Hemorrhagic Infarct of the Brain Without a Reopening of the Occluded Arteries in Cardioembolic Stroke

Jun Ogata, MD, Chikao Yutani, MD, Masami Imakita, MD, Hatsue Ishibashi-Ueda, MD, Yoshisuke Saku, MD, Kazuo Minematsu, MD, Tohru Sawada, MD, and Takenori Yamaguchi, MD

We examined the brains of 14 patients (four men and 10 women, mean age 68.9 years) who died from brain herniation after cardioembolic stroke with persistent occlusion of the internal carotid-middle cerebral arterial axis. Our examination showed hemorrhagic infarct in seven patients and pale infarct in the other seven, contradicting the commonly proposed pathophysiologic mechanism for the development of hemorrhagic infarct that the opening of previously occluded vessels makes an infarct hemorrhagic. Analysis of blood pressure after stroke revealed one or more surges of arterial hypertension or rapid rise of blood pressure in patients with hemorrhagic infarct without a reopening of the occluded artery. Such arterial hypertension was not always present in patients with pale infarct. Hemorrhage into an infarct with persisting occlusion of the proximal artery is assumed to occur when the involved blood vessels are exposed to the force of arterial blood pressure from the leptomeningeal collaterals. This occurs when arterial blood pressure rises after stroke in the presence of efficient leptomeningeal collaterals and before occlusion of these collaterals by a swollen cerebral hemisphere containing a large infarct. (Stroke 1989;20:876–883)

Fisher and Adams reported a high incidence of hemorrhagic infarct (HI) in their autopsy study of cerebral embolism. They usually found an embolus occluding the proximal artery in patients with pale infarct. In patients with HI, there was no embolus occluding the proximal artery, but fragments of the embolus in distal arterial branches were found. From these observations, Fisher and Adams proposed that the area of infarct becomes hemorrhagic when an embolus fragments and migrates distally, thereby opening the previously occluded vessel and exposing necrotic brain to the full force of arterial blood pressure. This concept has been further validated by autopsy and angiographic studies.

While pathologic examination of brains with HI in our hospital showed a reopening of the occluded artery in most cases, there were some cases in which HI occurred and the artery remained occluded. This observation seems to be compatible with that made by Jorgensen and Torvik, who found the entire area of HI lying distal to the embolus in seven cases. They suggested that some blood could have passed beyond the plug during its migration or pulsation and that blood flow could also have been established via collaterals. Mohr and Barnett also found in a few cases that HI occurred distal to the site of the persisting occlusion in the arterial bed exposed at best only to retrograde collaterals. Yamaguchi et al observed a few cases of massive HI in which complete embolic occlusion was confirmed at autopsy. The importance of retrograde collaterals as unobstructed arterial channels thus has not been emphasized as has been the importance of the reopening of the occluded artery as the mechanism causing HI to develop. The role of reperfusion via leptomeningeal collaterals in hemorrhagic transformation has been validated only in experimental models. Therefore, we analyzed clinical and pathologic findings to assess the mechanism that allows hemorrhagic transformation of an infarct with persistent occlusion in cardioembolic stroke.

Subjects and Methods
We evaluated clinical and autopsy findings of 14 patients who died from brain herniation after car-
TABLE 1. Clinical Findings of Patients With Hemorrhagic or Pale Brain Infarct

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Underlying heart disease</th>
<th>Duration of stroke (days)</th>
<th>Cerebral artery examined by angiography</th>
<th>Interval between stroke and angiography</th>
<th>Occlusion of cerebral artery demonstrated by angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80/M</td>
<td>NVAF with PMI</td>
<td>4.9</td>
<td>R CAG, L CAG, R VAG</td>
<td>&lt;6 hours</td>
<td>R ICA-MCA</td>
</tr>
<tr>
<td>2</td>
<td>62/F</td>
<td>RHD with MR, Af</td>
<td>2.1</td>
<td>R CAG, L CAG</td>
<td>&lt;6 hours</td>
<td>R ICA, L ACA</td>
</tr>
<tr>
<td>3</td>
<td>76/F</td>
<td>RHD with MR, Af</td>
<td>2.6</td>
<td>ND</td>
<td>&lt;6 hours</td>
<td>R ICA, L ACA</td>
</tr>
<tr>
<td>4</td>
<td>77/F</td>
<td>RHD with MSR, Ar, Af</td>
<td>1.1</td>
<td>ND</td>
<td>&lt;6 hours</td>
<td>R ICA, L ACA</td>
</tr>
<tr>
<td>5</td>
<td>72/F</td>
<td>MVP with PMI for A-V block</td>
<td>3.1</td>
<td>L CAG, L VAG</td>
<td>&lt;6 hours</td>
<td>L MCA, L ACA</td>
</tr>
<tr>
<td>6</td>
<td>52/F</td>
<td>RHD with MS</td>
<td>2.7</td>
<td>R CAG</td>
<td>&lt;6 hours</td>
<td>L MCA, L ACA</td>
</tr>
<tr>
<td>7</td>
<td>68/F</td>
<td>RHD with MSR, Af</td>
<td>5.3</td>
<td>L CAG, L VAG</td>
<td>&lt;8 hours</td>
<td>L MCA, L PCA</td>
</tr>
<tr>
<td>8</td>
<td>67/M</td>
<td>MVP</td>
<td>6.7</td>
<td>L CAG, R VAG</td>
<td>&lt;6 hours</td>
<td>L ICA</td>
</tr>
<tr>
<td>9</td>
<td>42/M</td>
<td>DCM</td>
<td>2.2</td>
<td>L CAG, R CAG, L VAG</td>
<td>&lt;6 hours</td>
<td>L ICA-MCA-ACA</td>
</tr>
<tr>
<td>10</td>
<td>78/F</td>
<td>RHD with MS, AS, Af</td>
<td>4.5</td>
<td>ND</td>
<td>30 hours</td>
<td>R ICA</td>
</tr>
<tr>
<td>11</td>
<td>67/F</td>
<td>SSS with PMI</td>
<td>2.3</td>
<td>R CAG, R VAG</td>
<td>&lt;6 hours</td>
<td>L ICA-MCA-ACA</td>
</tr>
<tr>
<td>12</td>
<td>75/F</td>
<td>RHD with MS, Af</td>
<td>5.2</td>
<td>L CAG, R CAG, L VAG</td>
<td>&lt;6 hours</td>
<td>L ICA-MCA-ACA</td>
</tr>
<tr>
<td>13</td>
<td>91/F</td>
<td>OMI, AMI with Af</td>
<td>5.1</td>
<td>ND</td>
<td>36 hours</td>
<td>L MCA</td>
</tr>
<tr>
<td>14</td>
<td>57/M</td>
<td>DCM with Af</td>
<td>10.8</td>
<td>L CAG, L VAG</td>
<td>36 hours</td>
<td>L MCA</td>
</tr>
</tbody>
</table>

M, male; NVAF, nonvalvular atrial fibrillation; PMI, pacemaker implantation; R, right; CAG, carotid angiography; L, left; VAG, vertebral angiography; ICA, internal carotid artery; MCA, middle cerebral artery; F, female; RHD, rheumatic heart disease; MR, mitral regurgitation; Af, atrial fibrillation; ACA, anterior cerebral artery; ND, not done; MSR, mitral stenosis and regurgitation; AR, aortic regurgitation; MVP, mitral valve prolapse; MS, mitral stenosis; DCM, dilated type of idiopathic cardiomyopathy; SSS, sick sinus syndrome; ECA, external carotid artery; OMI, old myocardial infarction; AMI, acute myocardial infarction.

diogenic thromboembolism with persistent occlusion of the internal carotid-middle cerebral arterial (ICA–MCA) axis. These patients included four men and 10 women, aged 42–91 years, with a mean age of 68.9 years. Patients were admitted a few hours after stroke and died within 2 weeks in the Stroke Care Unit of the National Cardiovascular Center from 1977 to 1988. We did not include in our study patients with the following clinical and pathologic findings: 1) cardiogenic thromboembolism showing a reopening of the occluded artery or migration of the embolus, 2) cerebral embolism whose embolic sources were the vegetations of nonbacterial thrombotic endocarditis or bacterial endocarditis, 3) treatment with anticoagulants or thrombolytic agents after stroke, 4) previous major strokes in the carotid system, 5) simultaneous development of significant embolism to the vertebral or basilar artery, and 6) macerated brain due to prolonged period of brain death. Treatment consisted of intravenous fluid replacement with dehydrating agents such as mannitol or glycerol. All patients were examined with computed tomography of the brain, and in 10 of 14, angiography of the brain was performed after stroke.

The neurologic status, vital signs, and blood pressure (BP) were examined and recorded every 2 hours. BP was measured with a standard mercury sphygmomanometer and an appropriately sized arm cuff. Because BP was analyzed in our study to assess the dynamic process of intracranial blood flow, BP values during the period of brain death, when intracranial blood flow can be absent or significantly reduced, were not used.

FIGURE 1. Diagrammatic representation of location of emboli in cerebral arteries in seven cases with hemorrhagic brain infarct.
At autopsy, the brains were removed and fixed in 10% formalin for 2–3 weeks. After fixation, arteries at the base of the brain were separated from the brain and histologically examined at approximately 3-mm intervals. The extracranial carotid and vertebral arteries were examined at approximately 5-mm intervals. The cerebrum was horizontally sectioned every 1 cm. Representative sections were taken from the brain for embedding and histologic examination with hematoxylin and eosin and other methods as needed. Special attention was paid to the source of the embolus to the brain in examining the heart, ascending aorta, and carotid and vertebral arteries.

Both hemorrhagic and pale infarcts of the brain were determined by gross examination as defined by Adams and Vander Eecken.2 The HI consists of an ordinary softening of tissue, the major portion of which is speckled by congested blood vessels and innumerable small hemorrhages. With pale infarct, the tissue is soft and swollen, with poorly demarcated anatomic structures. There are no hemorrhages, except occasionally at the margins of the infarct.

**Results**

Table 1 shows the clinical findings of the 14 patients with hemorrhagic or pale infarct of the brain. All 14 cases showed embolic occlusion of the cerebral artery proximal to the infarct.

Eleven patients showed a sudden onset of stroke while awake with a maximal deficit at the very beginning of the event. Three patients (Cases 5, 7, and 13) suffered neurologic deficits while in bed, 12 patients developed stroke at home, and two patients (Cases 2 and 14) developed stroke during hospital admission. In each patient, prothrombin time, active partial thromboplastin time, and platelet counts were normal. None of the patients showed severe anemia, suggesting that a bleeding disorder was not a factor.

**FIGURE 2.** Diagrammatic representation of location of emboli in cerebral arteries in seven cases with pale brain infarct.

**FIGURE 3.** Origin of right middle cerebral artery of Case 2 with hemorrhagic brain infarct. Lumen is occluded with fibrin platelet embolus. Bar=0.5 mm.
FIGURE 4. Diagrammatic representation of location of hemorrhagic and pale brain infarcts in 14 cases. Hemorrhagic infarct of occipital lobe associated with descending tentorial herniation in absence of embolic occlusion of posterior cerebral artery is not shown. Infarct of right cerebral hemisphere in Case 11 is shown on left side of diagram and noted with *.

FIGURE 5. Transverse section through basal ganglia of Case 3. Hemorrhagic infarct of territory supplied by right middle cerebral artery (MCA) due to occlusion of ipsilateral internal carotid artery and MCA can be seen. Petechiae are confined to cortical ribbon. Bar=2 cm.
The duration between the onset of stroke and cardiac arrest (or brain death if a period of brain death was present) was 3.1±1.4 days (mean±SD) (range 1.1–5.3 days) in patients with HI and 5.2±2.9 days (range 2.2–10.8 days) in patients with pale infarct.

Table 1 shows the time interval between onset of neurologic symptoms and angiography. The angiographic findings were proper for the site of the arterial occlusion, which was confirmed at autopsy. The internal carotid artery (ICA) was occluded at the carotid bifurcation in Cases 2, 11, and 12; a few centimeters above the carotid bifurcation in Case 9; and at its most distal portion in Cases 1 and 8. The middle cerebral artery (MCA) was occluded at its division of the cortical branches in four other patients. Separated from the ICA-MCA axis occlusion, the distal cortical branch of the anterior cerebral artery (ACA) was occluded in three and the posterior cerebral artery (PCA) in one patient. Branches of the left external carotid artery were occluded in one patient. Cross-filling of the left ACA as demonstrated by right carotid angiography was delayed in Cases 8 and 12, while cross-filling of the right ACA as demonstrated by left carotid angiography was sufficient in Case 1. There was some retrograde collateral filling to the leptomeningeal branches of the occluded MCA as demonstrated by carotid or vertebral angiography in Cases 5, 7, and 14. Leptomeningeal collaterals to the area of infarct were poor in the other patients. Capillary blush or early venous filling was not found in any of the patients.

Five of 14 patients had cerebral ischemic events before the last stroke. Three patients experienced a single episode of hemiparesis with minimal residuals 2 months (Case 1), 2 years (Case 2), and 19 years (Case 8) before death. Occlusion of the proximal portion of the left ACA was found in angiography in Case 2. Case 10 experienced a transient ischemic attack 7 years before death, at which time angiography showed transient occlusion of the right MCA. Case 11 developed right-sided quadrantanopsia 15 months and right hemiparesis 13 months before death, with some residuals.

Of the 14 patients, seven had rheumatic heart disease with valvular deformities. Of those seven, all except one showed atrial fibrillation. Two patients had a dilated type of idiopathic cardiomyopathy, and one of them showed atrial fibrillation. Two patients had mitral valve prolapse. A permanent pacemaker had been implanted in three patients. One patient showed old and acute myocardial infarction with atrial fibrillation and mitral ring calcification. Six patients (Cases 2, 3, 4, 6, 13, and 14) had congestive heart failure before stroke. There was mural thrombus in the atrium of the left atrium in four (Cases 4, 5, 12, and 13) and in the left ventricle in two (Cases 8 and 10).

Atherosclerotic changes of the arteries at the base of the brain were severe in one patient (Case 5), moderate in eight patients (Cases 1, 2, 3, 4, 7, 8, 12, and 13), and slight in five patients (Cases 6, 9, 10, 11, and 14). The atherosclerotic changes of the cerebral artery caused no occlusion or significant stenosis of the lumen that could have influenced the development of the infarct. The ascending aorta, aortic arch, and extracranial carotid and vertebral arteries contained no occlusive lesion or atherosclerotic plaques that would give rise to emboli.

The ICA-MCA axis was occluded with thromboembolic material in all cases (Figures 1 and 2). The arteries proximal to the infarct were macroscopically stuffed with emboli colored gray or brown. These emboli were microscopically composed of fibrin with some white blood cells and variable numbers of entrapped red blood cells (Figure 3). The arteries lodged with emboli showed no endothelial lesions, such as rupture of atheroma, that would produce local thrombus. Occasionally, early cellular reactions were found at the proximal or distal margin of the emboli. These emboli were associated with various lengths of retrograde and antegrade red thrombi.

Figures 1 and 2 show the site of occlusion with thromboembolic material in 14 cases. Besides the occlusion of the ICA-MCA axis, there was occlusion of the ipsilateral PCA, which branched off directly from the ICA in Cases 7 and 10. In Case 2, the proximal portion of the ACA contralateral to the last
embolic event was hypoplastic. Four cases exhibited embolus occluding the distal cortical branch of the ACA, 1-2.5 cm distal to the anterior communicating artery. Branches of the left external carotid artery were occluded with emboli in Case 12.

The pathologic and angiographic findings of the cerebral arteries showed a difference in the efficiency of collateral circulation to the area of infarct between cases with HI and pale infarct. Six of seven cases with pale infarct showed embolic occlusion of the distal ICA to MCA, obstructing the proximal portion of the ipsilateral ACA. In such cases, leptomeningeal collaterals from the ACA to the area of infarct must receive blood flow from the contralateral ICA crossing the anterior communicating artery. Also, of six cases with pale infarct caused by embolic occlusion of the distal ICA to MCA, one exhibited occlusion of the distal cortical branch of the ipsilateral ACA, and the other was associated with occlusion of the ipsilateral PCA. By contrast, five of seven cases with HI showed embolic occlusion at various sites of the MCA, providing efficient leptomeningeal collaterals to the area of infarct from the proximal portion of the ACA through the ipsilateral ICA.

All the cerebral hemispheres containing large infarcts were swollen with descending tentorial or subfalcial herniation. Most of them showed tonsillar herniation and secondary brainstem hemorrhage.

Seven brains contained HI in the area distal to the arterial occlusion (Figures 4, 5, and 6). Case 2 showed HI of the area supplied by the right MCA and pale infarcts of the area supplied by the right ACA and the small medial portion of the area supplied by the left ACA. Although the basal ganglia were involved in the infarct in Cases 1, 2, and 3, the basal ganglia were hemorrhagic in Cases 1 and 2 and pale in Case 3. Case 7 showed a frank hematoma measuring $4.5 \times 2.3 \times 2.3$ cm within the HI lateral to the basal ganglia.

There were innumerable discrete petechiae or confluent purpura confined principally to the cortical gray matter of the area of infarct, whereas the white matter involved in the infarct remained pale. The discrete petechiae appeared in the cortical gray matter, commonly more marked within the perisul-
Cal cortex than at the crowns of the gyri. In general, they were evenly distributed in the infarct, and there was no tendency to appear predominantly at the margin of the infarct (Figures 5 and 6). Microscopically, cortical gray matter showed small hemorrhages around small vessels and capillaries whose lumina were distended and overflowed with red blood cells. Many hemorrhages were observed to be confluent, thus making larger hemorrhages. These hemorrhages were observed only in the area of the infarct consisting of ischemic change of the neurons and glial reactions. Fragments of the embolus in the distal branches were not encountered in the ordinary histologic sections.

Seven brains contained pale infarct in the area of arterial occlusion (Figures 4 and 7).

Case 6 with HI of the area supplied by the MCA and ACA and three others (Cases 11, 13, and 14) with pale infarct of the area supplied by the MCA showed HI of the mesial and inferior sides of the ipsilateral occipital lobe. This HI was associated with descending tentorial herniation of the uncus and hippocampus in the absence of embolic occlusion of the PCA (Figure 7).

Six patients (Cases 3, 4, 5, 7, 12, and 13) had a history of hypertension. The mean of the mean blood pressure (MBP) obtained every 4 hours during each 12-hour period after stroke was plotted in Figure 8. In patients with HI, there was a rise of MBP after stroke except for Cases 3 and 7, who showed temporary fall of MBP in the first 24 and 36 hours after stroke. Case 1 showed several surges of hypertension.

Two patients with a dilated type of idiopathic cardiomyopathy (Cases 9 and 14) showed some rise in MBP after stroke, but overall BP values were in the normotensive or hypotensive range. Cases 10 and 11 with pale infarct showed progressive fall of MBP after stroke. Three patients (Cases 8, 12, and 13) who lacked collateral pathway from the proximal portion of the ACA through the ipsilateral ICA to the area of infarct showed a rise of MBP after temporary fall of MBP.

Discussion

For hemorrhagic transformation of a pale infarct to occur, there must first be ischemic insult of sufficient degree to induce disruption of the vascular wall followed by restoration of circulation to the injured vascular bed. Hemorrhagic infarct of the brain usually appears in patients with reopening of the artery occluded by thromboembolus.1-5 However, our study substantiated the existence of HI of the brain developing without a reopening of the occluded artery, implying other routes of reperfusion.3-6

In cases of HI without a reopening of the occluded arteries, the only possible route of reperfusion of the blood to the necrotic area is assumed to be the leptomeningeal arteries. Vander Eecken and Adams11 verified large and important arterial anastomoses on the surface of the brain between the three cerebral arteries. They observed four to eight anastomoses between the ACA and MCA, three to five anastomoses between the MCA and PCA, and up to two anastomoses between the ACA and PCA, with an average diameter of 311 μm. It is assumed that vessels in vasoparalysis within the necrotic brain tissue are exposed to the force of blood pressure via retrograde leptomeningeal collaterals.

The operation of this mechanism can be supported by the observation of blood pressure after stroke. Surges of BP into the hypertensive range or rapid rise of BP after stroke are likely to be associated with HI of the brain, with persisting occlusion of the proximal artery. To produce hemorrhagic transformation of an infarct, surges of arterial hypertension must occur before swelling of the brain becomes severe enough to cause herniation, which would obstruct all possible collaterals to the necrotic area. Cerebral lesions of patients showing surges of arterial hypertension after stroke would therefore
be pale when arterial hypertension occurred after the development of herniation. Because of distortion of the rostral brainstem in the case of massive cerebral infarct, BP usually rises because of increased sympathetic activity. The absence of BP rise in spite of increased sympathetic activity secondary to the intracranial events in some patients could be attributed to their decreased cardiac function.

Although chronic hypertension has no apparent relation to the development of HI or hematoma formation in patients with cardioembolic stroke in clinical or autopsy studies, there is a definite relation between blood pressure and HI using the method of analysis in our study.

The most feared complication of the early administration of anticoagulants to patients with embolic stroke is hemorrhagic transformation of an infarct or hematoma formation within the infarct. The cerebral embolism study group has reported that a large infarct is prone to become hemorrhagic spontaneously even without anticoagulants, and that excessive anticoagulation or acute hypertension contributed to hemorrhagic transformation in anticoagulated patients. These reports are compatible with our findings. Therefore, our observations strengthen the suggestions made by the Cerebral Embolism Study Group that special efforts to avoid excessive anticoagulation and to avoid hypertension are needed for patients with large embolic infarct.

In conclusion, HI, which requires efficient collateral pathways of blood flow and surges of arterial hypertension after stroke, was shown to develop even in the absence of the reopening of the artery occluded by cardiogenic thromboembolus. An experimental study is in progress to analyze the pathophysiologic mechanisms of hemorrhagic transformation of an infarct without a reopening of the occluded proximal artery (Y. Saku, J. Choki, R. Waki, J. Masuda, K. Tamaki, M. Fujishima, J. Ogata, unpublished observations).

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Key Words • cardiovascular diseases • cerebral hemorrhage • embolus
Hemorrhagic infarct of the brain without a reopening of the occluded arteries in cardioembolic stroke.

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Stroke. 1989;20:876-883
doi: 10.1161/01.STR.20.7.876

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