Preprocedural Therapeutic International Normalized Ratio Influence on Bleeding Complications in Atrial Fibrillation Ablation With Continued Anticoagulation With Warfarin

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Background: Safety of atrial fibrillation (AF) ablation in conditions of periprocedural therapeutic international normalized ratio (INR) in combination with heparin is still uncertain, and little is known about the pre-procedural therapeutic INR influence on bleeding complications (BC) in this method.

Methods and Results: The subjects were 150 consecutive patients who underwent catheter ablation for AF with therapeutic INR. The patients were classified into 2 groups, BC (Group BC) and no BC (Group No BC), by whether they did or did not have BC, respectively. Differences in various parameters, including pre- and post-procedural prothrombin time-INR and activated partial thromboplastin time (APTT), were compared between the 2 groups. None of the patients experienced stroke or transient ischemic attack. In the 22 patients (15%) who had BC (Group BC), 3 patients had major and 19 patients had minor BC. There were no significant differences between the 2 groups in pre-procedural INR, APTT, and amount of heparin administered during the procedure. However, post-procedural INR and APTT were significantly prolonged in Group BC (2.5±0.5 vs. 2.2±0.5, P=0.016, 65±45 vs. 44±11, P<0.0001 respectively). Multivariable analysis showed that post-procedural APTT was the only independent bleeding risk factor (P=0.022).

Conclusions: AF ablation with peri-procedural therapeutic INR in combination with heparin seems to be safe. Presence or absence of BC are not related to the pre-procedural INR level, but to post-procedural APTT. (Circ J 2013; 77: 338–344)

Key Words: Ablation; Atrial fibrillation; Heparin; Warfarin

Catheter ablation aimed at curing atrial fibrillation (AF) has become increasingly common, and its efficacy is established.1–3 Although the procedure is generally effective and safe,4,5 serious complications occasionally do occur, including death.6,7 The overall peri-procedural risk of thromboembolic events has been reported to be approximately 1.6–2.2% in focal AF ablations,8–10 and as high as 7% in linear AF ablations.11 Nevertheless, it has been common practice to interrupt warfarin before AF ablation procedures and use bridging with heparin or enoxaparin instead. Several recent studies have shown that continued use of warfarin in the periprocedural period with therapeutic international normalized ratio (INR) is effective or better in preventing thromboembolic events in AF ablation procedures.12–16 The focus of these studies was incidence of thromboembolic events when warfarin was continued, compared to bridging with heparin and analogs, and did not assess whether continued warfarin resulted in an increased number of bleeding complications (BC) at the expense of fewer embolic events. We hypothesized that BC could increase with periprocedural therapeutic INR. Administration of heparin in combination with warfarin is believed to provide a stronger anticoagulant effect, but optimal dose and timing of heparin administration is unknown. Therefore, the purpose of the current study was to assess the safety of AF ablation in conditions of peri-procedural therapeutic INR in combination with heparin, and to investigate the risk factors for BC when this method was used.
Ablation Protocol

Venous access was obtained at the right groin at 4 points in each patient. After a single trans-septal puncture, 3 long sheaths (SL0, St. Jude Medical, AF Division, Minnetonka, MN, USA) were introduced into the left atrium. The 4 pulmonary veins were imaged sequentially by an injection of contrast medium using 3-dimensional CARTO mapping systems (Biosense-Webster, Inc, Diamond Bar, CA, USA) were placed in the superior and inferior PV, respectively, and the left-sided and right-sided ipsilateral PV were circumferentially ablated. Radiofrequency current applications were applied with an ablation catheter (Thermocool, Biosense-Webster, Diamond Bar, CA, USA) using 3-dimensional CARTO mapping systems (Biosense-Webster). The power settings consisted of a temperature control mode, with a target temperature of 42°C and maximum power of 30 W at the LA posterior wall and 35 W at the anterior aspect of PV.

Irrigation rate was selected from 17 or 30 ml/min to achieve the desired power delivery. When the AF continued in spite of the PVI, additional linear ablations and complex-fractionated atrial electrogram ablations were performed, aimed at termination of the AF. Cardioversion was performed in the cases that could not be converted to sinus rhythm by ablation. After conversion to sinus rhythm, the cavo-tricuspid isthmus was also ablated to create bi-directional conduction block. If frequent atrial premature contractions (APC) occurred, we also performed focal ablation to remove the APC. The superior vena cava was also isolated if it was associated with frequent APC.

Peri-Procedural Anticoagulation

Oral warfarin was not interrupted. Heparin was not administered prior to the procedure in any patient. After the transseptal puncture, a heparin bolus (5,000 units) was administered to all patients. During the procedure, the infusion dose was adjusted to keep the activated clotting time (ACT) over 300 s. The ACT was examined every 30 min, and additional heparin was infused as needed as a bolus. After the ablation, heparin infusion was suspended, and heparin anticoagulation was partially reversed with 5 to 10 mg of protamine before sheaths were removed.

Definition of BC

A major BC was defined as one or more of the following: occurrence of cardiac tamponade or hemopericardium that was symptomatic or required intervention, need for transfusion, hematoma requiring intervention, massive hemoptysis, hemothorax, or retroperitoneal bleeding. Minor BC were defined as the occurrence of hematoma or any bleeding that was asymptomatic and did not require intervention. Thromboembolic complications were defined as occurrence of ischemic stroke, transient ischemic attack, peripheral embolic events, or deep vein thrombosis.

Statistics

All data are expressed as mean ± SD, and boxplot was used in the figure. Continuous variables were compared by Student’s t-test. Categorical variables were compared by chi-squared test and Fisher’s test. A 2-tailed P-value <0.05 was defined as statistically significant. Statistical analysis was done with JMP 10.0. Multivariable analysis was performed on items that could not be converted to sinus rhythm by ablation.

Study Subjects

This was a single-center retrospective study at Gunma Prefectural Cardiovascular Center. The subjects of this study were 150 consecutive patients with pre-operative INR greater than 1.8, who underwent catheter ablation of AF at the Gunma Prefectural Cardiovascular Center from July 2009 to August 2010. The AF was paroxysmal AF in 88 patients, and non-paroxysmal AF in 62 patients. Paroxysmal AF was defined as AF that terminates spontaneously in less than 7 days, and other persistent and longstanding persistent AF was defined as non-paroxysmal AF.

The mean age of the patients was 62±10 years (range, 30–79 years). There were 119 men and 31 women. The patients were classified into 2 groups, Group BC and Group No BC, by whether they did or did not have BC in the peri-procedural period, respectively. Differences in various parameters, including pre- and post-procedural PT-INR and activated partial thromboplastin time (APTT), were compared between the 2 groups.

A total of 22 patients (15%) had BC. Stroke/transient ischemic attack did not occur in any. The most common BC was minor bleeding categorized as other (neither hematoma nor arteriovenous fistula), which necessitated additional angioopressure after the procedure. Minor bleeding occurred in 12.6% of patients in this study. BC, bleeding complication.

Table 1. Dose of Additional Heparin Infusion After the Procedure

<table>
<thead>
<tr>
<th>Pre-procedural INR</th>
<th>Heparin dose</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8≤INR&lt;2.0</td>
<td>15,000 U/day</td>
<td>47</td>
</tr>
<tr>
<td>2.0≤INR&lt;2.5</td>
<td>10,000 U/day</td>
<td>72</td>
</tr>
<tr>
<td>2.5≤INR</td>
<td>5,000 U/day</td>
<td>31</td>
</tr>
</tbody>
</table>

Additional heparin was administered after the ablation procedure for 24 h. To minimize risk of bleeding complications, heparin dose was adjusted according to the pre-procedural INR. There were 31 patients who had INR greater than 2.5.

INR, international normalized ratio.

Table 2. Total Incidence of Bleeding Complications

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major BC</td>
<td></td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Pseudo aneurysm</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Minor BC</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Other minor bleeding</td>
<td>15 (10)</td>
</tr>
<tr>
<td>Total</td>
<td>22 (15)</td>
</tr>
</tbody>
</table>

A total of 22 patients (15%) had BC. Stroke/transient ischemic attack did not occur in any. The most common BC was minor bleeding categorized as other (neither hematoma nor arteriovenous fistula), which necessitated additional angioopressure after the procedure. Minor bleeding occurred in 12.6% of patients in this study.

BC, bleeding complication.

INR, international normalized ratio.
Figure 1. Comparison of serum international normalized ratio (INR), activated partial thromboplastin time (APTT), and D-dimer level before and after ablation during the procedure. INR, APTT, and D-dimer levels were checked in all of the patients the day before and after the ablation procedure. Both INR and D-dimer levels increased significantly the day after the procedure. APTT level was not changed.

Table 3. Clinical Characteristics of Patients With and Without Peri-Procedural Bleeding Complications

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=150)</th>
<th>Group BC (n=22)</th>
<th>Group No BC (n=128)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>62±10</td>
<td>63±7</td>
<td>61±10</td>
<td>0.43</td>
</tr>
<tr>
<td>Women</td>
<td>31 (21%)</td>
<td>9 (41%)</td>
<td>22 (17%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-PAF</td>
<td>60 (40%)</td>
<td>12 (55%)</td>
<td>48 (38%)</td>
<td>0.16</td>
</tr>
<tr>
<td>AST (IU/ml)</td>
<td>24±7</td>
<td>23±4</td>
<td>25±8</td>
<td>0.27</td>
</tr>
<tr>
<td>ALT (IU/ml)</td>
<td>27±14</td>
<td>23±8</td>
<td>28±14</td>
<td>0.16</td>
</tr>
<tr>
<td>eGFR (IU/ml)</td>
<td>67±15</td>
<td>65±13</td>
<td>67±16</td>
<td>0.65</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>42±7</td>
<td>45±8</td>
<td>42±7</td>
<td>0.032</td>
</tr>
<tr>
<td>EF (%)</td>
<td>63±11</td>
<td>62±12</td>
<td>63±13</td>
<td>0.99</td>
</tr>
<tr>
<td>CHA2DS2 score</td>
<td>0.6±0.8</td>
<td>0.5±0.7</td>
<td>0.6±0.8</td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.1±3.5</td>
<td>24.0±3.1</td>
<td>24.1±3.6</td>
<td>0.89</td>
</tr>
<tr>
<td>Heparin dose (U)</td>
<td>7,699±2,101</td>
<td>7,753±1,527</td>
<td>7,690±2,191</td>
<td>0.90</td>
</tr>
<tr>
<td>Pre-procedural D-dimer</td>
<td>0.36±0.16</td>
<td>0.32±0.07</td>
<td>0.36±0.17</td>
<td>0.22</td>
</tr>
<tr>
<td>Post-procedural D-dimer</td>
<td>0.44±0.25</td>
<td>0.43±0.11</td>
<td>0.44±0.23</td>
<td>0.84</td>
</tr>
<tr>
<td>Pre-procedural INR</td>
<td>2.2±0.4</td>
<td>2.2±0.4</td>
<td>2.2±0.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Post-procedural INR</td>
<td>2.3±0.5</td>
<td>2.5±0.5</td>
<td>2.2±0.5</td>
<td>0.016</td>
</tr>
<tr>
<td>Pre-procedural APTT</td>
<td>45±18</td>
<td>43±4</td>
<td>45±20</td>
<td>0.77</td>
</tr>
<tr>
<td>Post-procedural APTT</td>
<td>48±22</td>
<td>65±45</td>
<td>44±11</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

There were several significant differences between the groups with (BC) and without (No BC) bleeding complications after AF ablation. With respect to clinical characteristics, the patients with bleeding complications had a higher percentage of women and diagnosis of chronic AF. With respect to coagulation related parameters, patients with bleeding complications had a higher APTT after the procedure.

AF, atrial fibrillation; APTT, activated partial thromboplastin time; BC, bleeding complication; EF, ejection fraction; INR, international normalized ratio; LAD, left atrial diameter.
showed a P-value smaller than 0.1 by univariable analysis.

Results

Complication Rates for Stroke and Bleeding

None of the patients experienced stroke or transient ischemic attack. A total of 22 patients (15%) had BC (Table 2). Three patients had major and 19 patients had minor BC. The major BC were 1 cardiac tamponade and 2 pseudo-aneurysms of the femoral artery. In the patients with minor BC, 2 patients developed hematomas at the groin, 2 patients arteriovenous fistula, and the remaining 15 patients had minor bleeding that needed additional manual compression after the procedure. These 22 major and minor bleeding patients constituted group BC, and the remaining 128 patients, group No BC.

In the patient who developed cardiac tamponade, protamine and vitamin K were administered immediately to reverse the effects of warfarin and heparin. Vital signs stabilized with pericardiocentesis, and the patient recovered fully. The pericardial drain was removed the next day. The 2 patients with pseudoaneurysm were given a repeat manual compression until the pseudo aneurysms resolved completely, and neither required surgery. None of the patients with BC, including the patient with cardiac tamponade, required blood transfusion.

Change of the Serum INR, APTT, and D-Dimer Level Before and After the Procedure

To investigate changes in the clotting tendency and anticoagulant activity caused by the ablation procedure, we measured INR, APTT, and D-dimer the day before and after the procedure in all of the patients. We found INR to be increased significantly the day after the procedure (2.2±0.4 vs. 2.3±0.5, P=0.039). APTT level was unchanged. D-dimer levels were also increased significantly by the procedure (0.36±0.16 vs.
Distinguishing Characteristics of Patients Who Developed Bleeding Complications
We compared various clinical characteristics between the bleeding and non-bleeding patients (Table 3). Of the characteristics studied, Group BC had a significantly higher percentage of women (41% vs. 17%, P=0.02), and larger left atrial diameter compared to Group No BC (45±8 vs. 42±7, P=0.032). No other clinical characteristics, including age and hepatic function markers, were significantly different between the 2 groups. We next studied whether the 2 groups differed in any of the coagulation related parameters before, during, and after the procedure. In preprocedural values, there were no significant differences between the 2 groups in D-dimer, INR, and APTT. The total amount of heparin administered during the procedure was not significantly different between the 2 groups. However, we did find a difference in post-procedural values of INR and APTT, which was significantly greater in Group BC than in Group No BC respectively (2.5±0.5 vs. 2.2±0.5, P=0.016; 65±45 vs. 44±11, P<0.0001) (Figure 2).

Multivariable analysis was performed on the items that showed a P-value smaller than by univariable analysis, and the post-procedural APTT was shown to be the only significant predictor of BC in this study (Table 4).

Finally, we examined the relationship between pre-procedural INR and heparin dose in this study, and confirmed that patients who had lower INR (<2, n=50) needed more heparin than patients who had higher INR (≥2, n=100) (8,582±329 vs. 7,272±190, P<0.0005) (Figure 3).

Discussion
Main Findings
In this study, we examined bleeding risk in AF ablation under the condition of therapeutic INR and heparin administration. Fifteen percent of the patients developed some BC, but preprocedural INR was not different between patients who bled and those who did not, suggesting that BC in the peri-procedural period were not related to the pre-procedural INR (2.2±0.4 vs. 2.2±0.4, P=0.79). This result indicates that we can get hemostasis in the patients in whom warfarin works well. The safety of AF ablation with therapeutic INR was also shown in this study because our incidence of major BC was low at 2%, and when limited to critical BC such as cardiac tamponade, it was 0.67%, lower than the 1.22% reported in the past literature, in which oral warfarin was suspended and bridging therapy of heparin was used. Stroke or transient ischemic attack did not occur in this study. In conducting ablation with ongoing warfarin, INR levels should be kept in the therapeutic range because a lower level of INR necessitates a larger amount of heparin during the procedure, which might lead to a higher risk of both bleeding and thrombosis.

Clotting Tendency and Anticoagulant Activity Change Caused by the Ablation Procedure
Overall average INR, APTT, and D-dimer were checked in all of the patients before and after the procedure to investigate clotting tendency and anticoagulant activity change caused by the ablation procedure. INR level was significantly increased the day after the procedure by 4.5% (from 2.2 to 2.3) although the dosage of oral warfarin had not been changed. The reason for the increased INR is uncertain, but it might have been caused by administration of heparin or antibiotics during and after the procedure. Heparin might have prolonged the INR directly by affecting intrinsic anticoagulation, or indirectly by an antagonistic action on warfarin metabolism. Antibiotics administered peri-procedurally might also have prolonged the INR by an antagonistic action on warfarin metabolism. Overall average APTT level was not increased significantly after the procedure, and indicates that in most patients, the effect of heparin administered during the procedure was weakened or antagonized by the administration of protamine.

In AF patients, a close relationship has been shown between the fluctuation of INR level and change in D-dimer levels. Although average INR level was significantly increased the day after the procedure, the post-procedural average D-dimer level was also increased. This might reflect a clotting tendency
In this study, we added additional intravenous heparin for 24 h after the procedure. Thrombosis usually occurs during or immediately after the procedure, although late thromboembolic events have been reported in some cases.

### Risk of BC

To obtain more detailed data, we investigated BC including minor bleeding in this study. The majority of BC consisted of minor bleeding (15%), ie, those who needed manual compression again the day after the procedure.

Patients in Group BC had significantly increased APTT on the day after the procedure compared to Group No BC. Increased APTT was considered to be mainly provoked by the administration of heparin during and after the procedure. However, amount of heparin administration was not significantly different between these 2 groups, so we believe that the differences in APTT levels were caused by individual difference in reaction to the heparin. Patients who react to heparin excessively might have had more increased APTT. We hypothesize that many of the minor BC might have been caused by the inhibition of secondary hemostasis, evoked by an excessive response to administered heparin (Figure 4).

Incidence of minor BC was comparable to the 11% reported in the recent literature.

### Correlation Between the Bleeding Complications and Bleeding Risk Score

Several studies have analyzed risk factors for bleeding in patients taking oral warfarin. The HAS-BLED score (hypertension, abnormal renal/kidney function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) and ATRIA score (anemia, renal disease, age, prior bleeding, hypertension) are known as novel scores that provide a practical tool for assessing individual bleeding risk in real-world patients with AF. However, common items in these 2 scores (age, renal function, hypertension (CHADs2 score)) were not bleeding risk factors in this study. This might be because the mechanism of bleeding that occurs under regular oral warfarin use and that of BC that occur as a result of the procedure protocol are different.

### Heparin Administration

In this study, we added additional intravenous heparin for 24 h after the procedure. Thrombosis usually occurs during or immediately after the procedure, although late thromboembolic events have been reported in some cases. Atrial stunning is at maximum immediately after cardioversion and improves progressively with complete resolution within a few minutes to 4–6 weeks depending on the duration of the preceding AF, atrial size, and structural heart disease. To prevent thrombus formation, especially in the atrial stunning period immediately after the cardioversion of the AF, a temporary boosting of anticoagulation with heparin might be beneficial. We administered heparin in this study for this purpose.

Perhaps as a result, there were no thromboembolic events (stroke, transient ischemic attack) in the consecutive 150 patients in this study, although the patients in the studies by Wazni et al (n=150) and Di Brase et al (n=2,618) also suffered no thromboembolic events with therapeutic INR only and no heparin or analogs in the post-procedural period. Additional heparin administration might be an effective method for the prevention of thrombosis, although it might also increase the risk of BC. Heparin is a well-known drug, and it is also known for the variability of its effects in each patient.

Heparin is usually desulfated at the liver, and excreted by the kidney. Therefore, its half-life in blood is assumed to be prolonged in patients with hepatic or renal dysfunction. However, significant differences were not seen in this study with respect to hepatic and renal function indicators between the Groups BC and No BC in this study. This result suggests that APTT can be prolonged excessively by other factors in patients who have normal hepatic and renal function.

Recently several studies about AF ablation with the dabigatran were reported, and its efficacy and safety is under discussion. Heparin administration is usually used in the AF ablation with the dabigatran, so it is important to note the heparin influence in its combination therapy, as is the case with this study.

### Reversal of Anticoagulation Effect by Warfarin

In the case of cardiac tamponade, protamine and vitamin K were administered to reverse the effects of warfarin and arrest the bleeding. Although fresh frozen plasma and factor VIIa were readied to be on the safe side, they were not used. In cardiac tamponade in AF ablation with therapeutic INR, fresh frozen plasma and factor VIIa are said to be necessary. However, Rakaesh et al reported that only 35% patients needed administration of these 2 drugs. Protocols for reversal of anticoagulation in cases of cardiac tamponade need further study.
ameter. Significant prolongation of the heparin effect in women has been reported in the literature, and in some cases, was as long as 48 h. It might be one of the reasons a larger proportion of patients with BC was seen in women. The mechanism of the prolongation in women is unknown; however, increased levels of factor VIII as a result of estrogen is hypothesized to be one of the factors.

Sex-related differences in the risk factor profile of the patients with AF are shown in the J-TRACE study, and CHADS2 score was higher in women than in men. This suggests that women with AF might have a higher risk of BC in both catheter ablation and cerebral infarction.

It is unclear why larger left atrial diameter and permanent AF were related with BC. Larger left atrial diameter and permanent AF are usually associated with thromboembolism, so it is interesting that they might also be associated with higher risk for bleeding as well.

Study Limitations
Our study was a single-institution study with a small number of patients. Manual compression time after the sheaths removal differs by the operator; this might have influenced the proportion of patients with rebleeding.

Conclusions
AF ablation with peri-procedural therapeutic INR seems to be safe. Presence or absence of BC are not related to the pre-procedural INR level, but to post-procedural APTT.

References