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On the way to cure Atrial Fibrillation.

Radiofrequency ablation vs Cryoablation: *Iatrogenic Atrial Septal Defect after ablation procedures.*

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"If you don't go further than your front yard fence,

you will discover nothing"

Wright brothers

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ABSTRACT

Background. In recent years, Pulmonary Vein Isolation (PVI) has progressively increased its role in the treatment of drug resistant Atrial Fibrillation (AF). Traditionally these procedures are performed with a "point by point" ablation technique by means of radiofrequency (RF) energy; however, in the last years, the use of novel alternative technologies such as cryothermal balloon (CB) ablation is growing rapidly. Irrespective of the technique used, the first step in every PVI ablation is the access to the left atrium (LA) through a transseptal puncture (TS). In the RF ablation procedure, LA access is commonly achieved with a double TS puncture to insert both an ablation and a circular mapping catheter. In the CB ablation procedure, only a single TS puncture is usually required.

Objective. Our aim was to compare the incidence of iatrogenic atrial septal defect (iASD) between double transseptal conventional RF and CB ablation at 1-year follow-up evaluating its clinical significance.

Methods. We analysed and compared the presence of iASD and its clinical repercussion in a retrospective study of 127 patients, affected by drug resistant paroxysmal or early persistent AF, who underwent PVI by the means of either RF or CB ablation, between January 2008 and December 2012 in UZ Brussels hospital. Transoesophageal echocardiography was performed before each procedure. This study has been followed up for 1 year.

Results. The incidence of iASD at 1-year follow up following PVI was significantly higher in the CB group (22.2% vs 8.5%; p=0.03). Mean iASD diameter was larger in the CB group (0.60x0.50cm vs 0.44x0.35cm) without statistical significance. Only left to right atrial shunt was observed. No adverse events were recorded in these patients during the follow up.

Conclusion. The incidence of iASD at 1-year follow up following CB ablation procedure for PVI is significantly higher with respect to RF procedures. Although no adverse clinical events were recorded in patients with persistence of iASD, this complication should not be underestimated and systematic echocardiographic examinations might be advised in all individuals exhibiting this finding.

Keywords: atrial fibrillation, iatrogenic septal defect, cryoballoon, radiofrequency.

ABBREVIATIONS

AAD Antiarrhythmic drugs

AF Atrial Fibrillation

ASI: Agitated saline injection

AV: atrioventricular

CI: confidence interval

CTGF: connective tissue growth factor

DCC: direct current cardioversion

HF: Heart failure

IASD: iatrogenic septal defect

LV: left ventricular

PAF Paroxysmal atrial fibrillation

PV pulmonary veins

PVI pulmonary veins isolation

QQL quality of life

SR: sinus rhithm

SVC: Superior vena cava

TEE: transesophageal examination

TSP: transseptal puncture

TTE: transthoracic examination

PART 1: INTRODUCTION

1.Background

Atrial fibrillation (AF) is the most common arrhythmia occurring in 1-2% of general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to increase at least double in the next five decades as the population age[(1,2)].

AF has frequent and severe consequences in affected patients. It is strongly associated with increased morbidity and mortality[(1)]. Its prevention and treatment is one of the main goals of a cardiologist. Thus, the restoration and maintenance of normal sinus rhythm correlate with improved quality of life in these patients[(3)]. The arrhythmia is usually easy to diagnose electrocardiographically yet the "ideal" approach to the management of AF is still questionable. Traditionally, the first-line treatment of AF has always been pharmacological. Its desirable goal consists in restoring and maintaining sinus rhythm in order to relieve the patient from symptoms and reduce the risk of thromboembolic events. However, its effectiveness remains inconsistent. The likelihood of AF recurrence within 6 to 12 months approaches 50% with most drugs[(3)]. These facts together with the finding of ectopic beats originating from the pulmonary veins as one of the main sources of AF, have led to the development of new invasive techniques to cure AF such as percutaneous catheter ablation[(1,3–5)].

From all the techniques developed so far, radiofrequency ablation is the gold standard[(6)]. However, although it is an effective technique in maintaining sinus rhythm, this technique is associated with long procedural times and is often cumbersome[(2)]. Besides, lesions created by hyperthermia, inevitably involve some degrees of tissue disruption that increases the risk for perforation and thromboembolic stroke[7,8]. Therefore, as an alternative ablation treatment, cryoballoon ablation has emerged. Cryothermic lesion offers minimal tissue disruption and preserves basic underlying tissue architecture. In addition, it is associated with a similar success rates if compared to RF, and might be less time consuming[9] .

During the procedure, either cryoballoon ablation or RF, transseptal puncture (TSP) is the first step to achieve transatrial access[10]. Although it is extremely safe in the majority of cases, TSP might be associated with minor and major complications[11]. Among them, it is the potential permanency of iatrogenic septal defect (IASD)[10,12–14] . The aim of this study is to compare the incidence and clinical outcomes of iASD in AF ablation using either RF or Cryoballoon at one-year follow-up.

1.2 Definition of Atrial Fibrillation

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function, which leads to an increased long-term risk of stroke, heart failure (HF), thromboembolism, and all cause excess mortality[1,15]. Furthermore, the quality of life of these patients is impaired[3].

1.3 Epidemiology

AF represents the most common tachyarrhythmia that occurs in humans, with an incidence which almost doubles every decade after 55 years of age[1]. This results in a high prevalence of AF in individuals >70 years of age. Approximately 70% are between 65 and 85 years old[1,16]. As the population ages, AF represents an important public health problem.

1.4 Classification of AF

Several classifications have been proposed for AF even though none fully accounts for all aspects of this arrhythmia. One of the classification scheme recommended consists of distinguishing a first-detected episode of AF, either if it is or is not symptomatic or self-limited. It is recognized that there may be uncertainty about the duration of the episode and about undetected episodes. Every patient who presents with AF for the first time is considered a patient with *first diagnosed AF* (irrespective the duration or the presence and severity of the arrhythmia). If the patient has two or more episodes, AF is considered recurrent. If it terminates in a spontaneous way (usually it is self-terminating within 48 hours), it is called *paroxysmal atrial fibrillation* (PAF). Although AF paroxysms might continue for up to 7 days, the 48h timepoint is clinically important. When an AF episode is sustained longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion (DCC), it is called *persistent AF*. The category of persistent AF also includes cases of long-standing AF, usually referring to cases where the AF has lasted for more than one year[(1)].

The importance of this classification lies largely in the success rate after ablation. PAF's ablation yields a higher success rate if compared to the persistent, long-standing AF. This fact seems to be due to the reflection of an earlier stage in the PAF arrhythmia[(3,17)].

1.5 Pathophysiological mechanisms

There are different mechanisms involved as a cause of AF. For instance, an increased sympathetic or parsympathetic tone, or the replacement of atrial myocytes by interstitial fibrosis, which can be caused by genetic defects, inflammation, as well as structural changes associated with aging or atrial dilatation in any type of heart disease (valvular disease, hypertension, HF, coronary atherosclerosis)[1].

However, the onset and maintenance of AF is associated with focal mechanisms involving automaticity and multiple reentrant wavelets[18].

The demonstration of automatic focus for AF has been an important discovery, so the ablation of this source can extinguish AF, mainly PAF. The most frequent source of triggering AF have been found in pulmonary veins (PV)[18]. But, there are also other foci found in the superior vena cava (SVC), ligament of Marshall, left posterior free wall, crista terminalis, or coronary sinus[1,19].

As mentioned above, the most important structures that play a critical role in triggering AF in most of cases are PVs. From an embryological standpoint, this ectopic activity could be explained by the presence of pacemaker cells in PVs. It is found that the PVs have the same origin as the other cardiac conduction tissues and serve as foci of automaticity[20]. There are also studies that show the presence of transitional and Purkinje cells which are known to have intrinsic electrical activity[18,21]. Another hypothesis consists in the existence of slow conduction areas in the proximal part of the pulmonary veins in comparison to the adjacent left atrium. This fact suggest that on top of the ectopic activity, these electrophysiological properties of the pulmonary vein sleeves, could facilitate rapid re-entry and maintenance of AF[22].

Even though there are many factors involved in the onset and maintenance of AF, the degree to which changes in atrial architecture contribute to the initiation and maintenance of AF is not known. What it is currently known is that the duration of episodes is correlated with a decrease in atrial refractoriness, and all the factors mentioned above can influence to that abnormal atrial refractoriness[1].

1.6 Management of AF

Management of patients with AF consists in 3 different strategies[22]:

- ❖ Ventricular rate control.
- ❖ Assessment of the need for anticoagulation in order to prevent thromboembolism's events.
- ❖ Correction of the rhythm disturbance.

Depending on the patient's characteristics, the management strategy is discussed: type and duration of AF, severity and type of symptoms, associated cardiovascular disease, patient's age, medical conditions, short and long-term medical objectives, and pharmacological and nonpharmacological therapeutics options.

As mentioned previously, antiarrhythmic drugs are used as first-line treatment with the objective of maintaining sinus rhythm, thus avoiding long-term anticoagulation, thromboembolic risk is reduced and survival is improved. Although AAD might influence in the heart's electrical activity avoiding the onset and perpetuation of the AF, it is described that its long term effectiveness is shown only in a minority of cases[15]. Arrhythmias seem to recur within one to two years in at least 50% of patients despite AAD therapy. Furthermore, antiarrhtythmic drugs are also associated with cumulative adverse events over time[3,4].

These deceiving results and the demonstration of ectopic beats originating from the pulmonary veins have catalyzed the development of these invasive techniques. These nonpharmacological approaches developed such as percutaneous catheter ablation therapies pursue the challenge of curing AF[21,23–26].

1.6.1 Ablation therapies

Even though, it is not yet considered as first-line treatment, AF ablation has increasingly been used over the last decade. This is due to the demonstration of its superiority compared to conventional AAD therapy in terms of arrhythmia recurrence, quality of life, and arrhythmia progression[5,15,17]. Furthermore, according to a recent metanalysis, ablation is safer in terms of complications if compared to AAD[27].

1.6.1.1 Main technologies for pulmonary vein isolation

Due to the increasing number of PVI procedures performed daily in electrophysiological laboratories worldwide, many attempts of ablative techniques are being developed in order to take AF safer and more effective[24,26,28].

Radiofrequency versus cryoablation. Strenghts and limitations.

Currently, radiofrequency is the gold-standard for the catheter-based approach to AF ablation[7,8,29]. However, lesions created by hyperthermia (which is the energy RF works with), inevitably involve some degree of tissue disruption that increases the risk of perforation and thromboemolic stroke[30]. In addition, this cumbersome procedure uses a point-by-point technique, which makes difficult to create continuous lines, therefore potencially leaving conduction gaps. These gaps may facilitate recurrence of the arrhythmia. As an alternative treatment, cryoablation has appeared, which works by freezing the tissue. The resultant lesions preserve tissue's architecture, maintain good tensile strength and are minimally thromboembogenic. The latter consists in a functional destruction preserving the structure[8,30]. It is reported that cryoballon, delivering cryothermal energy is able to achieve PVI in virtually all veins, with similar success rate if compared to RF. Furthermore, it might be less time consuming[31].

With any ablative technology, the acute endpoint of electrical isolation can be achieved in almost 100% of veins at the end of all procedures. Nevertheless, a mean 25-30% of individuals develop clinical recurrence on the medium-long term follow-up after the first procedure[31,32]. The most likely explanation of it is electrical reconnection of the pulmonary veins[33]. Another possible cause of recurrence are the extrapulmonary vein foci[1,19,34]. These foci, potencially located anywhere in the atria can trigger AF in a minority of patients. However, localizing these triggers is difficult and often time consuming. Therefore, due to the abovementioned considerations, ablation of PAF mainly consists in PVI. There are also other factors, which might explain the variety of outcomes[35,36]. First, the success of AF procedure is highly dependent on the operator's skills and the experience. Second, up to date there is still no consensus on how to perform AF ablation[37]. Third, the classification of AF might in some cases differ with the electropathological stage of the disease. This fact could lead to classify as PAF patients who are affected by a more advanced stage of the disease. It is known that persistent and long standing persistent AF tend to reccur more often after AF ablation[38]. Another important factor that can lead to this discrepancy is the non-standardized follow-up after PVI. In fact, many centers, but not all, apply what is known as "blanking period". This is a period of time (normally around 2-3 months) when antiarrhythmic recurrence is not considered clinically relevant[(39,40)]. Furthermore, there is no consensus on post-ablation antiarrythmic medication protocol. Some centers continue medication up to 6 months after the procedure and some prescribe medications only in case of clinical recurrence. All these factors can have an impact on success rates. Additionally, the time to repeat procedure in case of recurrence is also a matter of debate[(41)].

Procedure and complications

Irrespective of the technique used, transseptal puncture (TSP), is the first step of every AF ablation procedure (apart from channelling the chosen vein (normally femoral vein) to reach the heart)[(10)]. In the RF ablation procedure, left atrial access is commonly achieved with a double TSP to insert both an ablation and a circular mapping catheter. In the CB ablation procedure, only a single TSP is required. Although extremely safe in the majority of cases in experienced hands, TSP might be associated with minor and major complications[(42)]. Among them, there is the iatrogenic septal defect (IASD), which is a small communication between both atria as a result of the puncture[(10,12–14)]. Although the clinical significance of persistent IASD has not yet been well-defined, IASD with interatrial shunting might be associated to paroxysmal embolism and stroke[(14,43).] It is also known that Patent Foramen Ovale and Atrial Septal Defects have been related apart from paradoxical embolism and cryptogenetic stroke, to left ventricular disfunction, pulmonary hypertension, migraine, decompression sickness and platipnea-orthodesoxia syndrome[44–46].

Finally, although the following listed complications have not been analysed in the current study, it should be noted that could also occur. For instance, pericardial effusion and tamponade, cerebral ischemic complications, PV stenosis, atrium-esophageal fistule, phrenic nerve injury and left atrial tachycardia[11]. It should be highlighted that all these complications have been already studied in previous studies. According to a recent survey conducted on more than 9000 patients who underwent AF ablation, complications occurred in roughly 4% of cases and not all centres were highly experienced[5]. As it is known, PVI is much safer and associated to lower rates of complications if performed by experienced operators.

2. Justification

As already mentioned, this study aims at comparing the incidence of iASD as well as its clinical significance between RF and cryoenergy catheter ablation in patients presenting with AF at 1-year follow up. PVI by catheter ablation is a highly effective therapy for the treatment of this arrhythmia, especially in those who are refractory to antiarrhythmic drug therapy[47,48]. Traditionally, these procedures are performed with a "point by point" ablation technique by means of RF energy[47]. However, in the last years the use of novel technologies such as CB ablation has grown rapidly on the grounds of improving the effectiveness in producing PVI[31].

During the procedure, either cryoballoon ablation or RF, transseptal pucture is the first step in order to reach left atrium. This transseptal puncture might hypothetically lead to permanency of IASD[10,12–14,43,49].

The literature on this topic is sparse, but iASD is a common complication after PVI. The most worrying clinical consequence is paradoxical embolism, secondary to right-to-left shunting. Although, the most typical shunting direction found in these patients is left-to-right shunting, this complication should not be underestimated. To our knowledge, there are no studies so far comparing the incidence of iASD by using either cryoablation or RF ablation.

Our final challenge is to be able to make up with the safest possible and curative technique to treat our patients.

PART 2: STUDY

2.1 Hypothesis

IASD has been reported as a complication of transseptal puncture, which is the first step of every AF ablation procedure to access left atrial. Several suggestions related to iASD have been made:

- It is believed that larger-diameter sheath might result in a higher rate of iASD, and the diameter of cryoballoon is 15F vs 8.5F in RF ablation. So, it should be found differences in the incidence of iASD depending on the technique used, being more incident in the Cryoballoon ablation group.
- It is suggested that in most of the iASD, the shunting found is left to right, and the paradoxical embolism, which is the most important concern related to iASD happens when it takes place right-to-left shunting. This means that no adverse clinical events should be found.

2.2 Objective

Mean objectives

This study aims to compare the incidence and clinical significance of iatrogenic Atrial Septal Defect at 1-year follow-up in 127 patients who underwent transseptal catheterization with either cryoballoon ablation or radiofrequency catheter ablation.

Secondary objective

- To investigate if there are any risk factors associated to the persistence of IASD.

2.3 Material and methods

2.3.1 Study design

It is a retrospective cohort study in which we observe and compare the incidence and clinical significance of persisent iASD in patients who underwent RF ablation or cryoablation for PVI.

2.3.2 Participants

The study population was made up of individuals affected by drug resistant paroxysmal or early persistent AF from the Heart Rhythm Management Center, Free University of Brussels, who have undergone PV isolation by means of CB ablation or RF ablation and a transesophageal echocardiography (TEE) examination during post ablation follow-up between January 2008 and December 2012. 127 patients from the database at the hospital who accomplished these characteristics were consecutively included in our retrospective analysis.

2.3.3 Inclusion and exclusion criteria

Exclusion criteria to the ablation procedure consisted of inability to undergo TEE, the presence of an LA thrombus at the preprocedural TEE, severe uncontrolled hcceart failure, contraindications to general anesthesia, or severe comorbility. Patients with a patent foramen ovale (PFO) prior to the index procedure were excluded from our analysis.

Inclusion criteria included patients affected by drug resistant paroxysmal or early persistent AF prior to the ablation procedure who underwent PVI by means of RF or CB ablation and a TEE examination during post ablation follow-up.

2.3.4 Sample size

A non-probabilistic consecutive sampling method has been used. All 127 patients who underwent PVI and a TEE examination during postablation follow up were the target population.

Even though the calculation of the sample size depends on the margin of error (0.05), on condifence interval (CI) (95%) and on the estimate rate of the study outcome, the latter is difficult to calculate in our case because there are a few studies about ASD in AF ablation. A previous study by Sieira et al at reported a 20% incidence of IASD at 1 year after cryoballoon ablation[(10)]. However, there is a great variability in the RF studies. Anselmino et al reported 5.6% at 1 year with one transseptal puncture[(43)], Rilling et al 3.7% at 1 year with double transeptal puncture[(12)], Hammerstingl 18% at 9 months with single TS puncture and 0% with double TSP[(13)].

If we assume a rate of 10% incidence in the total population of CB and RF patients with a margin of error of 5% and CI of 95%, we calculate that we need a sample of 138 patients. In our study, the sample is a bit lower (127 patients), however the margin of error is acceptable (5.2%). Therefore, increasing the population might hypothetally increase the precision but might not change substantially the incidence of IASD.

From these 127 patients, 82 patients belong to RF group and 45 patients to CB. So, assuming a IASD incidence of 5% in RF procedures and 25% in cases of CB according to literature, the power of the study is 83%.

2.3.5 Variables and measurements

Independent variable

Type of Intervention- catheter diameter

- Radiofrequency ablation (French)
- Cryoballoon ablation (French)

Dependent variable

- Presence of iASD evaluated by using transesophageal echocardiography.
- Clinical significance of IASD.

Associated variables

Sociodemographic variables

- Sex (Male/Female)
- Date of birth (years)

Clinical variables

- Paroxysmal AF
- Duration of symptoms
- Arterial hypertension (yes/no)
- Dyslipidemia (yes/no)
- Diabetes Mellitus (yes/no)
- Body mass index ($kg/m^{2)}$
- Structural heart disease (yes/no)
    - Coronary artery disease
    - Valvular cardiomyopathy
    - Hypertophic cardiomyopathy
    - Dilated cardiomiopathy

  - Absent

- Previous right atrial flutter ablation (yes/no)
- CHADS-VASC score

Echocardiographic variables

- Left atrial diameter (mm)
- Left ventricular ejection fraction
- Time to TEE (months)

Identification data

At baseline, sociodemographic data from each participant were collected.

Echocardiographic examination

All patients underwent TEE before the procedure, along with a transthorcacic examination (TTE). In particular, left atrial and left ventricular dimensions as well as valve function and ejection's fraction was examined. Interatrial septum with 2D and color Doppler flow was examined from multiple views. Atrial septal defect was defined as interatrial shunt confirmed by Doppler flow beside the fossa ovalis but not fulfilling the criteria for patent foramen ovale (PFO)(50).

Preprocedural CT scan

The anatomical aspect of the pulmonary veins is extremely variable and it is of utmost importance in the setting of PVI. Therefore, CT scans were performed prior to ablation in order to analyze the left atrial anatomy.

Ablation procedure: Cryoballoon Ablation

The CB ablation procedures were performed under general anesthesia. Following a single transseptal puncture, a circular mapping catheter (CMC) (Lasso, Biosense Webster, Inc., Diamond Bar, CA, USA) or a 20-mm diameter octapolar inner lumen mapping catheter (ILMC) (Achieve, Medtronic, MN, USA) were used to obtain baseline electrical information. Following the mapping, a 23 mm or 28 mm CB (Arctic Front, Medtronic) was inserted over the ILMC or the guidewire in the left atrium (LA). The choice of the balloon diameter was determined by the LA and PV anatomy observed on the preprocedural CT scan. However, whenever possible, the larger diameter CB was preferred. Once inflated and wedged in the PV ostium, dye was injected and vessel occlusion was evaluated according to a semiquantitative grading ranging from grade 0 (very poor occlusion) to grade 4 (perfect occlusion) in 2 different fluoroscopic projections. For each vein, cryoablation consisted of a minimum of 2 applications lasting 4 minutes each. In order to avoid phrenic nerve palsy, a complication observed during right-sided PVs ablation with CB, a quadripolar catheter was inserted in the superior vena cava and diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1200 ms cycle at an output of 20 mA. PV isolation was assessed either with the CMC or ILMC immediately and 20 minutes after the procedure. During the whole procedure, activated clotting time was maintained between 250 and 350 seconds with supplements of heparin infusion, as required.

Ablation procedure: Radiofrequency ablation

Radiofrequency ablation was performed as follows. After having accessed the left atrium with a double transseptal puncture, a 70 UI/kg heparin intravenous bolus was given. A selective PV angiogram was performed to assess all PV ostium positions. A CMC (Lasso; Biosense Webster Inc., Diamond Bar, California) was positioned into the proximal portion of the PV ostium to get baseline electrical information. Then an electroanatomic map of the left atrium was performed with a non fluoroscopic navigation system (CARTO; Biosense Webster Inc.). Radiofrequency ablation was performed with an open irrigated cool tip 3.5-mm catheter (NaviStar ThermoCool; Biosense Webster Inc.) in a power-controlled mode with a power limit of 35 W and at a maximum temperature of 48°C. Each application lasted a maximum of 60 seconds. Power was reduced to 25 W during ablation of LA posterior wall to prevent esophageal injury. The ablation strategy consisted in creating contiguous focal lesions at a distance of > 5 mm from the ostia of the PVs resulting in circumferential lines around ipsilateral PVs. During the whole procedure, activated clotting time was maintained at > 250 seconds by supplementing heparin infusion

Postprocedural management

All patients were dismissed the day following ablation. A TTE was performed in all individuals in order to exclude postprocedural pericardial effusion. Therapy with low molecular weight heparin (LMWH) was started the same day following ablation. Oral anticoalgulation (OAC) was started the day following the procedure. Patients were dismissed on both OAC and LMWH. When a target INR of 2-3 was reached, LMWH was stopped and only OAC was continued. OAC was continued for at least 3 months after the procedure. Antiarrhythmic therapy was administered for 3 months following the procedure and discontinued if the patient was free of AF relapse.

Follow-up

Clinical follow-up consisted in physical examinations, ECG and 24- hour Holter recording performed at 3, 6, 12 months and every 6 months after the first year. A blanking period of 3 months was considered for the study. Atrial fibrillation recurrence during the blanking period was taken into consideration for final analysis.

2.3.6 Statistical analysis

Data analyses are primarily focused on the baseline characteristics in both groups of patients to make them comparable. Next, we evaluated the procedural time depending on the technique used. Later, we analysed the iASD found, as well as, the diameter, and compared the iASD incidence according to the technique used. Finally, we tried to find predictors for the IASD persistence.

Data are given as mean and standard deviation (SD) for quantitative variables (age, duration of symptoms, CHADS-VASC score, body mass index, LA diameter, left ventricular ejection fraction, time to TEE), or as absolute values and percentages for qualitative values (gender, Paroxysmal AF, arterial hypertension, dyslipidemia, diabetes mellitus, structural heart disease, previous right atrial flutter ablation, IASD), as appropriate, with a 95% confidence interval.

A bivariate analysis has been made, in which continuous variables were compared using the Student's t-test or Mann-Whitney as appropriate and categorical variables were compared using chi-square or Fisher test. A p value of <0.05 was deemed statistically significant. Statistical analyses were conducted using SPSS software (SPSS v21, Chicago, IL, USA).

2.4 Ethical considerations

The Ethics Committee of the Investigation centre approved the protocol.

The protocol was carried out in accordance with the ethical principles for medical research involving human subjects established by Helsinki's Declaration, protecting the privacy of all the participants as well as the confidentiality of their personal information.

All patients gave written informed consent.

2.5 Results

Baseline characteristics

A total of 127 patients (92 males, 72%; mean age 60±11 years) were finally considered in our analysis. Specifically, 82 patients (58 males, 71%; mean age 61±9 years) having undergone RF ablation as index procedure and 45 patients (34 males, 76%; mean age 58±14 years) treated by CB ablation as first procedure. Baseline characteristics of both groups are listed in Table 1. No statistical differences between the 2 groups were found in terms of baseline population characteristics. Paroxysmal AF was documented in 54 patients in the RF group and 34 patients in the CB group (66% vs 76%, respectively; p=0.3) prior to the procedure. Mean time of AF in the whole study population was 40.9±50.6 months (44.2±48.1 months in RF group vs 34.9±54.9 months in CB group; p=0.4).

Preprocedural TEE

All patients underwent a TEE the day before procedure. Similar LA diameter (46±6mm in RF group vs 45±7mm in CB group; p=0.3) and mean left ventricular ejection fraction (58±10% in RF group vs 59±9% in CB group; p=0.8) were observed in both groups. Echocardiographic features are shown in Table 2.

Procedural parameters

Procedural time was significantly shorter in the CB group (181±53 minutes vs 109±56 minutes; p <0.001). Similar fluoroscopy times were observed between the 2 ablation procedures (31±20 minutes in RF group vs 28±14 minutes in CB group; p=0.5). In all patients, PVs were completely isolated at the end of procedure. In the CB ablation group, the 23 mm and 28 mm CB were used in 3 and 42 patients, respectively. Mean minimal temperatures were -53.2±10.2°C in the left superior PV (LSPV), -49.3±9.9°C in the left inferior PV (LIPV), -51.6±10.1°C in the right superior PV (RSPV), and -48.8±16.8°C in the right inferior PV (RIPV). After a mean 2.2 applications, veins were isolated. In 3 patients (right inferior PVs in 2 and left inferior PVs in 1) who underwent CB ablation, a focal touch-up with either a focal-tip cryocatheter (Freezor Max; CryoCath Technologies Inc., Montreal,Quebec, Canada) or an irrigated-tip RF catheter (NaviStar ThermoCool; Biosense Webster Inc.) was delivered. In the RF group, mean energy application time was 45±7 min/patient. During the CB ablation procedure, transient phrenic nerve palsy occurred in 3 patients (6.7%) and completely reverted in all cases before the end of procedure. In the RF group, one case of transient ST elevation secondary to air embolism (1%) and one case of pericardial tamponades requiring immediate drainage (1%) occurred.

Repeat TEE

During the follow up, an IASD was found in a total of 18 patients (14.2%). Particularly, an IASD was detected in 10 patients (22.2%) after CB ablation and in 8 patients (8.5%) after RF ablation procedure (p=0.03). In the whole study population, mean maximum and minimum IASD diameter were 0.54±0.27 cm and 0.44±0.26 cm, respectively. Specifically, mean maximum and minimum IASD dimension were 0.44±0.11 cm and 0.35±0.10 cm, respectively, in the RF ablation group and 0.60±0.33 cm and 0.50±0.33 cm, respectively, in the CB ablation group (p=0.2 for the maximum IASD dimension and p=0.3 for the minimum IASD dimension). All cases of IASD presented left to right interatrial shunt. In the study population, the main reason for performing a second TEE was a repeat PV isolation procedure for AF recurrence (n=112, 88.2%) followed by external cardioversion (ECV) in 12 patients (9.4%) and percutaneous LA appendage closure procedure in three patients (2.4%). In the RF group, a second TEE was performed for a repeat PV isolation procedure in 74 patients (90.2%) and for an ECV in 8 patients (9.8%). In the CB group, the main reason for performing a second TEE was a repeat PV isolation procedure due to AF recurrence (n=38, 84.4%; p=0.3); other indications for repeat TEE were external cardioversion (ECV) in 4 patients (8.9%; p=0.9) and percutaneous LA appendage closure procedure in three patients (6.7%; p=0.02). In the whole study population, the mean time from index ablation procedure to repeat TEE was 11.6±7.8 months. Specifically, the mean time from index procedure to repeat TEE was 11.9±7.8 months in the RF ablation group and 11.3±7.9 months in the CB ablation group (p=0.7). Six patients with IASD (4 in the CB group, 40%, and 2 in the RF group, 29%; p=0.6) received oral anticoagulation therapy during the follow up after the blanking period due to AF recurrence. No predictors of IASD were found in both groups (Table 3).

Follow up

Freedom of AF

After a mean total of 212 ablation procedures, 104 patients (93.7%) were free of AF at 18.9±15.3 months. The success rate for repeat RF ablation procedures was 90.5% (67 patients) and 97.4% (37 patients) for repeat CB procedures (p=0.18). In the RF group, among 8 patients having undergone ECV, 6 (75%) were free of AF at a mean follow up of 13.5±8.3 months; of the 4 patients having undergone ECV in the CB group, 3 (75%; p=ns) were free of AF at a mean follow up of 12.0±11.6 months. The 3 patients having undergone LA appendage closure secondary to the development of chronic AF and contra indications to oral anticoagulation therapy did not present adverse events during a mean follow up of 20.3±15.5 months.

Adverse events

Following the index procedure, no patients in both groups with persistent IASD presented a cerebral event.

In the CB group, one patient without IASD experienced an ischemic stroke without neurological sequelae after 52 months from the initial CB ablation procedure; this patient was 63 years old at the time of the stroke, in sinus rhythm and he wasn't doing OAC therapy. In the RF group, one patient without IASD suffered an ischemic stroke secondary to middle cerebral artery occlusion after 21 months from the initial RF ablation procedure; this patient was 64 years old at the time of stroke, in a persistent recurrence of AF and he was doing OAC therapy.

2.6 Discussion

The main finding of our study is that the incidence of IASD at 1-year is significantly higher following CB procedures if compared to RF ablation. To the best of our knowledge, this is the first study comparing the incidence of IASD between double transseptal conventional RF and CB ablation at 1-year follow up.

IASD following CB ablation

The persistence of IASD following CB ablation has been analyzed in 2 previous studies(10,14). Chan et al(14) identified IASD in 38% of patients at 6 months and 31% at 9 months in 13 consecutive patients having undergone PVI using CB ablation. Our group recently reported a 20% of IASD persistence in a series of 39 consecutive patients after 1 year from CB ablation[10]. Our current results are consistent with these previous reports identifying IASD in 22.2% of patients having undergone CB ablation at 1-year follow up with similar defect diameters (0.60x0.50 cm).

IASD following RF ablation

Some previously published reports investigated also the incidence of IASD following PVI by means of RF technology[12,13,43,51]. Obel et al reported an IASD incidence of 6.5% in patients having undergone PVI procedure achieved by double TS puncture after a follow-up period of 33 weeks[51]. Rillig et al found only 1 patient (3.7%) with a detectable IASD after 12 months from PVI[12]. Another study analyzed the persistence of IASD after a single TS puncture with passage of 2 electrophysiological catheters into the LA or double TS puncture reporting an incidence of 19% at 9 months; all defects were observed in the single TS puncture group[13]. Recently, Anselmino and co-workers also found a percentage of 5.6% of patients presented an IASD after RF ablation using single TS puncture at a median follow up of 12 months[43]. Our results are consistent with the literature showing a relatively low incidence of IASD (8.5%) following RF ablation achieved by double TS puncture.

The incidence of IASD between RF and CB ablation groups

The higher incidence of IASD in the CB ablation group might be explained by the larger sheath diameter (15F) compared with smaller sheats (8.5F) advanced through a double TS puncture in the RF ablation procedure. The larger outer diameter of the sheath inserted through the single TS puncture might be hypothetically more traumatic for the interatrial septum, although IASD diameters did not significantly differ between both groups. Of note, IASD dimensions following CB ablation were larger than those following RF ablation (0.60x0.50 cm vs 0.44x0.35 cm).

Clinical consequences

As described previously, the clinical significance of persistent IASD has not yet been well-defined. In this study no neurological complications related to IASD were observed during the follow-up period. Luckily, no right to left interatrial shunts were observed, which seem to be significantly more related to the paradoxical embolism. Predisposing morphological characteristics for the occurrence of paradoxical embolism have been extensively studied and characterized such as big diameters, spontaneous right to left atrial shunt and aneurismatic septum(52). In our series, the IASD found after PVI procedures did not fulfil this criteria. Otherwise, risks related to this complication should not be underestimated.

Echocardiographic follow up and IASD management

Although TEE examination was used in our study to assess IASD, less invasive methods might be alternatively used to identify IASD with similar accuracy during the follow up(53,54). Transthoracic echocardiogaphy with agitated saline injection (ASI) and provocative maneuvers such as Valsalva have been found to be equally reliable to diagnose an atrial septal defect. Moreover, TTE including novel 3D technologies might offer highly reliable measurements of IASD dimensions unless extremely small (< 2 mm)(55,56). Therefore, it might be advisable to perform TTE with ASI or alternatively 3D technology in the early phases of the follow up. Patients presenting IASD might undergo regular echocardiographic follow up in order to examine the behavior of the IASD over the time in terms of spontaneous reduction in dimensions. As the literature dealing with IASD after PVI using RF or CB ablation is still limited, it might be difficult to identify which patients would benefit of IASD closure. Thus, the latter should be performed according to current guidelines(57). No risk factors were found to be associated with IASD (Table 3).

2.7 Limitations

In regard to the limitations of this study, first, it should be considered that this study has a observational design. Besides, as all data have been collected in a single center, the results should not be generalized. The small number of patients and limited follow-up represent also limitations of our study. Moreover, we did not perform intermediate TEE examinations, which would have helped us in evaluating the rate and dimensions of IASD at different stages of the follow-up. All patients received OAC for at least 3 months after the procedure. This fact may also affect the occurrence of systemic embolism. No specific imaging technique has been used to rule out silent cerebral emboli. The use of this approach would have allowed us to make a more accurate diagnosis of asymptomatic cerebral events(58). Finally, TEE was performed without ASI (agitated saline injection) or Valsalva maneuvers in all patients. Performing the latter might have optimized the assessment of this complication(59).

2.8 Conclusion

The incidence of IASD at 1-year follow up following PVI was significantly higher in the CB ablation group compared with RF ablation group (22.2% vs 8.5%; p=0.03). Dimensions of IASD did not significantly differ between both groups. Only left to right atrial shunt could be observed. No clinical or procedural predictors of IASD were found in our series of patients. Although no adverse clinical events were recorded in patients with persistence of IASD, this complication should not be underestimated and systematic echocardiographic examinations might be advised in all individuals exhibiting this finding. Further studies with larger population and longer follow-up might be required to confirm our findings.

2.9 Cronogram

ACTIVITY	July 2014	August 2014	September 2014	October 2014	2015
Ethical committee					
Bibilography research					
Protocol elaboration					
Data collection					
Statistical analysis					
Results					
Final article elaboration					
Publication of data					

Activity	Investigators
Bibliography research	Marta Soriano
Protocol elaboration	Marta Soriano
Data collection	Juan Sieira, Giacomo Mugnai and Marta Soriano
Results analysis	HRMG (Heart Rhythm management

	group)
Final article elaboration	Giacomo Mugnai, Gian-Battista Chierchia and Marta Soriano
Publication of data	HRMG (Giacomo Mugnai, Juan Sieira, Giuseppe Ciconte, Ghazala Irfan, Yukio Saitoh, Burak Hunuk, Kristel Wauters, Claudio Tondo, Giulio Molon, Carlo de Asmundis, Pedro Brugada, Gian-Battista Chierchia and Marta Soriano)

2.10 Budget

Activity	Costs
Statistical analysis	1,000 €
Publication costs	2,000 €
Diffusion of the data	2,050 €
TOTAL	5,050 €

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TABLES

Table 1. Comparison of baseline characteristics between RF and CB ablation procedures

	RF ablation (n=82)	CB ablation (n=45)	P-value
Age, years	61±9	58±14	0.2
Men, %(n)	71% (n=58)	76% (n=34)	0.6
Paroxysmal AF, %(n)	66% (n=54)	76% (n=34)	0.3
Duration of symptoms, months	44±48	35±55	0.4
Arterial hypertension, %(n)	61% (n=50)	44% (n=20)	0.07
Dyslipidemia, %(n)	44% (n=36)	42% (n=19)	0.8
Diabetes mellitus, %(n)	12% (n=10)	2% (n=1)	0.06
CHADS-VASC score	1.7±1.4	1.4±1.2	0.2
Body mass index	27.7±4.5	26.6±3.7	0.2
Structural heart disease:			
- Coronary artery disease, %(n)	12% (n=9)	4% (n=2)	0.2
- Valvular cardiomyopathy, %(n)	4% (n=3)	2% (n=1)	0.7
- Hypertrophic cardiomyopathy, %(n)	1% (n=1)	4% (n=2)	0.2
- Dilated cardiomyopathy, %(n)	1% (n=1)	2% (n=1)	0.7
- Absent, %(n)	83% (n=68)	87% (n=39)	0.6
Previous right atrial flutter ablation, %(n)	26% (n=21)	24% (n=11)	0.9

Table 2. Comparison of echocardiographic characteristics between the 2 groups

	RF ablation (n=82)	CB ablation (n=45)	P-value
Left atrial diameter, mm	46±6	45±7	0.3
Left ventricular ejection fraction, %	58±10	59±9	0.8
Time to TEE, months	11.9±7.8	11.3±7.9	0.7

Table 3. Predictors of IASD persistence in the study population and in both RF and CB groups

	Study Population			RF ablation group			CB ablation group		
	No IASD	***IASD***	***P***	***No IASD***	***IASD***	***P***	***No IASD***	***IASD***	***P***
Age, years	59.6±11.2	59.2±10.4	0.9	60.6±9.1	59.9±8.2	0.5	57.7±14.6	58.7±12.1	0.8
Sex, (% male)	70.9	82.3	0.3	70.7	71.4	0.9	71.4	90.0	0.2
Paroxistic, %	69.1	70.6	0.7	64.0	85.7	0.2	80.0	60.0	0.2
HTA, %	55.4	52.9	0.9	61.3	57.1	0.8	42.9	50.0	0.7
Dyslipidemia, %	44.5	35.3	0.5	45.3	28.6	0.4	42.9	40.0	0.9
DM, %	9.1	5.9	0.7	12.0	14.3	0.9	2.9	0.0	0.6
LA diameter, mm	45.7±6.9	45.6±5.6	0.9	46.1±6.6	46.9±6.8	0.8	45.0±7.5	44.7±4.8	0.9
LVEF, %	58.4±9.4	63.5±8.1	0.1	58.9±9.5	64.6±9.4	0.1	57.5±9.4	62.8±7.5	0.1
Time to TEE, months	11.7±7.5	12.2±9.8	0.8	11.9±7.6	12.5±10.9	0.8	11.2±7.5	11.9±9.6	0.8

IASD: iatrogenic atrial septal defect, HTA: arterial hypertension, LA: left atrial, LVEF: left ventricular ejection fraction, TEE: transesophageal echocardiography