Predictors of recurrence after durable pulmonary vein isolation for paroxysmal atrial fibrillation

Michelle Lycke¹, Maria Kyriakopoulou¹,², Milad El Haddad¹, Jean-Yves Wielandts¹, Gabriela Hilfiker¹, Alexandre Almorad¹, Teresa Strisciuglio ¹, Jan De Pooter¹,³, Michael Wolf³, Philippe Unger⁴, Yves Vandekerckhove¹, René Tavernier¹, Jean-Benoît e Polain de Waroux¹, Mattias Duytschaever¹, and Sébastien Knecht¹*

¹Department of Cardiology, AZ Sint-Jan Brugge, Ruddershove 10, Bruges 8000, Belgium; ²Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium; ³Department of Cardiology, UZ Gent, Ghent, Belgium; and ⁴Department of Cardiology, CHU Saint Pierre, Brussels, Belgium

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Aims

Catheter ablation of paroxysmal atrial fibrillation (AF) reduces AF recurrence, AF burden, and improves quality of life. Data on clinical and procedural predictors of arrhythmia recurrence are scarce and are flawed by the high rate of pulmonary vein reconnection evidenced during repeat procedures after pulmonary vein isolation (PVI). In this study, we identified clinical and procedural predictors for AF recurrence 1 year after CLOSE-guided PVI, as this strategy has been associated with an increased PVI durability.

Methods and results

Patients with paroxysmal AF, who received CLOSE-guided PVI and who participated in a prospective trial in our centre, were included in this study. Uni- and multivariate models were plotted to find clinical and procedural predictors for AF recurrence within 1 year. Three hundred twenty-five patients with a mean age of 63 years (CHA²DS₂VASc 1 [1–3], left atrium diameter 41 ± 6 mm) were included. About 60.9% were male individuals. After 1 year, AF recurrence occurred in 10.5% of patients. In a binary logistic regression analysis, the diagnosis-to-ablation time (DAT) was found to be the strongest predictor of AF recurrence ($P = 0.011$). Diagnosis-to-ablation time $\geq$1 year was associated with a nearly two-fold increased risk for developing AF recurrence.

Conclusion

The DAT is the most important predictor of arrhythmia recurrence in low-risk patients treated with durable pulmonary vein isolation for paroxysmal AF. Whether reducing the DAT could improve long-term outcomes should be investigated in another trial.

Keywords

Atrial fibrillation • Pulmonary vein isolation • Predictors • Atrial fibrillation recurrence • Diagnosis-to-ablation time • Left atrium diameter

Introduction

Catheter ablation of paroxysmal atrial fibrillation (AF) reduces AF recurrence, AF burden, and improves patients’ quality of life.¹ Historically, pulmonary vein isolation (PVI) for paroxysmal AF has been associated with a 1-year success rate ranging from 50% to 80% in patients treated with PVI.² Over the years, a variety of possible predictive variables for AF recurrence after PVI have been evidenced³; however, data were flawed by the high rate of PV reconnection evidenced during repeat procedures after PVI.⁴

Recent PVI ablation techniques and technologies have emerged and have been associated with a higher clinical success rate.⁵–⁸ In particular, CLOSE-guided PVI is a point-by-point radiofrequency (RF) ablation strategy based upon contact force (CF)-guided delivery of closely spaced and optimized lesions close to the pulmonary vein (PV) ostia, targeting an inter-tag distance of $\leq$6 mm and an ablation...
What’s new?

- This study evaluates clinical and procedural predictors of atrial fibrillation (AF) recurrence in low-risk patients 1 year after the index ablation in a setting of durable pulmonary vein isolation (PVI).
- The identification of predictors that lead to AF recurrence after CLOSE-guided PVI is essential in order to achieve a better understanding of unsuccessful procedures and to improve patient selection.
- Our research indicates that in a setting of durable PVI a longer diagnosis-to-ablation time leads to higher chances of AF recurrence 1 year after the ablation.
- This finding stresses the potential positive impact of an early intervention, not only to achieve the best possible outcome but also to reduce patient burden as well as to reduce healthcare costs.

Methods

Study population

A total of 325 patients, treated with PVI in our institution for symptomatic paroxysmal AF, who previously agreed to participate in a prospective follow-up study using the CLOSE-protocol performed between February 2015 and October 2018 were included. Inclusion and exclusion criteria have been previously described.9,10,12–14 Baseline, procedural, and follow-up data were collected in all patients.

This trial was conducted in accordance with the protocol, current ICH-GCP guidelines, and applicable laws. The study was approved by the local ethical board (AZ Sint-Jan Brugge ethics committee, Approval 2517).

Patient and public involvement

There was no patient or public involvement for this study. Patients were not consulted regarding the study design, patient relevant outcomes, or study results. There was no patient or public involvement in the writing or editing process.

Study endpoints

The objective of the study was the identification of predictors for AF recurrence 1 year after the index ablation consisting of PVI using the CLOSE protocol. Patient (demographics, CHA2DS2-VASc score, cardiovascular, and medical history) and procedural characteristics were assessed. Atrial fibrillation recurrence was monitored with systematic follow-up visits and electrocardiogram (ECG) at 3, 6, and 12 months post-ablation. Moreover, either repetitive Holter (at 3, 6, and 12 months), weekly and symptom-driven trans-telephonic monitoring or continuous loop recorder were performed in all patients, depending on the different studies.9,10,12–14 A blanking period of 3 months was included, but a redo procedure was considered as a failure if it occurred within this period. Use of anti-arrhythmic medication after the blanking period was considered as a failure.

Ablation procedure

All procedures were performed under general anaesthesia with uninterrupted anti-vitamin K or direct oral anti-coagulants (last dose >12h before procedure). In all patients, oesophageal temperature was monitored during the procedure (SensiTherm, St Jude Medical Inc., MN, USA). Intra-venous heparin was administered after femoral vein access to achieve an activated clotting time >300 s. A decapolar coronary sinus (CS) catheter was introduced via the femoral vein and a single or double trans-septal puncture was performed with conventional long sheaths (SL0, St. Jude Medical Inc., MN, USA). A decapolar circular mapping catheter (Lasso®, Biosense-Webster Inc., CA, USA) and an 8-Fr open-tip irrigated RF catheter with tip-integrated CF sensor (Thermo cool SmartTouch®, Biosense-Webster Inc., CA, USA) were positioned in the left atrium (LA). Next, calibration of the RF catheter, respiratory gating, and 3D-mapping of the LA (Carto System®, Biosense-Webster Inc., CA, USA) were conducted.

All patients underwent CLOSE-guided PVI. This technique has been described extensively.15 Femoral access was achieved with ultrasound guidance in case of difficult puncture sites. Point-by-point RF delivery was performed aiming for a contiguous circle enclosing all PVs. Radiofrequency was delivered in a power-controlled mode (without ramping) using 35–40 W (EP Shuttle ST-3077, Stockert GmbH, Freiburg, Germany). The irrigation rate was 30mL/min. Radiofrequency was delivered until an AI of >400 was reached at the posterior wall and >550 at the anterior wall. In the case of dislocation, a new RF application reaching the AI target was applied. Maximal inter-tag distance between two neighbouring lesions was 6 mm. In case of intra-oesophageal temperature (T°) rise >38.5°C during posterior LA wall ablation, RF delivery was stopped at an AI of 300. In the absence of first-pass isolation, touch-up ablation was applied until PVI. In case of reconnection during the waiting time or during the adenosine test, the site of reconnection was located and treated with touch-up ablation until adenosine proof PVI was reached.

Follow-up

Patients were scheduled for repetitive follow-up visits 1 year after the ablation. Repetitive ECG’s were recorded at 3, 6, and 12 months for every patient. Patients were further monitored using repetitive Holter (after 3, 6, and 12 months), weekly and symptom-driven trans-telephonic monitoring, or continuous loop recorder. After the blanking period of 3 months, anticoagulation was continued according to the stroke risk (CHA2DS2-VASc score ≥1 (men) or ≥2 (women)), whereas antiarrhythmic drugs were always stopped. Restarted antiarrhythmic drug therapy was considered as a failure.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables are presented as counts and percentages (%). P-values <0.05 are considered to indicate statistical significance. Uni- and multivariate binary logistic regression analyses were conducted to determine predictors of AF recurrence 1 year after CLOSE-guided PVI. Following variables were included in the analysis: age, male gender, BMI, CHA2DS2-VASc score, presence of arterial hypertension, presence of diabetes mellitus, previous stroke, presence of congestive heart failure (CHF), presence of vascular disease, LA diameter, diagnosis-to-ablation time (DAT), total procedural time, total
Results

Patient and clinical characteristics

Table 1 represents patient and clinical characteristics. Patients presented with a mean age of 62.5 years. The majority of patients was male individuals (60.9%). Patients had a mean BMI of 27.1 kg/m² and presented with a median CHA2DS2-VASc score of 1 (IQR 1–3). Congestive heart failure, arterial hypertension, vascular disease, and diabetes mellitus was present in, respectively, 2.2, 35.7, 5.5, and 9.5% of patients. A history of stroke was present in 22 patients (6.8%). The median LA diameter was 41.3 ± 5.7 mm. The average LA diameter was 41.3 ± 5.7 mm. The median LA diameter was 41.3 ± 5.7 mm.

Procedural characteristics

The median total procedural time and total RF time were 120.0 min (IQR 85.0–154.5) and 28.0 min (IQR 22.7–32.8), respectively.

Cavitricuspid isthmus ablation was performed in 50/325 patients (15.4%). The median fluoroscopy time was 10 min (IQR 6.3–14.0) and mean DAP values were 8480.6 ± 12 708.3 mGy·cm². The first-pass isolation rate was 95.7%. Adenosine-proof PVI was achieved in all procedures (100%). Major procedural complications occurred in 6/325 patients (1.8%; four patients with vascular access site complications with surgical repair and/or with prolonged hospitalization, one patient with symptomatic left PV stenosis treated with percutaneous stenting, one patients suffered from a transient ischaemic attack 8 days after the ablation, Table 2).

One-year follow-up

In addition to an ECG (all patients), patients received either repetitive Holter (51.7%), weekly trans-telephonic monitoring (16.6%), or continuous loop recordings (31.7%, Table 3). Atrial fibrillation recurrence within the first year occurred in 34 (10.5%) patients (evidenced by Holter [23 (67.6%)]), trans-telephonic monitoring [7 (20.6%)] or continuous loop recorder [4 (11.8%)]. Median time to recurrence was 129 days (IQR: 101–211, Figure 1A). Reconnection of at least one PV was present in only 2 patients out of the 15 patients undergoing a redo ablation procedure.

Predictors for atrial fibrillation recurrence 1 year after CLOSE-guided pulmonary vein isolation

In the univariate analyses, both the DAT (Nagelkerke $R^2 = 4.7$, $P = 0.006$) and first-pass isolation (Nagelkerke $R^2 = 4.2$, $P = 0.004$) were found to predict 1-year recurrence (see Table 4 for details). The median DAT in the AF-free group was 12 months (IQR 10–78) in the AF recurrence group.
Over all, 54.3% of the patients presented with a DAT > 1 year. A log-rank test revealed a significant result \( (P = 0.025) \) when comparing with time the recurrence between patients with a DAT < 1 year and DAT > 1 year (Figure 1B). Results further showed a 1.8 times greater relative risk to develop arrhythmia recurrence in the latter group.

Figure 3 shows the ROC curve of the DAT. The area under ROC curve AUC, indicating the diagnostic accuracy of the DAT, was calculated as 0.65 (95%CI: 0.55–0.75). In patients with a DAT < 1 year the recurrence rate was 6.3% compared with 14.7% in case of a DAT > 1 year (the negative predictive value of DAT > 1 year is 93.7%).

When combined into a multivariate model with forward and backward analyses, the binary logistic regression model analysis revealed that the DAT was the sole independent predictor for AF recurrence 1 year after the index ablation \( (\beta = 0.028; P = 0.011, \text{Table 4}) \).

**Discussion**

**Main findings**

We evaluated predictors of AF recurrence after CLOSE-guided PVI in low-risk patients treated for paroxysmal AF. In the setting of durable PVI, the diagnosis-to-ablation time is the strongest predictor for 12-month AF recurrence. This suggests that reducing the DAT could result in improved long-term outcomes.

**Clinical predictors of atrial fibrillation recurrence**

Up to 50% of paroxysmal AF patients experience arrhythmia recurrence after PVI using non-contact force RF catheters or first-generation cryoballoons. The identification of variables predicting AF recurrence has been an important research topic over the past years, leading to the publication of a wide variety of possible predictive variables for AF recurrence after catheter ablation. One of the most important predictors is the DAT, as confirmed by our results in these selected patients with durable PVI and a lower recurrence rate (10–15%).

**Diagnosis to ablation time**

Several studies have already shown that the DAT was an important factor for AF recurrence. A recent study by Bisbal et al. reported that the DAT is independently associated with arrhythmia recurrence and redo ablations after the index procedure. A meta-analysis by Chew et al. also recently suggested that a shorter DAT (DAT < 1 year) is associated with a lower relative risk of AF recurrence compared with patients with a DAT > 1 year. We have found a nearly two-fold greater relative risk for AF recurrence in patients...
patients with a low baseline stroke risk. Kawaji et al.\textsuperscript{23} showed significantly lower rates of heart failure hospitalizations in patients with shorter DAT. Asides from these findings, recently published data of the EAST-AFNET 4 trial showed that earlier rhythm control (either with anti-arrhythmic drug therapy or catheter ablation) is associated with a lower risk of cardiovascular complications than patients who are referred to usual care.\textsuperscript{24} Therefore, we may conclude that longer DATs are associated with unfavourable outcomes.

**Other predictors**

Our results also indicate that the first-pass isolation rate may impact recurrence. However, in our sample we found a high first-pass isolation rate of 95.7%. This indicates that we were not able to isolate the PV’s with the first encirclement in only 14 patients (4.3%). Of those 14 patients, recurrence occurred in 5 (5 out of 14; 35.7%). On the contrary, recurrence was observed in 33 patients in whom first-pass isolation was achieved (33 out of 311; 10.6%). While the percentage of patients with recurrence is proportionally smaller in the first-pass isolation group, these numbers may be too small for actual conclusions. Therefore, more research is necessary in order to confirm this finding.

The LA diameter was another potential predictor reported in several studies.\textsuperscript{2,3} However, a systematic review could not find evidence to show that the LA diameter is an independent predictor of arrhythmia recurrence.\textsuperscript{3} Our analysis confirmed this finding. This could be due to the fact that our selected dataset included patients recruited in clinical trials where an enlarged atrium was defined as an exclusion criteria (LA>50 mm). We therefore found small LA diameters in our sample (mean of 41.3 mm).

Many other predictors have been reported with alternating success. Berruezo et al.\textsuperscript{25} identified the presence of arterial hypertension and the LA diameter as pre-procedural clinical predictors of AF after PVI. Letsas et al.\textsuperscript{26} evaluated clinical predictors of 72 patients in a cox proportional hazard regression analysis. They also found the presence of hypertension and large LA diameters to predict AF recurrence. They further identified the white blood cell count as an independent pre-ablative predictor. Bertaglia et al.\textsuperscript{27} reported that the presence of structural heart disease predicted early atrial tachyarrhythmia recurrence in a group of 143 patients undergoing PVI. Our study included only 2% patients with congestive heart disease and therefore no conclusion could be drawn from our data. A meta-analysis by Balk et al. evaluated multiple predictors including AF type, LA diameter, LVEF, gender, age, the presence of structural heart disease, and the presence of hypertension. They found that only the AF type demonstrated a potential link with AF recurrence. They did not find any evidence that the LA diameter or the presence of structural heart disease led to an increased risk of developing AF recurrence.\textsuperscript{3} A possible explanation of these mixed results relies in the fact that studies on AF recurrence include heterogeneous datasets whereas the ablation itself may include non-durable PVI strategies.

**Clinical implications: earlier pulmonary vein isolation?**

The identification of predictors that lead to AF recurrence after CLOSE-guided PVI is essential in order to achieve a better

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**Figure 1**

Figure 1 (A) Kaplan–Meier plot representing time to AF recurrence. (B) Kaplan–Meier plot representing time to AF recurrence according to a diagnosis-to-ablation time <1 year vs. ≥1 year. AF, atrial fibrillation.
understanding of unsuccessful procedures as well as to improve patient selection for CLOSE-guided PVI.

Our research indicates that a longer DAT leads to higher chances of AF recurrence 1 year after the ablation. As the DAT is a modifiable and actionable risk marker for AF recurrence, our results stress the potential positive impact of an early intervention, not only to achieve the best possible outcome, but also to reduce patient burden as well as to reduce healthcare costs.3,19 This is in line with recently published data of the EAST-AFNET 4 trial that showed that early rhythm-control therapy (treatment within <1 year after AF onset) was associated with a lower risk of death from cardiovascular causes, stroke, or hospitalization for heart failure or acute coronary syndrome.24 Our findings could obviously be true for any other PVI strategy (like the promising electroporation technique).6

Study limitations
Although this study reveals interesting findings, it has some limitations. First, it combines data from previous prospective study databases. Due to the retrospective design of the study and although all data were prospectively collected, we did not perform a power calculation. Results are therefore of explorative nature and should be confirmed in a second larger dataset. Next, the design is single centre and non-randomized. Furthermore, the study gathers mostly low-risk patients (paroxysmal AF without structural heart disease, small atria, and relatively young patients) and caution should be taken concerning the interpretation of the data for ablation of other types of AF patients. Moreover, patients who were included in this retrospective study previously participated in a prospective follow-up study in our centre. It is therefore possible that PVI was performed with more precaution and more closer observation compared with patients not included in a prospective trial, potentially leading to a risk of bias in recurrence rate. Finally, no estimation of the fibrosis was made (no systematic voltage map or MRI) and this could also be associated with a higher recurrence rate.

Conclusion
This study shows that the DAT is the most important predictor of arrhythmia recurrence in patients treated with durable PVI for paroxysmal AF. Whether reducing the DAT could improve long-term outcomes should be investigated in another trial.
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Data availability
Data are available upon reasonable request.

References