Catheter ablation (CA) of paroxysmal atrial fibrillation (PAF) has been established as a standard treatment option with a class I recommendation as indicated in the current guidelines. Long-term success rates of pulmonary vein isolation (PVI) can be estimated as high as 70% to 80% after 5 years using 1.5 procedures per patient. However, the mechanisms underlying persistent AF (persAF) are more complex. Patients are being treated with various ablation approaches (ie, PVI alone, linear lesions, electrogram-guided ablation targeting complex fractionated atrial electrograms) and clinical success rates of CA are limited. At present, no standard concept for CA of persAF has been established. In persAF, it seems reasonable to perform additional substrate modification beyond PVI to enhance clinical success rates. In contrast to ablation of PAF, in which the end point of electric isolation of the pulmonary veins (PVs) is recommended by the guidelines, the optimal end point of CA in the setting of persAF is still under debate. The stepwise ablation approach aiming at AF termination was introduced by Haïssaguerre et al in 2005. Long-term follow-up data on any ablation approach for persAF are limited.

In this study, we present 5-year follow-up data of patients with persAF undergoing stepwise CA aiming at AF termination.

Methods

Study Population
A total of 549 patients with persAF underwent CA using the stepwise approach at our institution in 2007 to 2009. Of these, 493 patients were included (Holter ECGs ≥ every 6 months). Mean follow-up was 59±16 months with 2.1±1.1 procedures per patient. Single and multiple procedure success rates were 20.1% and 55.9%, respectively (80% off antiarrhythmic drug). Antiarrhythmic drug–free multiple procedure success was 46%. Long-term recurrences (n=171) were paroxysmal AF in 48 patients (28%) and persistent AF/atrial tachycardia in 123 patients (72%). Multivariable recurrent event analysis revealed the following factors favoring arrhythmia recurrence: failure to terminate AF during index procedure (hazard ratio [HR], 1.279; 95% confidence interval [CI], 1.093–1.497; P=0.002), number of procedures (HR, 1.154; 95% CI, 1.051–1.267; P=0.003), female sex (HR, 1.263; 95% CI, 1.027–1.553; P=0.027), and the presence of structural heart disease (HR, 1.236; 95% CI, 1.003–1.524; P=0.047). AF termination was correlated with a higher rate of consecutive procedures because of atrial tachycardia recurrences (P=0.003; HR, 1.71; 95% CI, 1.20–2.43).

Conclusions—Catheter ablation of persistent AF using the stepwise approach provides limited long-term freedom of arrhythmias often requiring multiple procedures. AF termination, the number of procedures, sex, and the presence of structural heart disease correlate with outcome success. AF termination is associated with consecutive atrial tachycardia procedures.

Key Words: arrhythmia (heart rhythm disorders) | atrial fibrillation | catheter ablation | long-term outcome | success | stepwise approach

Catheter ablation (CA) of paroxysmal atrial fibrillation (PAF) has been established as a standard treatment option with a class I recommendation as indicated in the current guidelines. Long-term success rates of pulmonary vein isolation (PVI) can be estimated as high as 70% to 80% after 5 years using 1.5 procedures per patient. However, the mechanisms underlying persistent AF (persAF) are more complex. Patients are being treated with various ablation approaches (ie, PVI alone, linear lesions, electrogram-guided ablation targeting complex fractionated atrial electrograms) and clinical success rates of CA are limited. At present, no standard concept for CA of persAF has been established. In persAF, it seems reasonable to perform additional substrate modification beyond PVI to enhance clinical success rates. In contrast to ablation of PAF, in which the end point of electric isolation of the pulmonary veins (PVs) is recommended by the guidelines, the optimal end point of CA in the setting of persAF is still under debate. The stepwise ablation approach aiming at procedural AF termination was introduced by Haïssaguerre et al in 2005. Long-term follow-up data on any ablation approach for persAF are limited.

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Study Population
A total of 549 patients with persAF underwent CA using the stepwise approach at our institution in 2007 to 2009. Of these, 493
WHAT IS KNOWN

• Long-term outcome data after catheter ablation of persistent atrial fibrillation are rare and different approaches are being used.
• Little is known about prognostic factors for success.

WHAT THE STUDY ADDS

• Catheter ablation of persistent atrial fibrillation using the stepwise approach with the endpoint of atrial fibrillation termination provides limited long-term freedom of arrhythmias with single and multiple procedure success rates of 20.1% and 55.9% often requiring multiple procedures.
• Failure to terminate atrial fibrillation during index procedure, a high number of procedures, female sex, and the presence of a structural heart disease favor arrhythmia recurrence.

patients with persAF (long-standing persAF, n=119; 24.1%) were included in the study. Patients were eligible for study participation if AF episodes persisted for at least 1 month and required electric cardioversion to restore sinus rhythm (SR). Additionally, a sufficient long-term follow-up was required (see study protocol). Exclusion criteria were manifest hyperthyroidism, left atrium (LA) diameter >65 mm, life expectancy <1 year, and any previous ablation procedure.

Study Protocol

The index procedure for persAF was uniformly performed using the stepwise approach aiming at AF termination. Procedural success was defined as freedom from atrial tachycardia (AT)/AF with a duration >30 s in sequential Holter ECG, device interrogation, or tele-ECGs. Only those patients (493/549) were included having a follow-up >30 s in sequential Holter ECG, device interrogation, or tele-ECGs. After the ablation procedure, a blanking period of 3 months was established according to the guidelines. The study was approved by the institutional review board. All subjects gave informed consent. Follow-up was completed in October 2013.

Ablation Procedure

Details of the ablation procedure have been described previously. In brief, the first step of the ablation procedure was antral PVI with complete electric isolation of the PVs proved by a circumferential mapping catheter followed by ablation of complex fractionated electrograms. AF cycle length (CL) was continuously monitored inside the coronary sinus and inside the left atrial appendage (latter with a circumferential mapping catheter, mean >10 cycles measured). Targets for AF ablation consisted of complex fractionated atrial electrograms, as well as areas of short CL activity and local bursts, temporal activation gradient between proximal and distal ablation biopoles, or areas of local spatial centrifugal activation. The desired procedural end point was termination of AF, either directly to SR or via AT. Using the same criteria, mapping and ablation were performed within the coronary sinus and the right atrium if AF did not terminate (Figure 1). Subsequent ATs were specifically targeted, whereas linear ablation was performed if a macroreentrant mechanism was suspected. Linear lesions were always created with the end point of bidirectional block, evaluated by differential pacing. If AF termination failed, external electric cardioversion was used to restore SR after a 51-patient fluid administration via catheter irrigation or lack of target regions. The standard radiofrequency ablation setting consisted of a power output of 30 W using an irrigation rate of 10 to 30 mL/min (0.9% saline infused with the Cool Flow Pump, Biosense Webster, Diamond Bar, CA) for PVIs and the right atrium. Along the LA posterior wall, the maximum power was limited to 25 W. Within the coronary sinus, radiofrequency current was applied with a maximum of 25 W with a manually adjusted irrigation rate to keep the tip temperature <42°C.

Repeat Procedures

Indication for repeat procedure was put in place in case of symptomatic arrhythmia recurrences and patients’ preferences. As a first step of repeat procedures, electric isolation of the PVs was evaluated and re-established if required. If patients presented in SR, induction of either AT or AF according to the clinical recurrence was attempted using either programmed stimulation (AT) or atrial burst pacing until loss of 1:1 capture (AF). AT was defined as an organized atrial activity with CL of 2180 ms with monomorphic P waves on ECGs and consistent endocardial activation sequence. An AT with a stable CL was considered macroreentrant, when a consistent repeat postponing interval was observed or tachycardia CL could be demonstrated around the presumed circuit. Focal AT was recognized as an atrial activation originating from a discrete site activating the surrounding tissue centrifugally and demonstrating features consistent with a focal mechanism (centrifugal activation pattern, variation in AT CL≤15%, inconsistent postponing interval). Localized re-entry was defined as atrial activity confined to an...
area of continuous signals on the bi poles of the mapping catheter displaying ≥85% of tachycardia CL and showing consistent post-pacing interval ≤30 ms of the tachycardia CL after repeat entrainment pacing (at least twice at the same site). If patients presented with or were induced for AF, stepwise ablation was performed aiming at AF termination. If patients presented with AT or an AT was induced, ablation was performed according to the above-mentioned protocol, aiming at AT termination. In case of macroreentrant ATs, ablation lines were created aiming for complete conduction block along the line.

Follow-Up
Patients were followed clinically every 3 to 6 months with detailed symptom evaluation and a 12-lead ECG. Additionally, Holter ECGs were performed at least every 3 months for the first year after CA and afterward every 6 months. All patients received an additional questionnaire about arrhythmia symptoms and episode-duration, last known recurrence dates, and current medications and were contacted by phone calls if documentation was incomplete or unclear. In case of symptoms suspicious for arrhythmia recurrences without previous documentation, external ECG event recording was accomplished. Patients with implanted pacemakers or defibrillators were eligible to be followed by device interrogation. Antiarrhythmic drug (AAD) treatment was continued for 1 to 3 months after the procedure at the discretion of the operator. Long-term follow-up data were analyzed in the patients with complete follow-up only.

Statistical Analysis
Continuous variables are summarized by mean±SD or median (minimum–maximum) as appropriate. Categorical variables are represented by absolute and relative frequencies. To cope with censoring, event-free survival was plotted and estimated by Kaplan–Meier curves. Two-group comparisons were performed using Student t test. Recurrent events and covariate associations were investigated with univariable and multivariable Andersen and Gill models with robust estimates and Efron tie handling. If covariates were missing, multiple imputation was used to complete the data set. For multiple imputation, the fully conditional specification method was used and 10 different imputed data sets were generated. Finally, the pooled results are reported. For each of the variables, hazard ratios with corresponding 95% confidence limits and Wald test P values of the respective univariable or multivariable model are reported.

Throughout all calculations, a 2-tailed value of P=0.05 indicated statistical significance. Statistics were calculated using SPSS version 20 (SPSS Inc, Cary, NC) and Stata software version 13.0 (Stata, College Station, TX).

Results
Baseline characteristics of the study group are presented in Table 1. Known history of AF was 73 months (median, 48; 1–576) with a continuous AF episode duration of 14 months (median 6, 1–240). Patients had undergone 2 electric cardioversions on average (0–21) and were treated with 1.7 AADs (0–5) prior initial procedure, whereas 41% were on amiodarone. One third of patients showed a relevant structural heart disease (SHD; CAD, cardiomyopathy, or valvular heart disease).

Index Procedure
The mean procedure time of the index procedure was 197±56 minutes with a fluoroscopy time of 53±21 minutes and 126034±4410 J of radiofrequency energy application. Procedural details are summarized in Table 2. PVI was accomplished in all patients. The procedural end point of AF termination was achieved in 290 of 493 patients (59%). Of these, 46% converted directly to SR and 54% terminated into an AT. In 28 patients (5.7%), AF converted to SR with PVI. During index procedures, 148 of 493 patients (30%) showed ATs as consecutive arrhythmia (including right atrial flutter). A total number of 146 ATs (maximum 5 ATs) occurred. Of these, more than half were classified as typical macroreentrant ATs. Mitralissthmus-dependent flutter occurred in 5.5%, roof dependent ATs in 5.5%, and right atrial cavotricuspid isthmus flutter in 9.5% of 493 patients. Ablation was continued until termination and achievement of complete block via the respective lines. Other ATs were identified in the anterior LA, the septum, coronary sinus, and less frequently on other sites of both atria. In 52% of patients, electric cardioversion had to be performed to restore SR (either cardioversion of AF or AT). After initial ablation, 44% of patients were discharged without specific AADs, 38% on amiodarone, 5% on propafenone, and 13% on flecainide.

Repeat Procedures
The predominant indication for the second procedure was AF in 64% (n=206) and AT in 36% (n=115) of the cases. Of all 321 patients undergoing a second procedure, 48% presented in SR to the first redo procedure. In 55% of patients, any AT was observed during second procedure (n=1 in 26%, n=2 in 17%, n=3 in 8%, and n>3 in 4% of the cases). During second procedure, a mean of 2.3±1.3 PVs showed conduction recovery. The number of reconnected PVs declined with every repeat episode.
procedure (see Table 2). Dominant indication for procedure 3 was AT in 53% of the cases (remaining AF), for procedure 4 in 76% of patients, and for procedure 5, 6, and 7 in 91%, 25%, and 50% (Figure 2).

We analyzed all 493 patients for clinical and procedural factors that are associated with repeat procedures because of AT recurrences. The hazard for AT is significantly associated with the application of lines in the foregoing procedure \( (P=0.014; \text{hazard ratio [HR]}, 1.42; 95\% \text{ confidence interval [CI]}, 1.07–1.88)\), the amount of radiofrequency energy application \( (P=0.003; \text{HR}, 1.005; 95\% \text{ CI}, 1.002–1.008)\), and AF termination during the latter \( (P=0.003; \text{HR}, 1.71; 95\% \text{ CI}, 1.002–1.008)\), and AF termination during the latter \( (P=0.003; \text{HR}, 1.71; 95\% \text{ CI}, 1.002–1.008)\), and AF termination during the latter.
1.20–2.43). Also, the number of procedures ($P<0.001$; HR, 1.69; 95% CI, 1.45–1.97) was correlated with consecutive AT procedures. No significant association could be shown for the clinical parameters: age, sex, and LA size ($P=0.636$, 0.557, and 0.584), respectively.

Linear lesions have been performed in 112 of 321 patients (34.9%) during the second procedure (in 191/493 [38.7%] during index procedure). Termination (either into SR or AT) was achieved in 81% of patients during second procedure and in 87% to 98% during third to fifth procedure. Only 4 patients underwent a sixth or seventh procedure.

A detailed presentation of the repeat procedure periprocedural data is provided in Table 2. In 5 patients with indication for cardiac surgery, an endoscopical or open surgical AF ablation was performed as repeat procedure.

Long-Term Follow-Up

The mean follow-up duration was 59±16 months after the index procedure and 44±22 months after the last procedure. A total of 1042 procedures in 493 patients were analyzed (321 patients with ≥1 procedure) with a mean of 2.1±1.1 procedures per patient. Five-year success rates were 20.1% after a single procedure and 55.9% after the last documented procedure, respectively (Figure 3A and 3B). Based on Holter ECG results, 171 of 493 patients (34.6%) showed recurrent arrhythmia in long-term outcome, which was classified as PAF in 48 patients (28.1%) and persAF/AT in 123 patients (71.9%) after 1 or multiple procedures (outcomes after each procedure depending on types of termination are shown in Figure 2). At the end of follow-up, 42.8% of patients were off oral anticoagulation. Patients in stable SR presented off AADs in 79.8% of the cases at long-term follow-up. If AADs were needed, patients received Class Ic AADs in 10.5% or Class III AADs in 9.7% of the cases. The Kaplan–Meier estimate of 60 months arrhythmia and AAD–free survival with multiple procedures is 45.6% (95% CI, 40.4%–50.6%). The 60-month Kaplan–Meier curve and the distribution of AADs in the SR population are shown in Figure 4.

Time to Arrhythmia Recurrence

The median event-free time after index procedure was 12.8 months (95% CI 10.6–14.9). The recurrence rate during the first 12 months after index procedure was 47.8% (95% CI, 43.5–52.3), whereas further 22.8% of patients experienced

![Figure 3](image-url). Kaplan–Meier analyses demonstrating cumulative arrhythmia-free survival and estimates of 60-month arrhythmia-free survival with catheter ablation of persistent atrial fibrillation using the stepwise approach after (A) index procedure and (B) last documented procedure (in braces: number of events observed in corresponding time interval). CI indicates confidence interval.

![Figure 4](image-url). A, Antiarrhythmic drug (AAD) treatment at the time of last follow-up for patients in sinus rhythm. B, Cumulated AAD and event-free survival and Kaplan–Meier estimate of 60-month survival after last documented procedure (in braces: number of events observed in corresponding time interval). CI indicates confidence interval; and SR, sinus rhythm.
Factors Influencing Arrhythmia Outcome

Recurrent event analysis was performed for 1042 procedures of 493 patients. Univariable factors correlating with recurrence were failure to terminate AF during the index procedure irrespective of the mode of termination (direct SR versus in subsequent AT), number of procedure, larger LA diameter, and presence of SHD. AF episode duration, age, CHA2DS2Vasc (combined stroke risk score: congestive heart failure, hypertension, age>75 years, diabetes, prior stroke/transient ischemic attack, vascular disease; HTN, hypertension; LA, left atrium; and SHD, structural heart disease).

Table 3. Univariable and Multivariable Analysis of Associated Factors of Sinus Rhythm Maintenance

<table>
<thead>
<tr>
<th>Baseline Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, men</td>
<td>0.859</td>
<td>0.711–1.039</td>
<td>0.117</td>
</tr>
<tr>
<td>Age</td>
<td>1.006</td>
<td>0.996–1.016</td>
<td>0.237</td>
</tr>
<tr>
<td>CHA2DS2Vasc</td>
<td>1.050</td>
<td>0.996–1.107</td>
<td>0.069</td>
</tr>
<tr>
<td>HTN</td>
<td>1.062</td>
<td>0.870–1.296</td>
<td>0.554</td>
</tr>
<tr>
<td>SHD</td>
<td>1.223</td>
<td>1.021–1.464</td>
<td>0.029</td>
</tr>
<tr>
<td>Episode duration</td>
<td>1.002</td>
<td>0.999–1.006</td>
<td>0.172</td>
</tr>
<tr>
<td>Termination (initial procedure)</td>
<td>0.756</td>
<td>0.643–0.888</td>
<td>0.001</td>
</tr>
<tr>
<td>LA diameter</td>
<td>1.020</td>
<td>1.005–1.037</td>
<td>0.012</td>
</tr>
<tr>
<td>No. of procedure</td>
<td>1.164</td>
<td>1.063–1.273</td>
<td>0.001</td>
</tr>
<tr>
<td>Multivariable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, men</td>
<td>0.792</td>
<td>0.644–0.974</td>
<td>0.027</td>
</tr>
<tr>
<td>Age, mo</td>
<td>1.006</td>
<td>0.995–1.017</td>
<td>0.303</td>
</tr>
<tr>
<td>CHA2DS2Vasc</td>
<td>0.958</td>
<td>0.877–1.045</td>
<td>0.334</td>
</tr>
<tr>
<td>HTN</td>
<td>1.055</td>
<td>0.847–1.315</td>
<td>0.632</td>
</tr>
<tr>
<td>SHD</td>
<td>1.236</td>
<td>1.003–1.524</td>
<td>0.047</td>
</tr>
<tr>
<td>Episode duration</td>
<td>1.002</td>
<td>0.998–1.005</td>
<td>0.309</td>
</tr>
<tr>
<td>Termination (initial procedure)</td>
<td>0.782</td>
<td>0.668–0.915</td>
<td>0.002</td>
</tr>
<tr>
<td>LA diameter</td>
<td>1.012</td>
<td>0.996–1.029</td>
<td>0.146</td>
</tr>
<tr>
<td>No. of procedure</td>
<td>1.154</td>
<td>1.051–1.267</td>
<td>0.003</td>
</tr>
</tbody>
</table>

n=1042 procedures of 493 patients. CHA2DS2Vasc indicates combined stroke risk score: congestive heart failure, hypertension, age>75 years, diabetes, prior stroke/transient ischemic attack, vascular disease; HTN, hypertension; LA, left atrium; and SHD, structural heart disease.

Procedural Complications

Overall, 4.9% (n=27) of 549 patients experienced procedure-related complications during/after index procedure prolonging hospitalization. Of these, 2.7% (n=15) had peripheral vascular complications, such as arteriovenous fistula, pseudoaneurysm, or relevant groin hematoma (decrease in hemoglobin level >3 g/dL). Pericardial tamponade occurred in 0.4% (n=2) requiring percutaneous pericardial drainage. Embolic stroke was seen in 0.4% (n=2). In 1 patient, all neurological deficits recovered without sequelae, the other 1 recovered from hemiplegia but still suffers from aphasia. In another 0.4% (n=2), acute heart failure occurred after the procedure requiring transient intensive care therapy and 0.9% (n=5) were documented to have postinterventional pneumonia, all of them recovered with antibiotic therapy. One patient (0.2%) with a history of renal transplantation developed acute renal failure. No deaths, atrioesophageal fistulas or PV stenosis were observed. Overall, severe adverse events including embolic stroke and pericardial tamponade occurred in 4 patients (0.7%).

Discussion

Main Findings

This study provides important information to the field of CA for persAF. First, termination of AF during ablation can be achieved in the majority of patients using the stepwise approach. Second, 5-year follow-up results in limited freedom from AF/AT in 55.9% of patients with multiple procedures. Third, the effectiveness of a single procedure is insufficient. Furthermore, AF termination as a procedural parameter during the index ablation procedure, a lower number of procedures, and the clinical absence of SHD and male sex are associated with a favorable outcome.
Outcomes After PersAF Ablation

Although different groups have presented data on outcomes after PVI for PAF, there remains a paucity of data about the long-term efficacy of CA of persAF. Different patient cohorts along with variable ablation strategies for persAF hinder comparability of existing outcome data. Furthermore, follow-up times vary considerably and are mostly midterm to date.9,16,17,18,22,27 Multiple procedures (mean, 2; 1–7 in our study) or AAD support are often required to maintain stable SR. We report a limited 5-year multiple procedure success rates of 59% (20% on AAD) using the stepwise approach. However, AF termination can be achieved and the majority of patients (65%) do present with AT as a recurrent arrhythmia indicating a first step toward SR. Furthermore, a significant number of patients (n=165; 33%) with recurrences did not undergo repeat ablation because of AF regression to PAF (n=52) or symptom improvement (persAF, n=113; Figure 3). A higher rate of repeat CA may have resulted in improved outcomes. Tlz et al reported on 5-year outcome data using wide antral PVI alone for persAF (n=202) resulting in SR maintenance in 43.2% after multiple procedures (12% on AAD). Of note, PVI as the sole ablative strategy independently predicted arrhythmia recurrences favoring a supplemental substrate-based ablation strategy.17 Recently, 5-year outcome data of the stepwise approach (n=150) revealing AAD–free single and multiple procedure success rates of 15.3% and 64.7% with a termination rate of 80% during index procedure have been published. The lower risk profile patient population (CHA2DS Vasc ≥2 in 25% versus 65%) along with a slightly different follow-up monitoring (89% Holter versus 100%) might explain deviating outcome results compared with our data.18

Complication rates of our study are well in line with worldwide surveys. However, the periprocedural risks and the risk of cumulative radiation doses with multiple procedures have to be carefully considered although planning CA for patients with the stepwise approach.

Strategies for PersAF Ablation

Because the underlying mechanisms of persAF are poorly understood, various approaches for the interventional treatment of persAF are being used.9,10,12,15,17,22 A meta-analysis of 32 studies27 evaluated the impact of different ablation techniques on the outcomes of persAF. The authors concluded that persAF could be effectively treated with a composite of (1) extensive index CA, (2) repeat procedures, and (3) adjunctive pharmacological therapy. It revealed favorable outcomes for the stepwise approach. Also, the current guidelines emphasize that in persAF, ablation strategies beyond PVI should be considered.2

However, we are facing no more than limited outcomes, long procedure times and multiple procedures per patient. Therefore, further research is needed to develop more effective and specific patient tailored AF ablation strategies. Experimental and animal models suggested that focal AF sources or drivers may maintain the fibrillatory process.28,29 The CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial compared conventional ablation with rotor and focus mapping guided ablation followed by conventional ablation and showed improved short-term outcomes for the latter30. Also, panoramic noncontact mapping is aiming at identification of patient-specific AF driving sources.31 Of note, these first data derive from small, mixed AF populations (PAF, persAF) with lack of clinical long-term success to date. Moreover, termination rates varied considerably from 66% to 82%.

In our study, 66% of patients presented with AT as indication for repeat procedures. Linear lesions were created in 42% of procedures (n=438/1042) and clinical AT recurrences led to repeat ablation of the same line in ≤33% of repeat procedures. We showed that linear lesions, a high radiofrequency energy amount, and AF termination in the foregoing procedure, as well as a higher number of procedures, were associated with consecutive procedures because of AT. It is well known that complete conduction block of lines remains challenging and conduction recovery is commonly observed.32 Regional differences in atrial cellular electric properties because of conduction slowing or linear lesion gaps are considered to be proarrhythmic. Together with remodeling of atria, extended tissue ablation might not only provide a favorable condition for the development of ATs but also seem to result in a significant atrial substrate modulation avoiding perpetuation of AF. Additionally, AT recurrences (often based on macroreentrant mechanisms) can more easily be targeted during repeat procedures and are associated with favorable outcome when compared with CA for AF.28,33,34 Therefore, occurrence of AT can be considered a step forward to SR.

About LA transport function after CA of AF previous studies have shown that successful CA significantly decreases LA volumes and does not seem to adversely affect LA function.35 Latter was not only shown by echocardiography but also by MRI demonstrating recovery of active LA appendage emptying in the majority of patients.36

Prognostic Factors for Long-Term Success

Our data suggest that failure of AF termination during index procedure, the number of procedures and the clinical factors, such as female sex and the presence of SHD, are associated with an inferior long-term success.

Structural Heart Disease

One third of patients in our population had a relevant SHD (CAD, cardiomyopathy, or valvular heart disease). Any kind of SHD may trigger a progressive process of structural remodeling in the atria imposing an increased LA afterload resulting in LA stretching, enlargement, and fibrosis.37,38 Heart failure and known SHD were shown to increase the incidence of AF recurrences.39

Female Sex

Although AF being significantly less common in females, latter have a higher prevalence of underlying heart disease, a lower quality of life and treatment aims are harder to achieve. Additionally, women have a higher risk of ischemic stroke.40 In our study, female sex was associated with a worse outcome. Recently, some studies have examined the efficacy of CA for PAF in women but the findings have been inconsistent. Forleo et al41 showed that sex had no effect on the outcome of CA for AF,
whereas Patel et al.\textsuperscript{31} found lower success rates in females. Only 1 study evaluated the outcome for women after CA of persAF which revealed higher recurrence rates as shown in our study.\textsuperscript{43}

**AF Termination**

The data of this study indicate that procedural AF termination during CA of persAF with the stepwise approach independently increases the likelihood of long-term freedom from arrhythmias.

There is an ongoing debate whether AF termination is a direct procedure-related predictor for success and therefore to date termination is not incorporated or endorsed as an end point in the current guidelines.\textsuperscript{3} Several studies have shown that termination is predictive for long-term maintenance of SR.\textsuperscript{19–22,31} O’Neill et al. reported lower recurrence rates in patients with AF termination during index procedure (5% versus 39%). Termination to SR being associated with the highest single procedure success rate compared with AT or AF at the end of the procedure (42% versus 13% and 25%) was shown by Ammar et al. In contrast, Elayi et al. noted no impact of termination on SR maintenance. It did, however, predict the mode of arrhythmia recurrence (AT versus AF).

The question remains, whether failure to terminate AF is an epiphenomenon indicating a more pronounced atrial disease being less responsive to CA. Despite clear evidence-based data, in practice, currently termination is still a commonly used end point for persAF ablation not only during conventional complex fractionated atrial electrogram mapping but also when novel approaches as mentioned above are applied.\textsuperscript{30,31}

**Number of Procedures**

The fact that every repeat procedure lowered the long-term success rates may indicate a point of no return, where AF may no longer be accessible for rhythm control by CA. AF progression might be a reason for the decreasing effect of CA. Previous studies indicated the presence of baseline comorbidities/cardiomyopathies and the type of AF (persAF and long-standing persAF) being independent predictors for progression.\textsuperscript{44}

**Risk Prediction**

More clinical instead of procedural parameters, including novel factors like sleep apnea, obesity, or even MR imaging, for detection of atrial fibrosis would be desirable to screen for long-term success patients prior decision making for or against CA. We were not able to create a clinical futility score identifying patients for whom ablation is not advised, but patients with SHD and an episode duration of >12 months revealed poor outcomes with 60 months single and multiple procedure survival rates of 16% and 28%. It remains unclear if a clinical risk score would be able to estimate the extent of atrial remodeling, disease progression, and response to CA therapy.

For now, clinical factors identifying a less favorable outcome along with acute CA results during initial procedure and the mode of arrhythmia recurrence (AT/AF) should be incorporated when weighing up the patients’ long-term benefit from CA, especially after a failed first or second procedure.

**Late AF Relapse**

Although AF recurrences most often occur within the first 12 months after ablation, previous studies and our data show a slow but steady decline in arrhythmia-free survival thereafter, even after >1 year of apparent arrhythmia control (Figure 2).\textsuperscript{16–18} Failure of persAF ablation seems to be a combined consequence of inadequate trigger ablation, substrate modification, or conduction recovery of previously ablated substrates. However, progression of the AF underlying atrial disease itself that may only partly be halted by SR restoration should be considered as an important factor. Facing late recurrences in initially successfully treated patients, discontinuation of oral anticoagulation should carefully be considered, especially because we found 14% of patients with arrhythmias and a CHA\textsubscript{DS}2-Vasc score ≥1 being off oral anticoagulation at time of long-term follow-up.

**Limitations**

Patients in this single-center study were not randomized and the data analysis was retrospectively performed. Although the vast majority of patients presented with sustained forms of arrhythmias, the potential for under-recognition of silent arrhythmia recurrences during follow-up exists. Because of discontinuous Holter ECG monitoring, we are not able to provide data on AF burden prior and after CA.

**Conclusions**

The present data indicate that CA of persAF using the stepwise approach provides limited long-term freedom of arrhythmia recurrences often requiring multiple procedures. AF termination during index procedure, the number of procedures, sex, and the presence of SHD are prognostic factors correlating with long-term outcome. AF termination is associated with consecutive AT procedures.

**Disclosures**

None.

**References**


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