Cryoballoon Pulmonary Vein Isolation for the Treatment of Atrial Fibrillation and Issues in Follow-up Management

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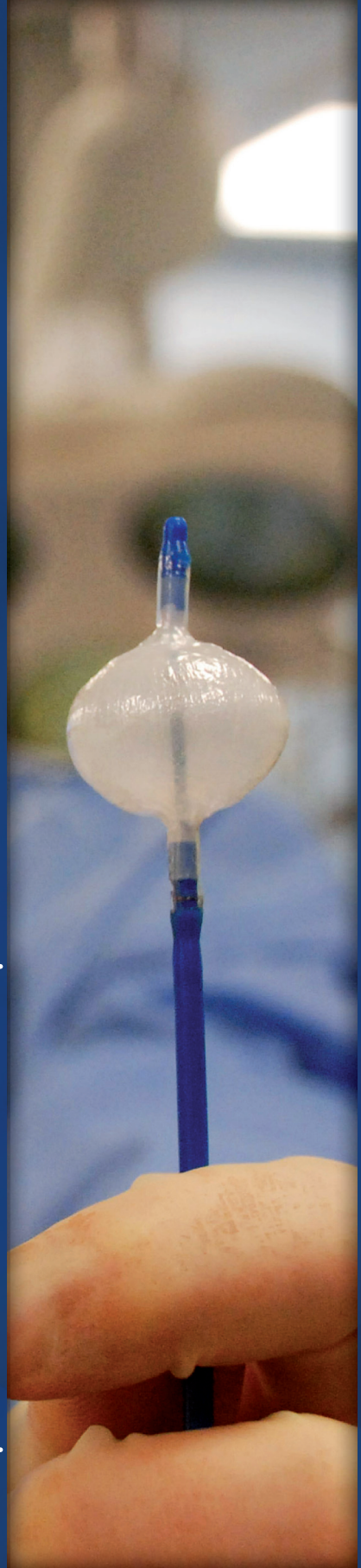

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Promotor: Prof. Dr. L. Jordaens

Overige leden: Prof. Dr. H. Crijns
Prof. Dr. W. van der Giessen
Prof. Dr. M. Simoons

Contents

Introduction

Introduction

Since the first publication proving the causal relation between electrically active muscular sleeves in the pulmonary veins (PV) and the triggering of paroxysmal atrial fibrillation (AF) by ectopic beats originating from them, numerous endocardial ablation techniques have been used to eliminate this arrhythmia(1-3). Although well established as a standard procedure in the treatment of atrial fibrillation, point-to-point radiofrequency ablation remains a challenging procedure, in which manual operator skills and experience is highly variable(4). This currently translates in variable success rates and high complication rates, making the risk-benefit evaluation of this procedure difficult to assess (5). Several devices have been engineered to simplify the circumferential ablation, with the aim of permitting less experienced operator to achieve the endpoint of PV isolation with reasonable procedure and fluoroscopy times, and without a higher risk of complications.

Principle of cryoballoon ablation

Cryothermal tissue destruction has been used for several decades in surgical and catheter based ablations. The principle of cryoablation is based on removing energy from the target tissue, creating an ice ball, thus disrupting the cellular membranes resulting in cell death. Important factors that determine the percentage of cellular survival after ablation are: freezing and thawing rates, the lowest temperature reached, and the duration of the freeze(6). Catheters and probes used for cryoablation employ internal expansion of liquid nitrogen to reach tissue temperatures of around -80°C. These temperatures are effective in creating well delineated lesions, with preservation of the underlying tissue architecture(7). In cardiac ablation, freezing tissue to a temperature of around -30°C can be used to create a completely reversible lesion. This technique, called cryomapping, can allow the operator to predict the effect of a permanent lesion before it is actually created(8). To create permanent lesions, tissue temperatures should reach as low as possible (ideally -80°C) for a minimum duration of 4 minutes to maximize cell death. It is evident that when performing a pulmonary vein ablation with a 4 or 8 mm cryocatheter, extremely long procedure times will result from the numerous and lengthy cryoapplications(9).
The concept of a catheter based, double lumen balloon, with a 23 or 28 mm diameter, occluding the pulmonary vein ostia, and delivering a circumferential cryolesion proved promising and was successfully tested in animals(10-11). The consideration to use cryothermal ablation was that it had proven to be a relatively safe alternative to radiofrequency ablation for other arrhythmias, conserving tissue architecture, and reducing the risk for thrombosis and pulmonary vein stenosis due to an excessive fibrotic reaction after ablation(7, 9).

Novel devices for ablation of atrial fibrillation

We will describe the range of the most important new devices currently available for pulmonary vein isolation, as to situate the cryoballoon technology in this emerging range of ablation devices.

High Intensity Focused Ultrasound Balloon (HIFU)

The HIFU-balloon is a balloon device, developed to deliver a circumferential lesion around the pulmonary vein when positioned at its ostium, by transmitting an anterior focused ultrasound beam into the tissue. The lesion creation is rapid and caused by direct mechanical tissue heating. Although its initial results seemed promising, with nearly 60% freedom of AF during long term follow-up(12), the first generation balloon catheter caused several major complications, including phrenic nerve paralysis(13-14) and lethal atriooesophageal fistula(15). Although further development led to a second generation device which was also tested in a clinical setting, complications remained at an unacceptable level, halting its use in clinical practice(16-17).

Endoscopic laser balloon ablation catheter

The laser balloon is a device designed to provide real-time endoscopic visualization, allowing the operator to deliver laser energy at specific locations around the antral pulmonary vein region. Reddy et al. reported on the first available generation of balloon, that allowed the operator to place large 90 to 120° ablation arcs around the balloon, but the reported complication rate limited its use in clinical practice(18). Currently, a second generation catheter, carrying a more compliant balloon with the capability to place point-like ablations has been tested by Dukkipati et al., and seems to be promising in an animal model(19).

Radiofrequency hot balloon catheter

This device was developed as a balloon based system that delivers radiofrequency energy around its surface heating the underlying tissue, and capable of ablating the PV-left atrial antral region. In an animal model, results have been published late 2001 by Tanaka et al., showing its potential for successful pulmonary vein isolation(20)w:rsid w:val=/, and after a small pilot study in 2003(21) in which Satake et al. found a high success without major complications, a large single centre trial was performed (Sohara et al.) confirming this in 100 patients(22). This device also directly heats the tissue by radiofrequency energy, and dragging it across the surface of the posterior wall, makes complete posterior wall isolation possible. Ablation of the posterior wall in general, however does not seem to improve outcome results in the treatment of atrial fibrillation(23). Currently, all data about this device originated from the pioneering centre that developed this and still awaits confirmation by larger multicentre trials.

Cryoballoon ablation

Our published literature about this device will be addressed as the main subject in this thesis. Two other important early publications however need to be considered as comparison to our own data. Neumann et al. described the results from a nonrandomized prospective 3-centre study in 346 AF patients of whom 293 were paroxysmal, and found 74% freedom of AF in the paroxysmal patients and 42% in the persistent patients, without any more use of antiarrhythmic drugs. As complications, two pericardial tamponnades were reported, and 26 right phrenic nerve palsies. All of the right phrenic nerve palsies recovered within one year, and were in most of the cases related to use of the 23mm balloon, since only 2 were caused by the 28mm balloon(24). The North American STOP-AF trial was presented during the 2010 American College of Cardiology meeting in Atlanta, and is an FDA controlled, multicentre trial comparing cryoballoon pulmonary vein isolation (n=163) to medical treatment (n=82). There was a procedural success in 98% of the cryoballoon arm, and an overall complication rate in the cryoballoon arm of 6,1%. Right phrenic nerve paralysis was observed in 28 subjects of which 4 persisted longer than 12 months. The combined endpoint of freedom of AF and non-failure of antiarrhythmic drug in the cryoballoon group was 69,9% versus 7,3% in the antiarrythmic drug arm. Success percentages in AF-ablation vary, not only in function of ablation strategy, but also in function of follow-up methodology. Therefore, the varying success rates of published literature on the cryoballoon needs to be interpreted in function of the methods and endpoints used. The following chapters in this thesis will try to clarify this.

Duty-cycled radiofrequency pulmonary vein ablation catheter (PVAC)

The PVAC device is a decapolar ablation catheter, designed to be placed at the pulmonary vein ostium, like a diagnostic circular mapping catheter, combined with a multichannel, duty-cycled RF generator by which electrodes can be selectively energized in predefined ratios of unipolar and/or bipolar energy. This combination allows for the creation of long contiguous lesions with each RF application. The catheter was first reported on by Boersma et al. in a report about 98 patients ablated with the system. Their report claimed an absence of procedure related complications and a freedom of AF after 6 months follow-up of 83% without the use of antiarrhythmic drugs(25). The protocol in this study however, did not incorporate CT or MRI during long-term follow-up to exclude pulmonary vein stenosis, a frequent complication of ostial radiofrequency pulmonary vein ablation(5). Only 11 patients had either a MRI or pulmonary vein angiography, all without evidence for stenosis. A report by Fredersdorf et al. in 21 patients, had a similar success rate, and confirmed the absence of pulmonary vein stenosis by CT or MRI at six months(26). Duytschaever et al. reported a freedom of AF after 3 months of 74% without antiarrhythmic drugs, without complications on clinical basis. However, in the last report, 19 patients had esophageal temperature monitoring during ablation, showing a temperature rise in 9 of them above 38,5°C, theoretically putting the patient at risk for developing a potential lethal atrio-esophageal fistel. Safety precautions are therefore necessary to employ this device, as the authors conclude(27).

High Density Mesh Ablator (HDMA)

The high density mesh ablator is an expandable variably shaped mesh electrode that allows mapping and radiofrequency ablation with 36 bipoles. Since the first animal experiments in 2007, in which the device performed safely, it has been used in human pulmonary vein isolation. Mansour et al. reported in 22 patients successful deployment of the device in the targeted pulmonary vein in 94,5% of cases, but was only able to isolate the targeted vein in 63% of cases with the HDMA. In only 40% of patients the pulmonary vein isolation could be achieved entirely with the 30mm(28). These results were confirmed by De Greef et al. showing that 76% of pulmonary veins could be isolated with the HDMA en 45% of procedures could be performed exclusively with the device(29). Although De Greef et al. reported clinical freedom of AF after one year of follow-up in a small group (n=11) of 64% in his initial publication, a later publication reporting about 64 patients, showed a freedom of AF of 19% in patients ablated with the 30mm HDMA (n=26) and 18% in patients ablated with the 35mm HDMA (n=38)(30). Steinwender et al. reported a similar low freedom of AF after one year follow-up of 29% in 35 patients, confirming that although the safety profile of this device is acceptable without an excess in pericardial effusion, phrenic nerve paralysis or mortality. It is severely limited in its long term clinical efficacy for prevention of AF recurrence(31).

Purpose of this thesis

The purpose of this thesis was to describe the effectiveness and complications of the cryoballoon for pulmonary vein isolation. To this end we have analyzed and published procedure characteristics, the short term and long term follow-up data, as well as the cardiac, cerebral and pulmonary complications. Before this technique became available, pulmonary vein isolation was performed by either intracardiac echography guided radiofrequency ablation(32) or segmental cryothermal ablation(9) in our centre. Both techniques proved to be technically challenging, long and with a high radiation exposure. The balloon concept had the potential of reducing the difficulty of the procedure, providing circumferential ablation with a shorter operator learning curve. Cryothermal energy had been used for year to treat a wide range of arrhythmias, both in electrophysiology and surgery, and had proven to be safe for endocardial ablation. Therefore, the decision to employ the cryoballoon technology in a large number of patients was carefully made, considering that balloon ablation technology could safely simplify pulmonary vein isolation.

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Chapter one

Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications and short term outcome

Van Belle Y, Janse P, Rivero-Ayerza MJ, Thornton AS, Jessurun ER, Theuns D, Jordaens L. Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. Eur Heart J. 2007 Sep;28(18):2231-7.

Abstract

Aim: To assess safety, feasibility and short term outcome of pulmonary vein (PV) isolation in paroxysmal atrial fibrillation (AF) with a cryoballoon.

Methods: We consecutively treated 57 patients with a double lumen 23 or 28mm cryoballoon. The acute results, complications and follow-up over the first three months were analysed, using a comprehensive and intensive follow-up period.

Results: During 57 procedures, 185 of 220 targeted PV's were successfully isolated using the cryoballoon (84%) (balloon group, 33 patients). In 33 veins (15%) an additional segmental isolation (hybrid group, 24 patients) was necessary with a standard cryocatheter to achieve isolation. The average procedure times were respectively 211 ± 108 and 261 ± 83 minutes (NS), the average fluoroscopy times 52 ± 36 and 66 ± 33 minutes (NS). The number of balloon applications did not differ between both groups : respectively a median 9 (4-18) and 10 (5-17) (NS). We observed four phrenic nerve paralysis after ablation of the right superior PV : two resolved immediately after cessation of the cryoenergy, one recovered after 3 months, one persisted up to 6 months. A daily transtelephonic rhythm recording showed a significant drop in mean AF burden from 24% to 10%, 8% and 5% during the three consecutive months of follow-up ($p<0.01$ versus baseline). No differences were observed between the treatment groups. 34 patients (60%) were completely free from AF after a single procedure.

Conclusion: Balloon cryoablation of the pulmonary veins with additional segmental isolation if necessary, is a good approach for patients presenting with paroxysmal AF, showing a significant reduction in AF burden after a single procedure. The major complication seems to be phrenic nerve paralysis after ablation of the right superior PV, but this is potentially reversible over several months.

Introduction

Isolation of the pulmonary veins (PVI), either segmental or circumferential, has become an important treatment of patients with atrial fibrillation (AF). Reports have been published that show up to 85% freedom of paroxysmal AF during long term follow up[1-9]. A large number of different approaches and techniques exist. The procedure remains technically challenging with a significant number of complications as thromboembolism[10], pulmonary vein stenosis[11,12], atrio-esophageal fistulae[13-17], and left atrial flutter[18]. Innovative new technologies are being developed to make isolation safer and easier.
Cryoablation has been promising because of low thrombogenicity and absence of PV-stenosis, but the longer procedure and fluoroscopy times have limited this approach to segmental isolation[19]. Recently, the development of balloon technology has opened the way for several novel approaches to isolation with new energy types (ultrasound, focused ultrasound, laser and cryo therapy). Cryoballoon experiments have been shown to be feasible and safe in animals[20,21]. Our aim was to publish our initial experience in humans, not only to describe the procedural success rate but also to assess short-term efficacy in treatment of paroxysmal AF. We have adopted an intensive follow up method, using daily event monitoring[22].

Methods

Patients

Patients with documented paroxysmal AF at two or more occasions were accepted as candidates. Exclusion criteria were: left atrial dimension > 50 mm measured in the parasternal long axis, as assessed with transthoracic echocardiography, valvular heart disease and advanced age.

Procedure

All patients were treated with a double lumen cryoballoon (Arctic front, Cryocath, Montreal, Quebec; figure 1). Both femoral veins and in some cases the left subclavian vein were used for venous access. A 10 Fr, intracardiac echocardiography catheter (Flexview, EPMed) was introduced through the left femoral vein and positioned in the right atrium. A decapolar catheter was placed in the coronary sinus. After the first ten cases, a double transseptal puncture was replaced by a single transseptal approach using a Brockenbrough needle, guided by both intracardiac echocardiography (ICE) and fluoroscopy. ICE was also used to ensure a posterior transseptal approach. A circular mapping catheter was advanced and positioned in the antrum of each pulmonary vein to record the presence of PV-potentials. After registration, the sheat was exchanged for a 14F steerable sheat. The mapping catheter was exchanged for a 23 or

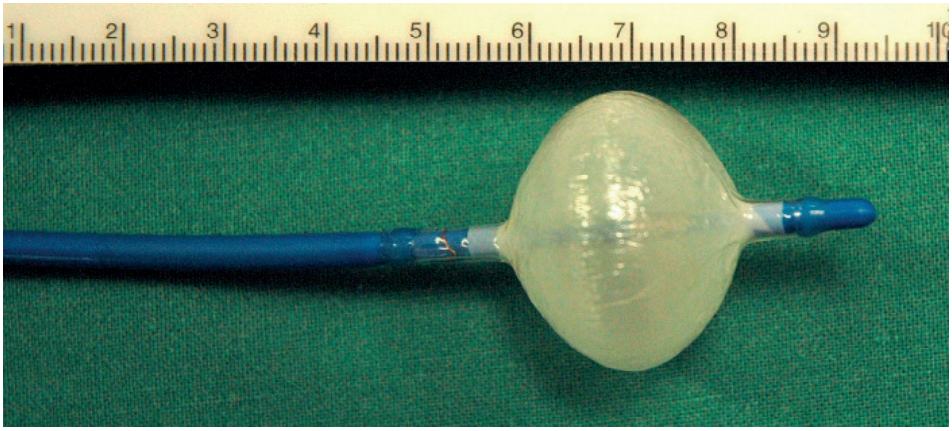

Figure 1. Distal end of a 23 mm, 10.5 F, double lumen cryoballoon catheter (Cryocath) after inflation.

28mm, 12F balloon catheter, positioned over an exchange wire to occlude the ostium of each PV (figure 2). Cryoenergy was given for 5 minutes per application. The applications per vein were directed towards the major side branches. Before targeting the right superior pulmonary vein (RSPV), a quadripolar catheter was positioned in the superior caval vein for continuous phrenic nerve stimulation during cryoapplication. At loss of capture, the ablation was instantaneously terminated. After targeting all PV's, the cryocatheter was exchanged for the circular mapping catheter to check for remaining electrical activity. If this registration showed persistence of the PV-potentials, the cryoballoon was introduced again, trying to maximize wall contact at the location of the remaining potentials (as guided by the circular catheter, ICE and fluoroscopy). If after this second ablation attempt the activity remained present, a conventional cryocatheter (Freezor Max, Cryocath, Montreal, Quebec) was used to perform a segmental isolation through the same transseptal puncture. If isolation could be achieved with the balloon, the patient was categorised as "balloon", if additional segmental isolation had to be performed he was categorised as "hybrid". These categories were included in further analysis. The day after the procedure a transthoracic echocardiogram was made to exclude pericardial effusion, and a chest X-ray to exclude pneumothorax and other thoracic complications.

All patients were treated with oral anticoagulation for at least one month before the procedure, aiming at an INR of 2.5-3.5. Two days before the procedure, patients were admitted and the oral anticoagulants were replaced by unfractionated heparin, aiming at a 3 times normal aPTT ratio. Two hours before the ablation heparin was stopped. After venous puncture, and before transseptal puncture a 5000 IU Heparin bolus was given. After transseptal puncture another 5000 IU Heparin was given and a continuous titrated infusion of heparin was started. During the procedure the activated clotting time (ACT) was monitored every 30 minutes, and kept above 350 s. After the procedure the patients were treated with heparin and oral anticoagulants were restarted.

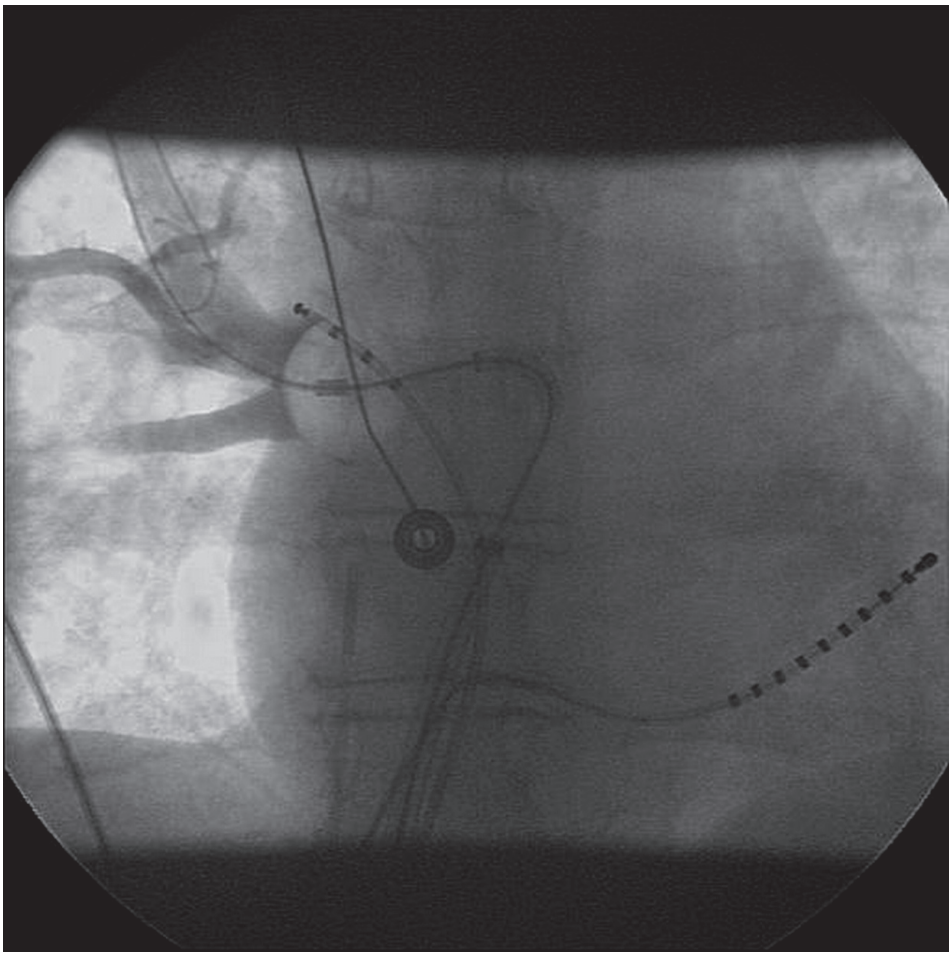

Figure 2. X ray while contrast fluid is injected, showing occlusion of the right superior pulmonary vein with the cryoballoon catheter. Quadripolar pacing catheter in the superior vena caval-right atrial junction. Multipolar mapping catheter in the coronary sinus. In the mid right atrium, an intracardiac echo catheter is visible.

Anti-arrhythmic drug treatment after ablation

During the three month follow up period after ablation all patients were continued on the antiarrhythmic medication they were taking before the ablation.

Follow up method

Before ablation patients were instructed to use an event recorder and to transmit daily at least one transtelephonic ECG-strip at a fixed hour, and when symptoms were present. This was started

one month before ablation and continued for three months afterwards. The heart rhythm on the ECG-strips was coded as sinus rhythm, atrial flutter, atrial tachycardia or atrial fibrillation. Atrial and ventricular premature beats and sinus tachycardia were coded, but are not reported, as they were infrequent. The heart rate during episodes of sinus rhythm was measured. Transmissions were coded as symptomatic or asymptomatic. The AF burden was defined as the percentage of days on which an AF episode was transmitted. Multislice CT scans were made before and at 3 months after ablation to evaluate the possible occurrence of PV stenosis as described before. PV stenosis was defined as a reduction of the diameter of more than 25%. Patients were seen at the outpatient clinic after 3 months.

Statistical analysis

Continuous variables are expressed as the mean value ± SD and were compared with the t-test. A chi-square test was used for categorical variables. Non parametric tests were used when appropriate. The learning curve was analysed in blocks of 10 patients. Data pertaining to number of applications, procedure and fluoroscopy times were documented for each subgroup. Statistical analysis of the hypothesis that procedure time and fluoroscopy times varied significantly between groups 1 to 5 was performed using the one-way analysis of variance (ANOVA).

Results

Patient data

A total number of 57 patients (44 male, 13 female), mean age 55 ± 9 years, underwent PVI with a cryoballoon. The mean LA dimension was 43±7 mm. The mean left atrial volume (calculated according to the ESC and ASE guidelines[23,24]) was 66±15 ml. Fourteen patients had previously undergone a cavotricuspid isthmus ablation for typical flutter. Three of the patients had thyroid

Table 1. Pulmonary vein diameters at baseline and at 3 months (mm)

	LSPV		LIPV		RSPV		RIPV	
	T	**F**	**T**	**F**	**T**	**F**	**T**	**F**
Baseline (mean)	17.3	21.5	13.8	18.6	17.6	19.7	17.4	19.3
SD	3.8	3.7	3.0	2.8	2.9	2.6	2.8	2.8
3 months (mean)	17.2	21.0	14.1	18.6	17.9	20.0	17.0	19.6
SD	3.5	3.6	3.8	1.4	3.0	2.8	3.2	2.6
p-value	NS	NS	NS	NS	NS	NS	NS	NS

F: frontal plane diameter, LIPV: left inferior pulmonary vein, LSPV: left superior pulmonary vein, NS: not significant, p-value: baseline versus 3 months, RIPV: right inferior pulmonary vein, RSPV: right superior pulmonary vein, SD: standard deviation, T: transverse plane diameter

disorders; hypertension was the underlying disease in 8, and hypertrophic obstructive cardiomyopathy in 2 patients. The mean PV-diameters are shown in table 1.
A total number of 18 patients had previously been treated with amiodarone, ten were still on the drug at time of ablation.
At least 3 months follow up was completed by all patients.

Procedures

During 57 procedures, registrations were made in 228 pulmonary veins, of which 220 showed PV potentials. All veins with potentials were targeted (LSPV: n=57, LIPV: n=53, RSPV: n=56, RIPV: n=54), and 218 were succesfully isolated. The median number of balloon applications per vein was 2 [range1-10], LSPV 3 [1-7], LIPV 3 [1-10], RSPV 2 [1-8], RIPV 2 [1-6]. A median of 9 [range 4-18] applications were given during the entire procedure. Of the 220 veins, 185 veins could be isolated using only the balloon (84%) in 32 patients (54%). There were no differences between the different veins: LSPV 48 (84%), LIPV 43 (81%), RSPV 46 (82%), RIPV 48 (89%) (NS). In the remaining 33 veins (15%) a standard cryocatheter was used to perform additional segmental ablation with a median of 2 [1-7] applications to achieve complete electrical isolation (hybrid approach). The number of balloon applications did not significantly differ from the balloon group : 10 (5-17) (NS). In 17/57 patients (30%) only one vein had to be targeted with a median number of 2 (1-5) applications; in 5/57 patients (9%) two veins were targeted and in 2/57 patients (4%), three veins were targeted.
When using a 23 mm cryoballoon (18 cases, 70 veins), 14 procedures (77%) and 52 veins (74%), were successful with just the balloon. With the 28 mm balloon (32 cases, 122 veins), 15 cases (47%) and 57 veins (47%) were successfully isolated. When using both balloons (7 cases, 28 veins), successful balloon isolation was achieved in 4 procedures (57%) and 16 veins (57%). The remaining required additional use of a conventional cryocatheter.
The average procedure time was 232±100 min and the average fluoroscopy time 58±35 min for the entire population (Table 2). Adding an additional segmental isolation did not significantly prolong fluoroscopy or procedure times.

Tabel 2. Procedure and fluoroscopy times

	Balloon isolation					Hybrid isolation				
Balloon size	**Procedure (p=0.06)**	**Rx (NS)**	**Veins**	**Patients**	**%**	**Procedure (p=0.06)**	**Rx (NS)**	**Veins**	**Patients**	**%**
23 mm	162±69	35±30	52	14	88	218±116	45±33	16	4	12
28 mm	224±130	64±38	57	15	47	269±76	69±33	65	17	53
23+28 mm	258±67	68±26	16	4	43	274±89	75±30	12	3	57
Total	211±108	52±36	125	33	58	261±83	66±33	93	24	42

Complications

In this series, two severe complications required prolonged hospitalization. One patient experienced a left sided hemothorax after hemorrhage due to puncture of the left subclavian vein. Another required surgical drainage of a pericardial effusion due to perforation of the left auriculum after transseptal puncture. None of these complications were attributable to the use of the balloon catheter. There were four cases of right phrenic nerve paralysis after application in the RSPV. At loss of phrenic nerve capture, ablation was immediately stopped. Two cases recovered after cessation of cryotherapy within the procedure. One recovered after 3 months (as documented with fluoroscopic evaluation of the diaphragm movement). One persisted for more than 6 months. The persistent phrenic nerve paralysis occurred during ablation with a 28mm balloon, the others when ablating with a 23mm balloon deep inside the RSPV.
One patient developed sustained atypical atrial flutter at three months after ablation. It responded to flecainide therapy, and did not recur. Two patients complained of hemoptisis within the first month after the procedure.

Analysis of the learning curve

When we compared the fifty last procedures in groups of ten, it was evident that procedure and fluoroscopy times fell significantly (figure 3). Procedure time fell from 375±87 to 137±40 min, fluoroscopy time from 105±30 to 21±7 minutes (both $p<0,01$). Furthermore, the number of balloon applications decreased significantly (table 3), whereas the proportion of patients requiring an additional segmental approach remained similar.

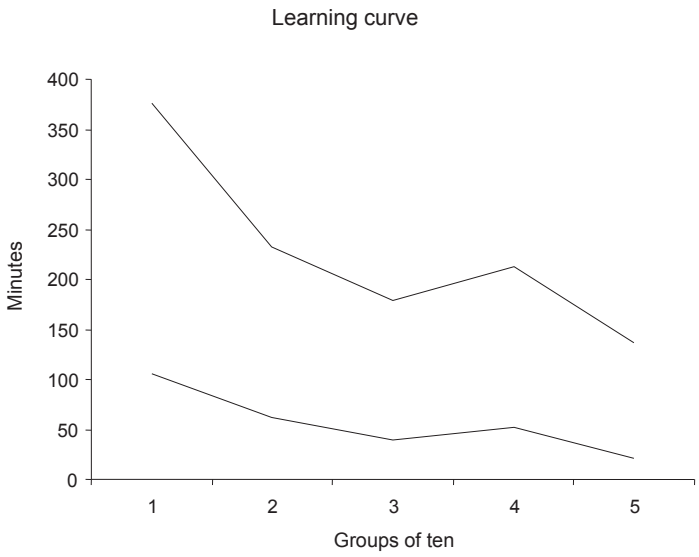

Figure 3. Procedure and fluoroscopy times (minutes) averaged per group of 10 consecutive procedures.

Table 3. Results in five consecutive groups of 10 patients

Patient number	1-10	11-20	21-30	31-40	41-50	p-value
Total number of veins	38	39	38	38	38	NS
Total number of veins with failed balloon isolation	11	7	4	4	4	NS
Total number of balloon applications	145	107	106	89	60	<0,01
Total number of conventional cryocatheter applications	18	28	10	6	15	<0.01
Patient number with additional cryoablation	5	4	4	4	4	NS

NS: not significant, p-value vs. baseline.

Event monitoring

All 57 patients who completed the follow-up, submitted daily rhythm strips 1 month before, and 3 months after the intervention. They sent in additional strips at the time of complaints (table 4). Before ablation 981 ECG rhythm strips were available for analysis. The average heart rate in sinus rhythm was 65±9 beats per minute in the month before ablation. In the rhythm strips, AF was recorded 246 times (25%), yielding a median AF burden of 14%. After ablation 3361 rhythm strips were transmitted and analyzed. The average heart rate in sinus rhythm during the first, second and third month was 68±8, 68±9 and 66±8 bpm respectively. The mean heart rate differed significantly from baseline during follow up (p<0,01 for the first two months). Results of rhythm recordings (number of strips showing AF and calculated AF burden) are presented in table 4. Overall, there was a significant reduction in AF burden from the first month on, persisting during the follow up period. When comparing patients who experienced recurrence with the ones showing no recurrence, there was no significant difference in baseline burden : respectively 0,29±0,31 and 0,21±0,32 (NS). Comparing the patients that underwent hybrid ablation with the balloon isolation patients showed no significant differences in AF burden during follow-up. The hybrid group however, had a significant reduction of AF burden from the first month onwards, whereas the balloon group shows a clear trend in AF burden reduction during the first two months and becomes significant during the third month of follow up (Table 5). 34 (60%) patients never experienced a recurrence AF after the ablation.

Table 4. Rhythm recording at baseline and during 3 months follow-up

	Baseline	1 month	2 months	3 months	Total FU
Number of recordings	981	1174	1182	1005	3361
Mean heart rate ± SD	65±9	68±8**	68±9**	66±8*	
AF recordings (n)	246	108	77	45	230
Mean AF burden ± SD	0,24±0,31	0,10±0,22**	0,08±0,21***	0,05±0,15***	0,08±0,20
Median AF burden (range)	0,14 (0-1)	0 (0-0,88)	0 (0-1)	0 (0-0,80)	0 (0-1)
Patients with AF (n)	57	18	16	13	23

AF: atrial fibrillation, nr: number, SD: standard deviation
*: p<0.06, *: p<0.05, **: p<0.01, ***: p<0.001 versus baseline

Table 5. AF burden

	n		PRE	1 M	2 M	3 M	POST
Balloon	33	Mean±SD	0,19±0,30	0,09±0,23	0,08±0,20	0,03±0,08	0,06±0,18
		Median (range)	0,06 (0-1)	0 (0-0,88)	0 (0-1)	0 (0-0,43)	0 (0-1)
		p-value		0,05	0,02	<0,01	<0,01
Hybrid	24	Mean±SD	0,31±0,33	0,11±0,22	0,11±0,23	0,09±0,21	0,10±0,22
		Median (range)	0,20 (0-1)	0 (0-0,75)	0 (0-0,81)	0 (0-0,80)	0 (0-0,81)
		p-value		<0,01	<0,01	<0,01	<0,01
Total	57	Mean±SD	0,24±0,31	0,10±0,22	0,08±0,21	0,05±0,15	0,08±0,20
		Median (range)	0,14 (0-1)	0 (0-0,88)	0 (0-1)	0 (0-0,80)	0 (0-1)
		p-value		<0,01	<0,01	<0,01	<0,01

1M: first month after procedure, 2M: second month after procedure, 3M: third month after procedure, n: number, PRE: baseline, POST: three month total, SD : standard deviation. P-value versus baseline.

Pulmonary vein diameter

All patients had multislice CT scans before and three months after ablation. No stenosis, as defined before, was seen at the evaluation at 3 months. Diameters are represented in table 1.

Discussion

We present data demonstrating the feasibility and efficacy of a cryoballoon in circumferential PV isolation. Circumferential RF ablation has long been shown to yield a high success rate in the treatment of patients with paroxysmal AF, yet proves to be a cumbersome endeavour with high procedure and fluoroscopy times[3,5]. RF applications in the left atrium are associated with several complications, including substantial mortality [4]. Previous studies have adopted cryothermia in an attempt to minimize complications since it produces homogeneous lesions, keeps the endothelium intact, and with a low thrombotic potential[25-30]. Tissue adherence during the applications limits this approach to segmental PV isolation[19,31,32].

Several authors have tried applying balloon technology with both ultrasound and high energy focused ultrasound, proving its potential for circumferential ablation, but at a high complication cost [33,34]. Combining the relatively safe cryothermal energy with a balloon, is the next step towards making circumferential isolation of the PV's a simple and safe technique. After its feasibility had been proved in animal experiments[20,21], we are now publishing the first human data in this field.

Acute success

Our data show a high feasibility in obtaining complete PV isolation with the cryoballoon, but also show that in a number of cases this seems impossible and additional conventional

cryocatheter ablation is required. We believe anatomical features are the main reason for this. Some patients had oval or slit-like shaped PV ostia and/or veins inserting onto the left atrium with a sharp angulation. In our experience it posed more difficulties to occlude these veins with a spherical shaped balloon. Although without reporting this, complete occlusion seems crucial in obtaining electrical isolation. We think that lack of blood flow allows the balloon to obtain lower temperatures. Incomplete occlusion, and blood flow warming the surface of the balloon, could produce reversible lesions[35-37]. The learning curve also shows that over time the number of balloon applications falls, indicating that operator dependent factors were present, along with simultaneous technical improvements of the device. The fact remains however that the lengthy cryoapplications add to the duration of the procedure and the use of an additional conventional catheter for a hybrid approach increases the cost of the overall procedure.

Complications using cryoenergy

The most frequently seen complication in our series was phrenic nerve paralysis. This was also the major limitation in balloon catheters using different energy sources [33,34]. Recently, it has been reported that this condition is temporary in the majority of the cases [38]. Stimulating the phrenic nerve with superior caval vein pacing has proven to be a valuable precaution during isolation of the right superior vein in our series. The reversibility of lesions with short cryoenergy applications remains to be proven at this site. All but one of the phrenic nerve paralysis were seen while ablating with a 23mm balloon deep inside the right superior pulmonary vein, and therefore we advise caution when using this balloon size in that region.

Outcome data

An intensive follow-up, aimed at detecting asymptomatic recurrence, shows 60% freedom of AF. Several authors consider the first three months a blanking period in which recurrence is common, while the effect of the procedure is delayed[39-41]. To our knowledge this has never been proven for transvenous catheter ablation of AF, and certainly not when using cryothermal energy. Moreover, there are reports that early recurrence after RF ablation is indicative of long term failure[42].

Limitations

In our series, patients received antiarrhythmic drugs before and after the procedure, which could be regarded as a limitation of the study. However, all of the patients had documented episodes of AF while taking their antiarrhythmic drugs before ablation. Continuing the drug therapy can be considered as a way to reduce a potential bias due to changes in pharmacological treatment.

The fact that the heart rate at month 3 was comparable to the baseline value, underscores that the baseline autonomic situation was present again, without a change in AF occurrence versus month one and two. We are currently continuing our long term follow up with cessation of antiarrhythmic drugs in patients who are free of AF after three months to further examine the recurrence rate in this group.

Conclusion

We consider cryoablation with a balloon as a feasible initial approach for patients presenting with paroxysmal AF. The technique has an acceptable learning curve. The most frequent complication is phrenic nerve paralysis when ablating the right superior pulmonary vein, but this proved to be reversible in some of the cases.

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Chapter two

Symptoms versus objective rhythm monitoring in patients with paroxysmal atrial fibrillation undergoing pulmonary vein isolation

Janse PA, van Belle YL, Theuns DA, Rivero-Ayerza M, Scholten MF, Jordaens LJ. Symptoms versus objective rhythm monitoring in patients with paroxysmal atrial fibrillation undergoing pulmonary vein isolation. Eur J Cardiovasc Nurs. 2008 Jun;7(2):147-51.

Abstract

Background: Pulmonary vein (PV) ablation is a treatment option for patients with atrial fibrillation (AF). The efficacy of treatment is often assessed by the evaluation of symptoms. However, a high proportion of AF episodes occur in the absence of symptoms as observed in pharmacological treated patients. The purpose of this study was to assess the association of symptoms and AF in patients who underwent PV ablation for the treatment of paroxysmal AF.

Methods: All consecutive patients scheduled for PV ablation received an event recorder 1 month prior to the ablation for the period of 4 months. Event strips were sent by telephone on a daily basis, and in case the patient suffered palpitations or other symptoms believed to be related to the arrhythmia.

Results: Forty-one patients (7 females; mean age 52 years (range 24 to 71 years)) sent a total of 3046 event strips (735 before ablation; 2311 after ablation). Before ablation, a total amount of 244 event strips were obtained of which were 85 (35%) were asymptomatic. After ablation, a total amount of 254 AF event strips were obtained of which 164 were asymptomatic (65%). Correlation between symptoms and rhythm was often absent during AF.

Conclusion: Our data demonstrate that for the evaluation of effectiveness of PV ablation, the lack of symptoms during follow-up is not a valid indication. Objective rhythm monitoring in order to detect asymptomatic AF should be performed.

Introduction

Atrial fibrillation (AF) is the most frequently encountered arrhythmia in the population and clinical practice[1]. A new, major challenge in the field of clinical electrophysiology is the potential curative treatment of AF. The growing knowledge of the initiating triggers, the perpetuating substrate and modifying factors has led to several potentially curative catheter ablation strategies[2-5]. However, variable success rates, roughly ranging from 60% to 90% have been reported. [6, 7] The efficacy of the procedure is not only dependent on the applied ablation strategy and the patient's characteristics, but also on the selected endpoints of follow-up[8]. In prior studies, absence of AF was documented by Holter[9, 10] and patient interviews. A major problem with AF is that AF episodes can occur in the absence of symptoms [7, 11, 12] Therefore, the purpose of this study was to compare symptoms as a parameter of recurrences with prolonged rhythm monitoring using transtelephonic ECG (T-ECG) in a group of patients undergoing echographically guided left atrial circumferential ablation

Methods

Study population

The study population consisted of 41 consecutive patients (pts) scheduled for intra cardiac echocardiographically guided circumferential isolation of the pulmonary veins (PV) by catheter ablation. The patients had highly symptomatic AF despite pharmacological treatment with at least 2 antiarrhythmic drugs. The clinical characteristics and demographic data are presented in Table 1.

Ablation procedure

Antral or left atrial circumferential ablation was performed guided by ICE, aiming at PV isolation, with disappearance of PV potentials. Two long sheaths were advanced into the left atrium after transseptal puncture guided by intracardiac echocardiography and fluoroscopy. Through the first sheath, a decapolar circumferential mapping catheter (Lasso^{TM}, Biosense Webster, Diamond Bar, CA, USA) was positioned in the antrum of the PV's. Through the second sheath, an 8-mm tip large-curve radiofrequency (RF) ablation catheter (Blazer, Boston Scientific Inc, Natick, MA, USA) was advanced into the left atrium. Antral PV isolation[13] was performed using RF energy between 30 and 70 Watts, based on micro bubble formation[14]. After isolation of all 4 PV's, the ablation catheter was placed in the superior caval vein (SVC) for additional isolation, except when phrenic nerve stimulation occurred at high output pacing. Patients were not sedated during the ablation but benzodiazepines and opiates were given throughout the procedure.

Table 1

Baseline Characteristics (n=41)	
Age (years)	52 ± 10
Male gender	34 (83%)
Left Atrial diameter (mm)	43 ± 5
Atrial flutter	12 (29%)
Medical history	
Hypertension	5 (12%)
Hyperthyroidism	3 (7%)
Cardiomyopathy	1 (2%)
Medical treatment	
Amiodarone	7 (17%)
Betablocker	29 (71%)
Digoxin	2 (5%)
Verapamil	2 (5%)
Flecainide	12 (29%)

Medical treatment at baseline was not changed until the 3 month follow up.

To ensure a minimum risk of thrombo-embolic complications during the procedure, activated clotting time (ACT) was monitored every 30 minutes with a target of > 350 seconds. Additional heparin infusion was given and titrated depending on ACT values. After the procedure patients were treated with heparin and oral anticoagulants were restarted. As soon as the PT-INR (prothrombin time international normalized ratio) was above 2.5 on 2 consecutive days heparin was stopped and discharge followed.

Transtelephonic ECG (T-ECG)

All patients received an event recorder (model ST-80 or model VS-20; Del Mar Reynolds Ltd, Hertford, UK) and were instructed how to transmit T-ECGs. One single-lead ECG with a fixed length of 1 minute could be recorded for each event. During a period of 30 days prior to ablation until 90 days after ablation, patients were prompted to record at least one T-ECG per day irrespective of symptoms. In case of palpitations or other symptoms believed to be related to AF, patients were instructed to transmit an additional T-ECG. Each transmitted T-ECG was accompanied by an oral description of symptoms experienced by the patient at the time of recording. Patients were free how to describe their symptoms. For each T-ECG, date, time, rate, rhythm, and eventual symptoms were noted and saved. The atrial arrhythmias were further classified as AF, atrial flutter (AFL), or supra ventricular tachycardia (SVT). The Holter analyses department and the electrophysiology research nurse did classification of T-ECG rhythms. In case of doubt an electrophysiologist was consulted. The AF and symptom burden were defined as the number of days on which AF or symptoms were present divided by the total number of days for which T-ECG information was available.

Outpatient clinic visits and follow-up

In the 30 days prior to ablation additional examinations were performed including a 12-lead 24-hour Holter, computer tomography of the thorax using contrast and transthoracic echo. The treating physician informed the patients in detail about the procedure and follow up. During this visit, which took place at the outpatient clinic, the patient was interviewed as well, in order to obtain a better understanding of the prevalence of AF. Patients were interviewed on subjective symptoms of AF using a 5 and 6-point Likert scale questionnaire, which addresses duration (6 point) and frequency (5 point) of AF episodes. This non-validated questionnaire was developed especially for patients undergoing a PV ablation. The research nurse who filled out all questionnaires interviewed patients. At 3 months follow-up this questionnaire was repeated, as well as the 24 hour Holter and the CT scan.

Statistical analysis

Continuous variables were expressed as mean ± SD, if normally distributed. Categorical variables were expressed as percentages. The Chi-square test was used for analysis of categorical variables. To adjust for multiple events per patient, the generalized estimating equations (GEE) method was used. A paired nonparametric exact method was used to compare the change in symptom frequency and duration scores over time for each patient. The level of statistical significance was set at 0.05. Statistical analyses were performed with SAS (version 8.2).

Results

Outcome measures: T-ECG's

A total of 3046 T-ECGs were transmitted by 41 pts (Tables 2 & 3). The target before ablation was 1240 T-ECGs (41 pts x 30 strips), and 3690 T-ECGs after ablation (41 pts x 90 strips). Actually, 39 pts transmitted 735 T-ECGs (59% of the target) before ablation while 41 pts transmitted 2311 T-ECGs (63% of the target) after ablation.

Before ablation 87 T-ECG's (out of 735 T-ECG's) showed asymptomatic AF (12%), sent in by 12 pts. After ablation 169 T-ECG's showed asymptomatic AF (7 %) sent in by 9 pts. Other asymptomatic atrial arrhytmias before and after ablation were also analysed and added 2%. With the chi- square analysis it was suggested ($p < 0.001$) that the number of asymptomatic AF episodes were relatively higher before than after ablation. Analysis performed with the GEE method to correct multiple episodes per patient confirmed the significant difference ($p < 0.001$). Symptoms reported by pts during T-ECG transmission before and after ablation were significantly related to the presence of AF ($p < 0.001$).

Table 2. Analysis of symptoms and rhythm as documented with transtelephonic recording (T-ECG) before ablation (n=735).

		T-ECG			
		AF	**SR**	**Other**	**Total**
Symptoms	Yes	156	31	9	196
	No	87	435	17	539
	Total	243	466	26	735

AF: atrial fibrillation; SR: sinus rhythm; Other: all atrial arrhythmias, including atrial flutter and atrial tachycardia. P< 0.001 with GEE analysis.

Table 3. Analysis of symptoms and rhythm as documented with transtelephonic recording (T-ECG) after ablation (n=2311).

		T-ECG			
		AF	**SR**	**Other**	**Total**
Symptoms	Yes	85	128	48	261
	No	169	1848	33	2050
	Total	254	1976	81	2311

AF: atrial fibrillation; SR: sinus rhythm; Other: all atrial arrhythmias, including atrial flutter and atrial tachycardia. P< 0.001 with GEE analysis.

Outcome measures: questionnaires

Questionnaires obtained before PV ablation reported a majority in weekly AF attacks in 22/41 pts (54%). During experienced recurrences, 31/39 (79%) reported that AF lasted for hours. This became significantly different after ablation (p<0,001) when the majority of all pts became completely asymptomatic (Figure 1). Only 2 patients reported a worsening condition with respect to frequency and 1 with respect to duration. An overall improvement was reported by 31/41pts (76%).

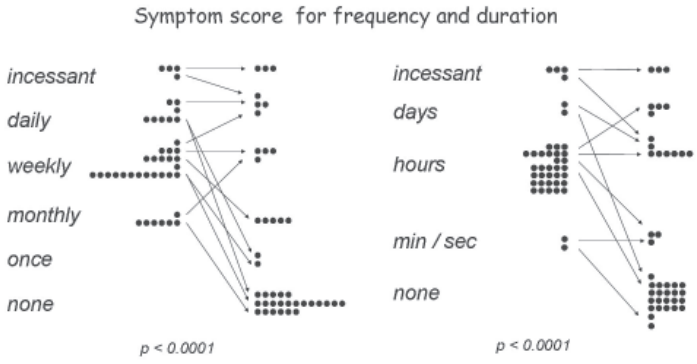

Figure 1. Questionnaire symptom scores with respect to frequency (left) and duration (right) of perceived arrhythmias. Each dot represents a patient with his evolution (arrow) before and after the procedures.

Outcome measures: questionnaires and AF in relation to T-ECG's

AF related symptoms as obtained by a questionnaire before and after ablation were compared with T-ECG's. At the 3 months follow-up visit, 31 pts reported an improvement of AF symptoms frequency. However, 18 pts still showed AF on the T-ECG's. Of those who did not feel an improvement only 6 out of 10 had AF on the T-ECG (Table 4).
A total number of 18 of the 26 pts, with an improvement with respect to duration, still showed AF on the T-ECG's. Of those without improvement only 5 out of 13 did not send in AF (Table 4). Both differences were not significant with respect to the proportion of patients. There was no significant difference when the number of episodes per patients was considered with GEE analysis.

Table 4. Number of patients who have AF on T-ECGs in relation to questionnaires (frequency and duration of AF) 3 months after ablation

Frequency	**AF on T-ECG (n=24)**	**No AF on T-ECG (n=17)**
No improvement	6	4
Improvement	18	13
Duration	AF on T-ECG (n=26)	No AF on T-ECG (n=13)
No improvement	8	5
Improvement	18	8

Discussion

The present study evaluated the accuracy of subjective and objective outcome measures in pts. who underwent PV ablation for the treatment of paroxysmal AF. In this study, a large proportion of episodes with AF occurred in the absence of complaints. Therefore, the major finding of this study is the high likelihood of over reporting success of PV ablation when it is based on subjective outcome measures.

Asymptomatic AF and transtelephonic ECG

During the analysis of T-ECG's it was noticed that many AF episodes were asymptomatic. Although this phenomena was previously reported by other investigators [7, 12, 15, 16], the proportion of asymptomatic AF in the T-ECG's was remarkable. This was before and after the procedure. Before ablation, about one third of AF was asymptomatic; after ablation the relation became inverted. Fortunately, the total arrhythmia burden decreased during follow-up. The high proportion of asymptomatic AF before the catheter ablation raises questions on patient selection in general. The inversion of symptomatic versus asymptomatic after PV ablation highlights the importance of objective criteria for reporting results.

Methodological considerations

As pts.recorded their heart rhythm only once a day for 1 minute (and additionally when symptoms occurred believed to be AF recurrences), a considerable amount of time remained during the day for asymptomatic AF recurrences. Objective methods commonly used to assess the presence or absence of AF are ECG, Holter, T-ECG or device implantation. However, all 4 have their limitations. A 12 lead ECG is very useful to determine the actual rhythm but it is easy to understand that this equipment cannot be used at home. This creates a great probability of missing an AF episode. The use of Holter recording is capable of identifying pts. with daily, weekly or permanent AF, as Holter recording is usually done 24 hours up to one week. In order to identify pts. with fewer AF episodes, it is useful to increase the frequency of follow up with the use of T-ECG's, in order to diminish the chance of asymptomatic AF recurrences outside a time window of Holter recording [17, 18]. When using daily T-ECG's, transmitted at fixed times and additionally during complaints, there is an increased chance to identify AF recurrences without noticeable complaints. The use of T-ECG was already used to recognize other arrhythmias than the arrhythmia which was targeted during ablation[19] but because of the growing knowledge that asymptomatic AF is likely to happen, nowadays many follow up procedures are performed with the use of T-ECG's [12, 15, 18, 20]. The use of an implantable device for objective AF documentation may be a very effective tool [11], but because of the limited investigations so far, further research on this topic should be considered[21].

Questionnaires

In order to assess information about AF and complaints related to AF, a patient interview or questionnaire at the follow-up visit can be performed. However, we showed that the success rate of PV ablation is higher as it is measured more subjectively and that many episodes with AF occur in the absence of complaints. Thus, the use of a patient interview or questionnaire in order to determine the absence of AF after a PV ablation should be considered as a limited method. Even when symptoms are present that can be related to AF recurrences such as dyspnea, dizziness, syncope, or palpitations, there is often no objective evidence confirming or rejecting the presence of AF. Questionnaires specifically designed for evaluating both AF recurrences and complaints related to AF are not yet validated[22]. Because we cannot rely on patient interviews or questionnaires to evaluate asymptomatic AF recurrences, there is a need for objective rhythm monitoring. The questionnaires we used were designed to obtain a better impression how complaints relate to objective rhythm monitoring. We did not use standardized quality of life questionnaires, but interestingly most pts. did report an improvement of quality of life during follow-up, which relates to the outcome of our questionnaires.

Nurse role

Because the growing number of patients with AF and the increased number of curative strategies such as PV ablations consequently leads to an increased workload at screening and follow up visits, there will be a need for specialised personnel. Well-trained specialised nurses or nurse practitioners in AF clinics can provide proper preparation and follow-up of PV ablation candidates. However, these nurses must be well instructed that the presence of AF and symptoms seemingly related to AF often do not correlate. Patients without symptoms can have AF and vice versa. Even a thorough patient interview done by an experienced professional cannot guarantee freedom of AF. The use of T-ECG's in combination with a patient interview or questionnaire is a useful method conducting a follow-up visit. However, there is a need to develop validated questionnaires specifically for AF, which can prove to be a valuable addition to objective rhythm monitoring [23]. Because of the high frequency of asymptomatic AF, it is in our opinion almost impossible to use questionnaires and patient interviews without objective heart rhythm monitoring, which is according to recent insights becoming the standard assessment of patients undergoing this kind of procedures [21].

Limitations

Patient compliance in sending T-ECG's was a major concern. We instructed patients as best as we could to encourage them sending daily T-ECGs. However, we do not know how many asymptomatic episodes were undetected, particularly due to sleep or briefness in duration, as all T-ECG's were patient activated. Of all reported symptoms, some comments seemed doubtful in relation to arrhythmia, like fever and painful feet. However, these symptoms were reported as being related to arrhythmia. Probably some patients underreported symptoms.

Conclusion

In conclusion, our data demonstrate that during evaluation of effectiveness of PV ablation, lack of symptoms during follow up is not a reliable indication of success. Objective rhythm monitoring should be performed in addition with questionnaires or patient interviews. Also, new validated questionnaires should be developed in the near future.

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Chapter three

One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation

Van Belle Y, Janse P, Theuns D, Szili-Torok T, Jordaens L. One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace. 2008 Nov;10(11):1271-6.

Abstract

Introduction: Isolation of the pulmonary veins (PVI) with cryoenergy delivered through a balloon is a new approach in the treatment of atrial fibrillation (AF), but long term follow-up is lacking.

Aim: To provide insight in the success rate and the incidence of recurrences.

Methods: Patients with symptomatic AF despite anti-arrhythmic drugs (AAD) were treated with cryoballoon PVI. Daily transtelephonic ECG monitoring, 24 hours Holter-ECG and an arrhythmia focused questionnaire were used to document AF.

Results:141 patients completed a follow-up of 457±252 days. Before ablation, Holter-ECG showed AF in 45%, including 16% continuous AF throughout the recording. Event recording revealed a median AF burden of 26%. The questionnaire showed a median of weekly AF-complaints lasting for hours. All but one patient had successful PVI with a single procedure. After ablation, AF (defined as lasting more than 30 seconds) was seen in 11% of Holter-ECG's, with 1% continuous AF. The event recording showed an AF burden of 9%. The median patient reported no more AF related symptoms. Recurrence during the first 3 months was predictive for later recurrence. A second procedure was performed in 24 patients. The freedom of AF was 59% without AAD after 1,2 procedures. Four right phrenic nerve paralysis occurred, all resolving within six months. No PV stenoses were observed.

Conclusion: PVI with a cryothermal balloon is an effective treatment for paroxysmal AF, resulting in a clinical success rate comparable to studies involving radiofrequency ablation. Temporary right phrenic nerve paralysis is the most important complication.

Introduction

Pulmonary vein isolation (PVI), has become an important treatment of patients with atrial fibrillation (AF). Reports have been published that show more than 80% freedom of paroxysmal AF during long term follow-up[1]. A large number of different approaches and techniques are currently routinely employed to achieve that goal, but the procedure remains technically challenging. The development of balloon cryoablation has recently proven to be safe and effective for PVI in animals[2-5] and humans[6]. While greatly simplifying the technical ablation aspects and showing 60% freedom of AF after a 3 month follow-up period follow-up period, long term results remained to be studied. The scope of our study is to report recurrences of AF during the first year, and complications after a cryoballoon PVI, using a wide array of follow-up modalities.

Methods

Inclusion

Between august 2005 and august 2007, a cryothermal balloon approach was used for all consecutive patients selected for circumferential PVI because of paroxysmal AF. All patients signed an informed consent. Inclusion criteria for ablation were symptomatic paroxysmal AF without major structural heart disease (normal left ventricular ejection fraction, no or only minor mitral insufficiency, normal to slightly enlarged left atrial diameter, assessed in the long parasternal axis). None of the patients had previously been ablated in the left atrium and all of them had episodes of AF despite concomitant anti-arrhythmic drug (AAD) treatment.

Screening before and assessment after ablation

Event recording
During one month before ablation, patients were instructed to use an event recorder for transmitting a daily transtelephonic 30 seconds ECG strip at a fixed hour. When symptoms were experienced, additional strips could be sent. This was continued until 3 months after ablation. The obtained ECG strips were coded as sinus rhythm, atrial flutter, atrial tachycardia, or AF. The AF burden was defined as the percentage of days on which an AF episode was transmitted. The compliance of patients with this follow-up method was monitored, and when no data were sent in, they were reminded to do so.

24-hour Holter
All patients were scheduled for 24-Holter recording at baseline and at 3 months follow-up. Thereafter, additional recordings were made at the physician's discretion as guided by patient

complaints. Each Holter was analysed for the presence of AF, runs of atrial tachycardia, atrial premature beats. Sustained AF was defined as lasting more than 30 seconds. If AF was present during the entire recording it was coded as continuous. The time in AF was measured.

QOL-questionnaire

All patients were asked to fill out a questionnaire pertaining their complaints before ablation and at 3 months after PVI. Both the frequency and the duration of AF-related complaints were graded according to a previously described and validated protocol[6, 7]. After ablation they were asked to grade their overall improvement at 3 months.

Outpatient screening and follow up

All patients were evaluated by one of two qualified physicians before ablation, and at 3 month intervals after ablation (LJ, YVB). At these times an extensive history, physical examination, and 12-lead ECG recordings were made. Transthoracic echocardiography and multislice CT were performed at baseline and at 3 months. Echocardiography was used to measure the left atrial dimensions and calculate the left atrial volume. Multislice CT was used to create a 3D anatomical reconstruction of the left atrium and to measure the ostial dimensions of the pulmonary veins. During these scheduled outpatient visits additional rhythm registrations and cardiac imaging was performed at the physician's discretion to investigate complaints or register recurrence of AF. The same was done at unscheduled visits at the outpatient clinic and at the emergency department,

Procedure

A detailed description of the cryoballoon ablation procedure has been given in a previous report[6]. A cavo-tricuspid isthmus ablation was performed in 7 patients because of documented isthmus dependent flutter. The cryoballoon size was selected upon availability until February 2007, and had to be larger than the PV diameter on the CT scan. From February 2007 on, the 28 mm size was preferred. Redo procedures were performed with the same protocol as the primary procedure.

Antiarrhythmic drugs

AAD's were stopped one week before ablation. After the PVI, patients were given their habitual drug regime until three months after ablation. If no recurrence during the first three months was observed, the AAD's were stopped. If recurrences were limited to the first month or if a reduction of AF-burden was obtained of more than 90%, AAD's were stopped at three months. If

not, either the drug regime was altered or a redo procedure was advised. If recurrence occurred after AAD cessation, they were restarted and altered if necessary.

Endpoints

Recurrence of AF was defined as the presence of at least one recording of AF after ablation, regardless of its origin (12-lead ECG, transtelephonic rhythm strip, 24-hour Holter recording, unsolicited tracing). Additional endpoints were improvement of QOL as perceived by the patient, reduction of AF burden with ≥90%, and disappearance of AF on the 24 hour Holter recording. The advice for a second procedure was based on presence early and late symptomatic recurrence under AAD. Finally, the results were reported according to the HRS/EHRA/ECAS recommendations[1].

Follow-up after the second procedure

The follow-up after a second PVI was performed in the same way as the first procedure, omitting the baseline Holter and event recording.

Statistical analysis

Continuous variables were expressed as mean ± SD if normally distributed, or otherwise by median. Continuous variables were evaluated using Student's *t* test or one-way analysis of variance. Categorical variables were expressed as percentages. The Chi-square test was used for analysis of categorical variables. A paired nonparametric test was used when appropriate. The Wilcoxon ranks test was used to compare the change in symptom frequency and duration scores over time for each patient. Actuarial event-free rates from atrial fibrillation were calculated according to the Kaplan Meier method and were compared by use of the log-rank test. The level of statistical significance was set at 0.05.

Results

Patient description

The first 141 consecutive patients treated with this technique at our institution, were included in this study. Two patients were excluded from the follow-up analysis: one was excluded due to equipment failure at the time of ablation, and one developed acute pulmonary oedema for which the procedure was aborted before ablation. The demographic data is presented in table 1.

Table 1. Patient demographics

Patient number (nr)	141
Male / Female	100/41
Age (years)	56±9
Follow-up duration (days)	457±242
Left atrial diameter (mm)	42±7
Valvular heart disease (nr)	5
Arterial hypertension (nr)	19
Thyroid disease (nr)	7
Amiodarone treatment (nr)	35

Primary procedure results

PVI was achieved in 139 patients within one procedure. This was done with a 23 mm balloon in 33 patients, a 28 mm balloon in 99 cases, while both sizes were used in 7 cases. A Freezor Max (Cryocath) was used to complete PVI in 56 patients (a total of 86 veins), on average 4±2 applications was needed to complete the isolation. The mean procedure time was 207 ± 79 min, the mean fluoroscopy time 50 ± 28 min. A total number of 1243 applications was given with the balloon, a mean of 9±3 per patient. With the Freezor Max 242 applications were given. Eight patients experienced pericardial effusion, including one due to rupture of the left superior pulmonary vein caused by distal cryoballoon inflation, one had a hematopneumothorax. Phrenic nerve paresis was observed in spite of precautions in 4 patients.

Follow up duration

The mean follow-up in this prospective study was 457±252 days, until March, 31st 2008.

Event recording

A total number of 2019 rhythm strips before, and 7986 after ablation were available, of which 534/2019 (26%) before, and 686/7986 (9%) after ablation showed AF. Of the entire group, 119 patients had reliably transmitted transtelephonic rhythm strips before and after ablation. On average, they transmitted 17±7 strips per month before ablation, and 20±9 strips/month after ablation. Of this group, 42 (35%) patients showed no AF episodes on the baseline event recording. Their AF-burden before and after ablation is represented in figure 1. The reduction in AF-burden was highly significant ($p<0,0001$) (table 2). In total, 66 patients (55%) did not have any recurrence of AF after ablation on this event recording ($p<0,005$). When looking at patients with recurrence, the AF burden still showed a significant reduction after ablation ($p<0,0001$). The baseline burden between those with and without recurrence did not differ significantly.

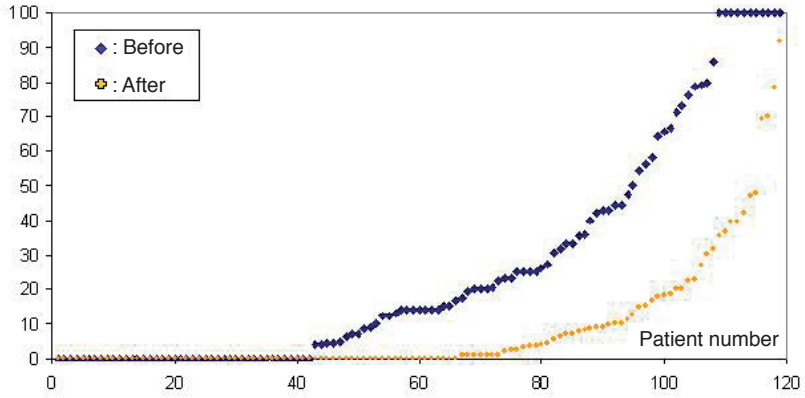

Figure 1. AF burden as calculated from transtelephonic ECG recordings sorted ascending by the burden before pulmonary vein isolation (before) and burden sorted ascending after isolation (after). The area between both curves represents the reduction in AF burden for the entire group.

Table 2. Results of event recording one month before, and 3 months after ablation

		Total Group			Recurrence			No Recurrence		
		before	**after**	**p**	**before**	**after**	**p**	**before**	**after**	**p**
Proportion with AF	**n**	**77/119**	**53/119**	**<0,005**	**41/53**	**53/53**	**NA**	**36/66**	**0/66**	**NA**
AF	Mean±SD	27±32	9±17		33±34	19±21		21±33	0	
Burden	Median	14	0	<0,0001	20	10	<0,0005	5	0	NA
(%)	(Range)	(0-100)	(0-92)		(0-100)	(1-92)		(0-100)	(0-0)	

Data from daily transtelephonic event recording for the patients with recordings before and after the intervention. Burden means the percentage of days with AF present in a recording. AF: atrial fibrillation; NA: not applicable; n: number; SD: standard deviation

24-hour Holter recording

In total, 128 patients had performed a 24-hour Holter recording before and 129 patients three months after ablation. Before ablation, 58 (45%) patients had AF documented on their Holter recording, of whom 21 (16%) patients had continuous AF during the entire 24 hours. After ablation, this decreased to 14 (11%) patients with AF on the Holter, of whom 1 (1%) patient with continuous AF during the entire 24 hours. The median time in AF for those with paroxysmal AF decreased from 19 % to 8 %. Heart rate during sinus rhythm did not change significantly before and after ablation (67±11 versus 68±10 bpm).

Quality of life

Patients assessed the frequency, duration and improvement of their complaints. The median scores (as explained in table 3) for frequency and duration before were respectively 3 (range 1-5) and 3 (range 1-5), being weekly episodes lasting for one or more hours. After ablation this

was significantly reduced to median values of 1 and 1 (ranges for both 1-5), being no more complaints ($p<0.01$). Paired data was available in 125 patients. After a three month follow-up period, 90 (72%) of patients considered themselves improved, 22 (18%) considered their symptoms as equal, and 13 (10 %) of patients considered their symptoms as worse.

Table 3. Score for AF episode frequency and duration

Score	Frequency of AF episodes	Duration of AF episodes
1	None	None
2	Monthly	Minutes/Seconds
3	Weekly	Hours
4	Daily	Days
5	Incessant	Incessant

AF: atrial fibrillation

Clinical long term follow-up results

From the initial procedure, until redo or march 31st 2008, an additional 597 rhythm strips and 191 Holter recordings were obtained from the entire group either at the routine follow-up visits or when presenting with complaints. On average a patient had 10±9 rhythm strips taken during the rest of his follow-up, and had 1,3±0,7 Holters performed after the initial three months.

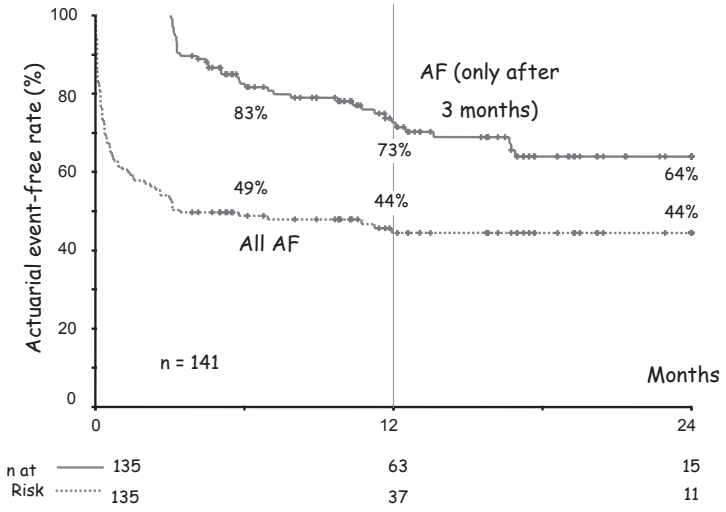

Figure 2. Event-free survival curve for atrial fibrillation (AF) after a single ablation procedure. The two curves represent the same patient population. The upper curve (AF only after 3 months) represents the event-free survival after a 3 month blanking period; the second curve (All AF) represents the event-free survival without the 3 month blanking period. The patient numbers of both groups are represented at the bottom.

Freedom from recurrent AF

Combining all these resources, actuarial event-free rates from any AF were calculated (figure 2). The event-free survival rate at 365 days was 44%. When all events in the first three months were blanked, and the curve was constructed from 90 days on, the event-free survival rate at 365 days was 73 % (p<0.0001). When patients with and without a recurrence in the first three months were compared (figure 3), it became clear that a recurrence in the first three months was highly predictive for recurrence after 3 months, whereas absence of events in the first three months was highly predictive for a low recurrence rate (logrank 23, p<0.0001).

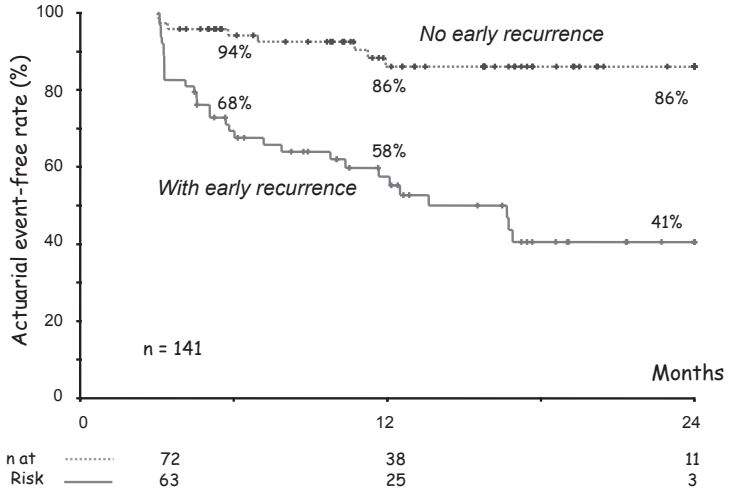

Figure 3. The event-free survival curve for atrial fibrillation (AF) after a single ablation procedure, employing three month blanking period. The upper curve (no early recurrence) is the patient population that did not have recurrence of AF during the blanking period. The lower curve (with early recurrence) represents the group that experienced recurrence of AF during the 3 month blanking period. Patient numbers of both groups are represented at the bottom.

Recurrence of AF and AAD treatment

After one procedure, 49% (68/139) were free from AF without AAD's. Of the remaining 51% (71/139) with AF recurrence, 27% (37/139) were advised to undergo a second procedure and 24% (34/139) continued on medical treatment due to a decrease in AF burden. In total 34% (47/139) continued on medical treatment, and 17% (24/139) agreed to undergo a second procedure. These data are represented in figure 4.

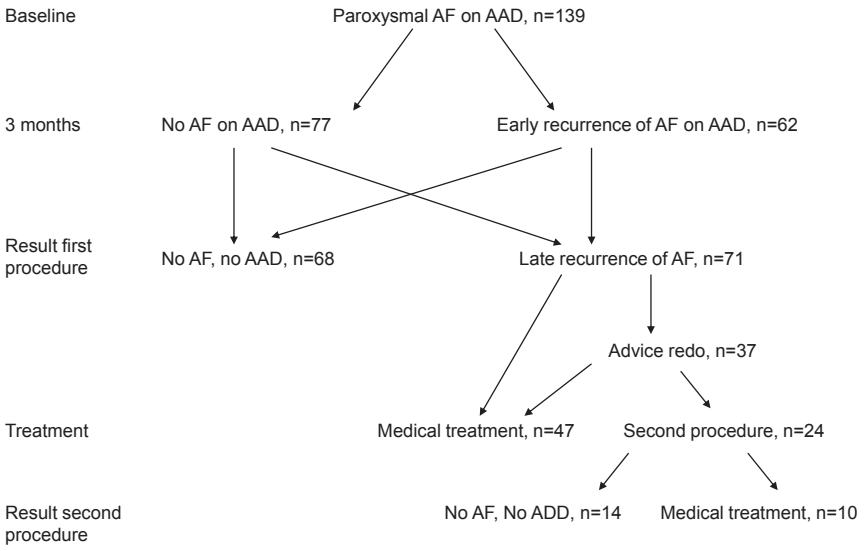

Figure 4. Graphical representation of the overall one year clinical outcome after a mean of 1,2 procedures, presented as patient numbers. AF, recurrence of atrial fibrillation; AAD, anti-arrhythmic drugs.

Recurrence of AF after a second procedure

Of the 37 patients to whom a redo procedure was advised (always after 3 months), 24 underwent a second procedure. On average, there was reconduction to 3±1 PV. Reconduction was found in 20/24 (83 %) left superior PV`s, in 22/24 (92 %) left inferior PV`s, in 17/24 (71 %) right superior PV`s, in 14/24 (58%) right inferior PV`s. During this second procedure all reconducting veins were successfully isolated with the same technique. The average follow-up after this second procedure was 225±137 days. During this follow up, 8 patients had an early recurrence, after a mean interval of 15 days; three had a late recurrence after 3 months, making the total number of patients with recurrence after a redo procedure 46% (11/24).

Overall recurrence of AF

After a mean of 1,2 procedures, 82/139 (59%) of patients were free from AF without AAD's and 57/139 (41%) of patients were under medical treatment, with a reduced AF-burden.

Long term complications

Multislice CT scan showed there was no significant difference in PV-diameter before and after the procedure. The mean PV diameter was 18.0 ± 3.8 mm before the procedure, versus 18.1 ± 3.7 mm after. Two patients complained of haemoptysis during the first month after PVI, but without

PV-stenosis on the multislice CT scan. In both of these patients the problem did not recur after temporary cessation of the anticoagulation therapy. The haematopneumothorax resolved completely. Two patients needed transfusion, because of a haematoma in the groin and a retroperitoneal bleeding respectively. Two arteriovenous fistula were reported. Four asymptomatic right phrenic nerve paralyses were observed, persisting at discharge. Three patients had recovery of their diaphragm movement at 3 months; all four had recovered at 6 months. One perimitral flutter was documented, and successfully ablated.

Discussion

We describe in this paper the clinical 1 year follow-up of a large consecutive group of patients treated with a cryothermal balloon approach. The major finding is that we had a clinical freedom from AF comparable to studies using radiofrequency ablation. Further, early recurrence was indicative for later clinical failure, and associated with reconduction to the veins.

Complications

The potential advantages of cryoenergy were already described in animals, and have been suggested for humans as well[3, 8]. No thromboembolism was seen in our group, which seems equivalent to similar radiofrequency populations. In contrast to ostial RF ablation[1], comparison of ostial PV diameters obtained from serial computed tomography shows again that cryothermal energy, although being delivered at the antral and ostial regions causes no pulmonary vein stenosis[8]. Although a rare complication in RF ablation, we found a 4% incidence of right phrenic nerve paresis, with complete recovery in all of them at the end of follow-up. A large multicentre study found this in around 8% of cases, also reporting complete recovery in all. This complication was also reported in different balloon delivery systems, independent of the energy used (ultrasound, high intensity ultrasound)[9, 10]. In RF-ablation the complete recovery of this nerve can only be expected in 66% and partial recovery in 17%[11].

Freedom of AF

The event-free survival in our analysis is comparable with data in the worldwide survey on RF ablation of paroxysmal and persistent AF[12]. After a single procedure 73% reported symptom improvement, coinciding roughly with the advice for a second procedure in 23%, which was given after objective recurrences in spite of AAD therapy after 3 months. Previously published cryoablation studies in literature show success rates varying between 56% freedom of AF after one year (including 21% on AAD)[8], and 71% freedom of AF after four years (including 22% on AAD) with a segmental isolation[13]. A cryoballoon study with a very limited number of patients

shows freedom of AF in 90% of cases after six months[14], whereas a multicentre study reveals sinus rhythm in 74% of patients after one year without AAD, in paroxysmal AF, and 42% without AAD in persistent AF[15]. Our study yields a lower success rate, with 59% being free from AF at one year without the use of AAD. This is probably due to a difference in follow-up method, since no large difference in patient characteristics is obvious.

Reconduction

Previous studies have shown AF recurrence to be associated with reconduction in the PV's[16-18]. This was also true for our study. In the patients considered for a repeat procedure, we found high rates of reconduction from the left atrium to the PV's.

Limitations

The major limitation of this prospective study is that it is observational, and therefore substantive conclusions can not be drawn regarding its relative advantages or disadvantages compared with radiofrequency ablation. For this a randomised head-to-head comparison would be required.
A second limitation is the less intense follow-up after the initial three month period. Although a large effort was made to document long term clinical efficacy, daily transtelephonic event recording over a very long period proved to decrease patient compliance dramatically, so that this was not a feasible method.

Conclusions

The data we present indicate that cryoablation with a balloon delivery system yields similar results to those reported on RF ablation, and comparable to other cryoballoon trials. An acceptable complication rate was observed.

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Chapter four

Focal AF-ablation after pulmonary vein isolation in a patient with hypertrophic cardiomyopathy using cryothermal energy

Van Belle Y, Michels M, Jordaens L. Focal AF-ablation after pulmonary vein isolation in a patient with hypertrophic cardiomyopathy using cryothermal energy. Pacing Clin Electrophysiol. 2008 Oct;31(10):1358-61.

Abstract

A 42-year old male patient, with a history of hypertrophic cardiomyopathy (HCM), an ECG pattern of ventricular preexcitation typical for mutations in the PRKAG2 gene, and highly symptomatic paroxysmal drug resistant atrial fibrillation (AF) underwent successful circumferential isolation of his pulmonary veins using a 28 mm double lumen cryoballoon. Because AF was still inducible with programmed stimulation, fractionated signals were targeted in the left atrium with a conventional cryocatheter. Ablation of an endocardial focus with fractionated potentials at the base of the left appendage terminated the episode and rendered AF non-inducible. No recurrence of AF was observed during a 10 month follow-up period.

Case presentation

A 42-year old male patient, with a history of hypertrophic cardiomyopathy (HCM) and highly symptomatic paroxysmal drug resistant atrial fibrillation (AF) was referred for pulmonary vein isolation. He had required cardioversion on two occasions over the last 12 months. His ECG (figure 1) showed a preexcitation pattern, however a previous EP-study had excluded the presence of an accessory pathway. Genetic testing revealed the patient to be carrying an unclassified variant in the PRKAG2 gene (c.1004T>C). Family screening showed the father to be of the same phenotype, also carrying the unclassified variant. Mutations in the PRKAG2 gene typically cause an accumulation of cardiac glycogen, leading to left ventricular hypertrophy, mimicking preexcitation on the surface ECG[1].

Transthoracic echocardiography revealed a left atrial diameter of 40 mm (measured in a parasternal long axis) and a septum measuring 25 mm, without LVOT-gradient. Three-dimensional CT reconstruction of the left atrium showed 4 individual pulmonary veins with a normal anatomy.

The procedure was performed under general anesthaesia after transesophageal echocardiography. Both femoral veins were punctured and an uncomplicated transseptal puncture was performed with an 8F sheath. A 20-polar circular catheter revealed PV-potentials in all of the veins during sinus rhythm. The transseptal sheath was exchanged for a 12F steerable sheath, and a 28 mm double lumen cryoballoon catheter (Arctic front®, Cryocath, Quebec) was advanced into the left atrium using an over-the-wire technique. Each vein was catheterised with the wire in every major side branch and the inflated balloon was positioned in the ostial region aiming to achieve complete occlusion of the targeted vein (figure 2). Several cryoapplications were given, each lasting for 5 minutes, in the different veins (LUPV : 2, LIPV : 2, RUPV : 4, RIPV : 1). After this, the balloon catheter was removed and the pulmonary veins were checked for electrical activity with the 20-polar circular catheter. As PV-potentials could be detected at the ridge between LUPV and LIPV, 2 more applications were given in the left atrial appendage. After confirmation of isolation of the veins, pacing inside the veins proved exit block to the left atrium. Induction of AF was then performed by burst pacing during 5 seconds with a cycle length of 200 ms. This was done at the anterior and posterior aspects of the LA, the lateral wall of the RA and inside the CS. Persistent AF could be induced from inside the CS. Electrical cardioversion was performed and the induction protocol was repeated, confirming the induction from the CS without the ability to induce elsewhere. During AF, an 8mm conventional cryocatheter (Freezor Max®, Cryocath, Quebec) was introduced into the left atrium. It was positioned in the inferior and anterior aspect of the left atrium, showing local potentials fluctuating between clearly separated nearly regular activation and high frequency continuous activity. When positioned at the anterolateral atrium near the mitral valve, below the ostium of the auricle, a continuous fragmented and high frequency activation pattern was locally observed (figure 3). A 5 minute application was

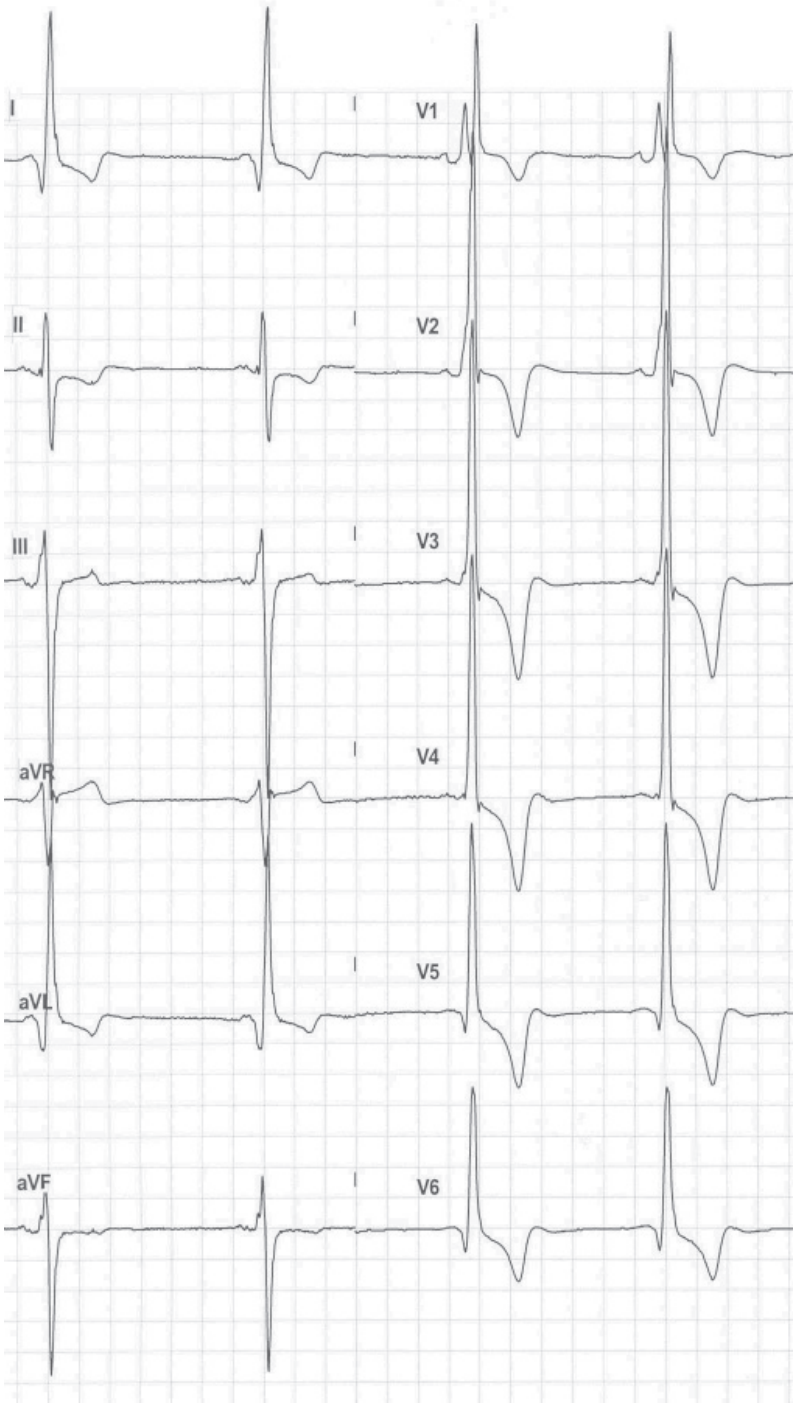

Figure 1. 12-lead ECG with the typical PRKAG2 pattern. The PR interval is 125 ms.

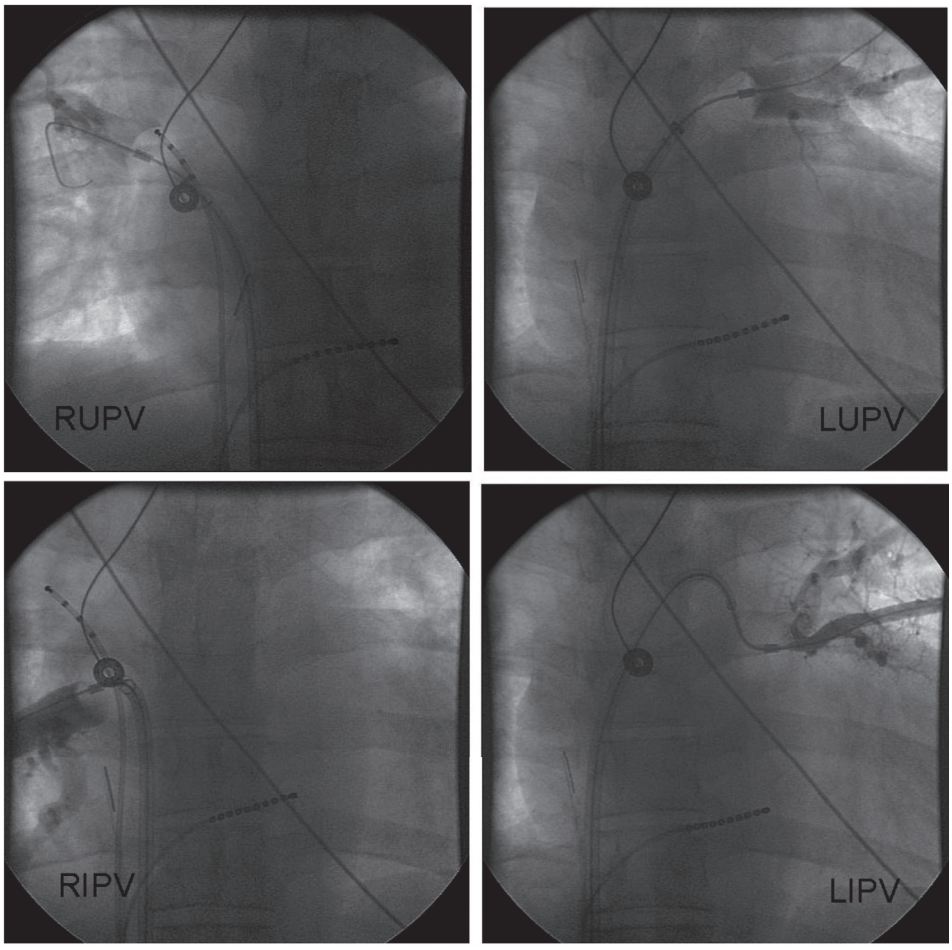

Figure 2. Consecutive balloon occlusion of all 4 pulmonary veins (LUPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, RUPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein).

given at the site, with termination of AF after 26 seconds (figure 4). After this application the induction protocol was repeated at the different sites, but burst pacing from the CS could no longer induce AF on 8 separate attempts. The procedure was terminated. Oral anticoagulation was continued and he was discharged the next day with a transtelephonic monitoring device. Daily rhythm strips were sent in during 3 months. The patient visited regularly at the outpatient clinic and a 24 hour holter monitoring was performed. After a follow-up period of 10 months, no AF recurrence could be detected and the patient has remained free of arrhythmia symptoms, while he suffered from daily episodes before ablation.

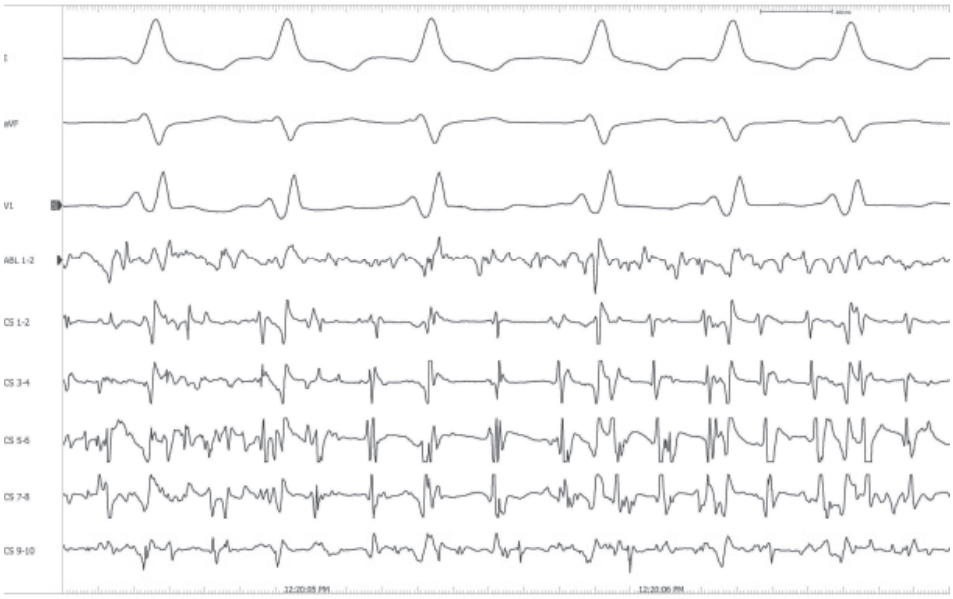

Figure 3. Continuous fragmented signal with a high frequency of activation on the mapping catheter near the ostium of the left atrial auricle during atrial fibrillation. Surface leads I, aVF and V1, mapping catheter (Abl) and CS leads (CS) are shown.

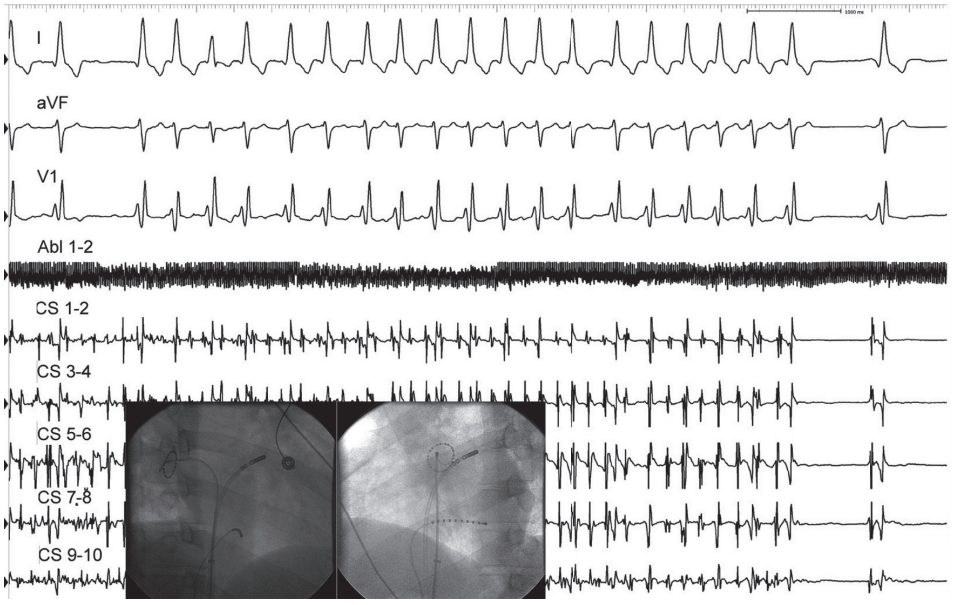

Figure 4. Termination of atrial fibrillation during application of cryoenergy at the site of fragmented potentials. The insert shows the ablation catheter in RAO and LAO. Abl = ablation; CS = coronary sinus.

Discussion

In this patient with left ventricular hypertrophy and an ECG pattern of ventricular preexcitation, typical for mutations in PRKAG2, AF was the main manifestation of his cardiac disease. No ventricular preexcitation was present[2-4]. It proved to be possible to treat his AF with catheter ablation.

This case is highly suggestive of the fact that a perpetuator of AF was present in the proximity of the distal CS. The localisation of both the inducing burst pacing and the successful application tend to suggest that the ligament of Marshall or the CS itself was responsible in this case. The fact that the ablation was performed from the endocardium of the LA on the other hand rather suggests a myocardial origin of the initiating focus, which would fit with the notion that AF occurs in HCM as an indicator of disease progression to the atria[5].

The ablation of fragmented signals has gained interest as an invasive therapy of AF[6].
Noninducibility after pulmonary vein isolation was comfirmed and was associated with the long term maintenance of sinus rhythm, as recently shown in literature[7].
In our case, a novel technique for circumferential cryoablation of the pulmonary veins by cryoballoon combined with focal cryoablation of a re-entrant source has proven to be successful in this patient with HCM[8]. Whether the driver originated from a focal region of diseased atrial myocardium or a nearby anatomical structure remains the question. Whether this was associated with this particular storage disease is another question.
AF is the most common arrhythmia in patients with HCM, and occurs in 20 to 25%, predicting morbidity and mortality[9]. Therefore, maintaining sinus rhythm is highly desirable in these patients. There are several reports describing the value of AF ablation for maintenance of sinus rhythm in patients with HCM. In a limited series (4 patients), the effectiveness was reported of pulmonary vein isolation for symptomatic paroxysmal AF, with a very high success rate (100%)[10]. In two later reports, describing HCM populations with paroxysmal and persistent AF (27 and 26 patients), the freedom of AF during long term follow-up was 70%[11] and 77%[12] respectively. In addition, it has been shown that sinus rhythm after AF ablation improves functional status and reduces the need for pharmacological treatment[12]. Therefore, we believe invasive management of HCM patients presenting with AF is highly recommendable.

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Chapter five

Electro-anatomical mapping of the left atrium before and after cryothermal balloon isolation of the pulmonary veins

Van Belle Y, Knops P, Janse P, Rivero-Ayerza M, Jessurun E, Szili-Torok T, Jordaens L. Electro-anatomical mapping of the left atrium before and after cryothermal balloon isolation of the pulmonary veins. J Interv Card Electrophysiol. 2009 Jun;25(1):59-65

Abstract

Introduction: The 28 mm cryoballoon catheter is a device used for pulmonary vein isolation (PVI). The aim of this study was to evaluate the extent of the ablation in the antral regions of the left atrium.

Methods and Results: Eighteen patients with drug refractory, symptomatic, paroxysmal AF were enrolled. A 3D electroanatomic reconstruction of the left atrium was made before and after successful PVI with the 28 mm cryoballoon. Markers were placed at the ostium. Sixteen patients were mapped. Fourteen patients had 4 veins each, and 2 patients had a common ostium of the left sided veins. All separate ostia were isolated in the antral region. The two common ostia showed ostial isolation. There was a significant difference in vein size between the common (29 and 31 mm) and the separate ostia (19 ± 4 mm) ($p<0,01$). The performance of an additional segmental ablation if balloon PVI did not eliminate all electrical activity, did not influence the extent of the ablation. The earliest left atrial activation during sinus rhythm was located in the superior septal region before ablation in all patients. After ablation, 2 patients showed a substantial downward shift towards the middle and inferior septal region respectively (NS). Four patients demonstrated a slight downward shift of the first activation.

Conclusions: In cryoballoon PVI, the majority of the veins undergo antral isolation. Veins with a diameter larger than the balloon, are isolated ostially. In individual cases, the left atrial activation sequence appears to be altered after ablation.

Introduction

The cryothermal balloon, or cryoballoon, is a novel technology, developed for pulmonary vein (PV) isolation. It is a catheter based device with the potential of performing a circumferential ablation, thus isolating the PV muscular sleeves in a limited number of applications. Since cryothermia causes no PV stenosis[1-3], the ablation can safely be performed at the ostial level of the pulmonary vein, but the question remains to what extent cryoballoon ablation modifies the left atrial substrate. After a large experience in animal testing was achieved by several authors[4-7], the first human results are promising as a treatment for paroxysmal atrial fibrillation (AF)[8]. The aim of this study was to evaluate the effect of the cryothermal balloon on the antral regions of the left atrium.

Methods

Inclusion

Patients with documented symptomatic paroxysmal AF despite antiarrhythmic drugs, at two or more occasions, were accepted as candidates for this study. Exclusion criteria were: left atrial dimension > 50 mm measured in the parasternal long axis, as assessed with transthoracic echocardiography, valvular heart disease and advanced age.

Pulmonary vein isolation procedure

The procedure was performed under conscious sedation. Both femoral veins were used for venous access. A 10 Fr, intracardiac echocardiography (ICE) catheter (Flexview, EP Med Systems, New Jersey, USA) (ICE) was introduced through the left femoral vein and positioned in the right atrium. A decapolar catheter was placed in the coronary sinus. A single transseptal puncture was performed using a transseptal needle (BKR1, St Jude Medical, Minnesota, USA) and an 8F sheath (Fastcath SL1, St Jude Medical, Minnesota, USA), guided by both intracardiac echocardiography and fluoroscopy. ICE was also used to ensure a posterior transseptal approach. A 6 Fr angiocatheter (Mach 1 MP2, Boston Scientific, Massachusetts, USA) was used to make a selective angiography of every pulmonary vein for locating the ostium. A circular mapping catheter was advanced and positioned in the antrum of each pulmonary vein to record the presence of PV-potentials. The position of the circular catheter was guided by ICE. If the patient was in AF at baseline, resistant to electrical cardioversion, he was excluded from the mapping study. A 4 mm mapping catheter was then used to create an electroanatomical reconstruction of the left atrium with a CARTO-system (Biosense Webster, California, USA) or an RPM-system (Boston Scientific, Massachusetts, USA). A high density voltage map was created of the antral

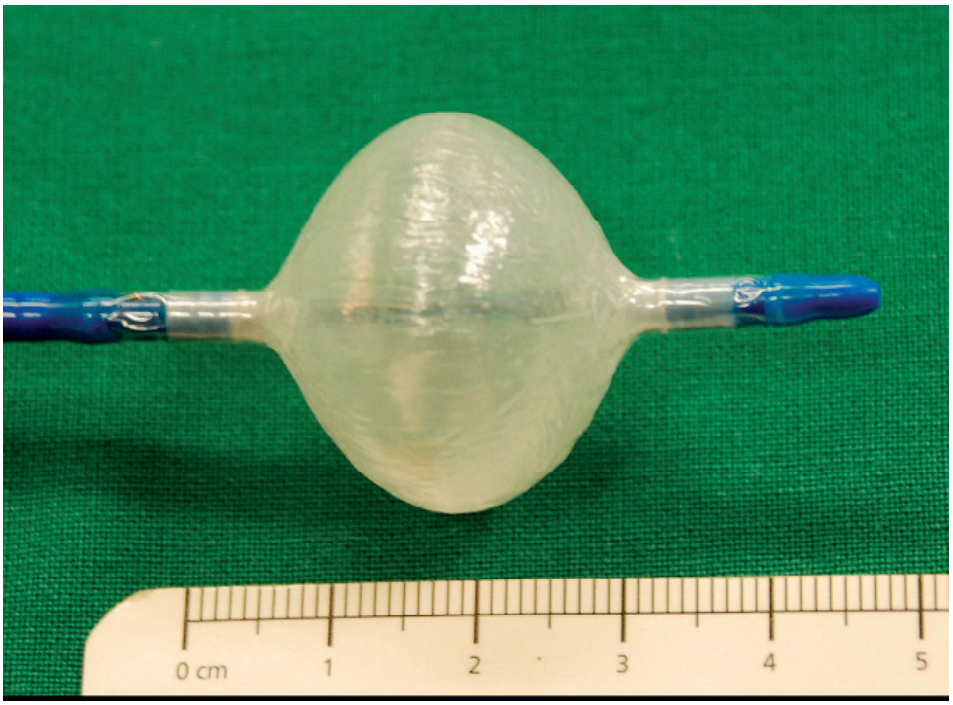

Figure 1. Inflated 28 mm double lumen cryoballoon

pulmonary vein region, as guided by the fluoroscopic images and the ICE. Tags were placed at the position of the ostial border of the pulmonary vein. After a satisfactory electroanatomical map was achieved, the sheath was exchanged for a 14 Fr steerable sheath (FlexCath, CryoCath, Montreal, Quebec). The mapping catheter was exchanged for a 28 mm, 12 Fr double lumen cryoballoon catheter (Arctic front, Cryocath, Montreal, Quebec) (figure 1), and positioned over an exchange wire to occlude the ostium of each PV. Cryoenergy was given for 5 minutes per application. The applications per vein were directed towards the major side branches, and a minimum of two applications per vein were given. If a common left ostium was present, ablation was performed with the 28 mm cryoballoon at least twice towards the major superior and inferior side branches, so a minimum of four applications were delivered. Before targeting the right superior pulmonary vein (RSPV), a quadripolar catheter was positioned in the superior caval vein for continuous phrenic nerve stimulation during cryoapplication. At loss of capture, the ablation was instantaneously terminated. After targeting all PV's, the cryocatheter was exchanged for the circular mapping catheter to check for remaining electrical activity. If this registration showed persistence of the PV-potentials, the cryoballoon was introduced again, trying to maximize wall contact at the location of the remaining potentials (as guided by the circular catheter, ICE and fluoroscopy) and an additional two applications were given per vein. If after this second ablation attempt the activity remained present, a conventional cryocatheter (Freezor Max, Cryocath, Montreal, Quebec) was used to perform a segmental isolation through

the same transseptal puncture. After obtaining isolation of all the veins, the 4mm mapping catheter was introduced in the left atrium and a new electroanatomical map was made with special attention for mapping the ablated regions and the activation of the earliest activation site of the left atrium. Throughout the procedure, the activated clotting time was monitored every 30 minutes and maintained above 350 seconds.

Analysis of the electroanatomical maps

The voltage map of the antral regions as guided by ICE was compared before and after ablation. The antral regions were evaluated for isolation. Local voltages of <0,05mV were considered as ablated tissue. The location of the first activation in the left atrium during sinus rhythm was determined before and after ablation.

Statistical analysis

An unpaired Student T-test was used for comparing the diameters of the pulmonary veins. A Wilcoxon Rank test was performed for evaluating the activation change of the left atrium.

Results

PVI

Eighteen consecutive patients were included. Two patients were excluded for mapping due to the presence of AF, with multiple recurrences after cardioversion. The procedure data is presented in table 1. Two patients had a common left sided ostium which was also targeted with the cryoballoon. Electrical activity was present in all of the veins. All patients underwent successful pulmonary vein isolation, with absence of PV-potentials at the end of the procedure. Mean procedure and fluoroscopy times were 174±39 and 30±12 minutes respectively. The procedure and fluoroscopy times for making the electroanatomical maps were deducted from the actual times since this was not essential in obtaining PV isolation. In 14 procedures only the cryoballoon was used, and 4 procedures required an additional segmental approach with a linear cryocatheter. No complications occurred in this series. No phrenic nerve paralysis necessitated early termination of any RSPV ablation, no paralysis was seen at the end of the procedures.

Mapping

Qualitative assessment of the electroanatomical maps revealed antral isolation in all veins that had separate ostia. In the right sided veins, the antrum was isolated in all instances, while on the

Table 1

Patient nr.	Mapping system	Balloon applications (n)	Segmental applications (n)	Fluoroscopy time (min)	Procedure time (min)	Largest diameter LSPV (mm)	Largest diameter LIPV (mm)	Largest diameter LCPV (mm)	Largest diameter RSPV (mm)	Largest diameter RIPV (mm)	Activation change
1	Carto	14	-	30	180	18,5	18,6	-	22,6	18,5	-
2	Carto	11	-	23	160	23,4	20,1	-	22,1	16,1	±
3	RPM	13	-	19	140	27,1	20,9	-	23,6	19,0	-
4	Carto	13	-	15	180	-	-	29,2	23,9	23,0	-
5	RPM	11	4	45	230	14,6	16,3	-	12,7	22,7	-
6	Carto	11	-	18	140	20,6	20,4	-	19,7	8,4	-
7	-	13	5	52	220	25,7	19,9	-	21	21,6	NA
8	Carto	12	-	37	180	19,6	17,8	-	16,4	17,6	-
9	RPM	11	-	22	120	18,8	17,9	-	23,7	19,4	+
10	Carto	10	-	26	100	22,9	18,2	-	18,1	13,5	-
11	Carto	9	3	45	240	17,8	15,7	-	21,1	18,4	±
12	Carto	13	-	21	180	-	-	31,1	23,7	18,3	-
13	RPM	14	2	53	220	24,3	18,3	-	12,7	24,9	-
14	Carto	15	-	36	200	22,6	16,3	-	21	12,7	+
15	Carto	11	-	25	150	24,2	16,6	-	18,6	12,0	±
16	Carto	13	-	16	140	23,7	15,9	-	14,6	16,1	±
17	-	13	-	34	180	25,4	17,3	-	18,6	24,9	NA
18	Carto	11	-	30	180	20,6	20,0	-	20,2	18,5	-

Procedure parameters

The pulmonary vein diameters were measured in both frontal and transverse CT slices, only the largest diameter is presented.

n: number

min: minutes

mm: millimetre

NA: not available

+: occurrence of large activation change

±: occurrence of minor activation change

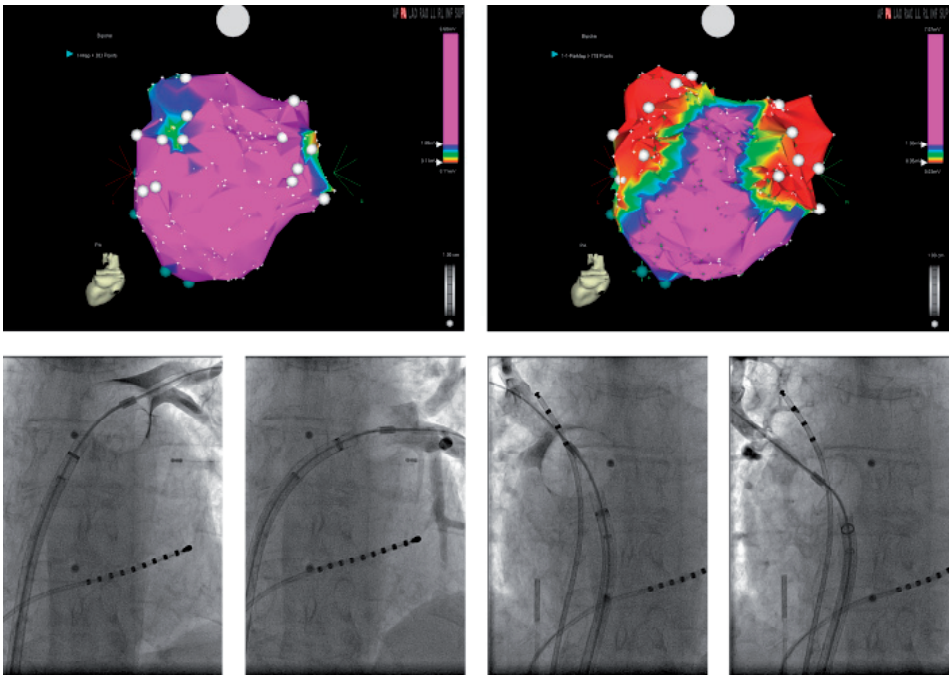

Figure 2. Postero-anterior view of a left atrial voltage map in a patient with four separate pulmonary vein ostia, before (upper left) and after (upper right) ablation. Low voltage areas (<0.05mV) are coloured red, white spherical markers are placed at the ostium. It is clear that the ablated region extends into the antrum. The fluoroscopic images (below) represent the cryoballoon occlusions during distal contrast injection before ablation: from left to right: left upper pulmonary vein, left lower pulmonary vein, right upper pulmonary vein, right lower pulmonary vein. A decapolar coronary sinus catheter is visible in all lower images; a quadripolar catheter is visible in the two lower right images for phrenic nerve pacing during ablation of the right sided veins.

left side, the pulmonary vein anatomy was the main determinant in absence of antral isolation: the two patients with a common left sided ostium showed ostial PVI. Figure 2 shows a typical example of a voltage map during sinus rhythm before and after ablation, with complete antral isolation, also shown are the fluorocopic images of the balloon occlusions in that same patient. Figure 3 shows a voltage map of a patient with a left sided common ostium: no antral isolation is observed around the left sided veins, only around the right sided veins. The mean of the largest diameter of the veins that showed antral isolation was 19±4 mm, while the two left common ostia were 31 and 29 mm in their largest diameter ($p<0,01$). The use of a linear cryocatheter for additional segmental ablation, if isolation could not be obtained with the balloon catheter, did not appear to influence the extent of the ablation in the antral region.

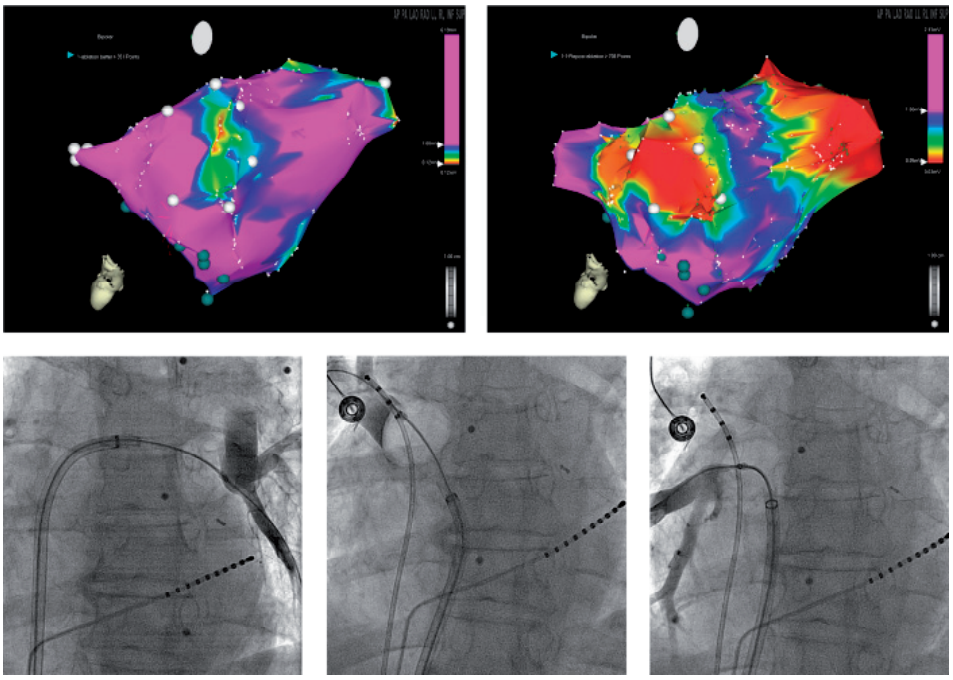

Figure 3. Cranial left anterior oblique view of a left atrial voltage map in a patient with a left sided common pulmonary vein ostium, before (upper left) and after (upper right) ablation. Low voltage areas (<0.05mV) are coloured red, white spherical markers are placed at the ostium. It is clear that the ablated region does not extend beyond the ostial markers. The fluoroscopic images (below) represent the cryoballoon occlusions during distal contrast injection before ablation: from left to right: left common pulmonary vein, right upper pulmonary vein, right lower pulmonary vein. A decapolar coronary sinus catheter is visible in all lower images; a quadripolar catheter is visible in the middle and right lower right images for phrenic nerve pacing during ablation of the right sided veins.

Activation of the left atrium

Before ablation, all of the left atria (n=16) showed their earliest activation site during sinus rhythm in the superior septal region. Activation mapping of the left atrium after ablation revealed a change in site of earliest activation in 2 patients (NS). One patient shifted his first activation point from superior towards the middle and one from superior towards the inferior region of the septum. In an additional 4 patients there was a minor change in activation, showing a downward shift as well, but which might have been due to a mapping artefact. An activation map is represented in figure 4, showing the patient switching from upper septum activation to lower septum activation of the left atrium.

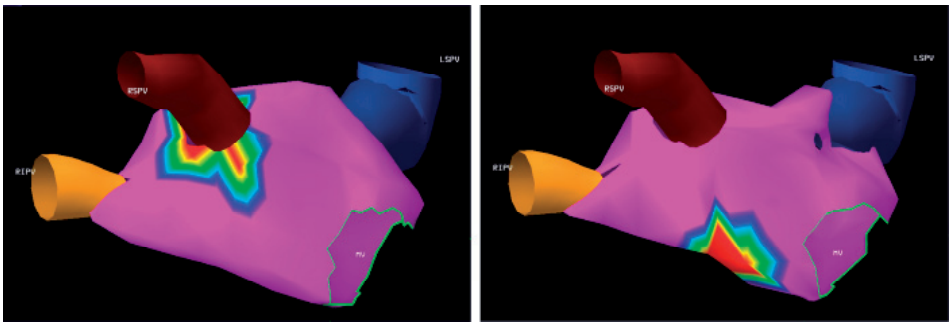

Figure 4. Activation map of the left atrium during sinus rhythm before (left) and after (right) ablation. The earliest activation times are represented in red. It is clear that the location of the earliest left atrial activation changes from high septal before, to low septal after ablation.

Discussion

In cryoballoon PVI, the majority of the veins undergo antral isolation. Veins with a diameter larger than the balloon, are isolated ostially. In individual cases, the left atrial activation sequence appears to be altered after ablation.

The main finding of antral isolation by the cryoballoon seems to contradict a recent report describing ostial PVI with several other balloon based ablation systems : high intensity focused ultrasound (HIFU, ProRhythm) and endoscopic laser balloon ablation system (EAS, Cardiofocus)[9]. We believe this important difference can be explained by the inherent difference in energy delivery. Both HIFU and EAS deliver energy in a linear circumference around the balloon, aiming to create a linear circle lesion. The cryoballoon on the other hand, is less direction dependent. The refrigerant jet inside the balloon is anteriorly directed to produce the lowest ablation temperatures in a large circular zone on the anterior one third of the balloon, thus creating a wider, planar circular lesion at the balloon-tissue interface. A report recently published on the level of pulmonary vein isolation for balloon based ablation systems, described a set of eight patients ablated with a 23 mm cryoballoon[10]. This showed only ostial isolation. Our study was exclusively performed with the 28 mm cryoballoon, which could account for the discrepancy between the two findings.

In at least two cases of our cohort, we saw that the preferential conduction path from the right to the left atrium seemed to change. This was not a consistent finding for the whole group. We believe that due to the proximity of Bachmann bundle to the antral region of the RSPV[11], in some cases the conduction over this structure is delayed as a result of the ablation, also confirming the ablation of left atrial muscle tissue in the septal region. This has been proven to improve outcome with radiofrequency ablation[12], but for cryothermal ablation the clinical impact of this remains to be determined.

Common left veins were targeted in a way similar to separate veins, with a minimum of two applications directed towards their respective superior and inferior side branches each. The ablation of a common left vein posed no additional technical difficulty and was successful in electrically isolating the vein, but proved to yield a lesion not extending into the antrum, although the operators tried to perform a similar antral ablation. We found the consistent larger ostial size as the only determining factor for this phenomenon. It seems logical that a larger balloon might solve this problem. What the effect of this relatively less extended lesion is on the long term clinical outcome remains to be determined.

From our study, it can be concluded that pulmonary vein isolation with the cryoballoon consistently yields isolation in the antral region of single vein ostia, thus not only isolating the muscular PV sleeves but also extending to an antral circumferential lesion. When ablation is performed of a common ostium, the ablation is not antral, but ostial.

It remains to be determined to what extent the ablation lesion remains permanent when mapped after a long term follow-up period. The long term persistence of a left atrial activation change and the clinical significance of this is also unclear.

Limitations

Only a qualitative assessment was made of the obtained mapping data. The main reason for this was that the proximal extent of the antral region is not always well defined in all patients. Image integration could have been helpful in this respect. Since the distal boundary of the antrum is more accurately defined by the ostium, ablation was more reliable when assessed qualitatively in reference to that boundary. Therefore, the presented data show that antral ablation was present in the reported cases, but do not imply that the entire antral region was ablated. In comparison to this, circumferential ablation with radiofrequency energy is aimed at delivering ablation energy inside the antrum, thus avoiding ostial pulmonary vein stenosis, and has not been proven to isolate the antral region to its full proximal extent. A randomised comparison to circumferential antral radiofrequency ablation would be necessary to compare any differences in the extent of the antral isolation.

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Chapter six

Transcranial measurement of cerebral microembolic signals during endocardial pulmonary vein isolation: comparison of three different ablation techniques

Sauren LD, Van Belle Y, DE Roy L, Pison L, LA Meir M, Van Der Veen FH, Crijns HJ, Jordaens L, Mess WH, Maessen JG. Transcranial measurement of cerebral microembolic signals during endocardial pulmonary vein isolation: comparison of three different ablation techniques. J Cardiovasc Electrophysiol. 2009 Oct;20(10):1102–7.

Abstract

Introduction: Isolation of the pulmonary veins (PVI) using high ablation energy is an effective treatment for atrial fibrillation (AF) with a success rate of 50-95%; however, postoperative neurological complications still occur in 0.5%-10%. In this study the incidence of cerebral microembolic signals (MES) as a risk factor for neurological complications is examined during three percutaneous endocardial ablation procedure strategies: segmental PVI using a conventional radiofrequency (RF) ablation catheter, segmental PVI using a an irrigated RF tip catheter and circumferential PVI with a cryoballoon catheter (CB).

Methods: Thirty patients underwent percutaneous endocardial pulmonary vein isolation. Ostial isolation was performed in 10 patients with a conventional 4 mm RF catheter (CRF) and in 10 patients with a 4mm irrigated RF catheter (IRF). A circumferential PVI was performed in 10 patients with a CB. Transcranial Doppler (TCD) monitoring was used to detect MES in the middle cerebral arties.

Results: The total number of cerebral MES differs significantly between the 3 PVI groups; 3908 cerebral MES were measured with use of the CRF catheter, 1404 cerebral MES with use of the IRF catheter and 935 cerebral MES with use of the CB catheter.

Conclusion: This study demonstrates a significant difference in cerebral MES during PVI with 3 different ablation procedures. The use of an irrigated RF, and a cryoballoon produces significantly fewer cerebral MES than the use of conventional RF for a PVI procedure, suggesting a higher risk for neurologic complications using conventional RF energy during a percutaneous PVI procedure.

Introduction

Atrial fibrillation (AF) is a highly prevalent cardiac arrhythmia, with an age-dependent increase in incidence. It is an independent risk factor for death and stroke [1]. Antiarrhythmic drug treatment and pulmonary vein isolation (PVI) are standard treatment options. PVI has become a mainstream treatment for AF whereby ablation energy is applied to electrically isolate the pulmonary veins [2, 3]. Catheter PVI procedures are efficacious with success rates approximating 80%. However, one of the complications of PVI procedure however is the occurrence of cerebroembolic complications in 0.5%-10% of the patients [2, 4, 5]. Several publications support an association between the number of cerebral MES and neurological impairment and stroke [4, 6-9]. Therefore in this study, the number of cerebral MES was considered as a risk factor of neurological complications and examined during three different catheter-based PVI approaches: (1) segmental isolation with a conventional radiofrequency (RF) ablation catheter (CRF), (2) segmental isolation with an irrigated RF tip ablation catheter (IRF), and (3) circumferential isolation with a cryoballoon catheter (CB).

Methods

Patients

A total of 30 consecutive patients suffering from drug-refractory and symptomatic AF undergoing a PVI were included in this study. We compared three separate cohorts in three different centres: Academic Hospital Maastricht (the Netherlands), Cliniques Universitaires de Mont-Godinne, Yvoir (Belgium) and Erasmus Medical Centre, Rotterdam (the Netherlands). Three groups were defined according to the ablation catheter used in each centre: (1) conventional RF catheter (CRF), (2) irrigated RF tip catheter (IRF), (3) cryoballoon catheter (CB).

Procedures

The investigation was approved by the Human Research and Ethics Committee of the Academic Hospital Maastricht (the Netherlands), Cliniques Universitaires de Mont-Godinne, Yvoir (Belgium) and Erasmus Medical Centre, Rotterdam (the Netherlands).

Segmental PVI

These procedures were performed under local anaesthesia and with femoral vein punctures. Two echoguided transseptal punctures were preformed and a steerable circular electrophysiologic catheter (Lasso®, Biosense Webster, Diamond bar, CA, USA) was positioned at the orifice

of the targeted veins. Ablation was performed at the atrio-venous junction at sites showing the earliest PV potentials. The introducers were continuously flushed to prevent the formation of thrombi on the catheter. Details about the segmental ablation have been published earlier [3].
The ablation catheter used for the conventional RF ablation was a 4-mm bidirectional RF ablation catheter (Saphire®, St.jude medical, Minnetonka, MN, USA). The maximum power limit for the RF ablation was set on 25W to 30W, with a maximum temperature limit of 55°C to 60°C.
The ablation catheter used for the irrigated tip RF ablation was a 4-mm externally irrigated tip catheter (Celius Thermo-cool®, Biosense Webster, Diamond bar, CA, USA). The maximum power limit for the RF ablation was set on 25W, with a maximum temperature limit of 48°C.

Circumferential cryoballoon procedure
The procedure was performed with femoral access and through a single transseptal puncture, guided by intracardiac echocardiography. The ablation was performed with a 28-mm double-lumen balloon catheter (Arctic front®, Cryocath, Montreal, Quebec, Canada), through a 14F transseptal sheath and positioned over an exchange wire to occlude the ostium of each PV. The introducers were continuously flushed to prevent the formation of thrombi on the catheter. Cryoenergy was given for 5 min per application of -80°C, with a minimum of 2 applications per vein. After ablation, a circular 20-polar catheter was positioned at the ostium of every vein to check for PV potentials. The procedural endpoint was the absence of pulmonary vein potentials in all of the targeted veins. If isolation could not be achieved with the cryoballoon, an additional segmental isolation was performed with a 8mm tip cryocatheter (Freezor Max®, Cryocath, Montreal, Quebec, Canada). Details on this approach have been published previously [10, 11].

Periprocedural anticoagulation management

All patients of all three groups were on oral anticoagulation for a minimum of 1 month before the procedure. This was stopped 2 to 3 days before the ablation. Transesophageal echocardiography was performed 24-48 hours before the procedure to rule out presence of intracardiac thrombi. The activated clotting time (ACT) was kept above 350 s during the entire procedure in the CRF procedures, between 200 and 250 s in the IRF procedures, and an ACT of 350 s was maintained in the cryoballoon procedures. After the procedure, oral anticoagulation was resumed with a target international normalized ratio between 2 and 3.

Transcranial Doppler (TCD) monitoring

TCD, (PMD 100, Spencer Technologies, Seattle, WA, USA) was used to monitor both middle cerebral arteries through the temporal windows for microemboli using two 2.0 MHz probes, fixed with a headband (Marc 600, Spencer technologies). The probes were by an experienced physician installed after the patient was positioned for both PVI procedures. Patients were monitored

continuously starting from 30 min before the procedure until termination of the procedure. TCD recordings were stored for later offline analysis. In our study the detection of cerebral MES was performed by a blinded trained physician according the guidelines of the consensus committee [12]. The TCD analyses were divided into different periods. The period from transseptal puncture until the first ablation was considered the placement period (placement period). The period during which ablation energy was delivered was classified as the ablation period. Due to the delay between emboli generation in the pulmonary veins and arrival of these emboli in the cerebral vessels, a 10-s period after the end of ablation was included in the ablation period in all of the different methods (ablation period). The period from the first ablation, until the end of the procedure, minus the ablation periods was considerate the manipulation period (manipulation period).

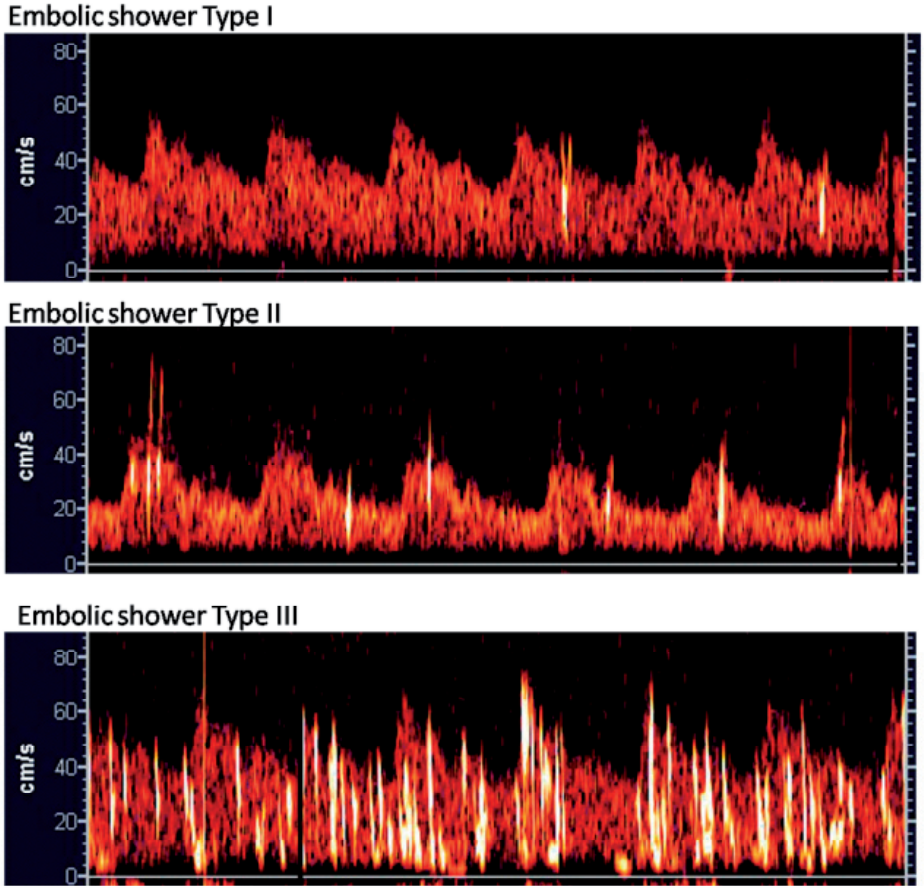

Figure 1. Examples of the 3 types of showers in the velocity spectrum of the Transcranial Doppler (TCD) screen.

Data analysis

The different patterns of cerebral MES were categorized according to previously defined criteria [4, 13, 14]. Type I embolic showers were defined as 1 to 10 cerebral MES in 1 minute of ablation. Type II embolic showers were defined as 11 to 60 cerebral MES in 1 minute of ablation. Type III embolic showers were defined as more than 61 cerebral MES in 1 minute of ablation. Figure 1 demonstrates the 3 mentioned types of embolic showers.

Statistical method

All data was analysed using the statistical software package SPSS® version 12.0 (SPSS Inc., Chicago, IL, USA). A Mann-Whitney U test was used to compare the 3 different types of embolic showers in the different ablation groups. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 30 patients were enrolled in this study. Table 1 presents patients' characteristics of the three PVI groups. There were no significant differences in the baseline characteristics.

Table 1. Patient's characteristics in the irrigated RF group, the conventional RF group and the cryoballoon group

	Conventional RF	Irrigated RF	Cryo balloon
N	10	10	10
Male	9	10	7
Age (year)	50 (11)	53 (14)	58 (11)
PAF/CAF	9/1	9/1	10/0
PFO	2	1	1
Previous TIA	0	0	1
Previous percutaneous ablation	3	1	2

PAF: paroxysmal atrial fibrillation, CAF: consistent atrial fibrillation, PFO= patent foramen ovale, TIA: transient ischemic stroke.

PVI procedures

A total of 741 energy applications were delivered in 30 patients: in the CRF group 318 applications, in the IRF group 314 applications, and in the CB group 109 applications. The CRF and IRF procedures had a significantly shorter total ablation time than the CB procedures ($P = 0.01$) (Table 2). The total procedural time was significantly longer in the CRF group (274 min) versus

Table 2. Procedure characteristics in the Conventional RF group, the irrigated RF group and in the cryo balloon group.

	CRF		IRF			CB			
	Mean	**SD**	**Mean**	**SD**	**CRF vs IRF**	**Mean**	**SD**	**CB vs CRF**	**CB vs IRF**
Ablation time (min)	24	10	16	9	p=0.347	79	42	P<0.0001	P=0.01
Time per ablation (sec)	45	15	34	17	p=0.008	300	0	P<0.0001	P<0.0001
Procedural time (min)	274	92	185	49	p=0.032	178	57	P<0.0001	P=0.711
ACT (sec)	371	106	210	33	p=0.017	364	90	P=0.909	P=0.05
Impedance (Ω)	200	10	115	14	p=0.04				
Power (W)	24	6	24	2	p=0.906				
Temperature (°C)	49	5	36	2	p=0.01				

IRF and CB group (185 min P = 0.032 and 178 min P < 0.0001). The ACT levels in the IRF group were significantly lower (ACT = 210) than in the CRF (ACT = 371, P = 0.017) and the CB groups (ACT = 364, P = 0.05).

Total number of cerebral MES

The number of cerebral MES in the three procedures are represented in Table 3.
The total number of cerebral MES differs significantly among the 3 groups. The number of cerebral MES detected during the entire PVI procedure was significantly lower in the IRF group (1404 MES) and in the CB group (935 MES), compared to the CRF group (3908 MES, respectively P = 0.0019, P = 0.001). The number of cerebral MES during the placement period was significantly higher in the IRF group (745 cerebral MES) compared to the other two groups (CB = 377 cerebral MES, P = 0.03; and CRF = 332 cerebral MES, P = 0.015). During the ablation period, less cerebral MES were generated in the IRF group (105 MES) and in the CB group (163 MES) compared to the CRF group (2566 MES, respectively, P = 0.01, P = 0.0001). When considering the number of MES per minute of ablation, the CB group demonstrated the lowest number of three cerebral MES per minute of ablation compared to both the other procedures. (CRF = 92 MES, P < 0.0001; IRF = 7 MES, P = 0.03).

Table 3. Number of microembolic signals in the conventional RF group, the irrigated tip RF and the cryo balloon group.

	CRF		IRF			CB			
	Mean	**SD**	**Mean**	**SD**	**IRF vs CRF**	**Mean**	**SD**	**CB vs CRF**	**CB vs IRF**
MES total	3908	2816	1404	981	p=0.019	935	463	p=0.001	p=0.186
MES placement period	332	193	745	467	p=0.015	377	297	p=0.624	p=0.03
MES ablation period	2566	2296	105	71	p=0.01	163	91	p=0.001	p=0.266
MES manipulation period	1010	733	554	601	p=0.143	395	186	p=0.027	p=0.874
MES per 1 minute of ablation	92	144	7	20	p<0.0001	3	5	p<0.0001	p=0.03

MES in the CB procedures

The number of MES during contrast injections and single point ablation in the CB group were analysed separately. On average 13 ± 2 cerebral MES were observed during each contrast injections in the CB procedure, resulting in an average of 132 ± 37 MES per procedure caused by contrast injections. Single segmental ablations with the freezer max did not contribute significantly to the total number of cerebral MES, as only 2 ± 1 cerebral MES were observed in the complete segmental ablation period, consisting of 8 applications.

Ablation characteristics and type of embolic showers in CRF procedures

Type I showers occurred during the CRF procedure at an average ablation application time of 41 s (±16 s), with an average temperature per ablation of 47°C (±4°C). Type II showers occurred at an average similar ablation application duration (44s ± 16s) but with a significant higher temperature of 49°C (±5°C) ($P = 0.025$). Type III showers occurred at significant higher ablation application time of 52 s (±11 s) than both type I and type II embolic showers ($P < 0.0001$) and at significant higher temperatures of 52°C (±5°C) than both other types of showers ($P < 0.0001$).

Discussion

This study demonstrates that cerebral MES are generated in patients undergoing catheter-based PV ablation procedures. However, the number of cerebral MES generated during PVI procedures is dependent on the type of the ablation catheter. The CB generates a lower number of cerebral MES during the ablation application than methods involving RF-based ablation catheters. When comparing the irrigated tip RF catheter and the conventional RF catheter, the former generates the lowest number of cerebral MES. The duration and temperature of each ablation application could play a role in the difference in generation of emboli when RF energy is used.

It has been proven that cerebral MES are an indicator of systemic and cerebral embolization, and are associated with a significant risk of neurologic damage [4, 6-9, 15, 16]. Lickfett et al [5] demonstrated with diffusion-weighted magnetic resonance imaging that 10% of patients undergoing PVI with a RF catheter had cerebral embolic lesions postprocedurally. Kilicislan et al and Marrouche et al [4] have shown that patients with cerebroembolic events had significantly higher numbers of cerebral MES, suggesting that without the knowledge of the constitution of those emboli, the cerebral emboli during catheter RF ablation are responsible for neurological complications. The method of detecting cerebral emboli cannot provide information of the composition of the observed emboli, but the moment of occurrence can provide an indication about the nature of the observed emboli. In cryoballoon ablation, a majority of MES are observed during the placement and manipulation phase and at end of each ablation. Since placement of a 14 Fr transseptal sheath and contrast injections during placement of the cryoballoon are involved in the placement and manipulation phases, it seems a reasonable hypothesis that the observed

MES during these phases are mainly caused by iatrogenic gas injection. At the end of the ablation phase, however, the balloon that occluded the PV ostium (trapping injected contrast inside the PV) is deflated. The cerebral MES detected at that moment could be the release of ice chips formed at the balloon-PV interface or the release of thrombi formed in the trapped blood column behind the occluding balloon. But it could also be the release of trapped contrast including some injected air which could be responsible for MES formation. Although the nature of the detected emboli in the CB procedures cannot be determined with certainty, it is clear from this study that a lower number of MES are detected during the CB procedure compared to the methods involving RF. The observed low number of MES during cryoenergy delivery with the cryoballoon and the absence of MES during with cryothermal segmental ablations confirms the previously proven low thrombogenity of cryoablation [17-20].

Both RF groups show a higher number of observed MES compared to the CB procedure during the ablation phase. It has been shown that RF energy is not only highly thrombogenic [17-19, 21, 22], but also causes the gaseous emboli to emerge due to tissue disruption and temperature rises [13, 14, 23]. Since this study confirms the significant correlation between increasing number of cerebral MES with higher power, duration and temperatures of the RF ablation, it confirms that the emboli are correlated with the energy delivery. In the CRF ablations the type III cerebral embolic showers may be prevented by reducing the duration of each ablation. It also shows that reducing the catheter tip temperatures by irrigated cooling is an effective means for reduction of cerebral MES, probably through prevention of thrombus formation as was suggested earlier [22, 24]. This shows that when using RF-energy for PVI, with a high number of ablation lesions in the left atrium, an irrigated tip catheter is preferable to a conventional RF catheter since systemic embolisation can have devastating consequences and is a frequently occurring complication [5, 6, 20, 25].

Study limitations

The activated clotting times during the ablation was not entirely uniform in all groups. The CRF and IRF maintained lower anticoagulation levels than the CB group which may pose a serious bias in this study. However, in the IRF group, although being the least anticoagulated, a significant lower MES were observed than in the CRF group, indicating the major determinant of MES was the method of power delivery, and not the anticoagulation level during the procedure.

The standard MES evaluation is the off-line evaluation of a recorded TCD signal by a human expert [12]; and although the agreement rates of MES detection by TCD are higher than the agreement rates for interpretation of computed tomography or magnetic resonance imaging [26, 27], a human dependency factor remains present by MES evaluation.

This study did not include a neurological examination of the patients. No observations were made of postprocedural neurological complications. However due to reports which have

demonstrated a correlation between cerebral emboli and brain damage [4-6, 8, 9, 15, 16, 28], a lower incidence of neurological complications in the cryoablation and the irrigated RF treated patients can be expected.

Conclusion

This study demonstrates that the generated cerebral MES during a PVI procedure are significant lower with the use of a CB catheter and a IRF catheter compared to the use of a CRF catheter. The risk of post-procedural neurological complications can therefore be expected to be higher with the use of a CRF catheter during a PVI procedure.

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Chapter seven

Adenosine testing after cryoballoon pulmonary vein isolation improves clinical outcome

Van Belle Y, Janse P, de Groot NMS, Schwagten B, Anné W, Theuns D, Jordaens L. Adenosine testing after cryoballoon pulmonary vein isolation improves clinical outcome. Submitted.

Abstract

Background: Adenosine infusion after pulmonary vein isolation (PVI) with radiofrequency energy reveals dormant muscular sleeves and predicts AF recurrence. The aim of our study was to determine whether adenosine could reveal dormant PV-sleeves after cryoballoon isolation and study its effect on recurrence of atrial fibrillation (AF).

Methods: Patients with paroxysmal AF underwent cryoballoon PVI. After PVI, adenosine 25mg was infused to test for dormant muscular sleeves in each vein. If reconnection under adenosine was shown, further cryoballoon ablation was performed until no more reconnection occured. Follow-up was performed with ECG, 24-hour Holterrecording, and a symptom questionnaire at 3 month intervals. Transtelephonic holtermonitoring was performed during one month before and three months after PVI. Patients that underwent cryoballoon PVI without adenosine administration were used as controls for comparison.

Results: In the study group (n=34, 24 male), adenosine revealed dormant sleeves in 9/132 (8%) veins, and 7/34 (21%) patients. All but one vein was further treated until the dormant sleeves were isolated. During a mean follow-up of 520±147 days, 23/34 (68%) patients were free of AF without antiarrhythmic drugs (AAD). In the control group (n=65, 46 male), 29/65 (46%) were free from AF without AAD. There were significantly less AF recurrences in the study group (p=0.04).

Conclusions: Adenosine administration after cryoballoon PVI reveals dormant muscular sleeves in 21% of patients. Clinical follow-up shows that adenosine testing is effective in reducing AF recurrence after cryoballoon ablation.

Introduction

Pulmonary vein isolation (PVI) has become the cornerstone of invasive treatment of atrial fibrillation (AF). Previous studies have shown that there is a high percentage of electrical reconduction from the atria to the pulmonary veins after circumferential ablation using radiofrequency current (RF) and that resumption of conduction to previously ablated pulmonary veins is responsible for recurrence of AF (1-2). It has also been proven that adenosine infusion after PVI reveals dormant muscular sleeves which are a predictor of late reconduction (3).
Adenosine activates adenosine sensitive potassium channels, restoring the resting potential to its normal value in myocytes with reversible thermal injury (4-5). Cryoballoon ablation has been proven to be effective in pulmonary vein isolation (6-7), but reconduction to the pulmonary veins is invariably present (100%) in patients who develop recurrences of AF (8). The scope of our study was to determine whether adenosine could reveal dormant PV-sleeves after cryoballoon isolation and gain insight in the long term outcome.

Methods

Study population

Patients referred to our centre for ablation of symptomatic paroxysmal AF resistant to antiarrhythmic drugs (AAD), at two or more occasions, were included. Patients with obstructive pulmonary disease, and severe valvular disease were excluded. Informed consent was obtained in all patients.
A control population with similar demographic characteristics was selected from patients who were ablated for AF with the cryoballoon during the same period as the study population. They were used to compare the freedom of AF after long term follow-up. For comparison the groups were labeled 'adenosine' and 'no adenosine'.

Pulmonary vein isolation procedure

The procedure was performed under conscious sedation or general anesthesia according to the patient preference. Both femoral veins were used for venous access. A 10 Fr, intracardiac echocardiography (ICE) catheter (Flexview, EP Med Systems, New Jersey, USA) was introduced through the left femoral vein and positioned in the right atrium. A decapolar catheter was placed in the coronary sinus. A single transseptal puncture was performed using a transseptal needle (BKR1, St Jude Medical, Minnesota, USA) and an 8F sheath (Fastcath SL1, St Jude Medical, Minnesota, USA), guided by both ICE and fluoroscopy. A 6 Fr angiocatheter (Mach 1 MP2, Boston Scientific, Massachusetts, USA) was used to make a selective angiography of every pulmonary vein for

locating the ostium. A circular mapping catheter was advanced and positioned in the antrum of each pulmonary vein to record the presence of PV-potentials. The sheath was exchanged for a 14 Fr steerable sheath (Flexcath, Medtronic, Minneapolis, USA), through which a 28 mm, 12 Fr cryoballoon catheter (Arctic Front, Medtronic, Minneapolis, USA), and positioned over an exchange wire to occlude the ostium of each PV. Cryoablation was performed for 5 minutes per application. A minimum of two applications per vein were given. Before targeting the right superior pulmonary vein (RSPV), a quadripolar catheter was positioned in the superior caval vein for continuous phrenic nerve stimulation during cryoapplication. At loss of capture, ablation was instantaneously terminated. After targeting all PV's, the cryocatheter was exchanged for the circular mapping catheter to register if remaining electrical activity was present. If this registration showed persistence of PV-potentials, the cryoballoon was introduced again and an additional two applications of 5 minutes were given. If after this second ablation attempt PV potentials remained present, a conventional cryocatheter (Freezor Max, Medtronic, Minneapolis, USA) was used to perform a segmental isolation through the same transseptal puncture. After isolation of all veins, registration of the electrical activity was made at the ostia during bolus administration of 25 mg of adenosine. If during adenosine administration reconduction to the pulmonary vein was confirmed, additional cryoablation was performed until this was no longer the case. Throughout the procedure, the activated clotting time was monitored every 30 minutes and maintained between 275 and 300 seconds.
The control population was ablated with the same method, except for the administration of adenosine.

Rhythm evaluation

Patients were instructed to submit daily rhythm strips, and additional strips when symptomatic, during one month before the ablation and three months after, with a transtelephonic holter monitoring system. These recordings were used to calculate an atrial fibrillation burden (AF burden), defined as the ratio of transmitted strips revealing AF and the number of days the patient was in possession of the recording device. A 24 hour Holter monitoring was performed before the ablation and repeated at three monthly intervals after ablation. The patients were evaluated at three monthly intervals by a cardiologist at the outpatient clinic, at which time an electrocardiogram (ECG) was performed, until at least one year after ablation. Unsolicited ECG tracings, performed for any reason outside the routine follow-up, were also taken in consideration. No blanking period for AF recurrence was applied.
A questionnaire was used to score palpitation symptoms for frequency and duration. Patients were asked to score this at baseline and at each outpatient visit during the follow-up. Frequency categories were subdivided into: no, daily, weekly, monthly, and yearly; duration categories into: no, minutes, hours, and days.

Drug management

Antiarrhythmic drug regime was discontinued five days before the procedure, and restarted the day after the procedure, until three months after ablation. If no recurrence was recorded during this period, AAD's were discontinued.
Oral anticoagulation (INR between 2,0 and 3,0) were stopped three days before the ablation. The day before the procedure a transesophageal echocardiography was performed to exclude the presence of a left atrial thrombus. Oral anticoagulantion was restarted the day after the procedure, until at least 6 months after ablation.

Statistical analysis

Continuous variables are expressed a mean ± SD if normally distributed, or otherwise by median and interquartile range. Continuous variables were analyzed with Student's t-test or the Mann-Whitney U test in case of non-normal distribution of data. Categorical data are summarized as frequency (percentage) and compared with a Chi square test. A two-sided *P* value < 0.05 was used for declaring statistical significance. A analyses were performed with SPSS for Windows (version 16.0, SPSS Inc, Chicago, Illinois, USA).

Results

Demographics

Patients with drug resistant, paroxysmal and symptomatic AF (n=34, 24 male, 57±12 years) were included in the study. The control population was a similar group of patients with drug resistant, paroxysmal and symptomatic AF, ablated during the same period with the cryoballoon (n=65, 46 male, 58±9 years). Demographic data are represented in table 1.

Adenosine revealing dormant conduction to the pulmonary veins: adenosine group

Administration of adenosine revealed dormant conduction to one or more PV's in 7 patients (21%), and 9 veins (8%): left superior pulmonary vein (LSPV) 1(3%); left inferior pulmonary vein (LIPV) 3(9%); right superior pulmonary vein (RSPV) 1(3%); right inferior pulmonary vein (RIPV) 4(12%). These results are represented in figure 1A and 1B. The average dose of adenosine administered per vein was 27±2 mg. There was no significant difference when considering reconduction in right veins versus left veins (NS), inferior versus superior veins and/or the RIPV versus other veins. All veins with dormant conduction were additionally ablated until adenosine could

Table 1. Demographic, procedure and follow-up data: comparison between the study group (adenosine) and the control group (no adenosine)

	Demographic data		
	Adenosine	**No Adenosine**	**p**
Male/Female (n)	24/10	46/19	NS
Age (years)	57±12	58±9	NS
LA diameter (mm)	45±7	42±6	0.05
Body Mass Index	28±5	26±5	NS
Years of AF (years)	7±5	7±6	NS
AF burden (%)	12±23	20±21	NS
	Procedure data		
Procedure time (min)	202±68	193±57	NS
Fluoroscopy time (min)	41±24	46±23	NS
Balloon applications (n)	11 (9-13)	9 (8-11)	0.013
	Follow-up data		
Follow-up (days)	520±147	539±214	NS
No AF, no AAD (n (%))	23 (68)	29(46)	0.04
AF recurrence (n (%))	11 (32)	34(54)	0.04
Reduced burden and/or AAD (n (%))	6 (18)	16(25)	NS
Re-intervention (n (%))	5 (14)	18(29)	NS

not reveal reconduction. The electrical activity revealed by adenosine in one vein (RIPV) could not be ablated by the operating physician within a reasonable timeframe, and the procedure was terminated before isolation under adenosine was achieved. These findings are summarized in Table 2.

Outcome of the ablation procedure: adenosine group

All study patients underwent successful pulmonary vein isolation with a median procedure time of 202±68 minutes and a fluoroscopy time of 41±24 minutes. General anesthesia was given in 13 (38%) patients, 21 (62%) were consciously sedated. The median number of balloon applications was 11 [9-13], and the left sided veins needed significantly more balloon applications than the right sided veins to achieve isolation: 3[2-7] versus 2[1-6] ($p<0,001$). An example of a cryoballoon occlusion of the right inferior pulmonary vein is shown in figure 2. The use of an additional linear cryocatheter was necessary in 9 patients (26%) and/or 14 veins (10%); in one patient however the linear catheter was used due to failure of the balloon console. There were significantly more linear catheters used in left sided veins than in right sided to complete the circular lesions: 9 (13%) versus 5 (7%) ($p=0.01$) (Table 2). Complete isolation of the four veins was achieved in all patients.

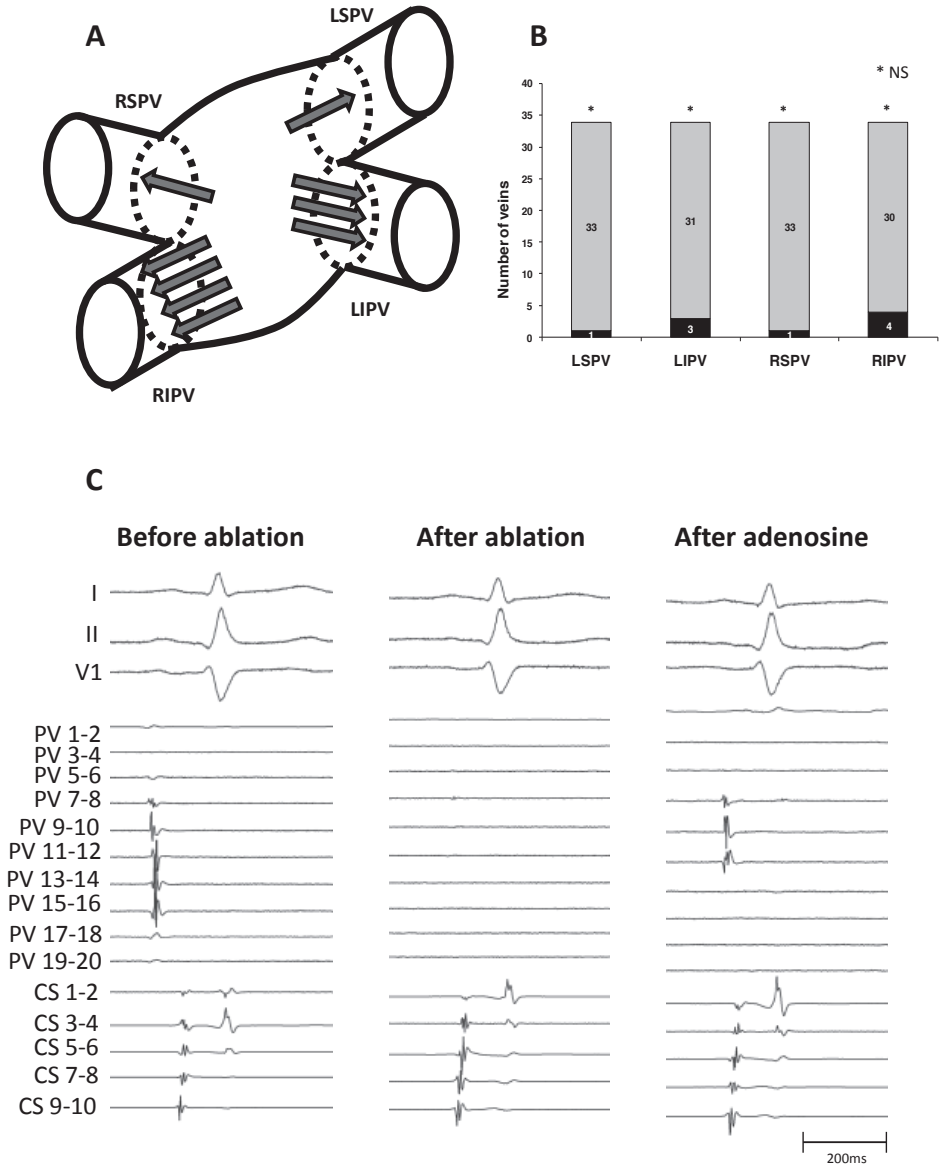

Figure 1. Reconnection of dormant pulmonary vein sleeves under adenosine administration after cryoballoon ablation - A. Schematic representation of the absolute number of reconnecting veins at the respective ostium. Each arrow represents a reconnecting sleeve. B. Bar graph representing the ratio of reconnection under adenosine in each vein. C. An example signals present in a right inferior pulmonary vein as measured with a 20-pole catheter at the ostium. Before ablation electrical activity is present in dipoles PV7-8 to PV15-16. After ablation no more electrical signals are present. After adenosine administration, electrical activity reappears on dipoles PV7-8 to 11-12.

Table 2: Procedure characteristics in the adenosine group

	LSPV	LIPV	RSPV	RIPV	Total
Balloon applications : median [range]	3 [2-6]	3 [2-7]	2 [2-4]	2 [1-6]	11 [8-16]
Linear touch-up : n (%)	5 (15)	4 (12)	2 (6)	3 (9)	14 (10)
Early reconduction adenosine: n (%)	1 (3)	3 (9)	1 (3)	4 (12)	9 (8)

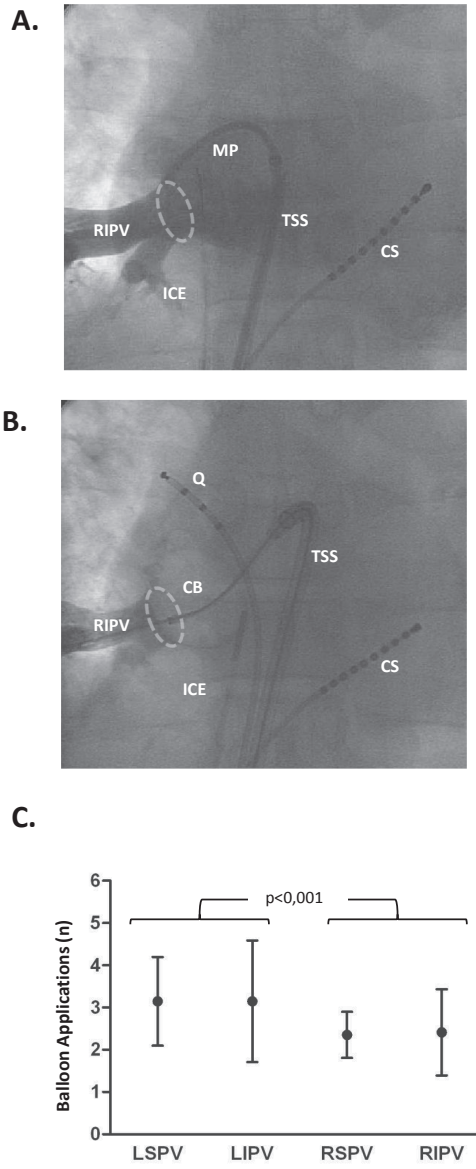

Figure 2. Cryoballoon pulmonary vein isolation - A. Fluoroscopic image (anteroposterior projection) of a selective contrast injection in a right inferior pulmonary vein through a multipurpose catheter positioned at its ostium (circle) in the left atrium. Also visible are a decapolar catheter in the coronary sinus, and a intracardiac echocatheter in the right atrium. B. Fluoroscopic image (anteroposterior projection) of an occlusion at the ostium of the right inferior pulmonary vein by a 28mm cryoballoon catheter, with distal contrast injection. Also visible are a decapolar catheter in the coronary sinus, a quadripolar catheter in the superior caval vein (used for phrenic nerve pacing during ablation), and an intracardiac echocatheter in the right atrium. C. Graph showing the average number of balloon applications necessary for isolation of the respective veins.
CS: coronary sinus catheter
CB: inflated cryoballoon catheter
ICE: intracardiac echography catheter
MP: multipurpose angiography catheter
Q: quadripolar catheter positioned for phrenic nerve capture in the superior caval vein
RIPV: right inferior pulmonary vein
TSS: transseptal sheat

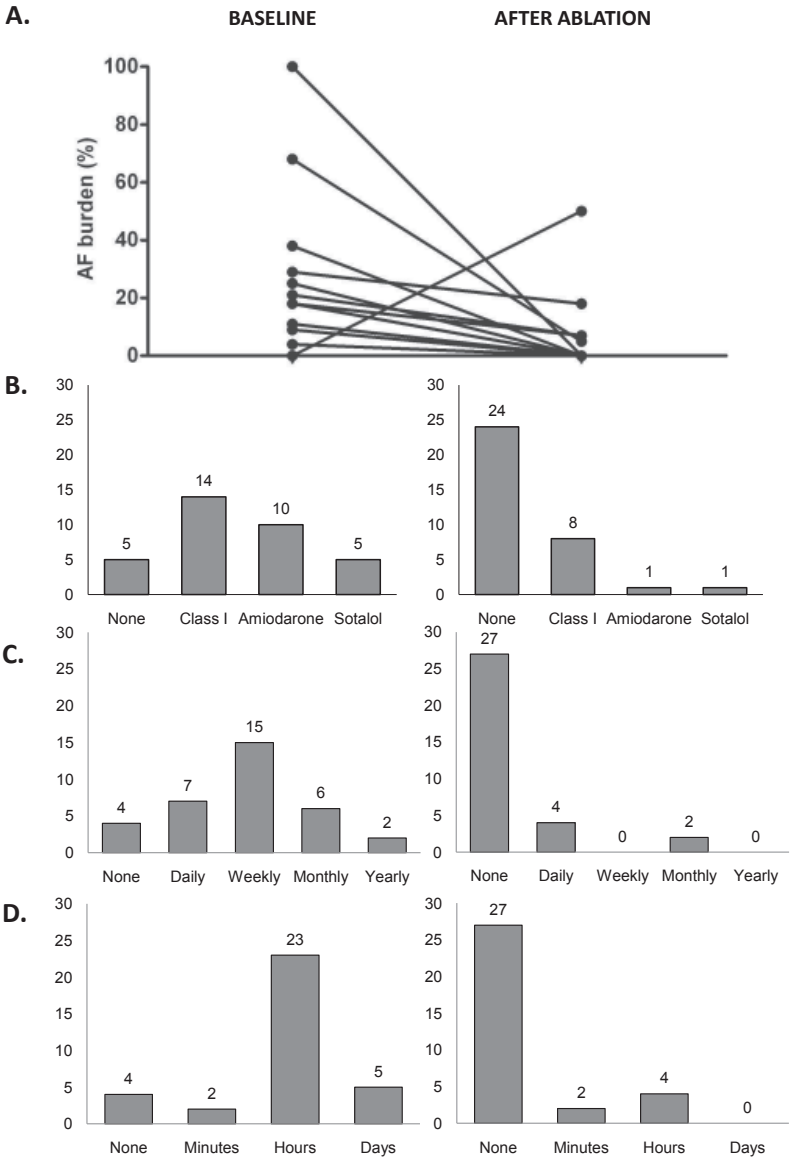

Figure 3. One year follow-up after cryoballoon pulmonary vein ablation for paroxysmal atrial fibrillation, with ablation of dormant pulmonary vein sleeves revealed by adenosine administration - A. Paired graph showing the baseline atrial fibrillation burden (%), paired with the burden after ablation. B. Bar graphs showing the antiarrhythmic drug use before and after ablation. The absolute number of patients is indicated above the respective bar. C. Symptom frequency of atrial fibrillation related complaints, as scored by a questionnaire. The two graphs show the frequency before and after ablation. D. Symptom duration of atrial fibrillation related complaints, as scored by a questionnaire. The two graphs show the duration before and after ablation.

Long term outcome after cryoballoon ablation: adenosine group

The follow-up period was 17±5 months. All results are graphically depicted in figure 3. At the end of follow-up, 23 (68%) patients were free from AF episodes, without AAD's. The average AF burden of the entire group decreased from 12% to 3% (p=0.01). Of the 11 patients who had recurrence of AF, 6 (18%) had a reduced AF burden of arrhythmia under the previously ineffective AAD regime, and were not reconsidered for reintervention (Figure 3A shows paired data of AF burden before and after the procedure). The remaining 5 patients with recurrence of AF despite AAD (14%) were planned for reintervention. The one patient, in whom dormant reconduction under adenosine had not been eliminated at the end of the ablation procedure, was also scheduled for reintervention. These results are summarized in table 1. The median time until the first recurrence after ablation was 9 [2-84] days. As shown in figure 3A, one patient exhibited an artificial increase in burden due to poor compliance with transtelephonic holter recording before the ablation (figure 3A).
Antiarrhythmic drugs were used by 29 (85%) patients at baseline: 14 (41%) class I AAD, 10 (29%) amiodarone, 5 (15%) sotalol. One year after ablation, only 10 (29%) were still on AAD: 9 patients due to recurrence of AF, 1 patient because of symptomatic supraventricular extrasystoles). Of the 24 (71%) patients that were free of AAD, 22 (65%) had no more AF, 2 (6%) had stopped AAD because they had a drastic reduction in AF burden (figure 3B).
The baseline symptom score showed that the average patient had a symptom frequency of weekly complaints, with duration of hours. One year after the procedure, the average patient had no more symptoms (Figure 3C and 3D).

Comparison to the control population: adenosine vs. no adenosine group

The adenosine group had a significantly larger left atrial diameter compared to the no adenosine group: 45±7 vs. 42±6 (p=0.05). There were no other significant differences between the groups at baseline. In both the adenosine and no adenosine groups, all patients were ablated until pulmonary vein isolation was achieved (NS). The number of balloon applications in the adenosine group was significantly higher than in the no adenosine group : 11 (9-13) vs. 9 (8-11) (p=0.013). No difference in procedure and fluoroscopy times was observed (NS).
Both groups had a comparable follow-up period. At the end of the follow-up, the freedom AF recurrence showed significantly less recurrence in the adenosine group: 68% vs. 46% (p=0.04) (Table 1). Figure 4 shows a Kaplan-Meier graph of AF-free survival in both groups.

Adverse events

In the adenosine group, one patient experienced a right phrenic nerve paralysis after cryoballoon ablation of the RSPV: this resulted in minor dyspnea complaints and resolved spontaneously

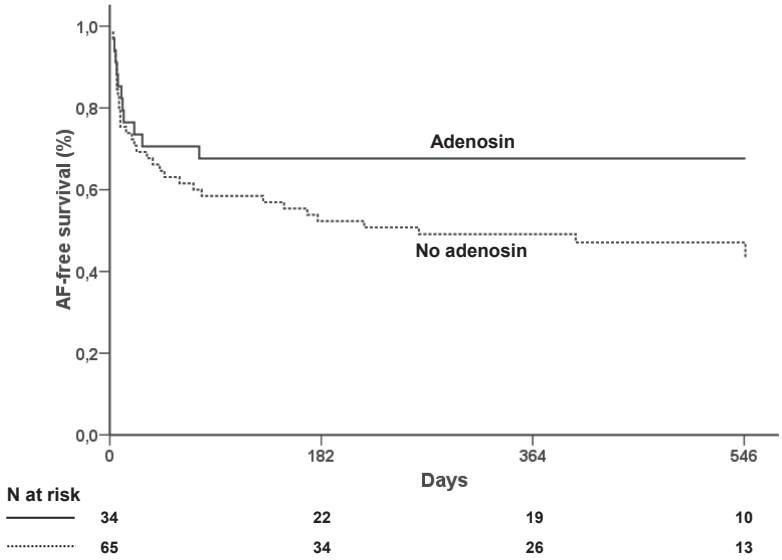

Figure 4. Kaplan-Meier graph representing the AF-free survival after pulmonary vein isolation without AAD in the adenosine vs. the no adenosine group.

within three months. Another patient experienced transient worsening of preexisting migraine during the first two weeks after the ablation. An extensive neurological diagnostic work up could not reveal a procedure related cerebral event.
In the no adenosine group one patient experienced a pericardial tamponnade after the procedure that was successfully treated with a percutaneous drain. A second patient experienced an asymptomatic phrenic nerve paralysis that spontaneously resolved within six months.
No other adverse events were noted in both groups.

Discussion

Our report shows that administration of adenosine after cryoballoon pulmonary vein isolation demonstrates reconduction to the PV sleeves in 9 out of 132 (8%) of the veins, and useful in 7 out of 34 patients (21%). The one year follow-up after one procedure, showed a freedom of AF without AAD of 68% (23/34 patients). There is a significant reduction in AF recurrence during the long term follow-up as compared to a control group, ablated without adenosine testing.

It has been proven that in pulmonary veins isolation by radiofrequency energy, transient conduction after administration of adenosine occurs in 25% to 35% of veins (3, 9). Since resumption of electrical activity in the muscular sleeves seems to be one of the most important factors for

recurrence of AF after isolation (1), it remains a challenge to achieve both continuous and permanent lesions during the first procedure. Ablation of dormant PV sleeves has proven to reduce recurrence of AF during follow-up (10-12). Most of the currently available studies have been performed using radiofrequency energy. It is therefore unclear what the clinical implications are for cryothermal ablation. Our study is in accordance with a recent report about a comparable number of patients, also demonstrating a lower number of dormant PV's demonstrated with adenosine after cryoballoon PVI, than one would expect in RF ablation (13); our study in addition shows a clear clinical benefit of adenosine testing. In cryoballoon ablation however, it has also been shown that reconduction is an important factor for recurrences of AF after PVI, with on average 3 PV´s showing recovery during a second procedure (8). Therefore, elimination of dormant PV sleeves could improve long term results. Building on these findings, we designed our study to answer the question whether adenosine could have the same predictive value in cryoballoon ablation as it has in radiofrequency ablation.

The mechanism by which adenosine causes reconnection of apparently isolated PV´s is by activating an outward potassium current through activation of a purginergic A1-membrane receptor (5). Reversibly damaged myocytes show a higher resting potential, deactivating the depolarizing voltage dependent sodium channels and thus inhibiting fast depolarization. By hyperpolarizing the muscular PV-cells that underwent reversible damage due to ablation, normal function of the sodium channels is restored, normalizing the conduction properties and revealing viable excitable tissue (4). A possible explanation for the difference in incidence of reconnection between radiofrequency and cryothermal PV isolation is the difference in amount of reversible damage around the permanent lesion. Radiofrequency ablation causes a temperature specific zone of reversible lesion around the ablation point (14-16). Cryothermal energy has been proven to cause little or no surrounding reversible injury after ablation (17-18). This is probably caused by the fact that the cryomapping effect at temperatures around -30°C is immediately reversible upon cessation of the application (19). The substrate that is sensitive for adenosine would therefore be absent or present in small amounts, resulting in the lower incidence.

We report a freedom of AF without AAD after one procedure of 68%, which is a significant increase in success compared to 46% in the control group without adenosine testing. It seems to prove, since adenosine testing (with subsequent ablation) is a proven method of increasing freedom of AF after radiofrequency ablation, that the same is true for cryoballoon ablation. There is a high discrepancy in published literature on recurrence of AF after cryoballoon ablation: success rates after a single procedure, range from 49%(8) to 74% (6). Two major differences in follow-up method are apparent in published literature on cryoballoon ablation: the use of a blanking period, and the modalities of rhythm monitoring after ablation. In this study, no blanking period was employed since early AF recurrence is a proven predictor of late recurrence (8, 20). HRS/EHRA/ECAS recommendations for follow-up after AF ablation still state that a blanking period of three months should be employed(21), but this is based on studies performed with

radiofrequency energy, which has a delayed effect, redering up to 60% of patients free of AF during long term follow-up after early recurrence(22). It is hypothesized that either the thermal injury of radiofrequency ablation(23), or a transient autonomic imbalance(24) is responsible for this. Unlike RF, cryothermal ablation causes tissue injury with preservation of tissue architecture(25), so it remains unclear at present whether a blanking period should be adopted for cryoballoon PVI.

As a follow-up method our study combines daily transtelephonic ECG, 24-hour Holtermonitoring and a symptom based questionnaire. Studies have shown that transtelephonic ECG and 7-day Holter have the same sensitivity for detecting AF episodes of about 70%(26). The addition of both 24-hour Holtermonitoring and a symptom based questionnaire should increase the sensitivity and therefore decrease the reported long-term freedom of AF (27), compared with reports using less follow-up modalities.

Limitations

This study focused on demonstrating the potential of adenosine for revealing dormant pulmonary vein sleeves after cryoballoon ablation. No blinded randomization was performed; instead a control population was used to assess the difference in outcome. No repeat procedures were performed in these patients to assess long term durability of the pulmonary vein isolation, to prove the predictive value of reconnection of sleeves under adenosine for late reconduction.

Conclusion

Adenosine administration after cryoballoon pulmonary vein isolation reveals dormant connections from the left atrium to the PV in 21% of patients. Additional ablation of dormant PV's gives a long term freedom of AF in 68% of patients after a single procedure. This is a significant increase compared to cryoballoon PVI without ablation of dormant PV's.

Acknowledgements

We would like to thank Yvette van Gestel for her assistance in preparing figures 2C and 3A.

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Chapter eight

Migraine accompagnée after transseptal puncture

Jordaens L, Janse P, Szili-Torok T, Van Belle Y. Migraine accompagnée after transseptal puncture. Neth Heart J. 2010 Aug;18(7-8):374-5.

Abstract

Migraine has never been reported as a complication of transseptal puncture for ablation of atrial fibrillation. We studied its incidence before and after such procedures after observing some striking new migraine in several patients. A total of 8% of procedures for pulmonary vein isolation with a 15 Fr sheath used for transseptal puncture were associated with new headache with ocular symptoms or migraine within 3 months. Exacerbation of pre-existing migraine was reported in another 7% of procedures. More complaints were seen in redo procedures. The questionnaires were performed at 3 months after the intervention and there was no more evidence of persisting flow over the atrial septum at that time, when most complaints had already disappeared. This has important implications for follow after ablation for atrial fibrillation.

Key words: Arrhythmia treatment; atrial fibrillation; catheter ablation; cryoablation; headache; migraine; transseptal puncture

Introduction

A patent foramen ovale (PFO) has been associated with cryptogenic stroke and migraine (1,2). Closure of the PFO has been advocated by some to treat migraine if conventional therapy fails, but the real benefit remains unclear (2). Today, an increasing number of cardiac interventions is done with transseptal puncture (TSP) of the interatrial septum. It is assumed that this puncture hole closes after the intervention. Most electrophysiologists are using multiple sheaths through the septum to perform pulmonary vein isolation. Migraine has never been reported as a complication of this procedure (3), but has been observed occasionally when TSP was used in conditions with a high right-sided pressure, creating a real right to left shunt (4). Nowadays, we are treating paroxysmal atrial fibrillation (PAF) with pulmonary vein isolation, using a cryothermal balloon, inserted through a single 15 Fr transseptal sheath (5).

Methods

The ablation procedure has been decribed in detail, and was followed with a structured follow-up of at least one year including a repeated questionnaire, to which all patients consented. Antiarrhythmic drugs, including beta-blockers and anticoagulant drugs were not changed from the pre-ablation dosages untill month 3. During the regular medical check-up at 3 months after the procedure, we submitted 87 consecutive patients (68 male, 29 female; mean age 55±10 years; persistent atrial fibrillation 11/87) to a systematic questionnaire (the relevant part is given in appendix 1) on having de novo, or exacerbated migraine or headache with ocular symptoms as scotoma, before the formal consultation was continued. We did the same after 13 re-interventions performed with the same technique during this time frame. De novo patients with headache were sent to the ophthalmologist and the neurologist to confirm the diagnosis, and to exclude ocular problems and embolism. A further work-up was left to the discretion of the attending cardiologist, in agreement with the patient.

Results

The prevalence of previous migraine or headache with ocular phenomena, as shown in table 1, was 16%. This concerned 9 male patients and 6 female patients, with a mean age of 52 $\pm$ 9 years. A total number of 15 patients reported new symptoms or exacerbations within 3 months. The patients with new symptoms (8% of the procedures) were 4 males and one female with a mean age of 46 $\pm$ 11 years. Exacerbations were almost as common as de novo symptoms in the 3 months after ablation (7%). Symptoms occurred more often after a redo procedure ($p<0,05$). Most complaints had disappeared when patients visited the outpatient clinic at 3 months after

Table 1. Migraine or headache with ocular symptoms after pulmonary vein isolation

Procedure type	Pre-existing	New	Exacerbation
First: n = 87	16	5	4
Redo: n = 13	3	3	3
Total: n = 100	16	8	7

the ablation. "Migraine accompagnée" was formally diagnosed in this way in one new patient, and in one with an exacerbation. Transoesophageal echocardiography, performed after 3 months in still symptomatic patients could not show a persistent hole with flow through the septum. One of the patients reported his symptoms spontaneously with a drawing of the ocular signs he had developed before he was interviewed (figure 1).

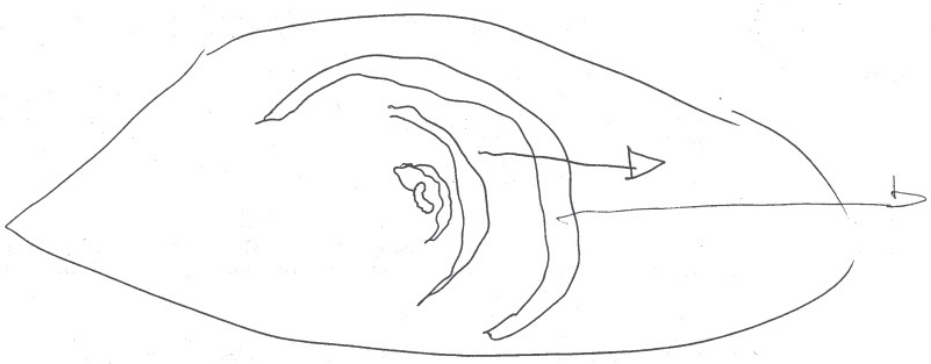

Figure 1. Drawing of a scotoma by a patient who developed visual phenomena preceding severe attacks of headache, after transseptal puncture for pulmonary vein isolation. Initially, the scotoma is small and centered in his visual field, to expand later and drift away to the lateral side of his vision over a course of 30 minutes.

Discussion

This observation certainly contributes to the ongoing controversy on the association of a PFO and migraine. The time course, and the repetitive character of exacerbation in some patients with a redo were very convincing. It has to be noticed that we report only on patients treated with a new cryo-ablation system with a 15 Fr sheath. We have observed headache during cryo-energy applications mainly at the left upper pulmonary vein as well, without a clear relation with the phenomena as described in this report.

We are aware that these results are not the result of data which were sampled with a questionnaire specifically designed to approach migraine in a scientific way, and we realise there is some bias after we had observed some patients with de novo headache. However, the questionnaires

(based upon a validated screening test) were collected prospectively, and were part of a larger interview (6). The reported prevalence (16%) is in line with existing data in the general population (7). We believe this study should be repeated with a well-structured questionnaire based on the International Headache Society Criteria.
Further, we are screening now all our patients with intracardiac echocardiography at the end of the procedure to assess whether the puncture site still shows transseptal flow.

Conclusions

We would like to emphasize that in the follow-up after isolation of the pulmonary veins for atrial fibrillation, attention should be given to the occurrence of migraine, ocular symptoms or headache. This is especially necessary after a re-intervention. This finding has consequences for the policy on anticoagulation after ablation. However, when studied at 3 months, no patients with manifest transseptal flow were detected. The higher occurrence of headache/migraine after a second procedure suggests that a scarred or previously damaged septum closes with more difficulties. Further neurological research on the effect of TSP in general, with the potential of silent embolism and stroke is stll needed.

Appendix 1. Section of the questionnaire focusing on headache

10. Did you have episodic headache, or headache before the ablation, which was so heavy you could not work, or associated with gastrointestinal symptoms, or aggravated by light, or associated with visual symptoms? If Yes , how often?
11. Did you have these symptoms after the ablation? If Yes, how often?
12. If you had such symptoms before and after the ablation, became they different afterwards? If Yes, please describe.

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Chapter nine

Hemoptysis after pulmonary vein isolation with a cryoballoon: An analysis of the potential etiology

Bhagwandien R., Van Belle Y., Schwagten B., Joos G., de Groot N., Jordaens L. Hemoptysis after pulmonary vein isolation with a cryoballoon: An analysis of the potential etiology. Submitted.

Abstract

In a series of 359 cryoballoon ablations with a complete registry of complications, hemoptysis after ablation was observed in 2 patients. One patient had pre-existing bronchiectasis; the other had no previous history of pulmonary disease. Both had clinically significant symptoms. In the first patient the guiding wire was very distal in one of the veins and exceptional low freezing temperatures were recorded in the left inferior pulmonary vein. Similarly, in the second patient exceptional low freezing temperatures were recorded in all 4 veins. Hemoptysis can occur after cryoballoon ablation.

Key words: atrial fibrillation; catheter ablation; cryoballoon ablation; hemoptysis; complications.

Introduction

Pulmonary vein isolation (PVI) has emerged as a successful therapeutic option in patients with paroxysmal atrial fibrillation with success rates varying between 65% and 85%(1-2). It has become general practice in patients with symptomatic recurrent paroxysmal episodes, resistant to anti-arrhythmic drugs(3). Although radiofrequency ablation is highly successful, major complications occur in 3,9-6% of the patients(4-5). These complications occur either peri-procedurally (e.g. vascular access accidents, cardiac perforation and tamponade, thromboembolic events, atrio-esophageal fistula, peri-oesophageal vagal plexus damage) or during long-term follow-up (e.g. pulmonary vein stenosis, development of new lesion related atrial arrhythmias). Cryothermal energy preserves the tissue architecture and reduces the thrombotic risk(6). The main complications of the cryoballoon in clinical use, are phrenic nerve palsy, and pericardial effusion(7-8). Until now no thromboembolic complications, no pulmonary vein stenosis, and no atrio-esophageal fistulas were described.

Case 1:

A 56-years old female patient was referred for PVI. She was known with symptomatic paroxysmal AF since 7 years. Her medication included flecainid slow release 200 mg odd, bisoprolol 2.5 mg odd and warfarin. The paroxysms of AF however, were unresponsive to medical treatment, resulting in significant patient discomfort. She had suffered in the past from recurring airway infections due to the presence of bronchiectasis. The electrocardiogram and echocardiogram showed no significant abnormalities. Her chest X-ray showed signs of bronchiectasis on both lower lobes.

PVI was performed with a 28 mm cryoballoon. During the procedure, iv heparin was given with an activated clotting time above 350 s. Table 1 shows the number and characteristics of the ablations in the 4 veins. In the right superior pulmonary isolation could not be achieved with only the balloon, and a segmental ablation with an 8mm cryocatheter was performed. When ablating the left inferior pulmonary vein the guiding wire was very distal in the vein (Figure 1), and a very low freezing temperature was observed during the third application.

At discharge, the patient had a normal echocardiogram and an unchanged chest X-ray. Oral anticoagulation was restarted, and dosed to reach an international normalized ratio (INR) of 2.5 to 3.5. Until the therapeutic INR was reached, low molecular heparin was given. A few days after discharge, she was re-admitted with hemoptysis. There were no signs of pulmonary infection, and the INR was within the therapeutic range. As the warfarin was discontinued for a short period, the hemoptysis disappeared. During the one year follow-up period after ablation, she had neither recurrence of hemoptysis, nor of AF.

Table 1: Pulmonary vein isolation: number and characteristics of the applications

		LSPV	LIPV	RSPV	RIPV
Patient 1	Application 1				
	Occlusion Grade (1-4)	3	3	2	2
	Inflation time (s.)	300	300	300	300
	Min. Temperature (C.)	-42	-35	-40	-39
	Application 2				
	Occlusion Grade (1-4)		3	2	3
	Inflation time (s.)		300	300	300
	Min. Temperature (C.)		-32	-39	-32
	Application 3				
	Occlusion Grade (1-4)		4	3	3
	Inflation time (s.)		300	300	300
	Min. Temperature (C.)		-76	-35	-34
	Application 4				
	Occlusion Grade (1-4)			3	
	Inflation time (s.)			300	
	Min. Temperature (C.)			-35	
	Application 5				
	Occlusion Grade (1-4)			4	
	Inflation time (s.)			300	
	Min. Temperature (C.)			-40	
	Application 6				
	Occlusion Grade (1-4)			2	
	Inflation time (s.)			300	
	Min. Temperature (C.)			-39	
	Freezor Max Applications			13	
	Pulmonary Vein Isolated	Y	Y	Y	Y
Patient 2	Application 1				
	Occlusion Grade (1-4)	4	4	4	4
	Inflation time (s.)	300	300	178	300
	Min. Temperature (C.)	-63	-74	-62	-65
	Application 2				
	Occlusion Grade (1-4)	4	4	4	4
	Inflation time (s.)	300	300	248	300
	Min. Temperature (C.)	-60	-67	-60	-65
	Pulmonary vein isolated	Y	Y	Y	Y

LSPV: Left Superior Pulmonary Vein; LIPV: Left Inferior Pulmonary Vein; RSPV: Right Superior Pulmonary Vein; RIPV:
Right Inferior Pulmonary Vein; Occlusion Grade: 1 No Occlusion, 4 Full Occlusion; S: Seconds; C: Degree Celcius.

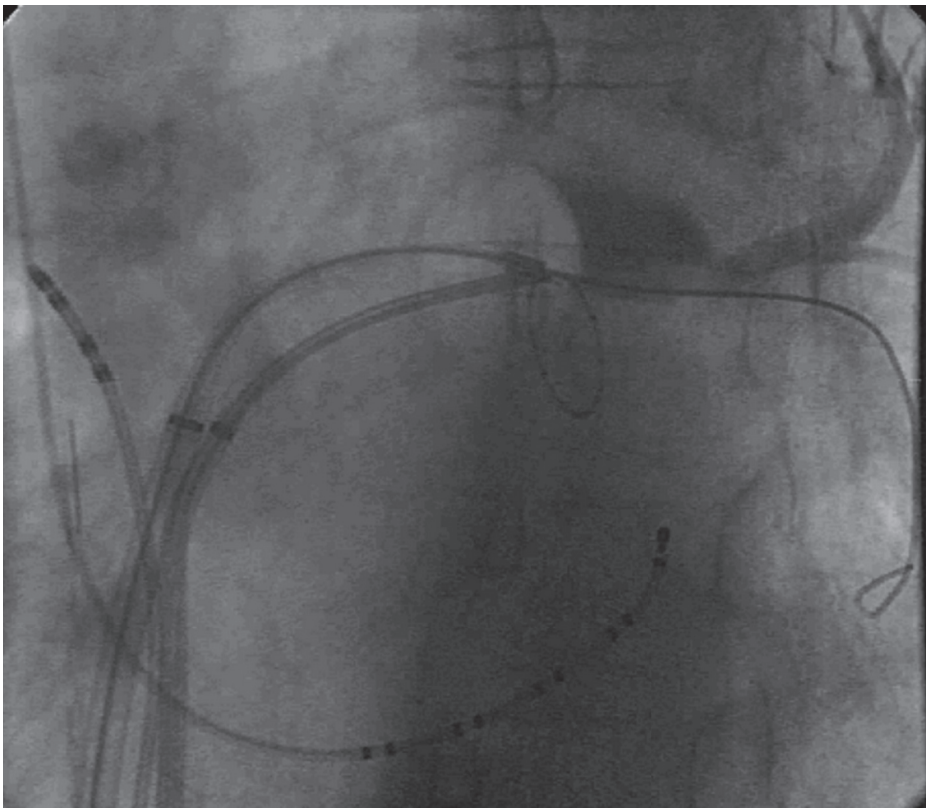

Figure 1. Cryoballoon ablation of the left inferior pulmonary vein. Left anterior oblique view. In this patient, a double transseptal puncture was performed. The guiding wire is directed inferiorly in a side branch of the vein.

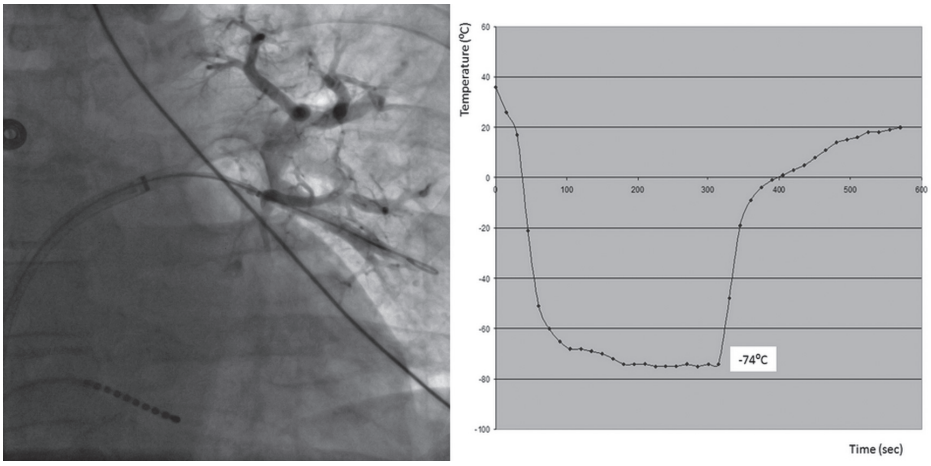

Figure 2. Application in the left inferior pulmonary vein, with the temperature curve as obtained from the freezing console. The occlusion is complete, and the contrast remains in the vein throughout the entire application. The lowest temperature is -74^{0}C.

Case 2:

A 48-years old male patient was referred to our out-patient clinic for PVI. He had symptomatic persistent drug-resistant AF for over a year. He had moderate regurgitation of the mitral valve with a mildly dilated left atrium.

PVI was performed using a 28 mm cryoballoon with an ACT between 280 and 300 s under iv heparin. All four pulmonary veins were successfully isolated, with extreme low freezing temperatures recorded in each vein (Table 1). During the procedure, it was also noted that the cryoballoon was positioned quite deep in the veins.

The next day, the patient had hemoptysis under iv heparin. The activated partial thromboplastin time was 73 s. The heparin was discontinued. Post procedural echocardiography was normal, but the chest X-ray showed a new consolidation in the left lower lobe (figure 3). The CT-scan of the chest confirmed the consolidation but showed no signs of pulmonary bleeding. The hemoptysis resolved spontaneously and did not reoccur after restarting warfarin.

During one year after ablation, there was no recurrence of the hemoptysis. The patient remained free from AF.

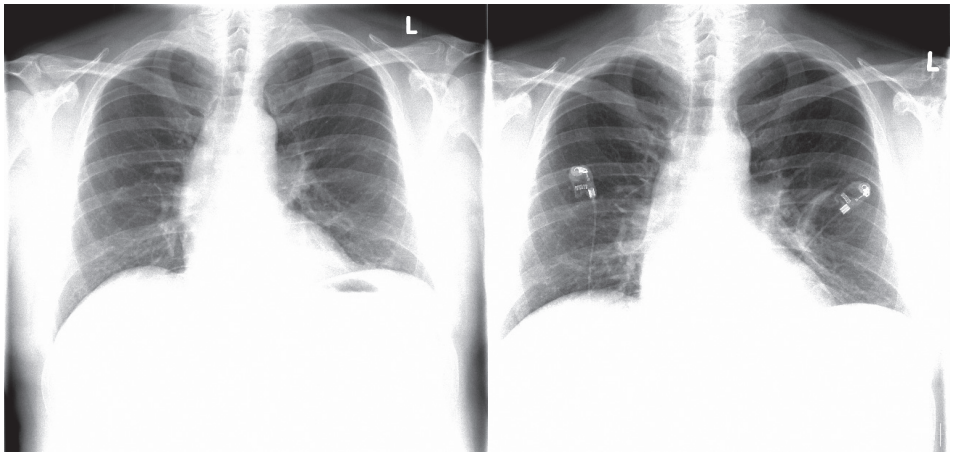

Figure 3. Chest X-ray before admission (A), and at the day after ablation (B), with a consolidation in the left lower lobe.

Discussion

To date, 359 patients in our centre had pulmonary vein isolation using a cryoballoon. In 2 patients we observed hemoptysis.. From studying these cases, it remains unclear what the mechanism is behind the hemoptysis. Several hypotheses can be suggested to explain the vascular damage causing the pulmonary hemorrhage.

It has been shown that hemoptysis can occur due to a pulmonary vein stenosis, as a long term complication of PVI. However, neither in segmental cryothermal PVI(9), nor in cryoballoon PVI(2), pulmonary vein stenosis has been reported as a complication. It is necessary for each vein to be occluded during several minutes to achieve isolation, and this might cause vascular damage in the pulmonary capillary tissue caused by a pressure rise. Ablation in an animal model could provide insight in the pathology supporting this hypothesis.

Direct damage to the tissue surrounding the pulmonary vein or deeper inside the lung could be caused by catheterising it with the guidewire or by inflation of the balloon. In these cases this is substantiated by the distal guide wire and/or balloon position in both. The very low freezing temperatures are correlated with complete occlusion of the vein(10) and to our experience also with distal positioning of the balloon. An argument against this is the fact that in both cases it took several hours to days for the hemoptysis to become clinically overt. When causing a vascular rupture through instrumentation, bleeding would be expected to occur immediately and be severe(11).

One of both patients suffered from bronchiectasis, a condition known to cause hemoptysis in about 27% of its initial clinical presentation. This condition, combined with the simultaneous use of warfarin and low molecular weight heparin, could also explain the hemoptysis in one patient, but does not apply in the second. In both patients however, the symptoms subsided when anticoagulation was stopped.

Currently, there is no certainty about the cause of hemoptysis after cryoballoon PVI, but these two cases should alert physicians performing this procedure that caution is to be maintained when manipulating either the balloon or the guide wire deep within the pulmonary vein. A temporary cessation of anticoagulants often suffices in resolving the problem.

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Chapter ten

Pulmonary infarction after pulmonary venous occlusion with a cryoballoon in a pig model

Van Belle Y., Bhagwandien R., Ferdinande L., te Lintel Hekkert M., de Groot N., Dunckers D., Jordaens L. Pulmonary infarction after pulmonary venous occlusion with a cryoballoon in a pig model. Submitted.

Abstract

Two pigs, submitted to ablation of the pulmonary veins with a 23mm cryoballoon were acutely sacrificed to assess the lesions in the heart. Both showed sharply delineated wedge shaped hemorrhagic lesions at the margins of the pulmonary tissue, suggestive for pulmonary infarction. Microscopic examination showed the presence of erythrocytes in the alveolar lumen, and thrombi in the small venous and capillary vessels. A double occlusion of the pulmonary vein ostia with a cryoballoon during 300 seconds may result in pulmonary infarction.
Key words: atrial fibrillation; cryoballoon; catheter ablation; cryoablation; pulmonary infarction; pulmonary veins.

Introduction

Cryoballoon ablation of the pulmonary veins is an effective treatment for atrial fibrillation (1-4). The major side effect of cryoballoon ablation is temporary right phrenic nerve palsy, due to the close proximity of the right phrenic nerve to the right upper pulmonary vein. No pulmonary vein stenosis and atrio-esophageal fistula have been reported (1-4). An animal study was designed in a porcine model to determine the optimal freezing duration for long term PV isolation, which is still a matter of debate. The effect temporary pulmonary vein occlusion with the balloon catheter on pulmonary tissue has not previously been studied. The unexpected pulmonary hemorrhagic lesions we found in the first two animals during these experiments are described in this report.

Methods

The study protocol was approved by the Ethical Committee for Animal Experiments of the Erasmus University, Rotterdam, the Netherlands. Pigs weighing between 50 to 60 kg, were treated under general anesthesia. The ablation was performed according to a protocol comparable with the clinical ablation performed in humans. Both femoral veins were cannulated under continuous heparine infusion. A transseptal puncture was performed guided by intracardiac echocardiography and fluoroscopy. Selective pulmonary vein angiographies were made and pulmonary vein signals were registered with a 20-pole circular catheter before ablation. The transseptal sheath was exchanged for a steerable 12F sheath through which a 23 mm cryoballoon was introduced the left atrium. The right superior, right inferior and left inferior pulmonary veins were separately occluded and ablated according to the protocol. Each vein was twice occluded during 300 seconds. After the ablation pulmonary vein signals were registered again. The 2 first animals were then immediately sacrificed. The heart and lungs were excised for fixation in formaldehyde. A microscopic analysis of the ablated regions was performed using Haematoxilin-Eosin, Trichrome Mason and Reticulin stains.

Results

Two pigs were sacrificed immediately after PV cryoballoon ablation was performed in three pulmonary veins with an occlusion of each vein for twice 5 minutes. At macroscopic inspection, both of the animals had sharply delineated wedge shaped hemorrhagic lesions at the pulmonary surface, suggestive for pulmonary infarction (Figure 1). Microscopic analysis confirmed this pathological finding. Figure 2 shows the trichrome Mason tissue preparation of a lesion. The hemorrhagic lesion is sharply delineated, with presence of erythrocytes in the alveolar lumen. The small veins and capillaries show thrombi and fibrin deposits.

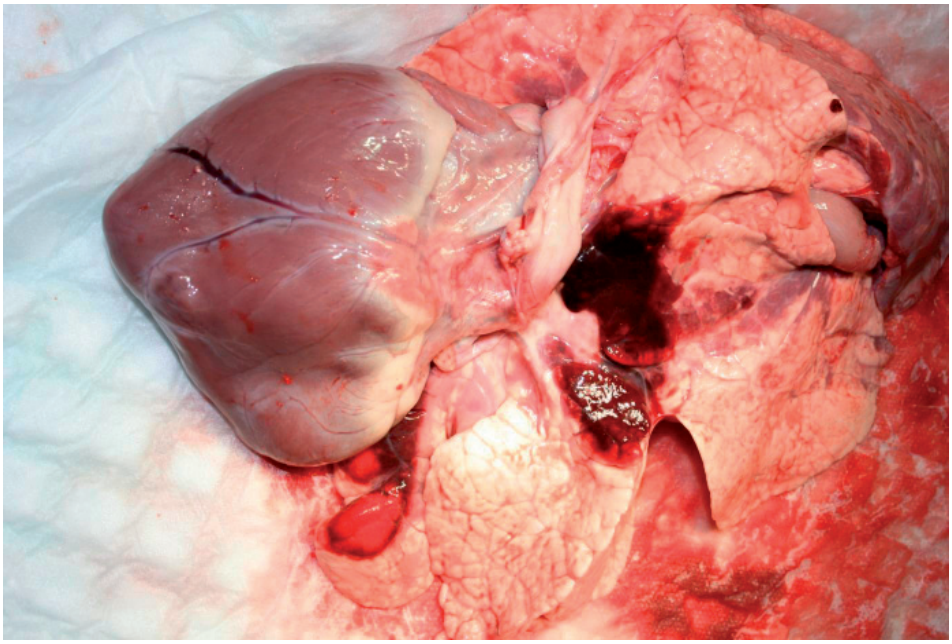

Figure 1. Macroscopic view of heart and lungs. The pulmonary tissue shows at least three distinct hemorrhagic lesions.

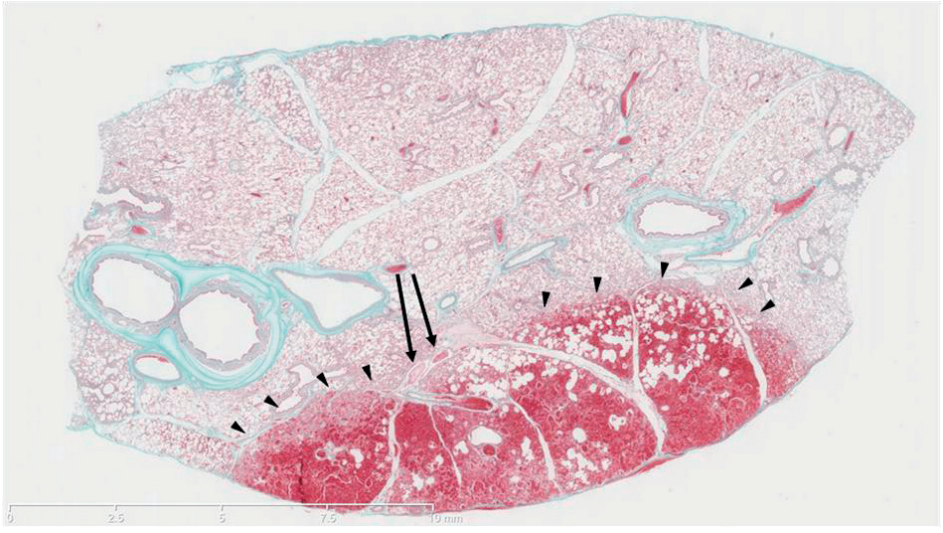

Figure 2. Microscopic section of a pulmonary lesion (Trichrome Mason staining). The large arrows point towards the capillary thrombi, the little arrows to the margin of the hemorrhagic lesion. Erythrocytes are visible in the alveoli.

Discussion

The findings presented here show that selective occlusion of the pulmonary veins with a cryoballoon for twice 5 minutes, can cause pulmonary infarction and hemorrhage in test animals. Currently, this occlusion period is standard for cryoballoon ablation in clinical patient care (1-3). Since pulmonary vein ablation emerged as a treatment for atrial fibrillation, PV stenosis has been reported in 0,4% of patients as a complication of ostial radiofrequency PV ablation, and can cause hemophtysis due to pulmonary bleeding especially in patients on anticoagulation(5). Although cryoballoon PV ablation causes no long term PV stenosis(4), the relative short obstruction of the PV's seems to cause pulmonary pathology that could result in similar symptoms. In reports about cryoballoon ablation, only one publication suggests pulmonary hemorrhage has occurred after ablation(4). Our findings should prompt physicians to be vigilant for this complication when performing the procedure.

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Chapter eleven

Reflections on reconduction after pulmonary vein isolation

Van Belle Y, Jordaens L. Reflections on reconduction after pulmonary vein isolation. Europace. 2009 Apr;11(4):400-1.

Comment on: Chierchia et al.=A0Early recovery of pulmonary vein conduction after cryoballoon ablation for paroxysmal atrial fibrillation: a prospective study. Europace. 2009 Apr;11(4):445-9

The cryoballoon has proven to be a formidable competitor in the field of novel technologies for ablation of atrial fibrillation. Several reports have shown this technique to be safe, and effective in treating atrial fibrillation, with 59 to 74% freedom of paroxysmal AF and 42% in persistent AF, after more than one year. Its major complication is temporary phrenic palsy caused by ablation of the right superior phrenic nerve[1-3]. In contrast to other balloon technologies, it is the only one which outcome results are currently extensively reported on in scientific literature, and seem promising. Two other balloon based devices, but employing a different energy source, have not proven to live up to safety standards : high intensity focused ultrasound balloon (HIFU) and the endoscopically-guided laser balloon. The HIFU was not only reported to have a high percentage of permanent phrenic nerve paralysis (which seems a problem inherent to any balloon concept)[4], but also evidence emerged that the dreaded atrio-oesophageal fistula was one of its major complications[5]. After that, the FDA-approved HIFU Ablation System Study (randomising ablation against antiarrhythmic drugs), was suspended. Similarly, the first generation of the endoscopically-guided laser balloon, did not survive early phase III testing, and it FDA approved ENABLE-study (comparing ablation against antiarrhythmic drugs) was terminated. Another investigational device (not a balloon catheter however) showing promising results seems to be the multipolar ablation catheter with duty-cycled bipolar and unipolar radiofrequency energy (PVAC), which has recently shown to have 83% freedom of AF at 6 months, and no major complications[6]. Two studies are currently underway on this, the TOPP AF trial (multicentre, randomising ablation against DC cardioversion for permanent AF), and a single centre trial for paroxysmal AF randomising against wide circumferential PV isolation. This shows that the current scientific interest in catheters capable of simplifying AF ablation is major, and that knowledge on these new devices is still scarse but urgently needed.

Reporting on the cryoballoon ablation in this issue of Europace, Chierchia et al. try to leap beyond merely reporting on AF recurrence, by shedding some light on the timespan for early recovery of conduction after pulmonary vein (PV) isolation. On this matter, a large volume of publications exist in radiofrequency ablation, but little is known in cryothermal ablation. It has long been known that in radiofrequency PV ablation, reconduction to the pulmonary veins is an important cause of recurrent atrial fibrillation. It is responsible for around 80% of recurrences of AF[7, 8]. Early reconduction after RF ablation of the PV's occurs usually within 60 minutes after ablation, and on average in 2 veins[9]. Therefore, a large number of operators take in account a 60 minute waiting period after PV isolation before rechecking conduction. Moreover, dormant or stunned PV sleeves can be made apparent using adenosine infusion[10] and ablating these have proven to be successful in prevention of recurrent AF. In a population with recurrence of atrial fibrillation after a successful cryoballoon isolation, repeat procedures have shown reconduction in 100% of patients, occuring on average in 3 PV's. Similarly to RF ablation, reablation yields a high freedom of AF after reablation[3]. However, although the mechanism for recurrence of AF seems to be the same (i.e. reconduction), the difference in ablation energy seems to have an

essential effect on the time to recovery of the ablated tissue. As shown in the report by Chierchia et al., early reconduction during the first 60 minutes, seems to be very rare, since it only happened in about 3% of ablated veins. The reconducting veins are all right inferior veins, the most difficult to occlude using this balloon device, showing that probably superficial cryomapping is responsible for this phenomenon, linked to the heat-sink effect the passing blood flow has on the endocardial surface. Reconduction after cryoablation occuring later during the clinical course, is probably not related to the degree of occlusion, but to anatomical or physiological determinants, such as heating of deeper lying PV tissue by nearby structures with a high blood flow. It has been previously reported that reconduction after cryoballoon ablation is more frequent in the left sided veins[3], probably due to the descending aorta directly underlying them and the close proximity of the mitral valve region, warming the deeper PV tissue. If lack of occlusion were responsible for late reconduction, this would have to be more frequent in the lower right sided vein. Tackling the problem of reconduction seems to be a balance between the power of the ablation and the risk of damaging adjacent structures. In this report one temporary phrenic nerve palsy was observed, roughly coinciding with the 3% expected incidence reported on in larger studies[2, 3]. The findings of Chierchia et al. pose another piece in a puzzle trying to find how and when recovery of conduction to the pulmonary vein takes place (if ever) after cryoablation, and focuses attention on the important challenge of preventing this. It is an essential study in understanding the temporal recovery sequence of the atrial myocardium after cryoablation and aids in determining crucial factors to optimize the cryoballoon ablation strategy.

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Chapter twelve

Atrial fibrillation during catheterisation

Van Belle Y, Scholten MF, Jordaens L. Atrial fibrillation during catheterisation, in: Textbook of Interventional Cardiovascular Pharmacology. Eds. N.N. Kipshidze, J. Fareed, J.W. Moses, P.W. Serruys. London, Informa Healthcare 2007. ISBN 978-1-84184-438-1.

Incidence and prevalence

It is evident that during all types of cardiac catheterisation (table 1) atrial fibrillation (AF) can occur and that several patients will present with preexisting AF. It is the most common type of arrhythmia in adults[1]. The prevalence goes from less than 1% in persons younger than 60 years of age to more than 8% in those older than 80 years of age[2]. The age-adjusted incidence for women is about half that of men.

The cardiac conditions most commonly associated with AF are rheumatic mitral valve disease, coronary artery disease, congestive heart failure, hypertension, hypertrophic cardiomyopathy, pericarditis, myocarditis and congenital heart disease. It also occurs in cardiopulmonary disease such as pulmonary embolism and chronic obstructive pulmonary disease. Noncardiac causes include hyperthyroidism, hypoxic conditions, surgery, and alcohol intoxication.A predisposing condition exists in more than 90% of cases; the remaining cases have what is called lone atrial fibrillation. Comparing with age-matched controls, the relative risk for stroke is increased 2- to 7-fold in patients with nonrheumatic AF, and the absolute risk for stroke is between 1% and 5% per year, depending on clinical characteristics. AF can be categorised as paroxysmal, persistent or permanent.

Table 1. Interventions associated with atrial fibrillation

Coronary artery disease
• Diagnostic coronary angiography
• Percutaneous coronary intervention
Valvular pathology
• Left-right catheterisation
• Balloon valvuloplasty
Cardiac arrhythmia
• Diagnostic supraventricular or ventricular induction
• Endocavitary ablation procedure (including pulmonary vein isolation)
• Pericardial ablation procedure
• Left auricular closure device
Congenital disease
• Transcatheter closure of atrial or ventricular septal defect
• Obliteration of anastomosis
Myocardial disease
• Endocardial biopsy
• Percutaneous transluminal septal alcoholisation

Therapeutic options

Several treatment options are available when confronted with AF dependent on its clinical effect and duration. The hemodynamic effects and/or cardiac ischemia due to a rapid ventricular rate can seriously complicate a catheter procedure and can even be life threatening in some instances. Therefore, one goal can be to alleviate the clinical repercussions of the arrhythmia in

order to finalise the procedure. The second goal is to restore sinus rhythm if possible. To achieve the first goal, a strategy called 'rate control' might be sufficient if allowed by the hemodynamic status. The second goal is more complex, but will be discussed as well. Whether sinus rhythm can be restored (rhythm control) is dependent on the risk for tromboembolic events.

Anticoagulation during catheter procedures in AF

During cardiac catheterisation, intravenous anticoagulation is given to prevent venous thrombosis and left-sided emboli. In some interventions, for example left-sided catheter ablations, a very high level of anticoagulation is required to prevent trombus formation on the site of intervention (cfr. Figure 1) The risk of trombosis and stroke is well known.
Patients with AF or atrial flutter (AFL) and impaired left atrial appendage (LAA) function are also potentially at high risk for thromboembolism and might therefore require anticoagulation[3]. Approximately 90% of atrial thrombi in non-rheumatic AF are found in the LAA[4]. Patients less then 60 years, without cardiovascular disease, however, have a low risk for stroke. Other factors, such as age and associated cardiovascular disease, therefore, play an important role. Platelet activation, on the other hand, probably does not play a significant role in thrombus formation in these patients[5]. Five large, randomised trials of anticoagulation were pooled by The Atrial Fibrillation Investigators [6] and risk factors for stroke were defined. Age was shown to increase

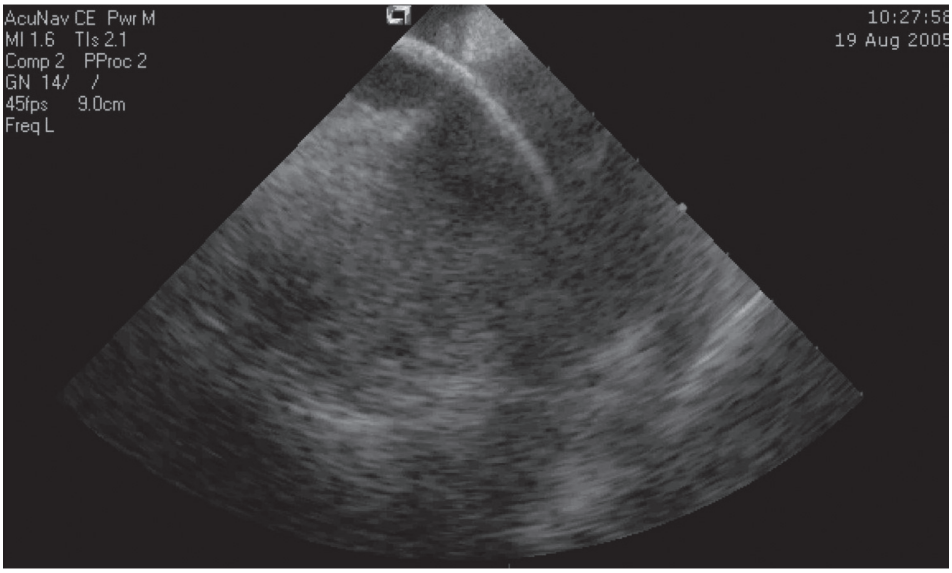

Figure 1. Intracardiac echocardiogram with transseptal sheath from right atrium (upper cavity) through the oval fossa in the left atrium. Attached to the sheath is a small clot, in spite of the administration of 5000 IU heparin before the puncture.

stroke risk by 1.4 per decade. Other risk factors include previous stroke or transient ischemic attack (TIA), hypertension, diabetes mellitus, congestive heart failure, ischemic or rheumatic heart disease, prior thrombo-embolism and female gender. Patients with rheumatic heart disease, prosthetic heart valves, prior thromboembolism and persistent atrial thrombus detected by transesophageal echocardiography are considered to be at highest risk[7, 8].
Echocardiography is useful in risk assessment for thromboembolism. Transesophageal echocardiography (TEE) is superior in detection of reduced flow velocities and spontaneous echo contrast in the left atrium and left atrial appendage[9]. Patients with AF and complex atherosclerotic plaques in the aorta have a substantially higher risk for stroke [10, 11].

Oral anticoagulation

Pooled data analysis for oral anticoagulation with coumadins (targeting an INR of 2.0 to 3.0) have shown a relative risk-reduction for stroke of between 62 and 70%[6, 12]. Several reports indicate that anticoagulation is actually underused in AF patients at high risk for thrombo-embolic complications[13, 14]. Possible explanations for this underuse are doubts about the effectiveness of anticoagulation, the fear of hemorrhagic complications such as intracerebral bleeding and the limitations of its use, such as frequent coagulation monitoring and interactions with other drugs. These fears also play a role in withholding oral anticoagulation at the time of catheterisation. In patients with bioprosthetic valves and AF, similar levels of anticoagulation to those mentioned above seem adequate. In AF associated with mechanical valve prostheses, levels of anticoagulation recommended are less standardised, but what is clear is that the risks for thromboembolism depend on the type of valve inserted and its position[15, 16]. Accordingly, the target INR for these patients should be individualised and the presence or absence of AF has little influence on this targeting. Thromboembolic events after cardioversion in atrial tachyarrhythmias have been reported in 1% to 7% of patients not receiving prophylactic anticoagulation[17, 18]. Anticoagulation is recommended for 3 to 4 weeks before and after cardioversion for patients with AF of unknown duration and for AF of more than 48 hours duration[7]. A reasonable alternative strategy is early cardioversion with a short period of anticoagulation therapy after exclusion of LA/LAA thrombi with TEE[7].

Anticoagulation in radiofrequency ablation of atrial fibrillation and flutter.

The treatment of AF entered a new era after the publication of the landmark observations of Haissaguerre et al[19]. Segmental ostial catheter ablation[20] and left atrial encircling ablation of the PVs[21] have both been reported to be successful in the treatment of AF. RF ablation is a highly effective therapeutic approach in the treatment of typical isthmus dependent atrial flutter[22].

RF catheter ablation is complicated by thromboembolism in about 0.6% of patients[23]. The risk of stroke from RF ablation may be higher in paroxysmal AF patients with prior transient ischemic attack[24]. As reflected by elevated plasma D-dimer levels, RF ablation has a thrombogenic effect that persists through the first 48 hours after the procedure[25]. Activation of the coagulation cascade in RF ablation procedures is not related to the delivery of RF energy, but is related to the placement of intravascular catheters and to the duration of the ablation procedure[26, 27]. Furthermore, RF lesions themselves have been shown to be thrombogenic in acute studies[28]. The risk of a thromboembolic complication is higher for left sided ablations (1.8%-2.0%)[23]. By administering intravenous heparin immediately after introduction of the venous sheaths, haemostatic activation is significantly decreased[29]. There is also a significant risk for thromboembolism in patients referred for ablation of typical atrial flutter who have not been appropriately anticoagulated[30]. Radiofrequency ablation of chronic atrial flutter is associated with significant left atrial stunning[31].

The NASPE Policy Statement on Catheter Ablation[32] suggest anticoagulation for at least 3 weeks prior to ablation for AF and atrial flutter for patients who are in these arrhythmias. Discontinuation of anticoagulants 2 to 3 days before the procedure is possible. For high-risk patients, heparin to cover this period should be considered[32]. Transesophageal echocardiography shortly before pulmonary vein ablation to exclude left atrial thrombi is done routinely in many services[33, 34]. Generally during left sided ablation, heparin should be administered, aiming at an activated clotting time (ACT) of 250-300 seconds. Higher levels of anticoagulation (ACT> 300 seconds) are used for pulmonary vein ablations[32]. Experienced groups continue anticoagulation therapy at least 3 months after a successful ablation[33, 35, 36].

Rhythm control: cardioversion

Early cardioversion may be necessary in patients with haemodynamic compromise (acute pulmonary oedema, worsening angina, or hypotension) in relation to uncontrolled AF (flow chart). Synchronized, direct current cardioversion is more effective and preferable to pharmacological cardioversion under these circumstances. Intravenous anticoagulation should precede and follow the cardioversion (figure 2).

The necessity for urgent cardioversion is less well established in haemodynamically stable patients with AF. It may be wise to postpone cardioversion till the procedure is finished, and to limit the antiarrhythmic interventions to rate control. Despite this wisdom, the management of these patients has traditionally been dominated by a drive to restore and maintain sinus rhythm – the so-called 'rhythm-control' strategy[37-39]. From a short term perspective, haemodynamic measurements may be more correct, and some procedures may require this. If cardioversion is performed in this, more or less elective, setting precaution to prevent emboli is warranted. TEE

may be helpful to take a better and faster decision; there are procedures with a transesophageal probe in place, and the threshold to cardiovert can be low.

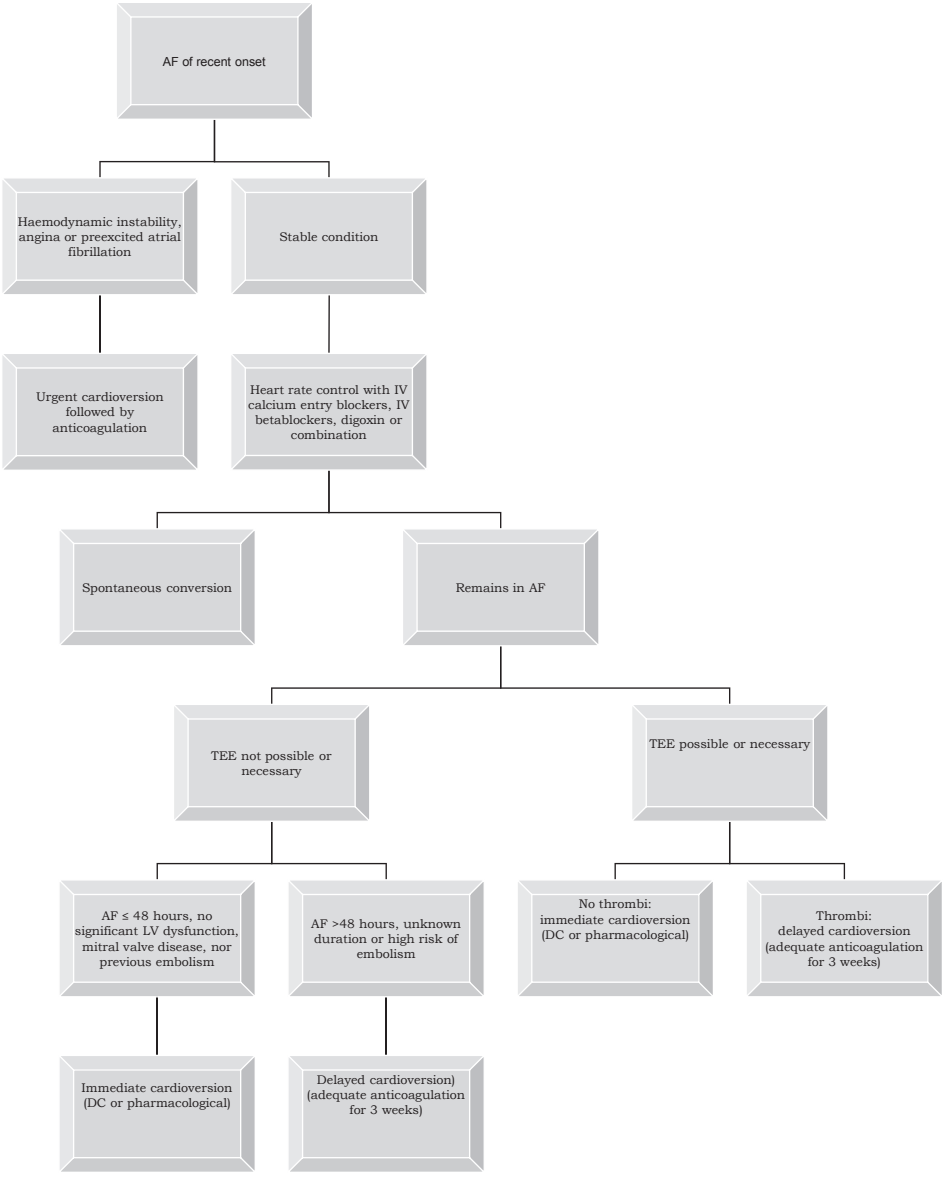

Figure 2. Flow chart for recent onset atrial fibrillation

Electrical cardioversion of atrial fibrillation

This can be performed with the conventional external paddles or patches or with intracardiac or intraesophageal electrodes. Good sedation with diazepam, or short acting anesthesia with a product as etomidate can be sufficient. Propofol has cardiodepressive characteristics, making it less desirable under certain conditions.

Pharmacologic cardioversion of atrial fibrillation

Pharmacological cardioversion appears to be most effective when initiated within 7 days after the onset of AF. A large proportion of patients with recent-onset AF experience spontaneous cardioversion within 24 to 48 h. This is less likely to occur when AF has persisted for more than 7 days.

A systematic review of randomized controlled trials in patients with newly detected AF identified a number of antiarrhythmic drugs for which there was statistically significant evidence of benefit[1]. In a limited number of comparative studies, flecainide was more effective than https://vpn.erasmusmc.nl/http/www.utdol.com/utd/content/topic.do?topicKey=Drug_L_Z/212980&drug=true propafenone and procainamide, propafenone was superior to amiodarone, amiodarone was superior to quinidine, and quinidine was superior to sotalol.

Recommendations for pharmacologic therapy, according to the duration of AF, and the doses that should be used were published in 2001 by a task force of the ACC/AHA[7]. In general, high doses of several drugs are more effective in producing cardioversion, but these doses are more prone to cause toxicity. As a result, DC cardioversion has largely replaced aggressive pharmacologic therapy for primary cardioversion. However, antiarrhythmic drugs are commonly used to facilitate DC cardioversion (e.g. Ibutilide) and after the procedure to maintain sinus rhythm.

An overview of effective drugs is given below. During procedures, the time to conversion also plays an important role.

Flecainide

- Class Ic agent that prolongs refractoriness and slows conduction in the atria, AV-node, His-Purkinje system, ventricles and accessory pathways. Predominantly blocks sodium channels in the activated state with rate-dependent block[40].
- Bioavailability 90-95%, t ½ 13-19 hours, 2/3 hepatic metabolisation, 1/3 renal excretion.
- Therapeutic levels 0.2 – 1.0 µg/ml, through level <1.0. Prolongation of PR and QRS intervals when therapeutic levels are achieved.
- Dosage: Oral, twice daily, initiation 100mg twice daily up to 150 twice, rare 200 mg twice. Intravenous : 1 to 2 mg/kg over 10 min, then 0.15 to 0.25 mg/kg/h
- Intravenous flecainide (150 mg) converts recent onset AF in 55 to 65 percent of patients[41].

- Cardiac proarrhythmic effects of flecainide include aggravation of ventricular arrhythmias and threat of sudden death as in the CAST study[42]. The proarrhythmic effect is due to nonuniform slowing of conduction. Monitoring the QRS-interval seems logical but no safety margins have been established. Furthermore late proarrhythmic effects can occur. In patients with preexisting sinus node or AV conduction problems, there may be worsening of arrhythmia. In AF or atrial flutter the drug can cause the atrial rate to fall, with a subsequent rise of the ventricular rate : it should therefore always be prescribed with an AV-nodal depressing drug such as digitalis, β-blockers, or verapamil to avoid fast AV conduction. Also, ventricular arrhythmias may be precipitated.
- *More effective than procainamide, sotalol, propafenone, and amiodarone[43-47].*

Propafenone

- Class Ic antiarrhythmic drug similar to flecainide, blocking sodium channels in both activated and inactivated state, additional weak betablocking effect.
- T ½ 2 to 12 hours, poor metabolizers 10 to 12 hours, steady state after 72 hours (t ½ of active metabolite
- Dosage: oral 450 to 600 mg, iv: 1.5 to 2.0 mg/kg over 10 to 20 min.
- Oral propafenone is an effective drug for conversion of AF to sinus rhythm[48, 49]. A review of the literature found that a single oral loading dose converted AF in 58 to 83 percent of patients, depending upon the duration of AF[50].
- Increased mortality and cardiac arrest recurrence when structural heart disease[51].
- *Useful in reducing the ventricular response[52].*

Ibutilide

- Class III antiarrhythmic drug, which prolongs repolarization by inhibition of the delayed rectifier potassium current (I_{kr}) and by selective enhancement of the slow inward sodium current. Ibutilide has no known negative inotropic effects[53].
- Only available as intravenous preparation
- T ½ 2 to 12 hours[54].
- Dose- and concentration-related increase in the uncorrected and rate-corrected QT interval
- Dosage: less than 60 kg — 0.01 mg/kg infused over 10 minutes. If the arrhythmia does not terminate 10 minutes after the end of the infusion, a second bolus (same dose over 10 minutes) can be given. More than 60 kg — 1 mg over 10 minutes. If arrhythmia does not terminate 10 minutes after the end of the infusion, a second bolus of 1 mg over 10 minutes can be given.
- The acute AF conversion rate is higher with ibutilide than with placebo and can be expected to occur about 30 minutes after infusion[55, 56]. It is efficacious in the termination of atrial fibrillation (AF) and flutter with both single and repeated intravenous infusions[54]. In patients with persistent AF or atrial flutter, ibutilide has a conversion efficacy of 44% for a

single dose and 49% for a second dose [56]. Efficacy is higher in atrial flutter than in AF and is related to an effect on the variability of the cycle length of the tachycardia[57] due to the phenomenon of reverse use dependence in that prolongation of refractoriness becomes less pronounced at higher tachycardia rates.

- Has the potential to provoke torsade de pointes. The rate of torsade de pointes ranged between 3.6 and 8.3 percent[55, 56, 58, 59] and may be more common in women [59]. Sustained episodes requiring cardioversion were seen in 1.7 to 2.4 percent. In addition to polymorphic VT, nonsustained monomorphic VT occurred in 3.2 to 3.6 percent [55, 56]. Therefore, continuous ECG monitoring for at least four hours after the infusion or until the QTc interval has returned to baseline.
- In comparative studies, ibutilide has been more effective for AF reversion than procainamide (51 versus 21 percent and 32 versus 5 percent)[60, 61] or intravenous sotalol (44 versus 11 percent) [53]. It is as effective as amiodarone in cardioversion of atrial fibrillation [1, 62].
- After cardiac surgery : dose-dependent effect in conversion of atrial arrhythmias with 57% conversion at a dose of 10 mg [63]
- The drug is more effective when given as pretreatment prior to cardioversion[64]

Dofetilide

- Useful, but not commercially available.

Amiodarone

- Class III antiarrhythmic agent with additional class I, II, III and IV actions. Prolongs action potential duration and effective refractory period in all cardiac tissues.
- Dosage : Oral : 1.2 to 1.8 g in divided doses until 10g, then 200 to 400mg per day or 30mg/kg as a single daily dose. Intravenous : 5 to 7 mg/kg over 30 min, then 1.2 to 1.8 g in continuous infusion over 24h, then 200 to 400 mg daily[1].
- Intravenous amiodarone has been reported to be effective, converting 60 to 70 percent of patients to sinus rhythm in some trials [65-67]. The efficacy has been evaluated in studies with different durations of AF.
- Oral amiodarone — A number of mostly small trials have evaluated the efficacy of oral amiodarone which, as with other drugs, appears to vary with the duration of AF [66, 68]. The SAFE-T trial of patients with persistent AF who were on anticoagulation therapy showed that patients randomly assigned to amiodarone or sotalol, had a higher frequency of cardioversion to sinus rhythm after one month compared to placebo. Patients who were still in AF underwent DC cardioversion of which efficacy was similar in all groups[69].
- Cardiac side effects : Torsade de pointes (<0.5%), severe bradycardia (1-year risk of bradycardia 2.4% on amiodarone vs. 0.8% on placebo. Non-Cardiac side effects : Pulmonary toxicity 1% per year with fatal cases : discontinue and treat symptomatically, hepatotoxicity 0.6%, periferal neuropathy 0.3%, hypothyroidism 6%, hyperthyroidism 0.9%. routine toxicity

screening is required. This includes periodic (usually every 6 months) measurement of thyroid (sensitive serum T4), hepatic (AST), and pulmonary function (chest x-ray), as well as clinical evaluation. [70]

Procainamide

- Intravenous procainamide converts 20 to 60 percent of cases to sinus rhythm, particularly if the AF is of recent onset. It can be used with caution (hypotension, QRS widening), when the more effective, previously described drugs are not available.

Quinidine

- Should not be used in emergency settings[71]

Sotalol

- Intravenous sotalol appears to be less effective than intravenous flecainide or ibutilide[47].
- Oral sotalol is less effective than quinidine for conversion of recent onset (<48 hours) AF and is comparable to amiodarone for conversion of AF of >48 hours in duration[69, 72].

Digoxin

- The rate of conversion with digoxin is no better than placebo. Digoxin may restore sinus rhythm when AF is due to heart failure[73, 74]. In this setting, reversion is the result of improved hemodynamics and a reduction in left atrial pressure.

Rate control: slowing conduction in the AV-node

Rate control can be effectively achieved using a betablocker, calciumantagonist and/or digoxin either in monotherapy or combined as necessary. Caution must be taken that combining intravenous betablocker and calciumantagonist may cause severe depression of the left ventricular function and AV-node. In the setting of heart failure digoxin may be prefereble since it has a positive inotropic effect, with diltiazem as a second choice agent.

Betablockers

Propranolol

- Noncardioselective betablocker with a plasma half-life of 1 to 6 hours and a hepatic metabolisation.
- Intravenous dose is 1 to 6 mg as needed.
- Contraindications include hypotension, second and third degree heart block, cardiogenic shock and overt cardiac failure, peripheral ischemia and bronchospasm.

- Multiple drug interactions have been described with numerous compounds due to interference with hepatic clearance.

Metoprolol
- β1-selective betablocker with a plasma half life of 3 to 7 hours and mainly hepatic elimination.
- Bolus 2.5 to 5 mg over 2 minutes, repeated at 5 minutes interval up to 15 mg.
- Contraindications: hypotension, second and third degree heart block, cardiogenic shock and overt cardiac failure and bronchospasm.
- Drug interactions: catecholamine-depleting drugs such as reserpine and MAO-inhibitors may have an additive effect in combination with betablockers. Drugs that inhibit CYP2D6 (quinidine, fluoxetine, paroxetine and propafenone) increase metoprolol concentration.

Esmolol
- Rapidly and very short acting betablocker (half life of 9 minutes).
- Bolus of 0.5mg/kg over one minute followed by 50 µg/kg per minute. After four minutes another bolus can be given and infusion increased to 100 µg/kg per minute. Infusion rate can be increase to a maximum of 200 µg/kg per minute, guided by clinical response.
- Contraindications include hypotension, peripheral ischemia, confusion, thrombophlebitis, skin necrosis from extravasation, bradycardia, second and third degree heart block, cardiogenic shock, overt heart failure and bronchospasm.
- Interactions with cathecholamine depleting drugs and increases digoxin blood levels.

Calciumantagonists

Verapamil
- Non-dihydropyridine calciumantagonist (Class IV AAD) that inhibits the calcium mediated depolarisation of the AV-node, increasing the nodal effective refractory period and reducing ventricular rate in AF.
- Can be given as a slow intravenous bolus of 5 to 10 mg over 2 to 3 min, repeated after 10 to 15 min. Acts within 5 minutes of iv administration. Plasma half life is 2-8 hours. Is metabolised in the liver by the P-450 system, with ultimately 75% renal and 25% gastrointestinal excretion.
- Contraindications are hypotension, cardiogenic shock, marked bradycardia, second or third degree AV-block, WPW-syndrome, wide complex tachycardia, VT and uncompensated heart failure.
- Multiple drug interactions have been discribed (decreased serum concentrations of phenobarbital, phenytoin, sulfinpyrazone and rifampin, increased serum concentrations of quinidine, carbamazepine, cyclosporin). Important in this setting is that a marked interaction

exists between digoxin and verapamil, increasing the serum concentrations of the former due to decreased renal excretion.

Diltiazem

- Non-dihydropyridine calciumantagonist (Class IV AAD) with similar action as verapamil.
- Initial intravenous dose is 0.25 mg/kg over 2 minutes followed by 0.35 mg/kg after 15 minutes as required. Continuous infusion rate after initial bolus of 5 to 10 mg/h may be further increased to 15 mg/h. Plasma half life is 3 to 5 hours, but may be longer in an elderly population.
- Contraindications are similar to verapamil.
- Drug interactions include rise in plasma concentration when concomittant administration with cimetidine and lowering of the concentration with barbiturates, phenytoin, rifampin. Digoxin levels may be variably affected, can rise.

Digoxin

- Digoxin is a cardiac glycoside acting through inhibition of the sodium pump (Na/K-ATPase) causing a transient increase in intracellular sodium which in turn promotes calcium influx by a sodium-calcium exchange mechanism resulting in an enhanced myocardial contractility. It also causes sinus slowing and atrioventricular nodal inhibition by parasympathetic activation, combined with a modest direct nodal inhibition. Digoxin inhibits sympathetic nerve discharge and inhibits renin release from the kidney with a natriuretic effect.
- Intravenous loading with 500 µg produces a detectable effect in 5 to 30 minutes and becomes maximal in 1 to 4 hours. Additional doses of 250 µg can be given with 6 to 8 hour intervals. Serum digoxin concentrations should be ranging from 0.8 to 2.0 ng/ml, however there can be a clinical benefit below this range. Sampling should be performed at least 6 to 8 hours after the last dose.
- Serum half-life is 36 hours, 70% by renal secretion, 30% hepatic/gastrointestinal.
- Contraindications are hypertrophic obstructive cardiomyopathy (increase in inotropism can increase outflow tract obstruction), atrial fibrillation in WPW-syndrome (can cause precipitation of the arrhythmia to VF by preferential conduction over the accessory pathway), significant AV-block or sick sinus syndrome, hypokalemia (causes increased digoxin sensitivity and supraventricular/ventricular arrhythmia), thyreotoxicosis, postinfarction status (increased mortality). Caution should be exerted in renal failure, and coadministration of other drugs depressing sinus node or AV-nodal function.
- Caution should be taken when administered in pulmonary disease because of the sensitivity to intoxication due to hypoxia, electrolyte disturbances and sympathetic discharge. Digoxin also experimentaly increases infarct size.
- Drug interactions are multiple but of special interest is the interaction with other AAD's such as quinidine and verapamil, both increasing the serum concentration.

- Diuretics may induce hypokalemia which sensitizes the heart to digoxin toxicity and stops the tubular excretion of the drug. Toxicity has gastrointestinal (nausea, vomiting, anorexia, diarrhea), neurologic (malaise, fatigue, confusion, insomnia, facial pain, depression, vertigo, colored vision) and cardiac (palpitations, arrhythmias, syncope) effects, hypokalemia is also common in the typical patient. Digoxin arrhythmias range from AV-block and bradycardia, due to increased vagal tone, to accelerated atrial, junctional or ventricular arrhythmias, due to increased automaticity of junctional tissue en His-Purkinje tissue. Bidirectional tachycardia is rare but very suggestive. Blood level and electrolytes should be checked to confirm. Lidocaine can be given to reduce ventricular ectopy without increasing the AV-block, phenytoin reverses the latter (dose of 100 mg intravenously every 5 minutes to a total of 1000 mg or side effects). When faced with severe ventricular arrhythmias and thus life threatening intoxication, Digoxin-specific antibodies can be administered.

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Chapter thirteen

Technical developments in imaging and ablation of AF

Van Belle Y, Thornton AS, Szili-Torok T, Jordaens L. Technical developments in imaging and ablation of AF. In: Maessen J. ed.: Hybrid Cardiac Interventions. 2009; ISBN 10:88-7711-641-2.

Ablation of atrial fibrillation (AF) is one of the main activities in clinical electrophysiology, and this seems to be logical, as the first randomized studies versus drug therapy show a benefit for catheter ablation[1]. However, one has to realize that no real long-term follow-up is available, and that the intervention is associated with potential life-threatening indications, including atrio-oesophageal perforation, which often comes late after the intervention, and is often lethal. Its incidence is probably underestimated, and the current policy document estimates it at `less than 0.25%`, which is frightening[2]. This is one of the reasons that ablation of AF can not be seen as an established technique, but should remain under continuous scrutiny, and has to be improved.

In general, the challenges for clinical electrophysiology are multiple: they are summarized in Table I. Several priorities can be set out: on-line accurate imaging is an important goal. Further, the use

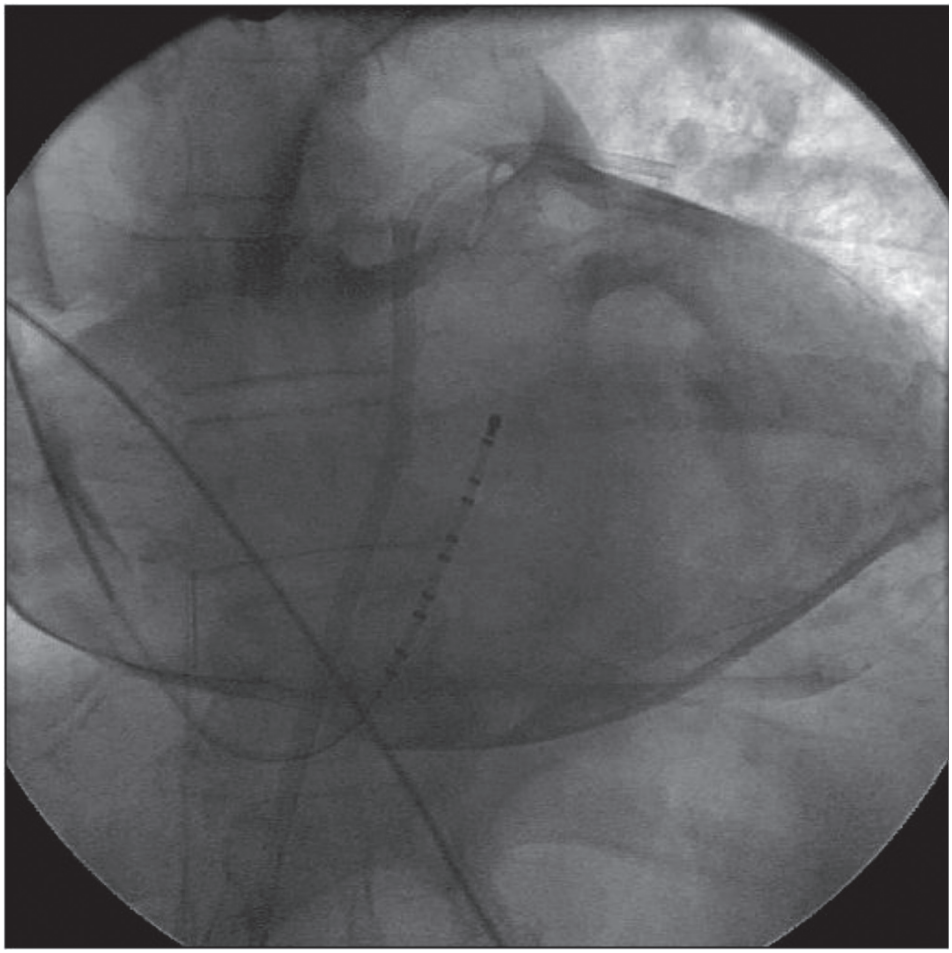

Figure 1. Pericardial effusion, after an imaging catheter was positioned in the left upper pulmonary vein. By using intracardiac echo the procedure could be brought to a successful ending.

of alternative energy sources might improve efficacy, and diminish the risk for perforation (figure 1). Finally, we would like to use safer catheters. The latter became possible by the use of robotics, mainly with magnetic navigation. In this chapter, we will focus on image integration, the use of balloon technology in order to simplify the approach of AF ablation, and finally on robotics.

Table I: Challenges for clinical electrophysiology

▪ Improving results, especially in AF
▪ Improving safety
▪ Understanding complex anatomy and mechanisms
▪ Better mapping
▪ Lesion assessment

Imaging modalities

Electroanatomical mapping

Electroanatomical mapping (EAM) systems (CARTO, NavX, RPM) have been around for more than a decade, and are very attractive in a complex cavity such as the left atrium. They have proven their value in the segmental ablation of AF. Creating a reconstruction of the endocardial surface by registering the catheter positions, together with the local electrogram voltage and activation time in relation to a reference electrode and showing the relative position of the ablation catheter, has rendered ablation more efficient and reduced fluoroscopy times[3].

Cardiac image integration

Image integration can be performed in several ways: EAM plus computed tomography (CT), magnetic resonance imaging (MRI), or with echo on top of all these techniques. An alternative is merging the CT or MRI with the actual fluoroscopic images.

CT/MRI with fluoroscopy
It has been shown that by combining CT with fluoroscopy alone (figure 2), catheter manipulation becomes easier and results of AF ablation improve[4].

CT/ MRI with EAM
Image integration of CT or MRI has been developed, allowing integration of an earlier acquired image set into the real-time (electroanatomical) mapping system. After segmentation of the 3D image, registration to a merged image is done by using landmark pairs (figure 3). This should allow the mapping system to represent a more detailed and accurate anatomical picture of the left atrial and pulmonary vein regions for ablation of AF (figure 4). There are several reports about the accuracy of the surface registration in the mapping system[5,6,7]. Using the mapping

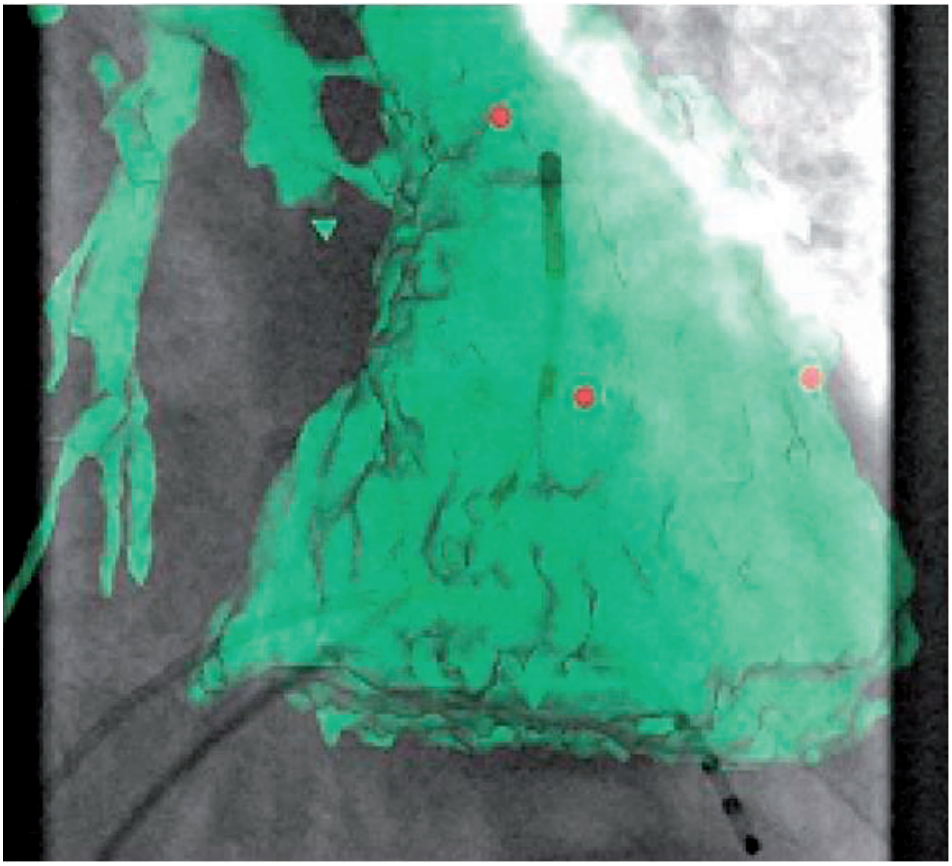

Figure 2. Image integration of fluoroscopy, with an ablation catheter in the right ventricular outflow tract, and a computed tomography of this region, in which the catheter is navigated.

system itself to determine the accuracy of the registered image it shows a very high degree of accuracy (2.1 to 4.7mm). However, when using intracardiac echocardiography (ICE) as an independent reference tool, larger spatial errors are reported (0.5 to 1.3cm), making CT/MRI integration rather inaccurate for ablation[8,9]. Optimizing accuracy also seems to be related to the respiratory and cardiac cycle, improving with expiration and end-atrial contraction CT or MRI data, and selecting the fiducial points (points used to register the previously acquired images to the electroanatomical map) at the posterior pulmonary vein surface[10]. A difference in atrial rhythm during acquisition of the radiologic images and the electroanatomical map does not seem to reduce accuracy of the registration process, but larger atrial size does[11,12]. As for clinical benefit of image integration, neither procedure outcomes nor follow-up data on recurrence of AF, suggest that CT or MRI image integration currently provide a significant benefit[13]. This is not surprising, as the merged product works with a static image, obtained before the procedure, with the patient having another position, blood pressure, left atrial filling etc.

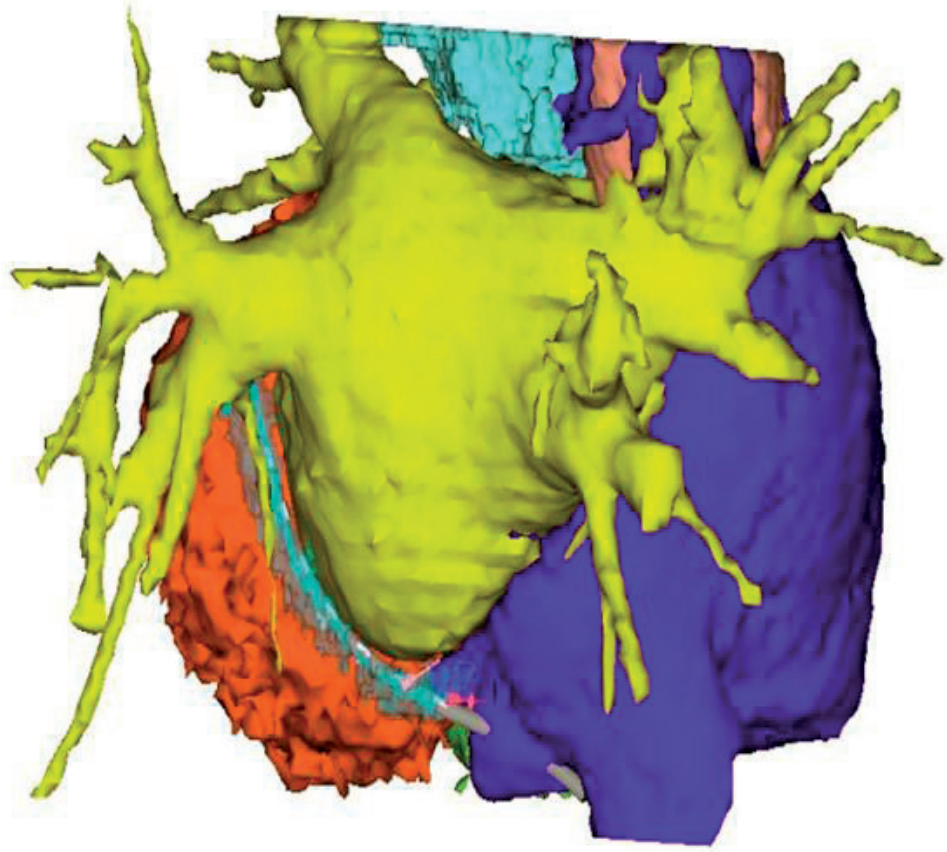

Figure 3. Segmented heart with the left atrium shown from the back. Observe the catheter in the coronary sinus.

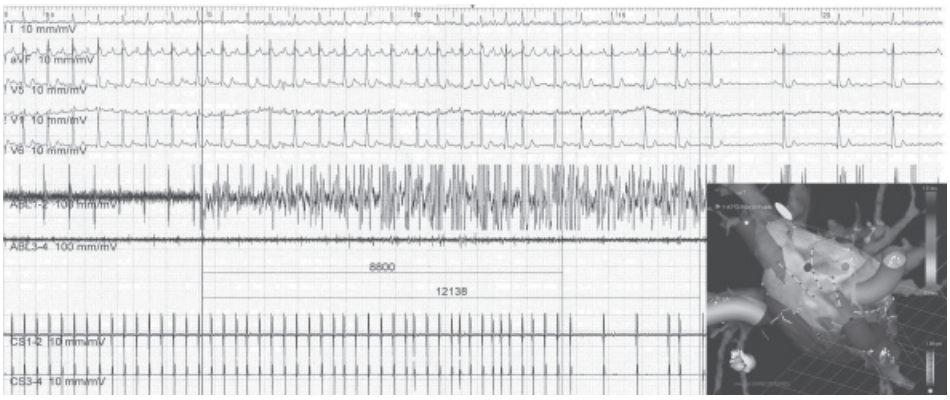

Figure 4. Ablation of a focal atrial tachycardia in the roof of the left atrium. The red area in the insert represents the earliest activation, where the ablation is carried out. Remark the crude representation of the pulmonary veins in the electroanatomical map (tubes, merged with the realistic CT image).

ICE with CT/MRI and EAM

A further step in increasing the accuracy of CT or MRI integration is using intracardiac echo (ICE) to reconstruct real time endocardial anatomy for image registration[14] . This technique has recently been reported on as being feasible and accurate for image integration. It is not yet known what the impact of this technique might be on procedural outcomes or clinical recurrence of AF, but it seems to increase the accuracy of image integration.

Intracardiac echocardiography

ICE has been used intensively to titrate radiofrequency during AF ablation, and to guide ablation lines. It is extremely helpful in our experience to guide transseptal puncture[15], and to avoid severe complication in the course of a procedure (figure 5). Furthermore, ICE can be used to judge the position of a catheter versus a pulmonary vein, the oesophagus, and of a balloon versus a vein. Venous occlusion can be assessed with colour Doppler.

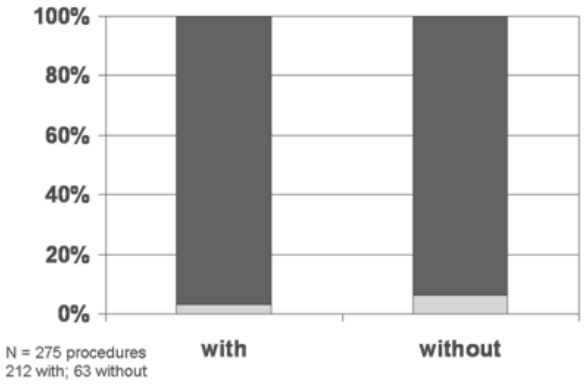

Figure 5. Pericardial effusion after transseptal puncture followed by cardiological or surgical intervention (in light blue colours) occurs more often when no intracardiac echo is used. Unpublished data 2003-2007.

Rotational angiography

Rotational angiography (RA) is a technique adopted from applications in neurovascular radiology and interventional cardiology, where it has been developed to reliably reconstruct 3-dimensional models of the vascular architecture. By injecting a large contrast bolus (approximately 60 to 90 ml) into the pulmonary trunk and rotating the X-ray camera 200 to 240 degrees from right to left anterior oblique at the time of contrast arrival in the left atrium, it is possible to recreate a 3D model of the left atrial body and the pulmonary veins. If simultaneously an amount of barium is swallowed, the location of the oesophagus can also be visualized[16]. If the 3D anatomical reconstruction is comparable to CT or MRI images, it can eliminate the need for these imaging modalities beforehand. This mode of visualizing left atrial anatomy has been proven

to be extremely accurate in comparison to preprocedural CT images[17], and will undoubtedly simplify patient preparation and reduce the cost of preprocedural investigations. Randomised data is needed however to asses the outcome benefit.

Electrical mapping tools

Advanced electrical mapping certainly has a future if complex signals (CFAE or CAFEs) will prove their point. Integration in other systems is likely.

Alternative ablation tools

Radiofrequency modifications

Several systems are now developed based on conventional or alternative radiofrequency delivery. Sometimes the tool for delivery was changed drastically (a balloon, a complex meshwork, an array) in order to deliver the heath to special sites or larger regions.

Other energy sources based on heat

Both the laser balloon and focused ultrasound (the HIFU-balloon) are based on thermal energy delivery. The initial investigation with the HIFU balloon was interrupted because of problems associated with the balloon approach (phrenic nerve paralysis and oesophageal problems)[18].

Cryoenergy

Pulmonary vein isolation with standard cryocatheters was disappointing, and not only in our hands[19]. This was especially disappointing, because cryoenergy (in contrast to radiofrequency) has the potential to preserve the continuity of the endocardium, therefore putting the patient at a lower risk for thrombo-embolism and perforation. However, with the cryoballoon a lot of the promises of cryoenergy seem to be fulfilled (figure 6)[20]. A single procedure is as effective as wide circumferential ablation, and the long term follow-up is promising, without deaths, oesophageal perforation or pulmonary vein stenosis[21,22,23].

Robotics

At this time, two different robotic systems are available: the Hansen system which uses a steerable sheath, which allows very precise manipulation. Perforations have been described,

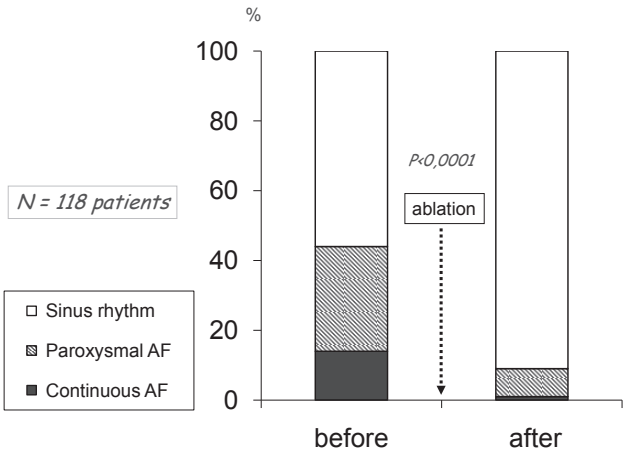

Figure 6. 24-hour Holter data in a series of 118 patients for whom paired Holter data were available before and after cryoballoon ablation. A remarkable reduction in the proportion of `continuous AF` is present.

but a learning curve certainly plays a role[24,25]. The introducer is quite thick, but the concept is very interesting. The Stereotaxis system works with two large permanent magnets, creating a magnetic field with a strength of 0.08 Tesla at the catheter tip which is also of magnetic material. This allows for the use of very soft catheters, and reduces the curl forces at the tip to 15 g, as compared to 45 g with conventional catheters. The potential advantages are outlined in Table II. Mapping of the atrium can be automated, with the computer dictating where the catheter should go. Most of our expectations for the system have been fulfilled, but for AF, we had to wait for a magnetic steerable irrigated tip catheter became available, as the conventional tip showed extensive charring in the left atrium[26]. Now that this is available, it is expected that we can proceed with this system easily to advanced mapping and ablation in the systemic atria of patients with a normal heart and in those with congenital heart disease[27].

Table II: Perspectives for magnetic navigation

▪ Precise remote catheter navigation
▪ Less traumatic
▪ Reproducible positioning
▪ Difficult anatomy
▪ Stability at the site of interest
▪ Less radiation exposure

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Summary

In chapter one, we assessed the feasibility, safety and short term outcome of pulmonary vein (PV) isolation in patients with paroxysmal atrial fibrillation (AF) with a cryoballoon. We showed that cryoballoon ablation is an effective method of pulmonary vein isolation in the majority of the patients, but that some need an additional segmental ablation during the same procedure to reach isolation. We have described the procedural characteristics, and the necessary learning curve to adopt this technique. The major complication of cryoballoon pulmonary vein isolation in our studies is phrenic nerve paralysis after ablation of the right superior pulmonary vein. This however, was in all cases a self limiting condition, persisting for several months, with limited discomfort. Using a comprehensive and intensive follow-up method combining daily transtelephonic rhytm monitoring, 24-hour Holter recording, and a standardised symptom questionnaire, we also showed that 60% of the patients experienced freedom of AF at the end of three months follow-up after a single procedure, and that the remaining patients had a significant drop in AF-burden.

In chapter two, we evaluated the accuracy of subjective and objective outcome measures in patients who underwent pulmonary vein isolation for the treatment of paroxysmal atrial fibrillation. A large proportion of episodes with atrial fibrillation occurred in the absence of complaints, confirming previous publications. If based on subjective outcome measures, the likelihood of over reporting the freedom of atrial fibrillation after pulmonary vein isolation is substantial.

In chapter three, we described procedural characteristics and freedom of AF after one year of follow-up in a large group of patients that underwent pulmonary vein isolation with a cryoballoon. We found that the major procedure related complications were pericardial effusion and right phrenic nerve paralysis. Serial CT-scans with repeated measurement of pulmonary vein diameter, proved that pulmonary vein stenosis does not occur as a long term complication when using the cryoballoon, in contrast to radiofrequency ablation in other series. During twelve months of follow-up, we found that around half of the patients were free of AF after one procedure, and after a second procedure in one fifth of cases added up to nearly two thirds. When adding freedom of AF under antiarrhythmic medication to this, the number of patients successfully treated amounted to nearly three quarters. Further analysis of the results showed that an AF recurrence during the first three months after the procedure was highly predictive of later recurrence of AF. Since the first three months after the procedure are considered as a blanking period for AF recurrence according to current guidelines, we analysed our data, adopting this blanking period, and found that the freedom of AF at 12 months substantially increased when omitting this data to 73% after one ablation. As we showed the predictive value of these early observations, the three month blanking period remains controversial in follow-up of pulmonary vein isolation with any technique. In the patient requiring a second procedure,

it was found that all of them had reconnection of three to four of the previously ablated veins, with a predominant reconnection of the left veins, compared to the right ones. The right inferior PV was the one most often permanently ablated in this group. This shows that anatomical and maybe physiological factors like blood flow have a major influence on the freezing characteristics inside the tissue and on recovery of partially ablated tissue.

In chapter four, we presented a case of a patient with a history of hypertrophic cardiomyopathy and an ECG pattern mimicking ventricular preexcitation typical for a mutation in the PRKAG2 gene, who underwent a cryoballoon pulmonary vein isolation for drug resistant paroxysmal AF. Because of induced of AF after isolation of the pulmonary veins, the ablation strategy was broadened to include ablation of complex fractionated electrograms, as potential drivers of AF in the atrium. This approach succeeded, showing that in this case, an atrial focus of high frequency electrical activity was sustaining the AF. Although the relation to the hereditary myocardial disease remains unclear, it is suggestive that in underlying disease conditions of the myocardial muscle, specific mechanisms could be responsible for initiating and/or perpetuating AF.

In chapter five, electroanatomical mapping of the atrial myocardium was performed before and after cryoballoon isolation of the pulmonary veins, in order to determine how far the lesion extended into the antral region of the pulmonary vein. It was shown that in patients with separate ostia of the pulmonary veins, the lesion extended into the antral region. In patients with a common ostium of the two left pulmonary veins, the ablation lesion was confined to the ostium. These were also the largest ostia, indicating that the size of the ostium was the major determinant of antral isolation. The electroanatomical mapping during sinus rhythm of the left atrium before and after pulmonary vein isolation also showed that in some cases, the ablation caused the earliest activation of the left atrium to shift downward on the septum. This indicates that some change in interatrial and intra-atrial conduction characteristics can occur due to the ablation.

In chapter six, we used transcranial Doppler, a non-invasive ultrasound monitoring method analysing the velocity spectrum of intracranial blood flow, during different endocardial ablation techniques for pulmonary vein isolation. This technique allows the detection of microemboli as specific signals in the velocity spectrum. For each ablation method, the total microembolic signal burden was calculated as an estimation of the total embolic load during the procedure. Compared to standard, non-irrigated, radiofrequency ablation, both irrigated radiofrequency and cryoballoon ablation had a significantly lower burden of microembolic signals, indicating that the potential for overt or subclinical neurological complications after performing either of the latter techniques is lower.

In chapter seven, adenosine infusion after pulmonary vein isolation, a technique shown to predict late recurrence of conduction to the ablated pulmonary vein sleeves and recurrence of AF, was adopted for cryoballoon ablation in order to determine its value in cryothermal energy ablation. Since the mechanism of damage caused to myocardial tissue is different from radiofrequency ablation, it was unclear whether adenosine infusion would show the same degree of reconnection and would be beneficial in preventing recurrence of AF. The study showed an incidence of reconnection that seemed lower than expected with radiofrequency ablation. When compared to a control group that was not tested with adenosine after ablation, the long term follow-up proved favorable for the treated study patients since a significantly higher percentage had freedom of AF. This technique will benefit a substantial number of patients otherwise requiring a second pulmonary vein isolation to achieve freedom of AF.

In chapter eight, the observation is described that exacerbation or de novo migraine complaints after pulmonary vein ablation using a large steerable transseptal sheat can occur in a substantial number of patients. Although the relation between transient headache complaints and a temporary atrial septal defect after the procedure remains elusive, this complication of large transseptal devices should be taken in consideration during the follow-up. This report also shows that in all cases, the symptoms are self-limiting within three months of the procedure.

In chapter nine and ten, we have described pulmonary complications of a cryoballoon pulmonary vein isolation, in experimental animals and in clinical patients. Pathologic examination of pulmonary tissue, after cryoballoon ablation in an animal model, showed hemorrhagic pulmonary infarctions, due to the selective occlusion of the pulmonary veins. Two patients developed temporary hemptysis after a cryoballoon pulmonary vein isolation.

In chapter eleven, twelve and thirteen, we have provided an overview of the technological advances in the ablation of atrial fibrillation and the treatment of atrial fibrillation during interventional procedures.

Currently, as the cryoballoon technology is widely adopted in clinical patient care, and is being more extensively researched, several shortcomings of the current technique remain to be clarified. A first future perspective for research could be to determine the minimal requirements for number and duration of freezing applications in the different pulmonary veins. The current freezing duration as advised by the manufacturer is largely empirically determined, and should be submitted to an extensive scientific evaluation. This could then be used to optimize the clinical freezing strategy, so that a maximum of success could be obtained with the least number of applications, minimizing procedure duration and complications. A second future perspective for research could be to develop a new generation cryoballoon that is more compliant in its shape, so that occlusion of the targeted vein would become easier. Currently, the balloon

occlusion of the veins remains subject to an operator learning curve, and variations in pulmonary vein ostium anatomy ranging from perfect circular to elliptic and even slit-like shapes. A more compliant balloon could therefore make occlusion and subsequent isolation easier. A third perspective for research is applying a very low threshold for detecting and reporting on complications, occurring during and after ablation with this device. Complications such as atria-esophageal fistula, which are rare after radiofrequency ablation, could be even rarer after cryoballoon ablation, but still, quantifying the incidence and predicting individual patient risk remain primordial for patient information and clinical follow-up. This of course, is an ongoing concern not only limited to this field of medicine. A fourth perspective for research could be to compare the results of cryoballoon pulmonary vein isolation to circumferential radiofrequency isolation in a randomized multicentre trial, so that the differences or equivalence in procedure characteristics, complications and patient outcome could be compared. It is needless to say, this should as well be performed for other new ablation devices, with the ultimate goal of selecting the best technology for the job, and treating patients with a maximum of success and a minimum of adverse events. The phrase 'Primum non nocere', which as a fundamental principle was developed during Hippocratic times, should still be an imperative thought in this matter.

Samenvatting

In hoofdstuk 1 hebben wij de haalbaarheid, veiligheid en korte termijnresultaten van pulmonaalvene isolatie met de cryoballon gerapporteerd bij patiënten met paroxismale atriale fibrillatie. Wij hebben aangetoond dat de cryoballon effectief is bij de meerderheid van de patiënten, maar dat sommigen additioneel een segmentale ablatie nodig hebben tijdens dezelfde procedure om isolatie van de pulmonaalvenen te verkrijgen. Wij hebben de karakteristieken van de ingreep beschreven en de noodzakelijke leercurve om deze techniek uit te voeren. De belangrijkste complicatie van deze techniek is rechter nervus phrenicus paralyse na ablatie van de rechter superior pulmonaalvene. Deze complicatie is een zelflimiterende aandoening in alle casussen die wij gevonden hebben, aanhoudend gedurende verscheidene maanden met weinig subjectieve klachten voor de patiënt. Gebruik makend van een volledige en intensieve methode voor follow-up waarbij wij dagelijks transtelefonische ECG registratie, 24-uurs Holter-registraties en een gestandaardiseerde vragenlijst voor symptomen hebben gebruikt, hebben wij aangetoond dat 60% van de patiënten volledig vrij zijn van atriale fibrillatie drie maanden na één procedure. De patiënten die hervallen, hebben minder en kortere episodes dan voorheen.

In hoofdstuk 2 hebben wij de accuraatheid van subjectieve versus objectieve parameters geëvalueerd in het klinische beloop van patiënten die een pulmonaalvene isolatie hebben ondergaan voor de behandeling van paroxismale atriale fibrillatie. Een groot deel van de episodes van atriale fibrillatie traden op in de afwezigheid van klachten wat eerdere publicaties bevestigt. Indien klinische evaluatie bij pulmonaalvene isolatie gebaseerd wordt op subjectieve eindpunten, zoals subjectieve klachten, bestaat het gevaar om de vrijheid van atriale fibrillatie na pulmonaalvene isolatie te overschatten.

In hoofdstuk 3 hebben wij de karakteristieken van deze ingreep en de vrijheid van atriale fibrillatie na 1 jaar opvolging beschreven in een grote groep patiënten die een pulmonaalvene isolatie hebben ondergaan met de cryoballon. Wij hebben gevonden dat de belangrijkste complicaties pericardeffusie en rechter nervus phrenicus paralyse zijn. Seriële CT-scans met herhaalde meting van de pulmonaalvene diameters hebben aangetoond dat pulmonaalvene stenose niet optreedt als laattijdige complicatie bij het gebruik van de cryoballon, in tegenstelling tot radiofrequentie ablatie. Na een opvolging van 12 maanden hebben we gevonden wij dat ongeveer de helft van de patiënten vrij is van atriale fibrillatie na één procedure, en dat het totale succes (na een tweede procedure bij één vijfde van de patiënten) ongeveer twee derden bedraagt. Wanneer wij de vrijheid van atriale fibrillatie onder antiarritmische medicatie hierbij toevoegen, loopt het aantal succesvol behandelde patiënten op tot ongeveer drie vierden. Verdere analyse van de resultaten heeft getoond aan dat een terugval in atriale fibrillatie gedurende de eerste 3 maanden na de procedure een hoge predictieve waarde heeft voor laattijdig recidief. Aangezien de eerste 3 maanden na een pulmonaalvene isolatie volgens de huidige consensus

documenten beschouwd wordt als een periode die niet noodzakelijk geanalyseerd dient te worden voor recidieven, hebben wij onze data ook geanalyseerd met in achtname van deze blindering. Wij hebben gevonden dat de vrijheid van atriale fibrillatie hierdoor op een termijn van 12 maanden in belangrijke mate toeneemt. Aangezien wij de voorspellende waarde van de vroegtijdige recidieven hebben aangetoond, blijft het 3 maanden "blinderen" controversieel in de opvolging van pulmonaalvene isolatie met eender welke techniek. In de patiënten die gezien zijn tijdens een tweede procedure, hebben we herstel van de geleiding vastgesteld in drie tot vier van de voorheen geisoleerde venen, met vaker geleidingsherstel in de linker venen vergeleken met de rechter. De rechter inferior pulmonaalvene is het vat dat het meest frequent permanent geïsoleerd blijft. Deze bevinding toont aan dat anatomische en misschien fysiologische factoren zoals bloeddoorstroming een belangrijke invloed uitoefenen op de vries-karakteristieken in het weefsel en op herstel van gedeeltelijk geableerd weefsel.

In hoofdstuk 4 hebben wij een casus gepresenteerd van een patiënt met een voorgeschiedenis van hypertrofe cardiomyopathie en een elektrocardiografisch patroon gelijkend op ventriculaire pre-excitatie, typisch voor een mutatie in het PRKAG2-gen. Hij onderging een pulmonaalvene isolatie voor paroxismaal atriale fibrillatie, onbehandelbaar met antiaritmische medicatie. Omdat na isolatie van de pulmonaalvenen het atriale fibrillatie nog steeds uitgelokt kon worden, werd de ablatiestrategie hieraan aangepast. Een ablatie van complexe gefractioneerde atriale electrogrammen werd uitgevoerd gezien deze mogelijk atriale fibrillatie kunnen onderhouden in de linker boezem. Deze aanpak bleek succesvol te zijn; aantonend dat in deze casus een atriale focus van hoogfrequente elektrische activiteit het atriale fibrillatie onderhield. Hoewel de relatie tussen de overerfbare myocardiale aandoening en het atriale fibrillatie onduidelijk blijft, suggereert deze casus dat erfelijke aandoeningen van het myocardiale spierweefsel specifieke mechanismen kunnen uitlokken voor het initiëren en/of onderhouden van atriale fibrillatie.

In hoofdstuk 5 hebben we electroanatomische reconstructies beschreven van de linker boezem, vóór en na pulmonaalvene isolatie met de cryoballon, om te zien tot hoever het uiteindelijke letsel zich uitbreidt in de antrale regio van de pulmonaalvene. Er werd aangetoond dat in patiënten met afzonderlijke ostia van de pulmonaalvenen, het letsel tot in de antrale regio reikt. In patiënten met een gemeenschappelijk ostium van de twee linker pulmonaalvenen blijft het ablatieletsel beperkt tot het ostium. Dit zijn tevens de grootste ostia, wat aantoont dat de grootte van het ostium, bepalend is voor al dan niet antrale isolatie. De elektroanatomische reconstructie tijdens sinusritme van de linker boezem, voor en na pulmonaalvene isolatie, toont ook dat in enkele gevallen de ablatie verantwoordelijk is voor het verschuiven van de linker boezem activatie van boven naar onder op het septum. Dit toont aan dat een verandering in de interatriale en intraatriale geleiding kan ontstaan door de ablatie.

In hoofdstuk 6 hebben we transcraniële doppler gebruikt, een niet-invasieve echografische monitoringmethode die het dopplerspectrum van de intracraniële bloedflow registreert, gedurende verschillende endocardiale ablatiemethoden voor pulmonaalvene isolatie. Deze techniek laat toe intracraniële micro-embolen als specifieke signalen in het dopplerspectrum te detecteren. Voor elke ablatiemethode werd het totale aantal micro-embolische signalen berekend als een schatting voor de totale hoeveelheid micro-embolen tijdens de procedure. Vergeleken met niet-geïrrigeerde radiofrequentie ablatie, veroorzaken zowel de cryoballon ablatie als de geïrrigeerde radiofrequentie ablatie een significant lagere hoeveelheid micro-embolische signalen. Dit toont aan dat het risico op een klinisch of subklinische neurologische complicatie in één van deze beide laatstgenoemde technieken, lager is.

In hoofdstuk 7 hebben we adenosine toediening na cryoballon pulmonaalvene isolatie geëvalueerd om zijn predictieve waarde voor herval in atriale fibrillatie bij deze techniek te onderzoeken. Het is een gegeven feit dat adenosine toediening het laattijdig hervatten van de geleiding naar de pulmonaal venen, met opnieuw optreden van atriale fibrillatie, kan voorspellen bij radiofrequentie pulmonaalvene isolatie. Aangezien het mechanisme van de schade door cryoablatie op het myocard verschilt van dat van radiofrequente ablatie, was het onduidelijk of adenosine toediening dezelfde voorspellende waarde zou hebben voor laattijdig optreden van atriale fibrillatie. De studie heeft getoond dat de incidentie van geleidingsherstel naar de pulmonaalvene lager leek dan wat geobserveerd werd met radiofrequentie ablatie. Wanneer er vergeleken werd met een controlegroep, bleek de studiegroep een significant betere vrijheid van atriale fibrillatie te vertonen tijdens de opvolging. Deze techniek is belangrijk in het voorkomen van een tweede ingreep na één pulmonaalvene isolatie, om vrijheid van atriale fibrillatie te bereiken.

In hoofdstuk 8 hebben wij de observatie beschreven dat het ontstaan of verergeren van migraine na een pulmonaalvene isolatie, met een lange stuurbare transseptale sheath, kan optreden in een belangrijk deel van de patiënten. Hoewel de relatie tussen voorbijgaande hoofdpijnklachten en een tijdelijk atrium septum defect onduidelijk blijft, dient toch aandacht te worden besteed aan deze complicatie en dient dit in acht te worden genomen tijdens de opvolging. Deze publicatie toont aan dat in alle gevallen de symptomen zelflimiterend zijn binnen drie maanden.

In hoofdstuk 9 en 10 hebben wij pulmonale complicaties beschreven na een cryoballon ablatie, zowel in proefdierexperimenten als in patiënten. Bij pathologische analyse van het longweefsel in een diermodel, vlak na een cryoballon ablatie, konden hemorrhagische longinfarcten teruggevonden worden, veroorzaakt door de selectieve occlusie van de pulmonaalvenen. Bij twee patiënten hebben we vastgesteld dat een tijdelijke hemoptysis is opgetreden na een cryoballon pulmonaalvene isolatie.

In hoofdstuk 11, 12 en 13 hebben we enkele overzichten gegeven van technologische ontwikkelingen in de ablatie van atriale fibrillatie en de behandeling van atriale fibrillatie tijdens invasieve procedures.

Terwijl de cryoballon technologie op veel plaatsen wordt toegepast voor de behandeling van patiënten, en verder uitgebreid onderzocht wordt, dienen verscheidene tekortkomingen van de huidige techniek nog verhelderd te worden. Een eerste perspectief voor toekomstig onderzoek is het bepalen van de minimale vereisten in het aantal en de duur van de vriesapplicaties. De huidige vriesduur, zoals geadviseerd door de producent, is grotendeels empirisch bepaald, en zou onderworpen moeten worden aan een grondige wetenschappelijke evaluatie. Deze bevindingen zouden gebruikt kunnen worden om de klinische vriesstrategie te optimaliseren, zodat maximaal succes bekomen wordt met het minste aantal applicaties. Dit zou zowel de duur als het aantal complicaties van de procedure kunnen verminderen. Een tweede perspectief voor onderzoek zou kunnen zijn een nieuwe generatie van cryoballon te ontwikkelen, die meer plooibaar is in vorm, zodat de occlusie van een pulmonaalvene gemakkelijker zou worden. Momenteel wordt het afsluiten van een pulmonaalvene bemoeilijkt door de leercurve van de operator, in combinatie met variaties in anatomische vorm van het ostium: dit gaat van perfect cirkelvormig, over elliptisch, tot spleetvormig. Een meer samendrukbare ballon zou daarom een occlusie en isolatie vergemakkelijken. Een derde perspectief voor onderzoek is laagdrempelig complicaties detecteren en rapporteren tijdens en na ablatie met dit apparaat. Complicaties zoals atrio-oesofagale fistels, die al zeldzaam zijn na radiofrequente ablatie, zouden zelfs nog minder kunnen optreden na cryoballon ablatie. Toch blijft het quantificeren van de incidentie en het voorspellen van het individuele risico van de patient primordiaal in het klinische beloop en voor informatieverstrekking aan de patient. Een vierde perspectief voor onderzoek zou kunnen zijn de resultaten van de pulmonaalvene isolatie met de cryoballon te vergelijken met circumferentiële radiofrequentie isolatie door middel van prospectief gerandomiseerd multicenter onderzoek. Dit zou toelaten procedure karakteristieken, complicaties en resultaten te vergelijken. Het is overbodig te vermelden dat dit ook geldt voor andere nieuwe ablatietechnieken, met als ultiem doel de beste technologie voor de ablatie te selecteren, en de patiënten met een maximuum aan succes te behandelen, doch met een minimum aan neveneffecten. De uitdrukking "Primum non nocere", die al als fundamenteel principe gold ten tijde van Hippocrates, zou nog steeds als dwingende gedachte hierin moeten gelden.

Curriculum vitae

Yves Van Belle was born on September 3 1972 in Sint-Amandsberg, Belgium. He obtained his medical degree from the University Gent in 1998, and started a cardiology training there. During his cardiology training, he worked as a research fellow for Clinical Cardiac Electrophysiology at the Academic Hospital Maastricht, the Netherlands, in 2003 and 2004. He became a cardiologist in 2005, after continued EP-training with Dr. Provenier at the Maria Middelares Hospital in Gent. Inspired and motivated by Prof. Dr. Luc Jordaens, he became a clinical fellow and PhD-student at the Electrophysiology department of the Thoraxcentre, Erasmus University in Rotterdam, that same year. He was appointed as a Erasmus MC staff member in 2006. He is married to Sandra Vandevoort and has two wonderful children Lise and Jules.

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