Predisposing Factors of Recurrent Embolization in Cardiogenic Cerebral Embolism

Masahiro Yasaka, MD, Takenori Yamaguchi, MD, Takeshi Miyashita, MD, Yung-Dae Park, MD, Tohru Sawada, MD, and Teruo Omae, MD

To elucidate the pathophysiology of intracardiac thrombus formation, serial two-dimensional echocardiographic examinations were performed on 30 consecutive patients with acute cardiogenic cerebral embolism in parallel with measurement of hematocrit and plasma levels of antithrombin III. The data from groups of patients with and without newly formed or enlarged thrombi were compared. Intracardiac thrombi were detected in eight of the 30 patients (27%), four at admission and four after admission. Enlargement of the thrombus was observed in four, and systemic embolization recurred in three of the eight. Antithrombin III levels already were low at admission in patients who later developed thrombi or had enlarged thrombi on serial examinations. When the development or enlargement of an intracardiac thrombus was detected by echocardiography, the diameter of the inferior vena cava was found to be reduced. At the same time, a decrease in antithrombin III and an increase in hematocrit were demonstrated. Intracardiac thrombi are frequently detected by repeated echocardiographic examination in patients with cerebral embolism. Dehydration seems to accelerate thrombus formation that is reflected by a decrease in antithrombin III. A low antithrombin III level at admission and/or a decrease in antithrombin III after admission may indicate the possible recurrence of embolism. (Stroke 1990;21:1000-1007)

It has been reported that approximately 90% of patients with cerebral embolism have heart disease as the source of the embolus1–3 and that cardiogenic cerebral embolism causes 15% of ischemic cerebral infarcts.4 Patients with embolic cerebral infarction have larger infarcts on computed tomographic scans and a poorer prognosis than those with atherothrombotic cerebral infarction.1 One of the reasons for the poorer prognosis is the recurrence of embolization.1,2,5,6 Recurrent attacks usually occur within 2 weeks after the initial event.4,6–8 Determination of the pathophysiology of recurrent systemic embolization is a problem of considerable importance, as it may enable us to develop treatment to prevent recurrent attacks.

Intracardiac thrombus formation and recurrent systemic embolization during the acute stage after cerebral embolism were studied with two-dimensional echocardiography, and the results were related to studies of blood coagulation.

Subjects and Methods

Thirty patients, 11 men and 19 women with a mean age of 63.1±12.5 years, who were admitted to the Stroke Care Unit of the National Cardiovascular Center within 48 hours after cerebral embolism were included in the study. Every patient with cerebral embolism who was admitted between June 1, 1986, and January 31, 1987, was included.

The diagnosis of cerebral embolism was made if the patients met at least two of the following criteria as reported previously1: 1) the sudden onset of clinical symptoms with the maximal focal neurologic deficit at the time of onset; 2) the presence of a probable or certain source of cardiac emboli, including a) valvular heart disease or myocardial disorders such as infective endocarditis or acute myocardial infarction or b) cardiac arrhythmias such as atrial fibrillation, sick-sinus syndrome, or frequent premature atrial contractions or premature ventricular contractions; and 3) evidence of embolization in other parts of the body. Because cardiac arrhythmias are commonly seen in elderly patients, this symptom was...
not considered as an independent item unless the presence of an embolus and/or the reopening of a previously occluded vessel were confirmed by cerebral angiography.

Two-dimensional echocardiograms were obtained with a commercially available real-time, phased array system (model SSH-60A with 3.75 MHz transducer, Toshiba Inc., Tokyo, Japan). Echocardiographic examinations were performed at the time of admission and at days 4, 7, 10, 14, 21, and 28 after the onset of cerebral embolism.

Patients were examined in the left recumbent or the supine position. The intracardiac chambers, especially the left atrial and ventricular cavities, were examined extensively by shifting, rotating, and tilting the transducer and by adjusting the gain control of the equipment if necessary. The echocardiographic diagnosis of an intracardiac thrombus was made when an echo of a mass with a clearly defined contour was observed inside the cardiac chambers, when the echo of endocardial surface was identified, and when the echo of the mass was visualized from several positions on the chest wall. A thrombus size was estimated as a square measure (mm²) on the view where the thrombus was best visualized. The thrombus was considered to have enlarged when it became 1.5 times larger than its previous size. A thrombus was considered to be mobile if part of the thrombus showed motion independent of that of the adjacent endocardium, either opposite in direction or freely erratic.

The left ventricular end-diastolic dimension and end-systolic dimension and the left atrial dimension were measured by M-mode echocardiography. The short diameter of the inferior vena cava was measured at the end of the expiratory phase at the level just below the junction of the hepatic vein and the inferior vena cava in the short-axis view by a subcostal approach in the supine position.

Coagulation studies, consisting of the measurements of hematocrit and plasma levels of antithrombin III, were performed within 48 hours and at days 4, 7, 14, and 28 after the onset of cerebral embolism. These studies also were done at days 10 and 21 after onset if an intracardiac thrombus was detected. Antithrombin III was measured by the chromogenic substrate method.

The water balance in each patient was determined each day after admission. We assumed that water derived from metabolism was 5 ml/kg/day and that insensible water loss was 15 ml/kg/day. The water balance was calculated as follows: infused volume plus oral water intake plus water contained in hospital food (1,750 ml/day on average) plus water derived from metabolism (5 ml/kg/day) minus urine volume minus insensible water loss (15 ml/kg/day). The use of diuretics also was monitored.

Continuous data were expressed as mean±SD, and the difference between two means was analyzed by the unpaired t test or the paired t test. The χ² test was also used.

### Table 1. Echocardiographic Findings

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Atrial fibrillation present</th>
<th>Atrial fibrillation absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic heart disease</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Prosthetic valve†</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy‡</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation alone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>27</td>
</tr>
</tbody>
</table>

*Patient showed frequent paroxysmal atrial contractions.
†Two patients underwent mitral valve replacement (Mitroflow valve and Björk-Shiley valve), and one underwent aortic valve replacement (Hancock valve).
‡One patient showed calcification of the aortic valves.

### Results

All 30 patients had heart disease that was considered to be a source of emboli (Table 1). Rheumatic heart disease was most commonly seen as an organic heart disease. All of the patients with rheumatic heart disease were found to have mitral stenosis on echocardiography. Twenty-seven of the 30 patients had atrial fibrillation.

In 25 of 30 patients, excellent echocardiograms were obtained in which the left atrial appendage was visualized. In the other five, however, visualization was poor (Figure 1). Among the 25 patients, the presence of an intracardiac thrombus was confirmed at admission in four (Figure 2). Six out of the remaining 21 patients were given anticoagulant therapy within 2 days after admission. Of the 15 patients who were not treated with anticoagulants, four developed fresh intracardiac thrombi after admission (Figures 3 and 4). Of the remaining 11 patients who were not treated with anticoagulants and who did not develop intracardiac thrombi, one died on day 5 after onset from brain edema. The 10 surviving patients constituted group A for purpose of data analysis.

A total of eight patients were eventually found to have intracardiac thrombi. Four had a thrombus at admission, and the other four developed a thrombus after admission (Figure 5). Thus, the incidence of detectable intracardiac thrombi was 27% (eight of 30 patients). The underlying cardiac diseases and the sites of thrombus formation varied. Five patients with rheumatic mitral valve disease and one with hypertensive heart disease had a mobile thrombus at the left atrial appendage (Figures 3 and 4); one patient with an acute anterior myocardial infarction had at admission a nonmobile thrombus at an akinetic portion of the left ventricular apex (Figure 2), and one patient with hypertrophic cardiomyopathy and ath erosclerotic aortic valve disease had at admission a tail-like 10-mm-long mobile thrombus that extended into the aorta from the aortic ring between the right and left coronary cusps. One of the five patients with
Total patients entered
Echocardiograms of good quality
Intracardiac thrombus detected on admission
Anticoagulation immediately after admission
Thrombus detected after admission
Enlargement of thrombus during admission

FIGURE 1. Block diagram showing characteristics of patients with cerebral embolisms. +, Presence; −, absence. *Group A: 10 surviving patients (one patient died on day 5 after onset) who had no intracardiac thrombi at admission, were not treated with anticoagulants, and did not develop intracardiac thrombi after admission. **Group B: Seven patients who experienced development or enlargement of intracardiac thrombi after admission.

Four of the eight intracardiac thrombi enlarged after admission. Two of the four thrombi enlarged two separate times during the study. One was the tail-like thrombus attached to the aortic ring, which was detected at admission. It was found to be enlarged at the examination on day 7 after onset, but at day 10 it was smaller; it was larger again at day 21. Another thrombus was at the left ventricular apex in the patient with myocardial infarction (Figure 2). This thrombus was detected at admission and enlarged twice, at days 4 and 14 after onset. In total, the development or enlargement of thrombi after admission was detected 10 times in seven patients; these patients constituted group B (Figure 1). Nine of these 10 developments or enlargements were seen within 14 days after the onset of cerebral embolism.

In three patients with an intracardiac thrombus, anticoagulant therapy was started immediately after the detection of the thrombus. In two of them, the thrombus gradually regressed. In the other patient, the thrombus disappeared abruptly on day 14 after onset, when embolization occurred.

FIGURE 2. Apical two-chamber (top panels) and apical short-axis (bottom panels) views of echocardiogram in patient with myocardial infarction. Mural thrombus (arrow) in apex was detected on admission (day 1). Enlargement of thrombus was demonstrated at day 4 and at day 14 after onset. LV, left ventricle; LA, left atrium.
Systemic embolization recurred in three of the eight patients with intracardiac thrombi (Figure 5). Each of the three patients had mitral stenosis with a mobile thrombus at the left atrial appendage. One of these was a 55-year-old woman in whom an intracardiac thrombus was not detected until day 7 after the onset of cerebral embolism. On day 10, a mobile intracardiac thrombus was observed, and anticoagulant therapy was started. However, embolization to the right upper extremity occurred on day 14. Immediately after embolization, the thrombus was no longer detectable by echocardiography. Another patient was a 38-year-old woman with no intracardiac thrombus detected either at admission and on day 4 after the onset of cerebral embolism. On day 7, she had a recurrent stroke, and a mobile thrombus was detected. The other patient was a 65-year-old woman, in whom no intracardiac thrombus was detected either at admission or on day 4 after the onset of cerebral embolism. On day 6, she suddenly developed an embolus to the left leg. A mobile thrombus was detected on day 7.

Measurements of the minor axis of the inferior vena cava diameter are shown for the 10 patients of group A in the left panel of Figure 6. There were no significant changes after admission. There were seven
patients in whom newly formed or enlarged intracardiac thrombi were detected after admission (group B). The changes in the minor axis of the inferior vena cava diameter that occurred in this group in the 7 days before the detection of the newly formed or enlarged thrombi are shown in the middle panel of Figure 6. The changes of inferior vena cava diameter between the studies done just before the detection and the studies done at the time of detection are shown in the right panel of Figure 6. When fresh thrombus formation or growth of a thrombus was observed, the diameter of the inferior vena cava was reduced significantly (from 15.7±2.8 to 12.8±2.3 mm, *p<0.01*).

There were no significant changes in left ventricular end-diastolic dimension, left ventricular end-systolic dimension, or left atrial dimension, from before the detection of a thrombotic change to after the detection (from 44.6±5.4 to 44.0±5.1 mm, from 30.3±5.6 to 29.5±6.0 mm, and from 49.7±7.4 to 48.0±6.7 mm, respectively). Fractional shortening calculated from left ventricular end-diastolic dimension and left ventricular end-systolic dimension at admission were 36.5±7.2% and 35.7±6.8% in group A and group B, respectively. There was no significant difference between the two groups.

There were no significant changes in hematocrit in group A patients during the 4 weeks, except for one patient with iron deficiency anemia whose hematocrit value rose with treatment after admission (Figure 7, left panel). On the other hand, the hematocrits in group B increased significantly at the time of appearance or enlargement of thrombi, when compared with hematocrits obtained shortly before detection (Figure 7, middle and right panels), from 41.3±4.3% to 44.8±6.4% (*p<0.01*).

The changes in antithrombin III levels after admission are shown in Figure 8. The plasma levels in group A remained above 90% of the normal control levels after admission in eight of 10 patients (Figure 8).
FIGURE 8. Graphs showing changes of plasma antithrombin III (AT III) levels. Left panel: Changes in group A, 10 surviving patients who were admitted with cerebral embolisms, had no intracardiac thrombi at admission, were not treated with anticoagulants, and did not develop intracardiac thrombi after admission. Middle panel: Changes in group B, seven patients who were admitted with cerebral embolisms and experienced development or enlargement of intracardiac thrombi after admission. The values are for AT III at the time of detection of thrombus growth and within 7 days before detection. ●, Thrombus detected; ○, thrombus enlarged. Right panel: Comparisons of the values for group B at the time of detection of thrombus growth and just before detection.*p<0.05 by paired t test.

In group B, however, there were changes in the levels in all patients during the 7 days before the development or enlargement of thrombi (Figure 8, middle panel). At the time of detection of a thrombotic change, antithrombin III decreased below 90% of control in most patients. When values obtained shortly before detection were compared with values obtained on the day of detection, a significant decline of antithrombin III levels was noted, from 97.8±10.8% to 85.9±10.2% (p<0.05) (Figure 8, right panel).

In addition, the levels of antithrombin III at admission already had been lower in group B (79.4±17.8%) than in group A (101.1±20.1%, p<0.05) (Figure 9). No patients in either group had malnutrition or hepatic dysfunction, which may decrease antithrombin III levels.

Diuretics were used in only two of 10 patients in group A, but in six of seven patients in group B. The difference in frequency was significant (χ² test, p<0.05).

Values for water balance (milligrams per kilogram per day) in groups A and B are shown in Figure 10. Because the appearance or enlargement of intracardiac thrombi were observed within two weeks after the onset of cerebral embolism in most cases, values for water balance during this period for patients in group A were considered as control data and compared with values for the day of detection of thrombotic activity in group B. Values for a single patient in group B were discarded because of inaccurate records. Water balance was negative in five of six patients of group B, whereas seven of 10 patients in group A showed positive water balance. The mean values for the two groups were significantly different between the two groups (unpaired t test, p<0.05).

Discussion

The criteria for echocardiographic diagnosis of intracardiac thrombi used for this study are essentially the same as those reported by Beppu et al. According to these criteria, the sensitivity of detection of intracardiac thrombi is such that small thrombi at the tips of the appendages, thin mural thrombi, and thrombi smaller than the resolving capacity of the instruments may not be visualized. The specificity, however, is reported to be so high that false positive diagnosis can be minimized if an
The appearance or enlargement of thrombi was observed 10 times in seven patients of group B. Most of the thrombotic activity was detected within 14 days after onset of the embolic stroke. These observations are consistent with the fact that the systemic embolism tends to recur most frequently during this period. 

The appearance and disappearance of intracardiac thrombi were found to occur during a relatively short period of time after embolism. Therefore, the more frequently the examination is repeated in the acute stage, the greater the incidence of detecting thrombi.

All the thrombi detected in this study were mobile except one. Recurrent embolization occurred in three patients with a mobile thrombus, indicating that mobile thrombi are fresh and may be easily detachable. Haugland et al reported that mobile thrombi of the left ventricle in patients with myocardial infarction tend to separate and embolize.

Decreased cardiac function is known to be one of the causes of an intracardiac thrombus. However, not all patients with decreased cardiac function develop intracardiac thrombi or have systemic embolization. Furthermore, it is often found that an intracardiac thrombus detected by echocardiography cannot be detected again. In our study, there were no significant differences in fractional shortening between group A and group B. Therefore, decreased cardiac function is not the sole factor in thrombus formation.

When a fresh thrombus or an enlargement of a thrombus was noted, a rise of hematocrit and reduction of inferior vena cava were detected. Furthermore, the appearance or enlargement of thrombi was observed mainly in patients with negative water balance, particularly in those taking diuretics. These findings suggest that dehydration may play an important role in the formation of intracardiac thrombi.

Fukuda and Nakamura reported that, in patients with rheumatic heart disease, the incidence of embolism was higher and antithrombin III levels were lower than in patients with other heart diseases (excluding ischemic heart disease). They suggested that low antithrombin III levels reflected a hypercoagulable state in patients with rheumatic heart disease. In our study, plasma levels of antithrombin III on admission were lower in group B than in group A. Moreover, when the appearance or enlargement of thrombi was confirmed by echocardiography, plasma levels of antithrombin III tended to decrease below 90%. This may indicate that coagulability in patients who later developed an intracardiac thrombus had already been accelerated at the time of admission and that enhanced intracardiac thrombosis resulted in a decrease of antithrombin III by consumption of antithrombin III in the cardiac chamber. Although we could not clearly differentiate group A from group B by the level of antithrombin III, as there was an overlap in those levels at admission between the two groups, we should at least keep in mind that patients...
with a low or progressively decreasing antithrombin III level are at high risk of intracardiac thrombus formation and embolization. In such cases, echocardiographic examination should frequently be performed to confirm the presence or absence of intracardiac thrombosis.

References
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