Regression of Intracardiac Thrombus After Embolic Stroke

Masahiro Yasaka, MD, Takenori Yamaguchi, MD, Takeshi Miyashita, MD, and Takashi Tsuchiya, MD

Using two-dimensional echocardiography, we studied the pathophysiology of intracardiac thrombus regression accompanied by anticoagulant therapy in 82 consecutive patients with acute cardiogenic cerebral embolism. We noted intracardiac thrombus in 15 patients; nine of the 15 were started on anticoagulant therapy with warfarin potassium to maintain the prothrombin time between 2.5 and 3.5 (international normalized ratio). Serial two-dimensional echocardiograms were obtained for these nine patients before and after anticoagulation, with the plasma levels of fibrinopeptide A, fibrinopeptide Bβ15-42, and D-dimer measured at the same time. In eight of the nine patients the intracardiac thrombi gradually decreased in size while the plasma level of fibrinopeptide A fell to within the normal range and the plasma levels of fibrinopeptide Bβ15-42 and D-dimer remained above the normal ranges. In the other patient the thrombus disappeared, with embolization to the right arm immediately after starting anticoagulant therapy. Mobile or small thrombi regressed earlier than nonmobile or large ones. We conclude that regression of intracardiac thrombus after anticoagulation may be based on the relative predominance of plasma fibrinolytic activity over anticoagulation-inhibited thrombin activity. (Stroke 1990;21:1540-1544)

Intracardiac thrombi can often be detected by serial two-dimensional echocardiography in patients with acute cardiogenic cerebral embolism.1 A number of recent studies1-11 have shown that intracardiac thrombi can regress during anticoagulant therapy in patients with or without cerebral embolism. The mechanism for this regression, however, has not been fully elucidated. We addressed this issue in nine patients with cerebral embolism and intracardiac thrombus by administering anticoagulants and taking serial two-dimensional echocardiograms at short intervals that paralleled measurements of prothrombin time and the plasma levels of fibrinopeptide A, fibrinopeptide Bβ15-42, and D-dimer.

Subjects and Methods

We entered into the study 82 patients (36 men and 46 women, mean±SD age 62.8±13.1 years) admitted to the Stroke Care Unit of the National Cardiovascular Center between June 1, 1986, and December 31, 1987, ≤7 days after cardioembolic stroke diagnosed according to the criteria of Yamaguchi et al.12

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Two-dimensional echocardiography was performed using a commercially available real-time, phased-array system with a 3.75-MHz transducer (SSH-60A, Toshiba Inc., Tokyo, Japan) ≤14 days after the onset of cerebral embolism and every month during hospitalization. In patients with intracardiac thrombus, two-dimensional echocardiography was performed before starting anticoagulant therapy and then every 24 hours until day 28 or the day when the intracardiac thrombus was no longer present if earlier. If the intracardiac thrombus did not disappear by day 28, additional echocardiographic examinations were performed once a week until either the thrombus disappeared or the patient was discharged from the hospital. The echocardiographic diagnosis of intracardiac thrombus was made when the echo of a mass with clearly defined contours was observed inside the cardiac chambers, the echo of the endocardial surface was identified, and the echo of a mass on the chest wall was visualized from several positions.4 Thrombus size was estimated in square centimeters on each echocardiogram taken from the same position from which the thrombus was best visualized. Sequential echocardiograms were compared. A thrombus was considered to be mobile if a part of it showed motion, either in the opposite direction or erratic, independent of the adjacent endocardium.

Coagulation studies consisted of measurements of the prothrombin time and the plasma levels of fibrino-
Table 1. Echocardiographic Findings in 82 Patients With Cardioembolic Stroke

<table>
<thead>
<tr>
<th>Finding</th>
<th>n</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic heart disease</td>
<td>27</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>7</td>
<td>6</td>
<td>1*</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>4†</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>4‡</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Atrial fibrillation only</td>
<td>27</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>70</td>
<td>12</td>
</tr>
</tbody>
</table>

*Frequent paroxysmal atrial contractions.
†Three with mitral valve replacement (one Mitroflow valve and two Björk-Shiley valves) and one with aortic valve replacement (Hancock valve).
‡One with calcification of aortic valve.

The plasma level of fibrinopeptide A was measured by enzyme immunoassay (Dimertest EIA, Agen Biomedical Ltd., Brisbane, Australia). We also measured the plasma levels of fibrinopeptide A, fibrinopeptide Bβ15-42, and D-dimer in 10 clinically healthy controls (five men and five women, mean ± SD age 54.3 ± 11.9 years).

No patient had previously received anticoagulant therapy. The decision to use anticoagulant therapy was nonrandom because it was made by the attending physician. For anticoagulation, warfarin potassium was given orally and the prothrombin time was maintained between 2.5 and 3.5.

Continuous data are expressed as mean ± SD. Means were compared by using the unpaired t test.

Table 2. Characterization of Patients With Intracardiac Thrombi

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Time (day)</th>
<th>Heart disease</th>
<th>Thrombus</th>
<th>Anticoagulant therapy</th>
<th>Period (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Site</td>
<td>Size (cm²)</td>
<td>Mobility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>APP</td>
<td>1.2</td>
<td>+</td>
</tr>
<tr>
<td>1/38/F</td>
<td>7</td>
<td>RHD+AF</td>
<td>APP</td>
<td>1.3</td>
<td>+</td>
</tr>
<tr>
<td>2/41/F</td>
<td>1</td>
<td>RHD</td>
<td>APP</td>
<td>2.5</td>
<td>+</td>
</tr>
<tr>
<td>3/43/F</td>
<td>74</td>
<td>RHD+AF</td>
<td>APP</td>
<td>2.0</td>
<td>–</td>
</tr>
<tr>
<td>4/44/M</td>
<td>14</td>
<td>RHD+AF</td>
<td>APP</td>
<td>3.2</td>
<td>+</td>
</tr>
<tr>
<td>5/58/F</td>
<td>10</td>
<td>RHD+AF</td>
<td>APP</td>
<td>25.6</td>
<td>–</td>
</tr>
<tr>
<td>6/70/F</td>
<td>60</td>
<td>MI</td>
<td>LV</td>
<td>3.4</td>
<td>–</td>
</tr>
<tr>
<td>7/55/M</td>
<td>1</td>
<td>MI</td>
<td>LV</td>
<td>8.4</td>
<td>+</td>
</tr>
<tr>
<td>8/69/M</td>
<td>10</td>
<td>MI</td>
<td>LAP</td>
<td>15.4</td>
<td>–</td>
</tr>
<tr>
<td>9/77/F</td>
<td>2</td>
<td>LAF</td>
<td>APP</td>
<td>3.0</td>
<td>+</td>
</tr>
<tr>
<td>10/42/F</td>
<td>2</td>
<td>RHD+AF</td>
<td>APP</td>
<td>3.2</td>
<td>–</td>
</tr>
<tr>
<td>11/82/F</td>
<td>1</td>
<td>MI</td>
<td>LV</td>
<td>1.2</td>
<td>+</td>
</tr>
<tr>
<td>12/71/F</td>
<td>2</td>
<td>HCM+AF, AOV</td>
<td>AOV</td>
<td>1.8</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AOV calcification</td>
<td>3.6</td>
<td>+</td>
</tr>
<tr>
<td>13/65/F</td>
<td>7</td>
<td>RHD+AF</td>
<td>APP</td>
<td>1.8</td>
<td>+</td>
</tr>
<tr>
<td>14/78/F</td>
<td>4</td>
<td>HHD+AF</td>
<td>APP</td>
<td>3.6</td>
<td>+</td>
</tr>
<tr>
<td>15/44/M</td>
<td>14</td>
<td>RHD+AF</td>
<td>APP</td>
<td>2.2</td>
<td>+</td>
</tr>
</tbody>
</table>

Pt, patient; time, onset of cerebral embolism to detection of intracardiac thrombus; period, start of anticoagulant therapy to disappearance of thrombus; M, male; RHD, rheumatic heart disease; AF, atrial fibrillation; MI, myocardial infarction; LAF, lone atrial fibrillation; HCM, hypertrophic cardiomyopathy; AOV, aortic valve; HHD, hypertensive heart disease; APP, left atrial appendage; LV, left ventricle; LAP, left atrial posterior wall.

*Discharged from hospital prior to disappearance of thrombus.
matic heart disease (Table 2); all six were found by echocardiography to have mitral stenosis and an intracardiac thrombus at the left atrial appendage. Two of the nine had old myocardial infarction with intracardiac thrombus at an akinetic portion of the left ventricular apex, and the remaining patient had no organic heart disease but had lone atrial fibrillation with a thrombus located at the posterior wall of the left atrium. In the nine patients receiving anticoagulant therapy, size of the intracardiac thrombus ranged from 1.2 to 25.6 cm² on the echocardiogram before starting anticoagulation (Table 2); in five of the nine patients the intracardiac thrombus was mobile.

Within 10 days after beginning anticoagulant therapy, the prothrombin time had generally increased to >2.5 and was carefully maintained between 2.5 and 3.5. In all nine patients the intracardiac thrombus regressed with anticoagulation (Figure 1). In eight of

![Figure 1](image1.png)

**Figure 1.** Four-chamber echocardiogram, apical view of patient with myocardial infarction. Mural thrombus (arrows) before anticoagulation (left) gradually decreased in size (center) and had disappeared by day 14 (right). LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium.

![Figure 2](image2.png)

**Figure 2.** Graph of changes in plasma level of fibrinopeptide A in nine patients with intracardiac thrombi receiving anticoagulant therapy. Shaded area, normal range (from 0 to control mean±2 SD).

![Figure 3](image3.png)

**Figure 3.** Graph of changes in plasma level of fibrinopeptide Bβ15-42 in nine patients with intracardiac thrombi receiving anticoagulant therapy. Shaded area, normal range (control mean±2 SD).
the nine patients the thrombus gradually decreased in size, with no systemic embolization. However, in one patient the thrombus abruptly disappeared on day 4 of anticoagulation and systemic embolization to the right arm occurred. In seven patients the intracardiac thrombus completely disappeared according to echocardiography; the remaining two patients had a non-mobile and large thrombus that gradually resolved, but did not completely disappear during the period of observation. Mobile thrombi tended to regress faster than nonmobile ones, and small thrombi seemed to regress faster than large ones (Table 2).

The plasma levels of fibrinopeptide A, fibrinopeptide Bβ15-42, and D-dimer in the 10 controls were 0.9±0.5, 2.7±0.9, and 88.5±34.5 ng/ml, respectively; in the patients before starting anticoagulant therapy the values were 14.8±9.8, 16.9±10.3, and 613.0±279.0 ng/ml, respectively (p<0.01 for all). Plasma levels of these substances had no clear correlation with size of the thrombus.

The plasma level of fibrinopeptide A decreased sharply after commencing anticoagulation, and reached an approximately normal value (control mean±2 SD) within approximately 10 days (Figure 2). However, plasma levels of fibrinopeptide Bβ15-42 and D-dimer gradually decreased after the beginning of anticoagulant therapy but were still higher than normal (control mean±2 SD) after day 10 (Figures 3 and 4). Mean ratios of the plasma levels of fibrinopeptide Bβ15-42 and D-dimer to that of fibrinopeptide A expressed as multiples of the control ratio (1.0) were compared before and 1, 2, 3, and 4 weeks (±2 days) after starting anticoagulant therapy (Figure 5). For both ratios, the mean values were <1.0 before and >1.0 after anticoagulation.

Discussion

Fibrinopeptide A, fibrinopeptide Bβ15-42, and D-dimer have been widely used to assess thrombin activity and fibrinolytic activity in vivo in patients with a variety of vascular diseases.14,16–20 High levels have been demonstrated in patients with mitral stenosis and an intracardiac thrombus and are considered to reflect a hypercoagulable state or a consumption coagulopathy within the affected cardiac chamber.20,21

In our study, the plasma levels of these substances were significantly higher in patients with intracardiac thrombus before anticoagulation than in the controls. This was considered to reflect a local consumption coagulopathy within the cardiac chambers containing thrombi. High plasma levels of fibrinopeptide A may reflect a hypercoagulable state that could contribute to intracardiac thrombus formation, while high plasma levels of fibrinopeptide Bβ15-42 and D-dimer suggest increased fibrinolytic activity. The ratios of the plasma

![Figure 4](image1)

**Figure 4.** Graph of changes in plasma level of D-dimer in nine patients with intracardiac thrombi receiving anticoagulant therapy. Shaded area, normal range (control mean±2 SD).

![Figure 5](image2)

**Figure 5.** Bar graph of mean ratio of concentrations of fibrinopeptide Bβ15-42 (filled bars) and D-dimer (open bars) to that of fibrinopeptide A, expressed as multiples of control ratio before and 1, 2, 3, and 4 weeks after commencing anticoagulant therapy (AC). Dashed line, control ratio.
levels of fibrinopeptide Bβ15-42 and D-dimer to that of fibrinopeptide A before starting anticoagulant therapy were <1.0 (Figure 5). This suggests that thrombin activity exceeded fibrinolytic activity, which is consistent with the results of Feinberg et al., who concluded from data on plasma levels of fibrinopeptides A, Bβ1-42, and Bβ15-42 and D-dimer that fibrin formation exceeded endogenous fibrinolysis during the acute phase of ischemic stroke, including cardiogenic brain embolism. Unfortunately, these authors did not mention intracardiac thrombus, but it is thought to be one cause of changes in plasma levels of these substances in acute cardioembolic stroke.

It has been reported that the plasma level of fibrinopeptide A decreases following anticoagulation and could be an indicator of anticoagulant therapy. We considered fibrin formation to be suppressed by anticoagulation in our patients because the plasma level of fibrinopeptide A was usually within the normal range during the first 10 days of anticoagulant therapy. Plasma levels of fibrinopeptide Bβ15-42 and D-dimer tended to decrease but in most patients did not reach the normal range. Ratios of the plasma levels of fibrinopeptide Bβ15-42 and D-dimer to that of fibrinopeptide A increased following anticoagulation, indicating that fibrinolytic activity greatly exceeded fibrin formation. This was quite different from the findings in patients with acute ischemic stroke who did not receive anticoagulants.

During anticoagulation, all intracardiac thrombi decreased in size or disappeared completely. Thus, the regression of intracardiac thrombi by anticoagulation appears to be due to a relative predominance of fibrinolytic activity over thrombin activity. Mobile or small thrombi resolved faster than nonmobile or large ones. It has been reported that mobile thrombi are fresh, and thus, the period required for regression of a thrombus is considered to depend on its age and/or size.

We conclude that the regression of intracardiac thrombi after anticoagulation may result from the relative predominance of plasma fibrinolytic activity over thrombin activity.

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References


Key Words • anticoagulants • echocardiography • fibrinolysis • thrombin
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