Secular Trends in Atherosclerosis of Coronary Arteries and Basal Cerebral Arteries in Japan

The Akita Pathology Study

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The atherosclerotic lesions of the coronary arteries and basal cerebral arteries in the circle of Willis were examined in the bodies of deceased men ages 30 and over who had been admitted to a local hospital in northeast Japan during 1966 to 1974 (243 men) and 1975 to 1984 (602 men). The autopsy rates during the two periods were 86% and 89%, respectively. The extent of atherosclerosis was determined blindly by one pathologist using a grading method of cross-sectional stenosis scoring for coronary arteries and Baker's method for basal cerebral arteries. The age-adjusted mean scores for atherosclerosis in the coronary arteries and basal cerebral arteries were 30% and 42% lower, respectively, in the 1975 to 1984 period than in the 1966 to 1974 period (p<0.001). There was also a fall in age-adjusted blood pressure levels at admission: 10 mm Hg for systolic and 4 mm Hg for diastolic blood pressure (p<0.001). The opposite trend was seen in mean serum cholesterol: a rise from 171 mg/dl to 177 mg/dl (p=0.018). Linear regression analysis indicated that blood pressure was positively associated with both atherosclerosis scores, controlling for age and serum cholesterol in both time periods (p<0.001). The association of serum cholesterol with the atherosclerosis scores was positive in both periods and statistically significant in 1975 to 1984. Similar findings were obtained when the analyses were conducted for cardiovascular disease (myocardial infarction and stroke) and for noncardiovascular disease, separately. The decline in atherosclerosis scores parallels the substantial fall in blood pressure levels, which may overwhelm the effect of the moderate increase in serum cholesterol level.

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In Japan, there has been a decline in mortality rates from stroke since 1970.1,2 Surveillance studies showed that the incidence rate of stroke declined between the 1960s and the 1970s.3-4 A decline in mortality rates from coronary heart disease has also been observed since 1972, although trends in the incidence rate varied between rural and urban populations. No trends of coronary heart disease incidence were reported from population surveys of rural communities,4-5 while increasing trends were seen in urban male employees.6 This study was conducted in a rural population in Akita Prefecture in northeast Japan where a declining mortality trend of coronary heart disease and stroke was also observed.5,7

Autopsy studies in New Orleans, Louisiana, have demonstrated a reduction in the extent of coronary atherosclerosis in Caucasian men between the periods, 1960 and 1964, and 1968 and 1972, which paralleled the decline in mortality rates from coronary heart disease.8 On the other hand, an autopsy study in Olmsted County, Minnesota, showed an increase in the percentage of persons with over 75% luminal diameter reduction of the coronary arteries between 1950 and 1979.9 No study in Japan, however, has examined secular trends in the atherosclerotic lesions of the coronary or cerebral arteries to associate them with cardiovascular mortality trends.

The Akita pathology study examined secular trends in atherosclerosis in both coronary arteries and basal cerebral arteries in Japanese men between 1966 and 1984 in an attempt to relate atherosclerotic changes to trends in mortality rates. This report describes the trends in the grades of these atherosclerotic lesions and the factors related to the trends.

Methods

The Akita pathology study is a hospital-based autopsy study that has been conducted in Yuri General Hospital since 1966. The hospital is located in the city of Honjo, surrounded by the Yuri area in Akita Prefecture 250 miles north of Tokyo. There is no other hospital with more than 20 beds in the area. Patients admitted to the hospital are predominantly from Honjo and the Yuri area. The census population of Honjo plus the Yuri area (500 square miles)
was 125,968 in 1970 and 127,175 in 1980. The primary industries include farming and light industry, and the population has been very stable.

The subjects studied consisted of all men who died in the hospital and on whom autopsies were performed. Men who did not live in the city of Honjo or the Yuri area were excluded. Between 1966 and 1984, autopsies were performed on 845 men ages 30 and over. Table 1 presents the number of men by disease and age group in the two periods, 1966 to 1974 and 1975 to 1984. The number of men in all age groups on whom autopsies were performed was 243 in 1966 to 1974 and 602 in 1975 to 1984. There was an increase over time in the number of autopsies in the older age groups, which may be due to an increase in the admissions of older persons. Because the population is stable, it is assumed that the rise in admissions was accompanied by a fall in out-of-hospital deaths at older ages. Although no data were available on the trends in the out-of-hospital deaths in these areas, it was likely that improvements in the ambulance system and medical insurance in the mid-1970s led to a rise in admissions at older ages.10 The proportion of all in-hospital deaths in which autopsies were performed was 86% in 1966 to 1974 and 89% in 1975 to 1984. The most frequent cause of death was stroke: 53% in 1966 to 1974 and 61% in 1975 to 1984. In both periods, 6% of deaths were due to myocardial infarctions. Accidents accounted for 5%, and violence accounted for 0.5% of all deaths.

The left main, left anterior descending, left circumflex, and right coronary arteries were fixed in 10% buffered formalin and were cut cross-sectionally at 5 mm intervals. The grade of stenosis in each section was visually estimated from 0 (no stenosis) to 4 (completely occluded). Then a total stenosis score was calculated by adding the maximum grades in 10 subregions of the arteries: the proximal, middle, and distal regions of the left anterior descending, circumflex, and right coronary arteries, as well as the left main coronary artery. The range of the total score could be between 0 and 40.11,12

The brains were fixed in 10% buffered formalin, and the grades of atherosclerosis in the basal cerebral arteries of the circle of Willis were scored according to Baker's method.13,14 The range of the total score could be between 0 and 88. All of the grading was performed within 1 year after death by one of the authors (M.K.), a certified pathologist, who was blinded to the subject's age, blood pressure, and serum cholesterol value.

First- and fifth-phase blood pressures were measured at admission for 99% of the subjects who died in the hospital by physicians or nurses using standard mercury sphygmomanometers. The first measurement of blood pressure was used for the analyses. For 89% of the hospitalized subjects, serum total cholesterol values at admission were available. Serum cholesterol was measured by the Liebermann-Burchard direct method.15 Quality control of the laboratory has been maintained by internal methods since 1966. A history of smoking was not available for most subjects.

For statistical analyses, Student's t test was used to compare atherosclerotic scores and continuous variables between the periods, 1966 to 1974 and 1975 to 1984. An analysis of covariance was used for the age-adjustment of these variables. Linear regression models were applied to determine the association of age, blood pressure, and total serum cholesterol with the atherosclerotic scores in each period. All p values presented were two-tailed. To estimate whether potential selection bias in hospital autopsy cases affected the study results, these analyses were conducted separately for two major groups of causes of death, i.e., myocardial infarction plus stroke (cardiovascular disease) and the others (noncardiovascular disease), as well as for all autopsy cases.

Results

Table 2 shows the mean values and standard errors of the atherosclerosis scores for the coronary and cerebral arteries by disease and age group in 1966 to 1974 and 1975 to 1984. For all autopsy cases, the mean coronary atherosclerosis scores were significantly lower in 1975 to 1984 than in 1966 to 1974 for all age groups except ages 50 to 59. The age-adjusted mean score for coronary
arteries in men ages 30 and over was 13.8 in 1966 to 1974 and 9.6 in 1975 to 1984, a 30% decline (p<0.001). A larger decline in atherosclerotic score was observed for cerebral arteries. The decline was significant for every age group. The age-adjusted mean scores for men ages 30 and over was 33.9 in 1966 to 1974 and 19.5 in 1975 to 1984, a 42% decrease (p<0.001). The distributions of atherosclerosis scores were also examined and found to be shifted downward over time. The proportion of coronary atherosclerosis scores ≥20 decreased in every age group; the age-adjusted proportions ≥20 were 21% in 1966 to 1974 and 19.5 in 1975 to 1984, a 42% decrease (p<0.001). The significant declining trends in the mean levels of atherosclerosis scores were observed for both cardiovascular and noncardiovascular disease cases. For cardiovascular disease cases, there was a 12 mmHg fall in systolic blood pressure, a 3 mmHg fall in diastolic blood pressure, and a 6 mg/dl rise in serum cholesterol level. The respective values for noncardiovascular disease cases were 13 mmHg, 10 mmHg, and 5 mg/dl.

Figures 1 and 2 illustrate the age-adjusted mean levels of the atherosclerosis scores by blood pressure category and by serum cholesterol category for all autopsy cases. Hypertension was defined as systolic blood pressure ≥160 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking antihypertensive medication. Normotension was defined as systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, or no antihypertensive medication use. All other combinations were regarded as borderline hypertension. There was a stepwise increase in the mean levels of the atherosclerosis scores for coronary and cerebral arteries across blood pressure categories in both periods. In each blood pressure category, the mean atherosclerosis scores decreased over time. There was a positive, but insignificant, trend in the mean levels of the atherosclerosis scores by blood pressure category and by serum cholesterol category for all autopsy cases. Similar trends were obtained for both cardiovascular and noncardiovascular disease cases. For cardiovascular disease cases, there was a 12 mmHg fall in systolic blood pressure, a 3 mmHg fall in diastolic blood pressure, and a 6 mg/dl rise in serum cholesterol level. The respective values for noncardiovascular disease cases were 13 mmHg, 10 mmHg, and 5 mg/dl.

The significant declining trends in the mean levels of atherosclerosis scores were observed for both cardiovascular and noncardiovascular disease cases. For cardiovascular disease cases, there was a 26% decline for coronary arteries and a 37% decline for the cerebral arteries. The respective percent decline for noncardiovascular disease cases was 44% and 58%.

The mean values and standard errors for systolic and diastolic blood pressure and total serum cholesterol in 1966 to 1974 and in 1975 to 1984 are presented in Table 3. For all autopsy cases, the mean values of both systolic and diastolic blood pressure were significantly lower in 1975 to 1984 than in 1966 to 1974 for ages 50 to 69, but not in the other age groups. The age-adjusted blood pressure levels declined 10 mm Hg for systolic and 4 mm Hg for diastolic blood pressure (p<0.001). The opposite trend was seen in mean serum cholesterol. Mean serum cholesterol increased in all age groups but was significant only for ages 30 to 49. The age-adjusted mean serum cholesterol increased 6 mg/dl (p<0.001). Similar trends were obtained for both cardiovascular and noncardiovascular disease cases. For cardiovascular disease cases, there was a 12 mmHg fall in systolic blood pressure, a 3 mmHg fall in diastolic blood pressure, and a 6 mg/dl rise in serum cholesterol level. The respective values for noncardiovascular disease cases were 13 mmHg, 10 mmHg, and 5 mg/dl.

A summary of the linear regression analyses is shown in Table 4. For all autopsy cases, atherosclerosis scores in both arterial trees were significantly associated with age and systolic blood pressure but not with serum cholesterol.
Table 3. Blood Pressure and Serum Total Cholesterol for Autopsied Men in Periods 1966 to 1974 and 1975 to 1984

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The values are the means±SE. The totals are the adjusted mean scores. Differences from the 1966 to 1974 values: *p<0.05, †p<0.01, ‡p<0.001.

CVD=myocardial infarction and stroke, Non-CVD=accident or violence and other diseases.

CORONARY ARTERY SCORE  

BASAL BRAIN ARTERY SCORE

Figure 1. Age-adjusted mean atherosclerosis scores in coronary and basal cerebral arteries, in the periods 1966 to 1974 and 1975 to 1984, by blood pressure category in men 30 years old and older.

in 1966 to 1974. In 1975 to 1984, these scores were positively associated with age, systolic blood pressure, and serum cholesterol. The findings were similar when the analyses were conducted separately for cardiovascular and noncardiovascular disease cases. The positive association between serum cholesterol and atherosclerosis scores, however, did not reach statistical significance for noncardiovascular disease cases in 1975 to 1984.
Figure 2. Age-adjusted mean atherosclerosis scores in coronary and basal cerebral arteries, in the periods 1966 to 1974 and 1975 to 1984, by serum total cholesterol category in men 30 years old and older.

Table 4. Summary of Linear Regression Results for Association of Risk Characteristics with Atherosclerosis Scores for Coronary and Basal Cerebral Arteries in Periods 1966 to 1974 and 1975 to 1984 In Men 30 Years Old and Older

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<td>0.0763†</td>
<td>−0.0048</td>
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<tr>
<td>Basal cerebral arteries</td>
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<tr>
<td>Age (yrs)</td>
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<td>0.5813†</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<td>0.1890†</td>
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<td>Serum cholesterol (mg/dl)</td>
<td>0.0520</td>
<td>0.1282†</td>
<td>0.0718</td>
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</table>

*p<0.05, †p<0.01, ‡p<0.001.

CVD = myocardial infarction and stroke, Non-CVD = accident or violence and other diseases.

Discussion

A significant decline in mean atherosclerosis scores for the coronary arteries and basal cerebral arteries was shown in this sample of autopsies of men who died in hospital in the periods 1966 to 1974 and 1975 to 1984. This trend parallels the trend of death from coronary heart disease and stroke between 1970 and 1980: a 17% decline for coronary heart disease and a 41% decline for stroke in Japan, and declines of 16% and 46%, respectively, in Akita Prefecture.35 This finding is consistent with the New Orleans study8 but not with the Olmsted County study.8 The decline in the atherosclerosis score was larger in basal cerebral arteries than in coronary arteries. This also parallels the larger decline in the rates of death by stroke than by coronary heart disease.

The weakness of the present study is the possible selectivity bias of hospitalized autopsy samples.16,17 Specifically, there might be differences in the severity and diagnosis mix of admitted cases between the periods 1966 to 1974 and 1975 to 1984. There was an increase over time in the number of older patients admitted. One way to correct for this selection bias is to restrict the autopsied samples to deaths from natural causes other than coronary heart disease and stroke.8,17 When we conducted separately the analyses for cardiovascular and noncardiovascular disease cases, the declining trends were observed for both disease groups. Furthermore, the trends were consistent in all age groups. Thus, these trends are not likely to be due to the selectivity of autopsy samples and probably reflect a real change.

A substantial decline in mean systolic and diastolic blood pressure was observed between the periods 1966 to 1974 and 1975 to 1984, although blood pressure measurement was not strictly standardized. A general population study in an adjacent community, Akita Prefecture, showed that there was a 15 mm Hg age-adjusted decline in systolic and a 4 mm Hg decline in diastolic pressure in men ages 40 to 69 between the periods 1963 to 1966 and 1980 to 1983.18 Other autopsy studies have demonstrated a positive association between blood pressure and atherosclerotic lesions.19,20 The present study also indicated a significant association of blood pressure at admission, with grades of
atherosclerotic lesions in the coronary and cerebral arteries. Therefore, a part of the decline in atherosclerotic lesions is probably attributable to the fall in blood pressure level.

Mean serum cholesterol increased significantly between 1966 to 1974 and 1975 to 1984. In the general population of an adjacent community, serum cholesterol levels rose from 157 mg/dl in 1963 to 179 mg/dl in 1980 to 1983. The increase in serum cholesterol level paralleled an increased intake of meat, eggs, and dairy products. A positive association between serum cholesterol and atherosclerotic lesions has been reported from various pathologic and epidemiologic studies. This study also showed the positive association of serum cholesterol with atherosclerosis in both time periods, but the association was statistically significant only in 1975 to 1984. The shallower slope and the associated lack of statistical significance in the earlier period may be due to in part to a lower atherosclerosis risk gradient with the lower serum cholesterol values.

The trend in serum cholesterol levels seems to be contrary to a decline in the atherosclerosis scores. However, it should be emphasized that the serum cholesterol level in 1975 to 1984 was still relatively low, and the increase was statistically significant only for men ages 30 to 49. Moreover, the serum cholesterol level has not been higher long enough. We assume that the substantial decline in blood pressure levels contributed much more than the moderate increase in serum cholesterol levels to the changes in the atherosclerosis scores. The results of the present study are comparable with the observation of a decline in stroke incidence with a fall in blood pressure and an increase in serum cholesterol in a rural Japanese community between the periods 1963 to 1966 and 1980 to 1983. Although this population study showed a continuously low incidence rate of coronary heart disease with no trend, the national data for Japan indicate a fall in the mortality rate from coronary heart disease since the 1970s. Information on smoking was not available in the present study. The national data on smoking trends indicate a slight decline in the prevalence of smokers for men ages 20 and over since 1965: 80% in 1965, 76% in 1975, and 65% in 1980. The trend in serum cholesterol levels seems to be contrary to a decline in the atherosclerosis scores. However, it should be emphasized that the serum cholesterol level in 1975 to 1984 was still relatively low, and the increase was statistically significant only for men ages 30 to 49. Moreover, the serum cholesterol level has not been higher long enough. We assume that the substantial decline in blood pressure levels contributed much more than the moderate increase in serum cholesterol levels to the changes in the atherosclerosis scores. The results of the present study are comparable with the observation of a decline in stroke incidence with a fall in blood pressure and an increase in serum cholesterol in a rural Japanese community between the periods 1963 to 1966 and 1980 to 1983. Although this population study showed a continuously low incidence rate of coronary heart disease with no trend, the national data for Japan indicate a fall in the mortality rate from coronary heart disease since the 1970s. Information on smoking was not available in the present study. The national data on smoking trends indicate a slight decline in the prevalence of smokers for men ages 20 and over since 1965: 80% in 1965, 76% in 1975, and 65% in 1980.

In conclusion, the decline in atherosclerosis scores in the Akita autopsy sample parallels the mortality trends of coronary heart disease and stroke in Japan. These trends also parallel the substantial fall in blood pressure levels, but not a moderate rise in serum cholesterol level.

Acknowledgments

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