Atrial Fibrillation Complexity Parameters Derived From Surface ECGs Predict Procedural Outcome and Long-Term Follow-Up of Stepwise Catheter Ablation for Atrial Fibrillation

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Background—The success rate of catheter ablation for persistent atrial fibrillation (AF) is still far from satisfactory. Identification of patients who will benefit from ablation is highly desirable. We investigated the predictive value of noninvasive AF complexity parameters derived from standard 12-lead ECGs for AF termination and long-term success of catheter ablation and compared them with clinical predictors.

Methods and Results—The study included a training (93 patients) and a validation set (81 patients) of patients with persistent AF undergoing stepwise radiofrequency ablation. In the training set AF terminated in 81% during catheter ablation, 77% were in sinus rhythm after 6 years and multiple ablations. ECG-derived complexity parameters were determined from a baseline 10-s 12-lead ECG. Prediction of AF termination was similar using only ECG (cross-validated mean area under the curve [AUC], 0.76±0.15) or only clinical parameters (mean AUC, 0.75±0.16). The combination improved prediction to a mean AUC of 0.79±0.13. Using a combined model of ECG and clinical parameters, sinus rhythm at long-term follow-up could be predicted with a mean AUC of 0.71±0.12. In the validation set AF terminated in 57%, 61% were in sinus rhythm after 4.6 years. The combined models predicted termination with an AUC of 0.70 and sinus rhythm at long-term follow-up with an AUC of 0.61. Overall, fibrillation-wave amplitude provided the best rhythm prediction.

Conclusions—The predictive performance of ECG-derived AF complexity parameters for AF termination and long-term success of catheter ablation in patients with persistent AF is at least as good as known clinical predictive parameters, with fibrillation-wave amplitude as the best predictor. (Circ Arrhythm Electrophysiol. 2016;9:e003354. DOI: 10.1161/CIRCEP.115.003354.)

Key Words: atrial fibrillation • catheter ablation • electrocardiography • follow-up studies • heart atria

Catheter ablation (CA) is a successful and widely used therapy in patients with paroxysmal atrial fibrillation (AF). Recently, a systematic meta-analysis confirmed that also patients with persistent AF benefit more from CA than from antiarrhythmic drug (AAD) therapy in terms of maintenance of sinus rhythm (SR). Depending on ablation procedure and rhythm follow-up, reported long-term success rates range from only 25% to 80%. Thus, development of diagnostic means to identify patients likely responding to CA is highly desirable. Several parameters have been suggested that predict success of CA in patients with persistent AF; for example, the duration of the AF episode or left atrial dimensions. However, the exact duration of the AF episode is often difficult to determine, and reports on predictive values of echocardiographic parameters are conflicting. A standard 12-lead ECG is available in every patient with persistent AF before ablation and may reflect the complexity of fibrillatory conduction in the atria during AF.

Not only AF but also structural heart diseases cause a steady and progressive process of structural remodeling characterized by atrial fibrosis with electric uncoupling between muscle bundles. The resulting increase in atrial conduction disturbances and thus complexity of the AF conduction pattern likely underlie the loss of efficacy of AAD treatment and recurrence after CA. Therefore, we sought to investigate AF complexity parameters derived from a standard 12-lead ECG to...
WHAT IS KNOWN

- A single catheter ablation procedure often fails to control persistent atrial fibrillation.
- Identifying patients who are likely to benefit is of interest.

WHAT THE STUDY ADDS

- Atrial fibrillation complexity and frequency parameters derived from the ECG are able to identify patients likely to benefit from catheter ablation.
- The F-wave amplitude is the most powerful ECG-derived predictor.
- Combining ECG-derived parameters with clinical predictors improves outcome prediction.

predict ablation outcome and compare them with known clinical predictors. Many different AF complexity parameters have been studied to predict rhythm outcome in different patient populations. However, in most of these studies, follow-up was limited or only 1 AF complexity parameter or lead was studied. Because of this lack of standardization of advanced ECG analysis, the aim of this study was to compare different time and frequency parameters and determine which parameters and combination of leads provide the optimal outcome prediction. In a training set of patients with persistent AF undergoing CA, we determined the best ECG parameters for prediction of acute outcome (ie, termination during the index ablation) and SR after long-term follow-up. Secondly, we validated these parameters in an external ablation cohort of similar patients with persistent AF. Finally, we compared the identified AF complexity parameters with known clinical predictors of success for both acute and long-term outcomes after CA for AF.

End Points

In both cohorts, the primary procedural end point was the termination of AF without AAD or direct current cardioversion. Termination of AF was defined as conversion of AF into atrial tachycardia, atrial flutter, or SR. In both cohorts, the primary long-term end point was defined as freedom from any documented symptomatic or asymptomatic atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) lasting >30 s after the last ablation procedure with or without AADs.

ECG Analysis

Surface ECGs were digitally recorded with a 1000-Hz sampling frequency during the entire procedure using an EP (electrophysiology) recording system (LabSystem PRO; Bard EP, Lowell, MA). A 60-s 12-lead ECG recording at the start of the procedure was exported for analysis, from which a 10-s ECG recording was selected for primary analysis. ECGs were filtered using a digital zero-phase band-pass filter between 1 and 100 Hz (third order Chebyshev, 20-dB stop-band attenuation) to remove baseline wandering and suppress high-frequency noise. Powerline interference, if present, was removed using a second order infinite impulse response notch filter, centered around 50 Hz. Ventricular signals were cancelled using a modified version of the adaptive singular value QRST cancellation. This method groups QRST windows before QRST template computation, using hierarchical clustering based on window correlation. During QRST cancellation, the signals were temporarily upsampled to 2000 Hz to improve alignment of the QRST templates. Before the analysis, an additional 3-Hz high-pass filter was used to avoid interference caused by the (possible residual) T wave.

The parameters computed on the ECG covered both the frequency domain and the time domain. Frequency domain parameters included dominant frequency (DF), organization index (OI), and spectral entropy (SE). Time domain parameters consisted of the mean fibrillation-wave amplitude (FWA) and sample entropy (SampEn). For the frequency domain parameters, a frequency power spectrum was estimated using Welch power spectral density estimate (3 segments; 4096 points; 50% overlap). The DF was defined as the frequency with the highest power between 3 and 12 Hz in this frequency spectrum. For the OI, the areas between the 2 largest peaks of the frequency spectrum were calculated using a 1-Hz frequency interval centered on each peak. The OI was defined as the ratio of the cumulative areas of these 2 largest peaks and the area of the entire power spectrum. To compute the SE, the spectrum was first normalized to produce a probability mass function, on which Shannon entropy was calculated to give an estimate of SE. For FWA, the mean amplitude of the extracted atrial signal was used. F waves were detected using peak detection with a minimal distance between 2 peaks of 100 ms and a zero crossing within each F wave. SampEn is a nonlinear regularity index. SampEn is calculated on the main atrial wave calculated by filtering with a 1-Hz band around the DF. The number of samples used for SampEn computation was 3 within a tolerance of r=0.35 times the SE.

Endocardial Signals

Endocardial signals were recorded from the left atrial appendage (LAA) and right atrial appendage (RAA) between ablation steps using a 10-pole circumferential mapping catheter (Lasso; Biosense-Webster, Diamond Bar, CA) or a quadripolar, irrigated tip ablation catheter (ThermoCool: Biosense-Webster). The signals were exported from the EP recording system and imported in custom-made MatLab
To preprocess the signals for robust DF measurements, we used the method suggested by Ng et al.\textsuperscript{18} First, the endocardial signals were filtered using a 40- to 250-Hz band-pass filter. The remaining signal was then rectified followed by a 20-Hz low-pass filter step.\textsuperscript{18} On this filtered signal, a fast Fourier transform was performed to provide a power spectrum on which the DF could be calculated. These invasive recordings were compared with simultaneous ECG recordings.

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS statistics 21 and MatLab R2013a. Continuous variables are reported as mean±SD or median and range. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Comparison between groups was performed using a Student \( t \) test or a Mann–Whitney \( U \) test in the case of a bimodal end point; the latter test was for non-normally distributed data. Categorical variables are reported as number and percentage and are compared using the Fisher exact test. To build the prediction models, a forward stepwise logistic regression analysis with a 5-fold cross validation was used. Cross validation was performed to get unbiased estimates of the model fit in the training set. Only parameters with a univariate \( P \) value \( \leq 0.10 \) were included in the models. For validation of the models, we used the same parameters and coefficients as identified in the initial training set. Correlations between endocardial and surface DF are calculated using Pearson’s correlation. Differences between ablation steps in patients with right-sided ablation are calculated using repeated measures ANOVA with Bonferroni correction for multiple comparisons. A \( P \) value of <0.05 was considered statistically significant.

**Results**

The training set comprised 93 patients. In 75 patients (81\%), the procedural end point of AF termination was achieved, and 72 patients (77\%) were in SR at the end of the median follow-up period of 6 (5–6.7) years with a median of 2 (1–3) procedures. The validation cohort consisted of 81 patients, and AF terminated in 46 patients (57\%). In 62 patients of the validation cohort, long-term follow-up data were available. After a median follow-up of 4.6 (4.3–5) years and 2 (2–4) ablations, 38 patients (61\%) were in SR. The study overview is presented in Figure 1, and the baseline characteristics of both cohorts are provided in Table 1.

**Table 1. Baseline Characteristics of the Training and the Validation Cohort**

<table>
<thead>
<tr>
<th></th>
<th>Training, n=93</th>
<th>Validation, n=81</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57±11</td>
<td>60±9</td>
<td>0.018</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>77 (83)</td>
<td>66 (81)</td>
<td>0.821</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7±3.8</td>
<td>28.3±4.4</td>
<td>0.033</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>36 (39)</td>
<td>59 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>13 (14)</td>
<td>14 (17)</td>
<td>0.548</td>
</tr>
<tr>
<td>HF, n (%)</td>
<td>21 (23)</td>
<td>20 (25)</td>
<td>0.743</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>8 (9)</td>
<td>5 (6)</td>
<td>0.543</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>6 (6)</td>
<td>8 (9)</td>
<td>0.407</td>
</tr>
<tr>
<td>Total AF duration, mo</td>
<td>66 (36–120)</td>
<td>60 (24–108)</td>
<td>0.078</td>
</tr>
<tr>
<td>Current AF episode, mo</td>
<td>13 (7–24)</td>
<td>10 (4–24)</td>
<td>0.059</td>
</tr>
<tr>
<td>Current use amiodarone, n (%)</td>
<td>24 (26)</td>
<td>30 (37)</td>
<td>0.110</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>58±13</td>
<td>57±12</td>
<td>0.860</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>48±8</td>
<td>47±6</td>
<td>0.617</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>260±72</td>
<td>223±54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF time, min</td>
<td>95±30</td>
<td>92±23</td>
<td>0.415</td>
</tr>
<tr>
<td>Termination during ablation, n %</td>
<td>75 (81)</td>
<td>46 (57)</td>
<td>0.001</td>
</tr>
<tr>
<td>Long-term SR, n (%)</td>
<td>72 (77)</td>
<td>38 (61)*</td>
<td>0.030</td>
</tr>
<tr>
<td>Follow-up duration, y</td>
<td>6 (5–6.7)</td>
<td>4.6 (4.3–5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of procedures</td>
<td>2 (1–3)</td>
<td>2 (2–4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( \text{AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction; RF, radiofrequency; and SR, sinus rhythm.} \)

*Out of 62 patients.
Prediction of AF Termination During Ablation
The best clinical predictor of the procedural end point was the duration of the current AF episode. Univariate differences between the patients with and without AF termination for both cohorts are presented in Tables I and II in the Data Supplement. The cross-validated prediction model with only clinical parameters had a mean area under the curve (AUC) of 0.75±0.16 containing the duration of the current AF episode and left atrial diameter. Figure 2 shows an example of lead V1 and the corresponding power spectrum of 2 patients. In the patient on the left, AF terminated during the procedure and long-term success of the ablation was achieved. In the patient on the right, neither acute termination nor long-term success could be achieved. Note the higher FWA, higher OI, and lower DF in the patient with success of CA. The ECG parameter providing the best prediction was the FWA. Logistic regression analysis allowing combination of different ECG parameters resulted in a model with a mean AUC of 0.76±0.15 containing FWA in lead aVR and the DF in lead aVF. Combining both ECG and clinical predictors revealed a model with a mean AUC of 0.79±0.13 containing FWA in lead aVR and the duration of the current AF episode. The predictive value of these models did not differ significantly. The models identified in the training set predicted acute outcome in the validation cohort with an AUC varying from 0.60 to 0.72. Table 2 provides a complete overview of the models. Interestingly, the model based on ECG parameters had a higher predictive value (0.72) than the one based on the clinical predictors (0.60).

Prediction of Long-Term Arrhythmia Outcome
The univariate differences for the long-term outcome are presented in Tables III and IV in the Data Supplement. The model, including clinical parameters, included the duration of the current AF episode and predicted SR after long-term follow-up with a mean AUC of 0.66±0.15. The model, including only ECG parameters, consisted of the FWA in

Table 2. Prediction Models

<table>
<thead>
<tr>
<th>Parameters Included</th>
<th>Training Set (Cross Validated), AUC</th>
<th>Validation Set, AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Termination during index procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>0.75±0.16</td>
<td>0.60</td>
</tr>
<tr>
<td>ECG</td>
<td>0.76±0.15</td>
<td>0.72</td>
</tr>
<tr>
<td>Combined</td>
<td>0.79±0.13</td>
<td>0.70</td>
</tr>
<tr>
<td>Long-term success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>0.66±0.15</td>
<td>0.61</td>
</tr>
<tr>
<td>ECG</td>
<td>0.69±0.13</td>
<td>0.63</td>
</tr>
<tr>
<td>Combined</td>
<td>0.71±0.12</td>
<td>0.61</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AUC, area under the curve; DF, dominant frequency; FWA, fibrillation-wave amplitude; and LA, left atrium.
lead V6 with a mean AUC of 0.69±0.13. The combination of these parameters predicted long-term SR with a mean AUC of 0.71±0.12 (not significantly higher). These models predicted long-term SR in the 62 patients in the validation cohort although the predictive value was lower than that in the training cohort (Table 2). Table 3 represents the prediction models for long-term outcome incorporating data from the electrophysiological procedure. Including the procedural end point (acute AF termination) in the long-term prediction models improved these models in both the training and validation sets.

### Correlation Between Endocardial Recordings and Corresponding Surface Leads
To investigate to what extent the ECG parameters measured noninvasively reflect the electrophysiological properties measured invasively, we correlated noninvasive DF with the activation rate in the right and left atria. In 54 patients of the training cohort, surface ECG recordings could be compared with simultaneous RAA recordings and in 51 patients with LAA recordings. Figure 3 shows an example of the DF in the right and left atria and on the surface leads V1 and aVL. In this patient, the activation frequency was higher in the right atrium than in the left atrium. These frequencies corresponded well to the frequencies in the leads V1 and aVL. Overall, the LAA DF showed a significant correlation with all surface leads, but the correlation was the strongest with lead I (r=0.733; P<0.001). In contrast, the RAA DF showed a highly significant correlation with lead V1 (r=0.870; P<0.001). The correlation coefficient decreased toward the leftward precordial leads as shown in Figure 4.

### Complexity Parameters During Ablation
To investigate how local changes of the AF cycle length and AF complexity alter the ECG parameters in various leads, we studied the behavior of the DF and FWA during CA. In 60 patients of the training cohort, ECGs were available for analysis after every ablation step. If AF terminated during a step, we examined the last ECG before termination. Overall, the DF decreased during every subsequent step. Figure 5 shows a representative example of a patient with a right to left frequency gradient with simultaneous endocardial recordings in the left atrial appendage (LAA) and the right atrial appendage (RAA) and surface ECG recordings. Top, Invasive recordings. Bottom, Noninvasive recordings.
example; note that the DF becomes lower in both leads V1 and I. The mean DF of the first ECG of all the patients combined was significantly higher compared with the last ECG ($P<0.001$) on all leads (Table V in the Data Supplement). Interestingly, not all leads behaved in the same way. In the 11 patients who needed right atrial ablation, overall, the DF in lead V1 decreased significantly during ablation. However, the DF decreased only after pulmonary vein isolation (PVI) and right atrial ablation but not after left-sided ablation (Figure 6). In contrast, the DF in lead V6 decreased during left-sided ablation steps but did not further decrease during right-sided ablation. In most leads, there was a significant difference between the FW A before and at the end of the ablation (Table VI in the Data Supplement). Also in the case of FW A, left and right-sided ablation differently affected the ECG leads. In patients with right atrial ablation, the FW A in lead V1 increased first after PVI and decreased thereafter, although not significantly. FW A in lead V6 decreases significantly during ablation and was affected most by PVI and left atrial ablation ($P=0.001$; Figure 6).

**Discussion**

This study shows that ECG-derived AF complexity parameters predict success of CA in patients with persistent AF. Their predictive performance in the training cohort is at least as good as previously identified clinical predictors. The best non-invasive AF complexity parameter for the prediction of both AF termination and long-term success is the FW A. The results could be successfully validated in an external ablation cohort supporting their general relevance for prediction of outcome in patients undergoing CA.

**Outcome Prediction Using Various ECG AF Complexity Parameters**

This study shows that a low FW A indicates a less favorable ablation outcome. A low FW A can be caused by an increase in heterogeneity in the atrium, for example, because of a higher number of waves and breakthroughs in patients with complex AF. This increased heterogeneity leads to more cancellation and hence the lower F waves. The predictive value of FW A for termination of persistent AF by ablation has been described before. However, these previous studies focused on lead V1 and did not provide a comparison with other AF complexity parameters or other leads. Furthermore, ECG analysis was done manually. An advantage of automated ECG analysis is that it enables analysis of smaller F waves in, for instance, lead V6 where manual FW A analysis is hardly possible. Furthermore, automated analysis might prevent a bias potentially introduced by choosing large and easily identifiable F waves. This may also explain the slightly lower FW A study in comparison with manually analyzed F waves. In line with a small previous study, our data show the importance of incorporating all available surface leads, including leftward oriented leads, despite their less favorable signal/noise ratio.

We studied a wide variety of time and frequency parameters and their predictive value. DF is the most frequently studied parameter in this respect, and as in our cohort, patients with a lower DF or longer atrial fibrillation cycle length have a more favorable rhythm outcome. SE and OI are calculated based on a larger part of the frequency spectrum than only the DF peak and, therefore in theory, could more reliably reflect disorganized electric activity. These parameters that measure

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**Table V**

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>aVR</th>
<th>aVL</th>
<th>aVF</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAA</td>
<td>0.277</td>
<td>0.220</td>
<td>0.415</td>
<td>0.452</td>
<td>0.620</td>
<td>0.499</td>
<td>0.870</td>
<td>0.796</td>
<td>0.644</td>
<td>0.457</td>
<td>0.486</td>
<td>0.336</td>
</tr>
<tr>
<td>LAA</td>
<td>0.733</td>
<td>0.571</td>
<td>0.300</td>
<td>0.596</td>
<td>0.686</td>
<td>0.409</td>
<td>0.616</td>
<td>0.464</td>
<td>0.590</td>
<td>0.599</td>
<td>0.676</td>
<td>0.694</td>
</tr>
</tbody>
</table>

**Figure 4.** Correlation between the invasively and noninvasively measured dominant frequency (DF). The table shows the Pearson $r$ for the DF in every lead with the invasive cycle length measured in the right atrial appendage (RAA) and the left atrial appendage (LAA). **Bottom,** Best correlation with the RAA frequency (with lead V1) and with the LAA (lead I).
the regularity or organization of the frequency spectrum, however, seemed to have limited predictive performance. They have been used to predict ablation outcome in a limited number of studies. In 1 study, stability of the frequency spectrum predicted AF termination during the ablation and freedom of atrial arrhythmias after a limited follow-up of 3 months. SampEn has not been used to predict ablation outcome before. In our study, SampEn showed a low predictive value.

Most importantly, we showed that a model, including AF complexity parameters, predicted acute and long-term outcomes not only in 1 specific cohort but also in a persistent AF patient cohort in a different center.

**Correlation Between Invasive and Noninvasive Parameters for Fibrillatory Rate**

To confirm that the ECG accurately reflects the electrophysiological properties of the fibrillating atrium, we directly compared simultaneous endocardial and ECG recordings. We demonstrate that the DF in the LAA correlates best with leftward leads on a standard ECG, such as lead I, aVL, or V6. Vice versa, DF in RAA correlates best with rightward leads, such as V1. Figure 3 shows results in a patient with a frequency gradient. Both the left and right atrial frequencies can be determined from the surface ECG. The highest peak in lead V1 equals the atrial frequency of the RAA, whereas the DF of aVL reflects the atrial frequency in the LAA. This finding further supports the notion that the electric information in individual leads may reflect the electric properties in different areas of the atria (left versus right), which may be useful for our understanding of the mechanisms of AF in individual patients.

**Evolution of the ECG During Stepwise Ablation**

If the ECG leads reflect activation frequencies in specific regions in the atria, the ECG should respond to local ablation...
steps, which have been demonstrated to change the atrial fibrillation cycle length nearby the ablation site. Overall, we found a decrease in DF during the ablation. Importantly, the extent of the decrease was clearly related to the location of the ablation. In patients undergoing ablation both in the right and the left atrium, there was a trend toward a larger effect of left atrial ablation on DF in V6, whereas the right atrial ablation had a larger effect on lead V1. This is consistent with a preferential prolongation of atrial fibrillation cycle length in the ablated area.

F waves are higher in patients in whom AF terminated during ablation, and SR during long-term follow-up was achieved. Therefore, a higher FWA might reflect a more organized AF pattern as discussed before. Because of the increasing organization of AF during ablation, we expected that FWA would increase during the ablation. Surprisingly, this was not the case. There was even a trend to a decrease in FWA. Also, here it is important to note the behavior of different leads. In lead V1, the FWA showed a slight increase after PVI but decreased during the subsequent ablation steps. The decrease was most pronounced after right-sided ablation. The FWA in lead V1 might have increased after PVI because of abolition of leftward oriented F-wave vectors after PVI, that is, vectors pointing away from V1. In lead V6, there was even a significant decrease in FWA with the largest contribution by left-sided ablation. The decrease in FWA during CA might be because of electric isolation of atrial tissue from the rest of the atrium during the procedure, thereby reducing the atrial mass contributing to the generation of F waves. The hypothesis that the FWA decreases because of the decrease in atrial mass is supported by studies investigating P-wave alterations during CA, with most of these studies reporting a shortening of the P-wave duration and decrease in P-wave area after CA as an indicator of a decreased atrial mass.28,29

Comparison With Clinical Predictors
New predictive markers for outcome are only useful if they outperform existing clinical markers that are easy to assess or if in combination with existing predictors, the outcome prediction can be improved. For this reason, we compared the predictive performance of our ECG markers with known clinical parameters of favorable rhythm outcomes, such as a shorter AF duration and a smaller left atrial diameter.4,5,7,8,30 Also, we showed that adding ECG parameters to known clinical parameters improves prediction. The prediction of success of CA using a combination of AF complexity parameters proved to be at least as good as the prediction using known clinical parameters. Although the duration of the current AF episode is an important parameter for outcome prediction, it can be difficult to assess because of the asymptomatic or slightly symptomatic nature of some AF episodes. Our study demonstrates that using objective ECG parameters may serve as a reasonable alternative for outcome prediction in the setting of CA in persistent AF.

Added Value of AF Termination During Index Procedure as a Predictor of Long-Term Outcome
As shown in Table 2, the predictive value of both clinical and ECG parameters is higher for the prediction of the acute rhythm outcome than that for the long-term outcome. It is not
surprising that (electrocardiographic) properties of the present AF episode are related more robustly to acute outcome of the index ablation than to the rhythm 5 years later. Still, the electric complexity before the index ablation predicted success in the long term. Recently, several studies identified termination of AF during the index procedure as a predictor of long-term maintenance of SR, suggesting that terminating AF may serve as an appropriate procedural end point.5,6 Indeed, the current data demonstrate that adding information about success of the first procedure substantially improved long-term prediction.

Clinical Implications

Although in paroxysmal AF, success of CA can be obtained in a high percentage of patients, in persistent AF, success rates are lower. The noninvasive atrial complexity parameters identified in this study may provide a useful tool to identify those patients with (long standing) persistent AF who likely benefit from CA and others in whom CA is less likely to be effective. Implementing ECG complexity together with other predictive parameters in an individualized stratification model could potentially prevent ablations in patients with a low chance of success during follow-up and thereby avoid unnecessary procedural risks. Alternatively, if a rhythm control strategy is still preferred in patients with a high AF complexity, more aggressive ablation regimens, such as extensive radiofrequency ablation or a hybrid surgical ablation, should be chosen as a first treatment option.31 The FWA was identified as the complexity parameter with the highest predictive value for both acute AF termination and long-term success. This parameter is both intuitive and easy to calculate from the ECG leads and could be implemented in clinical practice without large obstacles.

Limitations

Although this is the largest study so far investigating the predictive value a variety of ECG-derived complexity parameters in a population undergoing CA, the study population was still of limited size. Also, there is some evidence that alternative lead placement provides additional information about the fibrillatory process. However, in this study, we were limited to the standard 12-lead ECG and therefore not able to investigate whether a different lead placement improves prediction. For direct comparison between invasive and noninvasive complexity parameters, we were limited to the LAA and RAA measurements. Usually, the appendages have less complex electrograms than other locations in the left and or the right atrium. For this reason, we did not compare invasive complexity parameters, such as fractionation with the noninvasive parameters of complexity. As we used Holter monitoring for rhythm follow-up, we may not have detected some self-terminating episodes of AF. However, no persistent recurrence was documented in patients booked as SR. Also, we did not have specific information about the patients’ AAD therapies other than amiodarone. AADs and upstream therapy medication may influence the atrial remodeling process and suppress recurrences and thereby have affected our prediction models. Furthermore, we did not include the possible predictive value of blood biomarkers in our study. There is evidence that elevated cardiac biomarkers, such as B-type natriuretic peptide or markers of inflammation, predict ablation outcome.12,33 Also, the possible predictive value of single-nucleotide variants as shown before was not included in this study.34 Follow-up data in the validation cohort were available in only 77% of the patients. However, baseline characteristics did not differ between those patients and patients with complete follow-up. We were unable to study the relationship between ECG complexity parameters and effects of different sets of ablation lesions because the latter was not randomized that precluded an unbiased assessment. Finally, data from follow-up ablations are useful to analyze the mechanisms of arrhythmia recurrence and to correlate these mechanisms to AF complexity. However, data on follow-up ablations was too limited. Future research should address these research questions.

Conclusions

ECG-derived complexity parameters provide reliable information on the electrophysiological properties of the fibrillating atrium and can predict both acute termination of AF during CA and success of rhythm control during long-term follow-up. The predictive performance of ECG-derived parameters is at least as good as known clinical predictive parameters. Complexity analysis of the standard 12-channel ECG may help to identify patients in whom CA is likely to be effective and also those patients in whom SR cannot be maintained even after several CA procedures.

Acknowledgments

We thank Katrin Fuerst for her assistance in the data collection.

Sources of Funding

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Disclosures

Dr Schotten received research funding from the European Network for Translational Research in Atrial Fibrillation, the Center for Translational Molecular Medicine (COHFAReurope), the Netherlands Genomics Initiative (preseed grant), the Leducq Foundation (ENAFRA), the Dutch Heart Foundation (CVON), Roche Diagnostics (Switzerland), Bayer Healthcare (Germany), and Medtronic (United States). U. Schotten received consultant fees from Roche Diagnostics (Switzerland) and Bayer Healthcare (Germany).

References


Atrial Fibrillation Complexity Parameters Derived From Surface ECGs Predict Procedural Outcome and Long-Term Follow-Up of Stepwise Catheter Ablation for Atrial Fibrillation

Theo Lankveld, Stef Zeemering, Daniel Scherr, Pawel Kuklik, Boris A. Hoffmann, Stephan Willems, Burkert Pieske, Michel Haïssaguerre, Pierre Jaïs, Harry J. Crijns and Ulrich Schotten

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SUPPLEMENTAL MATERIAL

Results

The supplement tables 1 – 4 provide an overview of the univariate differences between the parameters both for the acute (tables 1 and 2) and long-term outcome (tables 3 and 4). Tables 1 and 3 represent the training cohort and tables 2 and 4 represent the validation cohort. Of the electrocardiographic parameters only significant differences of the parameters are listed here.

Supplement table 1: Univariate differences AF termination training cohort

<table>
<thead>
<tr>
<th></th>
<th>Termination</th>
<th>No Termination</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=75</td>
<td>N=18</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>56.1 ± 9.6</td>
<td>58.7 ± 14.8</td>
<td>0.480</td>
</tr>
<tr>
<td>Male gender</td>
<td>63 (84%)</td>
<td>14 (78%)</td>
<td>0.530</td>
</tr>
<tr>
<td>BMI</td>
<td>26.5 ± 3.8</td>
<td>27.9 ± 3.9</td>
<td>0.257</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (37%)</td>
<td>8 (44%)</td>
<td>0.578</td>
</tr>
<tr>
<td>CAD</td>
<td>11 (15%)</td>
<td>2 (11%)</td>
<td>0.696</td>
</tr>
<tr>
<td>HF</td>
<td>15 (20%)</td>
<td>6 (33%)</td>
<td>0.224</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>6 (8%)</td>
<td>2 (11%)</td>
<td>0.672</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (5%)</td>
<td>2 (11%)</td>
<td>0.370</td>
</tr>
<tr>
<td>OSAS</td>
<td>7 (9%)</td>
<td>3 (17%)</td>
<td>0.367</td>
</tr>
<tr>
<td>COPD</td>
<td>3 (4%)</td>
<td>1 (6%)</td>
<td>0.770</td>
</tr>
<tr>
<td>Total AF duration (months)</td>
<td>60 [10-240]</td>
<td>120 [12-204]</td>
<td>0.059</td>
</tr>
<tr>
<td>Current AF episode (months)</td>
<td>12 [2-84]</td>
<td>24 [8-168]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Episode &gt; 12 months</td>
<td>33 (44%)</td>
<td>14 (78%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Previous AAD use</td>
<td>2.7 ± 1.0</td>
<td>2.7 ± 1.0</td>
<td>0.970</td>
</tr>
<tr>
<td>Current use Amiodarone</td>
<td>18 (24%)</td>
<td>6 (33%)</td>
<td>0.416</td>
</tr>
<tr>
<td>Parameter</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58.0 ± 12.9</td>
<td>56.6 ± 13.3</td>
<td>0.677</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>46.5 ± 6.7</td>
<td>53.4 ± 9.7</td>
<td>0.010</td>
</tr>
</tbody>
</table>

**ECG parameters (only significant differences are shown)**

<table>
<thead>
<tr>
<th>Lead</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SE lead II</td>
<td>3.95 ± 0.51</td>
<td>4.25 ± 0.52</td>
<td>0.028</td>
</tr>
<tr>
<td>SE lead aVF</td>
<td>3.91 ± 0.49</td>
<td>4.19 ± 0.55</td>
<td>0.031</td>
</tr>
<tr>
<td>FWA lead I (µV)</td>
<td>27 ± 10</td>
<td>21 ± 9</td>
<td>0.010</td>
</tr>
<tr>
<td>FWA lead II (µV)</td>
<td>52 ± 18</td>
<td>37 ± 15</td>
<td>0.002</td>
</tr>
<tr>
<td>FWA lead III (µV)</td>
<td>56 ± 17</td>
<td>40 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>FWA lead aVR (µV)</td>
<td>32 ± 11</td>
<td>23 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td>FWA lead aVL (µV)</td>
<td>35 ± 10</td>
<td>27 ± 10</td>
<td>0.004</td>
</tr>
<tr>
<td>FWA lead aVF (µV)</td>
<td>52 ± 17</td>
<td>37 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>FWA lead V1 (µV)</td>
<td>62 ± 30</td>
<td>45 ± 21</td>
<td>0.026</td>
</tr>
<tr>
<td>FWA lead V4 (µV)</td>
<td>46 ± 18</td>
<td>37 ± 13</td>
<td>0.035</td>
</tr>
<tr>
<td>FWA lead V5 (µV)</td>
<td>39 ± 16</td>
<td>32 ± 9</td>
<td>0.046</td>
</tr>
<tr>
<td>FWA lead V6 (µV)</td>
<td>34 ± 13</td>
<td>27 ± 7</td>
<td>0.031</td>
</tr>
</tbody>
</table>

### Supplement table 2: Univariate differences AF termination validation cohort

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<tr>
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<th>Termination N=45</th>
<th>No Termination N=36</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>60 ± 9</td>
<td>60 ± 9</td>
<td>0.934</td>
</tr>
<tr>
<td>Male gender</td>
<td>39 (87%)</td>
<td>27 (75%)</td>
<td>0.381</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>28 ± 4</td>
<td>28 ± 5</td>
<td>0.865</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (78%)</td>
<td>24 (67%)</td>
<td>0.451</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td>8 (18%)</td>
<td>6 (17%)</td>
<td>0.977</td>
</tr>
<tr>
<td>HF</td>
<td>10 (22%)</td>
<td>10 (28%)</td>
<td>0.480</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>3 (7%)</td>
<td>2 (6%)</td>
<td>0.881</td>
</tr>
<tr>
<td>Stroke</td>
<td>5(11%)</td>
<td>3 (8%)</td>
<td>0.731</td>
</tr>
<tr>
<td><strong>Total AF duration (months)</strong></td>
<td>60 [24 – 120]</td>
<td>48 [18 – 96]</td>
<td>0.198</td>
</tr>
<tr>
<td>Episode &gt; 12 months</td>
<td>10 (22%)</td>
<td>19 (53%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Current use Amiodarone</td>
<td>13 (29%)</td>
<td>17 (47%)</td>
<td>0.061</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>58 ± 14</td>
<td>57 ± 10</td>
<td>0.821</td>
</tr>
<tr>
<td><strong>LA diameter (mm)</strong></td>
<td>46 ± 6</td>
<td>48 ± 6</td>
<td>0.287</td>
</tr>
</tbody>
</table>

**ECG parameters (only significant differences are shown)**

<table>
<thead>
<tr>
<th></th>
<th>Termination</th>
<th>No Termination</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF lead I (Hz)</td>
<td>6.00 ± 0.89</td>
<td>6.56 ± 1.32</td>
<td>0.027</td>
</tr>
<tr>
<td>DF lead aVR (Hz)</td>
<td>5.90 ± 0.78</td>
<td>6.38 ± 1.07</td>
<td>0.022</td>
</tr>
<tr>
<td>FWA lead I (µV)</td>
<td>24 ± 10</td>
<td>20 ± 8</td>
<td>0.028</td>
</tr>
<tr>
<td>FWA lead II (µV)</td>
<td>51 ± 20</td>
<td>39 ± 13</td>
<td>0.002</td>
</tr>
<tr>
<td>FWA lead III (µV)</td>
<td>53 ± 19</td>
<td>41 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>FWA lead aVR (µV)</td>
<td>30 ± 10</td>
<td>23 ± 6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FWA lead aVL (µV)</td>
<td>33 ± 12</td>
<td>27 ± 9</td>
<td>0.016</td>
</tr>
<tr>
<td>FWA lead aVF (µV)</td>
<td>51 ± 18</td>
<td>39 ± 14</td>
<td>0.002</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>FWA lead V1 (µV)</td>
<td>82 ± 32</td>
<td>51 ± 17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FWA lead V2 (µV)</td>
<td>63 ± 24</td>
<td>49 ± 23</td>
<td>0.009</td>
</tr>
<tr>
<td>FWA lead V3 (µV)</td>
<td>58 ± 21</td>
<td>45 ± 17</td>
<td>0.006</td>
</tr>
<tr>
<td>FWA lead V4 (µV)</td>
<td>49 ± 17</td>
<td>38 ± 14</td>
<td>0.003</td>
</tr>
<tr>
<td>FWA lead V5 (µV)</td>
<td>42 ± 15</td>
<td>33 ± 13</td>
<td>0.005</td>
</tr>
<tr>
<td>FWA lead V6 (µV)</td>
<td>35 ± 13</td>
<td>28 ± 11</td>
<td>0.012</td>
</tr>
</tbody>
</table>

**Supplement table 3: Univariate differences long-term success training cohort**

<table>
<thead>
<tr>
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<th>Long-term success</th>
<th>No long-term success</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>N=72</strong></td>
<td><strong>N=21</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>57 ± 11</td>
<td>56 ± 11</td>
<td>0.883</td>
</tr>
<tr>
<td>Male gender</td>
<td>61 (85%)</td>
<td>16 (76%)</td>
<td>0.362</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7 ± 3.9</td>
<td>27 ± 3.7</td>
<td>0.784</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (38%)</td>
<td>9 (43%)</td>
<td>0.657</td>
</tr>
<tr>
<td>CAD</td>
<td>11 (15%)</td>
<td>2 (10%)</td>
<td>0.503</td>
</tr>
<tr>
<td>HF</td>
<td>13 (18%)</td>
<td>8 (38%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>5 (7%)</td>
<td>3 (14%)</td>
<td>0.291</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (3%)</td>
<td>4 (19%)</td>
<td>0.008</td>
</tr>
<tr>
<td>OSAS</td>
<td>5 (7%)</td>
<td>5 (24%)</td>
<td>0.028</td>
</tr>
<tr>
<td>COPD</td>
<td>2 (3%)</td>
<td>2 (10%)</td>
<td>0.180</td>
</tr>
<tr>
<td>Total AF duration (months)</td>
<td>60 [36 – 108]</td>
<td>84 [57 – 174.5]</td>
<td>0.031</td>
</tr>
<tr>
<td>Current AF episode (months)</td>
<td>12 [6 – 22.5]</td>
<td>24 [12 – 57]</td>
<td>0.025</td>
</tr>
<tr>
<td>Episode &gt; 12 months</td>
<td>33 (46%)</td>
<td>14 (67%)</td>
<td>0.093</td>
</tr>
<tr>
<td>Previous AAD use</td>
<td>2.7 ± 0.9</td>
<td>2.5 ± 1.2</td>
<td>0.356</td>
</tr>
<tr>
<td>Current use Amiodarone</td>
<td>18 (25%)</td>
<td>6 (29%)</td>
<td>0.742</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 13</td>
<td>55 ± 13</td>
<td>0.282</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>47 ± 7</td>
<td>51 ± 9</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>ECG parameters (only significant differences are shown)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FWA lead I (µV)</td>
<td>27 ± 10</td>
<td>22 ± 9</td>
<td>0.043</td>
</tr>
<tr>
<td>FWA lead II (µV)</td>
<td>51 ± 18</td>
<td>41 ± 17</td>
<td>0.032</td>
</tr>
<tr>
<td>FWA lead aVR (µV)</td>
<td>32 ± 11</td>
<td>25 ± 9</td>
<td>0.017</td>
</tr>
<tr>
<td>FWA lead aVF (µV)</td>
<td>51 ± 17</td>
<td>42 ± 17</td>
<td>0.043</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------</td>
<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td>FWA lead V5 (µV)</td>
<td>40 ± 16</td>
<td>32 ± 11</td>
<td>0.030</td>
</tr>
<tr>
<td>FWA lead V6 (µV)</td>
<td>34 ± 13</td>
<td>27 ± 9</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Supplement table 4: Univariate differences long-term follow-up validation cohort

<table>
<thead>
<tr>
<th></th>
<th>Long-term success</th>
<th>No long-term success</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>N=38</td>
<td>N=24</td>
<td></td>
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<tr>
<td>Age (y)</td>
<td>61 ± 9</td>
<td>60 ± 10</td>
<td>0.614</td>
</tr>
<tr>
<td>Male gender</td>
<td>30 (79%)</td>
<td>19 (79%)</td>
<td>0.984</td>
</tr>
<tr>
<td>BMI</td>
<td>28.2 ± 4.3</td>
<td>28.7 ± 4.5</td>
<td>0.726</td>
</tr>
<tr>
<td>Hypertension</td>
<td>28 (74%)</td>
<td>17 (71%)</td>
<td>0.806</td>
</tr>
<tr>
<td>CAD</td>
<td>4 (11%)</td>
<td>6 (25%)</td>
<td>0.131</td>
</tr>
<tr>
<td>HF</td>
<td>5 (13%)</td>
<td>9 (38%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1 (3%)</td>
<td>2 (8%)</td>
<td>0.308</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (11%)</td>
<td>4 (17%)</td>
<td>0.482</td>
</tr>
<tr>
<td>Total AF duration (months)</td>
<td>60 [24 – 120]</td>
<td>48 [24 – 108]</td>
<td>0.778</td>
</tr>
<tr>
<td>Current AF episode (months)</td>
<td>9 [3 – 24]</td>
<td>18 [6 – 30]</td>
<td>0.167</td>
</tr>
<tr>
<td>Episode &gt; 12 months</td>
<td>11 (29%)</td>
<td>12 (50%)</td>
<td>0.070</td>
</tr>
<tr>
<td>Current use Amiodarone</td>
<td>14 (39%)</td>
<td>10 (42%)</td>
<td>0.704</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60 ± 14</td>
<td>55 ± 11</td>
<td>0.242</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>45 ± 4</td>
<td>51 ± 6</td>
<td>0.003</td>
</tr>
<tr>
<td>ECG parameters (only significant differences are shown)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DF lead I (Hz)</td>
<td>5.99 ± 0.93</td>
<td>6.68 ± 1.53</td>
<td>0.031</td>
</tr>
<tr>
<td>DF lead aVR (Hz)</td>
<td>5.86 ± 0.78</td>
<td>6.33 ± 0.85</td>
<td>0.031</td>
</tr>
<tr>
<td>DF lead V5 (Hz)</td>
<td>5.75 ± 0.74</td>
<td>6.17 ± 0.83</td>
<td>0.039</td>
</tr>
<tr>
<td>OI lead II</td>
<td>0.78 ± 0.10</td>
<td>0.72 ± 0.12</td>
<td>0.044</td>
</tr>
<tr>
<td>FWA lead II (µV)</td>
<td>51 ± 18</td>
<td>40 ± 14</td>
<td>0.019</td>
</tr>
<tr>
<td>FWA lead III (µV)</td>
<td>53 ± 19</td>
<td>41 ± 15</td>
<td>0.013</td>
</tr>
<tr>
<td>FWA lead aVR (µV)</td>
<td>30 ± 10</td>
<td>24 ± 7</td>
<td>0.011</td>
</tr>
<tr>
<td>FWA lead</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>p</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----</td>
</tr>
<tr>
<td>aVL (µV)</td>
<td>33 ± 12</td>
<td>26 ± 9</td>
<td>0.033</td>
</tr>
<tr>
<td>aVF (µV)</td>
<td>50 ± 17</td>
<td>40 ± 14</td>
<td>0.016</td>
</tr>
<tr>
<td>V1 (µV)</td>
<td>81 ± 32</td>
<td>53 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V2 (µV)</td>
<td>65 ± 27</td>
<td>45 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>V3 (µV)</td>
<td>59 ± 21</td>
<td>46 ± 14</td>
<td>0.002</td>
</tr>
<tr>
<td>V4 (µV)</td>
<td>49 ± 16</td>
<td>39 ± 14</td>
<td>0.013</td>
</tr>
<tr>
<td>V5 (µV)</td>
<td>42 ± 13</td>
<td>34 ± 14</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**Supplement table 5** Evolution of DF (Hz) during ablation

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>aVR</th>
<th>aVL</th>
<th>aVF</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre ablation N=60</td>
<td>6.51 ± 0.74</td>
<td>6.27 ± 0.74</td>
<td>6.36 ± 0.79</td>
<td>6.36 ± 0.68</td>
<td>6.34 ± 0.70</td>
<td>6.32 ± 0.78</td>
<td>6.61 ± 0.75</td>
<td>6.61 ± 0.74</td>
<td>6.43 ± 0.63</td>
<td>6.36 ± 0.70</td>
<td>6.41 ± 0.67</td>
<td>6.40 ± 0.70</td>
</tr>
<tr>
<td>Post PVI N=60</td>
<td>6.24 ± 0.66†</td>
<td>6.10 ± 0.66*</td>
<td>6.13 ± 0.77†</td>
<td>6.08 ± 0.68‡</td>
<td>6.11 ± 0.67†</td>
<td>6.10 ± 0.69</td>
<td>6.29 ± 0.71‡</td>
<td>6.35 ± 0.75†</td>
<td>6.15 ± 0.66†</td>
<td>6.10 ± 0.60†</td>
<td>6.01 ± 0.53‡</td>
<td>6.06 ± 0.63†</td>
</tr>
<tr>
<td>Post LA ablation N=56</td>
<td>5.80 ± 0.76‡</td>
<td>5.71 ± 0.74‡</td>
<td>5.89 ± 0.88‡</td>
<td>5.71 ± 0.75‡</td>
<td>5.93 ± 0.83</td>
<td>5.74 ± 0.77‡</td>
<td>5.99 ± 0.92†</td>
<td>6.01 ± 0.96†</td>
<td>5.79 ± 0.75†</td>
<td>5.78 ± 0.67†</td>
<td>5.78 ± 0.67</td>
<td>5.75 ± 0.71*</td>
</tr>
<tr>
<td>Post RA ablation N=11</td>
<td>5.77 ± 0.86</td>
<td>5.95 ± 0.98</td>
<td>6.24 ± 1.04</td>
<td>6.21 ± 0.72</td>
<td>6.26 ± 1.08</td>
<td>5.95 ± 1.01</td>
<td>6.06 ± 1.04</td>
<td>6.10 ± 0.72</td>
<td>6.04 ± 0.72</td>
<td>6.01 ± 0.77</td>
<td>6.08 ± 0.67</td>
<td>6.13 ± 0.65</td>
</tr>
<tr>
<td>Last ECG N=60</td>
<td>5.70 ± 0.71†</td>
<td>5.68 ± 0.76‡</td>
<td>5.81 ± 0.87‡</td>
<td>5.71 ± 0.74‡</td>
<td>5.86 ± 0.83‡</td>
<td>5.68 ± 0.77‡</td>
<td>5.87 ± 0.88‡</td>
<td>5.98 ± 0.89‡</td>
<td>5.84 ± 0.76‡</td>
<td>5.82 ± 0.69‡</td>
<td>5.81 ± 0.66‡</td>
<td>5.78 ± 0.70‡</td>
</tr>
</tbody>
</table>

Significant differences are between previous ablation step and only included the patients represented in both steps. Significant difference in row “last ECG” are with ECG “pre ablation”. * p<0.05, † p<0.01, ‡ p<0.001. Abbreviations: PVI: Pulmonary vein isolation, LA: left atrial, RA: right atrial, ECG: electrocardiogram.
**Supplement table 6 Evolution of FWA (µV) during ablation**

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>aVR</th>
<th>aVL</th>
<th>aVF</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre ablation N=60</strong></td>
<td></td>
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</tr>
<tr>
<td>I</td>
<td>29 ± 10</td>
<td>52 ± 16</td>
<td>57 ± 16</td>
<td>32 ± 10</td>
<td>37 ± 10</td>
<td>53 ± 16</td>
<td>64 ± 29</td>
<td>58 ± 27</td>
<td>60 ± 23</td>
<td>49 ± 15</td>
<td>41 ± 12</td>
<td>35 ± 10</td>
</tr>
<tr>
<td>II</td>
<td>27 ± 10</td>
<td>48 ± 16‡</td>
<td>53 ± 17†</td>
<td>30 ± 10‡</td>
<td>34 ± 12†</td>
<td>49 ± 16‡</td>
<td>69 ± 34*</td>
<td>60 ± 30</td>
<td>62 ± 27</td>
<td>48 ± 16</td>
<td>40 ± 12</td>
<td>34 ± 10</td>
</tr>
<tr>
<td>III</td>
<td>27 ± 10</td>
<td>46 ± 18</td>
<td>51 ± 18</td>
<td>28 ± 10</td>
<td>33 ± 12</td>
<td>46 ± 18</td>
<td>70 ± 39</td>
<td>57 ± 27</td>
<td>57 ± 21</td>
<td>45 ± 16</td>
<td>38 ± 13*</td>
<td>31 ± 10*</td>
</tr>
<tr>
<td>Post LA ablation N=56</td>
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<td>45 ± 15</td>
<td>49 ± 13</td>
<td>42 ± 10</td>
<td>33 ± 7</td>
<td>27 ± 5</td>
</tr>
<tr>
<td>II</td>
<td>26 ±10†</td>
<td>47 ± 18‡</td>
<td>51 ± 18‡</td>
<td>29 ± 11‡</td>
<td>33 ± 12‡</td>
<td>47 ± 18‡</td>
<td>68 ± 39</td>
<td>56 ± 26</td>
<td>57 ± 20</td>
<td>46 ± 16*</td>
<td>38 ± 13*</td>
<td>32 ± 11†</td>
</tr>
<tr>
<td><strong>Last ECG N=60</strong></td>
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</tr>
<tr>
<td>I</td>
<td>26 ± 10†</td>
<td>47 ± 18‡</td>
<td>51 ± 18‡</td>
<td>29 ± 11‡</td>
<td>33 ± 12‡</td>
<td>47 ± 18‡</td>
<td>68 ± 39</td>
<td>56 ± 26</td>
<td>57 ± 20</td>
<td>46 ± 16*</td>
<td>38 ± 13*</td>
<td>32 ± 11†</td>
</tr>
</tbody>
</table>

Significant differences are between previous ablation step and only included the patients represented in both steps. Significant difference in row “last ECG” are with ECG “pre ablation”. * p<0.05, † p<0.01, ‡ p<0.001. Abbreviations: PVI: Pulmonary vein isolation, LA: left atrial, RA: right atrial, ECG: electrocardiogram.