Viable Prediction for Atrial Fibrillation Recurrence After Catheter Ablation

Vinila Baljepally, Jesse Raffa, and Xiaopeng Zhao

Abstract. Introduction: Atrial fibrillation (AF) is the most common heart rhythm abnormality and the leading cause of stroke. Radiofrequency catheter ablation is used to treat AF but recurrence can occur after the ablation procedure, requiring repeat procedure. A new model to predict AF recurrence after ablation was developed through multivariate analysis. Methods: The variables include demographic, electrocardiographic, echocardiographic, and clinical parameters. In a retrospective review (n=82), 41 patients who underwent repeat ablation for recurrent AF were compared to 41 controls that underwent ablation only once. Results: Of the analyzed parameters, age, female gender and left atrial enlargement were not predictive, but P wave duration (PWD) and obstructive sleep apnea (OSA) were significant predictors of repeat ablation (p-value = 0.0003 and 0.0023, respectively). Based on the analyses, a simple decision tree model was developed, achieving a prediction accuracy of 87% (sensitivity=83%, specificity=90%). Conclusion: The developed PWD and OSA 2-predictor model has good accuracy and sensitivity, both of which make it a viable prediction model for AF recurrence after catheter ablation. The developed model will help doctors: (1) Avoid repeat procedure in patients at high risk of recurrence by exploring alternative treatments (2) Reduce costs by avoiding repeat procedure (3) Correct underlying issues prior to procedure in those at high risk (4) Objectively inform patients about recurrence so they can make an informed decision about whether to undergo the procedure. Adopting predictive models such as ours may therefore improve quality care and reduce costs for AF patients undergoing ablation.

I. Introduction

Atrial fibrillation (AF) is the most common heart rhythm abnormality and a leading cause of stroke affecting nearly 3 million people in the United States. More than 750,000 hospitalizations and 130,000 deaths occur each year because of AF. Incremental costs of AF are about $26 billion each year (Kim et al., 2011).

A normal heartbeat begins as a single electrical impulse that comes from the atria (Figure 1). The impulse sends out an electrical pulse that causes the atria to contract and move blood into the lower ventricles. The electrical current then passes through the AV node, causing the ventricles to contract and relax in a steady, rhythmic sequence (Laske et al., 2009). When AF occurs, the electrical impulse does not follow this order. Instead of one impulse moving through the heart, many impulses begin in the atria and fight to get through. These extra impulses cause the atria to fibrillate, quiver or twitch, in a fast and disorganized way. The chaotic atrial activity can cause several problems including stroke (Hunter, 2014).

Restoring regular sinus rhythm improves symptoms and prevents stroke. Although new developments aimed at treating AF are being explored actively (Camm et al., 2010), current treatment options for AF mainly are medications or radiofrequency catheter ablation. Medications are not very effective and can cause serious side effects (Verma & Natale, 2005); therefore the American College of Cardiology and the Heart Rhythm Society recommended ablation as the preferred treatment for AF (January et al., 2014). Ablation burns or freezes the abnormal tissue through radiofrequency energy and has a greater chance of reducing or eliminating AF (Camm et al., 2010).
While ablation can eliminate AF in 50 to 75% of the patients with a single procedure, many patients experience bothersome recurrence of AF and require repeat ablation (Santangeli & Marchlinski, 2014). Many risk factors for AF recurrence have been identified including age, high blood pressure, enlarged left atrial size, high white blood cell count, Tissue Doppler echo, as well as P wave factors on EKG (Budeus, et al., 2005; Camm et al., 2010; January et al., 2014; Khaykin et al., 2011; Neilan et al., 2013). In addition, obstructive sleep apnea (OSA) was also shown to be associated with the onset of atrial fibrillation as well as an increased risk of recurrence after ablation (Gottlieb 2014).

Thus, predicting which patients will develop recurrent AF after ablation is of great significance. A few prediction models have been developed in the literature to predict AF recurrence after ablation using P wave factors on ECG. Blanche et al. (2012) showed that P wave duration was significantly longer in patients with recurrence compared to those without. They also indicated that a P wave duration of 140ms can discriminate patients prone to recurrence with an overall accuracy of 58.8% (sensitivity = 69%, specificity = 53%, positive predictive value (PPV) = 45%, and negative predictive value (NPV) = 76%). Salah et al. (2013) evaluated various P wave indices to predict AF recurrence post ablation in paroxysmal AF patients. They found that AF recurrence was associated with longer mean P wave duration (122.9 ± 10.3ms vs 104.3 ± 14.2ms, p < 0.001) and larger P wave dispersion (40.7 ± 1.7 ms vs 36.6 ± 3.2 ms, p < 0.001), whereas P wave axis was not different between two groups. Using P wave duration ≥ 125ms as the prediction criterion, Salah et al. achieved an overall accuracy of 80.8% (60% sensitivity, 90% specificity, 72% PPV and 83.7% NPV). Using P wave dispersion ≥ 40ms as the prediction criterion, Salah et al. achieved 70.2% overall accuracy (78% sensitivity, 67% specificity, 51% PPV and 87.6% NPV).

There are several limitations of the existing studies, including: (1) Use of complex P wave characteristics on signal-averaged EKG, routine EKG and echocardiographic parameters etc. to assess risk of recurrence after ablation for AF. Such complex features are difficult to assess easily (2) Failure to include clinical factors such as obstructive sleep apnea (3) No mathematical model existed that includes clinical and EKG factors combined into one study.

We therefore developed a new viable prediction model combining simple clinical and surface EKG predictors that can be used easily to identify patients that may require repeat ablation. We explored multivariate analysis to identify patients at risk for repeat ablation by combining electrocardiographic (ECG), echocardiographic (Echo), and clinical factors. ECG factor included P wave duration (PWD); echocardiographic factor included left atrial enlargement (LAE); and clinical factors included age, female gender and obstructive sleep apnea (OSA). The objective of developing such a simplified model is to predict recurrence by using 2 or 3 easy to obtain simple parameters to assess risks of repeat ablation. Such an assessment will be hugely beneficial for multiple reasons including: 1) Avoid unnecessary procedures that may have a high rate of recurrence (2) Provide an opportunity to correct the underlying issues prior to the procedure in patients that are at high risk for recurrence and (3) Able to objectively inform patients who have a high rate of recurrence so that they can make an informed decision about whether to undergo the procedure based on their chance of recurrence. This may help them to explore alternative treatments before reconsidering the procedure. Overall, this will greatly help improve post-procedural care of AF patients who undergo ablation.
II. Materials and Methods

A. Patient Selection

A retrospective review of data on patients with paroxysmal AF who underwent elective ablation for AF at the University of Tennessee Medical Center from January 1, 2013 to October 10, 2015 was conducted. Only de-identified data, devoid of personal information such as date of birth, medical record number, address, phone numbers etc., were available for review. Of the available patients (n=82), 41 patients, who underwent repeat ablation for recurrence of AF, were used as cases. 41 randomly selected patients, who underwent ablation only once and did not require a second procedure, were chosen as controls. The study was approved by the Institutional Review Board at the University of Tennessee medical center. The study was exempt from requiring patient consent given that the study was retrospective in nature, and all available data were de-identified.

B. Selection of Variables

After consultation of experienced physicians at the University of Tennessee Medical Center, a few important predictors were identified, including P wave duration (PWD) on ECG, left atrial enlargement (LAE) by echocardiogram, age, female gender and obstructive sleep apnea (OSA). ECGs of all the 82 patients were reviewed. The ECG recorded before ablation procedure was the one used for statistical analysis. P-wave duration in lead V1 or lead II, (which ever yielded the widest P wave) was selected for measurement from standard 12 lead ECG during sinus rhythm (Figure 2). Scanning and digitizing of ECG signals from paper records using an optical scanner was performed for all ECG recordings. The onset and offset of the P wave were defined as the start of the upward deflection of the P wave pattern and its return to the isoelectric baseline (Salah, 2013). Echo reports were reviewed and left atrial size was documented. A left atrial size greater than 4.0 was considered as enlarged (Maceira et al., 2010). (Figure 3). Patients’ gender and history of OSA were noted. OSA was considered to be present when a doctor documented it in the chart or if the patient was using a continuous positive airway pressure (CPAP) machine.

![Figure 2: Calculating P-Wave Duration (PWD) from the beginning to the end of the P wave](image1)

![Figure 3: Left Atrial Enlargement by Echocardiogram- Normal Left Atrial Size by Echo on the left, compared to enlarged Left Atrium on the right.](image2)
III. Statistical Analysis

Categorical variables were described using percentages, whereas continuous variables were described using arithmetic means ± standard deviation (SD). The Chi Square test was used to compare categorical variables: gender, left atrial enlargement and obstructive sleep apnea. The Wilcoxon two-sample test was applied for comparison of nonparametric variables: age and PWD. A p-value < 0.05 was considered significant. To determine the relationship between variables and recurrence, univariate and multivariate logistic regression analyses were performed. To determine the predictors of recurrence of AF, multivariate logistic regression analyses were performed (Kleinbaum et al. 1998). First, a full model including all the candidate variables was conducted. Then, the backward selection method was employed to derive a simplified model by eliminating non-significant variables one at a time (Coder and Foreman 2014). The parameter estimated from the full model and the simplified model are presented as the odds ratio (OR) and 95% confidence interval (CI). A receiver operating characteristic (ROC) curve was generated to evaluate PWD and OSA as predictors of repeat ablation; the curve was also used to estimate different cut-off values for both were chosen to evaluate probability of undergoing repeat procedure. All statistical analyses were performed using MATLAB R2016a (Mathworks, 2016). All p-values were 2-sided, with P<0.05 considered statistically significant. To avoid overfitting, we conducted 10-fold cross validation using models in this work and compared the results to the previous models in the literature.

IV. Results

Statistics of the variables are shown in Tables 1. In the study cohort, the mean age is 64.6 years old, 50% of the subjects were female, 45.1% of the subjects had left atrial enlargement (LAE), 43.9% of the subjects had obstructive sleep apnea (OSA), and the mean P wave duration (PWD) was 119.3ms. The patients who underwent repeat procedure and those who didn’t had a similar age (64.8 ± 8.9 Vs 64.5±7.6). Since the incidence of AF is known to increase with age, it is interesting to note that age is not a significant predictor of repeat ablation (p-value=0.8723). Despite a higher percentage of females in the group with repeat procedure (58.8% vs. 41.5%), female gender was not a statistically significant factor for repeat procedure (p-value = 0.2195). Patients who required repeat ablation had presence of LAE (68.3% vs. 22.0 %, p-value < 0.0001) and longer mean PWD (144.6 ± 35.8ms vs 93.9 ± 23.1ms, p-value<0.0001), when compared with patients who underwent ablation only once. Among the patients who underwent repeat ablation, 70.7 % were diagnosed with OSA, while only 17.1% patients were diagnosed with OSA among those without repeat procedure.

Table 2 shows the results of multivariate
logistic regression using all the candidate variables. Age, female gender, and LAE are insignificant (p-value > 0.05), whereas PWD and OSA show strong predictability (p-value < 0.05).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.02</td>
<td>(0.93-1.12)</td>
<td>0.6728</td>
</tr>
<tr>
<td>Gender: Female vs. Male</td>
<td>1.64</td>
<td>(0.39-7.01)</td>
<td>0.5020</td>
</tr>
<tr>
<td>LAE: enlarged vs. Normal</td>
<td>3.82</td>
<td>(0.87-16.73)</td>
<td>0.0755</td>
</tr>
<tr>
<td>PWD (per 5 ms)</td>
<td>1.34</td>
<td>(1.16-1.54)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>OSA: Present vs. Absent</td>
<td>12.07</td>
<td>(2.89-50.45)</td>
<td>0.0006*</td>
</tr>
</tbody>
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Table 2: Multivariate logistic regression analysis using all candidate variables. The parameter estimates from the full model are presented as the odds ratio (OR) and 95% confidence interval (CI). A p value < 0.05 was considered significant*

Using backward selection, redundant predictors including age, female gender, and LAE were eliminated, which led to a simplified logistic regression model that included only PWD and OSA (Table 3).

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Table 3: Eliminating non-significant predictors using backward selection yields a simplified two-variable model. A p value < 0.05 was considered significant*

Longer P wave duration (PWD) and presence of obstructive sleep apnea (OSA) were significant predictors of undergoing repeat procedure. The odds ratio (OR) for PWD is 1.34 per 5ms, showing that the odds for AF recurrence is 1.34 times higher for every 5ms increase in PWD. The OR for OSA is 12.07, indicating that given the same PWD value, OSA increases the odds of AF recurrence by 12.07 times. Figure 4 shows the receiver operating characteristic curve for the two-variable logistic regression model. The area under curve for this model is 0.93.

To further evaluate the performance of our model, we conducted a 10-fold cross validation prediction using the two-variable logistic regression model. Although our model was unique in that it combined PWD with OSA, we wanted to compare our model with previous models in the literature.

Figure 4. ROC curve for the two-variable logistic regression model, where AUC=0.93.

Table 4: Comparison between our 2 - predictor model (PWD + OSA) and those by Blanche et al. (2012) and Salah et al. (2013), respectively. PWD (P wave Duration) vs PWD + OSA (Obstructive Sleep Apnea)

V. Discussion and Conclusions

Catheter ablation is the most effective treatment for AF. Recurrence can happen despite
successful ablation and therefore require repeat ablation. Independent predictors of AF recurrence after Radiofrequency Ablation have been identified in the literature, including age, left atrial size, Tissue Doppler echo, P wave factors on EKG and OSA. However, no previous studies exist where all three aspects—clinical, echocardiographic and EKG parameters—were combined into one study. While LAE has been considered an important factor for predicting AF recurrence post ablation, combining LAE and P wave duration does not improve the prediction power, likely because increased P wave duration is often caused by LAE. Thus, LAE does not provide additional prediction capability. Moreover, a viable mathematical prediction model that combines simple clinical and surface EKG predictors that can be used easily at the bed side to assess this risk has not been developed. By using multivariate analysis to study the influences of these factors and backward selection to eliminate redundant variables, we simplified the regression model to two predictors (PWD and OSA). The performance of the model was evaluated and compared to earlier models in the literature which used only a single predictor of PWD. Our model is more accurate for both the general cohort of patients with prolonged PWD and the cohort with OSA added (PWD + OSA). We believe adding OSA improved the accuracy of our model. Based on the results in Table 4, the model derived here can be represented by a simple decision tree (Figure 5). The overall accuracy was noted to be best in patients who have PWD >90 ms with OSA and a PWD>110 ms in those without OSA. Based on these criteria, the model can be optimized to achieve a higher sensitivity without seriously sacrificing the overall accuracy. Specifically, choosing the threshold as PWD>110ms, the model yields classification results with accuracy = 83%, sensitivity = 92%, and specificity = 79%. Considering the health risks of AF, a model with higher sensitivity may be more desirable to improve the quality of care. Thus, the decision tree in Figure 5 adopted the threshold 110ms for the OSA absent branch. With the model shown in Figure 5, we achieved greater than 90% sensitivity in predicting AF recurrence after catheter ablation surgery for patients with and without known OSA.

Our model is novel in that it uses 2 easily available factors: P wave duration (PWD) and obstructive sleep apnea (OSA) to accurately predict recurrence of AF. Our work is significant, since patients who have OSA can experience AF recurrence with an otherwise seemingly normal P wave duration. This is an important contribution of our study. Additionally, compared to existing criteria, combing P wave duration and OSA greatly improves the accuracy in predicting AF recurrence. Indeed, our study indicates that OSA is more predictive than age, female gender, and echocardiogram.

Limitations of our study include sample
size, single center and retrospective nature. A larger prospective study will eliminate any selection bias and validate the efficacy of the developed model. The model has potentials to be further improved by distinguishing the severity level of OSA and obtaining body mass index (BMI) in future work to increase the accuracy of the prediction.

By combining clinical and EKG parameters, our simple 2-predictor model provides an accurate assessment of risk for AF recurrence after ablation. This information will be valuable to physicians for multiple reasons: 1) High-risk patients who undergo ablation procedure can receive more frequent and intensive monitoring to detect AF recurrence as early as possible (2) Better patient selection of those at lower risk of recurrence (3) Appropriate utilization of resources by avoiding patients at high risk of recurrence (4) Treating underlying causes of recurrence such as OSA prior to repeat procedures to optimize success and prevent recurrence (5) Physicians may consider alternative treatments for high-risk patients (6) By reducing repeat procedure, AF-associated health care costs can be reduced significantly (7) Model helps doctors to discuss risk of recurrence more objectively, so patients at higher risk can make informed decision about whether to undergo a procedure, especially, a repeat procedure (8) Overall, application of our prediction model may help to improve quality of care for AF patients.

VI. Acknowledgements

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References
Gottlieb, D. J. (2014). Sleep apnea and the risk of atrial fibrillation recurrence: structural or functional effects?.