いがたい。結論として、高血圧の集団管理と個別管理はともに重要であり、補いあうものである。両者の効率的な運用は、高血圧の予防と治療および循環器病の予防に大きな意義を有している。

キーワード：高血圧，生活習慣，薬物療法，個別管理，集団管理，循環器病
（日循予防誌　39：132－138，2004）

はじめに

高血圧は、脳出血や脳梗塞などの脳血管障害、心筋梗塞や狭心症などの虚血性心疾患、心不全、不整脈といった心臓病、腎不全、さらに大動脈瘤や大動脈解離、閉塞性動脈硬化症といった種々の循環器病の主要な危険因子になっている。高血圧は自覚症状に乏しいことが多く、その管理の大きな目的は心血管系の合併症を予防して生命予後を改善することである。降圧治療により高血圧患者の予後が改善することについては確かなエビデンスがあり、血圧測定と降圧治療の普及により高血圧の診断と治療は容易になってきた。しかし、高血圧があっても診断されていない者、治療を受けていない者、血圧がコントロールされていない者は少なくない。ここでは高血圧の個別管理と集団管理について概説し、またそのための薬物療法や生活習慣改善について、原則や効果、限界などを含めて述べていきたい。

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I　個別管理と集団管理

1．高血圧の個別管理

高血圧の管理に関しては、個別管理と集団管理に分けて考えることができる。個別管理はhigh risk strategyであり、主に各々の高血圧者の血圧を正常化することにより心血管リスクを減少させるものである（図1）。血圧が高いほど脳卒中や心筋梗塞などの心血管リスクが増加することは明らかであり（図2,3）[1]、また降圧治療により高血圧患者の心血管予後、生命予後が改善することも確かめられている。高血圧者の病態は一様ではなく、適切な個別管理により個々の患者におけるリスクの低下が期待できる。これはまた、全体の予後も改善することを意味している。

高血圧の個別管理は、生活習慣改善（非薬物療法）および薬物療法が主となる。それらについては、後に詳述する。また、血圧は常に変動しており、検診や外来での随時血圧が各個人の血圧を正しく反映しているとは限らない。家庭血圧や24時

間血圧のモニタリングを取り入れることにより、よりよい高血圧の個別管理ができるであろう。また将来、遺伝子研究が進めば、生活習慣や薬物治療についてのより的確な個別管理が可能になろう。

しかし、正常高値血圧者はより低い血圧の者に比べて明らかに高リスクであるが、個別管理の対象にならないことが多い。この点で、高血圧者のみを対象とした個別管理では、全体からみた循環器病の予防において限界がある。また、治療中であっても血圧がコントロールされていない者は極めて多い。降圧治療により予後は改善するが、治療中の高血圧患者の予後は正常血圧者より不良であることも知られている。その原因として、不十分な降圧や治療開始の遅れ、他の心血管危険因子や臓器障害の存在などが考えられる。

2. 高血圧の集団管理

高血圧の集団管理はpopulation strategyであり、主に全体の血圧を下げることにより高血圧を予防あるいは改善し、心血管リスクを低下させるものである（図1）。人口集団の血圧が全体として数mmHg低下すれば、循環器疾患の予防にかなりの効果が期待できる。例えば、収縮期血圧が平均して5-6mmHg下がれば、脳卒中は約20%、心筋梗塞も10%以上減少するであろう。正常高値血圧者や軽症高血圧者は、相対リスクは高くはないが、絶対数が多いために心血管疾患のかなりの部分を占めている。集団管理はそれらにおける予後改善に大きな役割を果たすであろう。

高血圧の集団管理に関しては、検診などによる血圧測定の普及、高血圧についての啓蒙と教育、高血圧や他の心血管リスクファクターに対する生活習慣改善の教育と指導が中心となる。集団検診などにより高リスクの高血圧者を見い出すことは、各々への個別管理の適用にもつながる。日本ではすでに職場や学校、自治体などによる種々の検診がなされているが、全国民における定期的な血圧測定が望まれる。

しかし、集団管理にも限界がある。例えば重症高血圧者においては、血圧が数mmHg下がったところで心血管リスクはなおも極めて高い。また、高血圧者の病態や生活習慣は一様ではなく、血圧の変動も個人によって差が大きい。集団における随時血圧測定のみでは、白衣高血圧や仮面高血圧を見落とすことになるであろう。さらに、高血圧の予防と治療のためには学会や国をあげての啓蒙が重要であろうが、現在の状況で十分とは言いがたい。

結論として、高血圧の集団管理と個別管理はともに重要であり、補いあうものである。両者の効率的な運用は、高血圧の予防と治療および循環器病の予防に大きな意義を有している。

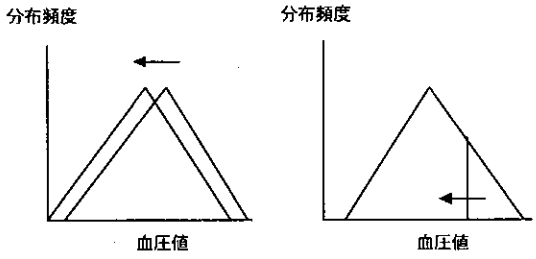

図1　高血圧管理のpopulation strategy(左)とhigh risk strategy

Ⅱ　高血圧の薬物療法

1. 大規模臨床試験によるエビデンス

薬物療法により高血圧患者の予後が改善することについては、これまでの多くの大規模臨床試験による確かなエビデンスがあり、その有効性は高齢者や収縮期高血圧においても証明されている[2]

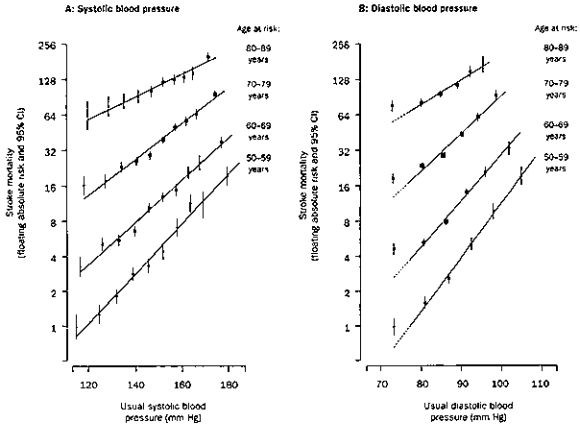

図2　観察的研究における血圧値と脳卒中死亡率のメタアナリシス（文献1による）

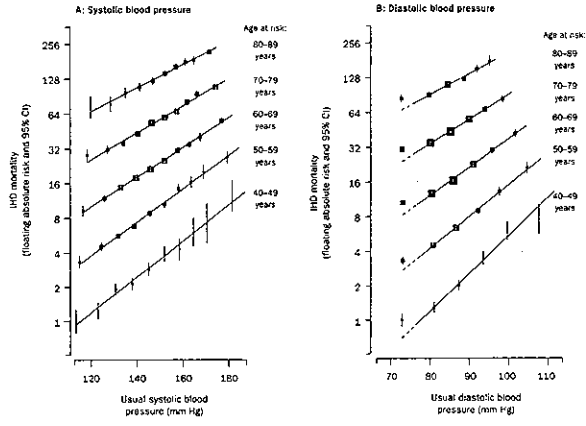

図3　観察的研究における血圧値と虚血性心疾患死亡率のメタアナリシス（文献1による）

(表1)。すなわち、降圧治療はプラセボに比較すると、脳卒中を30-40%、虚血性心疾患や心血管死亡を約20%、全死亡も10%以上減少させることが示されている。また、積極的な降圧は控えめな降圧より心血管イベントの予防に効果的であった[3]。

薬剤別に検討したメタアナリシスでは、利尿薬／β遮断薬に比較して、アンジオテンシン変換酵素（ACE）阻害薬の心血管予後への効果はほぼ同等であり、カルシウム（Ca）拮抗薬は脳卒中予防にやや優れ心疾患への効果は少し劣ることが示されている[3]。

最近発表された米国のALLHATは、4万人以上の高リスクの高血圧患者を対象に、利尿薬とCa拮抗薬、ACE阻害薬、α遮断薬の効果を調べた最大の臨床試験である[4]。α遮断薬は利尿薬に劣るとの理由で早期に中止されている。Ca拮抗薬とACE阻害薬は、利尿薬に比べて虚血性心疾患には差はなかったが、前者は心不全、後者は脳卒中、心血管イベント、心不全において劣っていた。ただし、ACE阻害薬は降圧効果も少し劣っていた。

アンジオテンシンⅡ受容体拮抗薬（AⅡ拮抗薬）についても、大規模臨床試験によるエビデンスが得られつつある。LIFE研究は、9,000人以上の左室肥大を伴う高血圧患者を対象としてロサルタンとβ遮断薬アテノロールを比べたもので、ロサルタン群は心血管イベントと脳卒中が少なく、心筋梗塞には差がなかった[5]。また、ロサルタンはアテノロールに比べて、副作用が少なく左室肥大の退縮に優れていることが示されている。

わが国では、降圧薬治療の大規模臨床試験によるエビデンスは、残念ながらほとんどない。しかし、これまでの臨床研究から、高血圧患者の予後への効果は利尿薬とCa拮抗薬、ACE阻害薬の間にあまり差はないことが示唆されている[6]。現在、JATOS、CASE-J、HOMED-BP、HOSPなどの無作為大規模臨床試験が進行中であり、その成果が期待される。

このように、高血圧に対する薬物治療の心血管予後への効果は、降圧自体が最も重要であると考えられる。降圧薬による差は、糖尿病性腎症など一部の病態を除いては明らかではない。AⅡ拮抗薬は他の薬剤より優れている可能性があるが、さらに知見の集積が必要であろう。老年者高血圧や家庭血圧での至適血圧も、今後の課題として残されている。

2. 薬物療法の原則

降圧薬による治療は、高血圧の個別管理において重要な位置を占めている。高血圧の治療においては、血圧値のみでなく臓器障害や他の心血管危険因子を考慮して方針を決定するが、非薬物療法には限界があり、多くの患者は薬物療法の適応となる。降圧薬には多くの種類があるが、主に用いられるものは、Ca拮抗薬、ACE阻害薬、AⅡ拮抗薬、利尿薬、β遮断薬、α遮断薬である[7]。他に、中枢性交感神経抑制薬や血管拡張薬も用いられる。

降圧薬は通常は少量から開始し、血圧値や副作用に注意しながら徐々に増やしていく。血圧の急激な低下は避け、数か月かけてコントロールすればよい。目標血圧値は140/90mmHg未満であるが、腎疾患や糖尿病を伴う場合にはより低くする(130/85 mmHg未満)。家庭血圧や24時間血圧はよい参考になるが、これらは一般に外来血圧より低いので、目標とする血圧値もやや低めとする。

降圧薬の選択にあたっては、各症例の病態を考慮して禁忌あるいは不適当なものを除外し、好適あるいは問題がない薬剤を選ぶようにする（表2)。長時間作用性の薬剤は、24時間の血圧コントロールと患者のコンプライアンスの点で優れている。最初に選択した降圧薬では不十分の場合には、①増量する、②他の群の薬剤に変更する、③他の群の薬剤を追加する、のいずれかにより血圧のコントロールに努める。単一の薬剤を大量に用いるより作用機序の異なる薬剤を少中等量で併用するほうが、降圧効果や副作用の点で好ましい。

3. 治療抵抗性高血圧

降圧治療によっても血圧がコントロールできない場合には、その原因を調べながら対策を立てる必要がある。3種類以上の降圧薬（利尿薬を含む）を用いても血圧のコントロールができないものを治療抵抗性高血圧という。その原因は様々であるが、患者、医師および高血圧自体のいずれかに問題があると考えられる。患者の問題としては、コンプライアンス不良で薬をきちんと飲まないことが最も多く、生活習慣が改善できないこともあげられる。医師の問題は薬の使い方が悪いことで、

表1　降圧薬治療を受けている患者とプラセボ投与患者における死亡率ならびに致死的および非致死的複合イベントにおける相対リスクの減少（文献2より）

	収縮期-拡張期高血圧		収縮期高血圧	
	リスク減少	P	リスク減少	P
死亡率				
全死亡率	-14%	<0.01	-13%	0.02
心血管性死亡率	-21%	<0.001	-18%	0.01
非心血管性死亡率	-1%	N.S.		N.S.
致死的あるいは非致死的イベント				
脳卒中	-42%	<0.001	-30%	<0.001
冠血管疾患	-14%	<0.01	-23%	<0.001

表2　降圧薬の積極的な適応と禁忌（文献7より）

	積極的な適応	禁　忌
Ca拮抗薬	高齢者、狭心症、脳血管障害、糖尿病	心ブロック（ジルチアゼム）
ACE阻害薬	糖尿病、心不全、心筋梗塞、左室肥大、軽度の腎障害、脳血管障害、高齢者	妊娠、高カリウム血症 両側腎動脈狭窄
AII受容体拮抗薬	ACE阻害薬と同様、特に咳でACE阻害薬が使用できない患者	妊娠、高カリウム血症 両側腎動脈狭窄
利尿薬	高齢者、心不全	痛風、高尿酸血症
β遮断薬	心筋梗塞後、狭心症、頻脈	喘息、心ブロック、末梢循環不全
α遮断薬	脂質代謝異常、前立腺肥大、糖尿病	起立性低血圧

不適当な用量や組み合わせ、血圧を上げる薬の併用などである。高血圧自体の問題としては、著しい白衣現象や二次性高血圧などがあげられる。

4. 新しいガイドライン

最近、米国および欧州より高血圧の診断や治療に関する新しいガイドラインが発表された。米国のものは、合同委員会の第7次報告（JNC 7）である[8]。後者は欧州高血圧学会（ESH）と欧州心臓学会（ESC）によるもので[2]、世界保健機構と国際高血圧学会（WHO/ISH）のガイドラインの改訂版と考えてよいであろう。

JNC 7は、血圧の分類と管理について新しい概念と原則を導入している。すなわち、正常血圧は120/80mmHg未満であり、120-139/80-89mmHgを前高血圧とした。高血圧は140/90mmHg以上で、160/100mmHgを境としてステージ1と2に分け単純化している。生活習慣の修正は、正常血圧者にも奨励し、前高血圧と高血圧者はこれを行うとした。薬物療法に関しては、積極的適応を除いてはサイアザイド系利尿薬を第一選択薬として推奨している。また、ステージ2の高血圧には、初回からの併用療法も勧めている。

ESH-ESCのガイドラインは、血圧の分類については従来通り、至適（120/80mmHg未満）、正常（120-129/80-84mmHg）、正常高値（130-139/85-89mmHg）、1度（140-159/90-99mmHg）、2度（160-179/100-109mmHg）、3度（180/110mmHg以上）の高血圧および収縮期高血圧（140以上/90未満）に分けている。降圧薬療法の主要な有用性は降圧それ自体によるので、主な降圧薬、すなわち利尿薬、β遮断薬、Ca拮抗薬、ACE阻害薬、AII拮抗薬は開始および維持に適しているとしている。降圧薬の妥当な併用も提示している。

このように、新しい2つのガイドラインはかなり異なっている。日本のガイドラインの改定は今後の課題であるが、降圧薬の選択などについてはESH-ESCのものがJNC 7より受け入れやすいように思われる。前高血圧の概念も高血圧予防の面からは評価できるが、JNC 7に従えば、高齢者で正常血圧の者は10%程しかいないことになるであろう。

III　生活習慣の改善

1. 生活習慣改善の原則

生活習慣改善（非薬物療法）は、高血圧の個別管理と集団管理の両者において重要である。生活習慣の改善は、食事や運動などにより血圧や他の心血管危険因子をコントロールするもので、高血圧の治療とともに予防にも大きな役割を有している。薬物治療との関係では、降圧薬治療に先だって開始し、治療中も継続することが推奨されている。

生活習慣改善についての日本高血圧学会によるガイドラインを表3に示す[7]。肥満者における減量、食塩制限、アルコール制限、運動と、禁煙、および高脂血症者における飽和脂肪とコレステロール制限が基本となる。これらのうち前4者は降圧を、後2者は心血管リスクの軽減を主な目的とする。非薬物療法は有用であるが、降圧効果が比較的小さいことと、実行と継続が困難な点が限界となっている[9]。

2. 各種の生活習慣改善とその効果

①食塩制限

食塩（ナトリウム）の摂取と高血圧との関係はよく知られており、食塩制限は高血圧治療の基本として重要である。日本人の食塩摂取量は1日約13gであり、世界的にみてもまだ多い。高血圧管理のガイドラインでは、日本は7g以下、欧米は6g未満を勧めている。食塩制限の効果は個人差があるが、1gあたり約1mmHgの降圧が期待できる。われわれの血圧モニタリングによる検討では、降圧効果は24時間を通して認められた[10]。また、食塩は血圧とは独立して心肥大や血管障害をもたらし、骨粗鬆症や腎結石、胃癌などにも関係している。

表3　生活習慣の修正項目（文献7より）

1）食塩制限7g/日(このうち調味料などとして添加する食塩は4g/日)以下。
2）適正体重の維持*
3）アルコール制限；エタノールで男性は20～30g/日(日本酒 約1合)以下、女性は10～20g/日以下。
4）コレステロールや飽和脂肪酸の摂取を控える。
5）運動療法(有酸素運動)**。
6）禁煙。

* 標準体重(22×[身長(m)]^2)の＋20%を超えない。
** 心血管病のない高血圧患者が対象。

これらの点からも食塩制限は重要と考えられる。

②体重の減量

肥満度と血圧との間には密接な関係があり、肥満を伴う高血圧者においては減量が重要となる。肥満とくに内臓肥満は、代謝異常を伴うことが多く（metabolic syndrome)、心血管リスクが大きい。減量にはカロリー制限が主となるが、運動も組み合わせることが望ましい。減量の降圧効果は明らかであり、1kgあたり1-1.5mmHgの血圧低下が期待できる。減量の降圧効果も24時間を通して認められる[11]。減量はまたインスリン感受性を改善し、糖・脂質代謝に好影響を及ぼすことから、心血管系リスク全体の軽減に有用性が大きい。

③運動

運動不足は、高血圧に関係することが示されている。また、身体活動量が少ない者は、心血管疾患や死亡のリスクが高いことが認められている。運動は減量にも有効であるが、これとは独立した降圧効果が認められている。高血圧の管理のためには、ウオーキングやサイクリングのような比較的軽い好気的運動を、定期的に（30-60分を週に数回）行うことが勧められる。介入試験のメタアナリシスでは、運動の降圧効果は約5mmHgで、高血圧者ではより大きいことが示されている[12]。運動はまた、体重の変化とは独立して糖・脂質代謝を改善する。

④飲酒制限

アルコールと高血圧の関係もよく知られている。高血圧管理における飲酒については、1日30ml（日本酒1合、ビール大1本に相当）以内、女性ではその半分が勧められている。観察的および介入的研究からは、アルコール10mlあたり血圧は約1mmHg変化する。しかし、アルコールと代謝産物は降圧作用も有している。われわれの研究では、アルコール制限により日中の血圧は下がったが、夜の血圧は逆に上昇し、24時間血圧は不変であった[13]。アルコールは脳出血、不整脈、心肥大などの危険因子であるが、一方では動脈硬化を抑制し虚血性心臓病の予防に働く。アルコール摂取量と循環器病死亡との間にはU型あるいはL型の関係が、全死亡との間にはJ型あるいはU型の関係が認められている[14]。したがって、大量飲酒者にはアルコール制限が望ましいが、飲酒を禁止すべきではない。

⑤禁煙

タバコは動脈硬化を促進し、虚血性心疾患の主要な危険因子となっている。喫煙者は非喫煙者に比し、循環器病、癌、全体の死亡率がそれぞれ1.5-2倍になることが示されている。また、禁煙はこれらのリスクを大幅に低下させる。すべてのガイドラインが、高血圧者に禁煙を強く勧めている。タバコと高血圧との関係は、疫学研究では認められていない。しかし、喫煙は血圧を急性に上昇させる。血圧モニタリングによる研究では、日中血圧は喫煙者が非喫煙者より高く、喫煙日は非喫煙日より高いことが認められている[15]。体重増加に注意を要するが、禁煙により血圧低下も期待できる。

⑥飽和脂肪とコレステロールの制限

高脂血症も虚血性心疾患の主要な危険因子であり、飽和脂肪とコレステロールの摂取制限は、高脂血症者における脂質代謝の改善のために重要である。血清総コレステロールおよびLDLコレステロールの低下には、飽和脂肪制限がコレステロール自体の制限より効果は大きい。トリグリセリドを低下させるには、脂質制限より糖質を主とするカロリー制限や運動が効果的である。HDLコレステロールは飲酒や運動により増加し、喫煙により減少する。

⑦ミネラル摂取

カリウム、カルシウム、マグネシウムといったミネラルは、摂取不足と高血圧との関係が示唆されている。これらの補給効果を調べた研究結果は一致していないが、カリウムはメタアナリシスでも比較的大きな降圧が示されている[16]。カルシウムとマグネシウムの降圧効果は小さい。われわれの血圧モニタリングによる研究でも、これらの摂取増加により有意な降圧が認められた[17]~[19]。した

がって、これらのミネラルは十分量を摂取することが勧められる。ただし、カリウムとマグネシウムは、腎不全を伴う場合には注意を要する。

⑧その他の食事

食事や生活に関するその他のことは、高血圧の一般的な治療法としてはあまり認められていない。しかし、魚油や食物線維の摂取による軽度の降圧が示されており、これらは脂質代謝などにも好影響を有している[9]。また、疫学研究においては、蛋白質の摂取量と血圧値との間に負の相関が認められている。

⑨食事全体の改善

高血圧の管理においては食事全体の改善も重要と考えられ、実際に有用性が示されている。例えば、米国のDietary Approaches to Stop Hypertension (DASH) 研究においては、果物と野菜および低脂肪の乳製品に富む食事 (DASH食) により、体重や食塩は変わらなくても血圧はかなり低下している[20]。この食事はミネラルを豊富に含んであり、線維や蛋白質も多い。DASH食は米国の新しいガイドラインにおいて推奨されている[8]。

⑩ストレス管理

持続するストレスや強いストレスは、高血圧や心血管事故の発症に関係する。また、仕事上のストレス (job strain) やストレスへの対応 (coping) も、高血圧との関連が示唆されている。ストレスマネージメントについては、リラクセーションやメディテーション、バイオフィードバック、ヨガなどの方法があるが、高血圧患者に対する降圧効果は確実ではなく、あまり実施されていない[9]。しかし、ストレスの多い生活はできるだけ避けることが望ましい。

3. 生活習慣改善の限界と問題点

食事や運動を中心とした生活習慣の改善は、血圧を下げ、他の心血管危険因子を是正し、副作用はほとんどなく、費用もかからない。したがって、高血圧の予防と治療のための個別および集団管理において強く推奨される。しかし、生活習慣改善には限界や問題点もある[9]。

1つは、血圧への効果があまり大きくないことである。厳重な食塩制限や大幅な体重減少が得られれば別であるが、通常は各々の降圧効果は数mmHgに過ぎず、それらを組み合わせても10mmHg程度であろう。したがって、生活習慣改善のみでは高血圧者において血圧の正常化は困難な場合が多い。

もう1つの、そしてもっと大きな問題は、実行と維持が難しいことである。高血圧の管理におけるコンプライアンス (遵守性) の点では、生活習慣改善は薬物療法にはるかに劣っている。特に、食塩制限と減量という最も効果的なものが守れず、長続きしないことが多い。

さらに、生活習慣改善と予後に関する成績が乏しいこともあげられる。高血圧治療の目的である心血管疾患の予防と生命予後の改善に関しては、観察的な疫学研究の結果からは期待できるものの、介入研究による臨床的なエビデンスはほとんどない。

おわりに

高血圧は普遍的な疾患であるが、その病態は個人によって異なっている。したがって、高血圧の個別管理と集団管理は各々重要であるが、一方のみでは限界があり、補いあう必要がある。個別管理に関しては、個々の患者に対する生活習慣改善の適切な指導や薬物治療が主となり、集団管理については、種々の団体やメディアによる啓蒙や教育、検診による血圧測定、生活習慣改善の指導が主となろう。両者の効率的な運用は、高血圧の予防と治療および循環器病の予防に大きな意義を有しており、さらなる充実が望まれる。

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