Embolic Attack in Patients With Atrial Fibrillation and Atrial Thrombus Depends on the Character of the Thrombus

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It is very important to prevent embolisms from left atrial thrombi (LAT). The present study was a trial for the management of patients with AT using 122 patients with atrial fibrillation and LAT who were followed for 1 year after transesophageal echocardiography. LAT were classified by their shape and mobility into the mobile ball type (MB, n=28), fixed ball type (FB, n=32) and mountain type (MO, n=42). The patients were given warfarin (INR: 1.5–2.0, n=43), aspirin 81 mg (n=74) and/or ticlopidine 200 mg/day (n=31). The embolic rate (ER) in the MB group was significantly higher than in the other groups [ie, MB 39.3% vs FB 15.6% (p<0.05), vs MO 2.4% (p<0.05)]. The ER in the FB group was significantly higher than in the MO group (p<0.05). Therapy with a combination of ticlopidine and aspirin reduced the ER in the patients with ball thrombi. The ER of the ball thrombus type group, especially the MB group, was very high in spite of therapy with anti-coagulants and/or anti-platelet agents, and such patients should be treated by early surgical intervention. However, the combination of ticlopidine and aspirin may be useful for preventing embolism. (Circ J 2003; 67: 203–208)

Key Words: Echocardiography; Embolism; Left atrial appendage; Thrombus

The presence of a thrombus of the left atrial appendage (LAA) together with LAA dysfunction on transesophageal echocardiography (TEE) are independent predictors of thromboembolism in patients with atrial fibrillation (AF)†. Dense spontaneous echocardiographic contrast in the left atrium (LA) or LAA is strongly associated with previously reported clinical predictors of stroke, linking them to thromboembolism through atrial stasis. Thus, these TEE findings are very useful, irrespective of the size of the thrombus, for predicting thromboembolism in patients with AF. We reported previously that a mobile ball type thrombus of the LAA in patients with AF is an important risk factor for cerebral or arterial embolism; but as we could not investigate treatment in that study, further study was needed to determine how patients with a LA thrombus (LAT) should be managed. Here we present the results of a trial for the management of patients with AF and LAT detected by TEE.

Methods

Subjects
Between January 1998 and December 2000, we recommended TEE examination for patients with paroxysmal or chronic AF who had a past history of clinical embolism, the complication of rheumatic heart disease or a LA diameter corrected for body surface area of more than 2.5 cm²/m², which had been obtained by M-mode echocardiography, because such patients are considered to be at high risk for embolism.†–6 Transthoracic echocardiography was performed as a screening procedure on all patients and 971 agreed to have the TEE examination. LAT were detected in 102 (10.5%) patients (67 men, 35 women; mean age, 68±8.9 years) who were enrolled in the present follow-up study with respect to embolic attack.

TEE Procedure
TEE was performed in the left lateral decubitus position using an Aloka 870 imaging system (Aloka Co, Tokyo, Japan) interfaced with a biplanar transesophageal 5-MHz transducer. The pharynx was anesthetized with a lidocaine spray and there were no complications from this procedure. Echocardiography images were recorded on videotape with an S-VHS recorder (model AG-7350, Panasonic).

Analysis of Echocardiographic Data
Two independent observers in each hospital who did not know the patients’ histories determined the shape, site, mobility, number and maximum dimensions of the LAT. A third observer established consensus in cases of disagreement. The maximum dimension in each case was deter-

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mined as the mean of the data from 2 observers.

**Classification of the LAT**  The shapes and mobility of LAT were classified as described in our previous paper:3 (1) mobile ball type (MB: the thrombus is shaped like a ball and is mobile with the heartbeat); (2) fixed ball type (FB: the thrombus is shaped like a ball, but is not mobile with the heartbeat); and (3) mountain type (MO: the thrombus is shaped like a mountain that has a broad base and is not mobile with the heartbeat) (Fig 1). Sometimes the MO type is difficult to distinguish. We only regarded a thrombus as present if a change in size, site or shape was observed when TEE was performed again within 2 months. If there was no morphological change, the patient was excluded from the study. With respect to location, the sites of the LAT were also classified as described previously:3 the interior, middle and entrance, as well as the exterior of the LAA.

The maximum diameter was used to specify the size of a ball-type thrombi, and the maximum length of the bottom or the height was used for the MO thrombi. If a patient had multiple thrombi, the largest thrombus was regarded as the size of the thrombi.

**Follow-up Study**

The patients with left atrial thrombi were followed for 1 year after the TEE while being treated with warfarin potassium (adjusted to obtain international normalized ratios of 1.5–2.0, n=43), aspirin 81 mg (n=74) and/or ticlopidine 200 mg/day (n=31); one or any combination of these drugs was prescribed to each patient, depending on the decision of each doctor.

We determined how the shape, site, mobility, number and maximum dimensions of the left atrial thrombi were related to embolism during the study period. We also investigated the relationships between the embolic rate and various factors, such as age, sex and smoking, and complications.

**Table 1 Clinical Characteristics and Embolic Attack**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No embolism (n=85)</th>
<th>Embolism (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68.8±9.8</td>
<td>66.1±8.9</td>
<td>NS</td>
</tr>
<tr>
<td>HT</td>
<td>58 (68.2%)</td>
<td>9 (52.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>37 (43.5%)</td>
<td>7 (41.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (11.8%)</td>
<td>4 (23.5%)</td>
<td>0.028</td>
</tr>
<tr>
<td>HL</td>
<td>21 (24.7%)</td>
<td>3 (17.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>20 (23.5%)</td>
<td>5 (29.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>CHF</td>
<td>15 (17.6%)</td>
<td>11 (64.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous MI</td>
<td>6 (7.1%)</td>
<td>1 (5.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous embolism</td>
<td>42 (49.4%)</td>
<td>11 (64.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>17 (20%)</td>
<td>9 (52.9%)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Data are expressed as the number of patients and their percentages except for age.

CHF, congestive heart failure; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; MI, myocardial infarction; Rheumatic disease, rheumatic heart disease.

**Table 2 Results of Transesophageal Echocardiography**

<table>
<thead>
<tr>
<th>Thrombus characteristics</th>
<th>No embolism (n=85)</th>
<th>Embolism (n=17)</th>
<th>Rate of embolism (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape and mobility*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobile ball</td>
<td>17</td>
<td>11</td>
<td>39.3†</td>
</tr>
<tr>
<td>Fixed ball</td>
<td>27</td>
<td>5</td>
<td>15.6‡</td>
</tr>
<tr>
<td>Mountain</td>
<td>41</td>
<td>1</td>
<td>2.4</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside</td>
<td>9</td>
<td>10</td>
<td>52.6§</td>
</tr>
<tr>
<td>Entrance</td>
<td>41</td>
<td>6</td>
<td>12.8</td>
</tr>
<tr>
<td>Middle</td>
<td>21</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Interior</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum size (mm)</td>
<td>14.5±7.2</td>
<td>14.8±10.3</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>1.2±0.53</td>
<td>1.3±0.59</td>
<td></td>
</tr>
</tbody>
</table>

*The shape and mobility of the thrombus was a risk factor for embolic attack (Cox’s proportional-Hazards regression model, p=0.046).
†The rate of embolism for the mobile ball type was significantly higher than that for the other types (mobile ball vs fixed ball p<0.05, vs mountain p<0.05).
‡The rate of embolism for the fixed ball type was significantly higher than that for the mountain type (p<0.05).
§The rate of embolism did not influence embolic rate.

The rate of embolism for the outside thrombi was significantly higher than that for other sites of atrial thrombi (chi-square test, p<0.01).
such as hypertension, hyperlipidemia, diabetes mellitus, old myocardial infarction, previous embolism, congestive heart failure and rheumatic heart disease. We also tried to clarify how the treatment affected the rate of embolic attack. A cerebral or arterial embolism was regarded as an embolic attack in this study. The diagnosis of brain embolism was made as described previously. Follow-up information was obtained by careful review of hospital records and direct contact with the patients or their primary physicians, including telephone interviews.

This study was approved by each hospital's review committee and the subjects gave informed consent.

Statistical Analysis

The values are expressed as means ± SD. The relation between embolic attack and clinical characteristics was analyzed by Cox’s proportional-Hazards regression model. The results obtained from TEE were analyzed by Cox’s proportional-Hazards regression model followed by Kaplan-Meier survival curve and Mantel-Cox log-rank test. The embolic rates of the sites of atrial thrombi were further analyzed by chi-square test. The relationship between the clinical characteristics and medications was analyzed by chi-square test. Comparisons between the efficacy of medications for the 3 types of thrombi were analyzed by chi-square test. The mean period until embolic attack after the TEE examination in each type of atrial thrombi was compared by unpaired Student’s t-test. A p value less than 0.05 was considered significant. All analyses were performed using Stat View software (Abacus Concepts, Inc, Calabasus, CA, USA).

Results

Clinical Characteristics and Embolic Attacks

Within 1 year after the TEE, 17 of 102 patients had embolic attacks (Table 1). Age, sex, hypertension, hyperlipidemia, diabetes mellitus, previous myocardial infarction or previous embolism did not influence the embolic rate, but smoking, congestive heart failure and rheumatic heart disease were risk factors.

TEE Results and Embolic Attacks

The TEE results are summarized in Table 2. The numbers of thrombi classified by shape and mobility were

28 MB, 32 FB and 42 MO. The numbers of thrombi at each site were 14 interior, 22 middle and 47 in the entrance of the LAA, and 19 external to the atrial appendage. There were no significant differences in the medications between the 3 types of thrombi. *There was no significant difference in the efficacy of each medication for preventing embolic attacks in the patients with mobile ball thrombi. However, the combination of ticlopidine and aspirin tended to reduce the embolic rate.

†There was no significant difference in the efficacy of each medication for preventing embolic attacks in the patients with fixed ball thrombi.

‡The combination of ticlopidine and aspirin reduced the embolic rate more than either aspirin or warfarin alone (p<0.05, p<0.05, respectively).

ASP, aspirin; TIC, ticlopidine; WAR, warfarin; Embolism (+), accesses of embolic attacks.

Table 3 Thrombus Morphology, Incidence of Embolism and Medications

<table>
<thead>
<tr>
<th>Thrombus type</th>
<th>ASP</th>
<th>TIC</th>
<th>WAR</th>
<th>ASP+TIC</th>
<th>ASP+WAR</th>
<th>TIC+WAR</th>
<th>ASP+TIC+WAR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile ball*</td>
<td>11</td>
<td>0</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Embolism (+)</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Embolism (−)</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Fixed ball†</td>
<td>8</td>
<td>1</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Embolism (+)</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Embolism (−)</td>
<td>8</td>
<td>1</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Mountain</td>
<td>11</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Mobile or fixed ball thrombi</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Embolism (+)</td>
<td>13</td>
<td>1</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td></td>
<td>44</td>
</tr>
</tbody>
</table>

Fig 2. Embolic event-free survival curves for all the patients. Kaplan-Meier survival curve and Mantel-Cox log-rank test showed that the rate of embolism for the mobile ball-type thrombus is significantly higher than that for the other types (mobile ball 39.3% vs fixed ball 15.6%, p<0.05, and vs mountain 2.4%, p<0.05; and fixed ball vs mountain, p<0.05).

The site of the atrial thrombus was not a risk factor for embolic attack according to Cox’s proportional-Hazards regression model analysis, probably because of the small number of patients in the study. However, it should be noted that the embolic rate of thrombi originating outside the LAA was higher than that for the other sites of atrial thrombi (p<0.01, chi-square test). The size or number of left atrial thrombi did not influence the embolic rate after the TEE examination (Table 2). The mean period until embolic attack after the TEE examination was 67±120.7 days for the MB, 235±139.1 days for the FB and 30 days for the MO (MB vs FB, p<0.05). It should be noted that 8 of 11 patients with MB thrombi had embolic attacks within only 3 days after the TEE examination.
Clinical Characteristics and Medications

Table 4 shows the relationship between clinical characteristics and medications. Of the patients with previous embolism, the number being treated with aspirin alone was significantly lower than those treated with warfarin alone, aspirin plus ticlopidine or aspirin plus warfarin. The age of the patients treated with aspirin was significantly lower than those treated with aspirin plus warfarin.

Medication and Embolic Attack

Medication as a factor related to embolic attack was analyzed by Cox’s proportional-Hazards regression model analysis and ticlopidine was found to be favorable for preventing embolic attack. The embolic rate in the group treated with regimens including ticlopidine was significantly less than in those group who were not prescribed ticlopidine (3.2% vs 22.5%, p<0.05).

Comparisons of the efficacy of the medications for the 3 types of thrombi were analyzed by chi-square test and no significant difference for preventing embolic attacks was found in the patients with MB thrombi, although the combination of ticlopidine and aspirin tended to reduce the embolic rate in those patients (Table 3). There was also no significant difference in the efficacy of the medications for preventing embolic attacks in the patients with FB thrombi (Table 3), although the combination of ticlopidine plus aspirin tended to be beneficial. Accordingly, the combination of ticlopidine and aspirin was effective in protecting against embolic attack in the combined group of patients with both types of ball thrombi (ie, ASP vs TIC and ASP: p<0.05; WAR vs TIC and ASP: p=0.05 (Table 3)). The efficacy of the medications for the patients with MO thrombi could not be examined because the embolic rates were very low (Table 2).

Discussion

Smoking, rheumatic heart disease and a past history of congestive heart failure were found to be risk factors for embolic attack, which, with the exception of smoking, has been reported previously. Inhalation of cigarette smoke exerts many effects on clotting factors, platelet function and other hematologic parameters that may play a role in atherosclerosis and public educate should alert people that smoking may be a risk factor for ischemic stroke, including embolic attack.

As for the relationship between embolic rate and thrombus type, the rate with the MB thrombi was significantly higher than with the other types, and the rate with the FB was higher than with the MO, which indicates that the MB is the thrombus shape with the highest risk for embolism. The mean period until embolic attack after the TEE examination in the patients with MB thrombi was significantly shorter than in those with the FB; 8 of 11 patients with MB thrombi had embolic attacks within 3 days of the TEE examination, which suggests that patients with ball thrombi, especially the MB, should be treated as soon as possible. It also should be noted that the embolic rate for thrombi external to the LA was significantly higher than for atrial thrombi originating from other sites.

There are many reports showing the efficacy of warfarin for preventing embolic attack in patients with AF but in the present study it was used in only 43 of the 102 patients. Although the reason for this relatively low rate of use is unclear, it may be related partly to the fact that the dose control of warfarin is somewhat troublesome and its efficacy is easily affected by dietary intake, including vitamin K. In the present study when patients were treated with warfarin alone for MB or FB thrombi, 7 of 19 cases had embolic attacks, whereas no attacks were observed in the 10 patients with FB thrombi who were treated with ticlopidine and aspirin, suggesting that the combination of ticlopidine and aspirin may be superior to warfarin for preventing embolic attack in AF patients with ball thrombi.

Ticlopidine was also found to be favorable for preventing embolic attack, but warfarin was not. The reason for this discrepancy about the efficacy of warfarin is not clear, but it is probable that the difference between our study and other reports may have resulted from different characteristics or numbers of patients. In previous studies patients with and without left atrial thrombi were enrolled, whereas only patients with left atrial thrombi were studied by us. Another possibility is that the international normalized ratio (INR) may be below in non-valvular AF patients.18 Low-intensity, fixed-dose warfarin (mean INR 1.3) plus aspirin was insufficient for preventing stroke in patients with non-valvular AF at high-risk for thromboembolism compared with adjusted-dose warfarin (target INR 2.0–3.0), which reduced stroke in high-risk patients. Prystowsky et al reported that for high-risk AF patients aged 75 years or younger, an INR range of 2.0–3.0 is safe and effective. However, the BAATAF study reported that
low-dose warfarin therapy (the target range for the pro-
thrombin-time ratio was 1.2–1.5-fold the control value, 
corresponding to an INR of 1.5–2.7 for the types of throm-
boplastin most commonly used) was highly effective for 
preventing stroke in patients with non-rheumatic AF.13 In 
Japan, a retrospective study evaluating the efficacy of 
warfarin for the secondary prevention of cardioembolic 
stroke caused by non-valvular AF found that warfarin ther-
apy with an INR less than 2.4 was desirable for avoiding 
hemorrhagic complications.14 Recently, Kimura reported 
that low-intensity warfarin therapy (INR: 1.5–2.0) was effi-
cacious in treating left atrial thrombus formation in patients 
with nonvalvular AF.15 Thus, the INR of 1.5–2.0 that we 
used in the present study does not seem to be extremely 
low or unsuitable for many AF patients.

There was a bias in the use of medications in the present 
study. The number of patients with previous embolism 
treated with aspirin was significantly lower than those 
treated with warfarin, aspirin plus ticlopidine or aspirin 
plus warfarin. The age of the patients treated with aspirin 
was significantly lower than those treated with aspirin plus 
warfarin. However, we presume that these factors may not 
have greatly affected the efficacy of the medications, 
because previous embolism or age were not risk factors 
for new embolism in this study. Nevertheless, it should 
be noted that the efficacy of warfarin for preventing embolic 
attack may be minimal in AF patients with left atrial throm-
bi, although it is still premature to say conclusively that the 
combination of ticlopidine and aspirin definitely protects 
against embolic attack in patient with a ball thrombus 
because of the small number of patients used in the present 
study and the non-randomized study design. It does seem 
reasonable that surgical removal of the thrombus and main-
tenance of the patients on anticoagulants reduces the likely-
hood of recurrent thrombus.16 We have had experience with 
2 patients, not included in the present study, who were free 
from embolic attack after surgical treatment, as expected. 
However the recurrence of left atrial ball thrombus has 
been reported after surgical thrombectomy followed by 
incomplete warfarin therapy.19

A difficult management problem has been posed for 
those patients undergoing open heart surgery who have had 
recent cardiogenic embolic stroke or central nervous sys-
tem dysfunction. There is always the risk that cardiopulmo-
nary bypass and heparinization may exacerbate the neuro-
logic injury. There is no clear data indicating what is the 
safest interval of time from the onset of neurologic symp-
toms to the time of surgery. Zisbrod reported the results of 
open heart surgery in patients with recent (2–28 days, mean 
12.7±7.9 days) cardiogenic embolic stroke and central nervous 
system dysfunction and it would appear that open 
heart surgery can be performed safely in patients with 
recent neurologic injury.20 Ting et al analyzed retrospec-
tively 106 consecutive patients who underwent valve re-
placement for left-sided infective endocarditis. The interval 
of time between valve replacement and the onset of neuro-
logical deficits in symptomatic patients or performance of a 
computed tomography scan in asymptomatic patients 
ranged from 1 to 49 days with a mean interval of 11.4 days. 
They reported that, in the absence of a hemorrhagic infarct, 
valve replacement can be performed with minimal risk of a 
perioperative stroke.21 Maruyama et al studied brain 
damage after open heart surgery in patients with acute 
cardiogenic stroke. The mean interval from the onset of 
cebral embolism to surgery was 5.3 (range 1–16) days.

They suggested that infective endocarditis and a large 
infarct appear to be possible aggravating factors when patients 
with recent cerebral embolism undergo open heart 
surgery.22 These results indicate that, in the absence of a 
hemorrhagic infarct and a large infarct, surgical thrombec-
tomy can be performed safely in patients with recent cere-
bral embolism. Further study is necessary to determine if 
the combination of ticlopidine and aspirin is beneficial, 
compared with surgical treatment, in patients with ball 
thrombi.

**Conclusion**

The embolic rate in the ball-type thrombus group, espe-
cially the MB group, was very high in spite of the adminis-
tration of anti-coagulants and/or anti-platelet agents, with 
the exception of those who received the combination of 
ticlopidine and aspirin. Therefore, it is recommended that 
these patients be treated by early surgical intervention, or at 
least by the combination of ticlopidine and aspirin to 
prevent embolism.

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