Cervico-Cephalic Arterial Thrombi and Thromboemboli in Moyamoya Disease — Possible Correlation With Progressive Intimal Thickening in the Intracranial Major Arteries

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SUMMARY Ninety-two thrombi and/or thromboemboli of cervico-cephalic arteries were confirmed histopathologically in 16 out of 22 patients with moyamoya disease. Included were 74 white thrombi mainly composed of fibrin and platelets, 9 organized thrombi and 9 mixed thrombi containing red blood cells. Thirteen microthrombi and one organized thrombus were located in the cervical arteries. Seventy-eight thrombi were present in the intracranial major arteries. Sixty-five were white microthrombi attached to the luminal surface of the arteries. The intracranial microthrombi were most frequently observed at the distal ends of the internal carotid arteries (29 thrombi). The fibrous thickening of the intima and edema in the innermost luminal surface were the most common vascular alterations associated with the thrombus formation. In two patients, thrombus formation was associated with fissure of the thickened intima and a dissecting aneurysm. We concluded that in patients with moyamoya disease the thrombi may be closely related to the development of intimal thickening in the intracranial arteries, particularly at the distal ends of the internal carotid arteries.

MOYAMOYA DISEASE is characterized by angiographic findings of bilateral stenoses or occlusion of the distal ends of the internal carotid arteries and an unusual vascular network at the base of the brain.1, 2 The typical abnormalities include fibrous or fibro-cel-

ular intimal thickening at the internal carotid bifurca-
tion.3-5 We report the histopathology of the thrombi frequently detected in the cervical and intracranial-
extracerebral arteries in patients with moyamoya disease. The pathogenesis and development of the intimal thickening of the intracranial arteries are also dis-
cussed.

Materials and Methods
Anatomical studies were done on 22 patients clini-
cally diagnosed as moyamoya disease and autopsied during the years 1970 to 1979. The age and sex of these patients are given in table 1. The postmortem protocol and clinical records on each patient were available. Histologic sections of the brain, blood vessels in the arachnoid space and cervical arteries including the in-
ternal carotid (ICA’s), external carotid (ECA’s) and common carotid arteries (CCA’s) and common carotid arteries (CCA’s) were routinely stained with hematoxylin and eosin (H&E), elastica van Gieson (EVG) and Mallory’s phosphotungstic acid hematoxylin (PTAH).

Results
In 16 out of 22 patients, 92 thrombi were located in the intracranial major arteries and cervical arteries.

The type of the thrombi and the sites are given in tables 1 and 2. Seventy-eight thrombi were located intracranially and 62 were in the anterior part of the circle of Willis. Twenty-nine thrombi in 10 patients were located at the distal ends of the ICA’s and posterior communica-
ting arteries (PCoA’s), and 23 in 6 patients were at the proximal segments of the middle cerebral arteries (MCA’s). Ten thrombi in 5 patients were observed at the anterior cerebral arteries (ACA’s). These thrombi were classified into three types; white thrombi (mainly composed of fibrin and platelets), organizing or organ-
ized thrombi (covered with new endothelial cells or containing recanalized small capillaries) and mixed thrombi (composed of red blood cells, fibrin and platelets). The white thrombi were most frequent among these three types (80%), and sixty-eight thrombi in 16 patients were micro- or small-sized thrombi attached to the luminal surface of the major arteries. Thirteen thrombi in 9 patients were relatively large and caused luminal stenoses or obstruction of the major arteries. Seven were of mixed type, three were organized and three were fresh white thrombi.

I. Thrombi in Intracranial Major Arteries
A. White Thrombi and Organized Thrombi
Sixty-one white thrombi and eight organized thrombi in 16 patients were verified histologically in the intracranial major arteries. These thrombi were most frequently located at the distal segments of the ICA’s and the PCoA’s. Five thrombi caused luminal stenoses or occlusion of the intracranial major arteries. A thrombus found at the right ACA in a 32-year-old man was attached to the thickened intima and was covered with endothelial cells (fig. 1). A thrombus located at the proximal segments of the right MCA of a 48-year-old man was attributed to a dissecting aneu-
rysrm of the MCA.6 Three thrombi caused luminal occlusion, despite a small size, as there was a marked stenosis of the arterial lumen due to fibrous intimal thickening (fig. 2a, b, c). All white thrombi, except

Received April 13, 1983; revision 1 accepted August 4, 1983.
these five, were microthrombi ranging from 10 μm to 50 μm thick and were frequently observed near the arterial bifurcations. The distinct localization of the thrombi was readily evident by means of longitudinal, serial or semi-serial sections of the arterial bifurcations, in each case. In an 8-year-old girl, the longitudinal sections revealed white microthrombi at the distal end of the ICA and at the proximal segment of the MCA (fig. 3). At the distal end of the right ICA in a 45-year-old man, white thrombi were attached to the thickened intima and extended to the proximal segment of the PCoA.

The most frequent intimal alterations associated with the thrombi, suggestive of a possible cause of the thrombosis, were fibrous intimal thickening and edema in the innermost luminal surface. In the left posterior cerebral artery (PCA) of a 48-year-old man, thrombus formation was noted in association with dissection of the thickened intima. A mural microthrombus was also noted on the luminal surface. In the left ICA (C-1 portion) of a 54-year-old woman, a microthrombus was observed within a small slit-like space in the markedly thickened intima (fig. 4). In the right ICA (C-2 portion) of an 18-year-old woman, a white microthrombus was attached to the intima presenting slight fibrous thickening (fig. 5).

Microthrombi, with or without organization, were also frequently seen in the MCA’s (23 thrombi). These thrombi were mainly located near the bifurcation of the ICA’s and at the proximal segments of the MCA’s (M-

**TABLE 1** List of Thrombi in 22 Patients with Moyamoya Disease

<table>
<thead>
<tr>
<th>No</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Type of thrombi</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>7</td>
<td>F</td>
<td>white</td>
<td>rt. ICA (C-3), lenticulostriate A</td>
</tr>
<tr>
<td>2.</td>
<td>8</td>
<td>F</td>
<td>white</td>
<td>ICA (C-1), MCA (M-1)</td>
</tr>
<tr>
<td>3.</td>
<td>16</td>
<td>F</td>
<td>mixed</td>
<td>rt. MCA (M-1)</td>
</tr>
<tr>
<td>4.</td>
<td>17</td>
<td>M</td>
<td>white</td>
<td>rt. PCoA</td>
</tr>
<tr>
<td>5.</td>
<td>18</td>
<td>F</td>
<td>white</td>
<td>rt. ICA (C-1, C-2), lt. ICA (C-1), rt. &amp; lt. PCoA’s, lt. PCA, BA</td>
</tr>
<tr>
<td>6.</td>
<td>27</td>
<td>F</td>
<td>white</td>
<td>lt. ICA (C-1)</td>
</tr>
<tr>
<td>7.</td>
<td>30</td>
<td>F</td>
<td>white</td>
<td>rt. PCA, rt. &amp; lt. PCoA’s, BA, lt. VA, lt. AICA</td>
</tr>
<tr>
<td>8.</td>
<td>32</td>
<td>M</td>
<td>mixed</td>
<td>rt. ACA (A-1)</td>
</tr>
<tr>
<td>9.</td>
<td>38</td>
<td>F</td>
<td>white</td>
<td>rt. ICA (C-2), lt. ICA (C-1), rt. ACA, rt. &amp; lt. VA’s, BA, rt. cervical ICA, rt. ECA</td>
</tr>
<tr>
<td>10.</td>
<td>41</td>
<td>M</td>
<td>white</td>
<td>lt. MCA (M-1), lt. PCoA</td>
</tr>
<tr>
<td>11.</td>
<td>41</td>
<td>F</td>
<td>mixed</td>
<td>lt. MCA (M-1)</td>
</tr>
<tr>
<td>12.</td>
<td>42</td>
<td>F</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>43</td>
<td>F</td>
<td>white</td>
<td>CCA, BA</td>
</tr>
<tr>
<td>14.</td>
<td>45</td>
<td>M</td>
<td>white</td>
<td>rt. &amp; lt. ICA’s (C-1, C-2), lt. PCoA, lt. PCA, rt. &amp; lt. MCA’s (M-1, M-2), rt. &amp; lt. ACA’s (A-1, A-2), ACA’s (M-1, M-2)</td>
</tr>
<tr>
<td>15.</td>
<td>46</td>
<td>F</td>
<td>white</td>
<td>lt. MCA (M-1), VA, CCA, ECA</td>
</tr>
<tr>
<td>16.</td>
<td>46</td>
<td>M</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>48</td>
<td>M</td>
<td>white</td>
<td>rt. MCA (M-1, M-2), lt. PCA</td>
</tr>
<tr>
<td>18.</td>
<td>48</td>
<td>M</td>
<td>white</td>
<td>rt. ACA (A-1), rt. ICA (C-1, C-2)</td>
</tr>
<tr>
<td>19.</td>
<td>52</td>
<td>F</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>54</td>
<td>F</td>
<td>white</td>
<td>lt. ICA (C-1), lt. MCA (M-2), Cervical ICA, CCA, ECA</td>
</tr>
<tr>
<td>21.</td>
<td>63</td>
<td>M</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>64</td>
<td>F</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

CCA = common carotid artery; ECA = external carotid artery; ICA = internal carotid artery; ACA = anterior cerebral artery; ACoA = anterior communicating artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; BA = basilar artery; VA = vertebral artery; SCA = superior cerebellar artery; AICA = anterior inferior cerebellar artery.

**TABLE 2** Type of Thrombi and Sites

<table>
<thead>
<tr>
<th>White</th>
<th>Organized</th>
<th>Mixed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA, ACoA</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>MCA</td>
<td>13</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>ICA, PCoA</td>
<td>29</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VA, BA</td>
<td>8</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>PCA, BA</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Cervical ICA, ECA, CCA | 13 | 1 | 0 | 14 |

Total | 74 | 9 | 9 | 92 |

**FIGURE 1.** Organizing thrombus attached to the thickened intima in the right ACA (A-1) of a 32-year-old man. The thrombus is covered with endothelial cells. H&E Χ117. Inset: Lower magnification of the ACA (A-1). PTAH Χ53.
FIGURE 2a. Longitudinal section of the distal end of the right ICA in an 18-year-old woman. White thrombus, 150 × 100 μm in size, located at the proximal segment of the ACA. H&E × 30. Inset: Mural microthrombus (or fibrin deposits) at the distal end of the ICA of the same patient (arrow). H&E × 28.


2c: Longitudinal section of the posterior part of the circle of Willis in a 45-year-old man. Left PCoA is obliterated by a fresh thrombus (arrow). There is focal intimal pod-like thickening at the bifurcations. PTAH × 10. Inset: White thrombus at the left PCoA. PTAH × 51.

FIGURE 3. Longitudinal section of the distal end of the ICA (C-I) in an 8-year-old girl. Fibrous thickening of the intima causes luminal stenosis. H&E × 17. Insets: left; microthrombus attached to the intima of the left ACA. H&E × 124. right; microthrombus at the apex of the ICA. H&E × 124. Arrows indicate the site of the thrombi.

1 portion). In a 46-year-old woman, a white thrombus (or focal fibrin deposits) was observed in the MCA (M-1) (fig. 6). Two organized thrombi were found in dilated lenticulostrate arteries of a 7-year-old girl.

B. Mixed Thrombi in the Intracranial Major Arteries

Nine mixed thrombi were found among 78 thrombi in the intracranial major arteries. These mixed thrombi were mainly located at the distal segments of the ACA’s, MCA’s and PCA’s and were always associated with proximal luminal stenosis or occlusion. A mixed thrombus found in the right MCA of a 16-year-old girl had obliterated the artery with concentric thickening of the intima. In the same patient, a dissecting aneurysm was verified histologically at the proximal segment (A-1) of the left ACA. A typical mixed thrombus was observed in the left ICA and PCoA of an 18-year-old woman. The head of the thrombus consist-
II. Thrombi in the Cervical Arteries

Thirteen microthrombi and one occlusive thrombus were confirmed histologically in the cervical arteries. A thrombus at the origin of the ICA of a 46-year-old woman occluded the artery and was organized by fibrous tissue containing many capillaries (fig. 8a). Twelve thrombi were microthrombi attached to the inner surface of the arteries, and one thrombus was within a slit-like space in the thickened intima of the ECA of a 54-year-old woman (fig. 8b). Two thrombi were found in the right CCA of a 46-year-old woman. One thrombus was attached to the luminal surface of the dense collagenous intima, and the other was associated with fissure of the atheroma and intramural hemorrhage (fig. 8c).

III. Thrombi in the Intracerebral Arteries

While occlusive thrombi were frequently found around the disrupted arteries and small perforating arteries in intracerebral hematoma and surrounding brain parenchyma in fifteen patients, thrombus formation was relatively rare in the brain parenchyma far from the hemorrhagic foci and in the contralateral cerebral parenchyma. Only three thrombi in 2 patients out of 22 were confirmed histologically, all were organized thrombi.5

Discussion

The essential lesions in moyamoya disease are stenoses or occlusion of bilateral distal ends of the ICA's due to fibrous or fibro-cellular thickening of the intima.1-5 Intimal thickening has been attributed to unusual proliferation of "Intimal pads" seen in individuals without vascular disease. These intimal pads are thought to be the histological basis for the development of cerebral atherosclerosis.5 The thrombogenic theory of atherosclerosis was originally suggested by Rokitansky.8 One hundred years later, Duguid suggested that atheroma might result from the organization of fibrin and platelets and the body and tail were composed of red blood cells and fibrin nets. A similar typical thrombus was found in the ACA and anterior communicating artery (ACoA) of a 45-year-old man (fig. 7).
mural thrombi. 8-11 Since the 1950's, a large number of investigators reported that experimental embolization of whole blood clots, fibrin clots and platelet-rich clots could induce atheroma-like lesions in pulmonary and systemic arteries. 12-19 It is generally agreed that the most essential factor in the pathogenesis of atherosclerosis is endothelial damage followed by the response of the intima to injury. 20-23 "Response to injury" hypothesis by Ross et al. 23 is one of the important theories in the atherogenesis. They suggested that platelets adhering to the denuded intimal surface could induce migration of the smooth muscle cells from the media into the intima and proliferation of the smooth muscle cells in response to the effect of platelet-derived growth factor. 23 24

Increased accumulation of plasma proteins in the intima following endothelial injury also has been considered a possible cause of atherosclerosis. 20 We consider that plasma components, particularly fibrinogen and fibrin, are important in the pathogenesis of atherosclerosis. 25 26 We reported that the intimal pads of the intracranial arteries contained fibrin-fibrinogen, even in fetuses and neonates, and the amount of imbibed fibrin-fibrinogen increased in density and extent with aging, consistent with the progression of the intimal thickening. 25 We also found that fibrin-fibrinogen promoted the growth of cultured rabbit aortic smooth muscle cells, in vitro. 28 Thus, the pathogenesis of the intimal thickening in moyamoya disease may be closely related to that of atherosclerosis; both are considered to initiate at the intimal pads and both involve smooth muscle cells and the matrix. It has been confirmed experimentally and clinicopathologically that intimal thickening could be the result of the incorporation of a thrombus into the arterial wall. 9 10 12-19 21 22 Moreover, embolized fibrin clots could cause fibrous intimal thickening. 14 15 Platelet-rich thrombi could be converted into lipid-rich foam cell lesions. 15 16 and embolized clots also form atheroma-like intimal lesions, under hypercholesteremic conditions. 18

We found 92 thrombi in 16 patients. White thrombi were most frequent among these 92 thrombi. The alter-

ations of the intima associated with the thrombus formation were fibrous intimal thickening with superficial edema, fissure of the thickened intima, and dissection of the vascular wall including dissecting aneurysm. In comparison to the results of our investigation on cerebral thrombosis complicated with atherosclerotic vessels, 27 intimal hemorrhage was extremely rare in moyamoya disease except for dissec-
ing aneurysm, in turn, mural microthrombi were rather frequent in moyamoya disease. Since the thickened intima of the intracranial major arteries in moyamoya disease was usually a lipid-poor fibrous lesion without foam cell accumulation and atheromatous components, especially in young patients, it is suggested that fibrin thrombi would more closely relate to the intimal thickening in moyamoya disease than in cerebral atherosclerosis. In fact, the majority of the thrombi verified histologically were white thrombi mainly composed of fibrinous materials.

Hosoda reported that hemosiderin deposition was confirmed in the thickened intima of the MCA in one patient out of ten. He speculated that the hemosiderin deposition was a result of thrombosis and the thrombosis might be related to the progression of the intimal thickening of the intracranial major arteries. Mural microthrombosis or fibrin deposition, however, has not been mentioned.

That the structure of the arterial wall, particularly the internal elastic lamina, at the distal ends of the ICA's were usually well preserved in each patient indicates that the stenosis or occlusion of the ICA's has not resulted from a congenital defect of the arterial wall but from acquired thickening of the intima. We did not find any evidence of arteritis in either the intracranial or systemic arteries.

The existence of microthrombi in the cervical arteries indicates that the thrombi located at the distal ends of the ICA's and perforating arteries might be thromboemboli from the cervical arteries. It might be also possible that the thrombi, particularly occlusive thrombi, are thromboemboli from the pulmonary vessels, heart or aorta. However, in 11 patients out of 22, we could not detect any possible sources of emboli except the CCA's and cervical ICA's, despite the microscopic investigation of the heart, lungs and systemic arteries including the aorta, brachiocephalic trunk and subclavian arteries.

It was not ruled out whether these microthrombi in the cervical arteries were the result of the intimal injury due to cerebral angiography. However, the finding that the majority of the thrombi were fresh, despite various intervals after angiography, indicates that the significance of these cervical microthrombi should not be minimized in patients with moyamoya disease. Furthermore, the presence of fresh microthrombi in cervical and intracranial arteries indicates that the thrombus formation actually had continued up to death of the patients.

In pediatric patients, progressive vascular changes have been well documented angiographically. Progression of the basal vascular network are closely related to the progression of the stenoses at the distal ends of the ICA's. Progressive vascular changes in adult patients also have been reported by several authors. Murphy reported a 29-year-old woman presenting progressive stenoses of the bilateral ICA's and ACA's. He emphasized that such progressive vascular changes were not common even in the adult patients with moyamoya disease. Both mural microthrombi and occlusive thrombi (or thromboemboli) could be responsible for the angiographical progression of the arterial stenoses.

The thrombus formation in cervico-cephalic arteries might lead to fatal cerebral ischemia. Despite a high frequency of thrombus formation, only one patient studied presented progressive and finally cerebral infarction. The thrombus formation in the patient was distributed in the distal ends of both ICA's and cerebral major arteries (ACA's, ACoA's, MCA's and PCoA's), and was most prominent among 16 patients with thrombi. Because of a rich collateral blood flow in brain parenchyma through "moyamoya vessels," fatal ischemic accidents were rare, despite the stenoses of the cerebral major arteries and thrombus formation.

Whether the microthrombi were the cause of the intimal thickening or secondary result of the intimal lesions is unclear. We considered that the formation of microthrombi in cervico-cephalic arteries could be one possible factor in the progressive intimal thickening of the intracranial arteries in moyamoya disease.

Acknowledgments

We wish to thank the following pathologists and doctors who contributed data on the autopsies related to this investigation: Prof. T. Nakashima (Kumamoto), Prof. H. Nakamura (Yonago), Prof. S. Seno (Okayama), Prof. K. Nakata (Osaka), Prof. R. Maeda (Osaka), Prof. Y. Harashima (Kyoto), Prof. A. Oshima (Wakayama), Prof. N. Komai (Wakayama), Prof. M. Takahashi (Gifu), Prof. G. Ohba (Kanazawa), Dr. Y. Kodama (Kure), Dr. T. Kitaoka (Hiroshima), Dr. Y. Nishihara (Fukuoka), Dr. H. Uchida (Kobe), Dr. T. Matsuo (Sumoto), Drs. K. Kotoh and M. Sasaki (Osaka).

We thank M. Ohara for comments on the manuscript.

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Cervico-cephalic arterial thrombi and thromboemboli in moyamoya disease--possible correlation with progressive intimal thickening in the intracranial major arteries.

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Stroke. 1984;15:264-270
doi: 10.1161/01.STR.15.2.264

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