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# Long term outcome after cryoballoon ablation of atrial fibrillation in a single center: results from a prospective study in 1002 patients

Elodie Laurent

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Année 2016

**Long term outcome after cryoballoon ablation of  
atrial fibrillation in a single center:  
results from a prospective study in 1002 patients.**

THESE PRESENTEE  
POUR L'OBTENTION DU DOCTORAT EN MEDECINE  
DIPLOME D'ETAT

**Elodie LAURENT**

*[Données à caractère personnel]*

Thèse soutenue publiquement à la faculté de médecine de Grenoble \*

**Le 10 novembre 2016**

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*« Quand tu arrives en haut de la montagne, continue de grimper »*

Proverbe tibétain

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## Liste des abréviations

AAD	Antiarrhythmic drugs
AF	Atrial fibrillation
AHI	Apnea-hypopnea index
BMI	Body mass index
ECG	Electrocardiogram
LA	Left atrium
LIPV	Left inferior pulmonary vein
LSPV	Left superior pulmonary vein
LVEF	Left ventricular ejection fraction
PNP	Phrenic nerve palsy
PV	Pulmonary vein
PVI	Pulmonary vein isolation
RF	Radiofrequency
RIPV	Right inferior pulmonary vein
RSPV	Right superior pulmonary vein

## Résumé

**Introduction :** L'ablation de la fibrillation auriculaire (FA) est un traitement efficace et recommandé en cas de FA réfractaire au traitement anti-arythmique, en particulier dans ses formes paroxystiques ou persistantes de courte durée. Cette étude analyse les résultats à long terme sur le maintien d'un rythme sinusal après isolation des veines pulmonaires par cryoablation.

**Méthodes :** Les patients avec une FA paroxystique (n=746) ou persistante (n=256) et échec d'un traitement anti-arythmique ont bénéficié d'une ou plusieurs procédures de cryoablation. Nous étudions l'efficacité et la sécurité de cette technique sur le court et le long terme. Tout épisode d'arythmie symptomatique ou de durée >30 secondes est défini comme une récurrence, après exclusion d'une période aveugle de 3 mois.

**Résultats :** Sur une cohorte de 1002 patients, 783 (79.7%) sont indemnes de récurrence à 3 mois de la procédure. Les données du suivi à long terme ont été recueillies chez 894 (89.3%) patients. Après un suivi médian de  $2.9 \pm 1.3$  ans, 599 (61.0%) patients ayant bénéficié d'une première procédure ne présentent pas de nouvel épisode de FA (taux de succès 66% si FA paroxystique, 47% si FA persistante). Les taux cumulés de succès après 2 et 3 procédures sont respectivement de 76% et 78%. Trois facteurs prédictifs de récurrence sont identifiés : la FA persistante ( $p < 0.001$ ), une oreillette gauche dilatée ( $p = 0.01$ ) et l'absence d'activité physique régulière ( $p = 0.01$ ). Un total de 190 (16.2%) procédures présentent une complication, dont 2.8% de complications majeures et 14.5% de complications mineures. La paralysie phrénique est la complication la plus fréquente, persistant plus de 6 mois chez 5 patients.

**Conclusion :** L'isolation des veines pulmonaires en utilisant un cathéter de cryoablation conduit à un fort taux de succès et une faible survenue de complications majeures. Les patients présentant une oreillette gauche dilatée, une FA persistante ou un manque d'activité physique régulière ont un moins bon pronostic.

**Mots-clés :** Fibrillation Auriculaire – Cryoablation – Récidive – Sécurité – Procédures répétées

## **Abstract**

**Aims:** Catheter ablation of AF is an efficient and recommended treatment in drug-refractory AF, especially concerning paroxysmal or “short-standing” persistent AF. The purpose of this study was to investigate long-term outcomes of freedom from AF after pulmonary vein isolation using cryoballoon ablation.

**Methods:** Drug-resistant patients with documented symptomatic paroxysmal (n=746) or persistent (n=256) AF underwent one or several cryoballoon ablation procedures. We analyzed the immediate and long-term procedural and clinical outcomes. Recurrence was defined as a symptomatic or documented arrhythmia episode of >30 seconds excluding a 3-month blanking period.

**Results:** Among a cohort of 1002 patients, 783 (79.7%) were free from AF at 3 months. End follow-up data was available for 894 (89.3%) patients. Over a median period of  $2.9 \pm 1.3$  years, 599 (61.0%) patients had no recurrence of AF after a single procedure (success rate of 66% if paroxysmal AF, 47% if persistent AF). The cumulative success rates after 2 and 3 repeat procedures were 76% and 78.2% respectively. Three statistically significant predictors of recurrence were identified: persistent AF ( $p<0.001$ ), dilated left atrium ( $p=0.01$ ) and lack of regular physical activity ( $p=0.01$ ). Complications were observed in 190 (16.2%) procedures, including 2.8% major complications and 14.5% minor complications. Phrenic nerve palsy was the most frequent complication, persistent over 6 months after discharge in 5 patients.

**Conclusion:** The pulmonary vein isolation using a cryoballoon catheter was completed with a high rate of long-term success and a low rate of major complications. Patients with dilated left atrium, persistent AF or lack of regular physical activity had lower AF-free survival rates.

**Key words:** Atrial Fibrillation – Cryoablation – Recurrence – Safety – Repeat procedures

## INTRODUCTION

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia within the adult population. According to the European (1) guidelines, catheter ablation of paroxysmal AF is now a reasonable (class IIa, B) initial rhythm-control strategy before antiarrhythmic drugs (AAD) therapy.

Catheter ablation has become a therapy of choice for drug refractory symptomatic paroxysmal AF (class I, A) and persistent AF (class IIa, C). Radiofrequency ablation is the most common method, and cryoablation is the second most frequently used technology. A randomized trial (2) including 762 patients compared these two technologies. Cryoballoon ablation was non-inferior to radiofrequency ablation with no differences regarding the safety.

The clinical success rate of paroxysmal AF cryoablation at one year is about 70% (3) and one study reported 53% of patients in sinus rhythm at five years (4). Only few studies have reported long-term outcomes of cryoballoon ablation. The rates of freedom from persistent AF at one year range between 45 to 67% (3) (5). Data on repeat procedures is lacking.

In this study, we investigated the long-term efficacy and safety of cryoablation in single and repeated procedures including patients with either paroxysmal or persistent AF.

## **METHODS**

### **Aim of the study**

The aim of this study was to analyze the efficacy and safety of cryoballoon ablation using long-term follow-up data in a large population. Secondary end-points were defined as: (i) short-term efficacy and safety of the procedures, (ii) outcomes of repeat procedures, (iii) predictors of AF recurrence.

### **Patient population**

#### **Inclusion criteria**

In this prospective monocentric observational study, we considered every consecutive patient who underwent a cryoablation procedure for AF between November 2007 and May 2015 in the Grenoble Alpes University Hospital. All patients had a symptomatic paroxysmal or persistent AF, and had failed  $\geq 1$  AAD previously. Episodes of AF lasting  $>7$  days were defined as persistent. The arrhythmia was confirmed by an electrocardiogram on each patient.

Baseline demographic and clinical characteristics were recorded for all patients including: age, gender, hypertension, diabetes mellitus, hyperlipidemia, cardiomyopathy (coronary artery and valvular heart diseases), prior arterial embolism, chronic obstructive pulmonary disease, sleep apnea, body mass index (BMI) and athletic patients (defined as a patient with more than 2 hours (h) a week of physical activity for  $>2$  years). Data related to oral anticoagulation and AAD were also considered.

### **Exclusion criteria**

Patients with either thrombus in left atrium (LA), contraindication to anticoagulation, LA diameter >50mm, mild to severe valvular heart disease, uncontrolled thyroid dysfunction or pregnant women were excluded from the study. The study was in compliance with the principles outlined in the Declaration of Helsinki and approved by an independent national ethical committee.

### **Pre-procedural management**

A transthoracic echocardiogram was performed on each patient so as to exclude any severe valvular cardiomyopathy and to evaluate left ventricular ejection fraction (LVEF) and the size of the LA. All patients systematically underwent a computed tomography scan with three-dimensional reconstruction of the LA to assess the detailed LA anatomy and to exclude any thrombi in the left appendage. Informed consent was obtained for each patient prior to the procedure.

Prior to the procedure, an effective anticoagulation for more than 3 weeks (international normalized ratio between 2-3 for vitamin K antagonist, or lack of observance with the direct oral anticoagulant) was required. In the rare cases where anticoagulation was not judged effective enough, a transesophageal echocardiography was carried out before the beginning of the procedure. The oral anticoagulant therapy was discontinued 24 h before the procedure, without being followed by enoxaparin administration.

### **Ablation procedure**

Patients were under sedation (using propofol and nalbuphin). Before transseptal puncture, an hexapolar catheter was introduced via the femoral access and positioned within the coronary

sinus. The transseptal puncture was achieved with a Brockenbrough needle with SL1-sheath under fluoroscopic guidance, before switching to the FlexCath® catheter. Briefly after having achieved LA access, heparin boluses were given to maintain activated clotting times between 250 and 300 s.

From 2007 to 2015 the technical procedure has evolved considerably. When the first generation cryoballoon was used, we advanced a circular mapping catheter in each pulmonary vein (PV) ostium to obtain the baseline electrical information. After withdrawing the mapping catheter, a 23 or 28 mm cryoballoon (Arctic Front Advance®, Cryocath) was advanced into the LA, inflated, and positioned in the PV ostium of each vein. Optimal vessel occlusion was confirmed when selective contrast injection showed total contrast retention with no backflow to the LA. Once occlusion was documented, cryothermal energy was started. Cryoablation was applied during 5 minutes (min) at least twice in each vein aiming for a trough temperature of -40°C to -45°C to be reached within the 120 s of each application. After treatment of all PVs, we reintroduced the Lasso catheter into each vein to check their complete electrical disconnection. If PV potentials remained present, extra cryoballoon applications were performed until complete pulmonary vein isolation (PVI). An irrigated radiofrequency (RF) catheter could also be used to perform further segmental isolation. During the first procedures the 23 mm cryoballoon catheter was often used, believing that the size had to be adjusted to the PV anatomy.

With the second generation cryoballoons, potentials were directly recorded during the cryoablation, using the Achieve™ Mapping Catheter. Distal coronary sinus pacing was accomplished to confirm the presence of left PV potentials. An Arctic Front® 28 mm (and rarely a 23mm) cryoballoon catheter was inflated and positioned in the PV ostium of each vein. Different cryoballoon positions were evaluated by injecting contrast into the vein distal to the balloon to ensure the most optimal PV occlusion. Cryoablation was applied during 5

min once in each vein and several procedures later 240 s once in each vein. The procedure usually began with the left superior PV (LSPV), followed by the left inferior (LIPV), the right inferior (RIPV) and the right superior PV (RSPV), respectively. In the presence of a PV common ostium, the cryoballoon was advanced first across the superior branch and then across the inferior branch.

The procedural endpoint was the complete electrical isolation of the PV based on the elimination of all ostial PV potentials. In order to avoid phrenic nerve palsy (PNP), a catheter was placed in the superior vena cava to continuously pace the phrenic nerve during the cryoablation of the right PVs. The phrenic nerve capture was monitored by intermittent fluoroscopy and tactile feedback was obtained following the placement of the operator's hand on the patient's abdomen. When phrenic nerve capture ceased or decreased, we immediately discontinued the cryoapplication. No further cryoenergy was delivered if PNP occurred.

Major complications were defined as vascular access complications requiring a surgery or a transfusion, cardiac tamponade and death. Minor complications included phrenic nerve palsy, air embolism and minor vascular access complications.

### **Post-ablation management**

Patients remained under continuous monitoring of an electrocardiogram for at least 18 h. Oral anticoagulation was initiated in the evening of the procedure. A transthoracic echocardiography was fulfilled for any patient complaining of a thoracic chest pain to exclude pericardial effusion. Patients were discharged the day following the ablation if the clinical status was stable.

## **Follow-up**

An appointment for a 48 h holter monitoring and a follow-up visit in our ambulatory department at 3 months were systematically scheduled. The duration of the AAD was adapted on a case-by-case basis, usually stopped at 2 months if the patient remained symptomless. The 48 h holter monitoring was implemented insofar as possible without any AAD. Oral anticoagulation had to be continued until the appointment at 3 months. The need for further anticoagulation was then evaluated, based on the CHA<sub>2</sub>DS<sub>2</sub>VASc score. Procedural success at the first medical visit was defined as the absence of symptoms of AF and the documentation of stable sinus rhythm during the 48 h ambulatory electrocardiogram (ECG). A blanking period of 3 months was considered for the study: any recurrence of AF during this period was not taken into account. At the beginning of the year 2016, every patient was contacted by mail or phone. Success of the procedure at the end of the follow-up was defined by the absence of arrhythmia-related symptoms, the absence of recurrence of arrhythmia mentioned by the cardiologist and no arrhythmia detected on ambulatory ECG ( $\geq 30$  s duration) during the follow-up. Any episode of AF, atrial flutter, or atrial tachycardia lasting for at least 30 s was defined as recurrence.

## **Statistical analysis**

Results were expressed as median  $\pm$  median absolute deviation. The median values were chosen rather than the mean values so as to exclude outliers and to ensure a better reproducibility. Cumulative survival rates free from AF were estimated using the Kaplan-Meier non parametric method and survival curves were compared using the log-rank test. A p-value  $< 0.05$  was considered statistically significant. All analyses were accomplished using the Python programming language (Python Software Foundation, <https://www.python.org/>, along with the matplotlib, numpy, scipy, pandas and lifelines libraries).

## RESULTS

### Baseline patient characteristics

A total of 1002 patients (75.4% men, mean age  $60 \pm 7$  years) with a history of paroxysmal AF (731 patients, 73%) or persistent AF (27%) underwent one or several cryoablation procedures. Among the patients with persistent AF, most of them (n=247, 96.5%) had an AF persisting less than 6 months before the procedure, defined as “short-standing” persistent AF. *Table 1* shows the baseline characteristics of the study population.

Most patients (95%) had an AF diagnosed  $>6$  months before the procedure. Arterial hypertension was the most common comorbidity (324 patients, 32%). Median CHA<sub>2</sub>DS<sub>2</sub>-VASc score was  $1 \pm 1$ . Cardiomyopathy was known in 157 (15.6%) patients, most frequently caused by ischemia (63 patients, 6.3%). A minority (6%) of patients had a decreased LVEF ( $<50\%$ ). A four distinct PV pattern was present in 857 (86%) patients. Among the 914 (91.2%) patients taking AAD before the first procedure, 382 (38%) received amiodarone and 386 (38%) had class Ic AAD.

**Table 1:** Baseline and follow-up characteristics of the study population (% of total population)

<b>Total n=1002</b>	
<b><i>Clinical parameters</i></b>	
Male	756 (75,4)
Age, y	60 ± 7
Age > 65 years	287 (28,6)
Hypertension	324 (32,3)
Type 2 diabetes	60 (6,0)
Dyslipidaemia	189 (18,9)
Cardiopathy	157 (15,7)
Coronary artery disease	63 (6,3)
Dilated cardiomyopathy	23 (2,3)
Valvular cardiomyopathy (1)	20 (2,0)
Hypertrophic cardiomyopathy	15 (1,5)
Rhythmic cardiomyopathy	25 (2,5)
Other cardiomyopathy	11 (1,1)
Paroxysmal AF	746 (74,4)
Persistent AF	256 (25,6)
« Short-standing» AF (2)	247 (24,7)
Mean CHA2DS2.VASc score	1 ± 1
Chronic obstructive pulmonary disease	43 (4,3)
Sleep apnea	141 (14,1)
Body mass index ≥30	181 (18,1)
Athletic patients (3)	398 (39,7)
<b><i>Echocardiographic parameters</i></b>	
LVEF 50-35%	52 (5,2)
LVEF <35%	10 (1,0)
Dilated left atrium (4)	242 (37,2)
<b><i>Anatomic parameters</i></b>	
PV common ostium	139 (13,9)
<b><i>Medication used before the first procedure</i></b>	
Antiarrhythmic drugs	914 (91,2)
Vitamin k antagonist	362 (36,1)
Direct oral anticoagulant	634 (63,3)

(1) Excluding mild to severe valvular heart disease

(2) Defined as a persistent AF diagnosed <6 months before the procedure

(3) Defined as patients practicing more than 2 hours a week of regular physical activity during 2 consecutive years.

(4) Defined as a left atrium diameter >40 mm. Among the population (650 patients) from which we had a data on the size of the left atrium

## **Procedural characteristics**

The median times of the total procedure and the fluoroscopy were respectively  $100 \pm 20$  min and  $14 \pm 5$  min. The median dose area product delivered was  $1.78 \cdot 10^3$  Gy.cm<sup>2</sup>. The total procedure time was reduced to  $90 \pm 20$  min with the use of the second generation cryoballoon (vs.  $120 \pm 25$  min with the first generation cryoballoon). The median minimal temperatures achieved were:  $-51 \pm 5$  °C in the LSPV,  $-47 \pm 5$  °C in the LIPV,  $-51 \pm 6$  °C in the RSPV, and  $-49 \pm 7$  °C in the RIPV. In case of the occurrence of a common ostium, the veins were treated separately. PVI was performed using either a 28 mm cryoballoon (965 (82%) procedures), a 23 mm balloon (85 (7.2%) procedures) or both cryoballoons (126 (10.8%) procedures). From June 2012, the second generation cryoballoon was used for all procedures.

When the achieve was visible, the median times to PVI were  $39 \pm 11$  s in the LSPV,  $32 \pm 13$  s in the LIPV,  $27 \pm 12$  s in the RSPV and  $39 \pm 17$  s in the RIPV. An additional RF ablation was applied during 151 (12.8%) procedures. An electric cardioversion was required at the end of 211 (17.9%) procedures (193 AF and 18 atrial flutter). Cavotricuspid isthmus ablation was achieved during the same procedure in 139 (13.9%) patients while 122 (12.2%) patients had already benefited from it during a previous procedure (patients with typical cavotricuspid-dependent atrial flutter identified on the ECG).

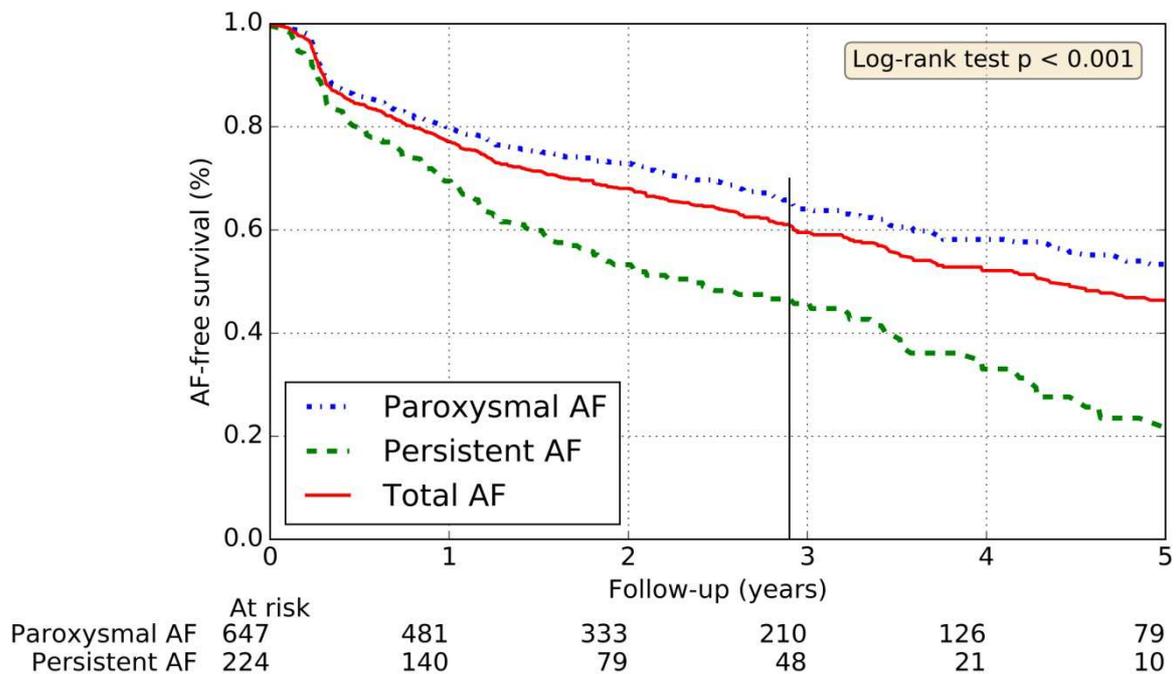
## **Three-month follow-up**

Clinical three-month follow-up was obtained in 783 of 982 (79.7%) patients (excluding the 20 patients who underwent a first RF procedure in another center). During the median follow-up time of  $106 \pm 15$  days (including the 3-month blanking period), 684 of 783 (87.4 %) patients were in stable sinus rhythm without symptomatic or documented episode of AF. AAD were discontinued in 542 (73.3%) patients.

## Long-term outcomes

Long-term follow-up data (median of  $2.9 \pm 1.3$  years, maximum follow-up 10.6 years) was available for 894 (89.3%) patients. After a single procedure, 599 (61%) patients remained free from AF with no need for repeat procedure. Rates of freedom from AF were significantly higher in paroxysmal AF (66%) than persistent AF (47%) ( $p < 0.001$ ) (Figure 1).

**Figure 1:** Rates of freedom from AF after a single cryoablation procedure.  
Thin vertical line: median follow-up time

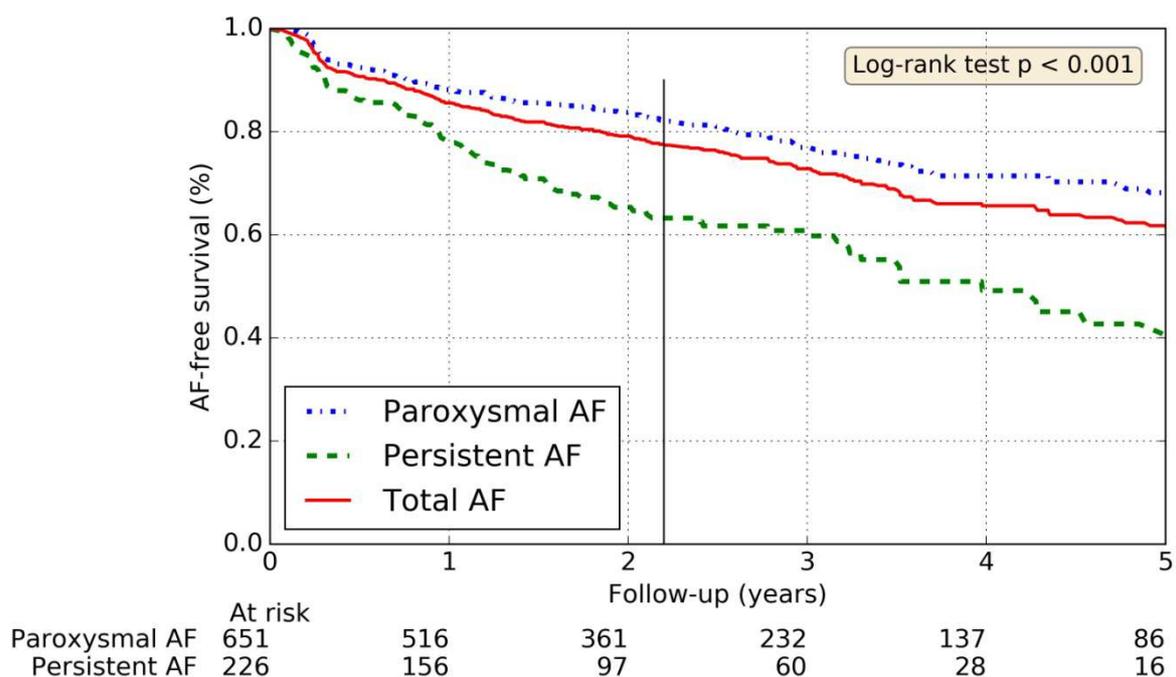


## Repeat procedures

The second and third procedures were performed after a median of  $333 \pm 174$  days and  $366 \pm 165$  days following the previous ablation, respectively. Over the 1002 patients, 792 (79%) had one AF ablation procedure, 177 (18%) had 2 procedures, 32 (3%) had 3 procedures and 1 patient had 4 procedures. PVI was achieved using only a RF catheter during 41

procedures. The first procedure was executed in another center using a RF catheter in 20 patients. These 61 procedures were excluded from the “procedural characteristics“ and “complications” study part. During 19 procedures, PVI was performed using both a cryoballoon and a RF ablation. When a macro-reentrant atrial tachycardia was detected, an additional anterior line, roofline, or posterior line could be deployed within the LA with the use of a mapping system (CARTO™). At the follow-up median time and after the blanking period, the cumulative success rates following 1, 2 and 3 repeat procedures were respectively 61%, 76% and 78.2%. After the last ablation attempt, 63% of patients were free from AF within the persistent AF population, versus 82% within the paroxysmal AF population (Figure 2).

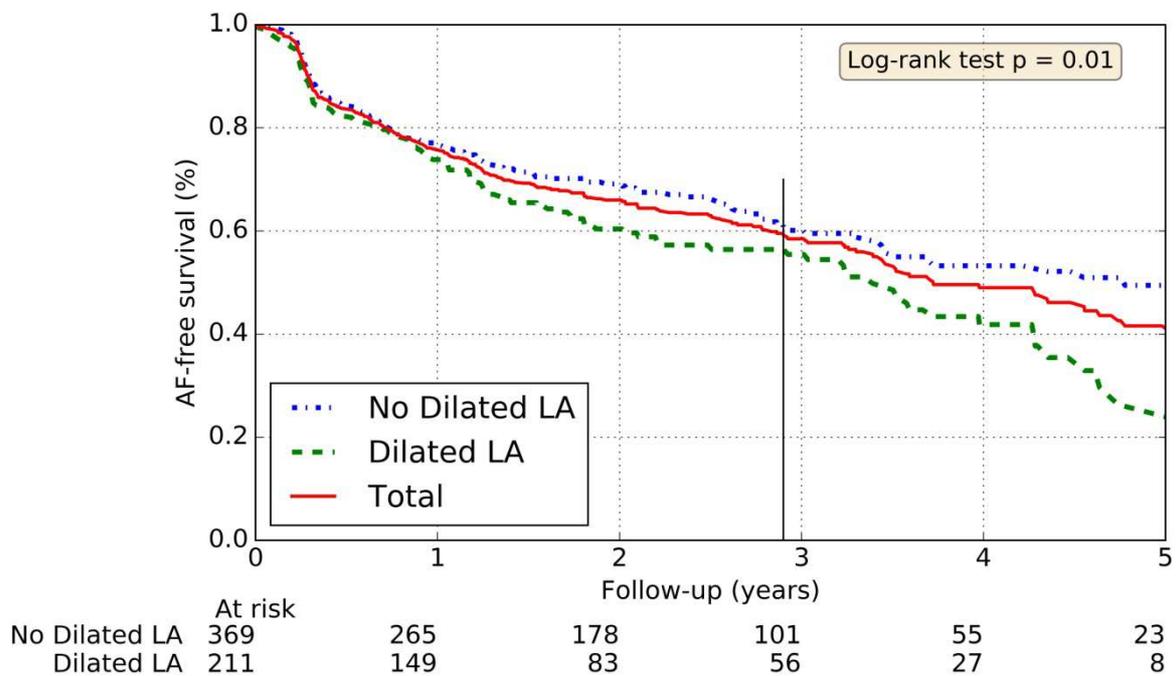
**Figure 2:** Rates of freedom from AF after last ablation attempt  
Thin vertical line: median follow-up time



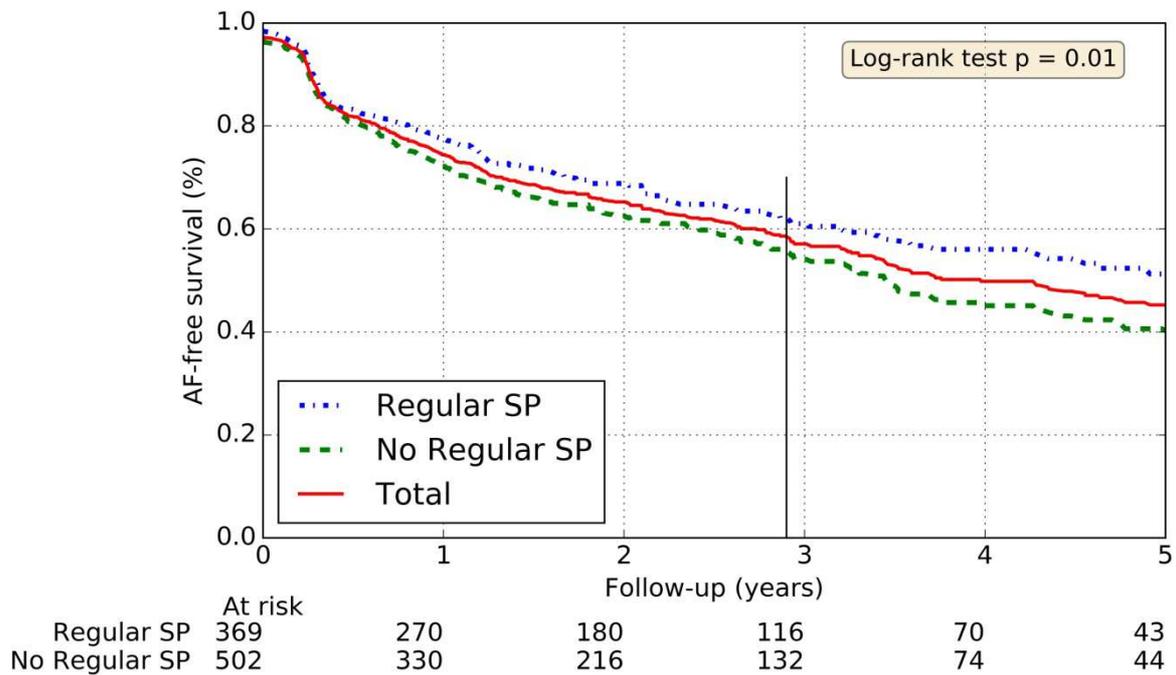
## Prediction of recurrence

The statistically significant predictors of AF free survival (after a single procedure) were the paroxysmal type of AF, the size of LA (dilated LA if LA diameter >40 mm) and the practice of regular physical activity (Figures 1 - 4). Obesity, age ≥65 year old and sleep apnea were not predictable of recurrent AF (p=0.33, p=0.28 and p=0.62 respectively).

**Figure 3:** Rates of freedom from AF depending on the left atrium size  
Thin vertical line: median follow-up time



**Figure 4:** Rates of freedom from AF depending on regular sport practice  
Thin vertical line: median follow-up time



## Complications

Complications were noted in 190 (16.2%) procedures, including 2.8% major complications and 14.5% minor complications. Some of the procedures had several complications. The most frequent complication observed was transient PNP which occurred in 97 (8.2%) patients. In 56.7% cases, PNP resolved completely before discharge. In 5 patients, this complication remained more than 6 months after discharge. The size (23 mm vs. 28 mm, 8.2% and 10.4% patients, respectively) and the use of a first or second generation cryoballoon (respectively 9% and 9%) were not predictors of PNP ( $p=0.6$  and  $p=1$ , respectively).

No atrioesophageal fistulae, stroke or procedure-related deaths were observed. Occurrences of complications are detailed in *Table 2*.

**Table 2:** Procedural related complications (excluding RF only procedures).

		1st procedure	2nd procedure	3rd procedure	All procedures
Major Complications	Cardiac tamponade	10 (1,0%)	3 (1,8%)	1 (3,7%)	14 (1,2%)
	Pericardial effusion medically treated	5 (0,5%)	1(0,6%)	0 (0,0%)	6 (0,5%)
	Vascular access complication at the right groin requiring surgery	8 (0,8%)	0 (0,0%)	0 (0,0%)	8 (0,7%)
	Hematoma requiring transfusion	1 (0,1%)	0 (0,0%)	0 (0,0%)	1 (0,1%)
	Procedure-related deaths	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)
	Other major complications (1)	4 (0,4%)	0 (0,0%)	0 (0,0%)	4(0,3%)
	<b>Total</b>	<b>28 (2,9%)</b>	<b>4 (2,4%)</b>	<b>1 (3,7%)</b>	<b>33 (2,8%)</b>
Minor Complications	Gaz embolism	5 (0,5%)	1 (0,6%)	0 (0,0%)	6 (0,5%)
	Vascular access complication at the right groin not requiring surgery	46 (4,7%)	3 (1,8%)	3 (11,1%)	52 (4,4%)
	Phrenic nerve palsy	90 (9,2%)	7 (4,2%)	0 (0,0%)	97 (8,2%)
	Other minor complications (2)	15 (1,5%)	1 (0,6%)	0 (0,0%)	16 (1,4%)
	<b>Total</b>	<b>156 (15,9%)</b>	<b>12 (7,2%)</b>	<b>3 (11,1%)</b>	<b>171 (14,5%)</b>
	Number of procedures with complication(s)	170 (17,3%)	16 (9,6%)	4 (14,8%)	190 (16,2%)

(1) Mediastinal effusion, infective endocarditis, massive haemoptysis, pleuropericarditis

(2) Haemoptysis, transient sinus bradycardia, pulmonary oedema, phlebitis, mycotic esophagitis

There were more complications during the first procedure (17.3%) than the second procedure (9.6%) ( $p=0.01$ ) especially concerning PNP (9.2% vs. 4.2% respectively,  $p=0.03$ ). No differences were noticed on the occurrence of complications between first-generation (19,7%) and second-generation (15.1%) cryoballoons ( $p=0.058$ ). However, the rate of minor complications was reduced with the second-generation cryoballoon ( $p=0.007$ ). Obesity was not a predictive factor for developing complications (17.2% vs. 16.0% if  $BMI < 30$ ,  $p=0.71$ ), including groin-site complications (4.75% vs. 3.87% respectively,  $p=0.61$ ). Five patients died during the follow-up (including one myocardial infarction).

## **DISCUSSION**

The main results of our study are : (i) after a single procedure, 61% had no AF recurrence at a median follow-up of 2.9 years (66% if paroxysmal AF and 47% if persistent AF, mainly including “short-standing” persistent AF); (ii) cumulative success rates after 1, 2 and 3 repeat procedures were respectively 61%, 76% and 78.2%; (iii) major complications were observed in 2.8% procedures; (iv) three statistically significant predictors of recurrence could be identified: persistent AF, dilated LA and lack of regular physical activity.

### **Long-term follow-up**

Rates of freedom from AF were highly similar to the rates achieved in previous studies (3) (4) (6). In Vogt et al study, the percentages of patients free from AF after 1, 2 and 3 repeat cryoablation procedures were respectively 74.9%, 76.2% and 76.9% (median follow-up 2.5 years). This study included a high majority of paroxysmal AF (96.7%) and repeat procedures were predominantly RF ablations. Catheter ablation for persistent atrial fibrillation is more challenging and is associated with less favorable outcomes. Some teams prefer the RF ablation catheter when treating persistent AF so as to perform additional lines on the LA. A recent study (7) found no reduction in the rate of recurrent atrial fibrillation when either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary-vein isolation. Extended ablation procedures require longer procedures, more ionizing radiation and potentially increase the risk of complications.

Only few data is reported concerning the long-term efficacy of catheter ablation of persistent AF. Multiple procedures or AAD are often required to maintain a stable sinus rhythm. Schreiber et al (8) reported on 5-year outcome data using RF for persistent AF (n=493) resulting in sinus rhythm maintenance in 20.1% after a single procedure and 55,9% after

multiple procedures. Our study is one of the first reporting the long-term efficacy of persistent AF using the cryoablation technique. We reported a median time to recurrence of 4.4 years (6 years for paroxysmal AF and 2.4 years for persistent AF). Between 2007 and 2015, we used different successive cryoballoon ablation catheters (first- and second- generation cryoballoons), following technological improvements. The second-generation cryoballoon catheter has shown improvement in long-term pulmonary-vein isolation, which may be attributed to the extensive wide-area circumferential ablation that is achieved.

### **Repeat procedures**

Regarding consecutive procedures, the improvement of the long-term success rate was lower for the last procedures. Very late recurrence of AF after years of sinus rhythm was not uncommon and may reflect disease progression. This might underline a point of no return, where AF may no longer be accessible for rhythm control by catheter ablation. Lack of success is likely due to underlying pathologies rather than the procedure itself. If so, the challenge would be to identify in advance this subgroup of patients who do not respond to PVI, and to propose them alternative treatments, rather than to attempt an incremental number of procedures. A certain amount of patients did not undergo repeat ablations because of AF regression (from persistent to paroxysmal) or symptom improvement.

### **Predictors of recurrence**

Many predictors of AF recurrence after cryoballoon ablation have been proposed. LA size and persistent AF were acknowledged factors (9). Early recurrence seemed to be a strong predictor of late recurrence of AF, questioning the existence of the blanking period (10). Other factors such as renal insufficiency, metabolic syndrome or in this present study lack of

regular physical activity have been suggested but needed to be confirmed by other studies (4). In our study, physical activity was defined as more than 2h a week of physical activity during two consecutive years. This population included all together young athletic patients and also older patients who used to be athletic. Another study with a less heterogeneous athletic population might need to be carried out before drawing any conclusions.

Procedural parameters were suggested to predict PV reconnection (11), (12): a time to PVI of >60 seconds, an interval thaw times at 0 °C of <10 seconds, vein occlusion score, and pulmonary vein size. Sleep apnea might be largely underestimated in our study, since the patients didn't get a systematic polysomnography. In Kawakami et al study, AF recurrence following PVI was three times higher in patients with  $AHI \geq 14$  (13). Treatment with continuous positive airway pressure has been shown to improve AF control in these patients.

In our study, the majority (84.3%) of the patients had no underlying cardiomyopathy. Structural heart disease can trigger a progressive process of structural remodeling in the LA and increase the incidence of AF recurrences. For now, these clinical factors should especially be taken into account to weigh up the patients' long term benefit from repeat procedures. The decision for catheter ablation should be based on the explanation of the potential benefits and risks, and the alternative such as AAD or acceptance of the current symptoms without rhythm-control strategy.

### **Complications/Safety findings**

Despite improvements in the procedural technique and increased effectiveness, safety remains a major concern when referring a patient for ablation. The safety of cryoablation in patients affected by AF has been well characterized in short-term follow-up studies (14), (15), (16). The acute complications observed were within the usual range for the procedure and did not

result in long-term limitations for the patients (5 out of 1002 patients had a PNP remaining more than 6 months). PNP was the most common complication. More refined phrenic nerve monitoring during right-sided pulmonary vein ablation might significantly reduce the occurrence of this complication. Ostial vein area and external RSPV-LA angle measurement showed excellent predictive value for PNP at the RSPV (17).

Repeat procedures were unexpectedly linked with fewer complications. This might be explained by the operator's experience and a reduce number of PV isolated during a repeat procedure. Most complications occurred during or immediately after the procedure. No atrioesophageal fistulae, stroke or procedure-related deaths were observed.

## **LIMITATIONS**

This was a single-centre prospective analysis with the inherent limitations of this study design. However, there was no selection bias since every consecutive patient undergoing cryoballoon ablation for AF was included. The results of this study could be limited by a potential variability of operators' experience. However, only five operators were involved in the procedures of this study. As mentioned in a previous study (18), cryoballoon seems to be less operator-dependent than RF. A blanking period of 3 months was considered for the study which can lead to an overestimation of a true success rate. Some patients were considered as a success even if they were still under AAD for another indication (beta blocker in arterial hypertension for example). Thus, results with AAD were difficult to interpret and may limit this study. Freedom from AF at the end of the follow-up was defined as the absence of symptoms of AF and the documentation of stable sinus rhythm during the 48h ambulatory ECG. Nevertheless, holter monitor was not available for all patients and these data was collected from the patient rather than the cardiologist himself.

## CONCLUSION

Thèse soutenue par Elodie LAURENT

### **Long-term outcome after cryoballoon ablation of atrial fibrillation in a single center: results from a prospective study in 1002 patients**

This prospective study included 1002 patients who underwent cryoballoon ablation for either paroxysmal AF or recent-onset persistent AF. At a median follow-up of  $2.9 \pm 1.3$  years, 599 (61.0%) patients had no recurrence of AF after a single procedure. The cumulative success rates after 2 and 3 repeat procedures were respectively 76% and 78.2%. Persistent AF was associated with a lower success rate. The rate of complications was relatively low and included a 8.2% incidence of PNP. Although most PNP reverted before discharge, this percentage remained quite high and immediate recognition was of utmost importance to avoid irreversibility.

Within the persistent AF population, 47% of patients were free from arrhythmia after a single procedure (66% in the paroxysmal AF population). These rates increased after repeat procedures (63% if persistent AF, 82% if paroxysmal AF).

Then, the patient must be well informed of the benefits and risks of the cryoballoon ablation technique and the possible necessity to undergo several procedures. Further, dilated LA, persistent AF and regular physical activity were identified as statistically significant predictors of recurrence. The latter should be looked for individually, and carefully taken into account before suggesting an ablation procedure.

VU ET PERMIS D'IMPRIMER  
Grenoble, le 10/10/2016

Le doyen  
J.P. ROMANET

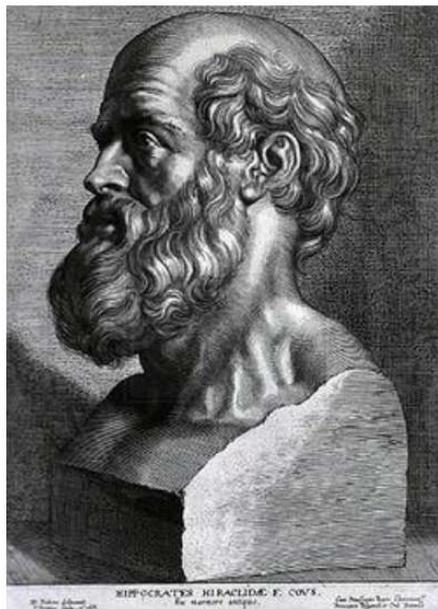
Le président de la thèse  
Professeur VANZETTO

Pour la Présidente  
et par délégation  
Le Doyen de Médecine  
Pr. Jean-Paul ROMANET

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## **SERMENT D'HIPPOCRATE**

*En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,*

*Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.*

*Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.*

*Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.*

*Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.*

*Je garderai le respect absolu de la vie humaine.*

*Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.*

*Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.*

*Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.*

*Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.*