The Pathogenetic Role and Treatment of Elderly Hypertension

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The clinicopathological study on the atherosclerosis and cerebrovascular and cardiac complications was carried out in 1561 consecutive autopsied cases in the elderly. The subjects were classified into 3 groups: 702 cases (45.0%) of normotension, 276 cases (17.7%) of systolic hypertension and 583 cases (37.3%) of diastolic hypertension. The acceleration of atherosclerosis by hypertension was prominent in sixties and seventies, less remarkable in eighties and almost none in nineties. The effect of hypertension was remarkable on cerebral artery, aorta and coronary artery in this order, and no difference was found between the systolic and diastolic hypertension groups. On the basis of atherosclerotic changes, strokes and myocardial infarction were prevalent in both these groups in comparison with the normotension group. The difference between the systolic and diastolic hypertension groups and the normotension group was prominent in sixties and seventies, but in eighties only the diastolic hypertension group showed a significant difference with the normotension group. The effect of hypertension was more remarkable on strokes than myocardial infarction. The lack of remarkable effect of hypertension on the cases over eighty may be attributed to the progression of atherosclerosis with age in normotensive cases.

The 4 year prospective trial on the effectiveness of the antihypertensive treatment was performed in 100 mild hypertensive patients of the aged, averaging 76.1 years. The matched pair group was selected by the age, sex and blood pressure. Cerebrovascular and cardiac complications were observed in 4 cases or 10.5% of 38 cases of the drug group, and in 9 cases or 22.0% of 41 cases of the placebo group. When the elevation of blood pressure over 200/110 mmHg, observed in 8 cases in the placebo group, were included as one of the cardiovascular complications, the complications in placebo group reached 41.5%, showing a significant difference. Other complications such as cancers, infections and bone or joint diseases, were observed in 12 cases or 31.6% in the drug group and in 17 cases or 41.5% in the placebo group. Blood pressure was decreased from 171/87 to 151/80 in the drug group in the 4 year period. The present study suggested that antihypertensive treatment was effective in the aged hypertension, and careful follow up was needed not only for cardiovascular complications but also for general health condition.

Key Words:

Hypertension in the aged
Atherogenetic role
Cerebrovascular and cardiac complications
Prospective antihypertensive treatment

DESPITE a lowering of many risk factors in the aged, the elderly hypertensive patients show the higher prevalence of cerebrovascular and cardiac complications, and the lower survival rate than the normotensive group^{1,2}

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TABLE I THE AGE AND SEX DISTRIBUTION OF NORMOTENSION (NT), SYSTOLIC HYPERTENSION (SHT) AND DIASTOLIC HYPERTENSION (DHT)

BP	Sex	Age				Total
		60	70	80	90	
NT	M	73	169	113	8	363
	F	69	147	97	26	339
						> 702 (45.0%)
SHT	M	10	60	46	7	123
	F	8	50	67	28	153
						> 276 (17.7%)
DHT	M	64	145	83	7	299
	F	30	110	116	28	284
						> 583 (37.3%)
Total	M	147	374	242	22	785
	F	107	307	280	82	776
						> 1561

Fig.1. Atherosclerosis of the aorta, cerebral and coronary arteries in normotension (N), systolic (S) and diastolic hypertensions (D). Black bar = severe, hatched bar = moderate, dotted bar = slight, open bar = minimum atherosclerosis, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

The role of hypertension as a risk factor is best evaluated by the clinicopathological correlations on the severity of atherosclerosis and the extent of cerebrovascular and cardiac complications in the consecutive autopsies of the aged. The other approach is to observe the effect of antihypertensive treatment on the cerebro-cardiovascular morbidity or mortality in the prospective study, although the decrease in blood pressure is thought to reveal little benefit on the cerebro-cardiac events^{3,4} and an inappropriate reduction

of blood pressure induces the ischemia of the target organs.⁵

Thus, the clinicopathological correlations in the elderly hypertension and the prospective study on the antihypertensive treatment was carried out to clarify the role of hypertension in the aged.

METHODS

Clinicopathological Study on the Role of Hypertension

In the clinicopathological study, 1561 consecutive autopsies over the age of 60 at the Tokyo Metropolitan Geriatric Hospital from 1972 to 1979 were divided into 3 groups by the blood pressure level before the onset of serious diseases. The normotension group, blood pressure below 160/90 mmHg, consisted of 702 cases (45.0%). The systolic hypertension group, the systolic pressure over 160 and diastolic pressure below 90 mmHg, consisted of 276 cases (17.7%). The diastolic hypertension group, the diastolic pressure of 90 mmHg or more, consisted of 583 cases (37.3%). The age and sex distribution of the patients is shown in Table I. Male and female ratio was equal as a whole, but female patients were more prevalent in older age. The percentage of diastolic hypertension was 30 to 40% in all decades over sixty, while the systolic hypertension increased from 6.8 and 7.5% to 31.8 and 34.8% (male and female), and normotension decreased from 49.7 and 64.4% to 36.4 and 31.7% with an increase of age from 60 to 90 years. The serum cholesterol levels decreased with advancing aged in both sexes, and no dif-

Fig.2. Atherosclerosis of the aorta in each decade.
Symbols are same as Fig. 1.

Fig.3. Cerebral atherosclerosis in each decade.
Symbols are same as Fig. 1.

ference was observed in male patients, but in female patients the diastolic hypertension group revealed higher serum cholesterol than the normotension group. The grade of atherosclerosis of aorta and cerebral artery was classified into 4 groups: severe, moderate, slight and minimum by macroscopic observation of the area of atherosclerosis and complicated lesions such as calcification or ulceration. The stenosis was also counted in the cerebral artery. The coronary artery stenosis was graded in the anterior descending and circumflex branches of the left coronary artery as well as right coronary artery by inspection of the percent narrowing of cross sectional area: 100% or pinhole (5), 75% (4), 50% (3), 25% (2), sclerotic plaque without stenosis (1),

and none (0). The sum of the largest score in 3 vessels was classified into 4 groups: 13–15 severe, 9–12 moderate, 5–8 slight, 0–4 minimum. The statistical analysis was carried out by Wilcoxon's rank sum test.

Prospective Study on the Antihypertensive Treatment

One hundred patients, the residents of the Tokyo Metropolitan Homes for the aged, showing normal activity of daily living and the blood pressure of more than 160/90 and less than 200/110 mmHg after withdrawal of previous antihypertensive medications were enrolled in the present study. The blood pressure reached a new level in a month.⁶ The matched pair group was

Fig.4. Coronary sclerosis in each decade. Symbols are same as Fig. 1.

selected by the age, sex and blood pressure levels during the drug-off control period of about one year. During this control period, 9 patients were dropped out; 6 because of blood pressure elevation and one each because of cerebral bleeding, cholelithiasis and moving out. Thus, remaining 91 patients were divided into 44 of the drug treated group and 47 of the placebo treated group. Average ages of male patients in each group were 74.9 and 75.7 years, and those of female patients were 76.3 and 77.9 years, respectively.

Patients were followed up once or twice a month for 4 years from 1975 to 1979. Patients who had blood pressure elevation over 200/110, occurrence of cerebrovascular or cardiac complications, other diseases which needed hospital admission, who died and who moved out from the Home were excluded from the present study.

In the drug treated group, thiazide diuretics (trichlormethiazide 1 to 4 mg) were used as basal antihypertensive drugs. Thiazide monotherapy was used in 35 cases out of 44 cases. In the remaining 9 cases, reserpine (0.3 mg), methyl-dopa (125 to 500 mg) and hydralazine (50 to 100 mg) were added by stepped care approach when needed.

RESULTS

Atherosclerosis and Hypertension

The grades of atherosclerosis of the aorta, cerebral and coronary arteries are illustrated in Fig. 1. The severe atherosclerosis of the aorta was found in 36.5% of normotension (NT), in

Fig.5. Cerebral and cardiac complications in normotension (N), systolic (S) and diastolic hypertension (D). Black bar = large, hatched bar = medium, open bar = small lesion, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

61.3% of systolic hypertension (SHT) and in 61.4% of diastolic hypertension (DHT), showing the significant difference between NT and both hypertension ($p < 0.001$). The severe atherosclerosis of the cerebral artery was observed in 23.0% of NT, in 50.4% of SHT and in 50.6% of DHT, also showing the significant difference between NT and both hypertension. No statistical difference was shown between SHT and DHT. The moderate and severe coronary stenosis was found in 34.8% of NT, in 48.7% of SHT and in 54.0% of DHT, showing an increase in coronary stenosis with blood pressure elevation.

The relationship between the atherosclerosis of the aorta and hypertension in each decade

Fig. 6. Cerebral bleeding in each decade.
Symbols are same as Fig. 5.

Fig. 7. Cerebral infarction in each decade.
Symbols are same as Fig. 5.

from sixties to nineties is shown in Fig. 2. The severe atherosclerosis of the aorta was found in 17.8% of NT, in 52.9% of SHT and in 46.2% of DHT in sixties, and in 34.5% of NT, in 58.6% of SHT and in 64.4% of DHT in seventies, showing the marked difference between NT and both hypertension. The severe aortic atherosclerosis was found in 49.5% of NT, in 63.6% of SHT and in 61.2% of DHT in eighties, and in 50.0% of NT, 65.7% of SHT and 85.3% of DHT in nineties. As the progression of atherosclerosis took place

in NT, the difference from the hypertension became less significant. The similar tendency of the cerebral atherosclerosis is shown in Fig. 3. The severe atherosclerosis of the cerebral artery was found in 10.5% of NT, 37.5% of SHT and in 37.9% of DHT in sixties, in 18.3% of NT, in 45.2% of SHT, and in 52.9% of DHT in seventies, in 35.5% of NT, in 54.0% of SHT, and in 53.3% of DHT in eighties, and 39.4% of NT, in 60.0% of SHT, and in 60.0% of DHT in nineties. The effect of hypertension on coronary sclerosis was less prominent than on cerebral artery especially over eighties as shown in Fig. 4. The severe and moderate coronary sclerosis was found in 21.2% of NT, in 41.1% of SHT and in 54.9% of DHT in sixties, and in 34.3% of NT, in 45.5% of SHT, and 57.7% of DHT in seventies, and in 41.9% of NT, in 54.0% of SHT, and 51.0% of DHT in eighties, and in 53.0% of NT, in 45.7% of SHT and in 42.9% of DHT in nineties. The agewise progression of atherosclerosis in NT was prominent both in cerebral and coronary arteries.

Cerebrovascular and Cardiac Complications in Hypertension

The prevalences of various sizes of cerebral bleeding, cerebral infarction and myocardial infarction are shown in Fig. 5. The cerebral bleeding of large and medium sizes was observed in 3.7% of NT, in 8.2% of SHT and in 14.2% of DHT. The cerebral infarction of large and medium size was found in 28.1% of NT, in 41.7% of SHT and in 43.4% of DHT. The myocardial infarction was found in 14.6% of NT, in 22.9% of SHT and in 23.9% of DHT. The cerebrovascular and cardiac complications were significantly higher in both types of hypertension than

TABLE II BLOOD PRESSURE AND LABORATORY DATA DURING THE CONTROL PERIOD

		Placebo		Drug	
		mean	SD	mean	SD
Blood pressure	systolic	166.1	4.3	171.3	4.2
(mmHg)	diastolic	85.5	2.2	86.5	1.9
Cholesterol	(mg/dl)	175.4	29.6	173.1	30.9
Urea nitrogen	(mg/dl)	19.0	9.3	18.0	3.7
Uric acid	(mg/dl)	5.2	1.4	5.5	1.0
Hemoglobin	(g/dl)	13.0	1.2	12.9	1.8
Cardiothoracic ratio	(%)	55.3	6.2	56.3	6.2
ECG score	*	1.1	0.9	1.3	0.9

* Score for the diagnosis of the severity of hypertension, presented by the Department of Medicine, University of Tokyo.

TABLE III CEREBROVASCULAR AND CARDIAC COMPLICATIONS DURING THE 4 YEAR PROSPECTIVE TRIAL

	Placebo (41)	Drug (38)
Death		
Cerebral infarction	1	1
Cerebral hemorrhage	0	1
Myocardial infarction	2	0
Sudden death	0	1
Admission		
Cerebral infarction	2	1
CHF, arrhythmia	2	0
Outpatient		
Cerebral infarction	1	0
CHF, arrhythmia	1	0
Total	9 (22.0%)	4 (10.5%)

NT, but there was no difference between SHT and DHT.

The relationships between the cerebral bleeding and hypertension at each decade from sixties to nineties are shown in Fig. 6. The cerebral bleeding of moderate and large sizes was found in 2.9% of NT, in 16.7% of SHT and in 19.5% of DHT in sixties, and in 2.3% of NT, in 8.7% of SHT, in 12.5% of DHT in seventies, and in 5.6% of NT, in 7.2% of SHT and in 14.6% of DHT in eighties, and in 9.1% of NT, in 5.8% of SHT in 8.8% of DHT in nineties. As shown in Fig. 7 the cerebral infarction of moderate and large sizes was found in 23.5% of NT, in 38.9% of SHT and in 34.4% of DHT in sixties, in 23.6% of NT, in 45.2% of SHT and in 43.3% of DHT in seventies, and in 35.9% of NT, in 39.3% of SHT and in 46.4% of DHT in eighties, and in 42.4% of NT,

in 40.0% of SHT and in 51.4% of DHT in nineties. The prevalences of cerebral bleeding and infarction were higher in SHT and DHT in sixties and seventies, and in DHT in eighties than in NT, but no difference was observed in nineties. The myocardial infarction (Fig. 8) was observed in 7.8% of NT, in 11.8% of SHT and in 18.3% of DHT in sixties, and in 14.8% of NT, in 20.0% of SHT and in 30.6% of DHT in seventies, and in 16.7% of NT, in 24.8% of SHT and in 21.3% of DHT in eighties, and in 29.4% of NT, in 31.4% of SHT and in 5.7% of DHT in nineties. The prevalence of myocardial infarction was higher only in DHT of sixties and seventies, and the role of hypertension on myocardial infarction was less prominent than cerebrovascular complications.

TABLE IV COMPLICATIONS DURING THE 4 YEAR PROSPECTIVE TRIAL

	Placebo	Drug
Case	47 (41)	44 (38)
Move out	6	6
<i>Cerebrovascular and cardiac complications</i>		
Death	3	3
Admission	4 9	1 4
Outpatient	2 (22.0%)	0 (10.5%) ns*
Elevated blood pressure	8	
Total	17 (41.5%)	4 (10.5%) p < 0.01
<i>Other complications</i>		
Death	4 17	4 12
Admission	13 (41.5%)	8 (31.6%) ns
Total complications	34	16
Follow up	7 (17.1%)	22 (57.9%) p < 0.001

* ns = not significant

TABLE V OTHER MISCELLANEONS COMPLICATIONS DURING THE 4 YEAR TRIAL

	Placebo (41)	Drug (38)
Death	4	4
cancer (esophagus 1)		(stomach 2) (lung 1) (gall bladder 1)
pneumonia	2	0
milliary tbc	1	0
Admission	13	8
arthrosis deformans	1	2
spondylosis deformans	1	2
fracture of femur neck	3	0
dementia, psychosis	3	0
cancer stomach 2		prostate 1
prostate hypertrophy	1	urinary tract infection 1
arteriosclerosis obliteraus	1	inguinal hernia 1
pneumonia	1	glaucoma 1
Total	17 (41.5%)	12 (31.6%)

Prospective Study on the Antihypertensive Treatment in the Elderly

The blood pressure level and laboratory data during the control period are shown in Table II. Average blood pressures were $166.1/85.5 \pm 4.3/2.2$ mmHg in the placebo group, and $171.3/86.5 \pm 4.2/1.9$ mmHg in the drug group, and showed no significant difference. In laboratory data cholesterol levels, blood urea nitrogen, uric acid,

hemoglobin concentration, cardiothoracic ratio, and ECG scores for LVH were comparable between the two groups.

The cerebrovascular and cardiac complications observed during the 4 year prospective trial are shown in Table III. Six cases of dropout due to moving out from the Home were observed in both groups, and 38 cases in the drug group and 41 in the placebo group were followed up.

Fig. 8. Myocardial infarction in each decade.
Symbols are same as Fig. 5.

Fig. 9. Course of blood pressure during the control and trial period in the total cases of drug and placebo groups.

Deaths in the drug group were attributed one each to cerebral infarction, cerebral hemorrhage and sudden death, and deaths in the placebo group consisted of 1 case of cerebral infarction and 2 cases of myocardial infarction. The morbid events which needed hospital admission in the drug group were one case of cerebral infarction. In the placebo group, 2 cases of cerebral infarction and 2 cases of congestive heart failure with arrhythmia were observed. One patient with cerebral infarction and one with congestive heart failure with arrhythmia were treated at outpatient department. As a whole, 9 out of 41 cases or 22.0% in the placebo group, and 4 out of 38 cases or 10.5% in the drug group were dropped out by cerebrovascular

or cardiac complications. This difference was not statistically significant. In addition to the cerebrovascular and cardiac complications dropouts due to blood pressure elevation were observed in 8 cases in the placebo group, and total dropouts in the placebo group were 17 cases or 41.5%. This prevalence was significantly higher than that of the drug treated group (Table IV).

Other complications were observed in 12 cases or 31.6% in the drug group, and in 17 cases or 41.5% in the placebo group. These were not significantly different. Therefore, cases without events were 22 cases or 57.9% in the drug group, and 7 cases or 17.1% in the placebo group, showing the significant difference. Other complications are shown in Table V. Four deaths in the

drug group were due to the cancers of stomach, lung and gall bladder, and 4 deaths in the placebo group were attributed to pneumonia, miliary tuberculosis and cancer of the esophagus. Morbid events were observed in 8 cases in the drug group and in 13 cases in the placebo group. Major causes for admission in these patients were bone and joint diseases, cancer, psychiatric disorder, infections, prostate hypertrophy and others.

The trends of mean blood pressure at each month are shown in Fig. 9. The average blood pressure in the drug group was lowered from 171/87 to 162/84 in the first year, 156/80 in the second year, 152/80 in the third year and 151/80 in the fourth year. The average decrease was 20/7 mmHg. Blood pressure in the placebo group changed little from 166/86 to 167/86 in the first year, but gradually declined to 162/82 in the second year, 159/80 in the third year and 150/78 in the fourth year due to the dropout of the hypertensive cases. In 22 cases of the drug group being followed up through 4 year trial period, blood pressure declined from 171/87 to 150/79 and the average decrease was 21/8 mmHg. In 7 cases of placebo group, the blood pressure during the control period was relatively low and gradually declined in the placebo period probably due to the aging.

In 16 thiazide treated patients and 11 placebo treated patients, hematocrit, serum protein, urea nitrogen, uric acid, sodium and potassium for 3 year trial period revealed no significant changes.

DISCUSSIONS

Atherosclerosis, Strokes and Myocardial Infarctions in Elderly Hypertension

The present study demonstrated that the acceleration of atherosclerosis by hypertension was prominent in sixties and seventies, less remarkable in eighties, and weak or none in nineties. The effect of hypertension was remarkable on cerebral artery, aorta and coronary artery in this order and no difference was found between the SHT and DHT. Ikeda et al.⁷ found the systolic blood pressure in the aged to show positive correlation with aortic, cerebral, renal and coronary atherosclerosis in this order. The diastolic blood pressure showed a close correlation with cerebral atherosclerosis, but a poor correlation with coronary, renal and aortic atherosclerosis. However, in the severe hypertension in the aged the arteriosclerosis of the arterioles was more

remarkable than that of the systolic hypertension.⁸ Murata et al.⁹ also found a positive correlation between the systolic pressure and the severity of atherosclerosis in the aorta ($r = 0.282$), coronary artery ($r = 0.319$) and cerebral artery ($r = 0.434$). The diastolic pressure was related only to the cerebral atherosclerosis ($r = 0.284$). On the basis of the atherosclerotic changes, strokes and myocardial infarction were prevalent in both SHT and DHT in comparison with the NT. The difference was prominent until seventies, and only the DHT showed the difference in eighties. The effect of hypertension was remarkable in the stroke than the myocardial infarction. The non-remarkable effect of hypertension over eighties could be attributed to the agewise progression of atherosclerosis and cerebrovascular and cardiac complications in NT. Thus, the systolic hypertension in the aged could not be disregarded as a natural trend of aging. Colandrea et al.¹ found that systolic hypertension had 2 to 3 times more heart attacks, strokes and other cardiovascular complications than normotension. Kannel et al.² revealed that the occurrence of strokes and other hypertensive complications was as directly related to the systolic as to the diastolic pressure, and emphasized that hypertension was the key remediable contributor to cardiovascular morbidity and mortality in the elderly.¹⁰ Tohgi et al.¹¹ found that the systolic pressure was significantly higher in cerebral bleeding in the aged, but not significant in cerebral infarction. The diastolic pressure revealed no difference between strokes and controls. In the multivariate analysis on the risk factors with the coronary arteriography, hypertension had a positive influence but not significant,¹¹ probably due to the selected patients for the angiography.

Antihypertensive Treatment in the Elderly

The present prospective study revealed that antihypertensive treatment in the elderly was effective in lowering the cerebrovascular and cardiac complication.

There has been dissenting views on the effect of the antihypertensive treatment in the elderly. Fry³ observed no increasing mortality rates with rising blood pressure in the over-sixties. Carter⁴ found the stroke recurrence to be 44% in placebo group, and 20% in drug treated group, but found no beneficial effect of the mortality over the age of 65. Jackson et al.⁵ presented unconsciousness and residual symptoms after the inappropriate

antihypertensive therapy in the aged and emphasized that the potent therapy might be unnecessary or harmful in the aged. The hypotensive stroke was also caused in the elderly by heart failure, occult hemorrhage, or multiple pulmonary emboli.¹³

The prospective study on the antihypertensive therapy in patients above 60 years was carried out by the European Working Party on High Blood Pressure in the Elderly (EWPHE).⁷ They observed 25/10 mmHg reduction of the blood pressure for 2 years in the absence of major electrolyte disturbances. But the terminating events were still being followed to prove the difference. Terasawa²¹ carried out the prospective study on 121 hypertensive patients in the aged. The prevalences of cerebrovascular disease, congestive heart failure and myocardial infarction for 5 year period were 17.1% in the drug group and 31.4% in the placebo group, showing no significant difference. The prevalence of morbid events in the drug group was similar to the present results, but that of the placebo group was higher than our data probably due to the difference of protocol in treating cases of the blood pressure elevation.

Svårdsudd et al.¹⁴ followed up hypertensive patients of 50 years old for 13.5 years and concluded that hypertension accelerates the cerebrovascular and cardiac events. The effect of antihypertensive treatment in mild hypertension was proved in the VA study in cases of diastolic blood pressure of 90 to 114 mmHg.¹⁵ The prevalence of morbid events was 11.8% in the drug group and 28.9% in the placebo group. When terminated cases on account of elevated blood pressure in the placebo group were summed up with the morbid events, total assessable events reached 39.2%. Since the average ages in the VA study were about 50 years, these effects were not applicable to the aged. However, the prevalences of morbid events were fairly similar to the present study in the aged. The VA study also confirmed the value of lowering the blood pressure in preventing both initial and recurrent vascular complications in the elderly.¹⁶ The USPHS study¹⁷ on the treatment of mild hypertension of younger population revealed no significant difference between the treated and control groups, indicating that treatment should be directed to other risk factors or general health control. However, the mild hypertension in the aged would trigger the cardiovascular events on the basis of atherosclerosis of the target organs. The treatment

should follow the stepped care approach¹⁸ with a small starting dosis, and should not lower the blood pressure abruptly. The hypertension detection and follow-up program cooperative group¹⁹ revealed that the control of blood pressure was better and five-year mortality was lower for the stepped care group compared to the referred care group. The target level of blood pressure should be determined individually by watching the general health condition of the patients. The blood pressure in the drug group of the present study reached around 150/80 mmHg. Taguchi and Freis²⁰ reported that the partial reduction of blood pressure in VA study was still effective in prevention of morbid events. The care should be taken on the electrolytes, blood sugar, uric acid, blood urea nitrogen and hematocrit to prevent the specific side effect in the elderly. The morbid events in the elderly hypertension were not only cerebrovascular or cardiac complications but also other complications such as bone and joint diseases, cancer, infection, psychiatric disorder and others, and the other complications were 2 or 3 times more prevalent than the cerebrovascular or cardiac complications indicating the need for the general health check up during the antihypertensive treatment.

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