Electrical isolation of pulmonary veins using cryothermal energy: study design and initial results

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Background. **Atrial fibrillation (AF) is the most frequently encountered arrhythmia. Radiofrequency pulmonary vein (PV) ablation is promising for symptomatic paroxysmal AF, but is associated with a significant risk of PV stenosis.**
Objectives. **To assess the efficacy of cryothermal PV ablation and the incidence of PV stenosis.**
Methods. **Highly symptomatic patients with paroxysmal or persistent AF were eligible for cryothermal ablation. Multislice spiral CT scans were performed before, and three months after ablation. AF burden was assessed using transtelephonic ECG recording and by telephonic enquiry.**
Results. **An attempt was made to isolate 27 PVs in 15 patients. In total, 20 PVs could be isolated (74% acute success). No significant difference in PV diameter was seen before and after ablation. Five out of 12 patients with paroxysmal AF were completely without AF after one ablation procedure. An additional two patients reported a significant reduction in symptoms. In the three patients with persistent AF no improvement was reported.**
Conclusion. **Cryothermal PV ablation was effective in isolation of the targeted PVs. It appears to be safe, as no PV stenosis was seen in this study three months after the ablation. Taking into account a learning curve, we consider the clinical results to be very promising. (*Neth Heart J* 2003;11:341-6.)**

Key words: atrial fibrillation, cryo-thermal ablation, pulmonary veins, stenosis

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Atrial fibrillation (AF) is the most frequently encountered sustained arrhythmia in clinical practice. The pulmonary veins are an important source of ectopic beats, which appear to be the main initiator of paroxysms of atrial fibrillation.[1] The myocardial architecture (arrangement of myocardial cells, fibrosis) in normal pulmonary veins is highly variable and responsible for non-uniform anisotropic properties.[2] Successful surgical treatment of AF always includes isolation of the pulmonary veins.[3,4] Empiric catheter-based pulmonary vein (PV) isolation appears to be a promising approach for maintaining sinus rhythm in patients with paroxysmal AF.[5,6] However, the procedure is associated with a significant risk (4 to 8.9% of treated patients) of pulmonary vein stenosis, defined as a luminal diameter reduction of 50% or more.[7-11] Luminal diameter reduction between 25 and 50% was found in 16% of treated patients.[7] PV stenosis can be life-threatening.[12] The aims of our study were twofold. Firstly we wanted to assess the efficacy of cryothermal PV ablation. A further objective was to measure the incidence of PV stenosis using cryothermal energy.

Methods

Patients with a history of problematic AF referred to the department of clinical electrophysiology were considered candidates for this single-centre prospective study. Initially, patients with persistent AF were also included. Entry criteria for paroxysmal AF included symptomatic episodes, occurring at least monthly, despite the use of more than two antiarrhythmic drugs. Exclusion criteria included severe valvular disease, marked left atrial enlargement (>50 mm, measured on M-mode echocardiography) and contraindications for oral anticoagulation. The day before the procedure a transoesophageal echocardiogram was performed to exclude left atrial thrombi. Antiarrhythmic drugs were continued.

Ablation

During the first ablation procedures an attempt was made to isolate the left upper PV (LUPV) and right upper PV (RUPV). A decapolar catheter was inserted in the coronary sinus (CS) via the left subclavian vein.

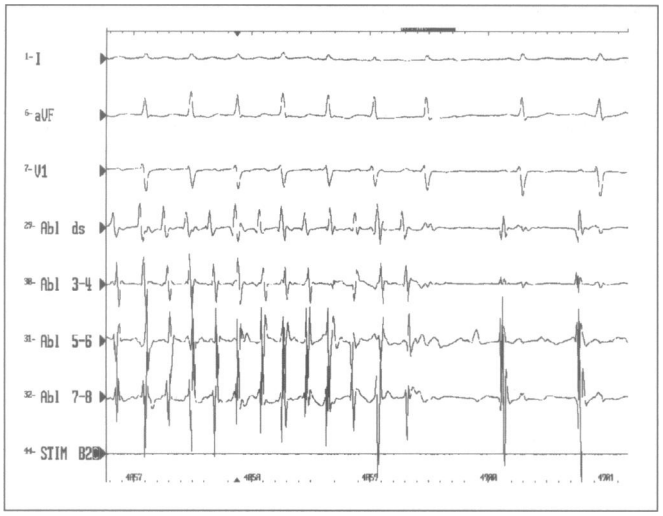

Figure 1. Basket catheter positioned together with the ablation catheter in the left upper pulmonary vein.

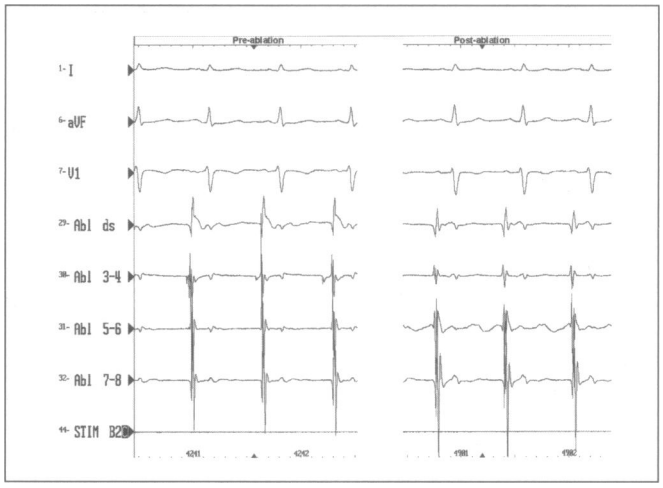

Figure 2. Pacing in the coronary sinus before and after successful ablation. In the left panel an atrial signal followed by a pulmonary vein potential is seen. In the right panel the pacing signal is only followed by an atrial signal.

A bipolar catheter was advanced in the right ventricular apex and was used as the reference catheter for a 3D positioning system (Localisa).[13] Double transseptal puncture was performed guided by intracardiac echocardiography.[14] After transseptal puncture the patients were heparinised, guided by the activated clotting time (ACT). After making a selective venogram a multipolar basket catheter (Constellation, Boston Scientific, Natick, MA, US) was advanced into the pulmonary vein (figure 1). The electrical connection between left atrium (LA) and PVs before and after ablation was studied while pacing from the CS (figure 2). Positioning of the ablation catheter within the PV was guided by fluoroscopy, electrograms and the Localisa system (figure 3).The pulmonary veins were ablated at the venoatrial junction, aiming at electrical isolation of the veins (figure 4). Ablation was performed with a 7-French 6 mm tip Freezor-Xtra cryocatheter (Cryocath Technologies Inc., Kirkland, Quebec, Canada). Applications lasted four minutes

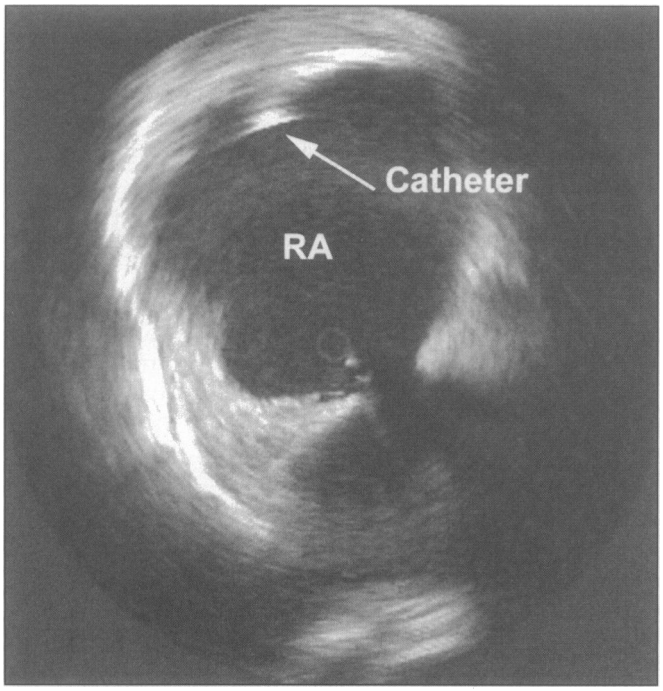

Figure 3. Use of the Localisa® 3D positioning system. On the left side of the image the positions of ablation applications in the right upper pulmonary vein are saved. On the right side of the image a ring of electrodes from the Basket catheter in the left upper pulmonary vein (LUPV) is made visible. The ablation catheter is seen within this ring at the position of the first cryothermal application in the LUPV.

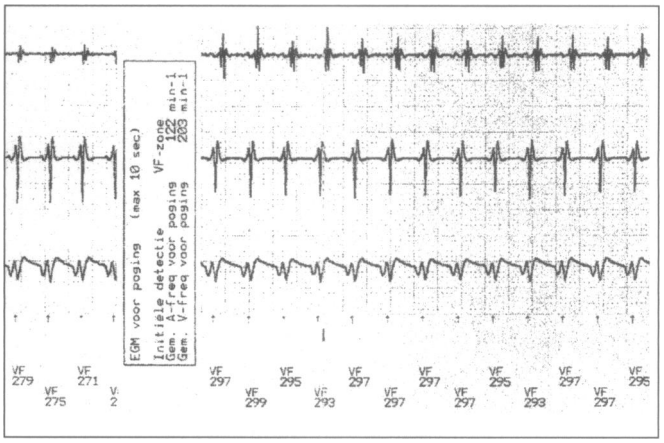

Figure 4. Disappearance of pulmonary vein potentials (PVP) during ablation. The first three atrial potentials during sinus rhythm are followed by a PVP. The last atrial potential is no longer followed by a PVP. This PVP did not return and this pulmonary vein was therefore successfully electrically isolated.

Table 1. Patient characteristics before catheter ablation.

No.	Gender	Age (years)	Paroxysmal/ persistent	Cardiac disease	Attack pattern	Cardioversions before	Cardioversions after
1	Male	63	1	-	M	15	1
2	Male	57	1	DCM	D	1	0
3	Male	56	1	-	D	0	0
4	Female	68	1	Thyroid	W	0	1
5	Male	51	2	-	P	3	0
6	Male	59	1	-	W	8	0
7	Female	62	1	Thyroid	D	0	0
8	Male	52	1	-	D	1	0
9	Female	40	1	Valv.	W	0	0
10	Male	56	1	H/DM	M	7	0
11	Male	50	2	H	P	1	0
12	Male	40	1	Thyroid	P	15	1
13	Male	53	1	Valv.	D	2	0
14	Male	45	1	-	D	1	1
15	Female	40	1	-	W	0	2

1=paroxysmal; 2=persistent; D=Daily, DCM=dilated cardiomyopathy; DM=diabetes mellitus; H=hypertension; M=monthly, Valv=valvular disease; W=weekly.

each. After the ablation, patients were hospitalised for at least two days and followed for early recurrences. Heparin was continued and anticoagulation treatment (acenocoumarol) started. If the patients remained symptomatic after three months the persistence of electrical isolation of the successfully treated PVs was to be confirmed, and the other PVs ablated.

Follow-up

In hospital recurrences of AF were documented. After discharge the patients were followed in the outpatient clinic on a regular basis. Transtelephonic ECG recordings were made weekly and in case of symptomatic arrhythmias. Furthermore at three months, the patients were interviewed by telephone by a research nurse

Table 2. Ablation data.

No.	LUPV	Diam. (mm)	Appl. (no.)	Isolated	RUPV	Diam. (mm)	Appl. (no.)	Isolated	LIPV	Diam. (mm)	Appl. (no.)	Isolated
1	+	18	2	+	-	17			+	17	3	+
2	+	15	13	-	+	15	NA	-	-	21		
3	+	19	16	+	-	19			-	19		
4	+	21	17	+	-	18			+	19	2	+
5	+	18	3	+	+	NA	8	-	-	17		
6	+	15	NA	+	+	19	10	+	-	15		
7	+	NA	6	+	+	NA	5	+	-	NA		
8	+	18	8	+	-	18			-	18		
9	+	NA	6	+	+	NA	5	+	-	NA		
10	+	NA	3	+	-	NA			+	NA	8	+
11	+	22	7	+	+	18	5	-	-	18		
12	+	22	NA	-	+	18	NA	+	-	17		
13	+	19	0		+	18	13	-	-	17		
14	+	21	11	+	+	19	8	+	-	13		
15	+	15	9	+	+	17	15	+	-	15		

Appl.=application; diam=diameter; LIPV=left inferior pulmonary vein; LUPV=left upper pulmonary vein; NA=not available; RUPV=right upper pulmonary vein.

Table 3. Additional procedure data and follow-up.

No.	Istmus	Remarks	Proc. time (minutes)	Fluroscopy (minutes)	Complications	Type	Attack pattern
1			249	72.8	yes	PE, no puncture	-
2			322	68.8			D
3			364	80.3			W
4			212	56.3			W
5			281	58.9			D
6			396	110	yes	hypotension	-
7			194	45.3			D
8			335	69.1			D
9			254	49.5			-
10	+		255	64.3			-
11	+		227	45	yes	ST elevation inferior	
12			297	59.4			D
13			297	55.1	yes	ST elevation inferior Amaurosis fugax	D
14	+	one left vein	299	53.6	yes	ST elevation inferior	-
15			272	50.2			M

D=daily, M=monthly, PE=pericardial effusion; Proc.=procedure; W=weekly; +=associated flutter ablation and cavo-tricuspid isthmus block achieved, -=no AF attacks after PV ablation.

about their subjective wellbeing. Before, and three months after the ablation, the diameter of all pulmonary veins was measured using multislice spiral CT scans. A one-year CT scan is scheduled in all patients.

Results

Patients

Results from the first ablation of the initial 15 patients included in this study are reported. Their demographic and clinical data are summarised in table 1. The mean age was 52.8 years (40 to 68 years), and four were female. Their mean LA size measured with M-mode echocardiography was 40.9 mm (30 to 48 mm). Ten patients had been cardioverted once or more in the past and six of them had daily attacks of AF.

Ablation

Acute results of the ablation are shown in table 2. An attempt was made to isolate 27 PVs, of which 20 veins could be isolated (74% acute success). The mean fluoroscopy time was 62.6 minutes and the mean procedural time 285 minutes (table 3). An average number of 7.71 (1 to 17) applications per vein was necessary.

Although it was the intention to treat only the LUPV and RUPV, because of procedural reasons the left inferior PV (LIPV) was occasionally targeted instead of the RUPV (n=2) or as a third PV (n=1).

Multislice spiral CT scan

Using multislice CT angiography (MSCT) of the treated vessels no significant difference in PV diameter before and three months after PV ablation was seen: LUPV 18.58x2.61 mm versus 18.13x2.10 mm; LIPV 17.17x2.12 mm versus 17.00x3.59 mm; RUPV 17.55x1.44 mm versus 18.19x0.95 mm.

Complications

Complications are shown in table 3. One patient had a pericardial effusion, not requiring puncture. Temporary ST-segment elevation in the inferior leads after selective angiography of the PV (LUPV and RUPV) was seen in three patients. In one patient a very short episode of blurred vision occurred on the second day after the procedure. No other complications occurred.

Follow-up

Mean follow-up was 276 days (104 to 426 days). Five of 12 patients (42%) with paroxysmal AF were completely without AF after one ablation procedure. An additional two patients (17%) reported a 50% reduction in symptoms. In the three patients with persistent AF no improvement was reported. The evolution in the AF burden is shown in table 3.

Discussion

It has been shown that extensions of atrial muscle surrounding the pulmonary veins (PVs) can have ectopic electrical activity able to trigger AF.[1,2,15-17] The long-term success rate of RF ablation (RFA) to cure AF by targeting these initiators using a focal approach is low (29%).[18] Empiric PV isolation appears to be a more effective approach to the maintenance of sinus rhythm.[5,6] Although distal isolation can be achieved with fewer lesions, ostial isolation is required in the

majority of patients to eliminate arrhythmogenic activity and AF.[18] It has become clear that electrical isolation of all four pulmonary veins from the left atrium provides the best cure rate. However, this is associated with a significant risk of pulmonary vein stenosis,[9-11] which has serious consequences, and can occur very late after the procedure (1 to 2 years).[8]

Cryothermal ablation

Cryothermal tissue injury is distinguished from hyperthermic injury, such as caused by RF energy, by the preservation of basic underlying tissue architecture and minimal thrombus formation. We hypothesised that using cryothermal energy would prevent the occurrence of PV stenosis. Cryothermal ablation, with a different set-up, was formerly used for this indication and seems to be safe.[19]

Results of PV ablation

Reported results of PV ablation show a large variability and are also dependent on the definitions used for the endpoints. Recently Oral et al.[20] reported results of PV ablation (with at least three PVs ablated) in 70 patients. After a mean follow-up of five months 70% of the patients with paroxysmal AF were in sinus rhythm (SR), compared with only 22% with persistent AF. A lower success rate of 51% after a mean follow-up of nine months was reported by Deisenhofer.[11] Gerstenfeld et al.[10] reported a very high recurrence rate of 68%. After 10.4±4.5 months, 85% of patients with paroxysmal AF and 68% of patients with permanent AF were in SR in a report by Pappone[21] using circumferential RF ablation.

Complications of PV ablation/PV stenosis

The risk of pulmonary vein (PV) stenosis after PV ablation is significant.[22,23] Metaplasia, proliferation, thrombosis and neovascularisation may lead to PV stenosis after RF energy application around or inside the PV ostia.[9] Pulmonary vein stenosis is potentially life-threatening.[24] The clinical manifestations of PV stenosis consist of chest pain, dyspnoea, cough, haemoptysis, recurrent lung infection and pulmonary hypertension. PV stenosis can be asymptomatic. Some patients may show late progression of PV stenosis during follow-up.[8,9] In a recent series of 380 ablated veins, the CT scans revealed 2 PVs (1%) with severe (>70%) stenosis, 13 (3%) with moderate (51 to 70%) stenosis, and 62 (16%) with mild (≤50%) stenosis.[7] In a recent report on 75 patients, Deisenhofer found stenosis of 25 to 50% in 9.3% patients and of >50% in 8.9% patients.[11] Others estimate the incidence of PV stenosis (defined as luminal diameter reduction >50%) detected by spiral computer tomography scan or three dimensional magnetic resonance angiography) at 0 to 7% per PV ablated.[9]

Moderate PV stenosis (50% narrowing) was observed in one of 136 consecutive patients (0.7%) after RF ablation of PV using an irrigated-tip catheter.[25] Using cryothermal ablation Rodriguez[19] found no stenosis after PV ablation in 53 veins. PV stenosis can be treated with balloon dilation, although the long-term course is unknown.[26]

Pericardial effusion

Pericardial effusion is reported in almost all reports about PV ablation.[27] Deisenhofer reported pericardial effusion in 4 of 75 patients (5.3%).[11] We suspect that catheter manipulation within the left or right atrium or damage to the thin-walled left atrial appendage is responsible.

Other complications of PV ablation

Other less frequently described complications such as phrenic nerve paralysis and reflex bradycardia were not observed in our series.[28]

Future perspectives

Several authors have explained the modest effect of PV ablation by the existence of non-PV foci.[29,30] Repeat ablation procedures are necessary in almost 50% of patients.[25] The role of concomitant cavotricuspid isthmus ablation and creation of a linear lesion (referred to as the 'lateral mitral isthmus line') between the ostium of the left inferior PV and lateral mitral annulus[25] needs to be defined. These lesions may reduce the amount of atrium available to support multiple wavelet reentry, changing the substrate for AF.

Conclusion

This report shows the initial results of the first patients in our department ever treated with PV ablation for paroxysmal AF. In 5 of 12 (42%) patients with paroxysmal AF no recurrences of AF occurred. An additional 2 of these 12 (17%) reported a 50% reduction in symptoms. Taking into account a learning curve, we consider these results promising. Cryothermal PV ablation appears to be a safe method. No PV stenosis was seen in this study three months after the ablation. Numbers are, of course, still too low to make firm conclusions. However the absence of pulmonary vein stenosis three months after ablation of 27 veins is encouraging. Furthermore this report is about the initial procedure in every patient. Of interest is that it appears there is a subset of patients who report a significant improvement in AF burden after PV ablation although AF did return. All patients with recurrence of AF were offered a second procedure to evaluate invasively the results of their first treatment and to extend the ablation to the two inferior PVs. ■

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