Periprocedural Stroke and Management of Major Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation

The Impact of Periprocedural Therapeutic International Normalized Ratio

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Background—Catheter ablation of atrial fibrillation is associated with the potential risk of periprocedural stroke, which can range between 1% and 5%. We developed a prospective database to evaluate the prevalence of stroke over time and to assess whether the periprocedural anticoagulation strategy and use of open irrigation ablation catheter have resulted in a reduction of this complication.

Methods and Results—We collected data from 9 centers performing the same ablation procedure with the same anticoagulation protocol. We divided the patients into 3 groups: ablation with an 8-mm catheter off warfarin (group 1), ablation with an open irrigated catheter off warfarin (group 2), and ablation with an open irrigated catheter on warfarin (group 3). Outcome data on stroke/transient ischemic attack and bleeding complications during and early after the procedures were collected. Of 6454 consecutive patients in the study, 2488 were in group 1, 1348 were in group 2, and 2618 were in group 3. Periprocedural stroke/transient ischemic attack occurred in 27 patients (1.1%) in group 1 and 12 patients (0.9%) in group 2. Despite a higher prevalence of nonparoxysmal atrial fibrillation and more patients with CHADS2 score >2, no stroke/transient ischemic attack was reported in group 3. Complications among groups 1, 2, and 3, including major bleeding (10 [0.4%], 11 [0.8%], and 10 [0.4%], respectively; P>0.05) and pericardial effusion (11 [0.4%], 11 [0.8%], and 12 [0.5%]; P>0.05), were equally distributed.

Conclusion—The combination of an open irrigation ablation catheter and periprocedural therapeutic anticoagulation with warfarin may reduce the risk of periprocedural stroke without increasing the risk of pericardial effusion or other bleeding complications. (Circulation. 2010;121:2550-2556.)

Key Words: atrial fibrillation • catheter ablation • embolism • stroke • transient ischemic attack • warfarin
Ablation Protocol

In group 1 patients, radiofrequency energy was delivered with an 8-mm solid-tip catheter (Biosense-Webster) with a target temperature kept constant at 55°C and power titrated upward in 5-W increments from 30 to 70 W while monitoring for microbubble formation.10,19 In groups 2 and 3, radiofrequency energy was delivered with a 3.5-mm open irrigated ablation catheter ( Biosense-Webster) with a maximum temperature of 42°C, power up to 45 W, and flow rate of 30 cm3/min.10,19,20

The ablation strategy was the same in all groups. Briefly, we performed pulmonary vein antrum isolation guided by a circular mapping catheter and by intracardiac echocardiography, along with empirical isolation of the superior vena cava.21 In patients with paroxysmal AF, the pulmonary vein antra and the portion of the posterior wall contained within the pulmonary vein area were targeted during the procedures with exit block as the end point.18,22 In patients with persistent and long-standing persistent AF, the electric isolation of the pulmonary veins was extended to the entire posterior wall down to the coronary sinus and to the left side of the septum.19,22 Ablation of complex fractionated atrial electrograms in the right and left atria and in the coronary sinus was also performed. In all patients, challenge with isoproterenol infusion up to 30 μg/min was performed to identify extrapulmonary vein triggers.

Methods

Between January 2002 and January 2009, data related to stroke and bleeding after RFCA procedures were prospectively collected from 9 centers performing the same ablation procedure with the same anticoagulation protocol over the study period. On the basis of the ablation catheter and the anticoagulation protocol used at the time of the procedure, we divided the study population into 3 groups: patients undergoing RFCA with an 8-mm catheter with warfarin discontinuation at the time of the procedure (group 1), patients undergoing RFCA with a 3.5-mm open irrigated catheter with warfarin discontinuation at the time of the procedure (group 2), and patients undergoing RFCA with a 3.5-mm open irrigated catheter without warfarin discontinuation at the time of the procedure (group 3).10,15

All patients included in group 3 had to show a “therapeutic” international normalized ratio (INR) the day of the procedure to meet the inclusion criteria. All patients signed informed written consent to participate in the study. The study was approved by the institutional review board.

Electrophysiological Study

Four venous accesses were obtained in each patient. The right groin accesses were used for transseptal catheterization. A double transseptal access was obtained via 2 separate puncture sites. A 20-mm decapolar circular mapping catheter was used for mapping (Lasso, Biosense-Webster, Baldwin Park, Calif); for ablation, an 8-mm-tip catheter (Celsius, Biosense-Webster) was used in group 1 and a 3.5-mm open irrigated-tip ablation catheter (Biosense-Webster) was used in groups 2 and 3.

A single left femoral 11F venous access was used to guide a 10F 64-element phased-array ultrasound imaging catheter (AcuNav, Acuson, Mountain View, Calif) in the right atrium.10,11,18 A single venous access in the right internal jugular vein was used to place a 14- to 20-pole catheter; the distal 7 to 10 poles were positioned in the coronary sinus along the mitral annulus, and the proximal 7 to 10 poles were placed along the crista terminals.

During the procedures, patients were anticoagulated with intravenous heparin with a bolus of 15 000 U in groups 1 and 2 and 10 000 U in group 3 just before the transseptal puncture. Then in groups 1 and 2, a continuous 1000-U/h infusion of heparin was started. The infusion was adjusted to maintain an activated coagulation time >350 seconds. In group 3, noncontinuous infusion was used. The transseptal sheaths were also infused with heparinized saline during the procedure.

Antiarrhythmic drugs were discontinued 5 days before the ablation. Patients on amiodarone discontinued the medication 6 months before the procedure.
Follow-Up
For the purpose of this study, all patients were assessed for complications during the initial 48 hours after the procedure. Follow-up was scheduled at 3, 6, 9, and 12 months. All patients had serial INR checks and were followed up by their referring physicians. Follow-up was scheduled at 3, 6, 9, and 12 months. All patients had serial INR checks and were followed up by their referring physicians. Complications were divided into 2 categories: hemorrhagic and thromboembolic. Major bleeding complications were defined as the occurrence of cardiac tamponade or hemopericardium that required intervention or caused symptoms, the need for transfusion, hematoma or any bleeding that did not require intervention or caused symptoms, the need for transfusion, hematoma requiring intervention, massive hemoptysis, hemotherax, and retroperitoneal bleeding. Minor bleeding complications were defined as the occurrence of hematoma or any bleeding that did not require any intervention and did not cause any symptoms. Thromboembolic complications were defined as occurrence of ischemic stroke, TIA, peripheral embolic events, or deep venous thrombosis.

Statistical Analysis
Continuous data are described as mean±SD and as counts and percent if categorical. Student t test, 1-way analysis of variance, χ² test, and Fisher exact test were used to compare differences across groups. When required, posthoc analysis was performed with the Tukey-Kramer multiple comparison method. Multivariable logistic regression was used to identify significant predictors of periprocedural stroke. All potential confounders were entered into the model on the basis of known clinical relevance or significant association observed in univariate analysis.

The controlling variables used in the model were age, hypertension, diabetes mellitus, coronary artery disease (CAD), congestive heart failure, prior cerebrovascular accident (CVA), and type of AF. Age was dichotomized at 75 years (≥75 years and >75 years) and entered into the model as an ordinal categorical variable. Analysis of variance inflation factor was used to examine the presence of multicollinearity of the covariates. Values of variance inflation factor exceeding 3.5 were regarded as indicators of multicollinearity. The odds ratio and 95% confidence interval (CI) of periprocedural stroke were computed. All tests were 2 sided, and a value of P<0.05 was considered statistically significant. Analyses were performed with SAS 9.2 (SAS Institute Inc, Cary, NC).

Results
A total of 6454 pulmonary vein antrum isolation procedures were identified. Of these procedures, 2488 were in group 1, 1348 were in group 2, and 2618 were in group 3. Compared with the other 2 groups, group 3 had a sicker population with a significantly higher prevalence of nonparoxysmal AF and CHADS2 (congestive heart failure, hypertension, age >75, diabetes mellitus, stroke or TIA) score ≥2 (P from multiple comparison <0.05). The demographic characteristics of these populations are presented in Table 1. In group 3, the mean INR on the day of the procedure was 2.68±0.62.

Transesophageal Echocardiography
Preprocedural TEE was performed in all patients with long-standing persistent AF (896 patients in group 1, and 310 patients in group 2). Among paroxysmal AF patients, 240 (21%) in group 1 and 115 (23%) in group 2 had preprocedural TEE. In patients with persistent AF, 228 (51%) in group 1 and 115 (23%) in group 2 had preprocedural TEE performed to exclude thrombus. None of the patients in group 3 had a TEE.

Thromboembolic Events
There were 19 strokes in group 1 (0.8%), 7 (0.5%) in group 2, and 0 in group 3. When stroke and TIA were considered together, 1.1% of group 1 and 0.9% of group 2 experienced the event. Group 3 patients did not experience stroke or TIA despite the higher prevalence of nonparoxysmal AF and a higher number of patients with CHADS2 score ≥2 (Table 2).
Hemorrhagic Events

In group 1, a total of 11 pericardial effusions (0.4%) were reported. Eight were documented during the procedure, and 3 occurred 1 to 4 weeks after the procedure. Only 1 patient required surgery. In group 2, a total of 11 (0.8%) pericardial effusions occurred (9 periprocedural and 2 after 1 to 4 weeks after the procedure). Two patients required surgery.

Twelve (0.5%) pericardial effusions were reported in group 3 (10 periprocedural and 2 after 1 to 4 weeks after the procedure). In this group, fresh frozen plasma with protamine was necessary to reverse the anticoagulation status. The mean INR when bleeding stopped was 1.8.

Three of the 12 patients with pericardial bleeding had termination of bleeding when the INR was <1.6. Surgery was necessary in 1 patient (Table 3). A median of 3 U blood was given in group 3. All patients requiring surgery had a steam pop during ablation along the mitral annulus.

The management strategy for pericardial effusions was compared between the on-warfarin (group 3) and off-warfarin (groups 1 and 2 combined) populations in Table 3. The incidence of pericardial effusion was comparable in the 3 groups (0.4% in group 1, 0.8% in group 2, and 0.4% in group 3; P=0.05).

In addition, the pericardial drainage was kept overnight and removed the next day in all patients except 1 woman who continued to accumulate clear fluid in the pericardial sac for 3 days and required treatment with steroids. All patients requiring pericardiocentesis were given antiinflammatory therapy for 2 weeks.

In all patients, an echocardiogram was performed at the end of the procedure. Five of 22 patients in the off-warfarin group and 2 of the 12 patients with pericardial effusions in the on-warfarin group presented late with a pericardial effusion that was not present immediately after the procedure. No treatment was required in 3 of the 5 patients in the off-warfarin group and in 1 of the 2 patients in the on-warfarin group. In the remaining 3 patients, the fluid was removed with a pericardial window in 2 cases and with percutaneous epicardial drainage in 1 patient.

Vascular access complications resulting in major bleeding were observed in 31 patients. In 12 patients, blood transfusion was required. Three patients had retroperitoneal bleeding; other bleeding complications included hematomas requiring no intervention but prolonged hospitalization, which was present in 16 patients.

Minor bleeding were observed more frequently in groups 1 and 2 than in group 3 (20%, 19%, and 4%, respectively; P<0.05). These data are summarized in Table 2.

Risk of Periprocedural Stroke/TIA

Patients were divided into 2 groups according to stroke/TIA outcome status, and univariate analysis was performed to compare their clinical characteristics. Male gender, CAD, diabetes mellitus, prior stroke/TIA, warfarin discontinuation, and CHADS2 score were found to be significantly associated with occurrence of periprocedural stroke (Table 4).

A multivariable analysis was performed with the logistic regression model (model 1). The significant confounders identified in the univariable test were included in the model. In addition, some other clinically important covariates (AF type, congestive heart failure, hypertension, and age >75 years) were added to the model despite their nonsignificant association in the univariate test. After adjustment for the above confounders, it was found that the anticoagulation strategy, AF type (nonparoxysmal AF), congestive heart failure, and diabetes mellitus were independent predictors of periprocedural stroke. The odds ratios from this model are presented in Table 5.

To avoid multicollinearity, a separate multivariable model was run by including CHADS2 score (categorized into 0, 1, 2), anticoagulation strategy, gender, CAD, and AF type (model 2). A CHADS2 score of 0 was considered the reference and was compared with the CHADS2 scores of 1 and 2. As observed in this model, CHADS2 score, anticoagulation strategy (on warfarin), gender, and AF type (nonparoxysmal AF) were independently associated with periprocedural stroke. Patients with CHADS2 score ≥2 had an odds ratio of 3.8; P<0.001) higher risk of experiencing periprocedural stroke compared with patients having a CHADS2 score of 1 and ≥4 times (odds ratio, 5.7; P<0.001) higher risk compared with those with a CHADS2 score of 0 (Table 6). In both models, AF type and the anticoagulation strategy were found to be strong predictors of periprocedural stroke.
Table 4. Univariate Analysis of Clinical Risk Factors for Stroke/TIA

<table>
<thead>
<tr>
<th>Variables</th>
<th>Stroke (n=41)</th>
<th>No Stroke (n=6413)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>26 (63)</td>
<td>4913 (77)</td>
<td>0.047</td>
</tr>
<tr>
<td>Age, y</td>
<td>58±9</td>
<td>56±11</td>
<td>0.275</td>
</tr>
<tr>
<td>AF type, n (%)</td>
<td></td>
<td></td>
<td>0.765</td>
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<tr>
<td>Paroxysmal</td>
<td>17 (41)</td>
<td>2634 (41)</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>15 (37)</td>
<td>1946 (30)</td>
<td></td>
</tr>
<tr>
<td>Long-standing persistent</td>
<td>9 (22)</td>
<td>1833 (29)</td>
<td></td>
</tr>
<tr>
<td>Patients with risk factors, n (%)</td>
<td>0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>2 (5)</td>
<td>1107 (17)</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>4 (10)</td>
<td>322 (5)</td>
<td>0.151</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (56)</td>
<td>3027 (47)</td>
<td>0.275</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>1 (2)</td>
<td>152 (2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (24)</td>
<td>860 (13)</td>
<td>0.061</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>10 (24)</td>
<td>254 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients off warfarin</td>
<td>41 (100)</td>
<td>3795 (59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients on warfarin</td>
<td>0 (0)</td>
<td>2618 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>10 (24)</td>
<td>2779 (43)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 (37)</td>
<td>2672 (42)</td>
<td></td>
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<tr>
<td>≥2</td>
<td>16 (39)</td>
<td>962 (15)</td>
<td></td>
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<tr>
<td>LVEF, %</td>
<td>51±9</td>
<td>53±8</td>
<td>0.609</td>
</tr>
<tr>
<td>LVEF ≤40%, n (%)</td>
<td>37 (90)</td>
<td>5924 (92)</td>
<td>0.551</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>45±7</td>
<td>45±7</td>
<td>0.961</td>
</tr>
<tr>
<td>LA diameter ≥40 mm, n (%)</td>
<td>31 (75)</td>
<td>4660 (73)</td>
<td>0.673</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

Discussion

Main Findings
This is the first large series of patients undergoing ablation of AF that shows that continuation of therapeutic warfarin during the procedure (RFCA) could reduce the risk of periprocedural stroke/TIA without increasing the risk of hemorrhagic events. The anticoagulation strategy, congestive heart failure, history of type 2 diabetes mellitus, and type of AF were independent predictors of stroke. After adjustment for CHADS2 scores, patients with CHADS2 ≥2 had the highest risk of experiencing the event, whereas patients with CHADS2 score of 0 had the lowest risk.

Of interest, group 3 consisted of a sicker population with a higher prevalence of stroke/TIA predictors. In addition, group 3 patients with long-standing persistent AF underwent a more aggressive ablation protocol, including defragmentation in the right and left atrium. Therefore, despite a more extensive ablation protocol and a higher prevalence of patients at risk for stroke, the absence of thromboembolic events in this group is of remarkable importance and is most likely related to the anticoagulation protocol in which warfarin was not discontinued because CVAs have been reported even with open irrigated catheters.

Previous Studies
Many previous studies have reported the incidence of periprocedural CVA with the use of either an 8-mm ablation catheter or a 3.5-mm open irrigated ablation catheter. We first reported the possibility of performing RCFA while maintaining therapeutic anticoagulation with warfarin. In this large series of patients, we observed that the combination of therapeutic anticoagulation with warfarin and the use of a 3.5-mm open irrigated catheter significantly reduced the risk for CVA/TIA without increasing the risk for bleeding.

The reported risks of stroke/TIA vary from 0.9% to 5% after RFCA. Studies have reported the incidence of TIA/stroke varying from 0.8% to 1.1% with the use of open irrigated catheters. Scherr et al reported a risk of periprocedural stroke of 1.4% despite the use of open irrigation catheters. Others have reported significant stroke risk reduction using a similar strategy. In a recent report, Hussein et al described 3 ischemic strokes using a similar strategy in >3000 patients. However, it should be emphasized that an INR of 1.8 was considered acceptable in their series. In our series, all patients in group 3 had an INR ≥2 on the day of the procedure.

Although the expert consensus document recommends a bridging strategy, our study and others confirm the limitations of such an approach. It appears that patients who discontinue warfarin may be exposed to an increased risk of stroke during the procedure even when the TEE excludes the presence of
thrombus. In addition, achieving a therapeutic INR after the procedure may take several days. During this time, patients may be at an increased risk of stroke/TIA and may not be adequately covered with the bridging strategy. Our multicenter report and the report by Hussein et al show that this anticoagulation approach is safe and efficacious in a large population of patients.

Our study found that anticoagulation strategy, nonparoxysmal AF, and higher CHADS2 scores were strongly associated with periprocedural stroke, whereas prior CVA, gender, and age did not show any impact. Patients with CHADS2 score $\geq 2$ were $\sim 5$ times more likely to experience the event compared with group 1 and 2 patients with a CHADS2 score of 0. The incidence of stroke was lowest among patients with CHADS2 score of 0, and each level of increase in CHADS2 score was associated with significantly higher risk. Our findings are consistent with those of Scherr et al using open irrigated catheters and warfarin discontinuation.

Minor Bleeding

Minor bleeding complications were significantly higher in the group of patients using the bridging anticoagulation protocol. This may increase the cost of this strategy. For the physicians who are concerned about the risk of vascular injury while inserting sheaths under full anticoagulation, ultrasound guidance might be useful.

Major Bleeding and Tamponade

In this patient population, the majority of bleeds have been related to cardiac tamponade. The management and incidence of this complication have not shown any statistical significant difference between groups. The prevalence of pericardial effusion during and after RFCA reported in the literature is $\sim 1.2\%$, which is similar to the rate found in all 3 of our groups.

Emphasis should be put on the different modalities of anticoagulation reversal. In groups 1 and 2, protamine was usually sufficient, whereas in group 3, fresh frozen plasma was necessary. In addition, patients on warfarin were more likely to have more blood removed from the pericardial space before stabilization and were given a larger amount of blood transfusion (Table 3). The need for fresh frozen plasma and blood units, although a potential disadvantage, is mitigated by the reduced risk of stroke/TIA.

Economic Point of View

Our strategy could also be cost-effective by reducing the number of TEEs performed and the extra cost for managing complications such as stroke and bleeding. In addition, patients belonging to groups 1 and 2 incurred the additional cost of low-molecular-weight heparin, which can be substantial. On average, before warfarin was therapeutic, patients had received 6 doses of low-molecular-weight heparin.

Study Limitation

The study was not randomized, although the data were collected in a prospective fashion. This can be considered an important limitation. However, the reduced stroke rate observed in group 3 despite a higher number of patients at risk is compelling.

Conclusion

Our results suggest that periprocedural therapeutic anticoagulation with warfarin can reduce the risk of procedural stroke without increasing the risk of bleeding complications.

Disclosures

Drs Al-Ahmad, Burkhardt, Lakkireddy, Sanchez, Cummings, Wang, Schweikert, Hongo, Horton, and Natale report receiving compensation from St. Jude Medical for participation in speakers’ bureaus. Drs Burkhardt, Horton, Sanchez, Lakkireddy, Khaykin, Verma, and Natale report receiving compensation from Biosense-Webster for participation in speaker’s bureaus. Drs Burkhardt, Horton, Khaykin, Verma, Wang, Cummings, Hongo, Al-Ahmad, and Natale report receiving compensation from Medtronic for participation in speaker’s bureaus. Drs Horton and Wang report receiving compensation from Hansen Medical for participation in speakers’ bureaus. Drs Grijswijkert, Hongo, Lewis, and Cummings report receiving compensation from Sanofi-Aventis for participation in speakers’ bureaus. Dr Schweikert reports receiving compensation from Glaxo-Smith-Kline for participation in its speakers’ bureau. Dr Wang reports receiving compensation from Lifewatch for participation in its speakers’ bureau. Drs Themistoclakis and Bonso report serving as a consultant/advisory board member for Biosense-Webster. Dr Gallghouse reports serving as a consultant/advisory board member for St. Jude Medical and Hansen. Dr Cummings reports serving as a consultant/advisory board member for St. Jude Medical and Corazon Consulting. Dr Burkhardt reports serving as a consultant/advisory board member for Stereotaxis. Dr Al-Ahmad reports serving as a consultant/advisory board member for Hansen Medical and Cyberheart. Drs Lewis and Hongo report serving as a consultant/advisory board member for Boston Scientific and Medtronic. Dr Al-Ahmad reports participation in a research grant from Siemens. Dr Natale reports participation in a research grant from St. Jude. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Periprocedural thromboembolic and hemorrhagic events are complications of percutaneous radiofrequency catheter ablation of atrial fibrillation. The management of anticoagulation before and after radiofrequency catheter ablation could play an important role in the prevention of these complications. The incidence of thromboembolic events varies from 1% to 5%, depending on the ablation and the anticoagulation strategy used in the periprocedural period. At present, although discontinuation of warfarin 3 to 5 days before ablation with and without bridging with low-weight heparin is the most frequently implemented protocol, the optimal anticoagulation management (minimizing thromboembolism while not increasing hemorrhagic complications) is not well established. We first reported radiofrequency catheter ablation of atrial fibrillation without discontinuation of warfarin. This is the first large series of patients undergoing ablation of atrial fibrillation with different anticoagulation protocols and with different ablation catheters showing that the continuation of therapeutic warfarin during the procedure (radiofrequency catheter ablation) reduces the risk of periprocedural stroke/ transient ischemic attack without increasing the risk of hemorrhagic events. Of interest, this anticoagulation protocol eliminates the need for a periprocedural transesophageal echocardiogram. A randomized controlled trial is necessary to confirm the results of our study.
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