Original Article

Influence of Hypertension on the Incidence of Cardiovascular Disease in Two Rural Communities in Japan: The Tanno-Soubetsu Study

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The purpose of this study was to determine the relationship between hypertension and onset of cardiovascular disease in Japan. As part of an ongoing epidemiological survey of cardiovascular diseases in Hokkaido, Japan, 1,798 subjects (806 males and 992 females; mean age in the initial year of the survey, 58.6 ± 11.8 years) were selected, after excluding subjects who had been taking antihypertensive drugs, from a total of 2,136 subjects who had undergone medical examinations in 1991 in the town of Tanno and in 1992 in the town of Sobetsu, two rural communities in Hokkaido. Height, weight, casual systolic and diastolic blood pressures in the sitting position and blood biochemical values of all subjects were measured, and the subjects were divided into blood pressure level groups according to the 1999 World Health Organization/International Society of Hypertension (WHO/ISH) criteria. The follow-up survey was concluded at the end of August in 1999. The endpoints in this study were onset of circulatory disease or death due to circulatory disease. During the follow-up period, circulatory diseases (ischemic heart disease or stroke) occurred in 94 of the subjects. The incidence rates of cardiovascular disease (per 1,000 persons/year) for subjects divided into blood pressure groups according to the 1999 WHO/ISH blood pressure classification were 6.24 for the optimal+normal blood pressure level group, 11.26 for the normal high blood pressure level group, and 15.83 for the grade 1–3 hypertension group. Thus, the incidence rate of circulatory disease increased as the blood pressure level increased, and there was a significant difference between the incidence rate in subjects in the grade 1–3 hypertension group and the incidence rate in subjects in the optimal+normal blood pressure level group ($p < 0.05$). In a Cox's proportional hazards model with onset of circulatory disease as the endpoint, diastolic blood pressure was shown to be an independent risk factor with a relative risk of 1.01. The results suggest that hypertension is an independent risk factor for onset of circulatory disease. (*Hypertens Res* 2007; 30: 677–682)

Key Words: prospective study, population-based, hypertension, onset of cardiovascular disease

Introduction

Hypertension has long been considered the most potent risk factor for cardiovascular diseases (1, 2). The diagnostic criteria for hypertension were recently revised, and the necessity of blood pressure management in order to prevent other concurrent diseases has been emphasized (3). Hypertension was found to be a significant risk factor for cerebrovascular and

ischemic heart diseases in the Framingham Heart Study in the United States (4). On the other hand, no significant correlation was found between the incidence of ischemic heart diseases and hypertension in the Hisayama study, although the incidence of cerebral infarction was found to increase with increase in blood pressure (5). Many studies have shown that the incidence of cardiovascular diseases increases with increase in blood pressure in the elderly (6–9). However, both the rate of death from cardiovascular diseases and the inci-

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dence of cardiovascular diseases were found to be not significantly correlated with systolic blood pressure (SBP) or diastolic blood pressure (DBP) in the elderly without a previous history of such diseases, as shown by Tervahauta *et al.* (10) and the Zutphen Elderly Study (11). Thus, there is no consensus among researchers as to the relationship between blood pressure and cardiovascular diseases in populations that include elderly individuals. It is possible that the influence of blood pressure on occurrence of ischemic and cerebrovascular diseases is different between Japanese and people in the United States and European countries.

In a previous study, we divided subjects into several categories based on blood pressure according to the guidelines of the World Health Organization/International Society of Hypertension (WHO/ISH) (12) and found that individuals who belonged to higher blood pressure categories had higher all-cause death rates and higher rates of death from cardiovascular diseases (13). Since death was considered to be the endpoint in our previous study, however, there remains the possibility that only patients with severe diseases were examined, and consequently the relationship between blood pressure and cardiovascular diseases was not duly evaluated.

In this study, we followed up the occurrence of cardiovascular diseases in a general population that included elderly individuals. For this purpose, we divided subjects into categories on the basis of their blood pressure according to the WHO/ISH guidelines and compared the incidences of cardiovascular diseases in the different categories. We thereby attempted to clarify the influence of blood pressure on cardiovascular diseases in Japanese subjects.

Methods

We have been carrying out a prospective epidemiological investigation of cardiovascular diseases in the towns of Tanno and Sobetsu in Hokkaido since 1976 (14). In this study, subjects who had cardiovascular diseases were excluded at baseline. Of the 2,136 inhabitants who underwent health examinations in 1991 and 1992, 338 receiving antihypertensive medication were also excluded. The reason for the exclusion of subjects treated with antihypertensive drugs was that most of them had cardiovascular diseases. The remaining 1,798, who could be divided into categories based on their blood pressure, were subjects of this study. The 1,798 subjects included 806 men who were 59.5 ± 11.2 years old on average in the first study year and 992 women who were 57.8 ± 12.1 years old on average in the first study year. In the first study year, there were 277 men and 304 women who were 65 years of age or older. Health examinations were carried out in fasting subjects early in the morning. Nurses interviewed the subjects, measured their height and weight, and calculated their body mass index (BMI). Three readings of blood pressure were taken for each subject with a mercury sphygmomanometer after resting in a seated position for at least 5 min. Thereafter, blood samples for analysis were col-

lected from a brachial vein. Items for analysis were age, BMI, casual SBP and casual DBP in the seated position, fasting plasma glucose concentration (FPG), and plasma concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C). Blood concentrations of these substances were determined by the following methods: FPG, by the glucose oxidase-electrode method; TC, by the cholesterol oxidase/dimethoxy-aniline hydroxy-3-sulfopropyl (DAOS) method; TG, by the glycerol-3-phosphate oxidase/DAOS method; HDL-C, by the dextran sulfate magnesium chloride precipitation method.

The subjects were divided into 6 categories based on their casual blood pressure in the seated position according to the WHO/ISH guidelines. Those with SBP below 120 mmHg and DBP below 80 mmHg were classified into a category with optimal blood pressure. Those with SBP between 120 and 130 mmHg and DBP between 80 and 85 mmHg were classified into a normal blood pressure category. Those with SBP between 130 and 140 mmHg or DBP between 85 and 90 mmHg were classified into a normal high blood pressure category. Those with SBP between 140 and 160 mmHg or DBP between 90 and 100 mmHg were classified into a grade 1 hypertension category. Those with SBP between 160 and 180 mmHg or DBP between 100 and 110 mmHg were classified into a grade 2 hypertension category. Those with SBP over 180 mmHg or DBP over 110 mmHg were classified into a grade 3 hypertension category. In this study, analysis was done in three groups: an optimal+normal blood pressure level group, a normal high blood pressure level group and a grade 1–3 hypertension group.

Follow-up was commenced on August 31, 1992 and terminated on August 31, 1999. The endpoints were onset of cardiovascular disease or death due to cardiovascular disease. Occurrence of strokes and ischemic heart diseases, *i.e.*, angina pectoris/cardiac infarction, and sudden cardiac deaths was detected by interview, at the health examinations, or by monitoring yearly changes in the ECG. The occurrence of the above diseases and deaths of the subjects who did not undergo the health examinations were detected by sending questionnaires to the subjects or the family members. For subjects who received medical treatment, we tried to obtain as much information as possible from the chief physicians about their diseases, particularly about clinical symptoms and findings in ECGs, CT scans and MRIs. We visited surviving family members or sent them questionnaires to confirm the deaths, and we obtained detailed information about the diseases of the decedents from chief physicians. We obeyed the law protecting individual information, and data of the subjects were treated very carefully.

Based on the data collected, the incidence of cardiovascular diseases was calculated for each blood pressure-based category. In principle, we conducted posthumous investigations or investigations after the occurrence of diseases only when the involved subjects or surviving family members gave their consent. Fortunately, we were not refused in any of these cases.

Table 1. Results of Examinations on the Subjects in Different Categories Formed on the Basis of Their Blood Pressure in the First Study Year

	Optimal blood pressure	Normal blood pressure	Normal high blood pressure	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension
Number of subjects	628	403	323	334	98	12
Sex (male:female)	260:368	188:215	151:172	154:180	47:51	6:6
Age (years)	55.7±12.8	57.1±11.4	60.2±10.2* [†]	62.3±10.1* ^{†,‡}	64.0±10.0* ^{†,‡}	63.3±9.5*
Body mass index (kg/m ²)	22.7±2.8	23.3±3.1*	24.0±3.0*	23.9±3.1* [†]	24.4±3.5* [†]	24.9±4.0*
Systolic blood pressure (mmHg)	109.4±8.0	123.9±3.4*	133.6±3.6* [†]	146.7±6.6* ^{†,‡}	166.8±10.2* ^{†,‡}	180.2±30.3* ^{†,‡}
Diastolic blood pressure (mmHg)	67.7±6.8	74.7±5.9*	78.4±6.5* [†]	88.3±8.0* ^{†,‡}	90.7±11.1* ^{†,‡}	93.7±12.4* ^{†,‡}
Fasting plasma glucose (mg/dL)	87.4±26.2	85.0±38.6	89.0±33.9	95.7±27.4* ^{†,‡}	100.9±22.1* ^{†,‡}	103.9±18.0*
Total cholesterol (mg/dL)	183.3±43.6	184.6±56.8	191.2±49.3*	195.1±30.9* [†]	194.4±30.9*	215.3±33.8*
Triglyceride (mg/dL)	109.2±78.2	128.1±103.5*	134.2±106.3*	149.5±114.1* [†]	150.4±86.2* [†]	191.9±99.9* [†]
HDL-C (mg/dL)	50.7±29.6	51.8±27.9	52.7±19.9	53.9±16.4	53.7±13.8	53.4±18.8

* $p < 0.05$ vs. optimal blood pressure; [†] $p < 0.05$ vs. normal blood pressure; [‡] $p < 0.05$ vs. normal high blood pressure. Atherogenic factors, such as age, body mass index, fasting plasma glucose, and lipids other than HDL-C increased with blood pressure. HDL-C, high-density lipoprotein-cholesterol.

Table 2. The Incidence of Cardiovascular Diseases per 1,000 Persons/Year in Each Category

	Optimal+normal blood pressure	Normal high blood pressure	Grade 1–3 hypertension
Sex (male:female)	448:583	151:172	207:237
Age (years)	56.3±12.3	60.2±10.2	62.7±10.0
Number of incidence	38	27	29
Observed persons/year	6,093.2	2,397.6	1,831.4
Crude incidence rate (per 1,000 persons/year)	6.24	11.26	15.83*

* $p < 0.05$ vs. optimal+normal blood pressure. The incidence of cardiovascular diseases per 1,000 persons/year was higher in higher blood pressure categories. Significant differences were noted in the incidence between the optimal+normal blood pressure group and the grade 1–3 hypertension group.

All numerical values are expressed as the means±SD. Differences between two groups were examined using Student's *t*-test. Relative risk of occurrence of cardiovascular diseases in individual categories was obtained as a value relative to that in the optimal+normal blood pressure group after adjusting for sex, age, and other parameters. For this purpose, a Cox's proportional hazards model was used. For statistical analysis, Statview Ver. 5.0 (Macintosh) was used. To compare frequencies, χ^2 -tests were performed. The significance level was set at $p < 0.05$.

Results

Table 1 summarizes the results of examinations for the subjects in different categories based on blood pressure in the first study year. Atherogenic factors, including age, BMI, FPG, and lipids other than HDL-C, increased with increase in blood pressure category.

The 1,798 subjects in the follow-up study included 806 men (mean age, 59.5±11.2 years) and 992 women (mean age, 57.8±12.1 years). Cardiovascular diseases occurred during

the follow-up period in 94 subjects (55 men and 39 women). Seventeen subjects died as a result of newly occurring cardiovascular diseases. Strokes occurred in 37 men and 27 women, and ischemic heart diseases occurred in 18 men and 12 women.

The incidence rate of cardiovascular disease per 1,000 persons/year was higher in the higher blood pressure categories: The incidence rates were 6.24 for the optimal+normal blood pressure level group, 11.26 for the normal high blood pressure level group, and 15.83 for the grade 1–3 hypertension group. There was a significant difference between the incidences in the optimal+normal blood pressure level group and the grade 1–3 hypertension group (Table 2).

The relative risk of occurrence of cardiovascular diseases in the individual groups, expressed as a multiple of that in the optimal+normal blood pressure level group, was calculated after adjusting for sex, age, FPG, TC and BMI using Cox's proportional hazards model. The relative risk increased in the higher blood pressure groups and there was a significant difference between the risk in the optimal+normal blood pressure level group and the grade 1–3 hypertension group (Table 3).

Table 3. The Relative Risk of Cardiovascular Diseases Adjusting for Sex, Age, Fasting Plasma Glucose, Total Cholesterol and Body Mass Index Using a Cox's Proportional Hazards Model

	Relative risk	<i>p</i> value	95% confidence interval
Optimal+normal blood pressure	1.00	—	—
Normal high blood pressure	1.19	0.3	0.89–1.20
Grade 1–3 hypertension	1.46	0.011	1.00–1.17

The relative risk increased in higher blood pressure categories, and there was a significant difference in the risk between the optimal+normal blood pressure group and the grade 1–3 hypertension group.

With regard to DBP, the relative risk of occurrence of cardiovascular diseases was 1.01, a significant value, in a Cox's proportional hazards model in which occurrence of cardiovascular diseases was taken as the endpoint and variables such as sex and age were included. This result indicates that DBP is an independent risk factor. In the groups having a DBP above 90 mmHg, the relative risk was 1.3-fold that in the optimal+normal blood pressure level group.

Discussion

The results of this study showed that in a relatively old cohort with a mean age of about 60 years, the risk for occurrence of cardiovascular diseases increased in the higher blood pressure groups. In the first stage of this study, we carried out analysis separately for occurrence of stroke and occurrence of heart diseases. However, we failed to reveal significant differences among the blood pressure categories for either the incidence or risk of stroke or heart disease. Since a tendency suggesting a close relationship between blood pressure and the incidence and risk of these diseases was noted in such analyses, we combined the two disease groups into one and studied the relationship between the blood pressure categories and occurrence of disease in this combined disease group.

The reason for the exclusion of subjects treated with antihypertensive medication was that many of them had cardiovascular diseases and that some antihypertensive drugs might not only have an inhibitory effect on but might also promote the onset of cardiovascular diseases *via* their effects on the metabolic and endocrine systems. However, we did not know the types of antihypertensive drugs the subjects were being treated with, and we therefore decided to exclude subjects taking antihypertensive drugs in order to eliminate the possible effect of blood pressure on the onset of cardiovascular diseases in those subjects.

The results of previous studies regarding the relationship between blood pressure and occurrence of cardiovascular diseases have been inconsistent. SBP (6, 9) and DBP (6) were found to have close positive correlations with the risk of cardiac infarction in men and women in the Framingham heart study (6), which included subjects aged 65–94 years, and also in a study by the Chicago Heart Association (9) with subjects aged 60–74 years. On the other hand, two other studies reported that there was no close correlation between DBP or

SBP and the incidence of cardiovascular diseases or the rate of death resulting from cardiovascular diseases (10, 11). The incidence of cardiac infarction has been reported to increase with decreases in SBP (15, 16) and DBP (11, 15, 16) in the aged.

Several possible reasons for the absence of an overt correlation between blood pressure and risk of cardiac infarction in the aged have been proposed. For instance, at the time of entry into a prospective study program, many elderly subjects might already have cardiac infarction (17), or they might have high blood pressure, thus obscuring the effect of blood pressure (18). Previous studies (10, 11, 15, 16) have shown a U- or J-shaped relation between blood pressure and the incidence of cardiovascular diseases (11, 19–21).

Diastolic blood pressure has been shown to decrease with advance of age because of increased arterial stiffness due to arteriosclerosis (22, 23). Since many old people have a combination of several diseases, they might have reduced diastolic blood pressure and as a result have a high death rate (18, 24). In addition, mechanisms are conceivable by which a reduction in blood pressure increases the incidence of cardiovascular diseases. Decrease in DBP, for instance, results in reduced blood flow in the coronal artery in patients with severe coronal stenosis and thereby increases the risk of death from ischemic cardiac diseases (18, 24).

The results of studies in Japan are inconsistent with those in other countries. The incidence of cerebral infarction increased with a rise in blood pressure in the first group in the Hisayama-cho study, whereas antihypertensive medication failed to reduce the risk of occurrence of ischemic cardiovascular diseases in the third group. Hypertension was reported to be a less potent risk factor for ischemic heart diseases than for strokes in Japan (5). In the present study, cardiovascular diseases, including strokes and ischemic heart diseases, occurred in 94 subjects during the follow-up period. The incidence of cardiovascular diseases increased in the higher blood pressure-based groups, and the incidence in the optimal+normal blood pressure group was significantly smaller than that in the grade 1–3 hypertension group. This study therefore indicates that hypertension increases the risk of cardiovascular diseases in the general population in Japan. Analysis of data for the 30 subjects in whom heart diseases occurred and for the 64 subjects in whom stroke occurred showed similar correlations between blood pressure and these diseases. The

findings described above indicate that the incidence of cardiovascular diseases has a positive correlation with blood pressure in the general population in Japan and that blood pressure is an age- and sex-independent risk factor for cardiovascular diseases, including stroke and ischemic heart diseases.

In studies in the United States and Europe, such as the Framingham heart study, on the other hand, the incidence of ischemic heart diseases had positive correlations with SBP and pulse pressure and had a negative correlation with DBP (25). Pulse pressure had a close positive correlation with ischemic heart diseases (26). In the present study, there was no consistent correlation between pulse pressure and occurrence of cardiovascular diseases. Diastolic blood pressure was a risk factor for cardiovascular diseases even in the subjects aged over 60 years when they had diastolic blood pressure above 90 mmHg.

As to subtypes of strokes, cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage (SAH) accounted for about 66%, 23% and 11%, respectively, of the strokes that occurred in the 64 subjects during the follow-up period. These percentages of subtypes are similar to those reported recently in Japan (27). It has been reported that smoking status was an independent determinant of multiple silent cerebral infarction in a high-risk community-dwelling population in Japan (28). The relationships between blood pressure and subtypes of stroke should be studied further.

No differences were found in the incidences of cardiovascular diseases among the 3 hypertension categories in the grade 1–3 hypertension group. When the risk of occurrence of cardiovascular diseases in the individual categories relative to that in the optimal blood pressure category was analyzed using a Cox's proportional hazards model, which enabled us to adjust for sex and age, relative risk showed a tendency to increase in the higher blood pressure categories. However, a significant difference from the optimal blood pressure category was revealed only in the grade 3 hypertension category. One possible explanation for this finding is that subjects in the grade 2 and grade 3 hypertension categories in the first study year received antihypertensive medication during the subsequent follow-up period and their blood pressure and other risk factors were controlled. It is possible that the reason for the lack of a statistically significant difference in relative risk between the grade 1 and grade 2 hypertension groups was not there was no relationship, but rather that the power of detection was too small. It was thought that age and sex were strong risk factors for the incidence of cardiovascular diseases, and that these factors attenuated the risk of hypertension as a byproduct of cardiovascular disease. In this study, analysis was therefore done in three groups: an optimal+normal blood pressure level group, a normal high blood pressure level group and a grade 1–3 hypertension group. It is therefore possible that the influence of blood pressure in the first study year on the incidence of cardiovascular diseases was unduly low. It is also possible that the number of subjects in

whom cardiovascular diseases occurred was not large enough to reveal statistically significant differences. Annual follow-up of these subjects should be continued hereafter.

The occurrence of cardiovascular diseases was confirmed by interviewing subjects or their family members, or by sending them questionnaires. The registered cases were those with newly occurring stroke, cardiac infarction or sudden death, which were confirmed by interviews with chief physicians and clinical records such as ECGs. There was a limitation with respect to determining the underlying cause of death, in that autopsies were not conducted.

In summary, a U- or J-shaped relation was not found between SBP or DBP and incidence of cardiovascular disease. Instead, the risk of occurrence of cardiovascular diseases increased with increase in blood pressure.

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