Impact of International Normalized Ratio and Activated Clotting Time on Unfractionated Heparin Dosing During Ablation of Atrial Fibrillation

Ismail Hamam, MD; Emile G. Daoud, MD; Jianying Zhang, PhD; Steven J. Kalbfleisch, MD; Ralph Augustini, MD; Marshall Winner, MD; Shane Tsai, MD; Troy E. Rhodes, MD, PhD; Mahmoud Houmsse, MD; Zhenguo Liu, MD, PhD; Charles J. Love, MD; Jaret Tyler, MD; Molly Sachdev, MD; Raul Weiss, MD; John D. Hummel, MD

Background—For ablation of atrial fibrillation, it is unclear how baseline international normalized ratio (INR) affects the dosing of unfractionated heparin (UFH).

Methods and Results—A retrospective review of 170 consecutive patients undergoing atrial fibrillation ablation with baseline activated clotting time (ACT) and INR values was performed. Patients were grouped according to INR <2.0 (G<2; n=129) and INR ≥2.0 (G≥2; n=41). Clinical variables, UFH doses, and ACT values were recorded. An equation was derived to calculate the first bolus of UFH required to achieve an ACT ≥300 seconds, and this was subsequently assessed in 168 patients. For the initial 170 patients, the baseline INR (2.47±0.31 versus 1.53±0.31) and ACT (185±26 versus 153±30 seconds) were significantly greater in G≥2 (P<0.001). The amount of UFH to achieve the first ACT ≥300 seconds was significantly higher for G<2 versus G≥2 (9701±2390 versus 8268±2366 U; P=0.0001). Baseline INR, ACT, and weight were predictors of the UFH dosage to achieve an ACT ≥300 seconds. An equation derived to achieve an ACT ≥300 seconds after a single bolus of UFH met this end point in 160 of 168 patients (95%).

Conclusions—Baseline INR and ACT, in addition to weight, are the only predictors of UFH dosage needed to achieve an ACT ≥300 seconds. A derived equation predicted the UFH dosage to achieve an ACT ≥300 seconds.

(Circ Arrhythm Electrophysiol. 2013;6:491-496.)

Key Words: anticoagulants ■ atrial fibrillation ■ catheter ablation ■ heparin ■ warfarin

The main goals of treating atrial fibrillation (AF) are to reduce symptoms and prevent thromboembolism and heart failure.1 Catheter ablation is often used to achieve these ends.2 Despite the improvement in techniques and proper anticoagulation periprocedure and postprocedure, the complication rate for catheter ablation of AF, including thromboembolism, remains significant.3 The incidence of periprocedural cerebrovascular accidents is reported to be as high as 1% to 5%, despite anticoagulation and transesophageal echocardiography.4,5 Furthermore, intracardiac echocardiography has noted intracardiac thrombus formation in the left atrium during catheter ablation procedures, with an incidence as high as 10.3%.6 Thus, it is important to maintain proper anticoagulation throughout the procedure with a target activated clotting time (ACT) ≥300 seconds.6,7 Multiple studies have shown that it is safe and effective to continue warfarin at therapeutic levels before, during, and after the procedure.8-10 Although this approach seems to decrease the amount of heparin required to achieve an adequate ACT, it remains a challenge to achieve an acceptable ACT with a single bolus of unfractionated heparin (UFH). The main purpose of this study was to assess the factors that affect the amount of UFH needed to achieve a therapeutic ACT ≥300 seconds. A second goal of this study was to assess a methodology used to calculate the initial bolus dose of UFH to achieve an ACT ≥300 seconds and validate this method.

Clinical Perspective on p 496

Methods

This is a single-center retrospective analysis performed at Ross Heart Hospital at The Ohio State University. We completed a review of all patients who underwent AF ablation between October 2009 and June 2011, regardless of the type of AF (paroxysmal, persistent, or long-standing persistent) or the technology used for AF ablation (radiofrequency or cryoballoon). Only patients who had their ACT measured before the administration of UFH were included. We excluded patients who had their first ACT reading measured only after administration of UFH and patients with incomplete or missing data for preprocedural international normalized ratio (INR), intraprocedural ACT readings, or UFH doses, leaving a total of 170 patients.

Received October 17, 2012; accepted May 9, 2013.

From the Division of Cardiology, Ohio State University Wexner Medical Center (I.H., E.G.D., S.J.K., R.A., M.W., S.T., T.E.R., M.H., Z.L., C.J.L., J.T., M.S., R.W., J.D.H.) and Center for Biostatistics (J.Z.), Ohio State University, Columbus, OH.

Editor for this article was Kenneth A. Ellenbogen, MD.

Correspondence to Ismail Hamam, MD, The Dorothy M. Davis Heart & Lung Research Institute, Ohio State University Wexner Medical Center, 473 W. 12th Ave, Suite 200, Columbus, OH 43210-1252. E-mail Ismail.hamam@osumc.edu

© 2013 American Heart Association, Inc.

Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org

DOI: 10.1161/CIRCEP.113.979088

491
Enrolled patients were divided into 2 groups based on the INR on the day of the procedure. G<2 included patients with a baseline INR of <2.0, whereas G≥2 included patients with an INR ≥2.0. In both groups, ACT readings and UFH doses (at 15-minute intervals per electrophysiology laboratory protocol) were recorded throughout the procedure.

In addition to demographic data, we also assessed the following clinical characteristics: left ventricular ejection fraction, left atrial size, presence of hypertension, diabetes mellitus, heart failure, coronary artery disease, type of AF, periprocedural use of warfarin, aspirin, clopidogrel, and antiarrhythmic medications (classes I and III). Baseline laboratory data included INR, serum creatinine, hemoglobin, and platelet count.

Periprocedural anticoagulation for AF ablation was left to the discretion of the electrophysiologist. This resulted in either discontinued or subtherapeutic warfarin dosing before the planned procedure, with enoxaparin bridging preprocedure and postprocedure until INR ≥2.0 (G<2), or continuation of therapeutic warfarin with INR ≥2.0 (G≥2). In G<2, warfarin was stopped 2 to 3 days before the day of the procedure, and the patients were started on subcutaneous enoxaparin 1 mg/kg BID 36 hours later or after left atrial thrombus was excluded with transeosophageal echocardiography. Enoxaparin injections were held on the day of the procedure and were resumed at a 0.5 to 0.7 mg/kg BID 4 hours after hemostasis was achieved. Warfarin was reinitiated the evening of the procedure. In G≥2, warfarin was continued throughout the periprocedural time, and no enoxaparin was prescribed. Patients taking uninterrupted warfarin periprocedurally, but with a subtherapeutic INR on the day of the procedure, were included in G<2. Patients who were on dabigatran were asked to hold 4 doses before the procedure and were included in G<2, given the low INR on the day of the procedure.

Patients had their baseline/preprocedural INR measured the morning of the procedure. Baseline ACT (Hemochron, ITC, Edison, NJ) was measured after femoral vein access and every 15 minutes after the initial dose of UFH. The initial UFH dose was empirically dictated by the electrophysiologist, in most cases, based on body weight. Subsequent dosing of UFH throughout the procedure was dictated by physician preference, with a target ACT to be >300 seconds. No ablation was performed until the ACT was confirmed to be >300 seconds. The ACT after the first dose of UFH in units and units/kg, the total units and units/kg of UFH given to achieve an ACT >300 seconds, number of UFH boluses given to achieve ACT >300 seconds, and total time in minutes needed to achieve the therapeutic ACT were recorded.

Major periprocedural complications were recorded in all patients, including major bleeding (defined as bleeding requiring blood transfusion, retroperitoneal bleeding, or groin hematoma that prolonged the hospitalization), pericardial effusion requiring drainage, and all thrombembolic complications, including pulmonary embolism, stroke, and transient ischemic attack.

The second part of the study was designed to assess an equation derived to calculate the initial bolus dose (in units/kg) of UFH to achieve an ACT ≥300 seconds. This equation was used by clinicians after its derivation in an attempt to arrive at an ACT ≥300 seconds more accurately after a single UFH bolus. A total of 168 patients who underwent AF ablation between April and September 2012 and who underwent AF ablation between April and September 2012 and who were given a dose of UFH derived from the equation based on both body weight and the baseline INR (Table 1) were assessed. Baseline demographic and clinical characteristics, in addition to baseline INR, ACT, initial dosage of UFH, and the resultant ACT calculated 15 minutes after the initial UFH administration, were recorded.

### Statistical Analysis

Baseline INR was dichotomized to 2 groups: high (G≥2) if INR ≥2.0 or low (G<2) if INR <2.0. Two variables, INR (G≥2) and INR (G<2) were generated as the distance from the clinical cutoff 2.0 multiplied by whether it belonged to the G≥2 INR or G<2 INR. Continuous variables are presented as mean and SD. The categorical variables were assessed as frequencies and percentages. The Student t test was used to compare normally distributed variables between the 2 INR groups. Pearson χ² or Fisher exact test was used to compare frequencies between the 2 INR groups for categorical variables.

Smooth curves by LOESS (locally weighted scatterplot smoothing) method was added to scatter plot to show how UFH dose (units/kg) was correlated to baseline INR, with different slopes before and after the cutoff 2.0. Correlations among covariates were examined, especially the association between initial UFH dose (units/kg) and each covariate in the univariate analysis. Multiple linear regressions were performed, and stepwise method (SAS procedure GLMSELECT, entry level 0.15 and stay level 0.05) was used to select the most influential covariates from the list of interest and the corresponding interaction terms with INR groups. The final regression model was fitted on the selected covariates, and an equation to calculate the initial dose of UFH was formed based on the parameter estimates. Multicollinearity was checked if covariates other than INR were selected into the final model. Residual plots and goodness-of-fit tests were used to check model assumptions, outliers, and model of fit. A P value of no more than 0.05 was considered statistically significant.

### Results

#### Baseline Variables

One hundred seventy patients met inclusion/exclusion criteria. Of the 170 patients, 95% (163 patients) were ablated using radiofrequency energy and 5% (8 patients) with cryoablation. There were a total of 129 patients in G<2 (patients with INR <2.0) and 41 patients in G≥2 (patients with INR ≥2.0). There were similar baseline clinical and demographic characteristics between the groups (Tables 2 and 3).
Baseline INR in G<2 was 1.53±0.31, and baseline ACT was 153±30. In comparison, in G≥2 baseline INR was 2.47±0.31 \((P<0.001)\), and baseline ACT was 185±26 \((P=0.0001)\).

A total of 3 (2.3\%) patients developed bleeding complications in G<2 (significant groin hematoma, upper gastrointestinal bleeding, and hematuria with hemoglobin drop), whereas there were no recorded bleeding complications in G≥2 \((P=0.32)\). There were no recorded thromboembolic complications in either group.

**Heparin Requirements**

Patients in G<2 were given a mean total dose of UFH to achieve an ACT ≥300 seconds of 13079±4469 U (132±49 U/kg), whereas G≥2 patients received significantly less UFH with a mean total dose of 8683±2173 U (91±23 U/kg; \(P=0.0001\) for units and units/kg). The mean first dose of UFH given to patients in G<2 was 9702±2390 U (98±25 U/kg) and in G≥2 was 8268±2367 U, \(P=0.001\) (86±26 U/kg; \(P=0.012\); Table 2). Importantly, 93\% (38) of the patients in G≥2 achieved ACT ≥300 seconds after a single dose of UFH in comparison with G<2, where just 51\% (66) of patients achieved a therapeutic ACT after the first dose \((P<0.0001)\). The patients in G<2 required an average of 1.98 boluses of UFH to achieve an ACT ≥300 seconds, which added ≈16 more minutes to achieve an ACT ≥300 seconds \((P<0.0001); \text{Table 3}\). In the univariate analysis, the total UFH dose required for therapeutic ACT is associated with baseline INR, baseline ACT, and body weight.

**Calculation of the Appropriate Heparin Dose in Units/kg to Achieve an ACT ≥300 Seconds**

By univariate analysis, the scatter plot of total dose units/kg versus baseline INR with smooth curve fitted by LOESS method implies that it may be appropriate and necessary to fit the linear model separately around the INR cutoff 2.0 (Figure 1). In the multiple linear regression procedure based on all the potential predictors and their interaction terms with INR groups, only the 2 cutoff-separated INR covariates INR (G≥2) and INR (G<2) are selected by stepwise model selection method to yield an initial ACT ≥300 seconds. Baseline ACT did not show added significance, which is most likely because of its multicollinearity with INR \((r=0.64)\).

The final equation to calculate the dose of UFH to yield an initial ACT ≥300 seconds with can be written as:

\[
\text{First dose in units / kg} = 90.51 - 93.68 \text{ (INR} - 2.0) - 10.44 \text{ (INR} - 2.0)\]

For interpretation simplicity, it can also be split into 2 equations, one for INR low group and another for INR high group, written as below:

In patients with INR <2.0 (G<2):

\[
\text{First dose in units / kg} = 90.51 - 93.68 \text{ (INR} - 2.0) - 10.44 \text{ (INR} - 2.0)\]

In patients with INR ≥2.0 (G≥2):

\[
\text{First dose in units / kg} = 90.51 - 93.68 \text{ (INR} - 2.0) - 10.44 \text{ (INR} - 2.0)\]

The 2 hypothesis tests on slopes different from zero showed significance \((P<0.0001)\) for INR (G<2), whereas it showed non-significance for INR (G≥2; \(P=0.380\)). The test on the difference between the 2 slope estimates for the 2 INR groups implied significance difference \((P<0.001)\). Lack of fit test indicates a goodness of fit of the model \((P=0.280)\). The residual plot showed the pattern close to randomness, symmetry, and normality, implying that the model assumption was not violated.

The equation suggests that when the baseline INR is <2.0, every 1 U below 2.0 will result in an increase of UFH dose by an average of 93.7 U/kg (or 9.4 for every 0.1 decrease from 2.0), whereas when INR is >2.0, every 1 U above 2.0 will result in an increase of UFH dose by an average of 10.4 U/kg (or 1.04 for every 0.1 increase from 2.0). To simplify the clinical application of these equations, the estimated UFH doses per kg based on this equation were laid out in a tabular format (Table 1).

**Clinical Validation of the Equation**

Subsequent to the analysis of the baseline 170 patients’ response to UFH dosing and development of a predictive equation for dosing of UFH, 168 patients undergoing AF ablation were given an initial bolus of UFH based on Table 1. Of the 168 patients, there were 65\% men, 51\% had paroxysmal AF, 75\% had hypertension, 18\% had diabetes mellitus, 40\% had coronary artery disease, and 62\% were on warfarin during their procedure. The mean age was 64±10 years, the mean body weight was 100.5±51.9 kg, the mean body mass index was 33±6, the mean ejection fraction was 54±9\%, baseline INR was 1.7±0.9, baseline ACT was 166±37 seconds, and the mean initial dose of UFH was 12,690±4,320 U. In each case, the total UFH initial dose was calculated by multiplying the patient’s weight (kg) by the recommended units/kg in the table. The resulting mean ACT after the initial UFH bolus was 364±26 seconds (Table 4). Importantly, 95\% (160/168) of patients required just 1 UFH dose to achieve ACT ≥300 seconds. Just 5\% (8/168) of patients did not achieve the target
ACT, and 3 of these patients had an ACT $\geq 295$ seconds, which was close to the target ACT of 300 seconds (Figure 2).

The 21 patients (12.5%) who had their ACT $\geq 400$ seconds after the first UFH dose were observed after the procedure for any complications. All of these patients were free of any significant complications and were discharged home next day.

In addition, we performed a detailed analysis of the first 53 patients, which shows that patients receiving the first heparin dose based on the derived equation required a mean of 4971±4387 U of UFH, 2.4±1.9 boluses throughout the entirety of their ablation. It was noted that 21% of these patients did not require any further UFH after the initial dose to maintain a therapeutic ACT throughout the procedure, whereas 60% of patients required 0 to 2 boluses to finish their entire procedure.

## Discussion

We found that INR, ACT, and body weight are highly correlated to the amount of UFH needed to reach an ACT level $\geq 300$ seconds, which is desired before proceeding with ablation of AF.

Using linear regression analysis, we developed an equation to calculate the dose of UFH to achieve an initial ACT reading of $\geq 300$ seconds after a single bolus, which seems to be remarkably accurate with 95% of patients reaching this target. Thus, our study seems to provide a method to calculate the UFH dosage based on the baseline INR and body weight to achieve a therapeutic ACT quickly and with 1 UFH bolus (Table 1).

When dosed empirically by the physician, the patients with INR $<2.0$ faired particularly poorly, with only 51% achieving an adequate ACT after a single UFH bolus. Anticoagulating these patients took longer to achieve the target ACT by $\approx 16$ minutes and may, in part, explain why patients undergoing AF ablation off warfarin or with subtherapeutic warfarin carry a higher periprocedural risk of thromboembolism. Not only did it take longer to achieve an adequate ACT in G$<2$, but these patients also required a larger amount of UFH to maintain proper anticoagulation throughout the procedure, which is consistent with prior findings. Because UFH usage has been associated with procedural bleeding complications, these findings imply that patients with INR$<2.0$ may be more susceptible to bleeding complications due to higher UFH requirement, as well as an increased risk of thromboembolic complications because of the delay in achievement of adequate anticoagulation during ablation.

In a prior study that predicted the UFH dose based on baseline INR, it was recommended to reduce the UFH dose by one third in those with an INR 2 to 3 and by two thirds in INR $>3$ for goal ACT $>250$ seconds. In a retrospective study of 427 patients, for a goal ACT $\geq 350$ seconds the optimal UFH dose for patients with INR $\geq 2.0$ is 77±18 and 106±40 U/kg for patients with INR $<2.0$. Although providing helpful guidance, these studies did not provide specific dosing based on an individual’s INR or body weight, both of which seem crucial for UFH dosing. To our knowledge, this study is the first to define a specific UFH dosage per kilogram body weight, adjusted for INR.

A linear correlation of the baseline ACT to baseline INR has previously been reported at the time of anticipated coronary intervention, and it was concluded that this is likely related to effects on the same coagulation factors. Our study reinforces these findings and leveraged this observation to show that the baseline ACT and INR are highly correlated with the baseline UFH dose that achieves an ACT $\geq 300$ seconds and to derive an equation to calculate an adequate UFH dose to achieve this goal. It has long been understood that body weight is an important factor affecting UFH dosing, but it is interesting to note that there were no other factors that we could identify which influenced the UFH dosage other than body weight, baseline ACT, and INR.

## Table 3. Baseline Categorical Variables Comparing G<2 and G$\geq 2$ Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>G&lt;2 (n=129)</th>
<th>G$\geq 2$ (n=41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>78% (100)</td>
<td>68% (28)</td>
<td>0.232</td>
</tr>
<tr>
<td>Type of atrial fibrillation (persistent)</td>
<td>35% (45)</td>
<td>41% (17)</td>
<td>0.446</td>
</tr>
<tr>
<td>Race (white)</td>
<td>96% (114)</td>
<td>98% (40)</td>
<td>0.664</td>
</tr>
<tr>
<td>Hypertension</td>
<td>69% (89)</td>
<td>73% (30)</td>
<td>0.611</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20% (26)</td>
<td>27% (11)</td>
<td>0.367</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13% (17)</td>
<td>22% (9)</td>
<td>0.174</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>24% (31)</td>
<td>24% (10)</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin on procedure day</td>
<td>68% (88)</td>
<td>63% (26)</td>
<td>0.569</td>
</tr>
<tr>
<td>Warfarin on procedure day</td>
<td>76% (98)</td>
<td>98% (40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pravastatin on procedure day</td>
<td>4% (5)</td>
<td>5% (2)</td>
<td>0.675</td>
</tr>
<tr>
<td>Antiarrhythmic on procedure day</td>
<td>57% (73)</td>
<td>46% (19)</td>
<td>0.251</td>
</tr>
<tr>
<td>Sedation (moderate)</td>
<td>70% (88)</td>
<td>59% (24)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

## Table 4. Baseline Variables and Results on the 168 Patients Who Were Given the First UFH Dose Based on Calculated Dose According to Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>Range</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>52–154</td>
<td>100.5±51.9</td>
</tr>
<tr>
<td>Baseline ACT</td>
<td>99–244</td>
<td>166±37</td>
</tr>
<tr>
<td>Baseline INR</td>
<td>1.0–3.4</td>
<td>1.7±0.9</td>
</tr>
<tr>
<td>First heparin dose</td>
<td>5000–24000</td>
<td>12690±4320</td>
</tr>
<tr>
<td>ACT after the first dose</td>
<td>242–474</td>
<td>364±26</td>
</tr>
</tbody>
</table>

ACT indicates activated clotting time; INR, international normalized ratio; and UFH, unfractionated heparin.
Limitations
Lack of randomization and the retrospective nature of the study are the main limitations of this study. A large number of the screened patients did not meet the inclusion criteria because of either a lack of recording the ACT before the time the UFH was given or missing data points. This made the actual studied population represent only 27% of patients who were ablated over the retrospective period analyzed. In addition, the 168 patients undergoing UFH dosing based on the derived equation were not prospectively chosen or randomized against a control group, which increases the risk of selection bias.

Another limitation of the study is that the dose of UFH and the number and timing of the boluses were left to the clinical judgment of the operator, except in the portion of the study that assessed the validity of the derived equation. In addition, there was no validation of the accuracy of the ACT reading against another ACT machine. Although the ACT machines in the laboratories were calibrated every morning against one another and before every case, we think that verifying the ACT on an additional machine or via 2 blood samples drawn at the same time leaves open the possibility that there is some error in our baseline assumptions and the derived equation.

The large number of patients assessed may decrease the risk of a meaningful error. Also, we did not perform detailed tracking as to how the ACT behaved after the first reading in all patients, given that in this study the primary end point was whether we were able to achieve a therapeutic/ideal ACT after a single dose of UFH.

It is also important to note that the equation used for dosage prediction works well only within the range of INR and weight in the data used for model building. It is also limited to the clinical goal of ACT ≥300 seconds.

Conclusions
In conclusion, we found that patients with therapeutic INR (≥2.0) had a lower total UFH requirement, lower bolus requirement, and were more likely to achieve an ACT ≥300 seconds with a single bolus. This confirms the findings from other studies. The unique findings from this study are that the patient’s INR is <2.0 and that a simple equation can accurately resolve this problem. The UFH dosage clearly requires adjustment for different INR to achieve an ACT ≥300 seconds, and use of this data should provide a more efficient means to achieve this end point safely and, hopefully, improve the safety of AF ablation.

Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Anticoagulation management is an important aspect to reduce the risk of thromboembolism related to catheter ablation of atrial fibrillation. Although it is preferred not to interrupt anticoagulation before an atrial fibrillation ablation procedure, there is still a need for reaching an activated clotting time >300 seconds before delivery of ablation current. This study completed a retrospective review to assess the clinical variables that may impact the dose of the first bolus of intravenous heparin to achieve a first activated clotting time >300 seconds. The only relevant features were body weight and the international normalized ratio on the day of the procedure. Based on this data, a formula that incorporates body weight and the international normalized ratio was designed, which readily calculates the single dose of heparin that will reliably achieve the first activated clotting time >300 seconds. This formula was then confirmed, and a simplified table was designed to facilitate calculation of the heparin dose and thus introduction of this methodology into clinical care.
Impact of International Normalized Ratio and Activated Clotting Time on Unfractionated Heparin Dosing During Ablation of Atrial Fibrillation

Ismail Hamam, Emile G. Daoud, Jianying Zhang, Steven J. Kalbfleisch, Ralph Augustini, Marshall Winner, Shane Tsai, Troy E. Rhodes, Mahmoud Houmsse, Zhenguo Liu, Charles J. Love, Jaret Tyler, Molly Sachdev, Raul Weiss and John D. Hummel

Circ Arrhythm Electrophysiol. 2013;6:491-496; originally published online May 17, 2013; doi: 10.1161/CIRCEP.113.979088

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/6/3/491