Hemorrhagic Transformation in Cerebral Embolism

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We studied the mechanism of hemorrhagic infarction after acute cerebral embolism in 160 patients by brain computed tomography and angiography. Hemorrhagic infarction during the month after the embolic event was evident in 65 patients (40.6%). Initial angiography a median of 1.5 (range 1–60) days after the event revealed occlusion of the cerebral arteries in 117 of 142 patients (82.4%), and reopening of the vessels was observed in 56 (94.9%) of 59 patients who had follow-up angiography a median of 20 (range 3–47) days after the event. The incidence of hemorrhagic infarction was higher in patients ≥70 years old (31 of 61, 50.8%) than in those aged 50–69 years (27 of 72, 37.5%) or <50 years (seven of 27, 25.9%) (≥70 vs. <50, p<0.05).

In patients with moderate or large infarcts, hemorrhagic infarction developed in 50.0% or 51.5%, respectively, while in those with small infarcts it developed in only 2.9% (p<0.05). No correlation was found between hemorrhagic infarction and history of hypertension or blood pressure during the acute stage of stroke. Thrombolytic and/or anticoagulant therapy did not affect the incidence of hemorrhagic infarction (40.0% with vs. 40.7% without therapy) but tended to cause massive hematoma. Our results indicate that hemorrhagic transformation in cerebral embolism is caused not only by reopening of the occluded vessels but also by other factors such as age and size of the infarct. Hypertension per se seems to be less important for hemorrhagic infarction. Anticoagulants and/or thrombolytic agents should be carefully administered in the elderly and in patients with large infarcts. (Stroke 1989;20:598–603)

The mechanism of bleeding into an ischemic lesion is still under dispute. Autopsy findings show that hemorrhagic transformation is more common in patients with embolic (51–71%) than in those with nonembolic (2–21%) stroke.1–3 Restoration of blood flow into an area of thromboembolic infarction is frequently followed by hemorrhage.1–3 The time from occlusion to reopening of the vessels must be considered since hemorrhagic transformation often occurs within 1–2 weeks after the stroke.5–10 Blood pressure during the acute stage also correlates with the incidence and severity of hemorrhagic infarction (HI).11–12

We examined repeated brain computed tomograms (CT scans) and cerebral angiograms in patients with acute cerebral embolism to clarify the relation between secondary hemorrhage and reopening of the occluded vessels and to identify the factors that may contribute to the development of hemorrhagic transformation.

Subjects and Methods

A total of 186 consecutive patients with acute cerebral embolism were admitted within 7 days after onset to the National Cardiovascular Center, Osaka, Japan, from August 1977 to December 1983. Cerebral embolism was diagnosed in those patients who had the abrupt onset of focal neurologic signs and symptoms with a probable source of emboli confirmed by echocardiography and/or electrocardiography (ECG) or evidence of single or multiple emboli to other organs. Patients with arrhythmia but no other evidence of heart disease and whose cerebral angiograms showed either occlusive changes suggestive of embolus or whose vessels supplying the area of infarction were patent and without localized arteriosclerotic narrowing were regarded as suffering embolic infarction. We excluded patients with severe arteriosclerosis in the carotid or cerebral arteries.

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Of the 186 patients, we excluded 16 because CT examination was not performed (in four) or was not repeated (in 12). We excluded another 10 patients because the infarcted area was not reliably detected by CT. The remaining 160 patients comprised 81 men and 79 women.

Brain CT examinations were performed on the first hospital day in all patients and were repeated at least every 10 hospital days during the first month and monthly thereafter. CT examination was performed using an EMI CT scanner (CT-1010, Middlesex, England) from August 1977 to July 1982 and a Toshiba TCT-20A (Tokyo, Japan) from July 1982 to December 1983. The size of the infarct was represented as the ratio of the maximum hypodense area to the entire ipsilateral hemisphere area on the same CT film (infarct index).7 Midline shift was defined as a shift of midline structures to the contralateral side on CT scans. HI was defined as an infarcted, hypodense area in or around which various degrees of hyperdensity appeared on unenhanced CT scans.

According to the pattern or degree of hyperdensity, HI was subdivided into four types: 1) petechial hemorrhage, with spotty and scattered hyperdense areas, usually along the cortical margin of the ischemic lesion, in which regional cerebral edema was mild and infrequent (Figure 1, top left); 2) diffuse hemorrhage, with irregular and inhomogeneous hyperdense areas in and around the ischemic lesion, usually accompanied by marked edema and frequent mass effect (Figure 1, top right); 3) small hematoma, with a homogeneous hyperdense area <3 cm in diameter in the ischemic area, in which mass effect was uncommon (Figure 1, bottom left); and 4) massive hematoma, with a large, homogeneous hyperdense area in the infarct ≥3 cm in diameter, accompanied by prominent mass effect (Figure 1, bottom right).

Soon after admission, conventional angiography of the neck and brain was performed in 142 (89%) of the patients; 71 patients (50.0%) were studied on the day of the stroke (Day 1), 21 (14.8%) on Day 2, 16 (11.3%) on Day 3, and the 34 others (23.9%) thereafter. A follow-up angiographic study was performed in 59 patients in whom the initial study revealed occlusion of the intracerebral vessels.

ECG was monitored in all patients to detect arrhythmia or signs of heart disease. A history of hypertension was sought from the patients and their physicians. Supine blood pressures were obtained on admission and at least four times daily during hospitalization. Twenty patients without HI on initial CT were given urokinase and/or heparin. Urokinase treatment was started on admission in 14 patients, and heparin was administered to nine patients within 1 week after onset and to one patient on Day 16.

Average infarct index, mean blood pressure, and average age in the HI and non-HI groups were compared using the $F$ test and Student's $t$ test. Source of emboli, sex, location of cerebral infarcts, and incidence of reopening of occluded vessels between HI and non-HI groups were compared using the $\chi^2$ test. The relation between antithrombotic therapy and development of HI was also assessed.

**Results**

Of the 160 patients, 65 (40.6%) demonstrated HI within 1 month after the ischemic insult; in 10 the first CT examination 1–4 days after the onset of stroke showed HI, while in 55 the initial CT examination 1–6 days after the stroke did not show HI but follow-up CT first showed HI 2–30 days after the stroke. In the patient that first showed HI at 30 days, the previous CT scan was done at 12 days. HI in 44 of 65 patients (67.7%) were observed within 10 days after the stroke, and no patient developed HI more than 1 month after the stroke. The rate of detection of HI on initial CT was not different for the two CT scanners. (CT 1010, 52 of 127, 40.9%, and TCT-20A, 13 of 33, 39.4%).

Sex ratios were almost the same in the groups, but the percentage of patients aged ≥70 years was somewhat greater in the HI than in the non-HI group (Table 1). The proportion of HI patients having a small infarct index (≤9%) was significantly smaller than that of non-HI patients, and the mean infarct index was greater (but not significantly so) for the HI than for the non-HI group. Midline shift was more common in the HI than in the non-HI group, although the incidence of a ≥2-cm midline shift was almost the same in the groups. The incidence of a history of hypertension, the mean blood pressure on admission and on Day 14, and the proportion of patients receiving antithrombotic drugs did not differ between groups.

Of the 65 patients with HI, 37 (56.9%) had petechial hemorrhages, 12 (18.5%) had diffuse hematomas, nine (13.8%) had small hematomas, and seven (10.8%) had massive hematomas. The incidence of HI increased with age and was significantly higher in those ≥70 (31 of 61, 50.8%) than in those ≤49 (seven of 27, 25.9%) years old ($p<0.05$, Figure 2); small or massive hematomas were more commonly observed in older patients. In patients who had an infarct index of ≥30%, the incidence of HI was significantly higher and hemorrhagic transformation with hematoma tended to be more frequent than in those with infarct indexes of ≤9%.

Although the incidence of HI was similar between those with (eight of 20, 40.0%) and those without (57 of 140, 40.7%) antithrombotic therapy, massive hematoma was more frequent in the former (four of eight, 50.0%) than in the latter (three of 57, 5.3%) ($p<0.05$).

Of the 160 patients with acute cerebral embolism, 138 (86.3%) had a cardiac source of emboli; valvular disease (53 of 138, 38.4%) and nonvalvular atrial fibrillation (45 of 138, 32.6%) were considered to be major causes. Infective endocarditis was also counted as a cardiac source of emboli after careful
FIGURE 1. Types of hemorrhagic infarction on computed tomograms. Top left: Petechial hemorrhage, spotty hyperdense areas localized on cortical surface, with mild cerebral edema. Top right: Diffuse hemorrhage, spotty or irregular hyperdense areas widely invading white matter, with mass effect. Bottom left: Small hematoma, homogeneous and localized hyperdense area of diameter ≤3 cm. Bottom right: Massive hematoma, large homogeneous hyperdense area of diameter ≥3 cm, with marked mass effect.

differentiation from the rupture of mycotic aneurysms or brain abscesses by angiography or enhanced CT. The incidence of HI by underlying disease for valvular disease was 20 of 53 (37.7%), for nonvalvular atrial fibrillation 24 of 45 (53.3%), for sick sinus syndrome three of 11 (27.3%), for
A total of 202 infarcted lesions were observed on CT scans in the 160 patients (Table 2), of which 146 (72.3%) were in the territory of the middle cerebral artery, 25 (11.3%) were in the territory of the anterior cerebral artery, and 21 (9.5%) were in the territory of the posterior cerebral artery. The incidence of hemorrhagic transformation ranged from 28.6% to 40.4%, and the regional difference was not significant.

The median interval from the ictus to the initial angiographic study in the 142 patients so examined was 1.5 days, with a range of 1-60 days (Table 3). Complete occlusion of the cerebral arteries was demonstrated in 117 patients (82.4%), while no vascular occlusion was evident in the other 25 patients (17.6%). The median interval from ictus to angiography was 1 (range 1-33) day in the former and 7 (range 1-60) days in the latter, which suggests that the occluded vessels of the 25 patients reopened before the initial angiographic study. Angiography was repeated a median of 20 (range 3-47) days after ictus in 59 patients, and 56 (94.9%) showed reopening of the vessels. Thus, when the 25 patients with no vascular occlusion on the initial angiogram were counted as cases of early reopening, 81 (25+56) of 84 (25+59) patients (96.4%) demonstrated reopening of the vessels. Among these 81, HI was found in 39 patients (48.1%). In contrast, HI occurred in one of the three patients with persistent occlusion on repeat angiography.

![Figure 2. Bar graph. Relation of incidence and type of hemorrhagic infarction (HI) in patients with cerebral embolism on computed tomogram (CT) to age, infarct index, and antithrombotic therapy. Number of patients in parentheses. *p<0.05.](http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/01.STR.5.6.601/-/DC1/fig2.jpg)
TABLE 3. Angiographic Findings and Incidence of Hemorrhagic Infarction in 142 Patients Suffering Acute Cerebral Embolism and Undergoing Angiography

<table>
<thead>
<tr>
<th>Angiographic findings</th>
<th>n</th>
<th>Median</th>
<th>Range</th>
<th>HI</th>
<th>no HI</th>
<th>% HI</th>
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<tr>
<td>No occlusion</td>
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<td>7</td>
<td>1-60</td>
<td>11</td>
<td>14</td>
<td>44</td>
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<tr>
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<td>1-33</td>
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<td>Repeat angiography</td>
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<td>20</td>
<td>3-47</td>
<td>28</td>
<td>28</td>
<td>50</td>
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<tr>
<td>Reopening</td>
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<td>20</td>
<td>3-44</td>
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<td>33</td>
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<tr>
<td>Persistent occlusion</td>
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<td>45</td>
<td>15-47</td>
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<tr>
<td>No repeat angiography</td>
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<td></td>
<td></td>
<td>22</td>
<td>36</td>
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</tbody>
</table>

HI, hemorrhagic infarction.

Discussion

Autopsy studies\(^1\)\(^-\)\(^3\) have demonstrated that hemorrhagic events occur in 51-71% of embolic strokes and thus are significantly more frequent than in nonembolic strokes (2-21% occurrence). We also have reported that HI by CT examination occurred in 45 of 115 patients with embolism (39%) and in two of 105 patients with thrombosis (2%).\(^3\) In contrast, recent sequential CT studies of cerebral embolism\(^9\),\(^10\),\(^13\) have revealed a lower incidence (2-26%) of hemorrhagic transformation than autopsy cases, probably due to differences in the severity of embolic stroke or insufficient CT examination for imaging small hemorrhages. A prospective study by Hornig et al\(^7\) has indicated that HI occurs more frequently (43%, in 28 of 65 cases) than previously thought in either acute embolic stroke or thrombotic events. In our study, consecutive patients with carefully defined cerebral embolism were examined with serial CT and angiography so that the overall prevalence of HI that we found (40.6%) more likely represents the natural course of acute embolic stroke than retrospective studies.\(^9\),\(^10\),\(^13\)

It is known that occluded vessels recanalize more commonly in embolic than in thrombotic stroke.\(^1\),\(^3\),\(^5\) Restoration of blood flow, which could cause diapedesis through ischemic endothelium or could disrupt the vessels in and around the infarcted area, is suggested to be a major cause of hemorrhagic infarction in some clinical and pathologic studies.\(^1\),\(^3\),\(^4\) In our study, however, 81 of 84 patients studied demonstrated opening of the vessels on initial angiography or reopening of the occluded vessels on repeat angiography, although hemorrhagic transformation was found in fewer than half of the patients. Thus, other factors in addition to reopening of the occluded arteries should be evaluated as causes of the initiation or development of hemorrhage.

Infarct size seems to be an important factor in secondary hemorrhage. CT and autopsy studies\(^2\),\(^7\),\(^8\),\(^14\)-\(^16\) have indicated that HI is closely related to infarct size. In our study, HI was more common in patients with large infarcts or midline shift of the brain. In their autopsy study, Lodder et al\(^2\) emphasized that HI was related more to infarct size than to stroke mechanism. Therefore, HI may indicate large infarcts and may predict ischemic stroke prognosis.

There are a few reports that demonstrate the effect of aging on hemorrhagic transformation. According to the analysis of 30 patients with cardiogenic brain embolism,\(^9\) the occurrence of HI was not affected by age. In contrast, our results show that HI occurs more frequently in older patients. However, age alone may not be an independent factor for developing HI since elderly patients could also have larger infarcts due to poorer collateral circulations.

HI is not necessarily associated with acute or chronic hypertension in humans,\(^15\),\(^17\) although some experimental studies\(^11\),\(^12\) indicate a correlation between the severity of HI and the level of blood pressure. In our study, blood pressure during hospitalization or a history of hypertension were not related to the incidence of hemorrhagic transformation, probably because valvular diseases and atrial fibrillation were major causes of cerebral embolism and ischemic or hypertensive heart diseases were less frequent.

Cardiogenic embolism produces a large infarct, resulting in frequent hemorrhagic infarction.\(^2\),\(^18\) We observed HI in up to 60% of our patients with cardiogenic embolism although the incidences of HI in each group with heart disease did not differ. Since almost all of our patients had cardiogenic embolism, it is not known how patients with "artery-to-artery embolism" might differ.

Many infarcts developed in the territory of the middle cerebral artery. However, there was no significant difference in the incidence of HI among the various vascular territories, suggesting that the location of embolic infarct is less important for hemorrhagic transformation.

The influence of thrombolytic or anticoagulant therapy in the acute stage of thromboembolism on clinical course is still controversial.\(^19\),\(^20\) Anticoagulant therapy reduces infarct size and prevents recurrent attacks during the first weeks\(^21\) and is suggested to be useful in cases of small or medium-sized infarcts.\(^8\),\(^13\),\(^22\) Some reports\(^23\)-\(^25\) however, have described a higher incidence of HI and an undesirable outcome as the result of anticoagulant therapy.
In contrast, our results demonstrate that the incidence of HI does not differ between patients with and those without thrombolytic and/or anticoagulant therapy. However, patients with such therapy seemed to experience larger and more severe hemorrhages than those without. Thrombolytic or anticoagulant drugs during the acute phase of cerebral embolism should be used carefully both in patients with large infarcts and in the elderly.

References

KEY WORDS • cerebral angiography • cerebral hemorrhage • embolism • tomography, emission computed
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