Pulmonary vein isolation of symptomatic refractory paroxysmal and persistent atrial fibrillation

A single centre and single operator experience in the Netherlands

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Aim. To investigate long-term outcome and to determine predictors of successful pulmonary vein isolation (PVI) in patients with symptomatic paroxysmal or persistent atrial fibrillation (AF) who are refractory or intolerant to antiarrhythmic drugs.

Background. The treatment of AF has traditionally been pharmacological aimed at rate or rhythm control. However, rhythm control remains difficult to establish. PVI is reported to be effective in selected patient groups.

Methods. Ninety-nine consecutive patients with a mean age of 54 ± 10 years who had paroxysmal or persistent AF were treated in the University Medical Center Groningen. All patients underwent PVI by the same electrophysiologist. Successful PVI was defined as absence of AF on Holter or electrocardiogram (ECG), and no symptoms of AF.

Results. After six months of follow-up, 60 (61%) patients were free of AF episodes, both on 96-hour Holter monitoring and on ECGs, and had no

symptoms related to AF. Thirty-nine of these 60 patients (65%) were no longer treated with any class I or III antiarrhythmic drugs. Independent determinants of successful PVI were paroxysmal AF (OR 18 [3.5-93], $p=0.001$), and left pulmonary vein ablation time >55 minutes (OR 15 [2.7-81], $p=0.002$). Left atrial (parasternal view 42 ± 6 vs. 40 ± 5 mm, $p<0.05$ and apical view 61 ± 9 vs. 58 ± 8 mm, $p<0.05$) and right atrial (59 ± 7 vs. 56 ± 5 mm, $p<0.05$) sizes decreased significantly in the successfully treated patients after six months of follow-up.

Conclusion. Independent determinants of a successful outcome after PVI are paroxysmal AF and a longer left atrial ablation time. (Neth Heart J 2009;17:366-72.)

Keywords: atrial fibrillation, pulmonary vein isolation, outcome

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Although large randomised controlled trials have shown that rate-control therapy is not inferior to rhythm-control therapy, rhythm control is indicated in specific patient populations.^{1,2} One of the main reasons for adopting rhythm control is symptoms caused by atrial fibrillation (AF), and subsequently a low quality of life.³ However, pharmacological rhythm-control therapy is only effective in maintaining sinus rhythm in 40% of all patients.⁴ Adverse effects of antiarrhythmic drugs are another important disadvantage.⁵ Nowadays, left atrial catheter ablation is widely used to prevent recurrences of AF. Pulmonary vein isolation (PVI) alone may exert its beneficial effects by eliminating triggers of AF, autonomic denervation of the left atrium, and eliminating part of the arrhythmogenic substrate. Additional linear ablation lines, e.g. at the left atrial roof and mitral isthmus, may abolish more substrate. PVI is reported to be effective in 60 to 85% of the patients, especially in patients with paroxysmal

short lasting episodes of AF.⁶⁻⁹ In about one third of the patients a second ablation procedure is necessary. The results reported in the journals are those achieved in high-volume centres in the USA, France, Italy and Germany performing different types of ablation procedures, with or without additional ablation lines.

The purpose of this prospective observational study was (1) to describe the success of PVI in a single operator referral centre in the Netherlands, (2) to determine predictors of success, (3) to determine beneficial changes of atrial sizes and ventricular function, and (4) to assess periprocedural complications.

Methods

Patient population

The present patient population consists of 99 consecutive patients with AF. All patients underwent PVI at the University Medical Center Groningen, Groningen, the Netherlands, in the period between March 2003 and June 2007. Patients were eligible for PVI if they met the following criteria: severely symptomatic paroxysmal or persistent AF despite the use of at least two antiarrhythmic drugs, or severe adverse events on rhythm-control drugs. Exclusion criteria were significant underlying heart diseases and age <18 years or >75 years. Hypertensive patients were not excluded if the blood pressure was under control.

Study design and follow-up

Patients were admitted to the hospital one to two days before the ablation. Oral anticoagulation was discontinued two days before the procedure and replaced by full-dose low-molecular-weight heparin. At admission, a transoesophageal echocardiography to exclude thrombi or spontaneous contrast in the atria, and an electronic beam tomography (EBT) or computed tomography (CT) to depict the left atrium and the pulmonary veins were performed. The EBT or CT scan was used during the procedure. Ablation was performed either during AF or sinus rhythm. Post ablation heart rhythm was monitored with 48-hour Holter registration. Antiarrhythmic drugs were continued for at least two months. No electrical cardioversions were performed directly post-pulmonary vein isolation. Oral anticoagulation was restarted after the procedure. Low-molecular-weight heparin was discontinued when an international normalised ratio (INR) >2.5 was achieved. Complications, i.e. haematoma, fistula, pericardial effusion, cardiac tamponade, pulmonary vein stenosis and thromboembolic complications, were carefully monitored. When no complications occurred, the patient was discharged from hospital after two days. At two and six months after discharge the patients were seen at the outpatient department. At each visit, any cardiovascular events were recorded, and a 12-lead ECG, transthoracic echocardiography, and 48-hour (at six-month visit a 96-hour) Holter registration were obtained. At the

six-month visit an EBT or CT scan was performed to assess pulmonary vein stenosis. When sinus rhythm was maintained for more than two months, the dose of antiarrhythmic drugs was lowered and eventually discontinued. Oral anticoagulant therapy was continued for at least six months.

Procedure of pulmonary vein isolation

All patients underwent circumferential PVI as described by Pappone¹⁰ by the same electrophysiologist. Catheters were introduced percutaneously in the right femoral artery and vein using the Seldinger technique. One decapolar catheter (Cordis-Webster, Miami, FL, USA) with 5-mm electrodes and 2-mm interelectrode spacing was placed in the coronary sinus. Using a long introducer sheath (Bard Channel, Lowell, MA, USA) and a transseptal needle (Bard, Lowell, MA, USA), one transseptal puncture was made, through which the ablation catheter was advanced to the left atrium. A bolus of unfractionated heparin was administered after the first transseptal puncture and subsequently an additional bolus of heparin after two hours. Coronary sinus stimulation was performed with cycle lengths of 700 ms during ablation, both in sinus rhythm and in AF. The left atrium was mapped and the pulmonary veins were reconstructed using CARTO[®] (Biosense-Webster, Diamond Bar, CA, USA). Then the CARTO[®] left atrium map was aligned to the EBT or CT scan reconstruction of the left atrium.

Endpoints

Primary endpoint was success of PVI after six months of follow-up. Success was defined as absence of AF, i.e. no evidence of AF, atrial flutter, or supraventricular arrhythmias on Holter monitoring or electrocardiogram >30 seconds, and no symptoms of AF. Secondary endpoints were changes in echocardiographic parameters and procedural complications (e.g. pulmonary vein stenosis, pericardial effusion, tamponade, transient ischaemic attack, stroke, bleeding, and oesophagus perforation). Two independent observers adjudicated success of PVI.

Statistical analysis

Descriptive statistics are presented as the mean $\pm$ standard deviation (SD) or median (range) for continuous variables and counts with percentages for categorical variables. In case of normally distributed variables the Student's t test and otherwise the Mann-Whitney U test was used. Paired t tests were used for comparison of the study population at different follow-up times. Multivariate stepwise logistic regression analyses were performed to determine predictors of maintenance of sinus rhythm during follow-up. Continuous variables were categorised on the median value. All univariate predictors with $p < 0.1$ were tested in a multivariate model. In the multivariate model a variable was excluded when $p \geq 0.05$. First-line interactions were investigated. All p values were two-sided,

Table 1. Baseline characteristics of the patients.

Patient characteristics	Total (n=99)	Success (n=60)	Failure (n=39)	P value
Gender (male)	80 (81)	49 (82)	31 (80)	0.79
Age (years)	54±10	53±10	54±10	0.61
Paroxysmal/ persistent AF	57 (58)/ 42 (42)	43 (72)/ 17 (28)	14 (36)/ 25 (64)	<0.001
Total AF duration (days)	2.300 (392-7.094)	2.247 (392-5.914)	2.352 (582-7.094)	0.94
No. of prior cardioversions	1 (0-20)	1 (0-14)	1 (0-20)	0.45
Symptoms				
- Palpitations	90 (91)	52 (87)	38 (97)	0.08
- Dyspnoea	39 (39)	22 (37)	17 (44)	0.53
- Fatigue	48 (48)	26 (43)	22 (56)	0.22
- Chest pain	29 (29)	15 (25)	14 (36)	0.27
- Dizziness	20 (20)	10 (17)	10 (26)	0.31
History of hypertension	55 (56)	33 (55)	22 (56)	0.81
Coronary artery disease	1 (1)	1 (1)	0 (0)	1.00
Cardiomyopathy	10 (10)	3 (5)	7 (18)	0.05
Significant valve disease (mitral regurgitation)	1 (1)	1 (1)	0 (0)	1.00
History of respiratory disease	9 (9)	5 (8)	4 (10)	0.74
Diabetes mellitus	1 (1)	1 (2)	0 (0)	1.00
Lone AF	24 (24)	16 (27)	8 (21)	0.63
BMI	29±5	29±5	28±5	0.41
Blood pressure (mmHg)				
- Systolic	130±16	129±17	131±16	0.59
- Diastolic	80±10	79±10	82±10	0.12
Echocardiographic measurements				
- Size of left atrium, long axis (mm)	42±6	42±6	41±7	0.84
- Size of left atrium, apical view (mm)	61±9	61±9	61±9	0.97
- Size of right atrium, apical view (mm)	58±7	59±7	56±7	0.07
- LVEDD (mm)	50±5	50±5	50±5	0.43
- LVESD (mm)	33±7	33±8	34±5	0.87
- Septal thickness (mm)	10±2	10±2	10±3	0.76
- Posterior wall thickness (mm)	10±1	10±1	9±1	0.10
- Fractional shortening (%)	34±10	34±11	33±7	0.40
Medication at screening				
- Coumarin	92 (93)	55 (92)	37 (95)	0.70
- Ascal	4 (4)	2 (3)	2 (5)	0.65
- Amiodarone	27 (27)	16 (27)	11 (28)	1.00
- Disopyramide	3 (3)	3 (5)	0 (0)	0.28
- Class 1C (Flecainide, Propafenone)	34 (34)	22 (37)	12 (31)	0.25
- Sotalol	12 (12)	6 (10)	6 (15)	0.53
- Beta blocker	49 (49)	31 (52)	18 (46)	0.68
- Diuretics	11 (11)	6 (10)	5 (13)	0.75
- ACE inhibitor or ARB	32 (32)	17 (28)	15 (39)	0.43
- Digoxin	4 (4)	2 (3)	2 (5)	0.65
- Verapamil or diltiazem	21 (21)	13 (22)	8 (20)	1.00
No. of previous antiarrhythmic drugs	1.±1.1	1.±1.1	1.±0.8	0.07
Rhythm baseline electrocardiogram				
- Sinus rhythm	78 (78)	47 (78)	31 (80)	1.00
- Atrial fibrillation	21 (22)	13 (22)	8 (20)	0.74

AF=atrial fibrillation, BMI=body mass index, LVEDD=left ventricular end-diastolic diameter, LVESD=left ventricular end-systolic diameter, ACE=angiotensin-converting enzyme, ARB=angiotensin receptor blocker, MI=myocardial infarction. Percentages shown in brackets.

Table 2. Procedure.

	Total	Success	Failure	P value
Septum puncture time (min)	20 (1-75)	21 (1-75)	15 (3-40)	0.12
Puncture radiation dose (cGycm2)	1993 (106-10,926)	1882 (142-10,926)	2236 (106-9744)	0.72
Mapping time (min)	37 (16-129)	38 (19-80)	31 (16-129)	0.21
Mapping dose (cGycm2)	1156 (8-6385)	1082 (145-6385)	1180 (8-3409)	0.74
Ablation time left PV (min)	55 (9-123)	61 (9-123)	45 (15-70)	0.001
Ablation dose left PV (Gycm2)	241 (4-2611)	258 (4-2611)	220 (54-2093)	0.84
Ablation time right PV (min)	54 (22-165)	54 (30-165)	53 (22-106)	0.72
Ablation dose right PV (cGycm2)	392 (32-3347)	358 (32-3347)	441 (75-2252)	0.21
Control ablation time (min)	20 (2-78)	20 (2-78)	27 (2-50)	0.62
Control ablation dose (cGycm2)	76 (1-1126)	79 (1-1126)	55 (5-725)	0.97
Total procedure time (min)	188 (100-294)	198 (112-294)	167 (100-262)	0.01
Total radiation dose (cGycm2)	4549 (943-15,743)	4431 (781-15,743)	5352 (943-13,068)	0.89
Complete conduction block after ablation	88/99 (90%)	58/60 (97%)	31/39 (80%)	0.01

PV=pulmonary vein.

and a p value <0.05 was considered statistically significant. Data analyses were performed using the Statistical Package for the Social Sciences 16.0 (SPSS 16.0).

Results

Patient characteristics

A total of 99 patients who underwent PVI were included (table 1). Mean age was 54 ± 10 years and 81% were male. Paroxysmal AF patients had a mean of 4.4 episodes per week with a mean duration of six hours. Hypertension was present in the majority of patients. Median history of AF was long (7.0 [1.0-36.4] years).

Outcome

A total of 146 procedures were performed in 99 patients. Of the 146 procedures, 47 (32%) were re-procedures. A total of 35 patients underwent one re-ablation, six patients underwent two re-ablations. The mean procedure time was 188 (100 to 294) minutes and the median radiation dose administered was 4549 (943 to 15,743) cGycm2 (table 2). In five of the 41 re-ablations a cavotricuspid ablation was also performed for ablation of a typical atrial flutter. In the successfully treated patients ablation time of the left pulmonary veins and total procedure time was longer, and complete conduction block after ablation was significantly more often present (table 2).

After six months of follow-up, 60 (61%) patients were free of AF episodes, both on 96-Holter monitoring and on ECGs, and had no symptoms related to AF. Of these 60 patients, 39 (65%) were no longer treated with a class I or III antiarrhythmic drugs. Figure 1 shows that the success of the procedure fluctuates between 60 to 70%.

Figure 1. Success and failure in paroxysmal and persistent AF during 2003-2007.

Independent determinants

Univariate analyses revealed that paroxysmal AF, ablation time of the left pulmonary vein (PV), cardiomyopathy, and palpitations had a relation with a successful outcome ($p < 0.1$). Baseline atrial sizes were not a determinant of success. The multivariate regression analyses revealed that paroxysmal AF and longer atrial ablation time of the left PV were independent predictors of a successful ablation for the total group (table 3).

Table 3. Independent determinants of successful pulmonary vein isolation.

	Univariate OR (95% CI)	Multivariate OR (95% CI)	P value
Paroxysmal AF	4.5 (1.9-10.7)	18 (3.5-93)	0.001
Ablation time left PV >55 min	5.0 (1.6-16)	15 (2.7-81)	0.002
Cardiomyopathy	4.2 (1.0-17.2)		
Palpitations	5.8 (0.7-48)		

AF=atrial fibrillation, CI=confidence interval, LA=left atrium, OR=odds ratio.

Follow-up

Left ventricular function was normal at baseline and did not change during follow-up (table 4). Significant decreases in atrial sizes were observed in the successfully treated patients (table 4). Holter monitoring revealed absence of AF after six months of follow-up in the success group (table 5).

Complications

Complications occurred in two of the 146 procedures (1.3%). In one patient pericardial effusion was complicated by a heart tamponade, which recovered after drainage. One patient had a stroke two weeks after the procedure. In four cases, pericardial effusion was suspected but on follow-up echocardiogram no effusion was found.

Discussion

The study shows that in a moderate volume referral centre, PVI can be effectively and safely performed.

PVI alone was more effective in patients with paroxysmal instead of persistent AF. Furthermore, a longer ablation time of the left PV was associated with a higher success rate.

Success of ablation

Success of PVI in our study was determined by type of AF and time of ablation. Paroxysmal AF and a shorter duration of AF are well-known parameters related to success of this strategy.⁶⁻⁹ In addition, we observed that a longer ablation time of the left PV determined outcome. This may be explained by several factors. First, a longer ablation time may increase the induction of continuous and transmural lesions required for success of the procedure. Comparably, Beukema et al. observed that patients with a successful outcome of PVI at long-term follow-up had higher troponin T plasma levels, compared to patients who remained in AF at long-term follow-up.¹¹ Second, it may relate to difficulties to transmurally ablate the left lateral

Table 4. Echocardiographic measurements.

	Baseline	2 Months	6 Months
Size of LA, long axis (mm)			
- Success	42±6	41±5	40±5*
- Failure	41±7	41±4	39±3
Size of LA, apical view (mm)			
- Success	61±9	60±8	58±8*
- Failure	61±9	62±8	60±5
Size of RA, apical view (mm)			
- Success	59±7	58±6	56±5*
- Failure	56±7	58±5	58±5
LVEDD (mm)			
- Success	50±5	50±5	50±5
- Failure	50±5	50±6	48±8
LVESD (mm)			
- Success	33±8	32±5	32±5
- Failure	34±5	32±7	32±5
Fractional shortening (%)			
- Success	34±11	37±8	37±7
- Failure	33±7	36±7	33±10

LA=left atrium, RA=right atrium, LVEDD=left ventricular end-diastolic diameter, LVESD= left ventricular end-systolic diameter *p <0.05 compared with baseline score.

Table 5. Holter measurements.

	Baseline	2 Months	6 Months
Sinus rhythm			
- Success	46 (79)	50 (94)	46 (100)
- Failure	30 (81)	19 (73)	14 (78)*
Atrial flutter			
- Success	5 (9)	- (0)	- (0)
- Failure	3 (8)	5 (19)*	2 (11)*
Atrial fibrillation			
- Success	7 (12)	3 (6)	- (0)
- Failure	4 (11)	2 (8)	2 (11)

*p<0.05 success group compared with the failure group at different time points. Percentages shown in brackets.

ridge between the orifices of the left pulmonary veins and the left atrial appendage, which is often challenging.¹² Transmural lesions can only be achieved at that location after long and extensive ablation, explaining the beneficial effects of longer left atrial ablation times. In the present study, baseline atrial diameters did not predict success. This is in contrast to other studies.¹³ This may relate to the number of patients included in the present study or the selection of patients. Baseline left atrial diameter was only modestly enlarged.

We report a success percentage of 60%. This is slightly lower than what is reported in the literature. A learning curve of the operator can explain this but also the fact that almost half of our patients had persistent AF. Success of PVI alone for ablation of persistent AF is lower compared with success rates observed in paroxysmal AF patients. Success rates of 21 and 45% in patients with persistent AF treated with PVI alone have been reported.¹⁴⁻¹⁶ Additional ablation lines and/or ablating complex potentials in addition to PVI critically increases the success rate in these patients.¹⁶ This emphasises that the type of AF is important in selecting patients for non-pharmacological rhythm-control therapy.

Atrial sizes post-pulmonary vein isolation

In accordance with prior ablation studies, atrial sizes significantly decreased in the successfully treated patients.^{11,17} Previous studies in patients who underwent serial electrical cardioversions and initiation of antiarrhythmic drugs also showed that maintenance of sinus rhythm reverted atrial enlargement.¹⁸ This is an essential finding as left atrial size is a powerful predictor of adverse events including mortality in patients with cardiovascular diseases.^{19,20} None of the rate- versus rhythm-control trials so far have shown a beneficial effect of rhythm control with regard to cardiovascular morbidity and mortality. All these studies, however, were hampered by low rates of long-term maintenance of sinus rhythm.^{1,2,21} Possibly, the

recently started ablation versus drug therapy for AF study (Cabana, ClinicalTrials.gov number NCT 00578617) may alter this consensus.

Role of atrial ablation for prevention of atrial fibrillation

Our report shows that PV is effective in curing patients with paroxysmal AF. There are more data on single-centre experiences, reporting similar findings about success and feasibility.²²

The Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) expert consensus statement on catheter and surgical ablation of AF states that when a patient fails on at least one antiarrhythmic drug, there is an indication for PVI.²³ This implies that PVI will become the therapy of choice in a larger group of patients and will result in more pulmonary vein ablations in the near future.

In the Netherlands, long waiting lists hamper early treatment of AF patients eligible for this therapeutic strategy. The long waiting list in part relates to the few electrophysiologists experienced in performing these procedures. Certainly, improvement of techniques and training will reduce procedure times and increase the number of patients that can be treated. Nevertheless, selection of patients who may benefit most from the ablation procedure is of crucial importance. At present, patients with paroxysmal AF, a shorter duration of AF and without a significant left atrial size enlargement seem to be the best candidates for PVI.^{13,16,23}

Limitations

In comparison with our colleagues in the USA, France, Germany and Italy, the population studied was smaller, 99 patients, and the time of ablation longer, reflecting less experience in performing PVI. Furthermore, half of the patient population suffered from persistent AF. PVI alone seems less effective for these patients.

Conclusion

Independent determinants of a successful outcome of PVI are paroxysmal AF and a longer ablation time. ■

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