Blood Stasis Secondary to Heart Failure Forms Warfarin-Resistant Left Atrial Thrombus

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SUMMARY

Anticoagulants such as warfarin are recommended for patients with atrial fibrillation (AF) to decrease stroke risk associated with thrombus formation in the left atrium (LA). In a subgroup of patients, however, warfarin is unable to prevent LA thrombus formation at therapeutic doses. This study characterized the clinical and echocardiographic features of patients having warfarin-resistant LA thrombus.

Of the 1364 nonvalvular AF patients examined by transesophageal echocardiography, 431 received warfarin. A total of 10 patients (2.3% of warfarin-treated patients) exhibited LA thrombus formation even during warfarin treatment at a dose and duration sufficient for increasing the prothrombin time–international normalized ratio (PT–INR) to the therapeutic range for ≥ 30 days. Categorical regression analysis revealed that decreased LA appendage (LAA) flow velocity, greater LA spontaneous echocardiographic contrast (LASEC), and lower left ventricular ejection fraction (LVEF) significantly contributed to residual LA thrombus (\(P < 0.05\) for all). Receiver operating characteristic (ROC) curve analysis indicated that higher right ventricular systolic pressure, which suggests LA pressure (area under curve, 0.85), LV mass index (0.81), and LA dimension (0.68), as well as lower LAA flow velocity (0.92) and LVEF (0.91) predicted warfarin-resistant LA thrombus formation (all \(P < 0.05\)).

These results suggest that blood stasis secondary to heart failure contributes to the formation of warfarin-resistant LA thrombus. We propose that therapies to increase LVEF should be administered together with warfarin for AF patients with heart failure to decrease stroke risk. (Int Heart J 2014; 55: 506-511)

Key words: Atrial fibrillation, Anticoagulants

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is associated with an increased risk of stroke and other thromboembolic events.\(^1,2\) Approximately 1 in 5 strokes is caused by AF, and stroke risk is 4- to 5-fold greater in patients with AF than in the general population.\(^2,3\) The CHADS2 score, a stroke risk index used in the updated National Registry of Atrial Fibrillation (American College of Cardiology/American Heart Association Task Force),\(^4\) and the CHA2DS2-V ASc score recently presented by the European Society of Cardiology,\(^5\) are used to quantify stroke risk in nonvalvular AF (NVAF) and, thus, the need for antithrombotic therapy. Both guidelines recommend antithrombotic therapy even for low-risk patients with a CHA2DS2-VASc score of 1.

Transesophageal echocardiography (TEE) yields high-resolution dynamic images of the left atrium (LA).\(^5,6\) Doppler TEE measurements of blood flow velocity in the LA appendage (LAA) and the presence of LA spontaneous echocardiographic contrast (LASEC) have been used to assess the severity of blood stasis, a risk factor for thrombus formation and stroke.\(^7,8\) Previous reports have shown that dense LASEC, decreased LAA flow velocity, and complex aortic plaques on TEE are independent risk factors for subsequent thromboembolic events.\(^9,10\) In fact, Takashima, et al reported that these TEE findings were stronger predictors of ischemic stroke than the CHADS2 score in patients with NVAF.\(^12\)

Antithrombotic therapy is often prescribed to NVAF patients to decrease stroke risk, and these antithrombotic regimens are usually sufficient to resolve or prevent LA thrombus formation. However, a small subpopulation of patients is resistant to antithrombotic drugs, necessitating additional treatments to prevent stroke. The clinical and echocardiographic features of these patients remain to be determined. Moreover, the morphological and hemodynamic characteristics of LA and other cardiac chambers in such patients have rarely been examined because such thorough analysis requires relatively invasive, low-throughput TEE. The present study aimed to describe the morphological and hemodynamic characteristics of the heart in AF patients with warfarin-resistant LA thrombus.

METHODS

Study subjects: This study retrospectively examined the transthoracic echocardiographic (TTE) and TEE findings of 1364 consecutive patients with NVAF treated between January 2001...
and April 2009 at our institution. The indication for TEE was based on either an evaluation of potential thromboembolic risk or identification of stroke secondary to confirmed cardiogenic embolism. Patients were classified into 4 groups according to the presence of an LA thrombus and use of antithrombotic therapy at the time of TEE examination: group 1, patients having an LA thrombus but not treated with warfarin; group 2, patients having an LA thrombus even under the therapeutic dose of warfarin; group 3, patients with no LA thrombus and no warfarin treatment; group 4, patients without LA thrombus and treated with warfarin. In groups 2 and 4, warfarin was administered for > 1 month and PT–INR checked at the time of TEE. Most group 1 patients were treated with antplatelet drugs until the early 2000s according to previous Japanese guidelines. Patients with mitral stenosis or mechanical heart valves were excluded. The study was approved by the institutional ethics committee of the Cardiovascular Institute.

**Echocardiography:** TTE was performed with a 3-MHz phased-array transducer and TEE with a 5-MHz multipline transducer (SSD-6500 and ProSound e10, Hitachi Aloka Medical, Ltd. Tokyo). The LA dimension (LAD) and left ventricular ejection fraction (LVEF) were determined from averaged TTE B-mode images acquired over 5 cardiac cycles. Right ventricular systolic pressure (RVSP) was estimated from peak tricuspid regurgitation jet velocities according to the following equation: RVSP = 4(V) + right atrial pressure, where V is the peak velocity (in m/s) of tricuspid regurgitation jet. In TEE analysis, each patient was studied in the fasting state without premedication except for topical anesthesia of the hypopharynx with lidocaine spray. LASEC was diagnosed by the presence of characteristic swirling, smoke-like echoes within LA or LAA distinct from the white-noise artifact. The severity of LASEC was defined as follows: 0 = none (absence of echogenicity); 1+ = mild (transient spontaneous echocardiographic contrast with optimal gain setting); 2+ = moderate (dense swirling pattern lasting up to 3 cardiac cycles); and 3+ = severe (intense echodensity and very slow swirling patterns in LA lasting > 3 cardiac cycles). The severity of LASEC was judged by 2 independent observers. LAA flow velocity profiles were obtained by pulse-wave Doppler echocardiographic examination at the orifice of the appendage. Peak outflow velocity signals within each R–R interval were averaged over a minimum of 5 cardiac cycles. Aortic atherosclerosis was defined as the presence of complex aortic plaques with any combination of mobile, pedunculated, and ulcerated morphologies, or a plaque thickness of ≥ 4 mm.

**Statistical analysis:** The data are presented as medians. Each parameter from the 4 groups was compared using the Kruskal–Wallis test followed by the Mann–Whitney U test for pair-wise comparisons. Categorical regression analysis was applied to determine echocardiographic factors to predict thrombus formation under warfarin therapy. A P value of < 0.05 was defined as statistically significant. Factors predictive of an LA thrombus (warfarin-resistant thrombus) in group 2 were also evaluated by receiver operating characteristic curves. All statistical analyses were performed using SPSS version 17.0 software (SPSS, Chicago, IL, USA).

**RESULTS**

**Clinical characteristics of patients:** Nonvalvular AF patients were divided into 4 groups according to the presence of LA thrombus development and warfarin administration (group 1: LA thrombus, no warfarin; group 2: LA thrombus with warfarin; group 3, no LA thrombus, no warfarin; group 4, no LA thrombus with warfarin). The clinical characteristics for each group are summarized in Table I. Of the 1364 NVAF patients enrolled, 431 (31.6%) were treated with warfarin, whereas the remaining 933 patients had never received antithrombotic therapy. Fifty-eight patients (4.3% of all enrolled NVAF patients) had an LA thrombus, and 10 of these patients were treated with the therapeutic dose of warfarin (0.7% of all patients and 2.3% of warfarin-treated patients).

For NVAF patients not treated with warfarin (groups 1 and 3), an LA thrombus (group 1) was more likely in cases with longer AF duration, heart failure, diabetes mellitus, prior stroke or transient ischemic attack (TIA), or higher CHADS2 score (Table I). In patients treated with warfarin for ≥ 1 month (groups 2 and 4), formation of an LA thrombus (group 2) was significantly associated with higher New York Heart Association (NYHA) classes and CHADS2 scores (Table I). Importantly, PT-INRs in the LA thrombus with warfarin group (group 2) were not significantly lower than those in the no LA

### Table I. Clinical Characteristics of Non-Valvular AF Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Thrombus (+) Warfarin (-)</th>
<th>Thrombus (+) Warfarin (+)</th>
<th>Thrombus (-) Warfarin (-)</th>
<th>Thrombus (-) Warfarin (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>n = 48</td>
<td>n = 10</td>
<td>n = 85</td>
<td>n = 421</td>
</tr>
<tr>
<td>Age</td>
<td>69.0 [60.3-78.0]</td>
<td>65.5 [61.3-71.3]</td>
<td>67.0 [59.0-74.0]</td>
<td>64.0 [56.0-72.0]</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>57.1</td>
<td>60</td>
<td>47.8</td>
<td>42.5</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35.7</td>
<td>30</td>
<td>13.0</td>
<td>17.9</td>
</tr>
<tr>
<td>Prior stroke or TIA (%)</td>
<td>26.2</td>
<td>20</td>
<td>10.9</td>
<td>10.3</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>2.0 [1.0-3.0]</td>
<td>2.0 [1.0-3.3]</td>
<td>1.0 [0.0-2.0]</td>
<td>1.0 [0.0-1.8]</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>38.1</td>
<td>40</td>
<td>30.4</td>
<td>23.3</td>
</tr>
</tbody>
</table>

*P < 0.015 group 1 versus group 3; *P < 0.05 group 2 versus group 4; Each parameter in 4 groups was compared with Kruskal–Wallis test. When this test indicated a significant difference, groups 1 and 3, and groups 2 and 4 were compared each other with the Mann–Whitney U test. AF indicates atrial fibrillation; BMI, body mass index; PT-INR, prothrombin time–international normalized ratio; and TIA, transient ischemic attack.
thrombus with warfarin group (group 4). Likewise, categorical regression analysis revealed that only NYHA class but not the titer of PT-INR independently contributed to form LA thrombus under warfarin administration (not shown).

**Echocardiographic characteristics:** Atrial morphology and hemodynamics were measured by TEE and TTE. LAA flow velocity was significantly lower and LASEC score was significantly higher in patients with LA thrombus formation (groups 1 and 2) than in those exhibiting no LA thrombus formation (groups 3 and 4) (Figure 1A and 1B). Interventricular septum thickness, posterior wall thickness, and LV diastolic diameter were not significantly different in these 4 groups, while LV systolic diameter was larger in patients with LA thrombus under anticoagulation therapy (group 2) than that in the other 3 groups \( (P < 0.05) \). Even under warfarin treatment, patients with an LA thrombus (group 2) had lower LAA flow velocity (Figure 1A) and LVEF (Figure 1C), as well as higher LASEC grade (Figure 1B), RVSP (Figure 1D), LV mass index (LVMI) (Figure 1E), and LAD (Figure 1F) than those without an LA thrombus (group 2 versus group 4; \( P < 0.05 \) by Mann–Whitney \( U \) test). Categorical regression analyses revealed that LASEC grade \( (P = 0.002) \), LAA flow velocity \( (P < 0.001) \), and LVEF \( (P = 0.005) \) were significantly associated with thrombus formation under warfarin therapy. The thrombus-positive patients did not exhibit more severe aortic atherosclerosis (not shown).

Receiver operating characteristic (ROC) curve analysis revealed that LAA flow velocity [area under curve (AUC) = 0.92, 95% confidence interval (CI) 0.87–0.97], LVEF (0.91, 0.86–0.96), RVSP (0.85, 0.79–0.91), LVMI (0.81, 0.66–0.96), and LAD (0.68, 0.53–0.82) were associated with formation of an LA thrombus under warfarin therapy (Figure 2).

Many reports have found a strong relationship between LAA flow velocity and LA thrombus formation.\(^9,14,15\) In our study, the maximum velocity of LAA flow in patients with LA thrombus not treated with warfarin (group 1) was 39 cm/s.

**Clinical and echocardiographic characteristics of patients with LA thrombus after antithrombotic therapy:** Of the 1364 patients with NVAF, 10 showed LA thrombus despite a therapeutic dose of antithrombotic therapy.\(^16\) Table II summarizes the clinical and echocardiographic variables of these 10 patients. Warfarin was administered for at least 1 month and PT–INRs were confirmed to be within the therapeutic range (1.6–3.0) during the month before TEE examination. The median duration of AF in group 2 (36 months) was not significantly different from that in warfarin-treated patients with no LA thrombus (group 4, 27.5 months). Similarly, the frequencies of the major underlying diseases associated with AF were not significantly different between patients with LA thrombus under warfarin treatment and patients with no LA thrombus (Table II). For the prediction of LA thrombus under warfarin administration, the AUC values of CHADS2 scores and NYHA classes \( \geq 2 \) were 0.77 (95% CI 0.63–0.90) and 0.88 (0.75–1.00), respectively.

**Figure 1.** Echocardiographic parameters of 4 groups of nonvalvular atrial fibrillation patients: group 1, left atrial (LA) thrombus, no warfarin treatment; group 2, LA thrombus, warfarin; group 3, no LA thrombus, no warfarin; group 4, no LA thrombus, warfarin. Kruskal–Wallis test indicated a significant difference among the 4 groups for all echocardiographic parameters. Mann–Whitney \( U \) test indicated significant differences between groups 2 and 4 for these all parameters \( (P < 0.05) \). A: LA appendage (LAA) flow velocity. B: LA spontaneous echocardiographic contrast (LASEC). C: Left ventricular ejection fraction (LVEF). D: Right ventricular systolic pressure (RVSP). E: LV mass index (LVMI). F: LA diameter (LAD). In each box-and-whisker plot, the bottom and top of the box are first and third quartiles and the band inside the box is the median. Upper and lower ends of whisker indicate highest and lowest datum within 1.5 times of interquartile range (IR), when all data exist within this range. Data that exceed 1.5 times of IR are indicated by circles and extreme values that are more than 3 times the IR are indicated by asterisks.

**Figure 2.** Receiver operating characteristic curves associated with warfarin-resistant left atrial (LA) thrombus formation. All parameters significantly predicted LA thrombus \( (P < 0.05) \). LAA indicates LA appendage; LAD, LA diameter; LVEF, left ventricular (LV) ejection fraction; LVMI, LV mass index; and RVSP, right ventricular systolic pressure.
Antithrombotic therapy is recommended to prevent cerebral embolism in patients judged by the CHADS2 score. However, a minority of patients exhibit residual LA thrombus despite appropriate antithrombotic therapy. A meta-analysis of 6 randomized clinical trials (SPORTIF III and V, BAFTA, RELY, ROCKET-AF, and ARISTOTLE) concluded that older age, female gender, previous stroke/TIA, vitamin K-antagonist naïve status, renal impairment, previous aspirin use, and higher CHADS2 score were associated with a higher relative risk of stroke on oral antithrombotic therapy. Nevertheless, Sugiura, et al suggested LVEF contributed (431). Nevertheless, Sugiura, et al suggested LVEF contributed to the formation of LA thrombus under antithrombotic therapy. In our study, the duration of AF was not significantly different between warfarin-treated patients with or without an LA thrombus (Table I). Although LAD was larger in patients with an LA thrombus, ROC analysis indicated that LVEF is a better predictor of warfarin-resistant LA thrombus than LAD (AUC 0.91, 95% CI 0.86–0.96 versus AUC 0.68, 95% CI 0.53–0.82) (Figure 2).

For many decades, warfarin was the only anticoagulant approved for AF. Several newer oral anticoagulant agents (dabigatran etexilate, apixaban, rivaroxaban, and edoxaban) have demonstrated an efficacy superior or equivalent to warfarin. These new oral anti-coagulant agents do not need routine monitoring while the PT-INR has to be monitored on a regular basis to avoid putting patients at increased risk of ischemic stroke and hemorrhagic events when using warfarin. Although these new drugs may increase the number of AF patients treated with anticoagulants, our study results suggest that LA thrombus may be resistant to anticoagulants in AF patients with heart failure (low LVEF). Thus, close monitoring including TEE, rather than isolated use of the CHADS2 score, is necessary regardless of the anticoagulant employed in low-LVEF patients.

Several clinical situations do not allow for use of anticoagulants, such the perioperative period. However, there are no confirmed guidelines to determine the relative risk of LA thrombus formation in NVAF patients when the administration of warfarin is suspended. We suggest that TEE parameters can help in such prediction. Among the 933 AF patients not treated with warfarin (groups 1 and 3), the maximum velocity of LAA flow in those with an LA thrombus (group 1) was 39 cm/s. Although this data was not analyzed statistically, this finding sug-

Table II. Characteristics of Thrombus-Positive Patients Under Warfarin Treatment

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age</th>
<th>Gender</th>
<th>Duration of AF (months)</th>
<th>PT-INR</th>
<th>LAA flow velocity</th>
<th>LASEC grade</th>
<th>LVEF</th>
<th>LVMI</th>
<th>RVSP</th>
<th>LAD</th>
<th>NYHA class</th>
<th>CHADS2 score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>M</td>
<td>180</td>
<td>73</td>
<td>1.81 (1.82)</td>
<td>3</td>
<td>35</td>
<td>176</td>
<td>33</td>
<td>61</td>
<td>IV</td>
<td>2</td>
<td>Tachycardia-induced cardiomyopathy s/o</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>36</td>
<td>36</td>
<td>2.29 (1.98)</td>
<td>2</td>
<td>20</td>
<td>169</td>
<td>42</td>
<td>48</td>
<td>II</td>
<td>3</td>
<td>Old myocardial infarction</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>F</td>
<td>36</td>
<td>36</td>
<td>3.58 (2.13)</td>
<td>1</td>
<td>13</td>
<td>132</td>
<td>50</td>
<td>51</td>
<td>IV</td>
<td>5</td>
<td>Tachycardia-induced cardiomyopathy</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>2.68 (2.05)</td>
<td>3</td>
<td>18</td>
<td>113</td>
<td>34</td>
<td>41</td>
<td>I</td>
<td>1</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>1.63 (1.81)</td>
<td>2</td>
<td>14</td>
<td>131</td>
<td>42</td>
<td>44</td>
<td>III</td>
<td>2</td>
<td>Recent myocardial infarction</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>204</td>
<td>36</td>
<td>1.94 (1.86)</td>
<td>3</td>
<td>13</td>
<td>27</td>
<td>81</td>
<td>36</td>
<td>44</td>
<td>II</td>
<td>Drug-induced cardiomyopathy</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>36</td>
<td>5</td>
<td>1.66 (1.74)</td>
<td>1</td>
<td>13</td>
<td>140</td>
<td>37</td>
<td>52</td>
<td>II</td>
<td>2</td>
<td>Tachycardia-induced cardiomyopathy</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>M</td>
<td>36</td>
<td>5</td>
<td>1.90 (1.67)</td>
<td>2</td>
<td>29</td>
<td>131</td>
<td>39</td>
<td>41</td>
<td>III</td>
<td>4</td>
<td>Tachycardia-induced cardiomyopathy</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>M</td>
<td>13</td>
<td>7</td>
<td>1.79 (1.79)</td>
<td>Unmeasurable</td>
<td>3+</td>
<td>47</td>
<td>128</td>
<td>42</td>
<td>52</td>
<td>II</td>
<td>Tachycardia-induced cardiomyopathy</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>F</td>
<td>2</td>
<td>2</td>
<td>2.53 (1.60)</td>
<td>1</td>
<td>10</td>
<td>28</td>
<td>201</td>
<td>35</td>
<td>44</td>
<td>IV</td>
<td>Cardiac amyloidosis</td>
</tr>
</tbody>
</table>

PT-INR values are at the timing of TEE examination and values in brackets are at one month before TEE examination. AF indicates atrial fibrillation; LAA, left atrial appendage; LAD, left atrial diameter; LASEC, spontaneous echocardiographic contrast in the left atrium; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RVSP, right ventricular systolic pressure; and Tx, treatment.

**DISCUSSION**
gests that an LAA flow velocity < 40 cm/s may enhance the possibility of thrombus formation when antithrombotic therapy is suspended. For such patients, we propose that an alternative antithrombotic therapy using a short-acting anticoagulant like heparin is necessary to compensate for suspension of warfarin during the perioperative period.

The present study has several limitations. First, although the total number of patients was large (1364), there were still only 10 exhibiting warfarin-resistant LA thrombus formation, limiting the statistical power of the study. Second, group 2 (patients with LA thrombus under anticoagulation therapy) includes several patients with lower PT–INRs in comparison to that recommended in the Japanese guideline for pharmacotherapy of atrial fibrillation. However, in our study, PT–INRs in the LA thrombus with warfarin group was statistically the same as those in the no LA thrombus with warfarin group and categorical regression analysis indicated that PT-INR is not an independent contributor of LA thrombus under warfarin administration. In addition, Inoue on behalf of the J-RHYTHM registry investigators recently reported that in 7,406 Japanese patients with NVAF, lower PT–INR values (between 1.5 and 1.99) were as effective as PT–INR values between 2 and 3 at preventing embolic events even in patients less than 70 years of age. Therefore, we believe our study groups are not inappropriate to analyze factors for LA thrombus formation under anticoagulation therapy. Third, classification of AF was not determined because this study included patients treated from 2001 to 2009, prior to the introduction of the current classification scheme (paroxysmal AF, persistent AF, and permanent AF). Fourth, our study was retrospective. We examined only NVAF patients examined by TEE, possibly introducing a selection bias because TEE is generally reserved for patients with a potential risk of thromboembolism. Thus, many of these NVAF patients may have a comparatively high risk for developing thromboembolic events. Fifth, inflammatory reaction and prothrombotic state may produce LA thrombus. However, inflammatory changes of LA endothelium and markers of coagulation were not evaluated in this study.

In conclusion, the present study results demonstrate that the LA blood stasis resulting from heart failure leads to thrombus formation even under antithrombotic therapy. For these patients, therapy to improve LVEF may be necessary to prevent thrombus formation or to dissolve existing clots. Moreover, the disappearance of LA thrombus should be carefully confirmed by TEE.

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