Pathologic Characteristics of Stroke and Myocardial Infarction in Japan – Akita Pathology Study –

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The Akita pathology study was conducted to examine risk characteristics of stroke and myocardial infarction, and trends of atherosclerosis in brain and coronary arteries. The subjects were 845 men aged 30 and over, examined among autopsied men admitted to a local hospital of northeast Japan between 1966 and 1984. The overall autopsy rate was 88%. Blood pressure and serum cholesterol at admission was compared according to type of stroke. To elucidate risk characteristics of myocardial infarction in Akita, the infarction cases were compared with those in Osaka (the second largest city in Japan). Grades of atherosclerosis for basal cerebral arteries and coronary arteries and grade of arteriosclerosis for intracerebral small arteries were determined blindly by one pathologist using a method of cross-sectional stenosis scoring. As expected, blood pressure levels were higher in all types of stroke than nonstroke. Serum cholesterol was lower in cerebral hemorrhage than in nonstroke, and was higher in infarction in cortical artery regions than in nonstroke. Cerebral hemorrhage showed the lowest proportion of significant stenosis in both basal and intracerebral penetrating arteries. Myocardial infarction in Akita had a higher prevalence of hypertension and a lower prevalence of high serum cholesterol, the higher proportion of scattered type of infarction (mostly subendocardial infarction) compared with myocardial infarction in Osaka. Age-adjusted mean scores for atherosclerosis in the coronary arteries and basal cerebral arteries declined 30% and 42%, respectively, between 1966–1974 and 1975–1984. There was a decline in age-adjusted blood pressure levels at admission: 10 mmHg for systolic and 4 mmHg for diastolic blood pressure, whereas mean serum cholesterol rose 6 mg/dl. There results indicated that hypertension and low serum cholesterol levels were associated with cerebral hemorrhage, and mostly hypertension with myocardial infarction in Akita. The deline in blood
pressure levels between the 1960's and 1980's may have contributed to the decreased atherosclerosis in both brain and coronary arteries. The effect of an increase in serum cholesterol for coronary atherosclerosis was overwhelmed by the large decrease in blood pressure levels.

Autopsy study, Serum total cholesterol, Secular trends, Atherosclerosis, Arteriosclerosis, Angioneurosis

INTRODUCTION

The relation between serum total cholesterol and myocardial infarction has been widely reported from Western countries(1). The contribution of serum total cholesterol to stroke, however, is controversial(2). Recent epidemiologic evidence suggests the association varies by type of stroke. Epidemiologic studies for Japanese(3-5) and Japanese Americans(6,7) showed that serum cholesterol was inversely associated with the incidence of cerebral hemorrhage, whereas studies from the United States(8,9) indicated a weak but positive association of serum cholesterol with cerebral infarction or total stroke. A 6-year followup study of 350,977 American men screened for Multiple Risk Factor Intervention Trial showed that serum total cholesterol was inversely associated with the death from cerebral hemorrhage, and positively associated with the death from cerebral infarction(10). However, few pathologic studies have examined the association of serum cholesterol with stroke type diagnosed by autopsy.

Contributions of serum cholesterol to myocardial infarction may vary among populations. We hypothesized that myocardial infarction in Akita is less associated with serum cholesterol than infarction in urban populations, or western countries. To examine this hypothesis, a comparative study was done for myocardial infarction from the Akita Pathology Study and infarction in an urban population.

During the past two decades, Japan experienced substantial changes in lifestyles leading to a decline of blood pressure levels and an increase in serum cholesterol levels(11). A decline in mortality from coronary heart disease and stroke was also observed(12). No study in Japan, however, has examined secular trends in atherosclerotic lesions of the cerebral or coronary arteries to associate them with cardiovascular mortality trends.


MATERIALS AND METHODS

The Akita pathology study is a hospital-based autopsy study conducted in Yuri General Hospital between 1966 and 1984 (13). The hospital is located in the city of Honjo, surrounded by the Yuri area in the Akita prefecture, 250 miles north of Tokyo. There is no other hospital with more than twenty 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.

Subjects were all men who died in hospital and were autopsied. Between 1966 and 1984, 845 men ages 30 and over were autopsied. Men who did not live in the city of Honjo or the Yuri area (n = 26) were excluded from this number. The proportion of all deaths that were autopsied was 89%. The most frequent cause of death was stroke: 59% of the total deaths. The proportion that were myocardial infarctions was 6%. The proportion that were accidents or violence was 5% and 0.5%, respectively.

Brains were fixed in 10% buffered formalin and grades of atherosclerosis in the basal cerebral arteries of the Circle of Willis were scored according to Baker’s method\(^{14,15}\). The range of the total score could be between 0 and 88. A Baker’s score of $>20$ was regarded as significant stenosis in the basal cerebral arteries. All of the grading was performed within a year from death by one of the authors (M.K.), a certified pathologist, blinded to subjects’ age, blood pressure and serum cholesterol values.

Hearts were fixed with 10% buffered formalin and the left main, left anterior descending, left circumflex, and right coronary arteries were cut cross-sectionally at 5 mm intervals. 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 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\(^{16,17}\).

There were 186 cerebral hemorrhage, 43 subarachnoid hemorrhage and 270 cerebral infarction. Penetrating artery infarction (n = 79) was defined as small infarction in the basal ganglion regions where the penetrating arteries are located. This type of stroke was mostly lacunar infarction. Cortical artery infarction (n = 58) was a larger infarction in the cortical artery regions with no hemorrhagic infarction, no cardiac embolus and no evidence of atrial fibrillation in the resting electrocardiogram. This type of stroke was mostly thrombotic infarction. Cortical artery infarction with evidence of possible embolic origin such as cardiac embolus, atrial fibrillation and hemorrhagic infarction was classified as embolic infarction (n = 97). Other types of infarction, mostly infarction in both penetrating and cortical artery regions was regarded as unclassified infarction (n = 36).

For men with cerebral hemorrhage, penetrating artery infarction or cortical artery infarction, grades of stenosis in intracerebral penetrating arteries in a basal ganglion region was also examined using a single microscopic slide of the coronal section of the cerebrum, including most of the putamen and globus pallidus. The percentage of stenosis for each artery of 100 to 300 microns in diameter was graded as 25% and more, or less than 25%. If half of more of the sections had stenosis 25% or more, we coded significant stenosis as being present, and otherwise entered a code in the database for no significant stenosis.

For a comparative study of myocardial infarction from the Akita Pathology Study and from an urban population, 54 myocardial infarction patients in Akita and 37 infarction patients admitted to the National Cardiovascular Center in Osaka (the second largest city in Japan) were used. Gross pathologic finding of myocardium was classified by spread of the necrotic regions. Infarction with necrotic regions of 1 centimeter and over in diameter, and mostly transmural infarction, was regarded as massive-type infarction. Only small regions of necrosis, and mostly subendocardial infarction, was classified as scattered type infarction.

First and fifth-phase blood pressures were measured at admission by physicians or nurses using standard mercury sphygmomanometers for 99% of subjects who died in hospital.
A resting electrocardiogram was obtained for 99% of the subjects. Total serum cholesterol value at admission were available for 89% of the subjects. Serum cholesterol was measured by the Liebermann-Burchard direct method. Quality control of the laboratory was maintained by internal methods since 1966. A history of cigarette smoking was not available for most subjects.

For statistical analyses, the Student t-test was used to compare atherosclerotic scores and continuous variables between 1966–1974 and 1975–1984. Analysis of covariance was used for age-adjustment of these variables. Linear regression models were applied to associate age, blood pressure and serum total cholesterol with the atherosclerotic scores in each period. All p-values presented were two-tailed.

**RESULTS**

**Risk Characteristics for Stroke by Stroke Type**

Table 1 shows age-adjusted mean values of blood pressure and serum total cholesterol in selected types of stroke and nonstroke. Mean age at admission was 62 for cerebral hemorrhage, 70 for penetrating artery infarction, 67 for cortical artery infarction and 63 for nonstroke. Cerebral hemorrhage showed the highest mean value of systolic and diastolic blood pressure, and the lowest mean of serum total cholesterol. Mean serum cholesterol for cerebral hemorrhage was significantly lower than nonstroke. Cortical artery infarction showed the highest mean value of serum total cholesterol, which was significantly higher than nonstroke. Penetrating artery infarction showed a similar level of serum cholesterol compared to nonstroke.

**Table 1** Age-adjusted mean values of blood pressure and serum total cholesterol in selected type of stroke and nonstroke for the autopsied men aged 30 and over.

<table>
<thead>
<tr>
<th></th>
<th>Cerebral hemorrhage (n = 186)</th>
<th>Penetrating A. infarction (n = 79)</th>
<th>Cortical A. infarction (n = 58)</th>
<th>Nonstroke (n = 346)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>185†</td>
<td>175†</td>
<td>174†</td>
<td>143</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>103†</td>
<td>98†</td>
<td>100†</td>
<td>84</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>165*</td>
<td>177</td>
<td>200†</td>
<td>174</td>
</tr>
</tbody>
</table>

* Differences from nonstroke: * p < 0.01, † p < 0.001

Distributions of serum cholesterol among the selected types of stroke and nonstroke are shown in Figure 1. Cerebral hemorrhage showed the lowest distribution of serum cholesterol, whereas cortical artery infarction showed the highest distribution. Distributions of serum cholesterol for penetrating artery infarction and nonstroke were located between cerebral hemorrhage and cortical artery infarction.

Figure 2 illustrates the proportion of significant stenosis in either basal or intracerebral arteries, or both, in cerebral hemorrhage, penetrating artery infarction and cortical artery infarction. Most of penetrating artery infarction and cortical artery infarction had significant stenosis in either basal cerebral or intracerebral small arteries. For cortical artery infarction,
the finding of significant stenosis in basal cerebral arteries only was common, while the finding of significant stenosis in intracerebral arteries only was rare. Cerebral hemorrhage showed a different pattern. No significant stenosis was found in 28% of cerebral hemorrhages. Among hemorrhage with significant stenosis, significant stenosis in intracerebral arteries only was also more common than stenosis in basal cerebral arteries only.

![Figure 1](image1.png)

**Figure 1** Distributions of serum total cholesterol among the selected type of stroke and nonstroke for the autopsied men aged 30 and over.

![Figure 2](image2.png)

**Figure 2** The proportion of significant stenosis in either basal or intracerebral arteries, or both, in cerebral hemorrhage, penetrating artery infarction and cortical artery infarction.
Comparison of Risk and Pathologic Characteristics of Myocardial Infarction Between Rural (Akita) and Urban (Osaka) Men

Table 2 presents risk and pathologic characteristics of myocardial infarction between Akita and Osaka men. Among myocardial infarction, the prevalence of hypertension, systolic blood pressure greater than or equal to 160 mmHg and/or diastolic blood pressure greater than or equal to 95 mmHg, and/or antihypertensive medication use, was much higher in Akita than in Osaka. The opposite trend was seen for the prevalence of a high blood cholesterol, serum cholesterol greater than equal to 220 mg/dl. There was a striking difference in gross pathologic findings in myocardial infarction between Akita and Osaka men. Massive type infarction was less common in Akita than in Osaka, while the opposite trend was seen for scattered-type infarction.

Table 2  Risk and pathologic characteristics of myocardial infarction between rural (Akita) men and urban (Osaka) men.

<table>
<thead>
<tr>
<th></th>
<th>rural men (n = 37)</th>
<th>urban men (n = 54)</th>
<th>Difference (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (%)*</td>
<td>92</td>
<td>41</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)**</td>
<td>14</td>
<td>59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gross Pathologic Type (%)</td>
<td></td>
<td></td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Massive</td>
<td>27</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Scattered</td>
<td>73</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

* systolic blood pressure >=160 mmHg and/or diastolic blood pressure, and/or with antihypertensive medication use

** serum total cholesterol >= 220 mg/dl

Trends in Atherosclerosis in Coronary and Basal Cerebral Arteries

Figure 3 shows trends in mean values of the atherosclerosis scores for the coronary and basal cerebral arteries by age group between 1966–1974 and 1975–1984. Mean coronary atherosclerosis scores were significantly lower in 1975–1984 than in 1966–1974 for all age groups except ages 50–59. The age-adjusted mean score for coronary arteries in men aged 30 and over was 13.8 in 1966–1974 and 9.6 in 1975–1984, 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. Age-adjusted mean scores for men aged 30 and over was 33.9 in 1966–1974 and 19.5 in 1975–1984 with a 42% decrease (p < 0.001). The declining trends in mean atherosclerotic scores did not change when myocardial infarction and stroke were excluded: a 45% decline for coronary arteries and a 58% decline for basal cerebral arteries.
Mean values of systolic and diastolic blood pressure and total serum cholesterol in 1966–1974 and in 1975–1984 are presented in Table 3. Age-adjusted blood pressure levels declined 10 mmHg for systolic and 4 mmHg for diastolic (p < 0.001). The opposite trend was seen in mean serum cholesterol. Age-adjusted mean serum cholesterol increased 6 mg/dl (p < 0.001). Similar findings were obtained when autopsy cases with stroke and myocardial infarction were excluded; a 13 mmHg fall in systolic blood pressure, a 10 mmHg fall in diastolic blood pressure and a 4 mg/dl rise in serum cholesterol level.

The result of linear regression analyses is shown in Table 4. Atherosclerosis scores in both arterial trees were significantly associated with age and systolic blood pressure but not with serum cholesterol in 1966–1974. In 1975–1984, these scores were positively correlated with age, systolic blood pressure and serum cholesterol. The findings were not altered when systolic blood pressure was replaced by diastolic blood pressure, and when autopsy cases with stroke and myocardial infarction were excluded.

Table 3 Mean values of blood pressure and serum total cholesterol for the autopsied men in 1966–1974 and in 1975–1984.

<table>
<thead>
<tr>
<th>Ages</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>Serum cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1966-74</td>
<td>1975-84</td>
<td>1966-74</td>
</tr>
<tr>
<td>30-49</td>
<td>148</td>
<td>151</td>
<td>90</td>
</tr>
<tr>
<td>50-59</td>
<td>175</td>
<td>158†</td>
<td>100</td>
</tr>
<tr>
<td>60-69</td>
<td>176</td>
<td>158‡</td>
<td>100</td>
</tr>
<tr>
<td>70+</td>
<td>166</td>
<td>163</td>
<td>93</td>
</tr>
<tr>
<td>Total§</td>
<td>169</td>
<td>159‡</td>
<td>96</td>
</tr>
</tbody>
</table>

Difference from the 1966–1974 value: * p < 0.05, † p < 0.01, ‡ p < 0.001
§ Age-adjusted mean scores

Figure 3 Trends in mean values of the atherosclerosis scores for the coronary and basal cerebral arteries by age group.
Table 4 Linear regression coefficients for the association of risk characteristics with atherosclerosis scores for coronary and basal cerebral arteries in 1966–1974 and 1975–1984, men ages 30 years and over.

<table>
<thead>
<tr>
<th></th>
<th>Coronary arteries</th>
<th>Basal cerebral arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1966-74</td>
<td>1975-84</td>
</tr>
<tr>
<td>Age (year)</td>
<td>0.207†</td>
<td>0.145†</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>0.086†</td>
<td>0.068†</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>0.006</td>
<td>0.076†</td>
</tr>
<tr>
<td></td>
<td>0.052</td>
<td>0.128†</td>
</tr>
</tbody>
</table>

* p < 0.05, † p < 0.001

DISCUSSION

The Akita pathology study showed a clear difference in serum total cholesterol levels between stroke types. The difference was particularly evident between cerebral hemorrhage and cortical artery infarction. Mean serum cholesterol was lower for cerebral hemorrhage and higher for cortical artery infarction compared to nonstroke. According to a population study in a neighboring community to the surveyed area, mean serum cholesterol was 175–179 mg/dl in the 1970’s and 1980’s(11). Thus, mean serum cholesterol seems to be lower for cerebral hemorrhage and higher for cortical artery infarction than for the free-living population from which the cases were drawn. This result is consistent with the findings of previous epidemiologic studies(3,7-10).

Distributions of stenosis in basal cerebral and intracerebral arteries also varied among stroke types. For cerebral hemorrhage, 29% of the cases showed no significant stenosis in either basal or intracerebral arteries, while the respective proportion of cortical artery infarction and penetrating artery infarction was less than 5%. A low proportion of stenosis in both basal arteries and intracerebral penetrating arteries, and a lower serum cholesterol level in cerebral hemorrhage imply that the disease process of cerebral hemorrhage is different from thrombotic infarction.

Previous pathologic studies showed that the pathogenesis of cerebral hemorrhage is the rupture of microaneurysm resulting from antigonecrosis (arteriolonecrosis, fibrinoid necrosis or lipohyalinosis) in intracerebral penetrating arteries(19,20). Pathologic findings of angionecrosis are the loss of medial smooth-muscle cells, the infiltration of blood plasma into the intima, the histolysis of internal elastic lamina and intimal collagen fibers, intimal fibrin deposition (fibrinoid degeneration) and luminal dilatation. Unlike atherosclerosis, there are no clear proliferative changes or lipid deposition in the intima. Disappearance of medial smooth-muscle cells contributes to the fragility of vascular wall which leads to microaneurysm in the presence of a high blood pressure.

We hypothesize that a very low serum cholesterol contributes to a fragile endothelium of intracerebral vascular walls, leading to the development of angionecrosis and cerebral hemorrhage in the presence of hypertension. There are several pieces of evidence which support this hypothesis. Men with cerebral hemorrhage had a higher degree of erythrocyte fragility, and lower cholesterol levels than age-matched controls in both serum and erythrocyte mem-
In vitro studies demonstrated increased osmotic fragility of erythrocyte membranes when the membrane cholesterol was reduced\(^{(21)}\). Stroke prone hypertensive rats had a lower cholesterol in both serum and erythrocyte membranes, and increased osmotic fragility of erythrocyte membranes compared to Wister-Kyoto rats\(^{(24)}\). A high-fat diet was reported to reduce the occurrence of stroke in stroke-prone hypertensive rats\(^{(25)}\). Furthermore, an animal study using Wister rats with a renal artery clamp showed that a diet-induced increase in the serum total cholesterol level from very low (118 mg/dl) to moderate (242 mg/dl) levels was associated with a significant reduction in the degree of angionecrosis\(^{(26)}\).

From a comparative study of myocardial infarction between Akita and Osaka men, we found that risk characteristics and pathologic findings differed between the two populations. In Akita, myocardial infarction was strongly associated with hypertension and was unlikely to be related to serum cholesterol levels. Over 70% of them were scattered-type infarction, mostly subendocardial infarction. On the other hand, myocardial infarction was more likely associated with high serum cholesterol levels, as with myocardial infarction in western countries. Most of them were massive-type infarction, mostly transmural infarction.

A significant decline in mean atherosclerosis score for the coronary arteries and basal cerebral arteries was shown between 1966–1974 and 1975–1984. This trend parallels the mortality trend of coronary heart disease and stroke between 1970 and 1980: a 17% decline for coronary heart disease and a 41% decline for stroke in Japan, a 16% and a 46% fall, respectively in Akita prefecture\(^{(27,28)}\).

A substantial decline in mean systolic and diastolic blood pressure was observed between 1966–1974 and 1975–1984. A general population study in an adjacent community of Akita prefecture showed that there was a 15 mmHg age-adjusted decline in systolic and a 4 mmHg decrease in diastolic pressure in men ages 40–69 between 1963–1966 and 1980–1983\(^{(11)}\). The present study also indicated a significant association of blood pressure with grades of atherosclerotic lesions in the coronary and cerebral arteries like other autopsy studies\(^{(29,30)}\). Therefore, a part of the decline in atherosclerotic lesions is likely attributable to the decrease in blood pressure level.

Mean serum cholesterol increased significantly between 1966–1974 and 1975–1984. In the general population of an adjacent community, serum cholesterol level rose from 157 mg/dl in 1963–1966 to 179 mg/dl in 1980–1983\(^{(16)}\). This study showed a significant positive association for the 1975–1984 sample. However, the association for the 1966–1974 sample did not reach statistical significance, perhaps in part due to a very low cholesterol level and a smaller sample size.

The trend in serum cholesterol seems to be contrary to a decline in the atherosclerosis score. The present study suggested that the contribution of serum cholesterol to myocardial infarction was small in Akita because of a lower cholesterol level than Osaka and western countries\(^{(11)}\). We assume that the substantial decline in blood pressure levels contributed more than the moderate increase in serum cholesterol levels to trends in atherosclerosis scores. A population study of an adjacent community\(^{(11)}\) showed continuously low incidence rates of coronary heart disease, with no trend, and the national data for Japan indicate a fall in the mortality rate from coronary heart disease since the 1970’s\(^{(30)}\).

Information on smoking was not available for the present study. According to the national data, there was a decline in the prevalence of current smokers for men ages 20 and over since 1965: 80% in 1965, 76% in 1975 and 65% in 1980\(^{(31)}\). If the trends is similar in our autopsied samples, the decrease in smoking prevalence may contribute in part to the decline in the atherosclerosis scores.
In conclusion, the present study confirmed a positive association of serum total cholesterol with cortical artery infarction and inverse association with cerebral hemorrhage. Yet, a causal relationship between low serum cholesterol levels and cerebral hemorrhage was not demonstrated. Further studies are needed to clarify the etiology of different types of stroke. 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 the moderate rise in serum cholesterol levels.

REFERENCES


