Cerebral Atherosclerosis in Japanese. 3. Predilection Site of Atherosclerotic Lesions

BY Y. KIKUCHI, M.D., H. YAMAMOTO, M.D., AND M. NAKAMURA, M.D.

Abstract: Four hundred twenty-three intracranial cerebral arteries (males and females) were obtained from the medicolegal autopsy cases. Special attention was given to the three sites and the circumferential distribution of lesions in order to investigate the effects of hydrodynamics on the development of cerebral atherosclerosis. The severest lesions were primarily found at the inner curvature at the terminal portion of the internal carotid artery, the medial portion at the origin of the anterior cerebral artery, and the posterior portion at the origin of the posterior cerebral artery. The present results obviously demonstrated the relationship between the predilection sites of atherosclerotic lesions and the shape of the cerebral arterial tree.

Additional Key Words: anterior cerebral artery, hemodynamic, posterior cerebral artery, internal carotid artery, thrombosis, hemorrhage

The most frequent cause of death in Japan is cerebrovascular disease. A recent survey of cerebrovascular accidents revealed that cerebral thrombosis is more frequent than hemorrhage, even in Japan. Whether this high incidence of cerebral thrombosis is related to high NaCl intake or to hypertension remains to be solved. We previously reported that the macroscopic severity of cerebral atherosclerosis in Japanese appeared to be equal to or slightly greater than that in Americans or Norwegians reported by Baker and his colleagues. The chemical composition of glycosaminoglycans and lipids in the cerebral arteries differs from that of other arteries. As is well known in oil technology, sludges in oil pipe are usually found at curvatures and branch points. These similarities between atherosclerotic development and oil sludge suggested to us that fluid dynamics in the arterial tree may contribute to the predilection site of atherosclerosis.

Detailed observations on the localization of atherosclerosis of the cerebral arteries are lacking. In the present study, the predilection site of atherosclerosis along the circumference at three selected sites of the cerebral arteries of Japanese has been examined macroscopically. The potential effects of fluid dynamics on the development of cerebral atherosclerosis is discussed.

Methods
Cerebral arteries from 423 cases were obtained at random from 2,238 consecutive autopsies at the Tokyo Medical Examiner's Office between April, 1965, and June, 1966. We have analyzed previously some of these data related to the primary cause of death, the atherosclerotic index evaluated by Baker's method, the relative frequency and intensity of cerebral atherosclerosis at various age periods, and the frequency and location of mild and/or severe atherosclerosis in these specimens. In the present study, special attention was given to the circumferential distribution of lesions at the three sites (A-A', B-B' and C-C' in fig. 1). The circumferential areas of the cerebral arteries at the three sites were divided into quadrants as follows: (1) A-A' (the terminal portion of the internal carotid artery) was divided into anterior portion (AP) and posterior portion (PP), and inner curvature (IC) and outer curvature (OC); (2) B-B' (the origin of the anterior cerebral artery) was divided into medial portion (MP), lateral portion (LP), superior portion (SP) and inferior portion (IP); (3) C-C' (the origin of the posterior cerebral artery) was divided into anterior portion (AP) posterior portion (PP), superior portion (SP) and inferior portion (IP). "Anterior" means frontal side, "posterior" means occipital side, "superior" means side of the brain parenchyma, and "inferior" means side of the base of skull.

The severity of sclerotic involvement of the four quadrants was compared on the basis of the thickness of lesions, and the number of cases showing the severest lesion at each quadrant was counted. Cases showing...
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ant. cerebral a. post. cerebral a. int. carotid a.

FIGURE 1

Three selected sites for observation in the circle of Willis. A-A': the terminal portion of the internal carotid artery, B-B': the origin of the anterior cerebral artery, and C-C': the origin of the posterior cerebral artery.

equivalent involvement in more than two quadrants were excluded from the study. The 852 arterial specimens in 423 cases were used for the present analysis. Difficult cases were discussed by both examiners (Y. K. and H. Y.) and then graded. X^2-test was used for statistical analysis.

Results

The 852 branches in 423 cerebral arterial specimens showed a nonuniform distribution of atherosclerotic lesions. Nonuniformly involved lesions were found in 368 cases at A-A', 236 at B-B', and 248 at C-C', respectively.

Results are summarized in the tables. A-A' is the terminal portion of the internal carotid artery, which is convex to the brain parenchyma and concave to the base of the skull. The severest lesion at A-A' was found at the inner curvature (IC) in 268 of 368 (73%) arterial specimens. The other quadrants were much less affected, i.e., PP 12%, AP 8% and OC 7%, respectively (table 1). The nonuniform distribution is statistically highly significant (P < 0.01).

B-B', the origin of the anterior cerebral artery, branches at nearly right angles from the internal carotid artery. Sixty-six percent of the severest lesions were located at the medial portion (MP). The nonuniformity of distribution also is highly significant (P < 0.01).

C-C' is an initial segment of the posterior cerebral artery, which branches off from the basilar artery. The branch point resembled a wide angle "Y" branching. The prevalent quadrant of the severest lesion was the posterior portion (PP) in 73% of the specimens, while the anterior portion exhibited only 4%. The nonuniformity also is statistically highly significant (P < 0.01).

These nonuniform distributions of the severest lesion were independent of sex (table 1). To establish the effects of age on the frequency of the predilection of cerebral atherosclerosis, the specimens were divided into three groups by decade: (a) decades 2 through 6, (b) decade 7, and (c) decades 8 through 10 (table 2). At A-A', the three groups showed a similar trend in nonuniform distribution. At B-B' the tendency for nonuniform distribution was most prominent in group "a" compared to groups "b" and "c" (P < 0.05 and P < 0.01, respectively). At C-C' the oldest group, "c," showed the least nonuniformity in three groups ("a" or "b" versus "c": P < 0.02).

The cerebral arteries also were divided into two groups on the basis of Baker's score: (α) 1 to 20 and (β) over 21 (table 3). At A-A' and C-C' the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Predilection Site of Atherosclerotic Lesion Along Circumference at the Selected Site of the Cerebral Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A-A'</td>
</tr>
<tr>
<td></td>
<td>AP</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>206</td>
</tr>
<tr>
<td>(8)</td>
<td>(72)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>(7)</td>
<td>(77)</td>
</tr>
<tr>
<td>Total cases</td>
<td>30</td>
</tr>
<tr>
<td>(8)</td>
<td>(73)</td>
</tr>
</tbody>
</table>

Each number represents number of cases demonstrating predilection of atherosclerotic lesion. Numbers in parentheses are percents. Abbreviations: see text and figure 1.

*Statistical significance of nonuniform distribution between quadrants (P < 0.01). Difference between male and female was not statistically significant.

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differences between the two groups of Baker's score were not clear. At B-B' the prevalence of the severest lesion at MP became less prominent with the higher Baker score of cerebral atherosclerosis (α versus β: P < 0.05).

**Discussion**

Atherosclerosis does not develop uniformly in the arterial tree. Several hypotheses have been advanced to explain the predilection sites of atherosclerosis from the point of the characteristics of the arterial wall. These focused on metabolic and histological aspects, or hemodynamic factors. Since we have no data on metabolism or on histological structure of the present materials, we will confine our discussion to the question of hemodynamic factors.

Since Cruveilhier (cited by Blumenthal) called attention to the possibility that hemodynamic factors might be a significant cause of atherosclerosis, stresses on the vascular wall have received increasing attention, even though some of the explanations have not been properly founded on engineering mechanics.

Burton emphasized the application of Laplace's law (wall tension = transmural pressure × radius), and Willis stated that the predilection site for atherosclerosis is due to increased wall tension on the inner curvature and at points of branching (fig. 2).

Texon proposed that an inwardly directed suction force generated by a "Bernoulli" mechanism is responsible for the development of atheroma. However, the maximum possible reduction of lateral pressure in his hypothesis is of negligible magnitude in normal arteries.

While many investigators have stressed the contribution of turbulence to atherogenesis, the question as to whether turbulence occurs normally in blood vessels other than the aorta has not been resolved. Stehbens observed streamlines in various-shaped glass tubes and speculated on the critical Reynolds number in the vascular system. He stated that while the critical Reynolds number in straight glass tubes is 2,000, it could be less than 200 in blood vessels, especially at bifurcations and curves. Further, he suggested that the maximum velocity rather than the mean velocity was the determining parameter in the development of turbulence.

Fox and Hugh advanced the concept, on the basis of their model experiments, that blood stasis resulting from boundary layer separation may accelerate the formation of a fibrin mesh and increase the deposition of fat, which then may be organized into an atheroma. However, the smooth curvatures and branching of normal vessels may inhibit flow separation.

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**Table 2**

Effects of Aging on Predilection of Atherosclerotic Lesion

<table>
<thead>
<tr>
<th>Decade</th>
<th>AP</th>
<th>IC</th>
<th>PP</th>
<th>OC</th>
<th>Total</th>
<th>MP</th>
<th>IP</th>
<th>LP</th>
<th>SP</th>
<th>Total</th>
<th>AP</th>
<th>IP</th>
<th>PP</th>
<th>SP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(α)</td>
<td>12</td>
<td>90</td>
<td>14</td>
<td>10</td>
<td>126</td>
<td>72</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>90</td>
<td>9</td>
<td>3</td>
<td>61</td>
<td>8</td>
<td>78</td>
</tr>
<tr>
<td>2–6</td>
<td>(10)</td>
<td>(71)</td>
<td>(11)</td>
<td>(8)</td>
<td>(124)</td>
<td>(80)</td>
<td>(8)</td>
<td>(7)</td>
<td>(6)</td>
<td>(100)</td>
<td>(8)</td>
<td>(4)</td>
<td>(78)</td>
<td>(10)</td>
<td>(92)</td>
</tr>
<tr>
<td>(β)</td>
<td>7</td>
<td>(7)</td>
<td>91</td>
<td>15</td>
<td>9</td>
<td>37</td>
<td>9</td>
<td>12</td>
<td>7</td>
<td>65</td>
<td>3</td>
<td>10</td>
<td>72</td>
<td>7</td>
<td>92</td>
</tr>
<tr>
<td>c</td>
<td>(8)</td>
<td>(7)</td>
<td>87</td>
<td>14</td>
<td>8</td>
<td>46</td>
<td>17</td>
<td>8</td>
<td>10</td>
<td>81</td>
<td>2</td>
<td>13</td>
<td>48</td>
<td>15</td>
<td>78</td>
</tr>
</tbody>
</table>

See footnote of table 1.

*a versus b: P < 0.05, a versus c: P < 0.01.
†a or b versus c: P < 0.02.

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**Table 3**

Effects of Severity of Cerebral Atherosclerosis on Predilection

<table>
<thead>
<tr>
<th>Baker's score</th>
<th>AP</th>
<th>IC</th>
<th>PP</th>
<th>OC</th>
<th>Total</th>
<th>MP</th>
<th>IP</th>
<th>LP</th>
<th>SP</th>
<th>Total</th>
<th>AP</th>
<th>IP</th>
<th>PP</th>
<th>SP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(α)</td>
<td>13</td>
<td>113</td>
<td>24</td>
<td>9</td>
<td>159</td>
<td>74</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>97</td>
<td>5</td>
<td>4</td>
<td>56</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>(β)</td>
<td>18</td>
<td>154</td>
<td>19</td>
<td>18</td>
<td>209</td>
<td>81</td>
<td>24</td>
<td>19</td>
<td>15</td>
<td>139</td>
<td>7</td>
<td>22</td>
<td>124</td>
<td>22</td>
<td>175</td>
</tr>
</tbody>
</table>

See footnote of table 1.

*a versus β: P < 0.05.
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a. high wall tension
b. low lateral pressure
c. disturbed flow
d. stasis
e. low shear
f. present results

FIGURE 2

Schematic illustrations of predilection sites of atherosclerosis by various theories or results of observation. (a) Willis,10 (b) Texon,11 (c) Murphy et al.,16 (d) Fox and Hugh,15 (e) Caro et al.,19 (f) present results in the circle of Willis (see fig. 1). L shows sites of relatively lower lateral pressure.

Murphy et al.16 and Mustard et al.17 noted that disturbed flow accelerates thrombi formation, and that organization of these elements into the vessel wall leads to the endothelial thickening. They also stated that the distribution of thrombi in extracorporeal shunt systems is similar to the loci of incipient atherosclerosis. Platelets also are capable of increasing vessel permeability.

However, several critical problems remain to be solved in the thrombogenic theory, e.g., lack of transitional form from mural thrombi to atherosclerotic plaque.

Rodbard18 concluded on the basis of his studies that reduced hydrodynamic drag facilitated subendothelial proliferation. Caro et al.19 regarded shear stress (= hydrodynamic drag) as a controlling and inhibiting (or retarding) effect rather than a causative one on the basis of their hypothesis, "shear dependent mass transfer mechanism." Other investigators have considered that increased shear may cause vessel injury and atherosclerosis.20,21

The above-mentioned hypotheses and/or results of observations have been applied to the circle of Willis (fig. 2). The terminal portion of the internal carotid artery (A-A') is a segment of a curve. The inner curvature is a predilection site of atheroma,10,11,15,16,19 which is coincident with our results. The origin of the anterior cerebral artery (B-B') is a branch point of nearly right angle. The severest lesion is primarily located at the medial portion, which coincides with the suggestions of Texon,11 Fox and Hugh,15 and Caro et al.19 The origin of the posterior cerebral artery (C-C') could be viewed as a point of wide "Y" branching. The predilection site predicted by the hypotheses of Murphy et al.16 and Fox and Hugh15 is the posterior portion, and is in agreement with the present data. However, Texon's hypothesis would place the predilection site in the anterior portion.

It is not possible to conclude from the present study which hypothesis is correct. Even though the operating hydraulic mechanisms would remain unknown, our analysis obviously demonstrated the relationship between the predilection sites of atherosclerotic lesions and the shape of the cerebral arterial tree.

Summary

The localization of atheroma along the circumference at three selected points of cerebral arteries was
examined. The severest atherosclerotic lesions were primarily located at the inner curvature at the terminal portion of the internal carotid artery, the medial portion at the origin of the anterior cerebral artery, and the posterior portion at the origin of the posterior cerebral artery.

Hemodynamic factors affecting this localization were discussed.

References
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