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)
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>
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</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>4t</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>4t</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 Bjork-Shiley valves) and one with aortic valve replacement (Hancock valve).
‡One with calcification of aortic valve.

peptide A, fibrinopeptide Bβ15-42, and D-dimer. Coagulation studies were performed before starting anticoagulant therapy and then twice a week until day 28 or the day when the intracardiac thrombus was no longer present if earlier. Prothrombin time was measured by Quick’s one-stage method using Thromborel S (Behringwerke AG, Marburg, F.R.G.) and expressed as the international normalized ratio.13 The plasma level of fibrinopeptide A was measured by enzyme immunooassay (Asserachrom FPA, Diagnostica Stago, Franconville, France), that of fibrinopeptide B/315-42 by radioimmunooassay (fibrinopeptide Bβ15-42 radioimmunoassay, IMCO Corp., Stockholm, Sweden),14 and that of D-dimer by enzyme immunooassay (Dimertest EIA, Agen Biomedical Ltd., Brisbane, Australia).15 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.

Results

All 82 patients had heart disease that was considered a source of emboli (Table 1). All 27 patients with rheumatic heart disease had mitral stenosis on echocardiography.

Intracardiac thrombus was detected in 15 patients (Table 2); anticoagulant therapy was started in nine (three men and six women, aged 38–77 [mean 55] years). Seven of the nine had suffered cerebral embolism ≤14 days before detection of the thrombus, none of the nine had infective endocarditis or hypertension, and in all nine the cerebral infarct was localized to regions supplied by the middle or posterior cerebral arteries (data not shown) according to computed tomography (CT) performed before commencing anticoagulation. Hemorrhagic infarction was not demonstrated on any CT scan. Six of the nine patients receiving anticoagulant therapy had rheu-

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<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Time (day)</th>
<th>Heart disease</th>
<th>Site</th>
<th>Size (cm²)</th>
<th>Mobility</th>
<th>Anticoagulant therapy</th>
<th>Period (day)</th>
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<tbody>
<tr>
<td>1/38/F</td>
<td>7</td>
<td>RHD + AF</td>
<td>APP</td>
<td>1.2</td>
<td>+</td>
<td>+</td>
<td>14</td>
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<td>APP</td>
<td>1.3</td>
<td>+</td>
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<td>74</td>
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<td>APP</td>
<td>2.5</td>
<td>+</td>
<td>+</td>
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<td>APP</td>
<td>2.0</td>
<td>–</td>
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<td>APP</td>
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<td>+</td>
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<td>APP</td>
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<tr>
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<td>1</td>
<td>MI</td>
<td>LV</td>
<td>3.4</td>
<td>–</td>
<td>+</td>
<td>56</td>
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<tr>
<td>8/69/M</td>
<td>10</td>
<td>MI</td>
<td>LV</td>
<td>8.4</td>
<td>+</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td>9/77/F</td>
<td>2</td>
<td>LAF</td>
<td>LAP</td>
<td>15.4</td>
<td>–</td>
<td>+</td>
<td>28*</td>
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<td>APP</td>
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<td>...</td>
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<tr>
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<td>1</td>
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<td>LV</td>
<td>3.2</td>
<td>–</td>
<td>–</td>
<td>...</td>
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<tr>
<td>12/71/F</td>
<td>2</td>
<td>HCM + AF, HCM calcification</td>
<td>AOV</td>
<td>1.2</td>
<td>+</td>
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<td>APP</td>
<td>1.8</td>
<td>+</td>
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<td>4</td>
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<td>+</td>
<td>–</td>
<td>...</td>
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<tr>
<td>15/44/M</td>
<td>14</td>
<td>RHD + AF</td>
<td>APP</td>
<td>2.2</td>
<td>+</td>
<td>–</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; F, female; 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.
Before 14 (day)

**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.

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 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.** 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 non-mobile 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. 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. 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
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, Bβ15-42, and Bβ15-42 and D-dimer that fibrin formation exceeded endogenous fibrinolysis during the acute phase of ischemic stroke, including cardioembolic 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 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 different from the findings in patients with acute ischemic stroke who did not receive anticoagulants.

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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