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Clinical and Electrophysiological Predictors of Arrhythmia Recurrences after Catheter Ablation for Atrial Fibrillation

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The mediocre teacher tells. The good teacher explains. The superior teacher demonstrates. The great teacher inspires.

William Arthur Ward

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Vorbemerkung

Bei der folgenden Dissertation wurde die Form der publikationsbasierten Promotion (gemäß TUM Promotionsordnung §6) gewählt, basierend auf zwei akzeptierten Erstautorenveröffentlichungen des Doktoranden. Den als Appendix beigefügten Originalarbeiten kann man jeweils die detaillierten Ausführungen zu Einleitung, Methoden, Resultaten und Diskussion entnehmen. Im folgenden einleitenden Textteil werden die beiden Publikationen zusammenfassend dargestellt, wobei auf die wichtigsten Methoden und Ergebnisse kurz eingegangen wird.

List of included journal publications

The present doctoral thesis is based on the following two first-authored journal publications

1) JP I

Buiatti A, Ammar S, Reents T, Semmler V, Kathan S, Hofmann M, Bourier F, Telishevska M, Kochbüttner K, Kaess B, Lennerz C, Kolb C, Hessling G, Deisenhofer I. **Dissociated Pulmonary Vein Activity After Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: A Predictor for Recurrence?** *J Cardiovasc Electrophysiol 2015 Jan;26(1):7-13.*

2) JP II

Buiatti A, Kaess B, Reents T, Semmler V, Telishevska M, Bourier F, Kornmayer M, Kottmaier M, Hessling G, Deisenhofer I. **Catheter Ablation for "Lone" Atrial Fibrillation: Efficacy and Predictors of Recurrence**. *J Cardiovasc Electrophysiol 2016 May;27(5):536-41.*

List of abbreviations

AAD	Antiarrhythmic Drug
AF	Atrial Fibrillation
AV	Atrio Ventricular
CA	Catheter Ablation
CL	Cycle Length
CS	Coronary Sinus
CV	Cardioversion
DPV	Dissociated Pulmonary Vein
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration Rate
ERP	Excitability Refractory Period
ESC	European Society of Cardiology
ICD	Implantable Cardioverter-Defibrillator
LA	Left Atrium
LIPV	Left Inferior Pulmonary Vein
LSPV	Left Superior Pulmonary Vein
MRI	Magnetic Resonance Imaging
OAC	Oral Anticoagulation
PV	Pulmonary Vein
RCT	Randomized Clinical Trials
RSPV	Right Superior Pulmonary Vein
SR	Sinus Rhythm

Contents

INTRODUCTION

Epidemiology of Atrial Fibrillation

Prevalence and Incidence in the General Population

Atrial fibrillation is a global health care problem with evidence suggesting an increasing prevalence and incidence worldwide[1]. This trend seems to be explained by the increasing age in the general population[2,3], the increasing prevalence of obesity, a better survival after a first cardiovascular event and a much-improved technology to detect AF, and other arrhythmias[4]. The prevalence of AF depends upon population characteristics, with differences apparent mostly due to age, sex, race and clinical setting[5]. Most of available clinical data are primarily derived from studies in which an electrocardiogram was obtained during an office visit rather than ambulatory monitoring. The prevalence of paroxysmal AF, which is more likely to be detected with ambulatory monitoring, is much higher[6].

AF is uncommon in infants and children and when present, almost always occurs in association with structural heart disease. Healthy young adults are also at low risk[1]. The prevalence of AF increases with age[7]. This relationship to age was demonstrated in the ATRIA study, a cross-sectional study of almost 1.9 million subjects in a health maintenance organization in the United States[8]. The overall prevalence of AF was 1 percent; 70 percent were at least 65 years old and 45 percent were ≥75 years old. The prevalence of AF ranged from 0.1 percent among adults less than 55 years of age to 9 percent in those ≥80 years of age. Similar patterns were reported in a European population-based prospective cohort study of 6808 subjects ≥55 years of age[9]. The prevalence of AF was 5.5 percent, ranging from 0.7 percent in those aged 55 to 59 years and 17.8 percent for those ≥85 years of age. AF prevalence and incidence in Asians and blacks are lower than in individuals with European

ancestry, despite a higher burden of comorbidities in blacks. Possible explanations comprise genetic, socioeconomic, and environmental determinants of health, which have not been completely evaluated[1,8].

The incidence of AF, similar to the prevalence, increases with advancing age. The risk increased with advancing age (from 0.5 per 1000 person-years before age 50 to 9.7 per 1000 person years after age 70). The lifetime risk for the development of AF was analyzed in a report from the Framingham Heart Study[7]. A total of 8725 patients were followed from 1968 to 1999 (176,166 person-years of follow-up); 936 developed AF. The risk of developing AF from age 40 to age 95 was 26 percent for men and 23 percent for women. Lifetime risk did not change substantially with increasing index age because AF incidence rose with age; the risk of developing AF from age 80 to age 95 was 23 percent for men and 22 percent for women.

Risk Factors for Development of Atrial Fibrillation

Among the many risk factors for development of AF, age is perhaps the most powerful, age-related fibrosis seems to play a key role. In western societies, elevated blood pressure and obesity are by far the most important modifiable risk factors for developing AF[10]. Combining the most important modifiable risk factors explains about 50% of the population attributable risk for AF development. There is therefore much room to further increase this number, and to obtain a better understanding on risk factors for AF development. It will also be important to assess whether the risk for develping AF can be attributed to phenotypic or genotypic differences. Large global studies using standardized assessment tools are needed to gain further insights in this area.

Most data on risk factors for new-onset AF are from the USA or other western populations[11]. It is unclear whether these associations are the same in other parts of the world, where the prevalence of obesity is much lower and where different risk factors for AF development may be present (e.g. Rheumatic heart disease). It is notable that many of the risk factors that have been associated with development of AF also

contribute to AF progression, recurrences of AF following ablation and complications associated with AF (e.g. stroke).

Unfortunately, very few randomized trials have investigated whether weight loss or intensive blood pressure control prevents the occurrence of new-onset AF in the population[12-16]. Posthoc data from randomized trials that did not pre-specify AF as an endpoint should be interpreted with caution, as they have a substantial risk of detection bias. There is therefore a clear need to include AF as pre-specified endpoint in future cardiovascular prevention trials.

Pathophysiology and Natural History of Atrial Fibrillation

Whereas AF may occur in the absence of known structural or electrophysiological abnormalities, epidemiological association studies are increasingly identifying comorbid conditions, many of which have been shown to cause structural and histopathological changes that form a unique AF substrate or atrial cardiomyopathy[17,18].

Mechanisms of Atrial Fibrillation: Interaction of Trigger and Substrate

Induction of AF requires rapid triggering propagating reentrant waves in a vulnerable atrial substrate. Premature atrial ectopy firing arising from myocyte sleeves within the PVs has been shown to be the most frequent trigger for AF[19]. It is now known that the PVs have unique electrical properties and a complex fiber architecture that promote reentry and ectopic activity to initiate AF. Catheter ablation of these ectopic foci reduced AF burden, demonstrating their role in AF genesis[20-22].

Besides the importance of triggers for AF, the presence of a susceptible atrial substrate is equally important in the maintenance of AF. Spectral analysis and dominant frequency mapping revealed that the dominant frequency and the highest dominant frequency were spatially distributed into the entire LA[23]. Perpetuation of AF is postulated to be sustained from reentrant waves, however the mechanism of reentry in AF is still controversial with two dominant hypothesis: reentrant rotors or multiple

independent wavelets. Atrial substrates that promote reentry are characterized by abnormalities of the atrial cardiomyocyte, fibrotic changes, and alterations in the interstitial matrix[24-27]. A combination of atrial fibrosis and alterations in cardiomyocyte function result in both a slowing of conduction velocity and shortening of ERP. Multiple animal models and human studies have revealed a close interplay of atrial myopathy, AF, and stroke via various mechanisms (e.g., aging, inflammation, oxidative stress, and stretch), which, in turn, lead to fibrosis, electrical and autonomic remodeling, and a pro-thrombotic state. The complex interplay among these mechanisms creates a vicious cycle of ever-worsening atrial myopathy and a higher risk of more sustained AF, arrhythmia recurrences and strokes, thus leading to worse outcome even after CA. Interestingly, although AF may lead to the initiation and/or progression of this myopathy, the presence of AF is by no means essential to the development or the maintenance of this myopathic state[28].

Natural History of Atrial Fibrillation and Impact on Prognosis

The common notion that AF begins with paroxysmal episodes while the electrical derangement adds to a vicious cycle in which "AF begets AF" has been evolving in the past 2 decades[25]. Studies in patients with pacemakers allowed for more robust assessment of AF burden and have shown that progression to more persistent AF subtypes is heterogeneous and still difficult to predict. Actually, most of available clinical data are still controversial. The Euro Heart Survey[29] followed 5,333 patients with AF for one year and found that 80% of patients with paroxysmal AF remained paroxysmal while 30% of patients with persistent AF progressed to permanent. One study[30] showed that up to 24% of patients with paroxysmal AF progressed to persistent AF in one year and that there was a progressive pattern of increasing arrhythmia burden in these patients except in the days prior to the development of persistent AF supporting the mechanism of tachy-mediated atrial remodeling. The complex natural history of AF highlights the existing uncertainty in the mechanisms and factors that regulate the clinical course of AF. Moreover, the natural history of AF may change over time as the risk factors contributing to its onset shift in prevalence and severity. Accordingly, in obese patients with AF, weight loss together with management of

other risk factors is strongly recommended to reduce AF burden and symptoms. Further obstructive sleep apnea treatment should be optimized to reduce AF recurrences and improve AF treatment results[1].

Nevertheless, AF is known to increase the mortality risk 1.5- to 2- fold[31] and the risk of stroke 5- fold[32]. However, prognosis of AF patients has been proved to be strongly influenced by improving of primary (e.g., better hypertension control) and secondary (anticoagulation) prevention treatments. Oral anticoagulation for stroke prevention is the mainstay of treatment in most patients with clinical AF[33]. However, the causal role of AF in the development of stroke and other adverse outcomes has been questioned[34]. Atrial myopathy is a new concept that describes patients with a diseased left atrium but without known AF. A diseased left atrium with or without the ability to develop or sustain arrhythmia episodes may potentially explain the lack of temporal relationship between arrhythmia episodes and adverse outcomes[35]. Studies aiming to improve outcomes by directly targeting the diseased left atrium will shed more light on this interesting concept.

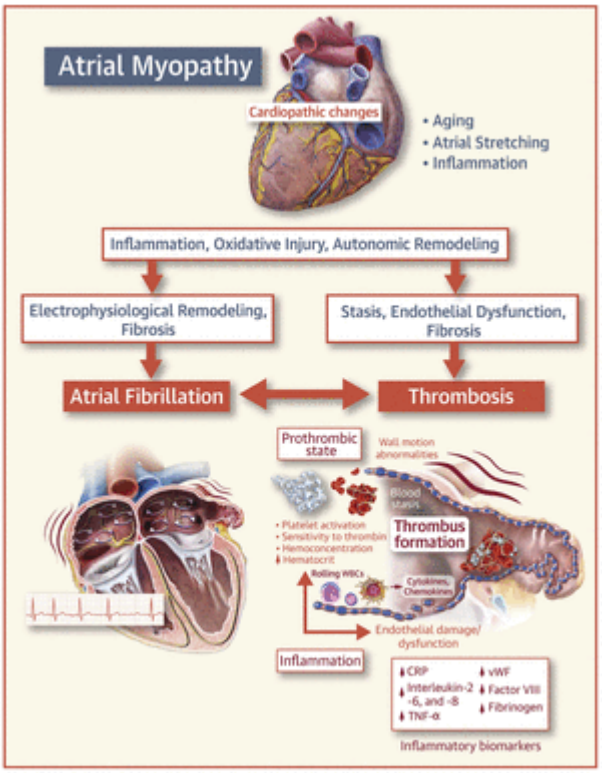

Figure 1: Atrial Myopathy. Its Relationship between Atrial Fibrillation and Strokes (from Shen A et al. Atrial Myopathy. J Am Coll Cardiol Basic Trans Science 2019;4:640-654)[35]

Another well-known adverse outcome among patients with AF is congestive heart failure, AF can cause tachycardia-mediated cardiomyopathy or worsening of preexisting heart failure[36]. Increasing evidence suggests that patients with AF also face a higher risk of cognitive dysfunction and dementia[37]. While this increased risk seems in part explained by the higher stroke risk among AF patients, the risk of cognitive dysfunction remains increased among AF patients without a history of clinical stroke, and studies are needed to address this important issue.

Finally, assessment of AF burden over time in various population studies is inconsistent leading to ascertainment bias and challenges in predicting the natural history of AF subtypes. Although the substantial progress over the last decade in understanding the significance of AF and its complications there is still a clear need for more evidence in this area. A growing number of patients with stroke are diagnosed with "silent" paroxysmal AF[38]. Therefore 2016 ESC guidelines[4] for management of AF recommend to interrogate pacemakers and ICDs on a regular basis for atrial high rate episodes. In patients with suspected AF further ECG monitoring is required to establish the diagnosis of AF, before starting any specific treatment. There is good evidence that prolonged ECG monitoring enhances the detection of undiagnosed AF, e.g., monitoring for 72 hours after a stroke, or even longer periods. By accepted convention, an episode lasting at least 30 seconds is diagnostic[1,4]. While the widespread availability of user-friendly long-term ECG recording devices has facilitated the detection of AF, it has created its own challenges. Advanced long-term monitoring in elderly high-risk individuals and pacemaker patients revealed a high number of individuals who have asymptomatic, 'subclinical' AF episodes. It is currently unclear which threshold to use to differentiate clinical from subclinical AF and whether the same treatment algorithms should be applied to patients with subclinical AF. Studies assessing the benefits and risks of oral anticoagulation in these patients are currently ongoing.

Catheter Ablation of Atrial Fibrillation

Current guidelines recommend CA of symptomatic paroxysmal AF to improve AF symptoms as first line therapy considering patients choice, in patients preferring further rhythm control therapy[4]. Previous RCTs[39-42] failed to demonstrate any significant mortality benefit of a pharmacologically based rhythm control strategy when compared with a rate control strategy. This has originally led to a widespread belief that restoration of SR does not improve prognosis. However, in-depth analysis of these trials demonstrated that the restoration of SR was associated with a 47% lower risk for death compared with continuing AF. On the hand, the use of AADs to restore SR was associated with a 49% increase in mortality rate, nullifying that substantial benefit achieved on establishment of SR from AF[43,44]. Therefore, pursuing SR by nonpharmacologic means is justified. Recently, a large RCT[45] was able to demonstrate that CA lowers morbidity and mortality as compared with medical therapy (rate or rhythm control) in patients with coexisting AF and medically managed heart failure. Most of available clinical data have proved the superiority of CA over medical therapy in establishing and maintaining SR in AF patients.

Indications for Catheter Ablation Therapy

The role of CA as first-line therapy, prior to a trial of a Class I or III antiarrhythmic agent, is an appropriate indication in patients with symptomatic paroxysmal or persistent episodes[1,4]. There have been three prospective RCTs[46-48] that have examined the relative efficacy and safety of first-line AF ablation vs medical therapy. The outcomes of these three trials have recently been summarized in a meta-analysis[49]. A total of 491 young, generally healthy patients with predominantly paroxysmal AF were randomized to AF ablation vs pharmacological therapy. CA of AF was associated with a significantly higher freedom from AF recurrence, as compared with drug therapy.

Even in young otherwise healthy patients with brady-tachy-syndrome CA should be considered as first-choice therapy, often without concomitant need of permanent pacemaker[1,50]. Otherwise, for these patients initiation of pharmacological

therapy would be inappropriate in the absence of a permanent pacemaker. Another specific population of patients in whom first-line AF ablation is often recommended as an initial approach are high-level competitive athletes with paroxysmal or persistent AF. They often have a marked resting bradycardia and are often against taking a medication[51,52]. Several studies have reported favorable outcomes of AF ablation in this subgroup of patients.

Catheter ablation of AF is a safe, effective and clinical acceptable therapeutic option in patients with AF and congestive heart failure. This applies both to patients suspected to having a arrhythmia-induced cardiomyopathy, due to AF with a rapid ventricular response, as well as to other populations of patients with AF and a structural cardiomyopathy. In this patients CA is associated with all-cause mortality benefit. Moreover, CA reduces cardiovascular hospitalizations and recurrences of atrial arrhythmia for patients with AF and congestive heart failure. In this subgroup younger patients and men appear to derive more benefit from CA[45,53].

Catheter ablation is not recommended for patients with asymptomatic long-standing persistent AF and the potential benefit of restoring SR for patients without symptoms are uncertain. Some of the variables that can be used to define patients in whom a lower success rate or a higher complication rate can be expected include the presence of concomitant heart disease, obesity, sleep apnea, LA size, patient age and frailty, as well as the duration of time the patient has been in continuous AF[54,55].

Isolation of Pulmonary Veins: Techniques and Endpoints

Current expert consensus acknowledges the importance of PV targets in the strategy of AF ablation and recommends that when PVs are targeted, complete electrical isolation should be achieved[20,56]. PV isolation alone is most likely to benefit patients with a normal heart and short episodes of paroxysmal AF[57]. Initially, PV ablation targeted observed triggers of AF inside the PVs. However, it was soon observed that RF injury inside the veins carried the risk for PV stenosis and that the clinical outcome was better when more PVs were isolated[21]. Based on such observations, the ablation strategy changed toward achieving systematic isolation of all four PVs by creating more proximal lesions in order to avoid lesions inside the

PVs. The veins can be isolated one by one, or ipsilateral veins can be isolated an bloc, two by two, by creating posterior and anterior lines joined distally. Electrical isolation requires at least entrance block into the vein and is shown by elimination of all PV potentials within the veins[58,59].

After initial success, up to one third of patients will have acute reconnection during the index procedure[1,4]. Therefore, PV isolation should be reconfirmed 20 to 30 minutes after the last energy delivery. The administration of isoproterenol, adenosine, or both to unmask PV reconnection can be useful. Residual atrial ectopy may be provoked by isoproterenol (up to 20 μg/minute), adenosine (6 to 24 mg), burst atrial pacing[60]. Residual atrial ectopy within the vein is common despite complete abatement of antral electrograms and this dissociated pulmonary vein activity with exit block has been suggested as a surrogate endpoint[61]. The completion of an anatomic encircling lesion set without assessment of the electrical effects does not reliably produce PV isolation and is not recommended. The role of inducibility testing as a procedural endpoint is still debated[62].

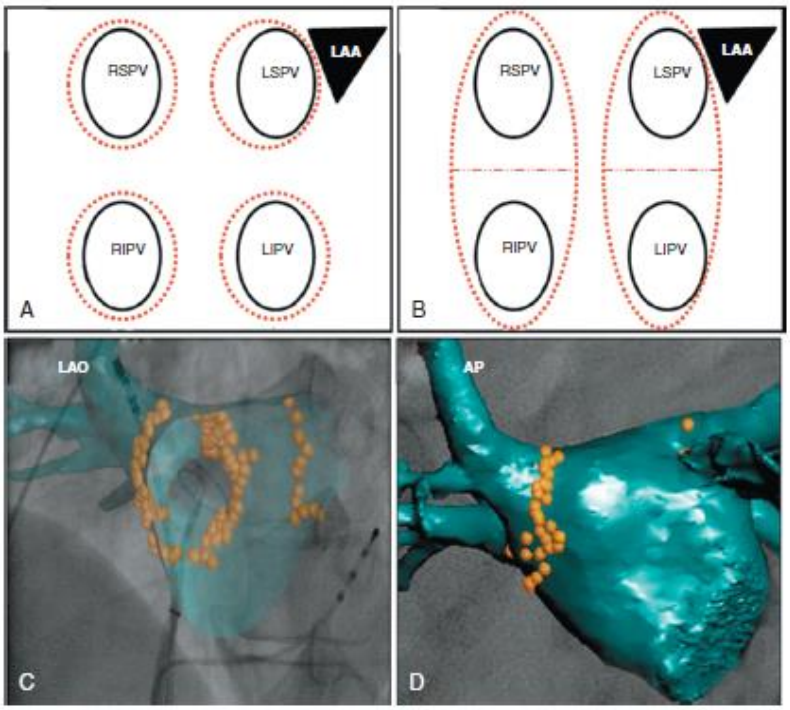

Figure 2: Circumferentially PVI. Schematic illustration of the lesion sets for segmental (A) and 2 × 2 (B) PV isolation. The dashed line in B represents optional ablation of the carina between the superior and inferior PVs. Note that for the 2 × 2 lesion set, the ablation line encroaches on the anterior aspect of the left veins due to the ridge between the PV and the left atrial appendage (LAA). C and D, Left atrial computed tomography overlay on

fluoroscopy with PV isolation 2 × 2. In C, the cutting plane allows visualization of the endocardium and the lesions (dots) on the posterior wall. AP, anteroposterior; LAO, left anterior oblique; LIPV, left inferior pulmonary artery; LSPV, left superior pulmonary artery; RIPV, right inferior pulmonary artery; RSPV, right superior pulmonary artery (from Huang et al. Catheter Ablation of Cardiac Arrhythmias, Second Edition 2011 – Philadelphia Copyright © by Saunders, an imprint of Elsevier)[63]

Follow-up Considerations after Catheter Ablation for Atrial Fibrillation

Outcomes and Efficacy of Catheter Ablation for Atrial Fibrillation

Acute isolation of the PVs should be achievable in 90% to 100% of cases. PV isolation is reported to achieve durable SR without the need of AAD in 59% to 93% of patients with paroxysmal AF[64]. It still debated whether additional lesions should be delivered after PV isolation in patients with paroxysmal AF. For most persistent AF cases, ablation of PV targets alone appears insufficient and strategies combining PV isolation and substrate modification are often adopted, achieving SR without AADs in 42% to 95% of patients[65]. In persistent AF, more than one ablation procedure is often needed to abolish AF; therefore patients should be informed that about half of them will require more than one procedure.

The benefits of CA are not judged solely by the absence of arrhythmia at follow-up. Many patients with a reduction of AF burden report symptomatic improvement, demonstrate better exercise tolerance, and have higher quality of life scores. The subgroup of patients with heart failure represents a population in whom AF ablation is particularly beneficial, with substantial improvement in quality of life and functional class associated with significant increase in left ventricular function[66,67].

Limited information is available regarding the outcomes of AF ablation in unusually young patients. At least two studies have reported on the outcomes of AF ablation in unusually young patients[68,69]. One of these studies defined young ablation patients as those under the age of 45 years; the other reported on outcomes of AF ablation for *lone* AF, defined as age < 65 years with no cardiac, pulmonary or structural heart disease. The authors reported that younger patients have lower rates of major complications compared with more typically aged AF patients. The largest study on AF ablation in younger patients was a multicenter German registry[69] in which 593

patients aged < 45 years were compared with 6550 patients aged > 45 years. In this study the younger patients had lower rates of complication, shorter hospital stays and lower rates of AF recurrences without AADs than older patients. Together, these studies suggest that AF ablation might be both safer and more effective in younger patients compared to older AF patients, although this result could be due in part to a lower burden of cardiac and noncardiac comorbid diseases.

Arrhythmia Relapses after Ablation

Early arrhythmia recurrences after AF ablation has been defined as any recurrence of AF > 30 seconds during the first 3 months of follow-up. Late recurrence has been defined as any recurrence of AF > 30 seconds between 3 and 12 months after the index procedure[1,4]. Early recurrences of AF after CA have been reported in up to 50% of patients within the first 3 months after ablation. Because these arrhythmias do not definitively indicate therapy failure over the long term, this period is also referred to as the blanking or therapy stabilisation period. Early recurrences of AF might be a transient phenomenon and reablation is not recommended in the first months after the index ablation[70]. Nevertheless, aggressive treatment of early recurrences might prevent electrical and structural remodeling, so that early electrical CV can be required to improve long-term outcome.

Arrhythmia recurrences after PV isolation are mostly due to PV reconnection[71]. When a repeat procedure is performed because of AF recurrence 95% to 100% of patients have resumption of conduction at the PV-LA junction. In contrast, among the patients who remain free from arrhythmia, 81% have no PV reconnection. Reisolation of PVs can lead to AF control in most cases of patients with paroxysmal AF, over long-term follow-up.

Predictors of Success following Ablation

While numerous clinical risk factors are associated with the development of AF (including age, hypertension, diabetes mellitus and heart failure, LA size), risk factors associated with recurrence are less well-established but likely include clinical and echocardiographic parameters. Factors that have been identified as predictors of a

poorer outcome, at least in some studies, included long-term persistent AF[72], sleep apnea and obesity[73], increased LA size[74], increased age, hypertension and LA fibrosis (detected by cardiac MRI)[75].

A systematic review[76] of predictors of AF recurrence after CA recently analyzed data from 33 studies reporting different prediction models of risk score to identify individual risk of recurrence after CA for AF. The most common model variables were left atrial parameters, type of AF and age, and to a lesser extent sex and eGFR. All model variables can be measured before ablation and therefore models could be used pre-procedurally to predict the likelihood of AF recurrence. This question may be of clinical interest, because early identification of potentially risk factors might contribute to better patient recruitment, in order to identify which patients are more likely to benefit from an ablation procedure for symptomatic AF. However, given the inconsistent and sometimes poor performance of the models to date, it is possible that incorporating other variables may improve model performance. Further studies are mandatory to predict recurrence based on clinical, electrophysiological, anatomical, imaging and serological characteristics. Future research on model development and validation will likely need to consider differences in underlying casual mechanisms to ensure that models appropriate fit to different patient groups.

Background and Objectives of Research

The research conducted in this publication-based doctoral thesis aimed to determine whether pre-procedural as well as intra-procedural parameters can predict outcome and success rate of CA for AF. Catheter ablation is becoming an effective therapeutic option for symptomatic drug refractory AF. This invasive therapeutic approach of AF has proved to improve symptoms and quality of life by reducing arrhythmia burden. However, recurrence of AF after CA remains a major problem and reported success rates show a wide variation. These clinical benefits are better sustained in patients who remain free of arrhythmia recurrences and need to be

balanced against the discomfort and complication risk of CA. Hence, there is a growing clinical need to identify patients at risk of developing AF recurrences after CA.

This project focused on predictive parameters for arrhythmia recurrence and thus for poorer outcome in two highly selected subgroup of AF patients usually supposed to be at lower risk for recurrences and thus to gain the best clinical benefit from an ablation procedure: namely pure paroxysmal AF and younger otherwise healthy patients with *lone* AF. We derived different parameters, respectively in a pre-procedural as well as intra-procedural setting. First, electrophysiological factors arising during the index procedure were examined, special regard was given to residual dissociated firing ectopy in PVs (otherwise known as DPV activity) after completing electrical isolation at PV-LA junction. The purpose of the study was to evaluate whether the presence of DPV activity was associated with a higher PV-LA reconnection rate and AF recurrence during follow-up, thus requiring a further more aggressive segmental approach, where appropriate, targeting the earliest breakthrough on the circular mapping catheter into the PVs. Second, we identified pre-procedural parameters predicting the risk of arrhythmia recurrences after CA in a highly selected subgroup of younger AF patients without cardiac disease. We analyzed safety and long-term efficacy of CA in these patients, mostly supposed to derive the best successful rate after CA. *Lone* AF is a descriptor that is applied to younger patients without clinical or echocardiographic evidence of cardiac disease. The rate of progression to persistent AF as well as arrhythmia recurrences seem to be very low in these patients. Nevertheless, there are very little data on efficacy and arrhythmia recurrence rate after CA in patients with *lone* AF.

We aimed to optimize risk stratification strategies incorporating clinical and electrophysiological parameters in order to improve patient selection criteria for CA and to identify selected group of patients eventually requiring more aggressive ablation strategies, as well. AF ablation is a maturing field and prediction models of clinical outcome are still poorly defined in available clinical studies. Over the past 10-12 years, a large number of RCTs have been completed addressing various aspects of AF ablation. However, the lack of standard terminology and definitions for end-point

recommendations, follow-up procedures and outcome reporting led to less rigorous and consistent data.

2. METHODS

Study Sample

We analyzed the center´s ablation database for patients undergoing a first CA for symptomatic drug refractory paroxysmal AF between May 2011 and September 2012 (n=243 consecutive patients; publication I) and for *lone* AF between May 2011 and December 2013 (n=76 consecutive patients; publication II). Exclusion criteria for the study included previous/current treatment with amiodarone, any previous LA ablation procedure, cardiac surgery, additional atypical atrial flutter and/or atrial tachycardia. In all patients a detailed medical history was taken by an experienced physician. All patients received a through physical exam, resting ECG and routine blood testing. Routine 2D echocardiography was performed using both parasternal and apical views. LA diameter was defined as the distance of the perpendicular line measured from the posterior LA wall to the anterior LA wall from M-mode of a parasternal short axis image at the level of the aortic valve. LA area was measured at apical four-chamber view by manual tracing of LA endocardial border. The presence of left ventricular hypertrophy or diastolic disfunction was defined as structural heart disease and excluded the diagnosis of lone AF (publication II). Patients with isolated left atrial enlargement were not considered as having structural heart disease and were thus enrolled in the study (publication II).

Procedural Work-up and Ablation Procedure (for both Publications)

All AADs except beta-blockers were discontinued for at least 4 weeks prior to the ablation procedure. All patients gave written informed consent to all imaging and invasive procedures. Patients had to be on OAC for at least 4 weeks prior to ablation and were kept under OAC during the procedure (continuous novel OAC or vitamin-K antagonist with intraprocedural INR levels of 2.0–2.8). At our institution, ablation is usually performed circumferentially, with an irrigated tip ablation catheter (Therapy

Cool PathTM, St. Jude Medical, St. Paul, MN, USA or Celsius ThermocoolTM, BiosenseWebster, Diamond Bar, CA, USA) by applying a maximum power of 25–30Wwith a flowrate of 30 mL/min. The ablation procedure consisted of encircling the ipsilateral PVs by a continuous circular lesion (0.5–1 cm antral to the ostium) with a circular mapping catheter in place. The electrical isolation of each vein was sequentially checked by leaving the circular catheter in each vein for a few minutes. If venoatrial electrical connections persisted, we performed further selective lesions inside the encircling lesion and between the veins guided by the activation sequence on the circular PV catheter, thus performing a combined approach of circumferential and segmental PVI. The electrophysiologic endpoint of ostial disconnection was an LA-PV conduction block consisting of entrance block with total elimination of the ostial PV potentials (during sinus rhythm and coronary sinus pacing).

Assessment of DPV Activity After PVI (Publication I)

After electrical isolation of all PVs, each PV was assessed for electrical disconnection and the presence of DPV activity. DPV activity was defined as slow intermittent potentials without a regular rhythm (as these may represent very slow conduction into the vein) and without any propagation into the LA (see Fig. 1, publication I). To define a slow activity, we put a cutoff for the CL of 1,000 milliseconds, according to our own clinical experience and to previous data[77]. According to our definition, a regular ectopic rhythm with a relative fast activity (CL <1,000 milliseconds) into the vein, even if dissociated, was no DPV activity. In case of these regular vein potentials, recorded on the circular catheter while performing the ablation procedure, additional radiofrequency energy was applied at the site of earliest activation. We defined as DPV activity only an irregular and slow automatic rhythm from the isolated vein recorded after waiting for a few minutes after placing the mapping catheter. We excluded single isolated ectopic beats eventually recorded while placing the mapping catheter into the vein, since these might be provoked mechanically by the catheter within the PV. The duration of monitoring DPV activity

during the procedure was at least 5 minutes, but only in few patients more than 20 minutes. The monitoring duration between superior and inferior PVs was similar. We did not routinely undertake any provocative maneuvers to check for DPV activity (i.e., isoproterenol administration). Intravenous adenosine to check for dormant LA-PV conduction was administered in a small subgroup of patients at the discretion of the operator. If spontaneous repetitive ectopy (bursts) or AF paroxysms were observed during the procedure, the initiating focus was localized by combining conventional mapping (CS activation pattern) and sequential mapping of the PVs with the circular catheter. Simple ectopic vein potentials like doubles or triplets were not considered as a triggering activity. A PV was defined as a "triggering vein" if the earliest local activation recorded from the circular catheter preceded the onset of the surface P wave and any other atrial intracardiac electrogram. Patients were classified into 2 groups. Group 1 consisted of patients in whom DPV activity with slow rhythm (>1,000 milliseconds) was demonstrated during sequential PV assessments with the circular mapping catheter placed at the PV-LA ostium after PVI. Group 2 consisted of patients without DPV activity after ablation.

Follow-up and Study Endpoints (for both Publications)

No AADs (except beta-blockers) were used during follow-up. Early recurrences were defined as clinical AF recurrence within a blanking period of 3 months. All patients with an early recurrence of sustained arrhythmia underwent electrical CV. After 3, 6, and 12 months, all patients had a follow-up visit including repetitive 7-day Holter ECG in our dedicated follow-up clinic. Patients who had symptoms without documented AF recurrence were provided a portable event recorder to identify the cause of their symptoms. Primary endpoint was defined as freedom from any atrial tachycardia (>30 seconds) after the first ablation procedure (blanking period of 3 months). Secondary endpoint was defined as freedom from any atrial tachycardia (>30 seconds) after the last ablation procedure (blanking period of 3 months).

Statistical Analysis

Data management and analyses were performed using SPSS version 19.0 (publication I) and 23.0 (publication II) (IBM Inc., Armonk, NY, USA). Data are presented as mean ± SD for continuous variables and proportions for categorical variables.

Publication I

Differences in mean values between patients grouped according to the presence of DPV activity after PVI were compared using unpaired t-tests; comparison of proportions between groups was performed using $\chi 2$ tests. A probability P value of <0.05 was considered statistically significant. A log-rank test was performed to compare distributions of event times between groups. Univariate Cox analysis was performed using clinical arrhythmia recurrence during long-term follow-up as dependent variable to investigate any correlation with clinical and procedural variables at baseline. Since none among the considered variables showed a significant relation with long-term outcome we did not perform any multivariate regression model analysis.

Publication II

Differences in mean values between patients grouped according to the presence of AF recurrence after ablation were compared using unpaired t-tests; comparison of proportions between groups was performed using $\chi 2$ tests. A two-sided $P < 0.05$ was considered statistically significant. A log-rank test was performed to compare distributions of event times between groups. Univariate regression analysis was performed to investigate the relation of clinical AF recurrence (dependent variable) with clinical variables at baseline. Significantly associated traits were then considered in a multivariable regression model.

3. RESULTS

Publication I

Ostial disconnection with disappearance of venous potentials by circumferential PVI was achieved in all 243 patients for 932 PVs. After PVI, 65 of 243 patients had at least 1 PV presenting with DPV activity (27%; Group 1). No DPV activity was present in 178 of 243 patients (73%; Group 2). A total of 112 of 932 (12%) isolated PVs showed DPV activity. There were no significant differences in baseline clinical characteristics between the 2 groups, except for age (Table 1 of publication I). There was no significant difference either in the anatomy of PVs or in LA dimension between the 2 groups. Regarding the arrhythmogenic potential of the PV, both superior PVs were more likely to present AF trigger activity during ablation, as well as DPV activity after electrical isolation: DPV activity was mostly documented in the LSPV (36%) and the RSPV (29%) followed by the LIPV (18%). DPV activity was observed bilaterally in 22 of 65 patients (34%). Among PVs with DPV activity we observed a significantly higher rate of triggering activity during ablation than among those without DPV activity (44/112, 39% vs. 13/820, 2%;p= 0.026). Thus, the triggering veins are more likely to have ongoing dissociated ectopy after isolation, however, without carrying out a higher risk of AF recurrence at follow-up (Table 2 of publication I). During a mean follow-up of 12 ± 7 months, sinus rhythm was observed in 50 of 65 patients (77%) in Group 1 versus 121 of 178 patients (68%) in Group 2 (P = 0.23). Also after exclusion of those patients (n=4) with arrhythmia recurrence during the blanking period, survival free from clinical relapses off AADswas comparable between 2 groups (69% vs. 78% in Group 1 vs. Group 2, respectively; PLog Rank = 0.17). Among 72 patients undergoing a repeat ablation (Group 1 n = 15, Group 2, n = 57), the majority (60/72 patients, 83%) presented with a recurrence of paroxysmal AF, whereas a progression to persistent AF (6/72; 8%) or atypical left atrial flutter (6/72; 8%) was less frequent. In Group 1, 13 of 15 (87%) redo patients had paroxysmal AF related to a recovered PV conduction. Among them, in only 5 patients the PV-LA

reconnection involved the same PVs showing ongoing DPV activity after first ablation (in 3 patients both superior PVs, in 1 patient all 4 PVs, in 1 patient the RSPV). In the remaining 8 patients, the PV-LA reconnection was observed in other PVs than those with DPV activity after first PVI. The remaining 2 patients did not present any recovered LA-PV conduction and developed clinically persistent AF (n = 1) and atypical atrial flutter (n = 1). In Group 2, paroxysmal AF probably due to reconnected PV was present in 47 of 57 (82%) patients. In 5 of 57 patients AF was associated to a triggering extra PV focus, without any PV reconnection. The remaining 5 patients (all with PV reconnection) clinically suffered from persistent AF or atypical atrial flutter. At univariate Cox analysis (Table 2 of publication I) none of the clinical and procedural variables considered at baseline was significantly related to a higher risk of clinical recurrences during long-term follow-up. All redo patients (N = 15; 100%) in Group 1 and 50 of 57 patients (88%) in Group 2 were free from AF after the repeat procedure (P = 0.26) at a mean follow-up of 16 ± 5 months after first PVI.

More detailed information about incidence and electrophysiological characteristics of DPV activity are provided in the paragraph *Results* of publication I.

Publication II

All 62 patients with paroxysmal *lone* AF underwent a circumferential PVI. All 14 patients with persistent lone AF were in AF at the beginning of the procedure and underwent a stepwise approach, with further substrate ablation. No difference was observed between patients with paroxysmal or persistent AF with regard to the baseline characteristics, except for depressive disorders. Patients with persistent AF suffered more often from depressive disorders (0/62 patients with paroxysmal AF versus 2/14 patients with persistent AF, P = 0.04). Procedure time (147 ± 68 versus 89 ± 27 minutes; $p < 0.01$) and radiofrequency (RF) time (65±21 versus 42±27 minutes; $p<0.01$) were significantly longer in patients with persistent lone AF compared to those with paroxysmal AF. One patient had sinus node dysfunction unmasked after the ablation which required pacemaker implantation. No death, stroke, or transient ischemic attack occurred. After a single ablation procedure, 56 patients (78%) were free from arrhythmia relapses after a mean follow-up time of 458 ± 344 days. Of the

20 patients with arrhythmia relapses all but 2 patients suffered originally from paroxysmal AF and experienced paroxysmal AF recurrence; the other 2 patients suffered originally from persistent AF and presented with persistent AF again after the first ablation. Among them, 15 patients (75% of redo patients) experienced early AF recurrences (<12 months after ablation) and 5 patients (25%) experienced late AF recurrences (> 12 months after ablation). Of note, patients with persistent AF were not more likely to suffer from relapses than those with paroxysmal AF ($p = 0.721$). Although in the univariate analysis an increased LA size was correlated with AF recurrences (Table 2 of publication II), in the multivariate analysis LA enlargement was not independently related to an increased risk of AF recurrences. Patients with AF recurrences were more likely to smoke ($p = 0.001$) and to have AV block I ($p = 0.001$), and suffered more frequently from early recurrences in the blanking period ($p = 0.001$), compared to those free from arrhythmia recurrence (Table 2 of publication II). All 20 patients with AF relapses underwent re-ablation (after a mean time of 235 days since first ablation), Figure 1 of publication II. During redo procedure, 16 patients (16/20, 80%) displayed electrical PV reconnection and a redo PVI was performed. In the remaining four patients without PV reconnection, extra-PV foci were detected and ablated in LA roof, mitral annulus, at the ostium of coronary sinus and in the superior vena cava, respectively. during a mean follow-up of 459±366 days after the last ablation (with a mean of 1.3 ablation per patient), n = 73 (96%) remained free of recurrences without antiarrhythmic drugs.

More detailed information regarding procedural data, primary and secondary outcomes of the study are further discussed in the paragraph *Results* of publication II.

4. DISCUSSION

Intraprocedural Predictors of Atrial Fibrillation Recurrence after Ablation (Publication I)

PV isolation is an essential first step in all the catheter ablation strategies for AF. Electrical isolation with PV-LA disconnection is a required end point, but the need of further ablation beyond antral electrogram abatement with further and points such as inducibility testing is not yet clear. Interestingly, after electrical isolation, up to 58% of PVs display slow, dissociated activity, and some sustain ongoing tachycardia dissociated from the left atrium in SR, emphasizing the arrhythmogenic potential of these structures. Accordingly, in our study PVs presenting AF trigger activity during ablation, were more likely to present DPV activity after electrical isolation. We observed a significantly higher incidence of DPV activity after isolation of triggering PVs compared to those in which an AF trigger was not identified. Although DPV activity can reflect a pronounced arrhythmogenic ectopic activity of the PV triggering AF a residual slow PV rhythm dissociated from LA activity is no predictor for clinical recurrence of AF during long-term follow-up. These findings are consistent with those of Doi et al[77]. A higher PV sleeve load in the triggering PVs compared to the overall mean PV sleeve load was observed by De Greef et al.[78], probably accounting for an increased expression of DPV activity despite PVI. Sleeves of myocardium extending from the LA into the PVs constitute the arrhythmogenic substrate for these structures. Myocardial sleeves of variable lengths, extending 2 to 25 mm distally into the vein from the ostium, are more developed in the upper than the lower PVs and are thickest at the LA-PV junction, tapering distally in a nonuniform manner. Currently, most leading centers perform circumferential antral ablation. However, the exact anatomic boundaries of the PV antrum are not absolutely defined but may be considered to be the area proximal to the venous ostium where PV potentials can still be recorded. It is this antral area, usually 5 to 10 mm around the perimeter of the PV os, that is the target for PV isolation. Nevertheless, due to the lack of evidence for prognostic significance

for ablation success, further ablation of such arrhythmogenic sleeves behind LA-PV junction into the veins is not recommended.

Recovered PV-LA conduction is the dominant finding at the repeat ablation and PVs with and without DPV activity were equally frequently reconnected. Our findings are in line with previous studies. Kim et al.[79], after randomly assigning patients following antral vein isolation to ablation of residual PV potentials, did not demonstrate an improvement in clinical outcome with adjunctive ablation. In contrast, Doi et al.[77] recently underlined the efficacy of additional RF ablation of DPV activity after PVI in order to prevent AF recurrence. Differences in the definition of DPV activity are probably the main reason for these conflicting results. We defined DPV activity only as low frequency, irregular potentials originating in the PVs. If rapid incessant electrical activity or low frequency potentials with constant and regular rhythm were still observed after PVI, we generally performed more extensive ablation at the PV-LA junction considering that the most probable mechanism was incomplete PVI with slow residual conduction. In contrast, we interpreted a very low frequency (<1 beat/s) electrical activity without a regular rhythm as focal firing within a completely isolated PV.

Clinical Predictors of Arrhythmia Recurrence after Catheter Ablation: Risk Stratification in a Pre-procedural Setting (Publication II)

The predictors of arrhythmia recurrence most commonly identified include type of AF as well as comorbid conditions, including hypertension, age, LA size, diabetes, valvular heart disease and left ventricular dysfunction, higher thromboembolic risk score. The optimal strategy for selecting patients with symptomatic AF for CA has yet to be established. This study attempted to assess the ability of common clinical variables to predict response to CA. Smoking, first-degree AV block, and early AF recurrence are associated with a higher risk of recurrence during long-term follow-up. The predictors of recurrence identified in this study must be balanced with the low morbidity and mortality associated with this high selected group of patients. Contrary to prior understanding, early recurrences of AF during the first 3 months following

ablation have been found to predict late recurrences of AF in this study. This findings are in line with previous studies. Khaykin et al[80] identified early recurrences as the only independent predictor of late recurrences in multivariate analysis. However, it is difficult to compare their findings to our own since the authors considered a mixed study population with paroxysmal as well as persistent AF. Apart from the differences in the ablation approach, there is still many concerns about the early use of antiarrhythmic therapy following ablation, a recommendation disputed by recent evidence. We were able to demonstrate that CA in young healthy *lone* AF patients is highly effective and safe, unexpectedly the outcomes are maintained at long-term follow-up, irrespective of AF type, preoperative history or LA enlargement. Therefore, it is reasonable to support the role of CA as first choice therapy for AF especially in such highly selected groups of patients. Our data are in line with previous studies[46-48] reporting on the efficacy and safety of radiofrequency ablation as first-line therapy for paroxysmal AF, compared with antiarrhythmic drugs. Reported success rate for AF ablation procedure had traditionally showed a wide variation, depending on type of AF, patients' characteristics, length of follow-up. However, our success rates after AF ablation in otherwise healthy patients are slightly better than long-term outcomes previously reported in literature[81], likely due to the very low cardiovascular risk profile.

Taken as role, these findings provide evidence to support the hypothesis that AF and its possible therapeutic approaches should be considered on the basis of the overall clinical context and patients' characteristics, and not only of isolated arrhythmia features. On the one hand, it is still unclear whether lone AF in apparently healthy patients should be considered as an epiphenomenon of a still latent pathology; on the other hand, one can argue that AF strictly relates only to atrial remodeling, but could be an early marker of a systemic cardiovascular comorbidity. In such a case, one can argue that an early ablation procedure could remove in advance the additional risk, imposed by AF, of a possible future cardiovascular disease.

5. Summary

Publication I

Dissociated Pulmonary Vein Activity After Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: A Predictor for Recurrence?

Abstract

Background: The role of dissociated pulmonary vein (DPV) activity after pulmonary vein isolation (PVI) is still poorly defined. We evaluated electrophysiological features and clinical impact on long-term outcome of DPV activity.

Methods: A total of 243 patients (mean age 63 ± 11 years; 63% males) undergoing PVI for paroxysmal atrial fibrillation (AF) were included. DPV activity was defined as a residual low frequency irregular PV rhythm. Patients were divided into Group 1 (presence of DPV activity; n = 65) or Group 2 (absence of DPV activity; n = 178).

Results: Of 936 isolated PVs, 112 PVs (12%) showed DPV activity. DPV activity was observed more frequently in PVs identified as AF triggers (P = 0.026). During follow-up (mean 12 ± 7 months), 15 of 65 patients of Group 1 (23%) and 57 of 178 patients of Group 2 (32%) had an arrhythmia recurrence (P = 0.23). At linear regression analysis, no independent predictor for clinical recurrence was identified. During the repeat ablation, 62 of 72 patients (86%) showed a recovered PV conduction without difference between the 2 groups. Clinically, all patients of Group 1 with PV reconnection (n = 13/15) had a recurrence of paroxysmal AF. In Group 2, 5 of 52 patients with reconnected PV developed non-PV related arrhythmias.

Conclusion: DPV activity occurred in 12% of PVs after PVI and was observed more frequently in PVs identified as AF triggers. DPV activity was not predictive for AF recurrence during follow-up. PV-left atrium reconnection involving PVs with DPV activity leads to AF.

Author Contributions

The first author conceived the main conceptual ideas, critically reviewed pre-existing literature, collected and analysed clinical data. With the help and consultation of the coauthors, the first author: performed the statistical data analysis and wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Publication II

Catheter Ablation for "Lone" Atrial Fibrillation: Efficacy and Predictors of Recurrence

Abstract

Background: Atrial fibrillation in otherwise healthy young patients has been termed "lone" atrial fibrillation (AF). The best treatment choice is still under discussion. The aim of this study was to report on efficacy and safety of catheter ablation.

Methods: Among 855 patients referred to our center between 2011 and 2013, 76 (9%) met the diagnostic criteria for lone AF (mean age 45±8 years;mean LA diameter 37±4 mm; paroxysmal AF 82%; persistent AF 18%). The primary endpoint was freedom from any atrial tachycardia after the first ablation; the secondary endpoint was freedom from any atrial tachycardia after the last ablation procedure without antiarrhythmic drugs.

Results: The primary endpoint occurred in 56 patients (74%) after a mean follow-up time of 444 ± 344 days. The secondary endpoint occurred in 73 patients (96%) after a mean of 1.3 ablations/patient during a follow-up time of 459 ± 366 days. The risk of AF recurrence was not influenced by AF duration or by the type of AF (paroxysmal versus persistent). In a multivariate regression analysis smoking (P = 0.001), first degree atrioventricular block (P = 0.001), and early (< 3 months) AF recurrence (P = 0.001) were independently associated with a higher risk of AF recurrence. Major peri-procedural adverse events did not occur. Conclusions: Catheter ablation in young healthy patients is highly effective and safe. The outcomes are maintained during long-term follow-up irrespective of preoperative AF duration. Patients with AF recurrence were more likely to smoke, have first degree AV block and early AF recurrence.

Author Contributions

The first author conceived the main conceptual ideas, critically reviewed pre-existing literature, collected and analysed clinical data. With the help and consultation

of the coauthors, the first author: performed the statistical data analysis and wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Bibliography

1. Calkins H et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm. 2017Oct;14(10):275-444.

2. Lip GY et al. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. BMJ. 1995;311:1361–3.

3. Benjamin EJ et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. Jama. 1994;271:840–4.

4. Kirchhof P et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct 7;37(38):2893-2962.

5. Staerk L et al. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circ Res. 2017 Apr 28; 120(9): 1501–1517.

6. Andrade J et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 2014 Apr 25;114(9):1453-68.

7. Lloyd-Jones, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation, 2004. 110(9): p. 1042-6.

8. Hylek EM et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001 May 9;285(18):2370-5.

9. Heeringa et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. European Heart Journal 2006 April 27;(8):949–953.

10. Allan, V. et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population based cohorts of 20 million participants. Thromb Haemost, 2017.

11. Miller, J.D., et al., Obesity, Exercise, Obstructive Sleep Apnea, and Modifiable Atherosclerotic Cardiovascular Disease Risk Factors in Atrial Fibrillation. J Am Coll Cardiol, 2015;66(25):2899-906.

12. Nalliah, C.J. et al. The role of obesity in atrial fibrillation. Eur Heart J 2016;37(20):1565-72.

13. Mahajan, R., et al., Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity. J Am Coll Cardiol, 2015;66(1):1-11.

14. Dublin, S., et al., Risk of new-onset atrial fibrillation in relation to body mass index. Arch Intern Med 2006;166(21):2322-8.
15. Gami, A.S. et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol, 2007; 49(5):565-71.
16. Tedrow U.B. et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (Women's Health Study). J Am Coll Cardiol, 2010;55(21):2319-27.
17. Huxley, R.R. et al. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2011;123(14):1501-8.
18. Wakili, R. et al. Recent advances in the molecular pathophysiology of atrial fibrillation. J Clin Invest 2011;121(8):2955-68.
19. Haïssaguerre M et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–666.
20. Chen SA, et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation 1999;100:1879–1886.
21. Valles E et al. Localization of atrial fibrillation triggers in patients undergoing pulmonary vein isolation: importance of the carina region. J Am Coll Cardiol. 2008;52:1413–1420.
22. Hoffmann E et al. New insights into the initiation of atrial fibrillation: a detailed intraindividual and interindividual analysis of the spontaneous onset of atrial fibrillation using new diagnostic pacemaker features. Circulation 2006;113:1933–1941.
23. Heijman, J. et al. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res 2014;114(9):1483-99.
24. de Vos et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol, 2010;55(8):725-31.
25. Wjifells M et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation, 1995;92(7):1954-68.
26. Walters E et al. Progression of atrial remodeling in patients with high-burden atrial fibrillation: Implications for early ablative intervention. Heart Rhythm, 2016;13(2):331-9.
27. Heijman J et al. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. Circ Res, 2014;114(9):1483-99.

28. Sugihara, C. et al. The development of AF over time in patients with permanent pacemakers: objective assessment with pacemaker diagnostics demonstrates distinct patterns of AF. Europace, 2015;17(6):864-70.
29. Nieuwlaat R et al. Atrial fibrillation management: a prospective survey in ESC Member Countries: The Euro Heart Survey on Atrial Fibrillation. European Heart Journal 2005;26(22):2422–2434.
30. Lubitz AL et al. Atrial fibrillation patterns and risks of subsequent stroke, heart failure, or death in the community. J Am Heart Assoc, 2013. 2(5):e000126.
31. Mijasaka Y et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year communitybased study. J Am Coll Cardiol, 2007;49(9):986-92.
32. Wolf PA et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–988.
33. Miller P et al. Are cost benefits of anticoagulation for stroke prevention in atrial fibrillation underestimated? Stroke, 2005;36(2):360-6.
34. Wang T et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107(23):2920-5.
35. Shen A et al. Atrial Myopathy. J Am Coll Cardiol Basic Trans Science 2019;4:640-654.
36. Grogan M et al. Left ventricular dysfunction due to atrial fibrillation in patients initially believed to have idiopathic dilated cardiomyopathy. Am J Cardiol. 1992;69:1570–1573.
37. Jakobs V et al. Atrial fibrillation and dementia. Trends Cardiovasc Med, 2015;25(1):44-51.
38. Boriani G et al. Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. Am J Med, 2015;28(5):509-18 e2.
39. Wyse DG et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–1833.
40. Roy D et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–2677.
41. Van Gelder IC et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834–1840.
42. Carlsson, J., et al., Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol, 2003;41(10):1690-6.

43. Hohnloser SH et al. Rhythm or rate control in atrial fibrillation. Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. Lancet. 2000;356:1789–1794.
44. Corley SD et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation. 2004;109:1509–1513.
45. Marrouche N et al. Catheter Ablation for Atrial Fibrillation with Heart Failure N Engl J Med 2018; 378:417-427.
46. Wazni et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA, 2005;293(21):2634-40.
47. Cosedis G et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med, 2012;367(17):1587-95.
48. Morillo C et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. JAMA 2014;311(7):692-700.
49. Hakalahti, A., et al., Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace, 2015; 17(3):370-8.
50. Hocini, M., et al. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. Circulation, 2003;108(10):1172-5.
51. Inada, K., et al., The role of successful catheter ablation in patients with paroxysmal atrial fibrillation and prolonged sinus pauses: outcome during a 5-year follow-up. Europace, 2014;16(2):208-13.
52. Chen Y et al. Pacing or ablation: which is better for paroxysmal atrial fibrillation-related tachycardiabradycardia syndrome? Pacing Clin Electrophysiol, 2014;37(4):403-11.
53. Tondo, C., et al., Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. Pacing Clin Electrophysiol, 2006;29(9):962-70.
54. Mohanty S et al. Catheter ablation of asymptomatic longstanding persistent atrial fibrillation: impact on quality of life, exercise performance, arrhythmia perception, and arrhythmia-free survival. J Cardiovasc Electrophysiol, 2014;25(10):1057-64.
55. Wu L et al. Comparison of Radiofrequency Catheter Ablation Between Asymptomatic and Symptomatic Persistent Atrial Fibrillation: A Propensity Score Matched Analysis. J Cardiovasc Electrophysiol, 2016;27(5):531-5.

56. Haïssaguerre M et al. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation. 2000;101:1409–1417.
57. Hocini M et al. Multiple sources initiating atrial fibrillation from a single pulmonary vein identified by a circumferential catheter. Pacing Clin Electrophysiol. 2000;23:1828–1831.
58. Ho SY et al. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 1999;10:1525–1533.
59. Nathan H et al. The junction between the left atrium and the pulmonary veins: an anatomic study of human hearts. Circulation. 1966;34:412–422.
60. Hachiya H et al. Clinical implications of reconnection between the left atrium and isolated pulmonary veins provoked by adenosine triphosphate after extensive encircling pulmonary vein isolation. J Cardiovasc Electrophysiol. 2007;18:392–398.
61. Weerasooriya R et al. Dissociated pulmonary vein arrhythmia: incidence and characteristics. J Cardiovasc Electrophysiol. 2003;14:1173–1179.
62. Matsuo S et al. Reduction of AF recurrence after pulmonary vein isolation by eliminating ATP-induced transient venous re-conduction. J Cardiovasc Electrophysiol. 2007;18:704–708.
63. Huang et al. Catheter Ablation of Cardiac Arrhythmias, Second Edition 2011 Elsevier
64. Chang SL et al. The efficacy of inducibility and circumferential ablation with pulmonary vein isolation in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2007;18:607–611.
65. Willems S et al. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. Eur Heart J. 2006;27:2871–2878.
66. Lutomsky, B.A. et al., Catheter ablation of paroxysmal atrial fibrillation improves cardiac function: a prospective study on the impact of atrial fibrillation ablation on left ventricular function assessed by magnetic resonance imaging. Europace, 2008;10(5):593-9.
67. Al Halabi, S. et al., Catheter Ablation for Atrial Fibrillation in Heart Failure Patients: A Meta-Analysis of Randomized Controlled Trials. JACC Clin Electrophysiol, 2015;1(3):200-209.
68. Leong-Sit, P., et al., Efficacy and risk of atrial fibrillation ablation before 45 years of age. Circ Arrhythm Electrophysiol, 2010.;3(5):452-7.
69. Chun, K.R., et al., Catheter ablation of atrial fibrillation in the young: insights from the German Ablation Registry. Clin Res Cardiol, 2013;102(6):459-68.

70 Lo LW et al Characteristics and outcome in patients receiving multiple (more than two) catheter ablation procedures for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2008;19:150–156.

71 Rajappan K et al. Acute and chronic pulmonary vein reconnection after atrial fibrillation ablation: a prospective characterization of anatomical sites. Pacing Clin Electrophysiol. 2008;31:1598–1605.

72. Jacobs, A.K. et al. The evolution and future of ACC/AHA clinical practice guidelines: a 30-year journey: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2014. 64(13): p. 1373-84.

73. Anderson, J.L., Evolution of the ACC/AHA Clinical Practice Guidelines in Perspective: Guiding the Guidelines. J Am Coll Cardiol, 2015;65(25):2735-8.

74. January, C.T., et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol, 2014;64(21):e1-76.

75. Marrouche, N.F., et al., Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA;2014. 311(5):498-506.

76. Balk, E.M., et al., Predictors of atrial fibrillation recurrence after radiofrequency catheter ablation: a systematic review. J Cardiovasc Electrophysiol, 2010;21(11):1208-16.

77. Doi et al. Efficacy of additional radiofrequency applications for spontaneous dissociated pulmonary vein activity after pulmonary vein isolation in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:894-901.

78. De Greef et al. Triggering pulmonary veins: A paradoxical predictor for atrial fibrillation recurrence after PV isolation. J Cardiovasc Electrophysiol 2010;21:381-388.

79. Kim ZH et al. Role of residual potentials inside circumferential pulmonary veins ablation lines in the recurrence of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2010;21:959-965.

80. Khaykin Y et al. Clinical predictors of arrhythmia recurrences following pulmonary vein antrum isolation for atrial fibrillation: predicting arrhythmia recurrence post-PVAI. J Cardiovasc Electrophysiol. 2011 Nov;22(11):1206-14.

81. Sawhney N et al. Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. Am J Cardiol 2009;104:366-372.

Dissociated Pulmonary Vein Activity After Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: A Predictor for Recurrence?

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Dissociated Pulmonary Vein Activity for Paroxysmal Atrial Fibrillation. *Background:* The role of dissociated pulmonary vein (DPV) activity after pulmonary vein isolation (PVI) is still poorly defined. We evaluated electrophysiological features and clinical impact on long-term outcome of DPV activity.

Methods: A total of 243 patients (mean age 63 ± 11 years; 63% males) undergoing PVI for paroxysmal atrial fibrillation (AF) were included. DPV activity was defined as a residual low frequency irregular PV rhythm. Patients were divided into Group 1 (presence of DPV activity; n = 65) or Group 2 (absence of DPV activity; n = 178).

Results: Of 936 isolated PVs, 112 PVs (12%) showed DPV activity. DPV activity was observed more frequently in PVs identified as AF triggers (P = 0.026). During follow-up (mean 12 ± 7 months), 15 of 65 patients of Group 1 (23%) and 57 of 178 patients of Group 2 (32%) had an arrhythmia recurrence (P = 0.23). At linear regression analysis, no independent predictor for clinical recurrence was identified. During the repeat ablation, 62 of 72 patients (86%) showed a recovered PV conduction without difference between the 2 groups. Clinically, all patients of Group 1 with PV reconnection (n = 13/15) had a recurrence of paroxysmal AF. In Group 2, 5 of 52 patients with reconnected PV developed non-PV related arrhythmias.

Conclusion: DPV activity occurred in 12% of PVs after PVI and was observed more frequently in PVs identified as AF triggers. DPV activity was not predictive for AF recurrence during follow-up. PV-left atrium reconnection involving PVs with DPV activity leads to AF. *(J Cardiovasc Electrophysiol, Vol. pp. 1-7)*

atrial fibrillation, catheter ablation, dissociated pulmonary vein activity, pulmonary vein isolation, recurrence

Introduction

Electrical pulmonary vein isolation (PVI) has evolved as the cornerstone of atrial fibrillation (AF) ablation.[1,2] It is commonly accepted that about 90% of the triggering foci initiating AF paroxysms are located inside or at the ostium of pulmonary veins (PV).[3-5] The reported success rates of PVI vary between 60% and 82%.[6,7] However, recovered PV conduction is reported in up to 80–95% of patients suffering from AF recurrence after PVI.[8,9]

Dissociated pulmonary vein (DPV) activity after successful PVI is sometimes observed inside the PV and seems to prove the achievement of electrical disconnection from the left atrium (LA).[10,11] DPV activity might also be interpreted as evidence for the arrhythmogenic nature of PV myocardium. Recent studies suggest that PVs with active triggers are more likely to have extensive circumferential muscular PV-LA connections and are more likely to be associated with early AF recurrence.[12]

The purpose of this study was to evaluate the incidence of DPV activity after PVI and to evaluate whether the presence of DPV activity is associated with a higher PV-LA reconnection rate and AF recurrence during follow-up.

Methods

Study Population

We analyzed the center's ablation database for patients undergoing a first circumferential PVI for paroxysmal AF between May 2011 and September 2012. Overall, 243 consecutive patients (mean age 63 ± 11 years; 63% males) were included in the study. Patients' clinical and electrophysiological characteristics are shown in Table 1.

Paroxysmal AF was defined according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society 2007 consensus statement on catheter and surgical ablation of AF.[13]

Exclusion criteria for the study included persistent AF, additional atypical atrial flutter and/or focal atrial tachycardia, previous/current treatment with amiodarone and any previous left atrial ablation procedure.

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TABLE 1
Baseline Clinical and Electrophysiological Characteristics of the Study Population

	Total Population N = 243	Group 1 DPV Activity N = 65 (27%)	Group 2 No DPV Activity N = 178 (73%)	P Value (Between Two Groups)
Age, years (mean ± SD)	63 ± 11	60 ± 12	64 ± 10	0.04
Male (%)	62%	66%	62%	0.55
BMI, kg/m² (mean ± SD)	27 ± 4	26 ± 4	27 ± 4	0.38
LA diameter, mm (mean ± SD)	43 ± 6	43 ± 6	42 ± 6	0.61
LA area, mm² (mean ± SD)	22 ± 4	22 ± 4	22 ± 4	0.90
Hypertension (%)	58%	60%	58%	0.82
Diabetes (%)	5%	3%	6%	0.34
Structural heart disease (%)	1%	2%	1%	0.79
Prior TIA/Stroke (%)	3%	2%	4%	0.29
$CHADS_2VASc$ 0 (%)	30%	34%	29%	0.43
$CHADS_2VASc$ 1 (%)	20%	15%	22%	0.26
$CHADS_2VASc$ 2 (%)	23%	26%	22%	0.48
No. of isolated PVs	932	253	679	–
Normal PV anatomy (%)	78%	83%	77%	0.30
Mean RF time, minutes (mean ± SD)	46 ± 27	42 ± 28	48 ± 24	0.10
Electrical cardioversion required after PVI (%)	3%	2%	3%	0.67

AF = atrial fibrillation; BMI = body mass index; LA = left atrium; PV = pulmonary vein; RF = radio frequency; TIA = transient ischemic attack.

AF-Ablation Procedure

Patients had to be on oral anticoagulation for at least 4 weeks before ablation and were kept under oral anticoagulation during the procedure. All antiarrhythmic drugs (AADs) were discontinued for at least 4 weeks before the ablation procedure, except β-blockers. PVI was performed as described earlier.[14] The ablation procedure consisted of encircling the ipsilateral PVs by a continuous circular lesion (0.5–1 cm antral to the ostium) with a circular mapping catheter in place. The electrical isolation of each vein was sequentially checked by leaving the circular catheter in each vein for a few minutes. If venoatrial electrical connections persisted, we performed further selective lesions inside the encircling lesion and between the veins guided by the activation sequence on the circular PV catheter, thus performing a combined approach of circumferential and segmental PVI.

The electrophysiologic endpoint of ostial disconnection was an LA-PV conduction block consisting of entrance block with total elimination of the ostial PV potentials (during sinus rhythm and coronary sinus pacing). Electrical PV isolation was achieved with an irrigated tip ablation catheter (Therapy Cool Path™, St. Jude Medical, St. Paul, MN, USA or Celsius Thermocool™, Biosense Webster, Diamond Bar, CA, USA) by applying a maximum power of 25–30 W with a flow rate of 30 mL/min.

No major complications occurred during the ablation procedure and during follow-up in any patient.

Assessment of DPV Activity After PVI

After electrical isolation of all PVs, each PV was assessed for electrical disconnection and the presence of DPV activity. DPV activity was defined as slow intermittent potentials without a regular rhythm (as these may represent very slow conduction into the vein) and without any propagation into the LA (Fig. 1). To define a slow activity, we put a cutoff for the cycle length (CL) of 1,000 milliseconds, according to our own clinical experience and to previous data.[15] According to our definition, a regular ectopic rhythm with a relative fast activity (cycle length <1,000 milliseconds) into the vein, even if dissociated, was no DPV activity. In case of these regular vein potentials, recorded on the circular catheter while performing the ablation procedure, additional radiofrequency (RF) energy was applied at the site of earliest activation. We defined as DPV activity only an irregular and slow automatic rhythm from the isolated vein recorded after waiting for a few minutes after placing the mapping catheter. We excluded single isolated ectopic beats eventually recorded while placing the mapping catheter into the vein, since these might be provoked mechanically by the catheter within the PV. The duration of monitoring DPV activity during the procedure was at least 5 minutes, but only in few patients more than 20 minutes. The monitoring duration between superior and inferior PVs was similar. We did not routinely undertake any provocative maneuvers to check for DPV activity (i.e., isoproterenol administration). Intravenous adenosine to check for dormant LA-PV conduction was administered in a small subgroup of patients at the discretion of the operator.

If spontaneous repetitive ectopy (bursts) or AF paroxysms were observed during the procedure, the initiating focus was localized by combining conventional mapping (CS activation pattern) and sequential mapping of the PVs with the circular catheter. Simple ectopic vein potentials like doubles or triplets were not considered as a triggering activity. A PV was defined as a "triggering vein" if the earliest focal activation recorded from the circular catheter preceded the onset of the surface P wave and any other atrial intracardiac electrogram.

Patients were classified into 2 groups. Group 1 consisted of patients in whom DPV activity with slow rhythm (>1,000 milliseconds) was demonstrated during sequential PV assessments with the circular mapping catheter placed at the PV-LA ostium after PVI. Group 2 consisted of patients without DPV activity after ablation.

Follow-Up and Study Endpoints

After 3, 6, and 12 months, all patients had a follow-up visit, including repetitive 7-day Holter ECG in our outpatient clinic. Patients who had symptoms without documented AF

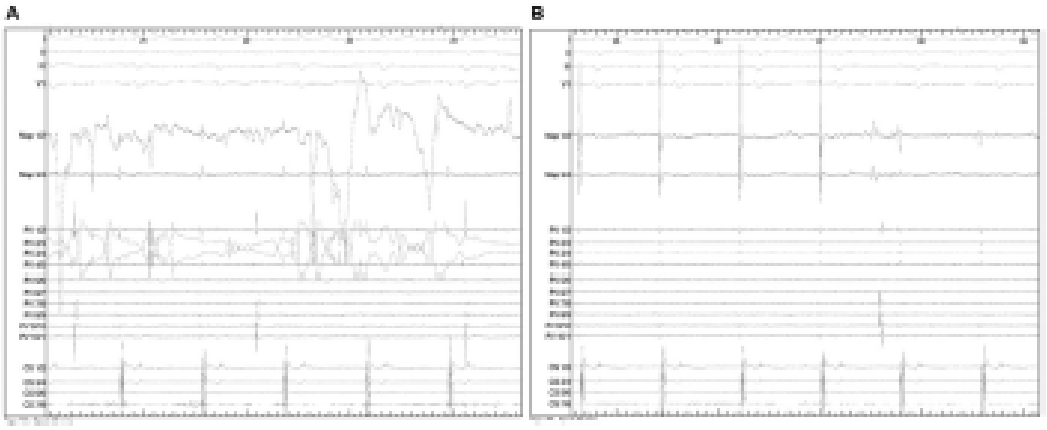


Figure 1. Surface ECG (leads I, II, III, and V1) and intracardiac recordings from the Orbiter catheter (PV 1/2–10/11) and the CS catheter placed in the right superior pulmonary vein and in the coronary sinus respectively. Panel A: Residual slow regular vein potentials during ongoing ablation. Panel B: Dissociated vein activity a few minutes after completing electrical isolation. Of note, the activation sequence on the circular PV catheter between 2 panels remains unchanged.

recurrence were given an event recorder to identify the cause of their symptoms. Primary endpoint was defined as freedom from AF (>30 seconds) off AADs after a blanking period of 6 weeks.

Statistical Analysis

Data management and analyses were performed using SPSS version 19.0 (IBM Inc., Armonk, NY, USA). Data are presented as mean ± SD for continuous variables and proportions for categorical variables. Differences in mean values between patients grouped according to the presence of DPV activity after PVI were compared using unpaired *t*-tests; comparison of proportions between groups was performed using χ^2 tests. A probability P value of <0.05 was considered statistically significant. A log-rank test was performed to compare distributions of event times between groups. Univariate Cox analysis was performed using clinical arrhythmia recurrence during long-term follow-up as dependent variable to investigate any correlation with clinical and procedural variables at baseline. Since none among the considered variables showed a significant relation with long-term outcome we did not perform any multivariate regression model analysis.

Results

Incidence of DPV Activity After PVI

Ostial disconnection with disappearance of venous potentials by circumferential PVI was achieved in all 243 patients for 932 PVs. While performing PVI, 116 of 243 (48%) patients showed an ongoing irregular fast dissociated activity (mean CL of 814 ± 108 milliseconds) and ablation was continued at the site where the latest electrical connections had been successfully eliminated. In 95 of 243 (39%) patients, a residual slow vein activity (mean CL of 1,211 ± 165 milliseconds) persisted with a constant rhythm potentially representing a very slow conduction into the vein. We performed further ablation at the site of earliest activation into the vein and obtained complete abolishment of those potentials in 30 of 95 (32%) patients; in 65 of 95 patients (68%) there was a change to a slow irregular dissociated activity (DPV activity). After PVI, 65 of 243 patients had at least 1 PV presenting with DPV activity (27%; Group 1). No DPV activity was present in 178 of 243 patients (73%; Group 2).

A total of 112 of 932 (12%) isolated PVs showed DPV activity. There were no significant differences in baseline clinical characteristics between the 2 groups, except for age (Table 1). There was no significant difference either in the anatomy of PVs or in LA dimension between the 2 groups. A left common PV (LCV) was identified in 9 of 65 and 35 of 178 patients (14% and 19%, for Group 1 and Group 2, respectively; P = 0.78).

Characteristics of DPV Activity

Of 932 isolated PVs, 820 (88%) showed no DPV activity whereas 112 PVs (12%) demonstrated DPV activity, accounting for 1.7 PVs with DPV/patient in Group 1.

Regarding the arrhythmogenic potential of the PV, both superior PVs were more likely to present AF trigger activity during ablation, as well as DPV activity after electrical isolation: DPV activity was mostly documented in the left superior PV (LSPV) (36%) and the right superior PV (RSPV) (29%) followed by the left inferior PV (LIPV) (18%). DPV activity was observed bilaterally in 22 of 65 patients (34%).

Among PVs with DPV activity we observed a significantly higher rate of triggering activity during ablation than among those without DPV activity (44/112, 39% vs. 13/820, 2%; P = 0.026). Thus, the triggering veins are more likely to have ongoing dissociated ectopy after isolation, however, without carrying out a higher risk of AF recurrence at follow-up (Table 2). A trigger activity was observed in 24 patients. Among them, 14 patients presented repetitive bursts, while the remaining 10 patients showed paroxysms of AF. An AF trigger was predominantly observed in the superior PVs (LSPV in 9 patients and RSPV in 9 patients), less frequently in the RIPV and in LIPV (trigger in 1 and in 3 patients, respectively), whereas the LCV was identified as the AF triggering PV in 2 patients.

In all patients in whom a triggering PV was observed, PVI resulted invariably in the elimination of ectopy and/or AF paroxysms.

TABLE 2
Univariable Cox Analysis to Investigate the Relation Between Clinical and Procedural Features at Baseline and the Risk of Clinical Arrhythmia Recurrence During Long-Term Follow-Up After the First PVI Procedure

Covariates	Hazard Ratio	95% CI	P Value
Age >60 years	0.13	−0.73–0.18	0.38
Gender	0.11	−0.07–0.17	0.44
LA dilatation	0.05	−0.12–0.12	0.97
CAD	0.05	−0.18–0.17	0.98
Diabetes	0.06	−0.33–0.21	0.68
Hypertension	0.13	−0.19–0.07	0.40
Presence of triggering PVs at index ablation	0.08	−0.27–0.15	0.56
DPV activity after PVI	0.15	−0.20–0.07	0.34
Electrical cardioversion required after PVI	0.30	−0.09–0.61	0.14

CAD = coronary artery disease; DPV = dissociated pulmonary vein; LA = left atrium; PVs = pulmonary veins; PVI = pulmonary vein isolation.

Clinical Outcome and Procedure Characteristics at Repeat Ablation

During a mean follow-up of 12 ± 7 months, sinus rhythm was observed in 50 of 65 patients (77%) in Group 1 versus 121 of 178 patients (68%) in Group 2 (P = 0.23). There was no significant difference regarding the timing of AF recurrence between the groups ($P_{Log\ Rank}$ = 0.12; Fig. 2). Also after exclusion of those patients (n = 4) with arrhythmia recurrence during the blanking period, survival free from clinical relapses off AADs was comparable between 2 groups (69% vs. 78% in Group 1 vs. Group 2, respectively; $P_{Log\ Rank}$ = 0.17).

Among 72 patients undergoing a repeat ablation (Group 1 n = 15, Group 2, n = 57), the majority (60/72 patients, 83%) presented with a recurrence of paroxysmal AF, whereas a progression to persistent AF (6/72; 8%) or atypical left atrial flutter (6/72; 8%) was less frequent.

In Group 1, 13 of 15 (87%) redo patients had paroxysmal AF related to a recovered PV conduction. Among them, in only 5 patients the PV-LA reconnection involved the same PVs showing ongoing DPV activity after first ablation (in 3 patients both superior PVs, in 1 patient all 4 PVs, in 1 patient the RSPV). In the remaining 8 patients, the PV-LA reconnection was observed in other PVs than those with DPV activity after first PVI. The remaining 2 patients did not present any recovered LA-PV conduction and developed clinically persistent AF (n = 1) and atypical atrial flutter (n = 1).

In Group 2, paroxysmal AF probably due to reconnected PV was present in 47 of 57 (82%) patients. In 5 of 57 patients AF was associated to a triggering extra PV focus, without any PV reconnection. The remaining 5 patients (all with PV reconnection) clinically suffered from persistent AF or atypical atrial flutter.

At univariate Cox analysis (Table 2) none of the clinical and procedural variables considered at baseline was significantly related to a higher risk of clinical recurrences during long-term follow-up.

All redo patients (N = 15; 100%) in Group 1 and 50 of 57 patients (88%) in Group 2 were free from AF after the repeat procedure (P = 0.26) at a mean follow-up of 16 ± 5 months after first PVI.

Characteristics of PV Reconnection at Repeat Ablation

At the repeat ablation, 149 PVs (16% of all isolated PVs) showed a recovered LA-PV conduction. All veins were again isolated by re-PVI. No significant differences were observed in the rate of reconnection between PVs with and without DPV activity (13/112, 11% vs. 136/820, 16%; P = 0.48; Fig. 3). Interestingly, in 2 of 136 reconnected veins without DPV at the first ablation we observed a DPV activity after reisolation. On the other hand, only 6 of 13 reconnected veins with DPV activity at first ablation still presented DPV after reisolation.

Discussion

Main Findings of the Study

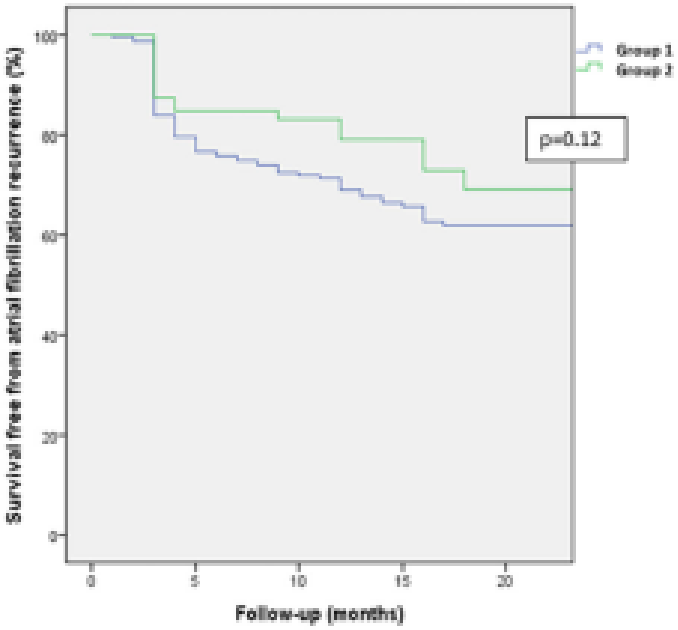
To the best of our knowledge, this is the largest series of patients evaluating incidence, electrophysiological characteristics and prognostic significance of DPV activity after first PVI, as well as the characteristics of recurrent arrhythmia in patients with and without DPV activity during follow-up. DPV activity occurs in 12% of PVs after PVI and is observed more frequently in PVs identified during ablation as AF triggers. DPV activity after PVI is no predictor for clinical recurrence of AF during long-term follow-up.

Incidence of DPV Activity

The reported incidence of DPV activity after PVI shows a broad variation from 9% to 63%,[16,17] which is mainly due to differences in definition, study population, and ablation approach. We observed a prevalence of DPV activity after PVI of 12%, which is similar to that reported by Weerasooriya *et al.*[10] in a series of patients treated with ostial isolation of the arrhythmogenic vein. Kabra *et al.*[17] reported a DPV activity after circumferential PVI in 91.7% of patients with paroxysmal AF. However, DPV activity in their study was classified as isolated ectopic beats, ectopic regular rhythm or PV fibrillation.

Characteristics of DPV Activity

Consistent with previous data,[18–21] we observed that the superior PVs were preferential sites for dissociated electrical automaticity. This might be due to anatomical factors and muscular sleeves that are supposed to be longer and thicker compared to those of the inferior veins.[18] Likewise, a comparable anatomical distribution was seen when looking at the triggering PVs. We observed a significantly higher incidence of DPV activity after isolation of triggering PVs compared to those in which an AF trigger was not



Patients at risk

Group 1	65	58	41	23	9
Group 2	178	133	103	23	9

Figure 2. *Kaplan-Meier curve of the freedom from arrhythmia recurrence. Survival free from arrhythmia recurrences off antiarrhythmic drugs was comparable between 2 groups. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

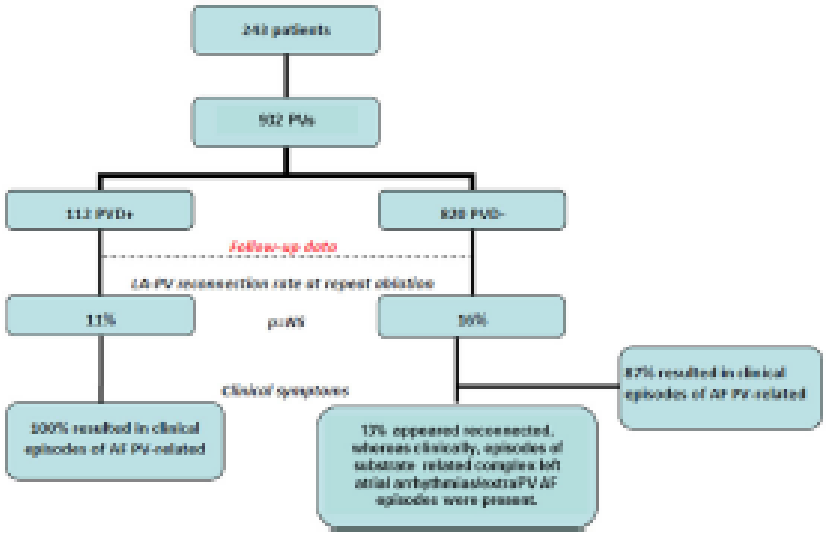


Figure 3. *The flow chart shows the occurrence of pulmonary vein reconnection at long-term follow-up between pulmonary veins with and without dissociated activity and its clinical significance during relapses. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

identified. These findings are consistent with those of Doi *et al.*[15] A higher PV sleeve load in the triggering PVs compared to the overall mean PV sleeve load was observed by De Greef *et al.*,[12] probably accounting for an increased expression of DPV activity despite PVI. Apart from differences in cellular electrophysiology, the PV area also shows salient features in gross anatomy and fiber geometry. Guerra *et al.*[22] specifically linked areas of PV wall thickening to high-frequency potentials and the origin of ectopic beats. At these anatomical sites, fibrosis and discontinuities might be more frequent, and these peculiarities may act in concert to facilitate arrhythmogenic PV activity.

Prognostic Significance of DPV Activity and Clinical Implications

In our study, DPV activity was no clinical predictor for AF recurrence during long-term follow-up. Besides, no other predictors for AF recurrence were identified. This might be explained by the fact that this was a series of AF patients otherwise relatively healthy. The findings are consistent with a previous analysis performed by our group.[23]

Recovered PV-LA conduction is the dominant finding at the repeat ablation and PVs with and without DPV activity were equally frequently reconnected. Our findings are in line with previous studies.[10,21] Kim *et al.*,[24] after randomly assigning patients following antral vein isolation to ablation of residual PV potentials, did not demonstrate an improvement in clinical outcome with adjunctive ablation. In contrast, Doi *et al.*[13] recently underlined the efficacy of additional RF ablation of DPV activity after PVI in order to prevent AF recurrence. Differences in the definition of DPV activity are probably the main reason for these conflicting results. We defined DPV activity only as low frequency, irregular potentials originating in the PVs. If rapid incessant electrical activity or low frequency potentials with constant and regular rhythm were still observed after PVI, we generally performed more extensive ablation at the PV-LA junction considering that the most probable mechanism was incomplete PVI with slow residual conduction. In contrast, we interpreted a very low frequency (<1 beat/s) electrical activity without a regular rhythm as focal firing within a completely isolated PV.

Neither DPV activity nor PVs that triggered AF were predictors of recurrence. This is in contrast with previous data reported by De Greef *et al.*,[12] identifying PVs triggering AF being a paradoxical predictor for AF recurrence after PVI. Differences in patient selection and the relatively low number of AF triggering PV in our cohort might explain the contrasting results.

The reconnection of triggering PVs as well as of PVs with DPV activity led in all cases to clinical recurrence of the index arrhythmia, i.e., paroxysmal AF. In patients without DPV activity at the first PVI and recovered PV conduction we observed more often left atrial arrhythmias other than AF and/or with an extra-PV mechanism. We identified 4 cases of atypical atrial flutter arising in the vicinity of the circumferential lesions with localized reentry through gaps in the lines or related to slow conduction zones beside the lines. In these patients, reconnection of PVs was not the mechanism for arrhythmia recurrence. Our findings support the idea that DPV activity—if it is a true dissociated rhythm—is a marker of a pronounced automaticity of PV myocytes, without prognostic significance for ablation success.

Limitations

After isolation, each vein was checked separately. Thus, we are not able to comment on the possible presence of a simultaneous DPV in ipsilateral veins. However, we performed a combined approach of circumferential and segmental PVI if LA-PV connections were still present after encircling both ipsilateral PVs. Thus, DPV in 1 PV but not in the other ipsilateral was a possible situation.

In our study, the incidence of AF trigger was smaller than previously described in the literature.[12] Different reasons may account for this observation. First, no provocative maneuvers were routinely undertaken in this study. Second, we have strictly defined a trigger activity, excluding any simple ectopy from the analysis. Moreover, propofol and opioids are known to suppress potential AF triggers. This may have led to further underestimation of the incidence of spontaneous triggers compared with nonsedated patients.

The follow-up available was comparable with previous studies.[15] An extended follow-up is certainly needed to make definitive conclusions regarding the prognostic value of ongoing DPV activity after successful PVI.

Conclusion

DPV activity occurred in 12% of PVs after PVI and was observed more frequently in PVs identified as AF triggers. DPV activity was not predictive for AF recurrence during follow-up. PV-LA reconnection involving PVs with DPV activity lead to AF as recurrent arrhythmia. Patients without DPV activity seem to be at higher risk for developing non-PV dependent, more complex atrial arrhythmia independently of PV-LA reconnection.

References

1. Writing Group Members: Samuel WL, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes Mark III, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM: 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2011;123:104-123.
2. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blomstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbuchel H, Heldal M, Kristensen SD, Kolh P, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Ratti PH, Schotten U, Van Gelder IC, Verheugt FW: 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-2747.
3. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J: Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-666.
4. Deisenhofer I, Schneider MA, Böhlen-Knauf M, Zrenner B, Ndrepepa G, Schneider S, Weber S, Schreieck J Jr, Weyerbrock S, Schmitt C: Circumferential mapping and electric isolation of pulmonary veins in patients with atrial fibrillation. Am J Cardiol 2003;91:159-163.
5. Ndrepepa G, Karch MR, Schneider MA, Weyerbrock S, Schreieck J, Deisenhofer I, Zrenner B, Schömig A, Schmitt C: Characterization of paroxysmal and persistent atrial fibrillation in the human left atrium during initiation and sustained episodes. J Cardiovasc Electrophysiol 2002;13:525-532.
6. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F: Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002;105:1077-1081.
7. Winkle RA, Mead RH, Engel G, Patrawala RA: Long-term results of atrial fibrillation ablation: The importance of all initial ablation failures undergoing a repeat ablation. Am Heart J 2011;162:193-200.
8. Cappato R, Negroni S, Pecora D, Bortivegna S, Lupo PP, Carolei A, Esposito C, Furlanello F, De Ambroggi L: Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. Circulation 2003;108:1599-1604.

9. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Gunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A: Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. Circulation 2005;112:627-635.
10. Weerasooriya R, Jais P, Scavee C, Macle L, Shah DC, Arentz T, Salerno JA, Rayband F, Choi KJ, Hocini M, Clementy J, Haissaguerre M: Dissociated pulmonary vein arrhythmia: Incidence and characteristics. J Cardiovasc Electrophysiol 2003;14:1173-1179.
11. Haissaguerre M, Shah DC, Jais P, Hocini M, Yamane T, Deisenhofer I, Chauvin M, Garrigue S, Clementy J: Electrophysiological breakthroughs from the left atrium to the pulmonary veins. Circulation 2000;102:2463-2465.
12. De Greef Y, Tavernier R, Vandekerckhove Y, Duytschaever M: Triggering pulmonary veins: A paradoxical predictor for atrial fibrillation recurrence after PV isolation. J Cardiovasc Electrophysiol 2010;21:381-388.
13. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, Haines DE, Haissaguerre M, Iesaka Y, Jackman W, Jais P, Kottkamp H, Kuck KH, Lindsay BD, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Natale A, Pappone C, Prystowsky E, Raviele A, Ruskin JN, Shemin RJ: HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) task force on catheter and surgical ablation of atrial fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. Europace 2007;9:335-379.
14. Ammar S, Hessling G, Reents T, Paulik M, Fichtner S, Schön P, Diller R, Kathan S, Jilek C, Kolb C, Hafner B, Deisenhofer I: Importance of sinus rhythm as endpoint of persistent atrial fibrillation ablation. J Cardiovasc Electrophysiol 2013;24:388-395.
15. Doi A, Satomi K, Makimoto H, Yokoyama T, Yamada Y, Okamura H, Noda T, Aiba T, Aihara H, Yasuda S, Ogawa H, Kamakura S, Shimizu W: Efficacy of additional radiofrequency applications for spontaneous dissociated pulmonary vein activity after pulmonary vein isolation in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2013;24:894-901.
16. Willems S, Weiss C, Rivinius T, Rostock T, Hoffmann M, Ventura R, Meinertz T: Dissociated activity and pulmonary vein fibrillation following functional disconnection: Impact for the arrhythmogenesis of focal atrial fibrillation. Pacing Clin Electrophysiol 2003;26:1363-1370.
17. Kahra R, Heist EK, Barrett CD, Donaldson D, Blondea D, Beinart R, Koruth J, Singh S, Ruskin J, Mansour M: Incidence and electrophysiologic properties of dissociated pulmonary vein activity following pulmonary vein isolation during catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2010;21:1338-1343.
18. Saito T, Waki K, Becker AE: Left atrial myocardial extension onto pulmonary veins in humans: Anatomic observations relevant for atrial arrhythmias. J Cardiovasc Electrophysiol 2000;11:888-894.
19. Miyazaki S, Kuwahara T, Kobori A, Takahashi Y, Takei A, Sato A, Isobe M, Takahashi A: Prevalence, electrophysiological properties, and clinical implications of dissociated pulmonary vein activity following pulmonary vein antrum isolation. Am J Cardiol 2011;108:1147-1154.
20. Jiang C, Fu J, Matsuo S, Nault I, Hong H, Jiang R, Liu Q, Fan Y, Sheng X, Zhang Z, Fu G: Dissociated pulmonary vein rhythm may predict the acute pulmonary vein reconnection post-isolation in patients with paroxysmal atrial fibrillation. Europace 2011;13:949-954.
21. Lee G, Kalman JM, Vohra JK, Teh A, Medi C, Ling LH, Kistler PM: Dissociated pulmonary vein potentials following antral pulmonary vein isolation for atrial fibrillation: Impact on long-term outcome. Heart 2011;97:579-584.
22. Guerra PG, Thibault B, Dubuc M, Talajic M, Roy D, Crépeau J, Nattel S, Tardif JC: Identification of atrial fenus in pulmonary veins using intravascular ultrasound. J Am Soc Echocardiogr 2003;16:982-987.
23. Fichtner S, Czudnochowsky U, Hessling G, Reents T, Estner H, Wu J, Jilek C, Ammar S, Karch M, Deisenhofer I: Very late relapse of atrial fibrillation after pulmonary vein isolation: Incidence and results of repeat ablations. Pacing Clin Electrophysiol 2010;33:1258-1263.
24. Kim YH, Lim HE, Pak HN: Role of residual potentials inside circumferential pulmonary veins ablation lines in the recurrence of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2010;21:959-965.

Catheter Ablation for "Lone" Atrial Fibrillation: Efficacy and Predictors of Recurrence

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Catheter Ablation for "Lone" Atrial Fibrillation. ***Background:*** **Atrial fibrillation in otherwise healthy young patients has been termed "lone" atrial fibrillation (AF). The best treatment choice is still under discussion. The aim of this study was to report on efficacy and safety of catheter ablation.**

Methods: **Among 855 patients referred to our center between 2011 and 2013, 76 (9%) met the diagnostic criteria for lone AF (mean age 45 ± 8 years; mean LA diameter 37 ± 4 mm; paroxysmal AF 82%; persistent AF 18%). The primary endpoint was freedom from any atrial tachycardia after the first ablation; the secondary endpoint was freedom from any atrial tachycardia after the last ablation procedure without antiarrhythmic drugs.**

Results: **The primary endpoint occurred in 56 patients (74%) after a mean follow-up time of 444 ± 344 days. The secondary endpoint occurred in 73 patients (96%) after a mean of 1.3 ablations/patient during a follow-up time of 459 ± 366 days. The risk of AF recurrence was not influenced by AF duration or by the type of AF (paroxysmal versus persistent). In a multivariate regression analysis smoking (P = 0.001), first degree atrioventricular block (P = 0.001), and early (< 3 months) AF recurrence (P = 0.001) were independently associated with a higher risk of AF recurrence. Major peri-procedural adverse events did not occur.**

Conclusions: **Catheter ablation in young healthy patients is highly effective and safe. The outcomes are maintained during long-term follow-up irrespective of preoperative AF duration. Patients with AF recurrence were more likely to smoke, have first degree AV block and early AF recurrence.** *(J Cardiovasc Electrophysiol, Vol. 27, pp. 536-541, May 2016)*

catheter ablation, lone atrial fibrillation, predictors of recurrence, recurrence

Introduction

Atrial fibrillation (AF) is the most common sustained rhythm disorder in adults.[1] Although the majority of patients is elderly and has cardiovascular comorbitidies, there is a minority of patients who develop AF at a relatively young age without any obvious structural heart disease. The term "lone atrial fibrillation" has been coined for this group of patients.[2]

Clinical risk stratification and therapeutic AF management are generally performed according to the nature and the extent of underlying heart disease and other concomitant diseases. Standardized therapeutic algorithms have been employed for estimating stroke risk (e.g., CHA2DS2-VASC) and for the assessment of symptoms (e.g., EHRA).[2]

However, the optimal therapeutic strategy for patients with lone atrial fibrillation is still unclear. Given the risk of complications and AF recurrence after an ablation procedure, antiarrhythmic drugs (AADs) are often considered as first-line therapy.[2,3] Nevertheless, there are very little data on the use of antiarrhythmics drugs, and no data on long-term efficacy of catheter ablation in patients with lone atrial fibrillation.

Therefore, the aim of this study was to report on safety and long-term efficacy of catheter ablation in this highly selected subgroup of AF patients.

Methods

Study Sample

We analyzed our center's ablation database for patients undergoing a first ablation for AF between May 2011 and December 2013. Patients were considered as lone AF if they were < 65 years of age and did not suffer from any cardiovascular comorbitidy, cardiopulmonary disease, or structural heart disease.[4] Patients treated with amiodarone or with a history of previous ablation were excluded from the study. Of 855 consecutive patients undergoing AF ablation, 76 (9%) met all criteria for lone AF and were included in the study. Baseline clinical and echocardiographic characteristics are shown in Table 1 (mean age 45 ± 8 years; mean LA diameter 37 ± 4 mm). Paroxysmal and persistent AF was defined according to 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation.[5]

Clinical Assessment of Comorbidities and Structural heart Disease

In all patients a detailed medical history (including smoking, depressive disorders, metabolic syndrome, drug intake,

Disclosures: None.

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TABLE 1

Baseline Characteristics of Patients Stratified by AF Recurrences During Follow-Up

	Patients			
	Total, n = 76	Without Recurrences, n = 56	With Recurrences, n = 20	P Value
Clinical characteristics				
Age, years (mean±SD)	45 ± 8	45 ± 8	44 ± 8	0.688
Male gender, n (%)	53(69)	38(68)	15(75)	0.777
BMI, kg/m^2 (mean±SD)	26 ± 4	26 ± 4	26 ± 4	0.884
AF history, months (mean±SD)	38 ± 36	34 ± 30	52 ± 53	0.199
Persistent AF (%)	14(18)	12(21)	2(10)	0.331
Endurance sport (%)	3(4)	2(3)	5(25)	0.223
Previous AADD (%)	12(16)	9(16)	3(15)	0.722
Smoke (%)	20(28)	11(20)	12(60)	**0.001**
Beta-blocker (%)	44(61)	35(62)	9(45)	0.773
Early recurrence (%)	21(29)	11(20)	13(65)	**<0.001**
Electrocardiogram				
AV block I, (%)	4(5)	1(2)	3(15)	**0.054**
BBB (%)	2(3)	2(3)	0	1.000
Echocardiographic parameters				
LA diam, mm (mean±SD)	37 ± 4	36 ± 3	40 ± 4	**0.001**
LA area, mm^2 (mean±SD)	19 ± 3	18 ± 2	20 ± 3	**0.005**

BMI = body mass index; AF = atrial fibrillation; ADD = antiarrhythmic drug; OAC = oral anticoagulants; AV = atrio-ventricular; BBB = bundle branch block; LA diam. = antero-posterior diameter of left atrium. Boldface indicates significance.

endurance sport practice) was taken by an experienced physician. All patients received a thorough physical exam, resting ECG, and routine blood testing (including electrolytes, renal function, total blood count, fasting glucose, thyroid function and C-reactive protein).

Routine 2D echocardiography was performed using both apical and parasternal views. LA diameter was defined as the distance of the perpendicular line measured from the posterior LA wall to the anterior LA wall from M-mode of a parasternal short axis image at the level of the aortic valve. LA area was measured at apical four-chamber view by manual tracing of LA endocardial border. The presence of left ventricular hypertrophy or diastolic dysfunction was defined as structural heart disease and excluded the diagnosis of lone AF. Patients with isolated left atrial enlargement were not considered as having structural heart disease and were thus enrolled in the study.

If coronary heart disease was suspected, treadmill testing and/or coronary imaging (using CT or coronary angiography) were performed.

Procedural Workup and Catheter Ablation

All AADs except beta-blockers were discontinued for at least 4 weeks prior to the ablation procedure. All patients gave written informed consent to all imaging and invasive procedures. Patients had to be on oral anticoagulation (OAC) for at least 4 weeks prior to ablation and were kept under OAC during the procedure (continuous novel OAC or vitamin-K antagonist with intraprocedural INR levels of 2.0–2.8). Preprocedural workup, including LA thrombus exclusion and CT scan for LA anatomy reconstruction, and ablation procedure were performed as previously described.[6]

In all patients with paroxysmal AF a circumferential pulmonary vein isolation (PVI) was performed as described earlier.[7] Briefly, the ablation procedure consisted of encircling the ipsilateral PVs by a continuous circular lesion (0.5–1 cm antral to the ostium) with a circular mapping catheter in place. The electrical isolation of each vein was sequentially checked by leaving the circular catheter in each vein for a few minutes. If veno-atrial electrical connections persisted, we performed further selective lesions inside the encircling lesion and between the veins guided by the activation sequence on the circular PV catheter, thus performing a combined approach of circumferential and segmental PVI.

In patients presenting with a recurrence of paroxysmal atrial fibrillation (during follow-up) and no PV reconnection, induction maneuvers (including burst stimulation and isoproterenol infusion) were performed to check for extra-PV foci initiating AF and/or triggering repetitive premature atrial complexes (PAC).

Patients with persistent AF underwent a modified stepwise approach, integrating circumferential PVI, substrate modification including an electrogram-guided ablation of complex fractionated atrial electrograms (CFAE), and linear lesions in case of macroreentries. Details of this ablation strategy and procedural endpoints were previously described by our group.[6,8]

Follow-Up and Study Endpoints

No antiarrhythmic drugs (except beta-blockers) were used during follow-up. Early recurrences were defined as clinical AF recurrence within a blanking period of 3 months. All patients with an early recurrence of sustained arrhythmia underwent electrical cardioversion (CV). After 3, 6, and 12 months, all patients had a follow-up visit including repetitive 7-day Holter ECG in our dedicated follow-up clinic. Patients who had symptoms without documented AF recurrence were provided a portable event recorder to identify the cause of their symptoms. Primary endpoint was defined as freedom from any atrial tachycardia (>30 seconds) after the first ablation procedure (blanking period of 3 months). Secondary endpoint was defined as freedom from any atrial tachycardia (>30 seconds) after the last ablation procedure (blanking period of 3 months).

Statistical Analysis

Data management and analyses were performed using SPSS version 23.0 (IBM Inc., Armonk, NY, USA). Data are presented as mean ± SD for continuous variables and proportions for categorical variables. Differences in mean values between patients grouped according to the presence of AF recurrence after ablation were compared using unpaired *t*-tests; comparison of proportions between groups was performed using χ^2 tests. A two-sided $P < 0.05$ was considered statistically significant. A log-rank test was performed to compare distributions of event times between groups. Univariate regression analysis was performed to investigate the relation of clinical AF recurrence (dependent variable) with clinical variables at baseline. Significantly associated traits were then considered in a multivariable regression model.

Results

Procedural Data and Acute Ablation Outcome

All 62 patients with paroxysmal lone AF underwent a circumferential PVI. An additional cavotricuspid isthmus (CTI) ablation was performed in four patients who had clinical episodes of typical atrial flutter. All 14 patients with persistent lone AF were in AF at the beginning of the procedure and underwent a stepwise approach. Termination of AF into sinus rhythm (SR) during ablation procedure (i.e., without external cardioversion) was achieved in 10 patients (71%). In four of them termination of AF was achieved with PVI followed by CFAE ablation; in the other six patients a stable atrial tachycardia (AT) arose during CFAE ablation and was successfully targeted and terminated by performing linear lesions. In the remaining four patients (29%) AF did not terminate into sinus rhythm under ablation, and external cardioversion was required to restore SR after the ablation procedure was completed.

No difference was observed between patients with paroxysmal or persistent AF with regard to the baseline characteristics, except for depressive disorders. Patients with persistent AF suffered more often from depressive disorders (0/62 patients with paroxysmal AF versus 2/14 patients with persistent AF, $P = 0.04$). Procedure time (147 ± 68 versus 89 ± 27 minutes; $P < 0.01$) and radiofrequency (RF) time (65 ± 21 versus 42 ± 27 minutes; $P < 0.01$) were significantly longer in patients with persistent lone AF compared to those with paroxysmal AF. One patient had sinus node dysfunction unmasked after the ablation which required pacemaker implantation. No death, stroke, or transient ischemic attack (TIA) occurred.

During the 3-month blanking period 24 (31%) patients experienced early AF recurrence and underwent external cardioversion.

Primary Endpoint and Relapse Characteristics

After a single ablation procedure, 56 patients (78%) were free from arrhythmia relapses after a mean follow-up time of 458 ± 344 days. Of the 20 patients with arrhythmia relapses all but 2 patients suffered originally from paroxysmal AF and experienced paroxysmal AF recurrence; the other 2 patients suffered originally from persistent AF and presented with persistent AF again after the first ablation. Among them, 15 patients (75% of redo patients) experienced early AF recurrences (< 12 months after ablation) and 5 patients (25%) experienced late AF recurrences (> 12 months after ablation).

Of note, patients with persistent AF were not more likely to suffer from relapses than those with paroxysmal AF ($P = 0.721$). Although in the univariate analysis an increased LA size was correlated with AF recurrences (Table 2), in the multivariate analysis LA enlargement was not independently related to an increased risk of AF recurrences.

Patients with AF recurrences were more likely to smoke ($P = 0.001$) and to have AV block I ($P = 0.001$), and suffered more frequently from early recurrences in the blanking period ($P = 0.001$), compared to those free from arrhythmia recurrence (Table 2).

All 20 patients with AF relapses underwent re-ablation (after a mean time of 235 days since first ablation), Figure 1. During redo procedure, 16 patients (16/20, 80%) displayed electrical PV reconnection and a redo PVI was performed. In the remaining four patients without PV reconnection, extra-PV foci were detected and ablated in LA roof, mitral annulus, at the ostium of coronary sinus and in the superior vena cava, respectively.

Secondary Endpoint: Outcome After Last Ablation

Of the 20 patients who had undergone re-ablation, 3 patients experienced another relapse (after the blanking period) of paroxysmal AF and 2 of them underwent a third ablation. Of the two patients undergoing a third ablation, one patient suffered from paroxysmal AF and underwent redo PVI and CTI ablation. No extra PV foci were detected. The other patient undergoing a third ablation suffered from persistent AF and experienced paroxysmal AF relapses after the third ablation. Amiodarone treatment was then started.

Thus, during a mean follow-up of 459 ± 366 days after the last ablation (with a mean of 1.3 ablation per patient), n = 73 (96%) remained free of recurrences without antiarrhythmic drugs.

Discussion

Main Findings

To the best of our knowledge, the present study is the first to investigate long-term outcomes after catheter ablation in patients with lone atrial fibrillation. The main findings of this study are that catheter ablation in young healthy lone AF patients is highly effective and safe, and the outcomes are maintained at long-term follow-up, irrespective of AF type, preoperative history or LA enlargement. For patients with symptomatic persistent lone AF a stepwise approach is highly effective and should be considered as initial ablation strategy. Smoking, first-degree AV block, and early AF recurrence are associated with a higher risk of recurrence during long-term follow-up.

Efficacy and Safety of Catheter Ablation in Lone AF as First-Line Therapy

The assessment of procedural risks and outcomes relevant to the individual patient is recommended before consideration of AF catheter ablation.[5] However, the ongoing effort to create a mechanistic classification for AF does not easily fit into the clinical work-up and therapeutic management of

TABLE 2

Potential Predictors of AF Recurrences: Uni- and Multivariate Regression Analysis

Variables	Univariate			Multivariate		
	B	95% CI	P	B	95% CI	P
Age	0.96	0.90;1.02	0.27			
Gender	1.07	0.32;3.54	0.91			
BMI, kg/m^2	1.01	0.88;1.17	0.81			
AF history, months	0.01	0.99;1.12	0.08			
Persistent AF	0.51	0.10;2.57	0.41			
Sport	3.73	0.49;28.32	0.20			
Previous ADD	1.17	0.27;5.00	0.82			
Smoke	0.37	0.16;0.57	**<0.01**	0.30	0.11;0.49	**<0.01**
Beta-blocker	0.79	0.25;2.45	0.68			
Early recurrence	0.42	0.20;0.60	**<0.01**	0.34	0.13;0.51	**<0.01**
AV block I	0.26	0.07;0.95	**0.02**	0.28	0.19;0.92	**<0.01**
LA area	0.37	0.23;0.86	**<0.01**	0.17	−0.10;0.60	0.16
LA diam.	0.37	0.01;0.06	**<0.01**	0.09	−0.18;0.37	0.43

BMI = body mass index; AF = atrial fibrillation; ADD = antiarrhythmic drug; AV = atrio-ventricular; LA area = left atrium area. Boldface indicates significance.

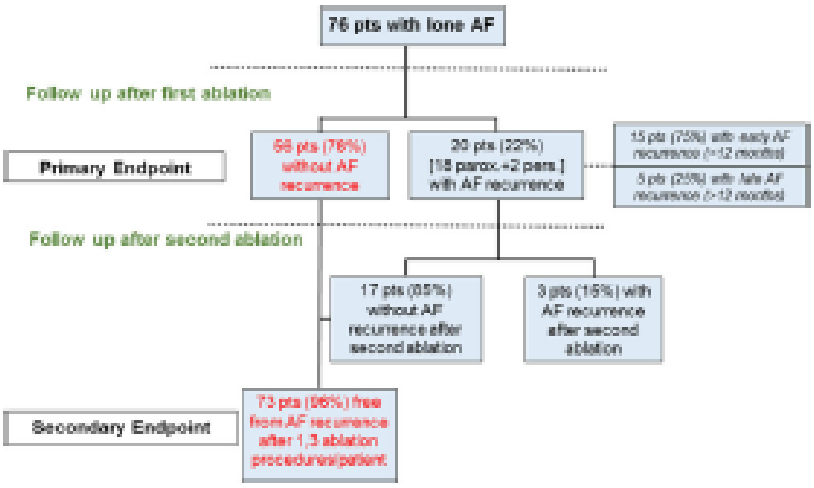

Figure 1. *The flow chart shows follow-up data after first ablation procedure. For a high quality full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

otherwise healthy AF patients with a lower procedural risk profile. According to the recent guidelines[2,3] in patients with AF and no structural heart disease rhythm control might be achieved by antiarrhythmic drugs or catheter ablation depending on the patients' choice. Nevertheless, catheter ablation is only recommended as first-line therapy for patients with paroxysmal AF. In a recent European Heart Rhythm Association (EHRA) survey[3] exploring work-up and clinical management of lone AF, 97% of the responding centers choose antirrhythmic drugs as the first therapeutic approach in symptomatic paroxysmal lone AF patients.

In the present study sample, 16% of patients with lone AF were unsuccessfully treated with antiarrhythmic drugs before undergoing ablation procedure. In our experience, catheter ablation as first-line therapy was highly effective and safe in patients with a very low cardiovascular risk profile. Our data are in line with previous studies[9-11] reporting on the efficacy and safety of radiofrequency ablation as first-line therapy for paroxysmal AF, compared with antiarrhythmic drugs. Reported success rate for AF ablation procedure show a wide variation, depending on type of AF, patients' characteristics, length of follow-up. Our success rates after AF ablation in otherwise healthy patients are slightly better than long-term outcomes previously reported in literature.[12] In recent randomized control trials,[13,14] survival free from recurrences at 1-year follow-up after ablation for paroxysmal AF varied from 70% to 86%, with 9% to 13% of patients requiring a second ablation. However, our results are not directly comparable with previous reported data. All previous studies also considered patients with structural heart disease and cardiovascular comorbidities, and separate analysis for this selected group of patients is lacking. Most redo patients in our study experienced clinical recurrences within the first year after ablation, only a minority of them suffered from late AF recurrence.

The initial ablation strategy for patients with symptomatic persistent lone AF was PVI only in most European centers reporting to the EHRA survey.[3] In concordance with the current guideline recommendation that patients with persistent AF should have additional substrate ablation we performed a stepwise approach including PVI, CFAE ablation, and linear lesions in case of regular and stable AT arisen during ablation. In our study, catheter ablation with a stepwise approach has proved to be highly effective and safe as first-line therapy also in patients with persistent AF, otherwise healthy, young, and with smaller LA.

Although recent literature[15] reports lower success rates of ablation procedures for persistent AF than for paroxysmal AF, we observed comparable success rate for both types of ablation procedures. The particularly high long-term success rate of ablation in persistent AF may be explained with the highly selected group of patients in our sample. Our data suggest that an ablation procedure as first-line therapy can achieve a successful outcome in young and otherwise healthy patients with AF, irrespective of the type of AF, AF history, and LA enlargement. Previous data of our group[6] showed a success rate varying from 42% to 13% at 12 months after ablation for persistent AF, depending on the acute ablation outcome. We observed a higher success rate for ablation of persistent AF in otherwise healthy patients, comparable to that for paroxysmal AF, and irrespective of the acute ablation outcome. Our data suggest that an ablation procedure and its estimated success rate should be considered on the basis of the overall clinical context and patients' characteristics, and not only of isolated arrhythmia features. However, in our study only a minority of patients suffered from persistent AF. Actually, selection criteria to identify which patients are more likely to benefit from an ablation procedure remain poorly defined; more studies and larger patients' samples are needed to better clarify this aspect.

On the one hand, it is still unclear whether lone AF in apparently healthy patients should be considered as an epiphenomenon of a still latent pathology;[16,17] on the other hand, one can argue that AF strictly relates only to atrial remodeling, but could be an early marker of a systemic cardiovascular comorbidity. In such a case, one can argue that an early ablation procedure could remove in advance the additional risk, imposed by AF, of a possible future cardiovascular disease.

Limitations

The study is subject to the limitations inherent in any retrospective study. Since we considered only a highly selected group of patients with AF, the study sample is relative small. However, to our knowledge, we analyzed the largest patient series with AF and no other cardiovascular comorbidities or structural heart disease. A direct comparison with existing data is difficult to interpret, since we considered a highly selected group of otherwise healthy patients, usually accounting for a lower proportion of study samples (ranging from 5% to 10% in most European countries[3]). Because of this specific lone AF population being apparently healthy, larger study populations with long follow-up times are needed to adequately describe, long-term outcomes. We observed high efficacy and safety of a more extensive ablation with a stepwise approach, as first-line therapy also in patients with persistent AF and smaller LA. However, given the small number of patients with lone persistent AF, more data are needed to confirm our observations. Despite regular screening, the detection of all episodes of AF recurrence is difficult to establish and therefore we may have underestimated the true incidence of AF relapses.

Conclusions

Catheter ablation in patients with lone atrial fibrillation is effective and safe and may thus represent a first-line choice in young and otherwise healthy AF patients. The results of ablation are maintained during long-term follow-up, irrespective of preoperative AF duration. Smoking, first-degree AV block, and early AF recurrence are associated with higher risk of recurrence during long-term follow-up.

References

1. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM: Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). Am J Cardiol 1994;74:236-241.
2. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH; ESC Committee for Practice Guidelines: Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:1360-1420.
3. Piccini I, Hocini M, Potpara TS, Todd D, Chen J, Blomström-Lundqvist; Scientific Initiative Committee, European Heart Rhythm Association: Work-up and management of lone atrial fibrillation: Results of the European Heart Rhythm Association Survey. Europace 2014;16:1521-1523.
4. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers: 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation—developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:1385-1413.
5. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1-e76.
6. Ammar S, Hessling G, Reents T, Paulik M, Fichtner S, Schon P, Diller R, Kathan S, Jilek C, Kolb C, Haller B, Deisenhofer I: Importance of sinus rhythm as endpoint of persistent atrial fibrillation ablation. J Cardiovasc Electrophysiol 2013;24:388-395.
7. Buiatti A, Ammar S, Reents T, Semmler V, Kathan S, Hofmann M, Bourier F, Telishevska M, Koch-Buttner K, Kanoo B, Lennerz C, Kolb C, Hessling G, Deisenhofer I: Dissociated pulmonary vein activity after pulmonary vein isolation for paroxysmal atrial fibrillation: A predictor for recurrence? J Cardiovasc Electrophysiol 2015;26:7-13.
8. Estner HL, Hessling G, Ndrepepa G, Luik A, Schmitt C, Konietzko A, Ucer E, Wu J, Kolb C, Pfluerner A, Zrenner B, Deisenhofer I: Acute effects and long-term outcome of pulmonary vein isolation in combination with electrogram-guided substrate ablation for persistent atrial fibrillation. Am J Cardiol 2008;101:332-337.
9. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, Gutleben K, Pisano E, Potenza D, Fanelli R, Raviele A, Themistoclakis S, Rossillo A, Bonso A, Natale A: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: A randomized trial. JAMA 2005;293:2634-2640.
10. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A; RAAFT-2 Investigators: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): A randomized trial. JAMA 2014;311:692-700.
11. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, Hansen PS: Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Engl J Med 2012;367:1587-1595.
12. Sawhney N, Anousheh R, Chen WC, Narayan S, Feld GK: Five-year outcomes after segmental pulmonary vein isolation for paroxysmal atrial fibrillation. Am J Cardiol 2009;104:366-372.

13. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, Santagostino A, LiVolsi L, Pappone N, Radinovic A, Manguso F, Santinelli V: A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: The APAF Study. J Am Coll Cardiol 2006;48:2340-2347.
14. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, Macle L, Daoud EG, Calkins H, Hall B, Reddy V, Augello G, Reynolds MR, Vinekar C, Liu CY, Berry SM, Berry DA; Thermo-Cool AF Trial Investigators: Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: A randomized controlled trial. JAMA 2010;303:333-340.
15. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P, Investigators SAI: Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med 2015;372:1812-1822.
16. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M: Lone atrial fibrillation: Does it exist? J Am Coll Cardiol 2014;63:1715-1723.
17. Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS, Badger CT, McCann CJ, Akoum N, Kholmovski E, Macleod RS, Marrouche NF: Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: Implications for disease progression and response to catheter ablation. Heart Rhythm 2010;7:1475-1481.