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The effect of hypertension, aging and benidipine on arterial elasticity in elderly hypertensives

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Advancing age;
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Summary
Four hundred and 16 subjects (average age, 56.2 years; range, 20—92 years; Men/Women, 207/209) undergoing annual health check-up were studied for the effect of aging and hypertension on arterial compliance or elasticity index, which were measured after a 10 min rest in the supine position using CR-2000. Thirteen additional elderly patients with hypertension were also studied at rest in the supine position 30 min before and after 8 mg benidipine oral administration at the beginning of treatment and then repeatedly studied after a 10 min rest over at least 4—7 weeks to examine the effect of benidipine hydrochloride 8 mg on arterial compliance in a similar manner. Systolic blood pressure and pulse pressure were increased in subjects above 40 years of age. Diastolic blood pressure was also increased up to 60 years of age but after 60 years of age, it was decreased or rather it plateaued. Above 40 years of age, large and small arterial compliance levels were significantly decreased with advancing age. Small arterial compliance was much more decreased than large arterial compliance. In hypertensive subjects, small and large arterial compliance levels were significantly decreased in comparison with normotensive subjects. Benidipine hydrochloride 8 mg was given orally every morning in elderly hypertensive patients for at least 1 month, and blood pressure and arterial compliance were measured every week using CR-2000. Benidipine hydrochloride decreased blood pressure and improved arterial compliance gradually and safely without any adverse effect. Therefore,

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benidipine hydrochloride is thought to be a useful antihypertensive drug for elderly hypertensives because of its potential to improve arterial function and perhaps arterial properties.

Introduction

Japanese people enjoy the longest life expectancy in the world. However, this longevity does not seem to be always a blessing to Japanese people because the number of diseased or debilitated elderly people has been increasing and the large healthcare expenditures. In Japan, cancer is known to be the number one killer, followed by heart disease and cerebrovascular disease. The second and third killers are closely related to vascular diseases, and thus the impairment of the heart and blood vessels should be prevented more aggressively for healthy longevity.

A simple method is necessary for the evaluation of vascular function, but there has been no easy and reliable method until now. Recently, an instrument for the analysis of vascular function (CR-2000) was invented using a tonometry sensor of radial pulse pressure [1]. Arterial compliance is analyzed by a personal computer program, based on the modified Wind-Kessel model. We examined the effect of hypertension, advancing age and benidipine hydrochloride on arterial compliance in participants of annual health check-ups and 13 additional hypertensive patients treated with benidipine 8 mg once a day.

Subjects and methods

Four hundred and 16 subjects (average age, 56.2 years; range, 20—92 years; Men/Women, 207/209) undergoing annual health check-ups were studied after a 10 min rest in the supine position to examine the effect of aging and hypertension on arterial compliance using CR-2000. In addition, 13 elderly patients with hypertension (average age, 74 ± 9 years; Men/Women, 8/5) were also studied after a 10 min rest in the supine position to examine the effect on vascular compliance of benidipine hydrochloride 8 mg administered orally every morning over at least 1 month in a similar manner.

The principle of measuring vascular compliance by CR-2000

Goldwyn and Watt [2] and Watt and Burrus [3] reported that this kind of measurement of vascular compliance is reasonable in humans, using the modified Wind-Kessel model. Zobel et al. [4] confirmed that this is a reliable method for the measurement of vascular compliance, using a pressure curve recorded by catheterization and cardiac output measured by dye-dilution method in a canine model. This concept was much more oriented to clinical practice and finally, CR-2000 was invented as a non-invasive instrument for arterial compliance or elasticity analysis. In CR-2000, a tonometry sensor is used to measure radial pulse pressure. Arterial compliance is analyzed by a personal computer program, based on the alternating current circuit, equal to the modified Wind-Kessel model [5]. A detailed description has been reported elsewhere. Briefly, the portion of diastolic decay of radial arterial pressure has been already found to fit very well to the following equation: $P(t) = a_1e^{-a2t} + a_3e^{-\alpha 4t} \times \mathrm{Cos}\,(a_5t + a_6)$. The parameters from a_1 to a_6 are computed from the alternating current circuit theory based on the pressure data of the diastolic decay and systemic vascular resistance, calculated using predicted cardiac output and mean arterial pressure. Arterial pressure was calibrated with an automatic blood pressure manometer on the opposite upper arm.

The equation of the measurement for arterial compliance is as follows:

Large vessel compliance $(C_1) = 2a_4[(a_2 + a_4)^2 + a_5^2]/Ra_2(a_2 + 2a_4)\,(a_4^2 + a_5^2)$.
Small vessel compliance $(C_2) = 1/(a_2 + 2a_4)\,R$.
Total vascular resistance (R) = predicted cardiac output/mean arterial pressure.

Statistics

Comparison among age groups was performed by one-way ANOVA and then Dunnett's method was used for multi-comparison. Comparison between hypertensive and normotensive subjects was performed by unpaired *t*-test. The effect of benidipine on arterial compliance and blood pressure was analyzed by repeated ANOVA measures, followed by linear contrast. Probability values less than 0.05 were regarded as statistically significant. Statistical analysis was performed using JMP version 5.1, StatView version 5.0 and SuperANOVA version 1.1.

Results

Systolic blood pressure and advancing age

According to age, the participants undergoing annual health check-ups (Table 1) were divided into the following six groups: less than 40, 40—49, 50—59, 60—69, 7—79, and 80 years or older. When compared among the six groups, systolic blood pressure significantly increased in the five older groups compared with the less than 40 years group (Fig. 1, †: $p < 0.01$).

Diastolic blood pressure and advancing age

Diastolic pressure, when compared among the same six groups, increased in the five older age groups except for the 60 years or older group. But it decreased or reached a

Table 1 Summary table of clinical characteristics.

Age (years)	56.1 ± 14.7	T chol (mg/dl)	203.4 ± 31.4
BMI (kg/m^2)	22.8 ± 2.9	TG (mg/dl)	91.8 ± 1.6
SBP (mm Hg)	125.9 ± 17.0	HDL-C (mg/dl)	58.9 ± 16.6
DBP (mm Hg)	72.8 ± 10.1	BS (mg/dl)	99.1 ± 15.1
PP (mm Hg)	53.0 ± 11.5	HbA1c (%)	5.2 ± 0.6
C_1 (mL/mm Hg^{-1} × 10)	12.6 ± 4.5	ANP (pg/ml)	12.5 ± 2.3
C_2 (mL/mm Hg^{-1} × 100)	4.9 ± 3.3	BNP (pg/ml)	14.5 ± 3.8

plateau in the 60 years or older group compared with the less than 40 years group (Fig. 2, †: $p < 0.01$).

Pulse pressure and advancing age

Pulse pressure, when compared among the same six groups, significantly increased in the four groups of 50 years or older compared with the less than 40 years group (Fig. 3, †: $p < 0.01$).

Advancing age and large artery compliance (C_1)

Large artery compliance, when compared among the same six groups, significantly decreased in the four groups of 50 years or older (Fig. 4, †: $p < 0.01$).

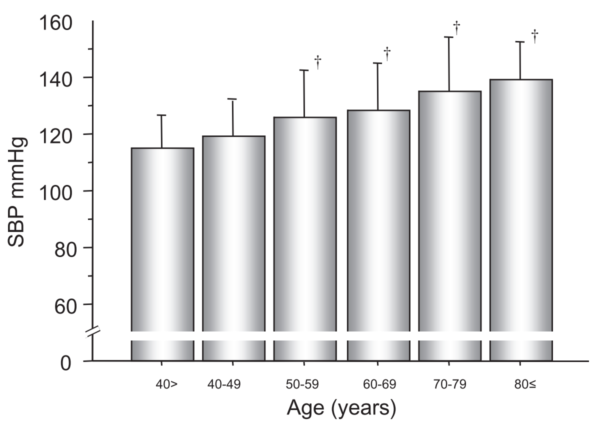

Figure 1 Changes in systolic blood pressure with advancing age $N = 416$.

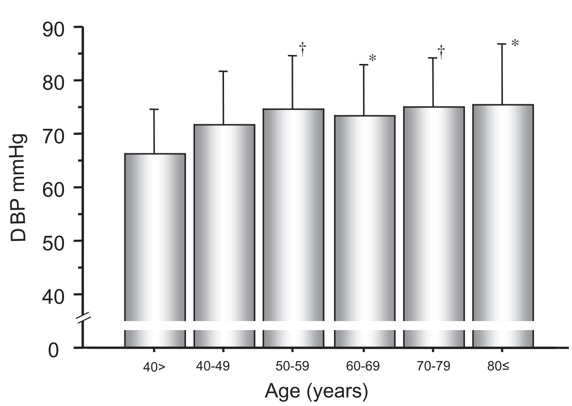

Figure 2 Changes in diastolic blood pressure with advancing age $N = 416$.

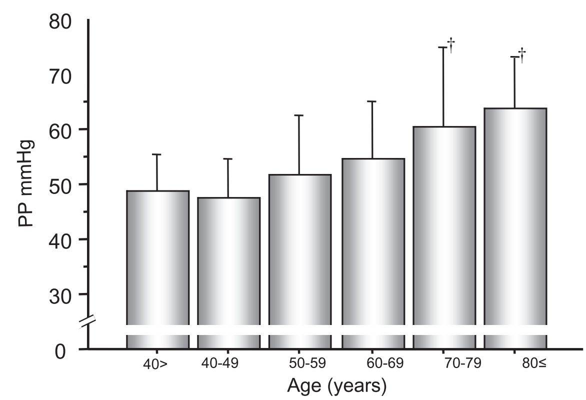

Figure 3 Changes in pulse pressure with advancing age $N = 416$.

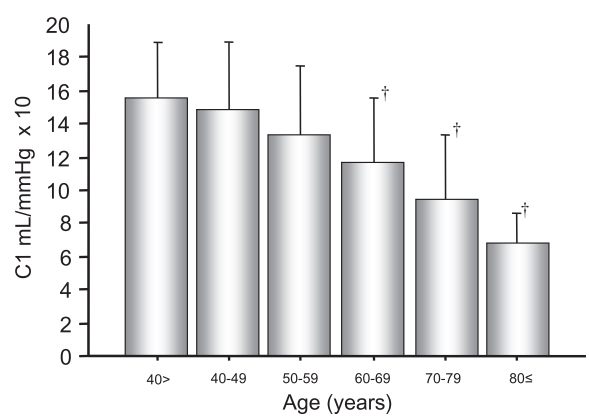

Figure 4 Changes in large artery compliance with advancing age $N = 416$.

Advancing age and small artery compliance (C_2)

Small artery compliance, when compared among the same six groups, more sharply decreased in the five groups of 40 years or older compared with large artery compliance (Fig. 5, ††: $p < 0.01$; †: $p < 0.05$).

Comparison of systolic blood pressure between hypertensive and normotensive subjects

Systolic blood pressure was 150.9 ± 8.9 mm Hg in hypertensive subjects ($n = 95$), and 118.5 ± 10.7 mm Hg in normotensive subjects ($n = 321$). Naturally, it was higher in hypertensives

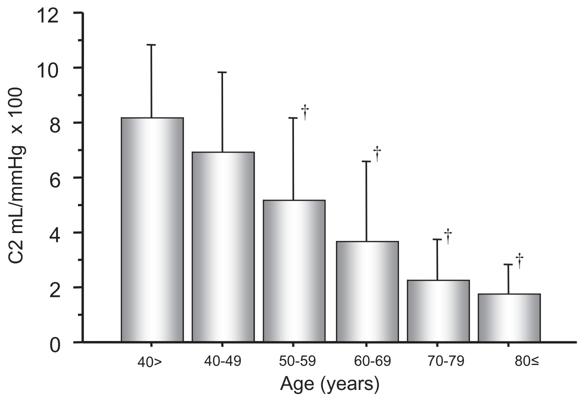

Figure 5 Changes in small artery compliance with advancing age $N = 416$.

than in normotensives (Table 2; hypertensives vs normotensives: $p < 0.0001$).

Comparison of diastolic blood pressure between hypertensive and normotensive subjects

Diastolic blood pressure was 82.7 ± 8.2 mm Hg in hypertensive subjects ($n = 95$) and 70.7 ± 8.7 mm Hg in normotensive subjects ($n = 321$). Naturally, it was higher in hypertensives than in normotensives (Table 2, hypertensives vs normotensives: $p < 0.0001$).

Comparison of large artery compliance between hypertensive and normotensive subjects

Large artery compliance was 8.6 ± 2.9 mL/mm Hg × 10 in hypertensives ($n = 95$) and 13.9 ± 4.2 mL/mm Hg × 10 in normotensives ($n = 321$). Naturally, it was lower in hypertensives than in normotensives (Table 2, hypertensives vs normotensives: $p < 0.0001$).

Comparison of small artery compliance between hypertensive and normotensive subjects

Small artery compliance was 2.4 ± 1.5 mL/mm Hg × 100 in hypertensives ($n = 95$) and 5.7 ± 43.3 mL/mm Hg × 100 in normotensives ($n = 321$). Naturally, it was lower in hypertensive than in normotensive subjects (Table 2, hypertensives vs normotensives: $p < 0.0001$).

The effect of benidipine on blood pressure and arterial compliance in elderly hypertensive patients

Thirteen hypertensive patients (age, 74 ± 9 years; M/F, 8/5) who visited our outpatient clinic and satisfied the criteria of hypertension as measured at least twice at visits more than 2 weeks apart were included in this study. Systolic blood pressure of the 13 hypertensive patients was 152 ± 11 mm Hg on average. Blood pressure was measured at rest in the supine position using CR-2000 30 min before and after oral administration of benidipine hydrochloride 8 mg, and at 1 week and at 4—7 weeks of treatment. Statistical analysis was performed by repeated ANOVA measures, followed by linear contrast for intra-group comparison. The significance level was set at $p < 0.05$. Systolic blood pressure significantly decreased after oral administration as shown in Fig. 6 and also diastolic blood pressure significantly decreased after oral administration as shown in Fig. 7. The antihypertensive effect of benidipine hydrochloride lasted in all the hypertensive patients treated orally, and blood pressure decreased mildly with no adverse effect. Arterial compliance was also improved by benidipine hydrochloride administration with no drug resistance throughout the study. Large artery compliance was improved at 1 week and 4—7 weeks as shown in Fig. 8 and small artery compliance was also improved at 4—7 weeks as shown in Fig. 9. Systolic blood pressure signif-

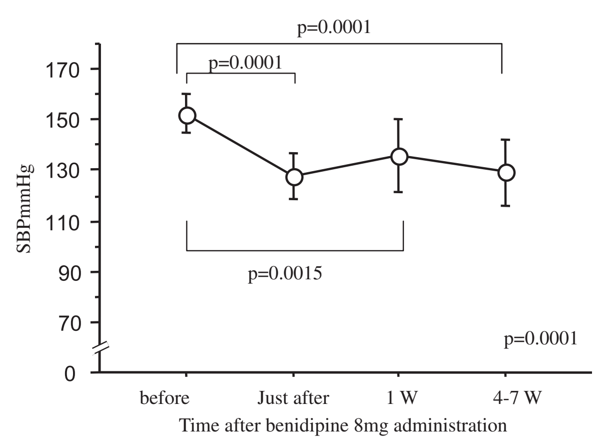

Figure 6 Time-course changes in systolic blood pressure after benidipine 8 mg administration $N = 10$.

Table 2 Clinical characteristics of subjects.

Parameters	Hypertensives ($n = 95$)	Normotensives ($n = 321$)	p-Value
Age (years)	65.2 ± 12.0	53.5 ± 14.3	$p < 0.0001$
BMI (kg/m^2)	22.9 ± 3.4	22.8 ± 2.7	ns
SBP (mm Hg)	150.9 ± 8.9	118.5 ± 10.7	$p < 0.0001$
DBP (mm Hg)	82.6 ± 8.1	69.9 ± 8.7	$p < 0.0001$
PP (mm Hg)	68.2 ± 9.4	48.5 ± 7.5	$p < 0.0001$
C_1 (mL/mm Hg × 10)	8.5 ± 2.9	13.9 ± 4.1	$p < 0.0001$
C_2 (mL/mm Hg × 100)	2.4 ± 1.5	5.7 ± 3.3	$p < 0.0001$
SVR (dyne s cm^5)	2296.0 ± 578.8	1668.4 ± 469.4	$p < 0.0001$

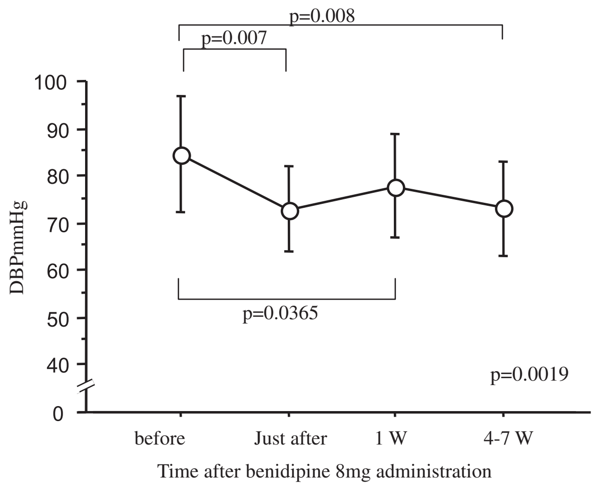

Figure 7 Time-course changes in diastolic blood pressure after benidipine 8 mg administration $N = 10$.

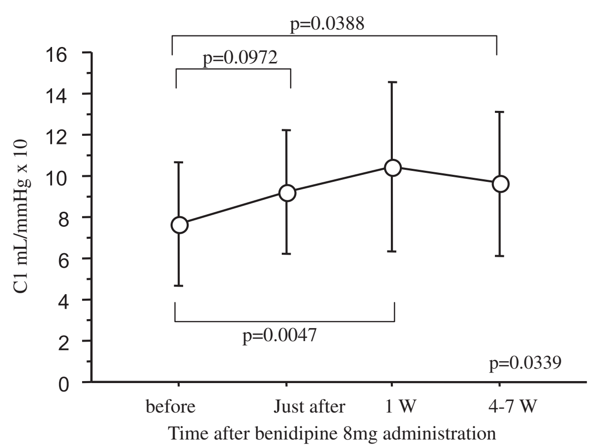

Figure 8 Time-course changes in large artery compliance after benidipine 8 mg administration $N = 10$.

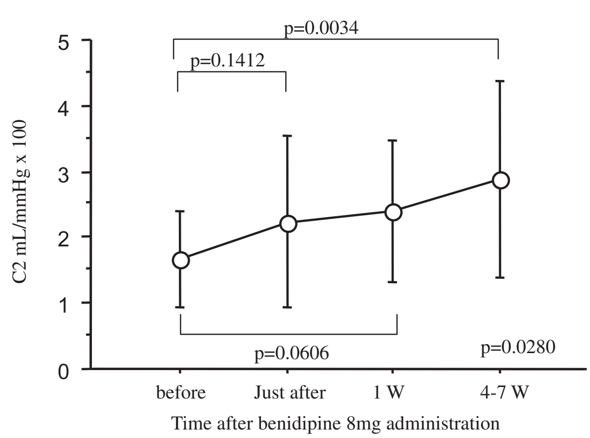

Figure 9 Time-course changes in small artery compliance after benidipine 8 mg administration $N = 10$.

icantly decreased from 152 to 129 mm Hg. Arterial compliance tended to increase 30 min after administration of 8 mg benidipine hydrochloride in association with lowered blood pressure, significantly increased at 1 week and at 4—7 weeks for the large artery level, and significantly increased at 4—7 weeks for the small artery level.

Discussion

Japan has become a more aged society than any other country has ever experienced. Today, cancer is the number one killer, heart disease is the second, and cerebrovascular disorder is the third in Japan. However, we must pay attention to vascular disorders because the second and the third killers are closely associated with it. And therefore, it is critical to detect early vascular impairment for organ protection. However, there has been no reliable non-invasive method to evaluate arterial function until now. The new instrument to evaluate arterial function non-invasively, CR-2000, is one of the handy screening instruments for arterial compliance. CR-2000 analyzes arterial compliance, based on the principle of the modified Wind-Kessel model, using a tonometry sensor. Systolic blood pressure gradually increased with advancing age, and diastolic blood pressure also increased with advancing age up to 60 years of age and decreased or reached a plateau over 60 years of age in this study, as has long been well known [6]. These results can be partly explained by stiffening of the aorta or arteriosclerosis with advancing age.

Telomere length of human leukocytes has been reported to be inversely related to pulse pressure, which was proved to increase with advancing age [7—9]. Oral administration of benidipine hydrochloride 8 mg for at least 1 month could decrease pulse pressure. To our knowledge, increased pulse pressure mainly reflects advanced sclerosis of the aorta [6,10]. In our participants undergoing their annual health check-up, large and small artery compliance proved to decrease with advancing age, especially after the age of 40—50 years, as assessed using CR-2000. This result may imply that vascular protection is necessary at least after the age of 40—50 years. In our participants, small and large artery compliance was decreased more in hypertensive subjects than in normotensive subjects and in particular, small artery compliance was much more decreased in hypertensive than in normotensive subjects. It is very likely that small artery compliance is early and easily impaired in comparison with large artery compliance [11]. In hypertensives, decreased arterial compliance does not always imply decreased distensibility of arteries but, in fact, results in decreased arterial function. Decreased arterial function is closely linked to increased cardiac afterload or arterial impedance whether the decreased arterial compliance is structural or functional. This kind of cardiac overload may accelerate cardiac hypertrophy and arterial impairment, if cardiac overload is not reduced. And therefore, combination of advancing age and hypertension can induce arterial impairment earlier and thus vascular protection should be considered much earlier. From this viewpoint, benidipine hydrochloride [12—14] 8 mg was orally administered to 13 elderly patients with hypertension for at least 1 month to examine the effect of benidipine hydrochloride on vascular function. Blood pressure gradually decreased as a result of benidipine hydrochloride administration. Large and small artery compliance levels were improved over time after benidipine hydrochloride administration. Both compliance levels tended to be improved even with the same arterial pressure. In other words, we can speculate some improvement actually occurs in both arteries during therapy by benidipine hydrochloride over time as well as blood pressure.

Conclusions

Benidipine hydrochloride decreased blood pressure safely and improved arterial compliance over time in elderly hypertensives. Vascular protection by benidipine hydrochloride administration may make patients with hypertension, especially elderly patients, survive longer by enhancing arterial function or by improving perhaps arterial properties.

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