Ipsilateral Circumferential Radiofrequency Ablation of Atrial Fibrillation With Irrigated Tip Catheter – Long-Term Outcome and Pre-Procedural Predictors –

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Background: Predictors of long-term outcome of atrial fibrillation (AF) ablation are unknown. The predictors of 5-year follow-up (FU) after single ipsilateral circumferential antrum pulmonary vein isolation (PVI) with irrigated tip catheter were investigated.

Methods and Results: In 356 patients (74% male) with AF (44% paroxysmal AF [PAF]) PVI was performed. Success was defined as absence of AF, atrial flutter or tachycardia (AFLAT) recurrence. A total of 161 patients (45%) were free of AFLAT. The univariate predictors of AFLAT recurrence were: type of AF (non-PAF vs. PAF, P=0.0001), size of LA (normalized left atrium area [NLA] ≥11.5 vs. NLA <11.5, P=0.0001), renal function (glomerular filtration rate [GFR] <68 ml/min vs. GFR ≥68 ml/min, P=0.001) and hypertension (HT vs. no HT, P=0.025). The independent predictors of AFLAT-free survival were non-PAF (hazard ratio [HR], 1.67; 95% confidence interval [CI]: 1.23–2.26, P=0.0005), NLA ≥11.5 (HR, 1.40; 95% CI: 1.03–1.90, P=0.007) and GFR <68 ml/min (HR, 1.70; 95% CI: 1.21–2.37, P=0.008).

Conclusions: Single PVI results in a moderate success rate in patients with AF during 5-year FU without the use of a 3-D mapping system. Higher success was observed in patients with PAF, non-enlarged LA and good renal function. (Circ J 2013; 77: 2280–2287)

Key Words: Atrial fibrillation; Catheter ablation; Circumferential pulmonary antrum isolation; Predictors of outcome; Pulmonary vein isolation

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia associated with significant morbidity and impaired quality of life. Medical therapy is of limited efficacy. Catheter ablation of AF is an important therapeutic modality for patients with AF.

The aim of catheter ablation for AF is to eliminate the triggers or substrate that initiate and maintain the disorder, to maintain sinus rhythm. Findings from several multicenter prospective clinical trials, systematic reviews, and meta-analyses have consistently shown that catheter ablation is more effective than anti-arrhythmic drug (AAD) therapy for maintenance of sinus rhythm. Furthermore, successful catheter ablation of AF was associated with improved symptoms and quality of life.

The published data suggest that, although sinus rhythm is better preserved after ablation procedures than with AAD, late recurrences are not uncommon. Despite the fact that the recent consensus guidelines emphasize the need for reporting of long-term results, most authors have presented follow-up (FU) data limited to ≤1 year. Recently published results of a 5-year FU are limited by ostial approach, usage of non-irrigated tip catheters, use of 3-D electroanatomical mapping and lower monitoring regime as recommended nowadays.

We present a very long-term outcome and its predictors in a cohort of patients after single ipsilateral circumferential antrum pulmonary vein isolation (PVI) with irrigated tip catheter using uniform approach without 3-D mapping system at a single center.

Methods

Patient Characteristics
To determine long-term outcome, we retrospectively followed a cohort of 356 patients who had PVI performed at Kerckhoff...
Heart Center, Bad Nauheim, Germany.

Inclusion criteria, at the time of procedure, were as follows: age between 18 and 80 years; symptomatic and drug-refractory AF documented on at least 2 electrocardiograms (ECGs) in a 3-month period preceding an ablation procedure; and signed informed consent by the patient.

Exclusion criteria were defined as acute reversible causes for AF, such as hyperthyroidism; known bleeding diathesis or intolerance of heparin or oral anticoagulation; attempted AF ablation in the past; left atrial (LA) thrombus; pregnancy or breastfeeding; abuse of drugs or alcohol; New York Heart Association (NYHA) class IV and other severe comorbidity.

Pre-Ablation Preparation
Medical history was obtained during outpatient clinic visit with a review of the medical records including ECGs and Holter ECG recordings of AF. The risk of ablation was discussed in detail, and all patients gave written informed consent before the procedure.

Three days before intervention, coumadin was stopped and replaced by s.c. low-molecular-weight heparin. All AAD, including amiodarone, were discontinued at least 3 days before ablation. Beta-blockers were allowed according to the protocol. Trans-esophageal echocardiography was performed to exclude LA thrombi.

Assessment of LA Size
All patients underwent transthoracic echocardiography to determine LA diameter. The LA size was assessed at admission on measurement of short- and long-axis in apical 4-chamber view. The normalized LA area (NLA) was calculated, as previously described. 21

AF Burden
Previous studies suggested that frequent and long AF episodes in patients with paroxysmal AF (PAF) predict poor outcome after PVI. 24 Patients with paroxysmal AF with >500 h in symptomatic AF within 3 months prior to admission were defined as “high burden” group and considered as non-paroxysmal AF (NPAF). 23

Catheter Ablation
Procedures were performed under conscious sedation and analgesia with appropriate doses of midazolam and dipidolor. During the catheter procedure, an infusion of heparin was maintained to achieve an activated clotting time >300 s. Measurements were performed every 30 min routinely.

The ablation procedure, without support of any 5-D electroanatomical mapping system, was performed with the high-density (HD) mapping HD Mesh Mapper™ (HDMM; Bard Electrophysiology, Lowell, MA, USA) catheter, described earlier. 25 It is a sole mapping catheter that is constructed not as an over-the-wire-system. 25 When placed in the antrum, its position is stable during the ablation procedure and allows for HD real-time mapping inside a PV. This offers the opportunity of a fully endocardial electrogram-guided circumferential antrum ablation with an additional ablation catheter.

In all cases we used bi-plane fluoroscopy with X-ray lamps set in left-anterior oblique 60° and right-anterior oblique 30° views.

After local anesthesia a 10- or 20-polar steerable catheter ( Biosense Webster, Diamond Bar, USA) was placed in the coronary sinus from the left femoral groin. Two trans-septal sheaths (SL-1 SJM™, steerable Agilis sheath SJM™ or Channel sheath Bard, Lowell, USA and Fast Cath 8F SJM, Minnetonka, USA) were introduced into the LA. For HD mapping, a 32-bipolar signal display was programmed and displayed on the LabPro EP recording system.

HDMM was placed in an antrum of a PV and a 7-F thermoablation catheter. The radiofrequency (RF) energy settings at the RF generator (HAT 300™; Osypka, Grenzbach-Wyhlen, Germany) were chosen between 15 and 35 W with a cut-off temperature of 42°C. During RF energy delivery, the ablation catheter was tracked around the equator of the spanned HDDM. Irrigated ablation of each PV was carried out in immediate proximity to, but definitely at the atrial side of the HDDM and/or the PV. A circumferential ablation line

| Data given as median (IQR) or n (%). ACEI, angiotensin-convert ing enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; HAT-C, high-density lipoprotein cholesterol; HMG-CoA, 5-hydroxy-3-methylglutaryl-coenzyme A reductase; LDL-C, low-density lipoprotein cholesterol; NLA, normalized left atrial area. |
After discharge from the hospital, patients were scheduled for quarterly FU visits. One year after intervention, FU visits were performed once a year. Seven-day Holter ECG recordings and a 12-channel ECG were obtained during each FU visit. Patients were asked to obtain an ECG at Kerckhoff Heart Center or outside when feeling palpitations at times out of Holter-ECG monitoring periods.

A blanking period of 3 months has been considered.

Endpoints
The endpoint for analysis was AF-free survival within 60 months FU, including all patients who had been followed for at least 6 months. As an index parameter for failure, time to first documented AF, atrial flutter, atrial tachycardia (AFLAT) episode >30 s documented on any kind of ECG was defined.

Statistical Analysis
The effect of discrete variables was studied using Kaplan-Meier survival analysis with log-rank test. The univariate association of continuous variables with outcome was analyzed using receiver operator characteristics (ROC) curves, and parameters were dichotomized on optimal cut-off. The impact of discrete variables on outcome was described with positive and negative prediction accuracy and hazard ratio. Continuous data are presented as median and interquartile range (IQR), and categorical variables as numbers and percentages.

To avoid potential over-fitting of the model, only the parameters identified as being significantly associated with outcome on univariate analysis were included in the multivariate Cox regression model, calculated using the step-down procedure. Two-tailed P <0.05 was considered statistically significant.

FU
After discharge from the hospital, patients were scheduled for quarterly FU visits. One year after intervention, FU visits were performed once a year. Seven-day Holter ECG recordings and a 12-channel ECG were obtained during each FU visit. Patients were asked to obtain an ECG at Kerckhoff Heart Center or outside when feeling palpitations at times out of Holter-ECG monitoring periods.

A blanking period of 3 months has been considered.

Post-Ablation Management
I.v. flow of heparin was continued to achieve a partial thromboplastin time of 60–80 s. Prior to discharge from the electrophysiological laboratory, all patients underwent transthoracic echocardiography to exclude pericardial effusion. Oral anticoagulation with coumadin was started 1 day after PVI, targeting an international normalized ratio of 2.0–3.0 for at least 3 months.

was performed around the mapping catheter at each PV, overlapping ipsilateral ablation lines. In patients with sinus rhythm, at the beginning of a procedure, only PV antrum isolation was performed. In patients with AF, at the beginning of a procedure, the first step of the procedure was PV antrum isolation. When AF stopped spontaneously during PVI at the antrum, the procedure was finished after confirming isolation of the PVs. If AF continued, a stepwise approach including mitral isthmus line, roof line, ablation of complex fragmented signals and finally isolation of superior vena cava was implemented in the same procedure. When sinus rhythm could not be obtained during the procedure, cardioversion and re-mapping at sinus rhythm was planned at the end of the procedure. No AF induction or isoproterenol challenge was performed.

The acute endpoint for the procedure was elimination of PV antrum potentials recorded from the HDMM and/or both exit and entrance block from the PV. When residual signals existed, the pair of electrodes was paced with maximum output of 10 V at 2.9 ms. If the location could be captured, the energy delivery was continued to a point when capture was lost. In the case of missed capture, the residual signal was indexed as a far-field.

| Table 2. Predictors of Outcome After Single RF Ablation |
|---|---|---|---|---|
| | AUC | 95% CI | P-value |
| Continuous variables (ROC analysis) | | | |
| History of AF | 0.492 | 0.425 | 0.558 | 0.8042 |
| Age | 0.486 | 0.426 | 0.546 | 0.6504 |
| BMI | 0.550 | 0.485 | 0.615 | 0.1402 |
| BSA | 0.487 | 0.422 | 0.553 | 0.7080 |
| LA long axis diameter on 4-chamber view | 0.533 | 0.473 | 0.593 | 0.2903 |
| LA short axis diameter on 4-chamber view | 0.581 | 0.522 | 0.640 | 0.0084 |
| LA area | 0.600 | 0.541 | 0.659 | 0.0011 |
| NLA | 0.612 | 0.554 | 0.670 | 0.0005 |
| Creatinine | 0.537 | 0.476 | 0.597 | 0.2355 |
| GFR | 0.580 | 0.520 | 0.639 | 0.0096 |
| LVEF | 0.554 | 0.494 | 0.613 | 0.0803 |
| Discrete variables | | | |
| NPAF | 1.473 | 1.226 | 1.771 | 0.0001 |
| Hypertension | 1.374 | 1.040 | 1.814 | 0.0250 |
| Diabetes | 0.874 | 0.583 | 1.309 | 0.5550 |
| NLA ≥11.50 | 1.392 | 1.166 | 1.663 | 0.0001 |
| GFR <68 ml/min | 1.451 | 1.164 | 1.809 | 0.0010 |
| Multivariate Cox regression model | | | |
| NPAF | 1.703 | 1.261 | 2.298 | 0.0005 |
| NLA ≥11.50 | 1.505 | 1.199 | 2.024 | 0.0068 |
| GFR <68 ml/min | 1.581 | 1.125 | 2.222 | 0.0084 |

AUC, area under the curve; CI, confidence interval; HR, hazard ratio; NPAF, non-paroxysmal atrial fibrillation; RF, radiofrequency; ROC, receiver operating characteristic. Other abbreviations as in Table 1.
Results

Baseline and Procedural Characteristics
In this retrospective study we included 356 patients who underwent PVI with HDMM. Baseline characteristics of the cohort are summarized in Table 1. The median cumulative time of the procedure was 2.8 h (IQR, 2.2–3.2 h), with a median fluoroscopy time of 41.8 min (IQR, 30.5–65.9 min).

Even though all patients had PVI during the first procedure, additional LA lesions were created in 129 patients (36%; 106
NPAF patients and 23 PAF patients with high AF burden, respectively): mitral isthmus line in 112 (31%), roof line in 105 (29%), lesions along coronary sinus in 48 (13%) and fragmented signals at the posterior area of the LA in 25 (7%), respectively. Superior vena cava was additionally isolated in 8 patients (2%). Intra-procedural cardioversion was performed in 101 patients (28%; 11 in PAF, 90 in NPAF).

Eighty-eight patients (25%) with severe symptoms during AF recurrence were, according to the protocol, on AAD at some points of FU.

### Table 1: Procedure Details

| Procedure               | Total | Events | Censored | N (%)  |
|-------------------------|-------|--------|----------|--------|
| Mitral isthmus line     | 112   | 40     | 51       | 56.7%  |
| Roof line               | 105   | 155    | 108      | 41.1%  |
| Lesions along CS        | 48    | 194    | 159      | 45.0%  |
| Fragmented signals LA   | 25    | 194    | 159      | 45.0%  |
| Total                   | 356   | 40     | 51       | 56.7%  |

### Figure 3. Renal function and 5-year outcome.
Kaplan-Meier event-free survival curve after a single catheter ablation. The cut-off of 68 mL/min for GFR was calculated from receiver operating characteristic curve analysis. AF, atrial fibrillation; AFLAT, atrial fibrillation, atrial flutter, atrial tachycardia; GFR, glomerular filtration rate.

### Figure 4. Hypertension and 5-year outcome.
Kaplan-Meier event-free survival curve after a single catheter ablation. AF, atrial fibrillation; AFLAT, atrial fibrillation, atrial flutter, atrial tachycardia.
Arrhythmia-Free Survival and Predictors of Long-Term Outcome After a Single Procedure

One hundred and sixty-one patients (45%) were free of AFLAT on 5-year FU after the initially successful procedure. The cut-offs of 11.5 for NLA and of 68 ml/min for glomerular filtration rate (GFR) were calculated from ROC curve analysis (Table 2).

After a single procedure, the univariate predictors of AFLAT recurrence (Table 2) were: type of AF (Figure 1), size of LA (Figure 2), renal function (Figure 3) and hypertension (Figure 4).

The independent predictors of AFLAT-free survival after first procedure were NPAF, NLA ≥11.5 and GFR <68 ml/min (Table 2).

Complications

Major complications occurred in 23 patients (6.5%). Cardiac tamponade (n=4; 1.1%) could have been managed by pericordial puncture without any sequel. Pericordial effusion (n=17; 3.7%) needed no intervention. Two patients (0.6%) developed transient ischemic attack in the early days after intervention. PV stenosis in 1 patient (0.3%) was resolved by implantation of a GENESIS PTA stent (Cordis, Miami, FL, USA) with a diameter of 10 mm. That patient has been stable since. In 27 patients (8%) the ablation resulted in LA tachycardia that resumed after additional procedures. There were no procedure-related deaths, air embolism, atrio-esophageal fistula or stroke.

Discussion

The emerging need for reporting of long-term success of catheter ablation for AF has been emphasized in the latest expert consensus statement. Herein, we report the longest FU to date of ipsilateral circumferential ablation of AF with irrigated tip catheter and HD Mesh Mapper™ as a mapping tool. In 5-year FU after a single procedure, overall freedom from AFLAT recurrence was 45% and independent predictors of very late AFLAT recurrence were type of AF, LA size and renal function, that is, factors related to structural atrial remodeling. One year success rates in the present study are consistent with prior reports. During this time, we observed a gradual decrease in arrhythmia-free survival. We noted that the rate of decline in freedom from AFLAT after the first intervention stabilized after the initial 12 months, although it did not entirely reach a plateau. Outcome longer than 3 years after RF ablation has been described in few reports. The present data are comparable to previously described 3- and 4-year success rates. Gaita et al followed 204 patients for 3 years and reported freedom from AFLAT after a single procedure in 29% of PAF and 19% of NPAF patients treated with PVI only, and in 53% of PAF and 41% of NPAF treated with PVI plus left linear lesions, respectively. In a 4-year FU of a group of 110 patients with PAF, Fiala et al reported that 56% of them were free from arrhythmia after a single RF procedure, without AAD. Similar results were presented by Bertaglia et al, in PAF and NPAF patients after PVI plus mitral isthmus lesion, with 58% of patients free from AFLAT after 4 years. Still, almost 19% of those patients were on continuous therapy with AAD. Ouyang et al, who used 3-D electroanatomical mapping, noted a single-procedure success rate of 46% at 5-year FU; that is, almost as good as was obtained in the present study without such support. Recently published data by Weerasooriya et al noted even lower effectiveness of RF energy, with 39%, 26% and 29% of patients free from AFLAT after a single procedure at 1-, 2- and 5-year FU, respectively. The limitations of the study were ostial approach in a more selected group (younger, healthier, non-obese patients with relatively smaller atria and paroxysmal or recent progression to persistent AF) and monitoring for AFLAT recurrence, not as extensively performed as currently recommended. According to the present data, 5-year freedom from AFLAT recurrence after a single PVI ablation was 57% in PAF. The outcome for NPAF (36%) was less satisfactory but still better than after ostial PVI as determined by Weerasooriya et al.

Predictors of Very Late Recurrence After Circumferential Ablation of AF

Many factors (type of AF, LA size, age, sleep apnea and obesity, hypertension, LA fibrosis detected on magnetic resonance imaging [MRI], diabetes, rise in right atrium magnetic strength) have been proposed as predictors of poorer outcome after PVI. The most consistent predictor of very late recurrence was type of AF, followed by LA size. We found that the independent predictors of very late recurrence of AF after circumferential RF ablation were: type of AF, size of LA, and impairment of renal function. Hypertension was associated with outcome on univariate analysis only. We did not study sleep apnea and did not have MRI data on LA fibrosis. Other, previously proposed, predictors such as age, gender, AF duration and prior AAD were not important in the present cohort.

Type of AF is widely recognized, in most reports, as a known predictor of success. It is well accepted that the development of AF requires both a trigger and a susceptible (anatomical or functional) substrate. Most triggers originate in the LA-PV junction. Eliminating the triggers, and the part of the substrate located near the LA-PV junction, in PAF patients (with functional rather than anatomical substrate) by circumferential PVI results in a high success rate. Failure of PVI in this group is rather a result of incomplete isolation of LA-PV triggers or existing non-LA-PV triggers (eg, vein and ligament of Marshall, posterior wall of LA, superior vena cava) that were not identified and electrically isolated during ablation. In NPAF patients, with anatomical substrate, sole circumferential PVI is rarely sufficient to eliminate AF, even with additional lesions within LA (eg, mitral isthmus line, roof line or complex fractionated atrial electrograms [CFAE]). Improvement of the success rate in NPAF needs deep and wide injury within the LA, which can be achieved after multiple procedures.

The importance of LA size, as a single independent predictor of success, partly supports the concept of the critical mass hypothesis proposed by Moe and verified by Damiano et al. We believe it is true for NPAF patients. There are some controversies in PAF. Some authors suggest that LA size may not be the most important factor in selected PAF patients, because enlargement of the LA might be an “acute result of atrial tachycardiomypathy” without structural substrate within the LA. In such PAF patients, with enlarged LA but low AF burden, sole PVI may stop AF and result in positive LA remodeling. Such attempts would justify early intervention and PVI as first-line therapy for AF. We believe that enlarged LA is not a synonym for structurally changed LA, especially in PAF patients.

A lower success rate in patients with impaired renal function has also been previously described. Renin-angiotensin-aldosterone system (RAAS) stimulation, in patients with impaired estimated GFR (eGFR), causes cardiac remodeling and increases the arrhythmogenic substrate. Myocardial fibrosis slows down impulse propagation velocities.
heterogeneous depolarization facilitates an anisotropic re-entry phenomenon. Decreased eGFR has been associated with arrhythmogenic substrate properties of the LA, that is, low LA voltage and long activation time, regardless of the size of LA. Those findings were associated with electrical remodeling of LA. In our opinion, the observed change in voltage and activation time, even in non-enlarged atria, is instead the premise for structural remodeling. Hypertension is a well-established risk factor for AF development and an independent predictor of AF recurrence in the general population. It is also proposed as a predictor of poorer outcome after PVI but only a few studies report hypertension to be a single independent predictor of outcome at an average of 41, 13.1 and 8.7 months. Hypertension results in impaired left ventricle diastolic function and, as a consequence, LA volume overload, which itself makes LA more prone to fibrillation. Additionally, activation of RAAS in hypertensive patients may provoke structural remodeling within the LA. The present data show that, in very long FU of 5 years, hypertension has not been identified as a single independent predictor of very long-term outcome after PVI, that is, its effect on structural changes in the LA might be overestimated. We should instead consider hypertension as one of the factors predisposing to AFLAT recurrence in patients with already existing substrate for AF.

All identified independent factors are connected with deep remodeling within the LA structure. Single ipsilateral circumferential PV antrum isolation (eliminating focal triggers), even with additional lesions (linear lesions, CFAE), may reverse electrical remodeling but it cannot be expected to stop or reverse structural remodeling.

Clinical Implications

Clinical implications of the present results are substantial with regard to the care of AF patients after RF ablation. First, empirical long-term FU data should be presented to patients to inform the decision-making process and provide reasonable expectations. Second, ongoing surveillance is warranted, even if catheter ablation was deemed initially successful. Incidence of late recurrence may be related to the extent of ECG monitoring and earlier recurrence may be missed in selected patients with no or minimal symptoms. Clinical evaluation should be performed on a regular basis and any complaint of “heart palpitations” or suspected silent AF should be addressed. Finally, attention to control patient-related AF risk factors remains an integral part of AF management after the ablation procedure.

A higher, than currently reported, cardiac perforation rate was in all cases caused by injury of the LA appendage with HDMM. The HDDM cannot be navigated over a wire, which increases the risk of perforation. Angiography of the PV is mandatory for a safer introduction of the stiff catheter into the PV.

Study Limitations

This study had the following potential limitations. First, this was a single-center, non-randomized, retrospective report with the limitations characteristic of this study design. There was no selection bias for study inclusion, however, because all consecutive patients undergoing catheter ablation for AF at Kerckhoff Heart Center were included for analysis. Second, the present results were further limited by potential variability of operator experience with the stepwise ablation approach. Third, according to the latest Consensus Report, the FU results are presented without consideration of recurrences during the blanking period. This could lead to an overestimation of the true success rate. Fourth, FU was based on clinical evaluation and Holter-ECG recordings. Although the vast majority of patients presented with sustained forms of arrhythmia recurrences (AFLT), some asymptomatic non-sustained arrhythmia episodes may have been missed. Any missed asymptomatic AFLAT should have occurred equally across all subgroups and is not likely to have changed the present conclusions. And fifth, MRI was not routinely performed after the 3-year FU to detect asymptomatic PV stenosis, although patients were specifically questioned with regard to PV stenosis symptoms and imaging was performed to rule out a suspected diagnosis.

Conclusions

A single PVI procedure without the use of a 3-D mapping system results in a moderate success rate during 5-year FU. The success rate, however, is comparable to those procedures with the use of a 3-D mapping system. Higher success was observed in patients with PAF, non-enlarged LA and good renal function. The long-term outcome success in patients at risk (NPVF, enlarged LA, impaired eGFR) was acceptable but subsequent procedures might be needed in many of them to cure AF. Hypertension should instead be addressed as a concomitant factor that further aggravates the outcome of catheter ablation in AF patients. Although most recurrences occurred in the first 12 months, a slow but steady decline in arrhythmia-free survival was noted thereafter. Such long-term FU results should be openly discussed with patients and thoroughly considered when presenting the merits of an ablation approach to AF patients.

Disclosures

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