Clinical Features of Recurrent Embolization in Acute Cardioembolic Stroke

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Background and Purpose: Recurrent embolization is a serious problem in acute cardioembolic stroke. However, the clinical features and predisposing factors of recurrent embolization have not yet been fully elucidated.

Methods: Subjects were 227 consecutive patients (128 men and 99 women, aged 68.6±13.2 years) with acute cardioembolic stroke who did not receive anticoagulant therapy during the first 14 days after stroke onset. We assigned the subjects to two groups according to the occurrence or nonoccurrence of recurrent attacks within 14 days of the stroke onset. We assessed their clinical features, coagulation study results, and underlying heart disease.

Results: Recurrent brain or systemic embolization during the first 14 days after onset was noted in 46 patients (20.3%, group A) but not in the other 181 (group B). Recurrent embolization was more frequently noted at an early phase than at a late phase during the initial 14 days. Mortality was higher in group A (19.6%) than in group B (8.8%). The mean plasma level of antithrombin III (77.8±19.5%) at admission in group A patients was significantly lower than that in group B patients (87.9±15.5%). After admission, hematocrit decreased in group B patients but slightly increased in group A patients, in whom diuretics were more commonly used. Rheumatic heart disease and prosthetic valves, in addition to the presence of intracardiac thrombi, were seen more commonly in group A patients, whereas atrial fibrillation without organic heart disease and myocardial infarction were more frequent in group B patients.

Conclusions: Low plasma levels of antithrombin III, dehydration, the use of diuretics, and the presence of rheumatic heart disease, prosthetic valves, and intracardiac thrombi seem to be predisposing factors for recurrent embolization. Immediate anticoagulation may be considered in acute cardioembolic stroke patients if such predisposing factors are demonstrated. (Stroke. 1993:24:1681-1685.)

Key Words • antithrombin III • cardioembolic stroke • dehydration • embolism

Recurrent embolization, one of the most serious problems in patients with cardioembolic stroke (CES),1–6 most frequently occurs within 2 weeks of the initial event.5–8 To prevent recurrent embolization and ensure the effective management of patients with acute CES, it is important to clarify the predisposing factors. We investigated the timing and incidence of recurrent embolization during the first 14-day period of onset in 227 patients with acute CES who did not receive anticoagulation. We then compared the clinical profiles of patients who developed recurrent embolization during this 14-day period with those of patients without recurrence.

Subjects and Methods

Between 1985 and 1991, 412 patients were admitted consecutively to the Stroke Care Unit of the National Cardiovascular Center, Osaka, Japan, within 7 days of nonseptic CES onset. Of these patients, 185 received immediate anticoagulant therapy within 14 days of the initial stroke onset. Because the efficacy of immediate anticoagulation was still under dispute and we had no protocol or specific criteria for immediate anticoagulation, the initiation, kind, mode, and amount of anticoagulant therapy varied according to the primary physician. As a result, 227 patients received no anticoagulant or antiplatelet therapy during the first 14 days; these patients were entered into the current study. This group comprised 128 men and 99 women with a mean±SD age of 68.6±13.2 years and a mean interval from onset to admission of 1.6 (median, 1) days. They were older than the 185 patients (62.7±13.2 years) who received anticoagulation therapy (Table 1). As for underlying heart disease, in the untreated group there were more patients with atrial fibrillation and fewer with prosthetic valves than in the treated group. There were no other differences in underlying heart disease.

The diagnosis of CES was made if the patients met the first of the following criteria and at least one of criteria 2 through 5 (which are based on our previous reports1–3): (1) newly developed neurological deficit and presence of a certain embolic source in the heart, including valvular heart disease, prosthetic valves, cardiomyopathy, myocardial infarction, or atrial fibrillation; (2) sudden onset of clinical symptoms with the
maximal focal neurological deficit; (3) evidence of embolization in other parts of the body; (4) angiographic features such as visualization of an embolic shadow and reopening of the previously occluded vessel; and (5) computed tomographic (CT) features such as hemorrhagic infarction and a sharply margined hypodense area involving the cortex.

Electrocardiograms and transthoracic two-dimensional echocardiograms were obtained for all subjects at admission. Cerebral angiography was performed in 143 patients (63.0%): conventional or intra-arterial digital subtraction arteriography was performed in 121 patients and intravenous angiography in 22. Distinctive findings of cerebral embolism, such as reopening, embolic shadow, capillary blushing, or early venous filling, were confirmed in 115 cases. Brain CT examinations were performed on the first hospital day in all patients and were repeated two or more times during the observation period.

We investigated the stage at which recurrence occurred during the first 14 days and the incidence of recurrent embolization. Recurrence of brain embolism was diagnosed when additional focal neurological deficits developed after the initial attack. Embolization to other parts of the body was diagnosed on the basis of clinical symptoms, signs, angiographic findings, or autopsy.

We also compared the clinical profiles of the patients with subsequent recurrence within 14 days of the onset (group A) and those without recurrence (group B). The variables investigated were age, sex, blood pressure at admission, consciousness level at admission, and infarct size due to the initial attack, coagulation studies, and underlying heart disease. The use of diuretics was also monitored. The patient’s level of consciousness was evaluated at admission and classified into four categories: awake, drowsy, stuporous, and comatose. The infarct size was measured using the brain CT scan obtained between 24 and 48 hours after onset or that performed on admission in patients admitted more than 48 hours after onset. Size was defined as follows: small, an infarction of less than 1 cm hypodensity; medium, 1 cm to 3 cm hypodensity; and large, more than 3 cm hypodensity. Coagulation studies consisted of prothrombin time, activated partial thromboplastin time, and plasma levels of antithrombin III and fibrinogen that had been measured at admission. Prothrombin time was measured by Quick’s one-stage method using Thromborel S (Behringwerke AG, Marburg, FRG) and expressed as an international normalized ratio.10 Plasma levels of antithrombin III were measured by the chromogenic substrate method (Substrate S-2238, KabiVitrum AB, Sweden).11 Hematocrit was measured at the time of admission for patients in both groups and on the day of recurrence for group A or around day 14 for group B. Changes in hematocrit values were expressed as ∆hematocrit, calculated by subtracting the hematocrit value at admission from that on the day of recurrence in group A patients and from that at day 14 in group B patients.

Continuous data were expressed as mean±SD. We used the χ² test for analysis of discrete variables and the unpaired t test for analysis of continuous variables.

### Results

Recurrent brain or systemic embolization during the first 14 days after onset was noted in 46 (20.3%, group A) but not in the other 181 (group B) of the 227 study subjects. Brain embolism was observed in 31 patients (13.7%) and systemic embolization to other parts of the body in 19 (8.4%), including 4 with simultaneous brain and systemic embolism.

Twenty-nine of the 31 patients developed recurrent brain embolization abruptly when they were awake. In the other 2 patients with severe disturbance of consciousness, recurrence was noted by follow-up neurolog-

### Table 1. Baseline Characteristics of 227 Nonanticoagulated and 185 Anticoagulated Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Nonanticoagulated</th>
<th>Anticoagulated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>227</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Men/Women</td>
<td>128/99</td>
<td>101/84</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>68.6±13.2</td>
<td>62.7±13.2</td>
<td>.0001</td>
</tr>
<tr>
<td>Underlying heart diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>57 (55)</td>
<td>53 (51)</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32 (11)</td>
<td>21 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>8 (8)</td>
<td>14 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>5 (4)</td>
<td>9 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>7 (7)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>NS</td>
</tr>
<tr>
<td>Prosthetic valves</td>
<td>2 (2)</td>
<td>13 (11)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>17 (17)</td>
<td>9 (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation only</td>
<td>97 (97)</td>
<td>58 (58)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

NS indicates not significant. Values in parentheses indicate patients with atrial fibrillation.
ical examinations. Twenty-four of the 31 attacks occurred in a vascular territory different from that of the initial attack; the remaining 7 occurred in the same territory fed by the internal carotid artery. In one of these 7 patients, systemic embolization developed at the same time. Two of the 7 patients experienced recurrence after full recovery of the initial neurological deficit, and the other 5 developed rapid deterioration of consciousness and hemiparesis. Five of the 7 recurrent lesions demonstrated on CT were located apart from the initial lesions; 1 involved the initial lesion, and 1 involved a lesion adjacent to the initial one.

Of the 19 patients with systemic embolism, 9 had embolization to the limbs, 8 to the mesenteric artery, and 4 to the kidney. Two patients had more than two simultaneous embolizations to different sites. All patients with embolization to the limbs exhibited cyanosis, decrease in skin temperature, and loss of pulses distal to the occlusion. The presence of emboli was confirmed by arteriography in 5 patients and by autopsy in 2 of the remaining 4 patients.

All 8 patients with mesenteric artery embolism had severe abdominal pain, paralytic ileus with decreased bowel sound, and bloody stool. The diagnosis was confirmed by arteriography in 3 patients and autopsy in 5.

In 4 patients, fresh renal infarction was accompanied by gross hematuria; confirmation was by autopsy in each case.

Recurrent embolization was more frequently noted at an early phase (5 days or less), especially within 2 days, than at a late phase (over 5 days) of the first 14 days after the initial attack (Fig 1).

Clinical features in both groups are shown in Table 2. There were no differences in age, blood pressure, consciousness level, or infarct size (demonstrated by brain CT). However, women were more commonly found in group A than in group B. The mortality rate in group A (19.6%) was significantly higher than that in group B (8.8%; χ² test, P<.05). Diuretics were more frequently used in group A (58.7%) than in group B (27.1%; χ² test, P<.01).

Rheumatic heart disease and the presence of a mechanical prosthetic valve were more common in group A patients, whereas atrial fibrillation alone was more frequently observed in group B patients. Rheumatic heart disease was present in 36 women (63.2%) and 21 men (36.8%), and this difference was significant (χ² test, P<.01). This trend was not observed for other heart diseases.

Plasma level of antithrombin III (77.8±19.5%) at admission in group A patients was significantly lower than that in group B patients (87.9±15.5%; nonpaired t test, P=.0004) (Fig 2). There was no difference in hematocrit at admission between group A (40.7±5.6%) and group B (41.7±5.1%). However, hematocrit at the time of recurrence in group A (41.5±7.3%, measured in 36 patients) was higher than that at day 14 in group B (39.3±5.8%, measured in 165 patients) with marginal significance (nonpaired t test, P=.054), and the mean Δhematocrit was negative in group B (−2.5±5.1%) and significantly lower than that in group A (0.9±4.6%; nonpaired t test, P=.004), which was positive. There were no differences in prothrombin time, activated partial thromboplastin time, and fibrinogen levels between the two groups.

Discussion

There were some differences in age and underlying heart disease between the 227 nonanticoagulated patients and the 185 anticoagulated patients. It has been reported⁴ that advanced age is one of the risk factors for promoting hemorrhagic complications in immediate anticoagulation and that recurrence is frequently seen in patients with prosthetic valves and less common in those with atrial fibrillation alone. Therefore, a primary physician’s decision for acute anticoagulant therapy might be affected by this information. Although there were some differences in baseline characteristics between the two groups, we believe that the 227 patients were an appropriate study population for elucidating the predisposing factors of recurrent embolization.

It has been demonstrated that recurrence of embolization, with an incidence of 13% to 20%, tends to occur during the first 14 days after onset of CES and worsens the prognosis of patients with cerebral embolism.⁵,⁶,⁸,¹² However, it has not been exactly determined when during the first 14 days after onset the recurrence tends to occur. The Cerebral Embolism Study Group¹⁻³ aggregated 33 episodes of acute recurrent embolization from their data and previous reports. They found that the risk of reembolism was slightly higher during the first 6 days after onset. Our data also demonstrated that recurrent embolization tended to develop within the first few days of the 2-week postonset period and was associated with high mortality. Because recurrence is more likely to occur close to the time of the initial CES onset, it may be expected that immediate anticoagulation treatment would effectively reduce the incidence of recurrent attacks and mortality if started as soon as possible after initial onset.

In this study, recurrence was frequently seen in patients with rheumatic heart disease, mechanical prosthetic valves, or intracardiac thrombus. The Framingham Study¹⁴ reported an 18-fold increase in stroke occurrence in patients with mitral stenosis and atrial fibrillation compared with matched controls. The Cerebral Embolism Task Force⁵ investigated a number of previous reports and concluded that embolization recurs in 30% to 75% of patients with rheumatic heart disease at an annual rate of almost 10% and that the
stroke risk in anticoagulated patients with mechanical prosthetic valves was 2% to 4% per year. Intracardiac thrombus is a dangerous direct source of emboli. In a previous study, we performed serial two-dimensional echocardiography in 30 consecutive patients with acute cardioembolic stroke and found intracardiac thrombi in 8. Recurrent embolization occurred in 3 of the 8 patients within 14 days of CES onset. The 22 patients without intracardiac thrombus did not experience recurrence during this period.

On the other hand, atrial fibrillation without other clinical evidence of organic heart disease and myocar-
Fig 2. Graph showing plasma levels of antithrombin III in groups A and B.

dial infarction was not closely associated with recurrent embolization. Because of the low incidence of recurrence associated with atrial fibrillation and the possible hemorrhagic complications that accompany immediate anticoagulation, it may be preferable to delay the start of anticoagulant therapy, with the following exceptions: in patients with atrial fibrillation alone, the presence of mobile thrombi (which cause embolization easily) at the left atrial appendage\(^\text{15}\) revealed by transesophageal echocardiography\(^\text{16}\); and in patients with myocardial infarction, the presence of mural thrombi demonstrated by transthoracic echocardiography or ultrafast CT.\(^\text{15,17}\)

The proportion of women was higher in group A than in group B, probably due to a high incidence of women with rheumatic heart disease in the former group.\(^\text{18}\)

Dehydration has been implicated in the acceleration of intracardiac thrombus growth in the cardiac chamber.\(^\text{15}\) In the current study, group B showed a negative Δhematocrit, whereas that of group A was positive. This may indicate the existence of dehydration at the time of the first embolism that was corrected in group B but continued or was accelerated in group A, which in turn might be related to the recurrence of embolization. The use of diuretics might play a role in the promotion or continuation of dehydration.

Plasma levels of antithrombin III were already lower in patients with subsequent recurrence than in those without, which was consistent with the findings described in our previous report.\(^\text{15}\) These low levels of antithrombin III are considered to result in large part from consumption of antithrombin III due to increased thrombin activity in the cardiac chamber.\(^\text{17,19}\)

Our data demonstrate that the presence of low plasma levels of antithrombin III, dehydration, rheumatic heart disease, mechanical prosthetic valves, and intracardiac thrombi are strong predisposing factors for recurrent embolization. Although immediate anticoagulation is still under dispute, it may be considered in patients with acute CES if the above-mentioned predisposing factors are demonstrated and hemorrhagic complications or promoting factors of hemorrhagic infarction (such as hypertension, large brain infarction, and advanced age) are not present.

Acknowledgment

This study was partially supported by a grant from Japan Cardiovascular Research Foundation.

References

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*Stroke*. 1993;24:1681-1685
doi: 10.1161/01.STR.24.11.1681

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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