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Predictors of Success After a First Circumferential Pulmonary Vein Isolation For Atrial Fibrillation

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Abstract

Background: To identify and characterise pre-procedural and procedural parameters which predict maintenance of sinus rhythm after a first circumferential pulmonary vein isolation (CPVI) for recurrent atrial fibrillation (AF).

Methods: 100 patients (54±10 yrs) undergoing CARTO-guided CPVI for symptomatic drug refractory, paroxysmal or shortstanding persistent AF were studied. The endpoint was complete electrical isolation within the encircled regions. 3D left atrial (LA) volume was measured by CARTO geometry. Follow-up examinations (symptoms, ECG, 24-hour ECG recording) were performed at 1 and 3 months and every 3 months thereafter.

Results: After the first CPVI, 71 patients (71%) were free of AF without antiarrhythmic drug therapy (follow up:28±11 months). The only independent and significant predictors for freedom of AF after the first CPVI were duration of AF history and 3D LA volume ($p<0.05$). However, a significant overlap in durations of AF history and 3D LA volumes between failures and successes was observed.

Conclusions: (1) Using the "circumferential pulmonary vein isolation" approach, the first catheter ablation leads to resolution of arrhythmia in ≈ 70% of symptomatic AF patients. (2) Independent predictors for freedom of AF after initial CPVI are duration of AF history and 3D LA volume. (3) Due to considerable overlap between failures and successes, these parameters can not be used to identify patients who should not undergo CPVI or in whom an additional ablation beyond CPVI is required. On the other hand, our results do suggest that an ablation strategy early in the course of AF disease can influence successful outcome.

Introduction

Since the initial identification of the left atrium/pulmonary vein (LA/PV) junction as an important site for initiation and perpetuation of atrial fibrillation (AF), a wide spectrum of catheter-based therapies for treating AF has been developed, mostly using the LA/PV junction as an endocardial RF abla-

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tion target.[1-5] Percutaneous catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement.[6] The common denominator for all procedures and prerequisite for success seems to be achieving long-term electrical isolation of the PVs.[7]

Percutaneous PV isolation (whether ostial or circumferential) is associated with good clinical outcome in 70-90% of the patients with paroxysmal or shortstanding persistent AF.[3-9] Nevertheless, identifying predictors of success is important to (1) avoid a costly, possibly dangerous procedure in patients not suited for this technique (non-responders) or to (2) apply a more complex ablation strategy (additional lines, targeting fractionated electrograms) in selected patients. Although previous studies, reporting on predictors of success after catheter ablation of AF, identified left atrial size as an independent predictor of AF recurrence after catheter ablation, only limited data are available on predictors after circumferential PV isolation (CPVI).[10-26] Moreover, in all studies left atrial size was assessed by 2D transthoracic echocardiograpy.

Therefore we aimed to investigate in a cohort of 100 patients (1) which pre-procedural and procedural characteristics are likely to influence clinical outcome after a single CPVI procedure, (2) whether 3D LA volume -assessed by CARTO geometry can predict clinical outcome after CPVI and (3) whether observed independent predictors can be used to screen out patients who should not undergo CPVI.

Materials and Methods

Patient Data

The patient population consisted of 100 consecutive patients referred for percutaneous catheter ablation of AF between July 2003 and August 2006 (Table 1). Each patient had been in follow-up for symptomatic paroxysmal (3.8±2.8 episodes per week) or shortstanding persistent AF. The duration of AF history, defined as the time since first ECG documentation of AF was 6.2±6.4 years. Pharmacological treatment with 2.6±1.0 types of class I and/or III antiarrhythmic drugs (AADs) had not been able to provide symptom control. Arterial hypertension was present in 23%, structural heart disease in 15% of the patients.

Table 1 Patient characteristics

Age (y)	54 ± 10
Male (N)	83 (83%)
AF type (N)	
Paroxysmal	80 (80%)
Persistent	20 (20%)
Duration of AF History (y)	6.2 ± 6.4
Number of AADs (N)	2.6 ± 1.0
Amiodarone (N)	42 (42%)
VKA (N)	47 (47%)
History of endurance sports (N)	10 (10%)
Arterial hypertension (N)	23 (23%)
Structural heart disease (N)	15 (15%)
Ischemic heart disease	5 (5%)
Hypertrophic cardiomyopathy	4 (4%)
Valvular heart disease	4 (4%)
Other (dilated, ethanol)	2 (2%)
3D LA volume (ml, Carto)	92±25

Legend: AF=atrial fibrillation, AADs=antiarrhythmic drugs, VKA=vitamin K antagonists, LA=left atrium

CT Acquisition

Of the 100 patients, 60 underwent an ECG-gated cardiac CT examination prior to the procedure. Equipment selection was done on the basis of availability, with a preference for a 16-slice CT (N=52, 16 slice CT, Philips Brilliance, Best; N=8, 4 slice CT, Siemens Volume Zoom, Erlangen). Depending on the equipment used, ECG gating was set up to acquire images at +75% or -35% of the RR interval, respectively. Contrast injection protocols were optimized for filling all cavities. In 11 patients, metoprolol tartrate 2.5 to 5 mg was used intravenously to slow down sinus rhythm to a target heart rate of 65 bpm.

Left atrial cavities were segmented in the Advantage Workstation software (software version AW Suite 5.5.3e, GE Medical Systems, Milwaukee, WI, USA). Left and right pulmonary veins were morphologically evaluated. Pulmonary ostium morphology was evaluated from an endocavitary point of view as described in the literature: a patient was considered to have distinct pulmonary

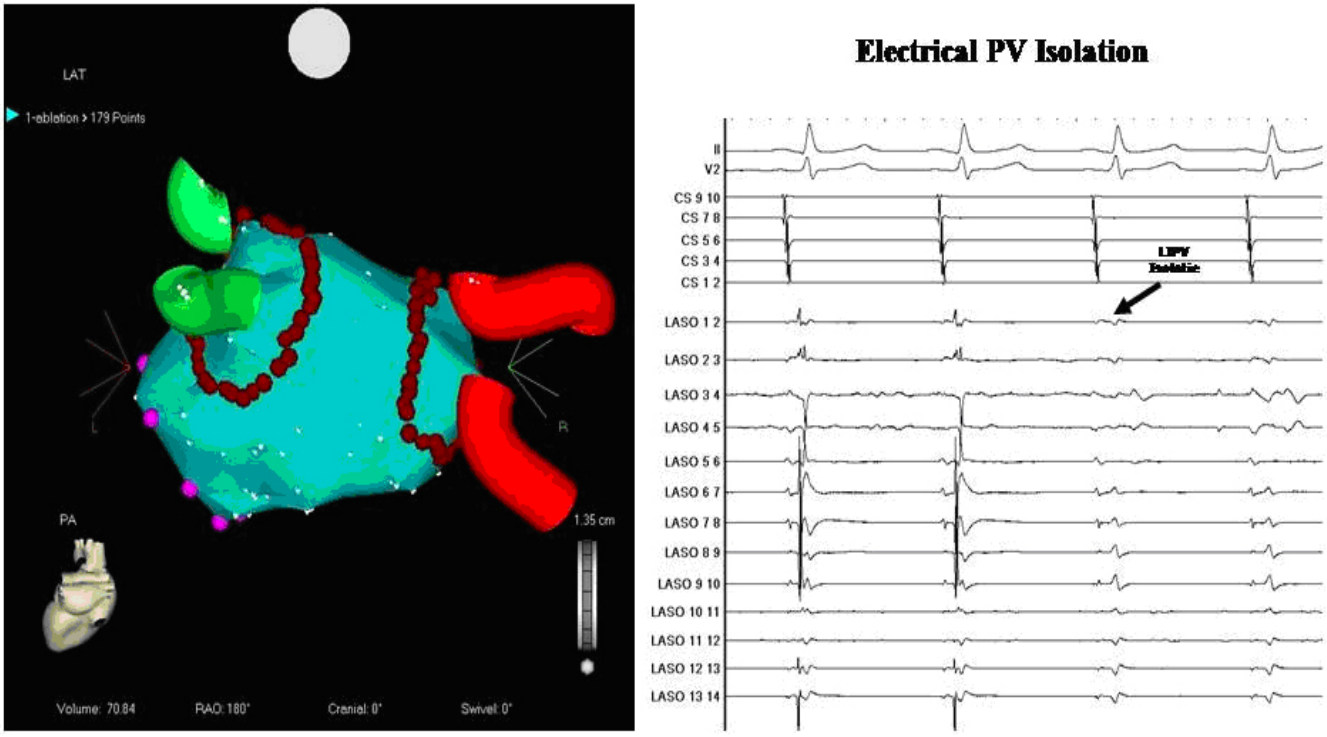
vein ostia, if the individual PVs entered the atrium at markedly different angles and did not share a common region.[27]

A detailed segmentation of left and right ventricle, left and right atrium, including pulmonary veins, aorta root, pulmonary trunk was performed before the procedure for all CT datasets using a specialised software package (CartoMerge, Biosense Webster, Diamond Bar, CA, USA).

Left Atrial Mapping Procedure

The procedure was performed under general anaesthesia using continuous propofol infusion for sedation, cisatracurium for neuromuscular blockade and remifentanil for analgesia. All patients were in sinus rhythm before and during the procedure. After obtaining vascular access, two 12 French (F) and one 6F sheath were positioned in the right and left femoral vein. A standard 6F steerable decapolar catheter (Bard Electrophysiology) was positioned in the coronary sinus. Two long vascular sheaths (SL0, St Jude Medical) were introduced, via the 12F sheaths, into the right atrium, after which a double trans-septal puncture was performed. Immediately prior to puncture an intravenous loading dose of 10.000IU heparin was given. After puncture a continuous infusion of heparin was started to maintain an activated clotting time (ACT) above 350 seconds. Via the trans-septal sheaths we introduced (1) a deflectable quadripolar 3.5-mm irrigated tip diagnostic/ablation catheter (NaviStar ThermoCool, Biosense Webster, Johnson & Johnson) and (2) a 10 to 14-pole variable loop mapping catheter. A real-time 3D electro-anatomical map of the LA, including the left atrial appendage, and mitral annulus, was constructed with the use of the non-fluoroscopic navigation system (CARTO, Biosense-Webster, Johnson&Johnson). The PV ostia were identified by fluoroscopic visualisation of the catheter tip during pullback from the PVs, confirmed by simultaneous impedance decrease and the appearance of characteristic LA potentials. In 60 patients, CartoMerge software was used to integrate a CTbased 3D LA surface reconstruction into the virtual electro-anatomical map following three steps: (1) manual alignment of both datasets "with the naked eye" to superimpose the CT image on the CARTO map, (2) automatic visual alignment using 1 landmark on the posterior left superior PVLA junction and (3) surface registration determining the optimal fit between the two

Figure 1: Left panel: Carto-guided PV encircling (PA view). Right panel: example of PV isolation recorded by circular mapping catheter



datasets by comparing average distance between all points.

Circumferential Pulmonary Vein Isolation

Radiofrequency (RF) energy was delivered in a unipolar mode from the distal electrode of the ablation catheter to a cutaneous patch. Each lesion was created with an application of 20-35W during 30 seconds, with the RF generator (Stockert, Biosense Webster, Johnson & Johnson) with a temperature limit of 48°C. During RF delivery normal saline was infused at a rate of 20 mL/min.

The septal and lateral PVs were encircled 1 to 2 cm away from the ostia (except for the ostial ridge between LSPV and left atrial appendage) by creating point-by-point lesions (Figure 1, left panel, PA view). In order with the ablation sequence, the circular mapping catheter was positioned at the ostium of the corresponding vein. PV potentials (PVPs) were identified using pacing manoeuvres at the left atrial appendage and distal coronary sinus, by observation of automaticity and by using typical electrogram morphology, as described elsewhere.[28] The end-point of ablation was complete abolishment of local PV electrograms recorded with the mapping catheter (PV isolation). A representative example of PV isolation in the LIPV is shown in Figure 1 (right panel). In case PVPs remained after anatomical encircling, ablation was applied at the circumference of the ablation circle (at "bridging" potentials), using the circular mapping catheter as a reference to identify the point of earliest breakthrough. After isolation, a waiting time of at least 30 minutes was respected for each vein.

At discharge, anti-arrhythmic drugs (sotalol 80 mg bid or flecainide 100 mg bid) were given for 3 months. Irrespective of CHADS2 risk score for stroke, oral vitamin K antagonist (VKA) therapy was given for at least 3 months with a target INR of 2-3.

Follow-up Evaluation

Each patient was scheduled for routine follow-up examination at 1 and 3 months and every 3 months thereafter. Mean follow-up duration was 28±11 months (range 15 to 59 months). At each follow-up examination, a Holter monitoring was performed. After 3 months of follow-up, anti-arrhythmic drugs were discontinued. If no pre-procedural indication for VKA existed, anticoagulation was stopped as well. CT scanning for the evaluation of PV stenosis was performed in 7 patients exhibiting shortness of breath, coughing or exercise intolerance.

A successful outcome was defined as freedom from both symptomatic and asymptomatic AF, without antiarrhythmic drug therapy, at any follow-up with a blanking period of 1 month. Early recurrence of AF was defined as any recurrence of AF that occurred within the first month after the ablation procedure.

Statistical Analysis

All continuous data are expressed as mean ± standard deviation (SD). Categorical values were compared using the chi-square and Fisher's exact test. Individual determinants of outcome were analysed with binary logistic regression, entering all theoretical explanatory variables into the model in one step. Student's t test was used to compare means of 2 normal populations. An alpha level of 0.05 was defined as the threshold for rejecting the null hypothesis. All statistical analyses were performed using the Excel software package (Microsoft, Redmond, USA) and software from the R project for statistical computing (http://www.r-project.org). Receiver operator curves were constructed using Graph Pad Prism 4.0.

Results

Patient Population

Clinical characteristics are given in Table 1. Mean 3D LA volume was 92±25 ml on the CARTO map. Based on CT data (N=60), a classical configuration of 2 right-sided pulmonary veins (RPV) was found in 46 (77%) patients and 2 left-sided pulmonary veins in 51 (85%) of patients. A right middle PV was present in 11 (18%) patients, with 4 right PVs in another 3 patients (5%). On the left, a left common PV was found in 6 patients (10%), an additional left middle vein in another 3 (5%) patients.

Mapping And Ablation Data

A 3D electro-anatomical map of the LA was created in 30±12 minutes with an average of 139±32 points. CartoMerge segmentation of all relevant thoracic cavities could be achieved in 12±8 minutes. Registration of the CT dataset with the electrophysiological map was accomplished in all patients. The average point-to-point distance between CARTO and CT surface reconstructions was 2.8±0.6 mm with an average standard deviation of 2.2±0.7 mm.

The average time required for CPVI was 4.4±0.9 hours with a mean fluoroscopy time of 29±16 minutes (radiation dose 136±90 centiGray per cm2). After 115±27 RF applications (RF time 53±10min), electrical isolation was achieved in 384 out of 387 separate PVs (99.2%). Isolation of all PVs could be obtained in 97 out of 100 patients (97%). A significant ablation-induced vagal reflex (defined as sinus bradycardia < 40 bpm, AV block, asystole or hypotension), was observed in 14 patients (14%), preferentially during RF delivery at the left posterior LA-PV junction. Hemodynamically significant pericardial effusion requiring pericardiocentesis developed in 3 patients (3%). We observed one transient thromboembolic stroke.

Clinical Outcome And Predictors Of Success

After the first CPVI, 71 patients (71%) were free of AF without antiarrhythmic drugs. In the group with recurring AF, 5 patients were asymptomatic. An early recurrence of AF (after 12±8 days) was observed in 25 patients (25%). In table 2 pre-procedural and procedural parameters are compared between patients with a successful and failed first ablation. Age, sex, clinical type of AF, arterial hypertension, structural heart disease or history of endurance sport did not differ between groups. No particular anatomy on CT or the use of CT itself

Figure 2: Duration of AF history and 3D LA volume (Carto) compared between failed and successful CPVI procedures. $p < 0.05$ for both comparisons

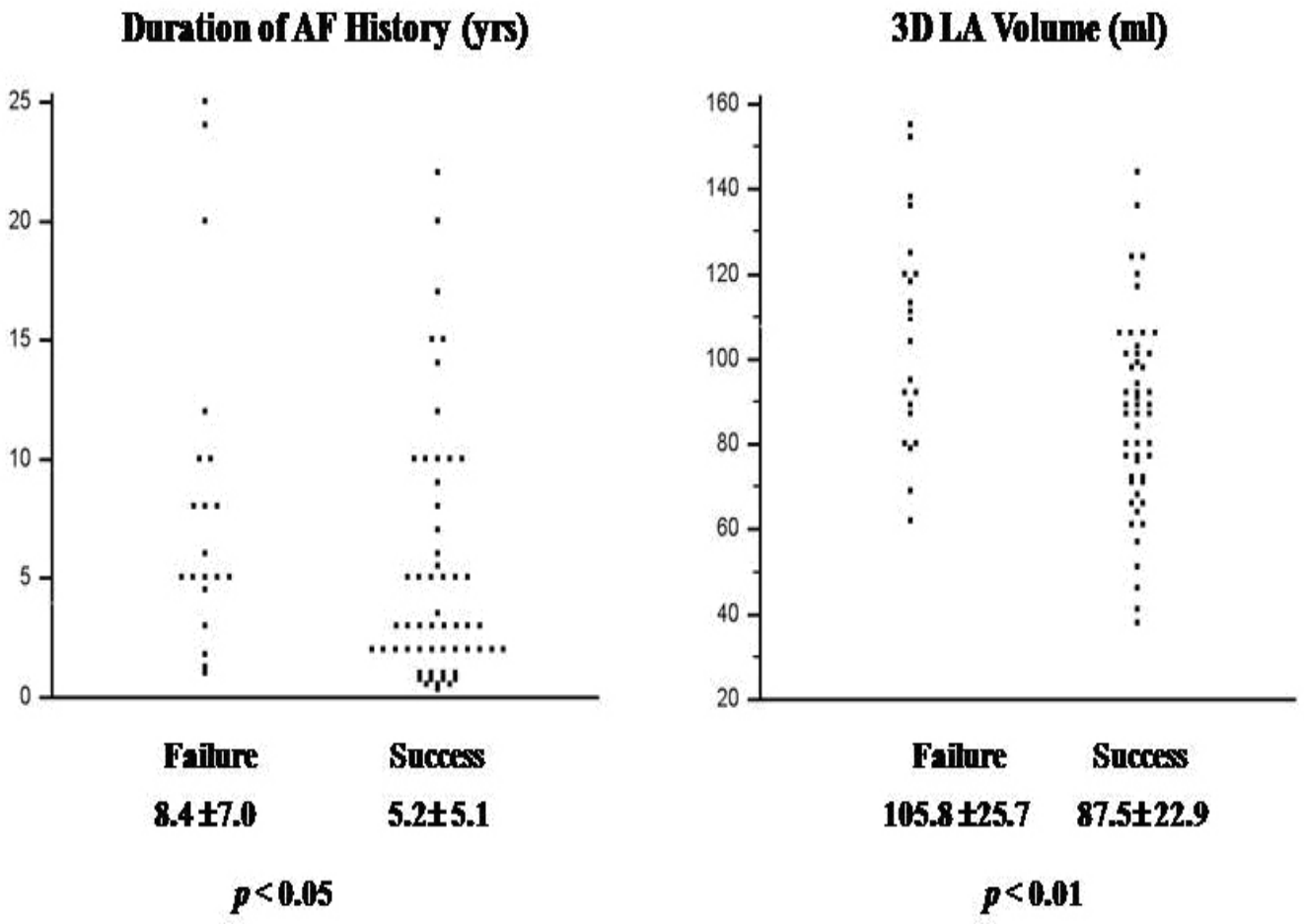
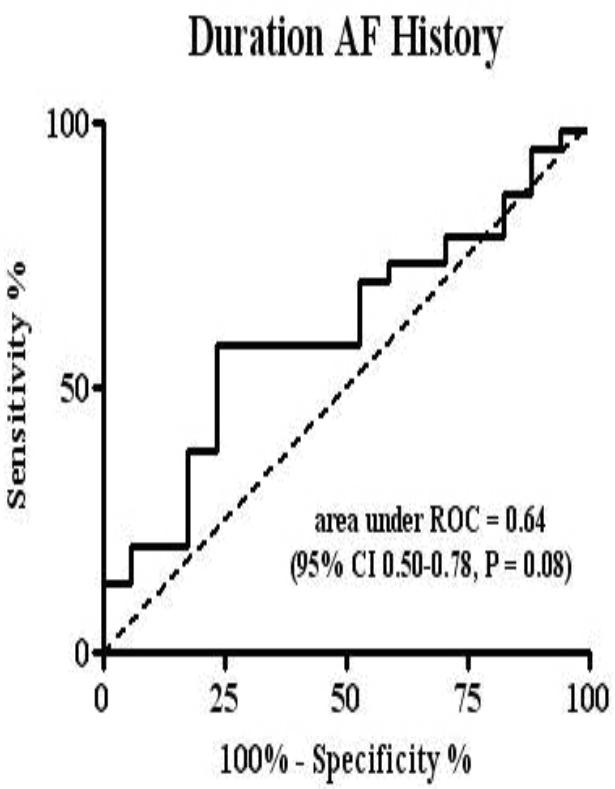
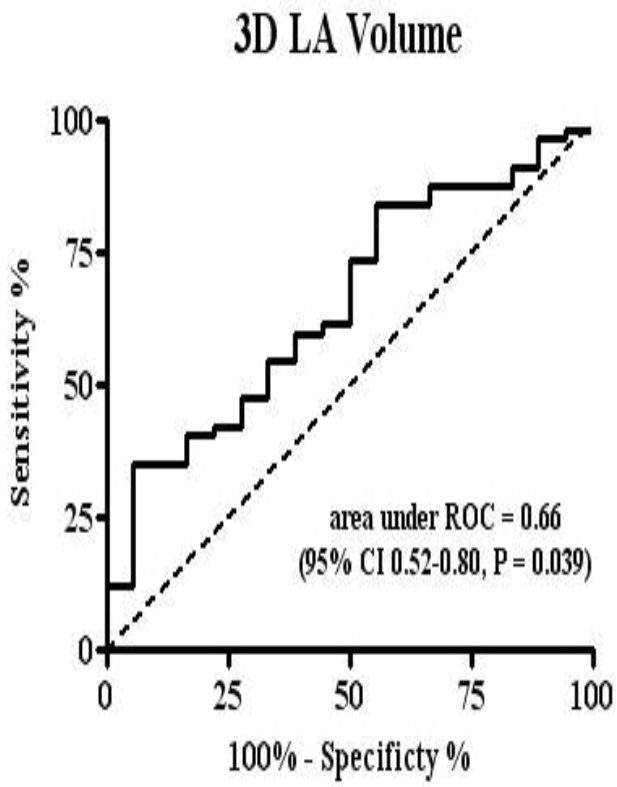


Figure 3: ROC-curves for duration of AF history and LA volume suggesting a low overall diagnostic accuracy of these predictors





was predictive for clinical outcome after CPVI.

Early recurrence of AF was also not predictive for clinical outcome (17 out of 25 patients with early recurrence were free of AF, 68%). The number of RF applications was not significantly different between the successful and failed ablation group either. The occurrence of an ablation-induced vagal reflex was equal in both groups (14% in both groups). In contrast, duration of AF history was significantly less in the successful group (8.4±7.0y versus 5.2±5.1y, p<0.05, Table 2). Similarly, 3D LA volume was significantly smaller in the successful group (105.8±25.7ml versus 87.5±22.9ml, p<0.05). Binary logistic regression analysis, showed that duration of AF history and 3D LA volume were significant and independent predictors of a successful outcome (Table 3). However, as plotted in Figure 2, there is a marked overlap in the durations of AF history and 3D LA volumes between failures and successes. In Figure 3, the ROC curves for the duration of AF history and 3D LA volume are plotted. Clearly both curves approach the line of identity with an area under curve of respec-

Table 2 Univariate comparison between successful and failed ablation

	Success (N=71)	Failure (N=29)	p
Age (y)	54.9 ± 9.7	53.5 ± 9.8	0.54
Male (N)	59 (83%)	24 (83%)	0.8
Paroxysmal (N)	58 (82%)	22 (76%)	0.7
AHT (N)	16 (26%)	7 (24%)	0.93
SHD (N)	12 (17%)	4 (14%)	0.93
History of Endurance sports	9 (13%)	2 (7%)	0.63
Duration AF History (y)	5.2 ± 5.1	8.4 ± 7.0	0.03
3D LA volume (ml, Carto)	87.5 ± 22.9	105.8 ± 25.7	0.003

Legend: AHT=arterial hypertension, SHD=structural heart disease

Table 3 Logistic regression analysis results, predictors of successful outcome

	Odds ratio	95% Confidence intervals	p
Duration of AF History	0.90	0.81-0.99	< 0.05
3D LA volume (ml,Carto)	0.97	0.94-0.99	< 0.05

tively 0.64 and 0.66 suggesting a low overall diagnostic accuracy of these tests. Data on sensitivity, specificity, positive predictive value and negative predictive value for different cut off values are given in table 4. When the duration of AF history is very short (one year or shorter), CPVI will result in maintenance of normal sinus rhythm during follow up in 92% of the cases (positive predictive value). However, if ablation would only be considered in this subgroup of patients only 20% of the patients with a potentially successful outcome would be treated (sensitivity). Data on 3D left atrial volume are similar: the chance of a successful outcome after CPVI in the presence of a small atrium (80 ml or less) are high (positive predictive value 88%) but this represents only a minority of patients that can potentially be ablated with success (sensitivity 39%). Overall, the negative predictive value of the duration of AF history or 3D LA volume is low (26% to 33%).

Discussion

Main Findings

Using the "circumferential pulmonary vein isolation" approach, the first catheter ablation leads to resolution of arrhythmia in almost 70% of symptomatic AF patients with an acceptable risk of complications. Duration of AF history and 3D LA volume are the only independent predictors for freedom of AF after the first CPVI, but a significant overlap between failures and successes is observed.

Predictors Of Clinical Outcome After Catheter Ablation Of AF

Previous studies on clinical and procedural predictors for successful ablation of AF (either segmental PV isolation, circumferential PV ablation or circumferential PV isolation) show varying results.[10-26] In Table 4 we listed all studies identified by comprehensive MedLine search for peer-reviewed English original papers published over the last five years reporting on independent predictors of recurrence of AF after catheter ablation. As in our study, age and gender do not influence outcome after catheter ablation of AF, irrespective of the chosen approach. This is in agreement with recent reports on good clinical outcome after catheter ablation of AF in septuagenarians.[29] The presence of short standing persistent AF (in stead of paroxysmal AF) seems not to be a predictor of failure if circumferential PV ablation or isolation is chosen as ablation strategy. In these patients however segmental ostial catheter ablation seems to be less effective when compared to the results of this technique in paroxysmal AF. The presence of arterial hypertension or limited structural heart disease does not influence clinical outcome.

In contrast to our observations, duration of AF history was not a consistent predictor of AF recurrence in other studies. This discrepancy could be explained by the wide range (0.5 to 30 years) in duration of AF history in our study. In six studies, LA size (assessed by 2D transthoracic echocardiography) was a consistent independent predictor of AF recurrence after catheter ablation, irrespective of the chosen strategy.[3, 8, 21, 22, 6] These observations are confirmed by our study in which 3D LA volume measured by CARTO geometry, was an independent predictor of recurrence after a first CPVI approach.

The influence of the duration of AF history and 3D LA volume on AF recurrence are in line with results in a AF surgery. Grubitzsch et al reported that AF duration and LA diameter were the only independent predictors of sinus rhythm after ablation of AF in valvular heart surgery independent of the type of valve disease.[30] Likewise, LA size and duration of AF history have also been shown to predict recurrence of AF after electrical cardioversion of AF. Probably both parameters reflect a higher degree of atrial remodeling either due to AF per se (AF-induced remodeling) or progression of underlying structural heart disease. Atrial

Table 4 Sensitivity, specificity and predictive values for different cut-off values

	Sens	Spec	PPV	NPV
Duration AF Hx ≤ 1yr	20%	94%	92%	30%
Duration AF Hx ≤ 4yrs	56%	76%	89%	33%
Duration AF Hx ≤ 8yrs	77%	29%	79%	26%
LA volume ≤ 80ml	39%	83%	88%	30%
LA volume ≤ 100ml	66%	50%	80%	32%
LA volume ≤ 120ml	89%	16%	77%	33%

Legend: Hx= history, Sens= sensitivity, Spec= specificity, PPV = positive predictive value, NPV negative predictive value

remodeling promotes perpetuation of the arrhythmia and increases the likelihood of recurrence by electrical, contractile and structural changes.[31] More specifically, Sanders et al showed that atrial remodelling shifts the driver away from the PV regions resulting in non-PV mediated AF.[32, 33] As such, percutaneous ablation targeting only the LA/PV region might be insufficient. On the other hand it is possible that the likelehood of reconnection after successful PV isolation is higher in enlarged atria. Data by Sauer et al showed that acute reconnection during an ablation procedure was more likely to occur in larger left atria.[18]

Clinical Implications

Due to considerable overlap between durations of AF history and 3D LA volumes between failures and successes, these parameters can not be used to screen out patients who should not undergo CPVI. Furthermore ROC curves for these two parameters clearly illustrate that no cut-off point with acceptable sensitivity and specificity can be set for any of the two parameters that would identify a subgroup of patients that can be ablated successfully. However, it is clear that patients with a short AF history duration and small 3D LA volume have a high likelihood of success after a single CPVI with no need for any additional ablation targets (AF duration ≤1 years, 92% sinus rhythm during follow up; LA volume ≤ 80 ml, 88% sinus rhythm during follow-up). Of course, this would be applicable to only a minority of patients presenting with AF (20% and 39% respectively). On the other hand our results do support the concept of an early ablation strategy in the course of paroxysmal or short standing persistent AF. This approach is already incorporated in the recent guidelines on the management of AF stating that catheter ablation is an accepted alternative treatment strategy after failure of one single antiarrhythmic drug. Changing to a second anti-arrhythmic drug strategy offers limited benefit and might result in delayed catheter-based intervention.

Furthermore our data imply that, in the presence of enlarged atria or long-lasting AF history, ablation targeting the LA/PV region might not be enough to achieve long-term cure. As such the physician can opt either to avoid possibly hazardous ablation or to perform a more complex ablation (additional linear lesions, fractionated electrograms, non-PV foci). Our data also imply that the decision to extend the procedure can be based upon CARTO guided calculation of 3D LA volume at the beginning of the procedure.

Limitations

The main limitation of our study is that we conducted an observational, albeit prospective investigation. Another limitation is the absence of stringent arrhythmia monitoring after ablation (transtelephonic monitoring, implantable loop recorders). As such patients with asymptomatic recurrences of AF could be miscategorized as being successfully ablated. Finally, not all potential predictors of recurrences of AF were analysed. However, we focused on clinical and periprocedural parameters that can easily be obtained in all patients.

Conclusion

A single circumferential pulmonary vein isolation results in resolution of arrhythmia in ≈70% of patients with paroxysmal or short standing persistent symptomatic AF. Duration of AF history and 3D LA volume are independent predictors of successful outcome but due to considerable overlap between failures and successes, these parameters can not be used to identify patients who should not undergo CPVI or in whom an additional ablation beyond CPVI is required. Our results suggest that an ablation strategy early in the course of AF disease can influence successful outcome.

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