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COMPARISON OF THE CONTACT FORCE SENSING RADIOFREQUENCY AND THE CRYOBALLOON ABLATION EVALUATING CLINICAL OUTCOME AND PRESENCE OF IATROGENIC ATRIAL SEPTAL DEFECT

Ph.D. thesis

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LIST OF ABBREVIATIONS

AAD=antiarrhythmic drug

AF=atrial fibrillation

AI=ablation index

ASD=atrial septal defect

AV=atrioventricular

BMI=body mass index

CAD=coronary artery disease

CF=contact force

CT=computed tomography

CTCA=computed tomography coronary angiography

CVA=cerebrovascular accident

DC=direct current

EAM=electro-anatomical mapping

ECG=electrocardiogram

ECV=electrical cardioversion

FTI=force-time integral

FU=follow-up

HF=heart failure

HPSD=high-power, short-duration

IASD=iatrogenic atrial septal defect

ICE=intracardiac echocardiography

LA=left atrium

LCPV=left common pulmonary vein

LIPV=left inferior pulmonary vein

LSPV=left superior pulmonary vein

LV=left ventricular

LVEF=left ventricular ejection fraction

MRI=magnetic resonance imaging

NOAC=non-vitamin K antagonist oral anticoagulant

OAC=oral anticoagulant

PCI=percutaneous coronary intervention

PFO=patent foramen ovale

PV=pulmonary vein

PVI=pulmonary vein isolation

RIPV=right inferior pulmonary vein

RSPV=right superior pulmonary vein

TIA=transient ischaemic attack

TOE=transoesophageal echocardiography

TS=transseptal

TSP=transseptal puncture

TTE=transthoracic echocardiography

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1 INTRODUCTION

Catheter ablation of atrial fibrillation (AF) has been a continuously evolving procedure since its introduction in the 1990s. However, there is still insufficient reliable information on the development of AF and the maintaining mechanisms, and there is extensive active research in this field of electrophysiology. Catheter ablation treatment has stimulated and responded to this growing body of knowledge. Over the last decade, many novel ablation strategies have developed, leading to technological advances, new catheter designs, innovations in electro-anatomical mapping (EAM) systems, and the advent of alternative energy sources. Nowadays, catheter ablation treatment of AF offers a safe therapeutic option for an increasingly wide range of patients and has an improving short- and long-term clinical success rate. The two most widely used catheter ablation techniques for AF patients, contact force (CF) sensing radiofrequency (RF) catheter ablation and cryoballoon (CB) ablation, are routinely applied at our Electrophysiology and Pacemaker Therapy Department at the Gottsegen National Cardiovascular Center. Their comparison from different perspectives became the basis of my research since my university studies.

1.1 Atrial fibrillation

1.1.1 Definition

AF is a supraventricular arrhythmia with irregular atrial activation and accordingly ineffective atrial contraction. An entire 12-lead electrocardiogram (ECG) recording or a single-lead ECG tracing of ≥30 seconds verifying heart rhythm with no discernible repeating P waves and irregular RR intervals are diagnostic of clinical AF (1).

1.1.2 Epidemiology

AF represents the most common sustained cardiac arrhythmia worldwide, currently affecting between 2% and 4% of the general population (2). The most important risk factors of AF are increasing age, hypertension, diabetes mellitus, heart failure (HF), coronary artery disease (CAD), chronic kidney disease, obesity, and obstructive sleep apnoea (3-7). Patients with AF demonstrated a higher risk of thromboembolic events and all-cause mortality.

1.1.3 Classification

The traditional classification based on presentation, duration, and spontaneous termination of AF episodes categorizes five patterns: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF (8). In addition, based on the clinical presentation, symptomatic and asymptomatic AF are distinguished.

The novel approach in AF management prefers the structured characterization of AF to the traditional classification. The structured characterization of AF includes clinical assessment of stroke risk, symptom status, the burden of AF, and evaluation of substrate, which would help to give prognostic and clinical information and facilitate optimal management of AF patients (9).

1.1.4 Electrophysiological mechanisms

The electrophysiological mechanism of AF is based on the interaction between an initiating trigger and the underlying atrial substrate. A „trigger" is a rapidly pacing focus (such as the pulmonary veins (PVs) or non-PV triggers like the superior vena cava, coronary sinus, left atrial appendage, ligament of Marshall, crista terminalis, and left atrial posterior free wall). The „substrate" develops electrophysiological, mechanical, and anatomical characteristics of the atria that maintain AF (10).

AF is a progressive arrhythmia characterized by a gradual worsening over time. Progression from shorter, infrequent episodes to more sustained events will lead to atrial electrical and structural remodeling, contributing to the further maintenance of AF.

Electrical remodeling includes changes in the function of ion channels disturbing atrial myocardial activation and conduction. Structural remodeling refers to alterations in the tissue architecture, both microscopic (e.g., fibrosis) and macroscopic (e.g., atrial dilatation).

AF is characterized by rapid and chaotical atrial electrical activation leading to impaired atrial function. Numerous electrophysiological mechanisms were described like the classical mechanisms of a single ectopic focus, single circuit re-entry, multiple wavelet re-entry, and a more recent theory of stable rotors, unstable fibrosis-linked rotors, and epicardial–endocardial dissociation. There are undoubtedly many different mechanisms involved in the development of AF, but these complex electrophysiological mechanisms are still not wholly understood (11, 12).

1.1.5 Diagnostic evaluation

The diagnostic algorithm for AF includes a detailed medical history taking and identification of comorbidities, AF pattern, AF-related symptoms, thromboembolic risk, and left ventricular (LV) dysfunction. The symptoms associated with AF range widely (e.g., fatigue, tiredness, shortness of breath, palpitations, and chest pain). It is recommended to quantify the patient's symptoms on a valid symptom scale (13). A 12-lead ECG, laboratory tests (thyroid and kidney function, serum electrolytes, full blood count) and transthoracic echocardiography (TTE) are required for standard investigation. In selected AF patients, long-term ambulatory ECG monitoring or additional imaging modalities [transoesophageal echocardiography (TOE), computed tomography coronary angiography (CTCA), brain computed tomography (CT) or magnetic resonance imaging (MRI), cardiac magnetic resonance of the left atrium (LA)] are also required. Regular follow-up (FU) of AF patients is recommended to continue the optimal treatment strategy.

1.1.6 Management of atrial fibrillation

The integrated management of AF requires a complex approach, including optimized stroke prevention, symptom control with rate and/or rhythm control, and management of cardiovascular risk factors and comorbidities (1).

1.1.6.1 Stroke prevention

AF increases the risk of stroke depending on various thromboembolic risk factors. The optimal thromboembolic/stroke prevention management requires the patient’s individual risk assessment. The most commonly used clinical risk-factor-based CHA_2DS_2-VASc score summarizes the main stroke risk factors such as congestive HF, hypertension, elderly age, diabetes mellitus, previous stroke, vascular disease, and female sex in AF patients (14). AF patients with low-risk (CHA_2DS_2-VASc score=0 in men or 1 in women) do not need any stroke prevention therapy in the vast majority of cases, except in specific clinical situations such as around electrical cardioversion (ECV) or ablation procedure. Anticoagulation should be considered in AF patients with one risk factor (CHA_2DS_2-VASc score=1 in men or 2 in women). Anticoagulation therapy is recommended in patients with higher thromboembolic risk (CHA_2DS_2-VASc score $\geq$ 2 in men or $\geq$ 3 in

women). Non-vitamin K antagonist oral anticoagulants (NOACs) are generally recommended as first-line therapy. AF patients with prosthetic mechanical heart valves or moderate-to-severe mitral stenosis should take vitamin K antagonist (VKA) high time in the therapeutic range (1).

The bleeding risk monitoring is also essential when using oral anticoagulants (OACs) in AF patients. The HAS-BLED score is widely used to identify patients with high bleeding risk (15). A high bleeding risk score (HAS-BLED score ≥ 3) in the absence of absolute contraindications to OAC should not lead to withholding anticoagulation. However, these patients need to be followed with more surveillance, especially in specific clinical situations such as percutaneous coronary intervention (PCI).

1.1.6.2 Symptom control – rate and rhythm control

1.1.6.2.1 Rate control

1.1.6.2.1.1 Pharmacological rate control

Rate control in AF patients directs to improve symptoms associated with excessive heart rates and prevent tachycardia-induced cardiomyopathy. Initially, lenient rate control (heart-rate target <110 bpm) is recommended until symptoms require stricter rate control (16, 17). Pharmacological rate control strategies aim to increase atrioventricular (AV) node refractoriness to reduce ventricular rate during AF. The drugs used to prolong AV node refractoriness are beta-blockers, non-dihydropyridine calcium channel blockers, and digitalis glycosides.

1.1.6.2.1.2 Non-pharmacological rate control

AV node ablation with pacemaker implantation is a highly effective treatment option for AF patients with high ventricular rates resistant to pharmacological rate control, especially in the elderly or those with severe comorbidities. The „ablate and pace" strategy is associated with improved symptoms, quality of life, and physical stress tolerance (18, 19). In selected HF patients, AV node ablation may also result in improved LV systolic function (20, 21). The type of pacing therapy depends on patient characteristics (22, 23). Biventricular pacing or His bundle pacing may be a beneficial treatment option to prevent pacing-induced ventricular dyssynchrony and consequent HF (24-26).

1.1.6.2.2 Rhythm control

1.1.6.2.2.1 Pharmacological rhythm control

Rhythm control therapy aims to restore and maintain sinus rhythm (SR) and is recommended to improve symptoms and quality of life in symptomatic AF patients (27, 28). Antiarrhythmic drugs (AADs) are mainly Class IA (quinidine, disopyramide), Class IC (flecainide, propafenone), and Class III (amiodarone, dronedarone, sotalol, dofetilide) agents. They can be used to reduce AF recurrences and maintain SR acutely or on a long-term basis. The choice and dosing of AADs should be based on underlying structural heart disease and comorbidities, considering the frequency and severity of AF (29, 30). The decision to initiate long-term AAD therapy should be based on a balance between symptom burden and possible side effects, taking into account the patient's preferences.

1.1.6.2.2.2 Non-pharmacological rhythm control

Synchronized direct current (DC) ECV can be performed as an emergency procedure in a hemodynamically unstable AF patient or in a non-emergency situation. Pre-treatment with AADs may increase the success rate of elective ECV (31).

Catheter ablation for AF is a well-established rhythm control strategy and is the most common cardiac ablation procedure performed worldwide. The ablation procedure is a safe and superior alternative to pharmacological rhythm control to maintain SR and improve symptoms (32-43). Catheter ablation of AF is discussed separately in detail in the next section.

Surgical AF ablation aims to eliminate AF using surgical lesions in the left and/or right atria to block electrical conduction. From the classic „gold standard" Cox-Maze procedure, the surgical treatment of AF has been revolutionized through improvements in endoscopic imaging, ablation technology, and surgical instrumentation (44-46). Hybrid surgical and catheter ablation procedures merge minimally invasive epicardial ablation with a percutaneous endocardial approach.

1.1.7 Cardiovascular risk factors and comorbidities

Cardiovascular risk factors and comorbidities can strongly influence the development of AF. It is, therefore, crucial to identify and manage risk factors and concomitant diseases. The most important lifestyle modifications are eating a healthy diet, doing regular physical activity and avoiding alcohol consumption. Optimal management of common comorbidities such as hypertension, HF, CAD, diabetes mellitus, and sleep apnoea can reduce the burden of AF and improve symptoms (47).

1.2 Catheter ablation of atrial fibrillation

1.2.1 The evolution of ablation strategies

The first catheter ablation in humans was performed by Scheinman and colleagues, who pioneered the invasive treatment of arrhythmias in 1981, initially by delivering high-energy DC shocks and later using RF energy catheters (48). In 1998, the seminal work by Haissaguerre and coworkers showed that a rapidly firing focus originating from sleeves of muscle in the PVs could be the cause of AF (49). These findings led to the development of pulmonary vein isolation (PVI) as a basic ablation strategy for AF. The electrical isolation of the PVs was initially performed by segmental ostial PVI and then replaced by the more efficient circumferential PVI (50-52). Although the exact pathomechanism of AF remains unknown, advances in catheter ablation treatment have stimulated the understanding of the mechanism of AF initiation and persistence. In addition to electrically isolating the PVs, wide-area circumferential ablation was also used to modify the substrate near the PVs, which can be complemented with linear ablation lines (e.g., roofline, mitral isthmus line, posterior line, posterior box) (53, 54). Mapping and ablation of complex fractionated electrograms is another strategy that aimed to modify the atrial substrate thought to be critical to the perpetuation of AF (55). Ganglionated plexi ablation achieves autonomic denervation by affecting both the parasympathetic and sympathetic components of the autonomic nervous system and may improve PVI outcomes (56). Non-PV triggers are well-known arrhythmogenic sites and possible trigger sites of AF emerging from the superior vena cava, left atrial posterior free wall, crista terminalis, coronary sinus ostium, ligament of Marshall, left atrial appendage, and interatrial septum

(57-59). In addition, common arrhythmias such as AV node re-entry, Wolff-Parkinson-White syndrome, or atrial tachycardia can also occasionally trigger AF (60).

1.2.2 Indications of catheter ablation

Catheter ablation of AF is an effective way to maintain SR in patients with paroxysmal or persistent AF. AF catheter ablation may eliminate or reduce arrhythmia-related symptoms and improve the quality of life. (37) As the effect of catheter ablation on mortality and major cardiovascular events is not yet understood, its indications are still limited to symptom reduction in most patients. More substantial evidence on the impact of ablation treatment on major cardiovascular events was evaluated in the EAST trial. Early rhythm-control management was associated with a lower risk of adverse cardiovascular events than usual care among patients with early AF and cardiovascular conditions (61).

PVI should be considered as first-line rhythm control therapy as an alternative to AADs in patients with paroxysmal or persistent AF, taking into account the risk-benefit ratio and patient choice. First-line catheter ablation of AF is recommended in patients with tachycardia-induced cardiomyopathy to improve LV function and should be chosen in selected patients with HF and reduced LV function to reduce hospitalizations and improve survival (62, 63). AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to AAD (IA) or beta-blocker (IIa) treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF (1).

1.2.3 Ablation techniques

According to the current AF guidelines, electrical isolation of the PVs is the cornerstone of AF catheter ablation and the only established endpoint for the first ablation procedure (64, 1). PVI can be achieved by point-by-point lesions with RF energy or using single-shot devices like CB (ArcticFront Advance™; Medtronic, Inc., Minneapolis, MN, USA), laser balloon (Heartlight™; CardioFocus, Marlborough, MA, USA), RF hot balloon (Hayama Arrhythmia Institute, Kanagawa, Japan) and the „Globe" multi-electrode contact mapping and ablation system (Globe; Kardium Inc., Burnaby, BC, Canada) in the PV antrum. In order to simplify the ablation procedure and improve outcomes, catheter ablation technologies and catheter designs are under continuous development, and several

alternative energy sources are currently available (65, 66). Pulsed-field ablation is a novel, non-thermal ablation technology that uses high-voltage, very short-duration electrical pulses to damage tissue through a mechanism of irreversible electroporation. It has the advantage that the myocardium is very sensitive to this type of injury, while collateral structures appear relatively resistant to damage protecting surrounding intra- and extracardiac structures (67).

1.2.3.1 Radiofrequency ablation

Point-by-point ablation with an irrigated-tip RF catheter is the most widely used technology for AF ablation (68, 69). Combining RF ablation with a 3D EAM system can significantly reduce the fluoroscopy dosage and provide additional information to create a LA activation and voltage map (see Figure 1.) (70).

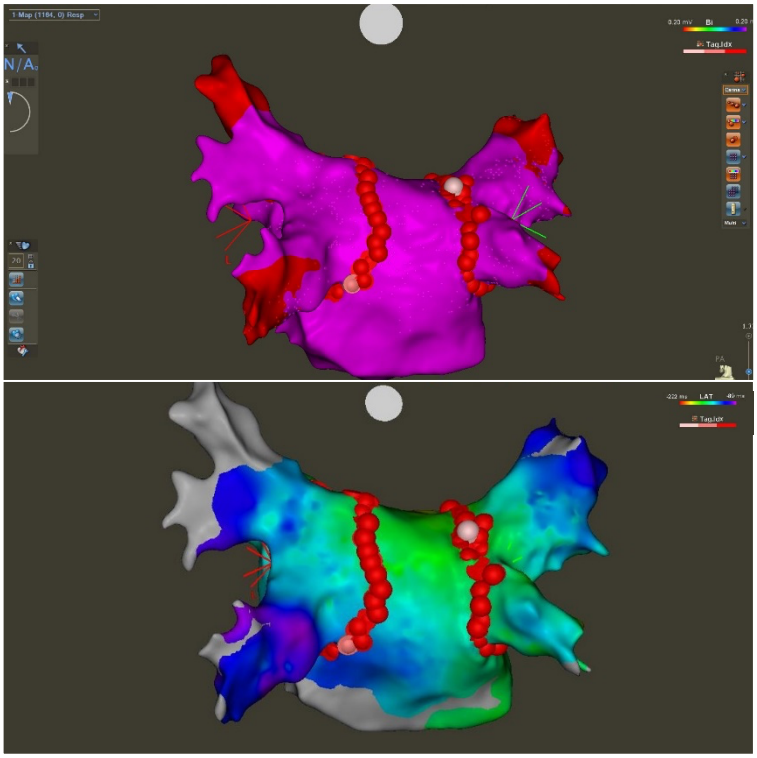

Figure 1. Pulmonary vein isolation with contact force sensing radiofrequency ablation technique using the CARTO 3D electroanatomical mapping system. Pre-ablation electroanatomical voltage map (up) and activation map (down) of the left atrium and the ablation lines before remapping of left atrium. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center.

Based on these electro-anatomical maps, RF ablation can also be used to treat additional substrates of AF, such as atrial tachycardia, atrial flutter, or non-PV triggers. Despite the numerous technological advances, it remains challenging to create durable, continuous, transmural lesions with RF ablation. With the recently developed CF sensing ablation catheters, the operator can optimize tissue heating and thus achieve a more durable lesion set and improve procedural outcome (71, 72). The ablation index (AI) is a novel quality marker of ablation lesion that utilizes CF, time, and power in a weighted formula and can predict lesion size and depth for RF energy delivery. Several clinical trials have demonstrated that AI-guided ablation leads to shorter ablation times, lower PV reconnection rates and thus higher clinical success rates (73). The „high-power, short-duration" (HPSD) ablation is an emerging strategy applying alternative ablation generator settings characterized by a higher power and shorter duration. Using the HPSD approach, a wider but shallower lesion formation can be achieved, with non-inferior complication rates and shorter procedure and fluoroscopy times (74).

1.2.3.2 Cryoballoon ablation

CB ablation is a single-shot ablation modality that has become the most commonly used alternative ablation method for PVI. The second-generation CB catheter has been improved with technical modifications: the number of injection ports has been increased and they have been positioned more distally along the axis of the catheter, resulting in a wider and more uniform freezing zone on the surface of the CB compared to the first-generation catheter. The „FIRE AND ICE" multicentre study showed the non-inferiority of CB compared to RF ablation in terms of efficacy and safety in paroxysmal AF patients (40). Recent studies have also demonstrated good clinical outcome in patients with persistent AF (75, 76). Although the CB technique is a faster and simpler procedure than RF ablation, it may have the disadvantage of a significantly higher radiation dose due to the PV angiography required to demonstrate the PV occlusion by the balloon. The learning curve of the CB technology is steep, and the procedure is less operator-dependent; hence less experienced operators can achieve PVI in low-to-medium volume electrophysiology centers (77, 78). The fixed size and shape of the balloon make it less adaptable to different PV anatomies. However, there are conflicting data on how anatomical variants such as the presence of a left common PV trunk affect the success of

CB ablation (79). Pre-procedural imaging may be helpful in the appropriate patient selection for CB technology. Furthermore, as the CB is a single-shot device suitable only for isolating the PVs, additional ablation targets require replacing the ablation set-up.

1.2.4 The technique of transseptal puncture

Transseptal puncture (TSP) provides a direct route to the LA via the interatrial septum and is an integral part of AF ablation. There are slight differences in the mode of TSP for different ablation techniques. RF ablation usually requires two long sheaths delivered into the LA either by a single TSP using a „sliding technique" or by a double TSP. During CB ablation, only a single TSP is needed, but a larger diameter long sheath is inserted into the LA. TSP can have potentially serious complications such as pericardial effusion or tamponade, aortic puncture, or left/right atrial free wall perforation occurring in approximately 1% of procedures, but is considered a safe intervention for experienced operators. In low-volume centers, the use of intracardiac echocardiography (ICE) alongside fluoroscopy can minimize the complication rate of TSP (80, 81)(Figure 2.). The presence of a persistent iatrogenic defect in the atrial septum following AF ablation may associate with the risk of stroke or other cerebrovascular events (82).

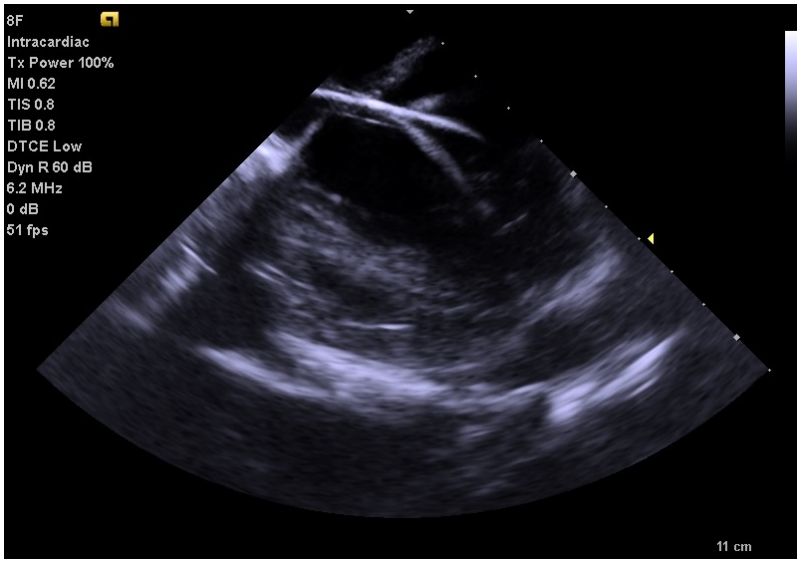

Figure 2. Intracardiac echocardiographic image of two long sheaths in the left atrium after transseptal puncture with „sliding" technique during radiofrequency ablation. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center.

1.2.5 Iatrogenic atrial septal defect after ablation

Iatrogenic atrial septal defect (IASD) is defined as an atrial septal defect (ASD) caused by TS cardiac interventions. The emergence of IASD is inevitable and therefore generally accepted. IASD is a relatively common phenomenon after left-sided cardiac procedures, but not much is known about IASD-related morbidity and complications (83). ASD closure is recommended for right ventricular dilatation due to significant shunting in case of no pulmonary arterial hypertension or LV disease, regardless of the onset of symptoms. ASD closure should be considered in patients with suspicion of a paradoxical embolism in the absence of pulmonary arterial hypertension or LV disease and in patients with 3-5 WU pulmonary vascular resistance when a significant left-to-right shunt is present (84). There is no data in the case of IASDs, but it seems reasonable to assume that similar recommendations must apply. The spontaneous closure rate of IASDs after catheter ablation of AF is high, so IASD closure is only necessary in sporadic cases (85). The presence of IASD can lead to paradoxical embolism and stroke, especially in the setting of thrombi in the venous system. However, limited data are available on the risk of cerebrovascular accidents (CVA) in patients with IASD. In addition to AF ablation, IASD can frequently occur following other structural interventions such as left atrial appendage closure or MitraClip (Abbott, Chicago, IL) implantation (86).

1.2.6 Complications of atrial fibrillation ablation

Complications of AF ablation are uncommon, but life-threatening complications can occur in 2-3% of patients (87). Patients vulnerable to major complications are the elderly, women, obese patients, those with structural heart disease, and those undergoing redo procedures (88). Periprocedural mortality is 0.01% and is most often caused by cardiac tamponade, oesophageal perforation/fistula, or thromboembolic event (89). In the case of cardiac tamponade, emergency pericardiocentesis and suspension of anticoagulation are sufficient in most patients. However, urgent surgical intervention may be required in some cases, so an in-house cardiac surgical background is strongly recommended. Oesophageal perforation is a rare but devastating complication. Symptoms such as sepsis, stroke and dysphagia usually appear 1-6 weeks after the ablation procedure, and the most appropriate diagnostic methods are CT or MRI scan of the esophagus. Once the diagnosis of the atrio-oesophageal fistula is made, early surgical repair is essential because of the

high mortality rate (90). Periprocedural thrombotic events such as stroke occur in less than 1% of the patients, and periprocedural anticoagulation management can play a role in reducing these complications (91). Other serious complications include PV stenosis, which occurs mainly after RF ablation (92), and persistent phrenic nerve palsy, which is the most common CB-related complication, but its incidence can be significantly reduced by pacing the phrenic nerve or monitoring diaphragm movement (93). Vascular complications including groin hematoma, retroperitoneal hematoma, pseudoaneurysm, arteriovenous fistula, and hemothorax due to venous access are the most frequent complications regardless of the ablation technique.

1.2.7 Clinical outcome

Catheter ablation for AF is a safe and effective treatment modality to prevent AF recurrences and reduce AF burden both as first-line and second-line therapy (94). The main goal of AF ablation is to improve the quality of life in patients with symptomatic AF. Secondly, ablation therapy may improve clinical outcome in patients with concomitant cardiovascular diseases as part of early rhythm control therapy. According to the latest guidelines, the definition of success in AF ablation is freedom from any atrial arrhythmia, defined as AF, atrial flutter, or atrial tachycardia lasting more than 30 seconds without AAD treatment in symptomatic or asymptomatic patients (1). The efficacy of AF ablation can also be measured by AF burden, which is the proportion of time spent in AF during the monitoring period. AF burden can be determined by continuous monitoring with an implantable loop recorder, a pacemaker, or an implantable cardioverter-defibrillator. Various factors, such as AF type and duration, age, presence of comorbidities (e.g., hypertension, obesity, metabolic syndrome, sleep apnoea), LA anatomy, and other structural abnormalities, may influence the outcome of AF ablation. Regular FU is needed to determine the clinical success of ablation. Monitoring arrhythmia recurrence during outpatient visits may be performed by intermittent ECG, Holter, patch recordings, external or implantable loop recorder, smartphone monitor, or smartwatches. In patients with paroxysmal AF, the first catheter ablation after a 3-month blanking period has a 60-70% success rate at 12-18 months FU (32). Long-term arrhythmia-free survival rates increase after repeated ablations compared to a single procedure. For persistent AF, the success rate gradually decreases, usually to around 50% after a single procedure (95).

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2 OBJECTIVES

As a practicing electrophysiologist fellow, the focus of my interest was in the clinical outcome of AF ablation for the various ablation techniques used in our center.

Therefore, our primary aim was to compare the efficacy and safety of the two most common ablation techniques, the CF sensing RF ablation and the second-generation CB ablation, with medium- and long-term clinical FU of our paroxysmal AF patients. We performed a single-center, retrospective study including patients with paroxysmal AF undergoing catheter ablation procedure for the first time. We evaluated the main procedural parameters and the clinical FU data obtained over two years after the index procedure (96, 97).

Secondly, our research project aimed to investigate the presence of IASD after AF ablation. Published data on the occurrence and clinical significance of IASD following PVI with different ablation techniques are limited. Therefore, our prospective study called "EVITA" (**EV**aulation of **I**atrogenic a**T**rial sept**A**l defect) aimed to describe the incidence and echocardiographic characteristics of IASD diagnosed by TOE following CF sensing RF or CB ablation at 3 months and 12 months FU visits. In addition, we sought to examine the incidence of CVAs caused by paradoxical embolism associated with post-interventional IASD (98).

3 METHODS

Study protocols were approved by the Hungarian Ethics Committee and were following the declarations of Helsinki.

3.1 Study group

3.1.1 "Clinical outcome" patient group

This non-randomized, retrospective, single-center study included 98 symptomatic patients with drug-refractory, paroxysmal AF from September 2012 to December 2013, who underwent PVI using either RF energy with CF sensing ablation catheter (ThermoCool SmartTouch, BiosenseWebster Inc., Diamond Bar, CA, USA; n=58) or the CB catheter (Arctic Front Advance, Medtronic, Minneapolis, MN, USA; n=40) for the first time.

3.1.2 "EVITA" patient group

Our prospective, single-center cohort study enrolled 94 consecutive, symptomatic, drug-refractory patients with paroxysmal AF between July 2014 and September 2016. An index procedure of PVI using the CF sensing RF catheter (n=48) or the CB catheter (n=46) was performed in all cases. In all patients, only PVI was achieved without cavotricuspid isthmus ablation. Exclusion criteria were regarded as previously performed TSP, previously documented ASD or patent foramen ovale (PFO), congenital heart disease, pregnancy, LA thrombus before the procedure, and any contraindications to TOE and/or ablation procedure.

The ablation technique of choice in both patient groups depended on the operator's preference, in agreement with the patient. However, all RF and CB ablation procedures were accomplished by the same operator.

3.2 Periprocedural protocols

All patients received therapeutic anticoagulation four weeks before the ablation procedure. In the „clinical outcome" study group, anticoagulation therapy was administered without interruption, regardless of the chosen drug. In the „EVITA" study group, anticoagulation with VKAs was discontinued before the procedure until INR < 2. NOACs were stopped the evening before the procedure. In the early postprocedural period, therapeutic anticoagulation with enoxaparin or NOAC was used after sheath extraction. After the procedure, anticoagulation was continued for at least three months or longer, depending on the CHA_2DS_2-VASc score. If the CHA_2DS_2-VASc score was 0 or 1, OAC therapy was stopped at the 3-month outpatient visit. AADs were given without interruption and were continued for three months after ablation and then stopped in both study groups.

Before the procedure, all patients underwent TTE to determine LV function and atrial dimensions and exclude structural and/or valvular disease. The day before ablation, TOE was performed to exclude left atrial (LA) thrombus, confirm an intact atrial septum and assess LA and PV anatomy.

All patients provided written informed consent before the procedure.

3.3 Transseptal puncture and ablation technique of cryoballoon ablation

All CB ablation procedures were performed using the second-generation 28 mm CB catheter (Arctic Front Advance™, Medtronic, Minneapolis, MN, USA). A single interatrial puncture was sufficient for CB ablation because the circular mapping catheter (Achieve Mapping Catheter™, Medtronic, Minneapolis, MN, USA) for PV electrogram monitoring was advanced through the central lumen of the balloon. TSP was accomplished with a Brockenbrough needle (BRK-1™, St. Jude Medical, St. Paul, MN, USA) placed in the SL0 standard transseptal (TS) sheath (SL0™, St. Jude Medical, St. Paul, MN, USA) under fluoroscopic and/or ICE guidance. The inserted SL0 sheath was then replaced by a steerable TS sheath (FlexCath Advance™; Medtronic, Minneapolis, MN, USA) with an inner diameter of 12 Fr and an outer diameter of 15 Fr over the wire. After that, the CB and the circular mapping catheter were inserted into the LA and positioned in each PV ostium through the sheath. The next step was the complete occlusion of the PVs by PV angiography with contrast injection into the PVs. If contrast

leakage was detected, the balloon could be repositioned. Initial cryoablation of 240 seconds was applied to each vein at temperatures no colder than minus 55-60°C. If complete isolation of PVs was not achieved based on the intracardiac electrograms, further cryo applications were performed. In order to prevent phrenic nerve damage, the diaphragmatic motion was routinely monitored during cryoablation of the right superior pulmonary vein (RSPV).

3.4 Transseptal puncture and ablation technique of radiofrequency ablation

For the RF ablation procedures, CF sensing ablation catheters (Navistar Thermocool SmartTouch®, Biosense Webster Inc., Diamond Bar, CA, USA) and the CARTO® system (BiosenseWebster Inc., Diamond Bar, CA, USA) for 3D EAM were employed. Two different TSP techniques were used during the procedure: a single and a double TSP method.

A single TSP technique with Brockenbrough needle and SL0 TS sheath was performed in 30/48 (62.5%) patients under fluoroscopic and/or ICE guidance. Subsequently, a multipolar, steerable, circular mapping catheter (Lasso®Nav, Biosense Webster Inc., Diamond Bar, CA, USA) was placed in the SL0 TS sheath, positioned in the left superior pulmonary vein (LSPV), and the sheath was retracted into the right atrium. Then, in the „EVITA" study group, from a separate femoral venous puncture, an 8.5 Fr long steerable sheath (Agilis^{TM} NxT, St. Jude Medical, St. Paul, MN, USA) was inserted over the wire in the superior vena cava, gently redrawn, and stabilized against the interatrial septum. In the „clinical outcome" study group, two non-steerable sheaths were used during the procedure. After the guidewire of the sheath was inserted into the LA at the previous TSP site, the second long sheath was also guided into the LA through the TS defect along the shaft of the Lasso catheter.

A double TSP approach was used in 18/48 (37.5%) patients where the second long sheath could not be passed through the interatrial septum using guidewire alone. In these cases, after insertion of the Lasso catheter into the SL0 TS sheath, a second TSP with a Brockenbrough needle was applied to gain second access to the LA using non-steerable or Agilis steerable long sheath. In the next step, the CF-sensing ablation catheter was guided into the LA in this long sheath. The RF ablation catheter was set to power-controlled mode, with a maximum power of 25 W on the posterior wall and 35 W in the

other regions of the LA. A maximum temperature of 48°C was adjusted. CF parameters were measured in real-time, including the amplitude and orientation of real-time CF, average force (Fav in gram-force, g) and force-time (FTI) integral. The ablation settings were the following: a minimum time of 20 seconds, a maximum range of 4 mm, a force over time of 50%, and a minimum force of 10 g. The upper limit of CF was 50 g force to avoid complications. Currently, in accordance with the latest technological innovations, we are performing AI-guided PVI with less than 6 mm interlesion distance based on the CLOSE protocol.

Conscious sedation was used during all ablation procedures (midazolam up to 5 mg and fentanyl up to 200 micrograms). Before the first TS access, complete anticoagulation with intravenous heparin bolus was given and repeated as necessary to achieve an activated clotting time of above 300 seconds.

Figure 3. shows the position of the TS sheaths and ablation catheters during RF and CB procedures.

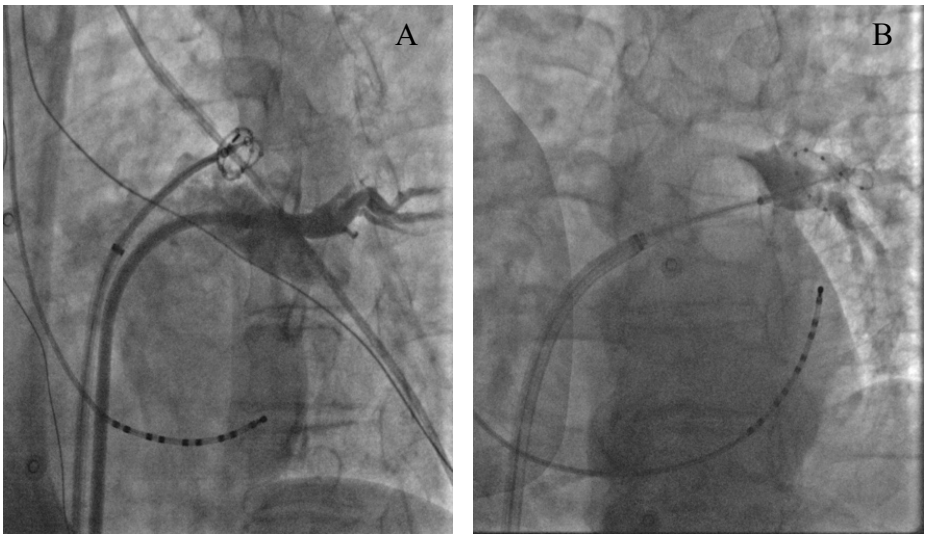

Figure 3. Fluoroscopic LAO 30° views of the position of the transseptal sheaths during radiofrequency (SLO and Agilis) (A) and cryoballoon (FlexCath) (B) procedure. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center

3.5 Follow-up

At 3, 6, and 12 months after the ablation procedure, and every 6 months after that, all patients were recalled for outpatient clinical visits, including physical examination, 12-lead ECG, 24-hour Holter and/or 1-week transtelefonic ECG monitoring. Patients were interviewed by telephone between these outpatient visits, during which they were asked about their symptoms related to AF using standardized questionnaires. A 3-month blanking period was used in the studies. AF recurrence was defined as atrial tachycardia/AF/atrial flutter lasting >30 seconds, and any symptoms similar to previous AF episodes were considered as AF recurrence. The success rate was defined as the percentage of patients with no documented AF episodes during the FU period or no evidence of AF recurrence after the blanking period. In the "EVITA" group, we focused on neurological status during outpatient clinical visits and reviewed all medical documentation to detect CVAs following ablation procedures. CVA was defined as stroke or transient ischaemic attack (TIA) during the FU period.

3.6 Transoesophageal echocardiography

In all patients in the "EVITA" group, TOE was obtained at the 3-month FU to confirm persistent IASD. In patients who were proven to have IASD at the 3-month FU, TOE was repeated at the 12-month FU. TOE scans were recorded using standard echocardiography equipment (IE 33, Philips Medical, Andover, MA, USA). The interatrial septum was examined from multiple views between the middle and upper esophagus at angles between 0 and 120°. For detection of persistent IASD, we used the color Doppler technique and peripheral venous infusion of echo contrast solution at rest and during Valsalva manoeuver. The incidence, diameter and shunt flow of IASD was assessed at 3 and 12 months after CB (single TSP) or RF (single or double TSP) catheter ablation. In addition, the main clinical [sex, age, hypertension, body mass index (BMI)] and echocardiographic parameters [left ventricular ejection fraction (LVEF) and LA diameter] were compared in patients with and without IASD at the 3 and 12-month FU, who are hereafter known as patients in the „IASD" or „NoIASD" group.

3.7 Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and comparisons between groups were made using the two-sided t-test after testing for normal distribution with the method of Kolmogorov and Smirnov. Among patients with successful ablation procedures, the probability of freedom from AF was calculated using Kaplan and Meier survival analysis, and differences between groups were determined with the log-rank statistic test. Binary endpoints were multivariate modeled using logistic regression, and time-to-event endpoints were determined using a Cox proportional hazard model. Continuous covariates were first augmented with restricted cubic splines and checked for deviations from linearity. A value of $p < 0.05$ was considered significant. All analyses were performed in the R statistical software package version 3.6.0 (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

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4 RESULTS

4.1 Baseline demographic and clinical characteristics

Both study groups included symptomatic patients with paroxysmal AF refractory to at least one AAD undergoing catheter ablation for the first time. The „clinical outcome" study group involved 98 patients [33 (33.7%) women, mean age=60.2±9.6 years] who underwent AF ablation from September 2012 to December 2013. Catheter ablation was performed using the CB technique [n=40 (40.8%)] or the CF sensing RF catheter [n=58 (59.2%)]. The „EVITA" study group enrolled 94 consecutive patients [30 (31.9%) women, mean age=60.0±9.7 years]. The procedure of PVI with CF sensing RF [n=48 (51.1%)] or CB catheter [n=46 (48.9%)] was achieved between July 2014 and September 2016. The investigated clinical and echocardiographic parameters did not differ between the different ablation technique groups (RF or CB) in any of the study groups. Baseline data in the two study groups are shown in Table 1 and Table 2.

Table 1. Baseline data of patients in the „clinical outcome" study group. Abbreviations: AF=atrial fibrillation, CB=cryoballoon, NOAC=non-vitamin K antagonist oral anticoagulant, RF=radiofrequency

„Clinical outcome" study group (*n*=98)			
	RF (*n*=58)	CB (*n*=40)	*p* value
Women, *n* (%)	20 (34.5)	13 (32.5)	n.s.
Age (years)	61.2 ± 9.3	59.0 ± 10.1	n.s.
Hypertension, *n* (%)	30 (51.7)	17 (42.5)	n.s.
Diabetes mellitus, *n* (%)	3 (5.2)	2 (5.0)	n.s.
Hyperlipidemia, *n* (%)	19 (32.8)	14 (35.0)	n.s.
Coronary heart disease, *n* (%)	7 (12.1)	5 (12.5)	n.s.
Congestive heart failure, *n* (%)	10 (17.2)	9 (22.5)	n.s.
Body mass index	27.9 ± 4.5	31.2 ± 4.9	n.s.
Duration of AF (months)	58.0 ± 42.8	50.1 ± 39.6	n.s.
CHA_2DS_2-VASc score	2.2 ± 1.6	2.7 ± 1.9	n.s.
HAS-BLED score	1.8 ± 1.2	2.0 ± 1.8	n.s.

„Clinical outcome" study group (*n*=98)			
	RF (*n*=58)	CB (*n*=40)	*p* value
Left ventricular ejection fraction (%)	62.0 ± 9.2	61.3 ± 10.1	n.s.
Left atrial diameter (mm)	42.1 ± 4.6	41.3 ± 4.0	n.s.
Medication prior to ablation			
Beta blockers, *n* (%)	55 (94.8)	40 (100.0)	n.s.
Propafenone, *n* (%)	24 (41.4)	12 (30.0)	n.s.
Sotalol, *n* (%)	2 (3.4)	0 (0.0)	n.s.
Amiodarone, *n* (%)	2 (3.4)	1 (2.5)	n.s.
Acenocoumarol, *n* (%)	40 (68.9)	29 (72.5)	n.s.
NOACs, *n* (%)	5 (8.6)	4 (10.0)	n.s.

Table 2. Baseline data of patients in the „EVITA" study group. Abbreviations: AF=atrial fibrillation, CB=cryoballoon, RF=radiofrequency NOAC=non-vitamin K antagonist oral anticoagulant, RF=radiofrequency

„EVITA" study group (*n*=94)			
	RF (*n*=48)	CB (*n*=46)	*p* value
Women, *n* (%)	17 (35.4)	13 (28.2)	n.s.
Age (years)	60.5 ± 9.6	60.4 ± 9.8	n.s.
Hypertension, *n* (%)	33 (68.8)	31 (67.4)	n.s.
Diabetes mellitus, *n* (%)	8 (16.7)	3 (6.5)	n.s.
Hyperlipidemia, *n* (%)	17 (35.4)	22 (47.8)	n.s.
Coronary heart disease, *n* (%)	15 (31.3)	9 (19.6)	n.s.
Congestive heart failure, *n* (%)	16 (33.3)	8 (17.4)	n.s.
Body mass index	30.2 ± 5.6	29.2 ± 4.2	n.s.
Duration of AF (months)	45.0 ± 38.9	61.1 ± 59.6	n.s.
CHA_2DS_2-VASc score	2.8 ± 2.0	2.1 ± 1.6	n.s.
HAS-BLED score	1.8 ± 1.4	1.7 ± 1.1	
Left ventricular ejection fraction (%)	60.9 ± 9.4	63.3 ± 7.7	n.s.
Left atrial diameter (mm)	43.0 ± 7.4	41.5 ± 6.9	n.s.

4.2 Procedural Data

In both study groups, the procedure time, which is defined as the time from venous puncture to removal of sheaths, was significantly shorter with CB ablation than with RF ablation (in the „clinical outcome" study group: CB: 74.3±17.0 min vs. RF: 120.1±49.2 min, $p<0.05$; in the „EVITA" study group: CB: 66.0±18.3 min vs. RF: 99.0±25.5 min, $p<0.001$). In the „clinical outcome" study group, fluoroscopy times were similar using both ablation techniques (CB: 14.4±7.1 min vs. RF: 16.0±5.5 min, $p=0.45$). In contrast, in the „EVITA" study group, fluoroscopy time was significantly shorter in the RF group (CB: 11.6±4.4 min vs. RF: 8.6±5.7 min, $p=0.004$). There was no significant difference in radiation exposure between the ablation groups in the „clinical outcome" study group (CB: 666.7±379.7 vs. RF: 557.7±353.1 $cGycm^2$, $p=0.11$). However, in the „EVITA" study group, CB ablation resulted in a higher radiation exposure to control PV occlusion after contrast administration (CB: 988.1±770.4 vs. RF: 620.1±554.6 $cGycm^2$, $p=0.016$). In the „clinical outcome" study group, 98% (39 out of 40) of patients in the CB group and 96% (56 out of 58) of patients in the RF group had a complete PVI during the procedure. The 28 mm CB was used during all CB procedures. Left common pulmonary vein (LCPV) was confirmed in 3/40 patients in the CB group. The mean number of CB applications per PV was 1.5±0.8 for LSPV, 1.3±0.6 for left inferior pulmonary vein (LIPV), 1.5±0.8 for RSPV, 1.7±0.9 for right inferior pulmonary vein (RIPV) and 2.0±1.3 for LCPV. The minimum balloon temperature indicative of balloon-tissue contact was significantly „warmer" in the inferior PVs: LSPV: -49.5±6°C vs. LIPV: -44.6±7°C ($p<0.05$) and RSPV: -50±7°C vs. RIPV:-41±10°C ($p<0.001$).

The CF and FTI values indicating real-time catheter-tissue contact were continuously monitored during the RF procedures. Using non-steerable sheaths, lower FTI values were observed in the anterior and inferior region of the left pulmonary veins and in the posteroinferior part of the right pulmonary veins than in the other PV regions (illustrated in Figure 4.).

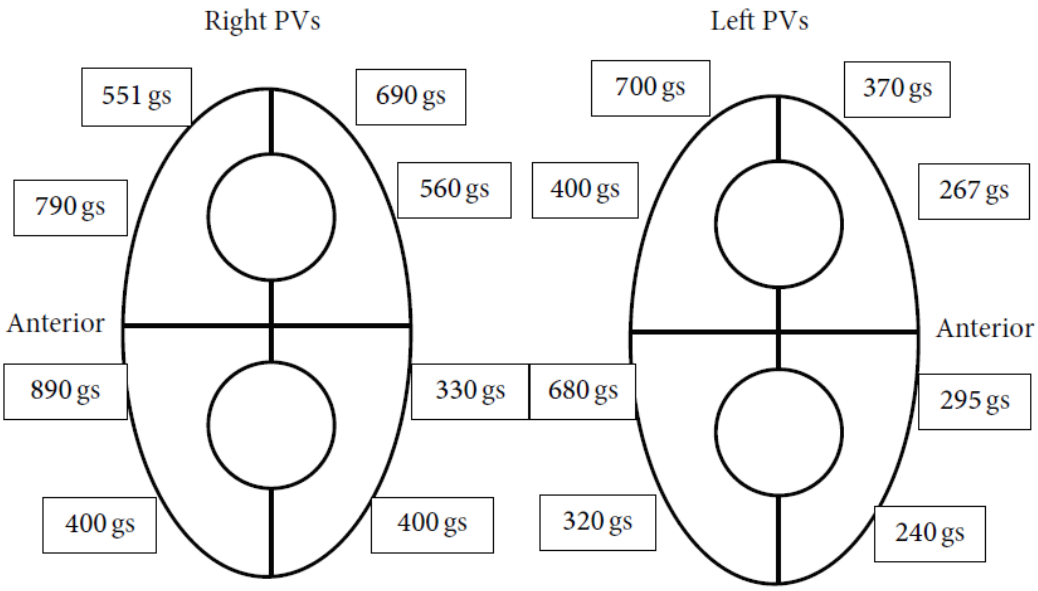

Figure 4. Distribution of mean force-time integral (FTI) values (gs) per PV quadrant in the RF group. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center

The periprocedural complication rate was low in both studies. In the „clinical outcome" study group, there was one case of pericardial tamponade requiring pericardiocentesis during RF ablation and 3 cases of phrenic nerve palsy during CB ablation, two of these resolved entirely during the procedure and one resolved after 12 months. In the „EVITA" study group, 2 patients in the CB ablation group developed phrenic nerve palsy that resolved during the procedure, and no major complications occurred during RF ablation. No death, stroke, or TIA occurred during any of the procedures.

4.3 Iatrogenic atrial septal defect

In the „EVITA" study group, we examined the incidence of IASD at 3 and 12 months after index ablation, compared the clinical characteristics of patients with and without IASD, studied factors predictive of IASD and the association between AF recurrence and IASD prevalence.

4.3.1 Incidence of IASD at the 3 and 12-month follow-up

At the 3-month TOE examination, IASD was observed in 17/94 (18.1%) patients. Nine of forty-eight (9/48) (18.8%) patients had IASD in the RF group. In the RF group, IASD was detected in 6/30 (20%) patients after single TSP compared to 3/18 (16.7%) patients after double TSP, with no significant difference (p=0.780). The incidence of IASD in the CB group was 17.4% (8/46 patients). No significant difference was found in the 3-month IASD incidence between the RF and CB ablation groups (p=0.866). The mean IASD diameter was 2.2±1.1 mm in the RF group (range 1-5 mm) and 2.5±1.4 mm in the CB group (range 1-7 mm)(p=0.624). All IASDs showed spontaneous left-to-right shunt flow by both color Doppler and microbubble contrast study. Based on the 12-month repeat TOE examination, the IASDs evaluated at the 3-month FU had a spontaneous closure rate of 82.4% (14/17 patients), 8/9 (88.9%) patients in the RF group, and 6/8 (75%) patients in the CB group. Two of 46 patients in the CB group (4.3%) and 1/48 (2.1%) patients in the RF single TSP group had persistent IASD (p=0.529) (see Figure 5). Table 3. summarises the incidence of IASD 3 and 12 months after the procedure in the CB and RF groups, and within the RF group using a single or double TSP technique.

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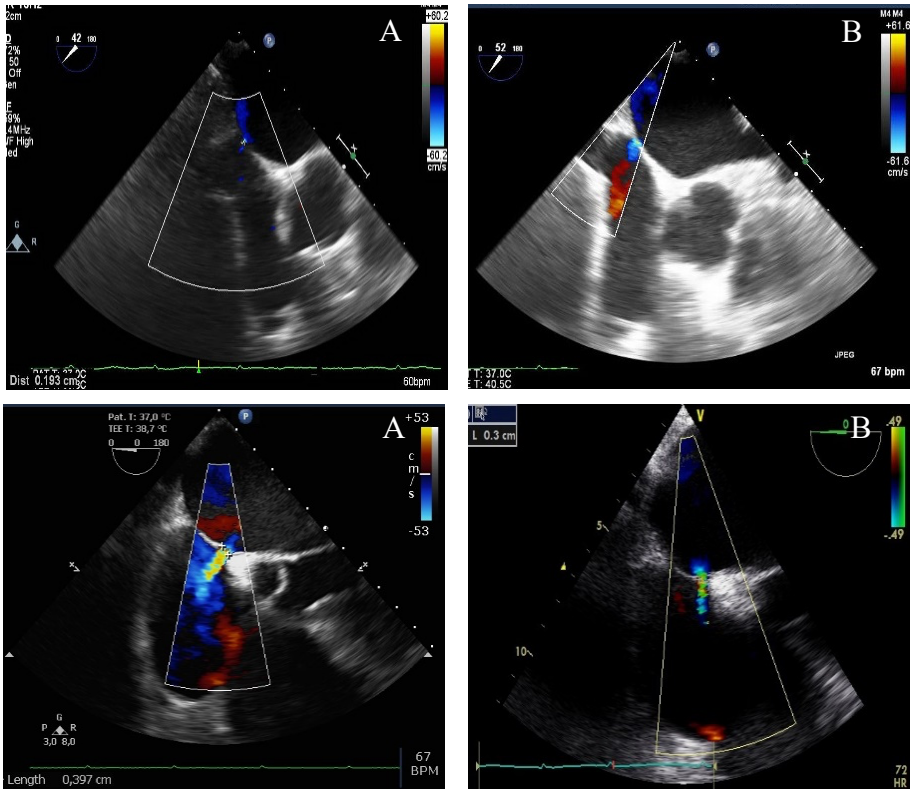

Figure 5. Persistent iatrogenic atrial septal defect with left-to-right shunt detected by transoesophageal echocardiography in a patient at 3-month (A) and 12-month (B) follow-up after radiofrequency (top) and cryoballoon (bottom) ablation. Electrophysiology Laboratory, Gottsegen National Cardiovascular Center

Table 3. Incidence of iatrogenic atrial septal defect at the 3-and 12-month follow-up. Abbreviations: CB: cryoballoon, IASD: iatrogenic atrial septal defect, RF: radiofrequency, TSP: transseptal puncture

IASD incidence at 3- and 12-month follow-up		
	3 month, *n* (%)	12 month, *n* (%)
Study population (*n*=94)	17 (18.1)	3 (3.2)
RF (*n*=48)	9 (18.8)	1 (2.1)
RF, single TSP („sliding technique") (*n*=30)	6 (20.0)	1 (3.3)
RF, double TSP (*n*=18)	3 (16.7)	0 (0.0)
CB (*n*=46)	8 (17.4)	2 (4.3)

4.3.2 Clinical characteristics of patients with and without IASD

Among the clinical parameters examined in the study group, BMI demonstrated a significant difference. Patients with IASD at the 3-month FU had a significantly higher BMI than patients without IASD at this time [(32.4±6.1 vs. 28.9±4.2) (p=0.01)]. The „IASD" and „NoIASD" groups did not show differences in the main echocardiographic parameters. Table 4. illustrates the clinical and echocardiographic characteristics of „IASD" and „NoIASD" patients during the 3- and 12-month FU periods.

Table 4. Risk factors of iatrogenic atrial septal defect at the 3-month and 12-month follow-up. Abbreviations: IASD: iatrogenic atrial septal defect, LVEF: left ventricular ejection fraction

Study population at 3-month follow-up (*n*=94)			
	NoIASD (*n*=77)	IASD (*n*=17)	*p* value
Women, *n* (%)	25 (32.5)	5 (29.4)	n.s.
Age (years)	59.5 ± 9.4	64.7 ±10.0	n.s.
Hypertension, *n* (%)	53 (70.1)	11 (70.6)	n.s.
Body mass index	28.9 ± 4.2	32.4 ± 6.1	*p*=0.01
LVEF (%)	51.8 ± 5.2	59.4 ± 8.7	n.s.
Left atrial diameter (mm)	41.3 ± 6.2	42.9 ± 5.3	n.s.
Study population at 12-month follow-up with patients who presented with IASD at 3-month follow-up (*n*=17)			
	NoIASD (*n*=14)	IASD (*n*=3)	*p* value
Women, *n* (%)	5 (35.7)	0	-
Age (years)	63.2 ± 10.1	71.4 ± 6.6	n.s.
Hypertension, *n* (%)	9 (64.3)	2 (66.7)	n.s.
Body mass index	32.5 ± 6.4	31.6 ± 5.0	n.s.
LVEF (%)	58.8 ± 9.2	63.0 ± 4.2	n.s.
Left atrial diameter (mm)	43.7 ± 7.7	40.5 ± 5.4	n.s.
Stroke/paradoxical embolism	0	0	-

4.3.3 Predictors of IASD at the 3-month FU

In the multivariate model of IASD at the 3-month FU, ablation method, sex, and LA size were not predictive of the occurrence of IASD (p=0.8956, p=0.4380 and p=0.8538, respectively), but age was predictive (p=0.0489, 7.1% higher odds of having IASD at 3 months for each year increase in age, 95% confidence interval: 1.00–1.15).

4.3.4 Relationship between IASD and AF recurrence

In the multivariate model for AF with IASD as a – time-varying – covariate, the effect of IASD was not significant on the hazard of the onset of AF (p=0.3210) after controlling for age, sex, LA size, and ablation method.

4.4 Cerebrovascular events

In the „EVITA" study group, anticoagulation was discontinued at the 3-month FU visit in 58/94 (61.7%) of patients, depending on the CHA_2DS_2-VASc score. In patients at low risk of stroke (CHA_2DS_2-VASc score 0 in men or 1 in women), OAC therapy was stopped at the 3 month-FU. No patients with IASD had a cerebrovascular event after the index PVI procedure in any ablation group.

4.5 Atrial fibrillation recurrence

Clinical FU was 24 months in the „clinical outcome" study group and 12 months in the „EVITA" study group, which all patients completed. Freedom from AF without AAD treatment in the „clinical outcome" study group 12 months after ablation was 77.5% (45/58) in the RF group and 80.0% (32/40) in the CB group, and 65.5% (38/58) in the RF group and 67.5% (27/40) in the CB group at the 24-month FU. In the „EVITA" study group, 34/48 (70.8%) patients in the RF group and 31/46 (67.4%) patients in the CB group were free from AF recurrence without AAD therapy at the 12-month FU (p=0.72). No significant difference in clinical success rate was observed between the two ablation groups in either study group. The arrhythmia-free survival in the „clinical outcome" study group for the two ablation techniques is shown in Figure 6.

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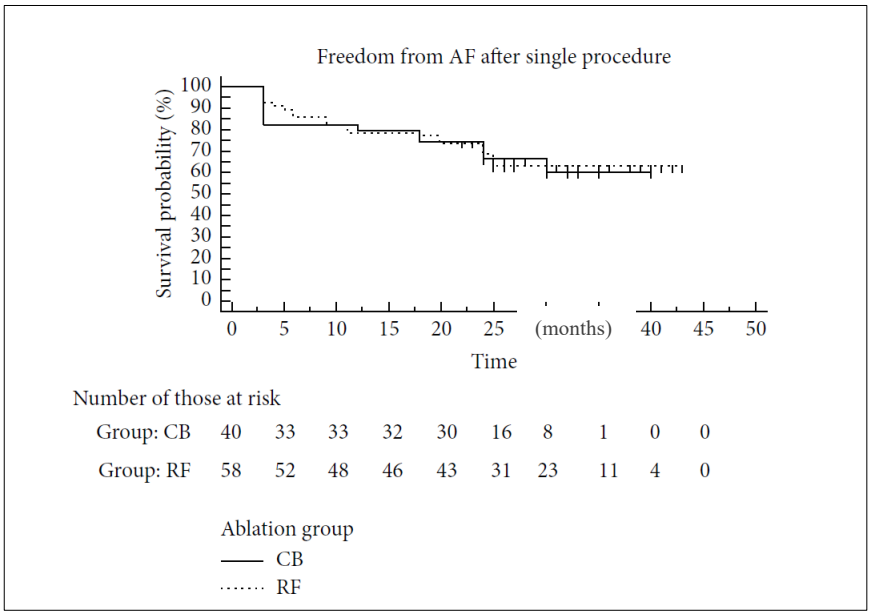

Figure 6. Kaplan-Meier survival analysis shows the time to AF recurrence after a single ablation procedure in the CB (solid line) and RF (dotted line) groups. Abbreviations: AF=atrial fibrillation, CB: cryoballoon, RF: radiofrequency

4.6 Redo ablation procedures

In the „clinical outcome" study group, a total of 22 symptomatic patients unresponsive to AAD therapy suffering from AF recurrence underwent a redo ablation 13.3 ± 7.8 months after the initial ablation procedure [15/58 (25.8%) patients in the RF and 7/40 (17.5%) patients in the CB group]. In the „EVITA" study group, a total of 9 patients required redo ablation, 6/48 (12.5%) patients after RF and 3/46 (6.5%) patients after CB ablation, a mean of 10.4±4.6 months after the index procedure (p=0.33). All redo procedures were performed using RF energy in either study group.

4.7 Pulmonary vein reconnections

In the „clinical outcome" study group, in the RF group, 37 of the 60 PVs (61%) in 15 patients (2.5 per patient), while in the CB group, 10 of the 28 PVs (35%) in 6 patients (1.4 per patient) showed PV reconnection gaps (p=0.01). The reconnection rates per vein in the RF group were: LSPV: 53% (8/15), LIPV: 66% (10/15), RSPV: 40% (6/15) and RIPV: 87% (13/15). In one patient undergoing CB ablation, all PVs were isolated despite

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documented symptomatic episodes of paroxysmal AF, and therefore non-PV foci were ablated. In the CB group, inferior PVs (LIPV and RIPV) were frequently reconnected (12/14 veins in total, 86%), whereas conduction gaps were documented in the superior PVs (RSPV and LSPV) in only one patient.

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5 DISCUSSION

5.1 Clinical outcome of atrial fibrillation ablation using cryoballoon or contact force sensing radiofrequency catheter

5.1.1 Medium-and long-term follow-up

To the best of our knowledge, our working group reported the most prolonged FU results comparing second-generation CB ablation and CF sensing RF ablation in paroxysmal AF at the time of publication. As a single-center, retrospective study, the clinical interpretation of our results is limited, but is in line with major international studies.

Our study did not show a significant difference between CF sensing RF catheter ablation and second-generation CB ablation in terms of 12-month and 24-month arrhythmia-free survival (in the "clinical outcome" study group: RF: 77.5% vs. CB: 80.0% at 12 months and RF: 65.5% vs. CB: 67.5% at 24 months). A postprocedural "blanking period" of 3 months was defined, during which any atrial tachyarrhythmias had not been taken into account when reporting the results of the procedure. Atrial arrhythmias are very common in these first 3 months after ablation. Acute inflammatory changes may be responsible for the early onset, as the application of ablative energy to atrial tissue has a pro-inflammatory and potentially arrhythmogenic effect. (99) Current literature suggests that early recurrence of atrial tachyarrhythmia strongly predicts late recurrence of AF after CF sensing RF or CB ablation, and therefore shortening the blanking period may be recommended. (100, 101) The success rate of ablation treatment in patients with paroxysmal AF similar to our patient population, symptomatic and refractory to at least one AAD, has been investigated in several major clinical trials (94). A difficulty in determining the efficacy of ablation is that different trials have defined arrhythmia recurrence in various ways and have used differing monitoring methods during the FU period. Several clinical studies have investigated the efficacy and safety of ablation treatment for drug-refractory AF. In the SMART-AF trial, similar results were presented; the 12-month success rate was 74% with CF sensing RF catheters (102). Some studies reported a second-generation CB catheter ablation with 80% or even higher clinical effectiveness at 1 year (103, 104). The "FIRE AND ICE" multicentre, randomized trial followed patients with paroxysmal AF undergoing RF and CB ablation for an average of

1.5 years using transtelephonic ECG and Holter monitoring. During the study, AF recurrence rates were 34.6% and 35.9% in the CB and RF groups, respectively, thus confirming the non-inferiority of CB ablation compared to RF ablation with similar safety profiles. Although the representation of advanced generation catheters was not equal in this study [first-generation CB (24%) and second-generation CB (76%) in the CB group and non-CF sensing RF (76%) and CF sensing RF (24%) in the RF group] (40). The recently published The Cryoballoon vs. Irrigated Radiofrequency Catheter Ablation: Double Short vs. Standard Exposure Duration (CIRCA-DOSE) trial was a prospective, multicenter, randomized clinical trial using implantable loop recorder monitoring to compare the effectiveness of different ablation technologies in drug-refractory paroxysmal AF. During a 12-month FU period, the overall arrhythmia-free rate was 53.9% after RF ablation and 52.2% after 4-minute CB ablation (105). A common finding in major clinical trials is that ablation treatment was significantly more effective than AAD in preventing arrhythmia recurrence in patients whose ablation was chosen as a second-line treatment strategy. Several factors may have played a role in the effectiveness of different ablation techniques in our study. The effectiveness of the CF sensing RF ablation technique in our study may have been influenced by the use of a non-steerable long sheath. The development of steerable sheaths, which are now routinely used, has been shown to improve ablation target access and to provide better catheter-target contact (106). CB technology is also evolving; third- and fourth-generation CB catheters are now available (107, 108). In our study, we used the second-generation CB catheter designed to achieve significantly lower temperatures and faster isolation than the first-generation device (109). We performed a 4-min-duration freezing cycle for isolation of all PVs without bonus freeze. This approach is used in most electrophysiology centers (110), but there is also literature data on cryoablation with freeze-thaw cycles of 3 minutes with excellent results (111, 112).

5.1.2 Procedural data

Based on our study, second-generation CB ablation was found to be a significantly shorter procedure in terms of the time from the venous puncture to sheath extraction being significantly lower than RF ablation (CB: 74.3±17.0 min vs. RF: 120.1±49.2 min, $p<0.05$). Our procedural data are comparable to those available in the literature (113, 40).

5.1.3 Pulmonary vein reconnection

The recurrence of arrhythmias after the first AF ablation is predominantly due to reconnection of previously isolated PVs. In the study of Ciconte et al. the rate of late PV reconnection was significantly lower following second-generation CB ablation (20.4% of all PVs; 1.2 per patient) when compared with CF sensing RF ablation (36.1% of all PVs; 1.8 per patient) as index procedure. Anatomical reconnection patterns around the PVs differed between the two ablation groups (114). In our study, higher reconnection rates were found both in the CB group (35%, 1.4 per patient) and in the RF group (61%, 2.5 per patient) (p=0.01). Following CB ablation, reconnection of inferior PVs was observed in the vast majority of cases. The presumed reason for this is the straight orientation of the CB catheter towards the superior veins, which allows better vessel occlusion, lower nadir temperature and better tissue-balloon contact. Whereas in case of difficult occlusion of the inferior PVs, a "pull-down" technique is required to achieve electrical isolation. The cryoballoon nadir temperature provides reliable information about the balloon-tissue contact. The minimum balloon temperature reached during cryoablation of inferior PVs in our study was significantly "warmer" than the values measured in the superior PVs. With regard to CF sensing RF ablation, the aim of the EFFICAS I multicentre study was to demonstrate the correlation between CF and FTI parameters during the initial procedure and the occurrence of conduction gaps later. At 3-month follow-up, 65% of patients showed at least one conduction gap, which was correlated with minimum CF and FTI values (115). We found that the dominant sites of PV reconnection were the anterior-inferior segments of the left PVs and the inferior and inferoposterior parts of the RIPV. The lowest FTI values measured in all left anterior positions are in line with the results reported in the EFFICAS I study, where 46% of patients was ablated with the use of a steerable sheath. Extended usage of steerable sheaths may result in higher CF values and lower PV reconnection rates in these PV segments.

5.1.4 Complications

No death, stroke, or TIA occurred in our study. Pericardial tamponade developed in one patient during CF sensing RF ablation (1.7%) and phrenic nerve palsy in 3 patients during CB ablation (7.5%). In the pericardial tamponade case, pericardial puncture was required, but no cardiac surgery was performed, and the patient did not suffer any residual damage.

Two of the phrenic nerve palsies detected in the CB group were transient and resolved spontaneously before hospital discharge; in one patient, the phrenic nerve injury resolved during 1-year FU. Our complication rates are comparable to previously published literature data (40).

5.1.5 Strengths and limitations

Our retrospective, single-center analysis revealed that the second-generation CB ablation and the CF sensing RF ablation have a similar clinical outcome during the 2-year FU period. Therefore, our results on clinical success rates are comparable to the findings in the literature. The strength of our study is that all RF and CB procedures were completed by the same operator, so interobserver variability was not a relevant consideration. Nevertheless, a limitation of our study is that the choice of ablation strategy was not randomized but was influenced by operator preference. However, based on literature data, both ablation techniques can be used with similar safety and efficacy in patients with paroxysmal AF (40, 105, 116, 117), and there were no significant differences between ablation groups in our study regarding the main demographic parameters.

5.2 Evaluation of iatrogenic atrial septal defect after atrial fibrillation ablation

To the best of our knowledge, our prospective study was the first to investigate the incidence of IASD after CB or RF ablation using single or double TSP techniques confirmed with TOE at 3- and 12-month FU and the cerebrovascular event rate associated with persistent IASD. Moreover, this was the first study to compare the occurrence of IASD following single or double TSP during RF ablation.

Our study has identified several key findings. First, the incidence of IASD was relatively common at 3 months after AF ablation in the RF (18.8%) and CB (17.4%) groups, but the chosen ablation technique did not significantly influence the incidence of postinterventional IASD. Second, the occurrence of IASD after RF ablation was not affected by the single or double TSP approach. Third, the vast majority of IASDs (82.4%), regardless of ablation technique, showed spontaneous closure rates during the 12-month FU period. Fourth, persistent IASDs after ablation were not found to be associated with an increased risk of cerebrovascular events in our study. Finally, there was no correlation between the presence of IASD and AF recurrence during the FU period.

5.2.1 Comparison of IASD incidence after RF and CB ablation

Nowadays, TS catheterization is performed most commonly for AF ablation to access the LA and isolate the PVs. Depending on the different ablation techniques, the method of TSP may also vary. During CB ablation, a single TSP is performed, and then a larger outer diameter of 15 Fr steerable TS sheath is passed into the LA. RF ablation can be achieved with a single TSP ("sliding" technique) or a double TSP using two 8 Fr TS sheaths. Before this study, only one working group had published their findings comparing the presence of IASDs after ablation using different ablation techniques: Mugnai et al. reported the occurrence of IASDs in the 1-year FU period after CB or RF ablation using the double TSP technique. A significantly higher incidence of IASD was confirmed in the CB group (22.2%) than in the RF group (8.5%) (118). Following the publication of our study, Yang et al. recently reported their results showing that the incidence of IASD in the cryoablation group was significantly higher than in the RF ablation group at 3-month FU (24.1 vs. 11.8%, $p<0.05$). At one year after the procedure, the incidence of IASD was still higher in the CB group than in the RF group (15.6 vs. 6.6 %, $p<0.05$). In this study, IASD affected LA function and increased the risk of AF recurrence (119). Concerning RF ablation, one retrospective study examined the incidence of IASD (5.6%) with TOE at a median FU of 12 months (120). Nevertheless, several clinical studies were designed to investigate CB-related IASD using TOE in the postprocedural FU period. Chan et al. first studied IASDs at 9-month FU after CB ablation and discovered persistent IASD in 31% of the cases (121). They then published their 6-year FU results, which showed that roughly one-fifth of patients undergoing CB ablation develop persistent IASD. For septal defects larger than 10 mm, percutaneous closure may be necessary due to a significant left-to-right shunt (85). According to a study by Sieria et al., CB ablation-related IASD can occur in up to 20% of patients after 1 year (122). In the study of Davies et al., IASD was revealed in 25.9% of the patients at a median FU time of 553 days (123). Linhart et al. published their long-term results in 2018; the IASD occurrence following CB procedure was 37% after 2.9 years (124).

The wide range in the incidence of IASDs in the referred studies may be due to the different inclusion criteria. For example, a heterogeneous patient population was used, PFO or ASD was not excluded before the procedure, and in some studies, IASD was assessed by TTE rather than TOE. Our study's lower rate of IASD may be explained by

our inclusion criteria, such as the inclusion of only patients with paroxysmal AF, and exclusion of patients with preprocedural PFO or ASD.

5.2.2 Clinical importance of IASD

IASD following TSP is increasingly recognized and may be an unknown nuance around AF ablation because its clinical significance remains not fully clarified (82, 125). Closure of the septal defect at the time of index procedure is only required in sporadic cases, as residual IASD usually closes spontaneously in the vast majority of patients during medium- and long-term FU (126). The risk of cerebrovascular events strongly determines the clinical importance of IASD. In our cohort, none of the patients had a stroke or TIA during the 12-month FU period. Consequently, the presence of IASD was not associated with an increased risk of cerebrovascular events in this study, but in the absence of events, statistical power is controversial, and larger patient population and longer follow-up are needed to assess this question. In our study, the spontaneous closure rate of IASD was high (82.4%) between 3 and 12 months of FU visits. Therefore, the risk of IASD-related cerebrovascular events would be the highest in the early postprocedural period, in the first 3 months after AF ablation. However, in these months, all patients routinely receive OAC therapy based on our protocol, which may offset the increased risk of paradoxical embolism. This question may be relevant for patients with low thromboembolic risk (CHA_2DS_2-VASc score of 0-1), because in this patient group, anticoagulation is usually discontinued 3-12 months after ablation. There is limited data available in the literature about the risk of cerebrovascular events associated with IASD (127, 128). Singh et al. investigated the incidence of postprocedural IASD and the associated cerebrovascular events after Watchman device implantation using a 12 Fr TS sheath in the PROTECT-AF study. They found a high spontaneous closure rate of IASDs that was not associated with an increased stroke or systemic embolization rate during the 12-month long FU period (129). In addition, silent cerebral embolism associated with TS procedures, particularly AF ablation, is becoming increasingly recognized (130). In conclusion, well-designed studies are needed in the future to understand the relationship between persistent IASD after TS interventions, anticoagulation treatment, cerebral brain imaging data, and changes in cognitive function, and thus to provide more information on the clinical relevance of IASD.

5.2.3 Risk factors of persistent IASD

A recent study found that hypertension, LA diameter and LA dwelling time are risk factors for IASD, while statin and ACEI/ARB drugs may reduce IASD (119). Another study identified that atrial septal angle, assessed by preprocedural CT examination, maybe a valuable predictor of persistent IASD (131).

In this study, patients with IASD at 3 months had a higher BMI than patients without IASD. Age was a significant predictor of IASD at 3-month FU, with older patients having a higher odds of IASD at 3 months. The other investigated parameters showed no further differences between the groups in our study. The results of the few studies in the literature examining predictive factors for IASD range widely, in most cases without identifying any predisposing factor for IASD.

5.2.4 Strengths and limitations

The strengths of this prospective study are listed below. First, only patients with paroxysmal AF were included in our study group, and therefore the study has a homogeneous patient population. Second, all patients had a TOE before the procedure, and a confirmed PFO or ASD was considered as exclusion criteria. Third, the single TSP technique during cryoablation was compared with both single and double TSP methods used in CF sensing RF ablation. Furthermore, we examined IASD with TOE not only at the 3-month outpatient visit but also at 1-year. Finally, the study provides a systematic FU focusing on neurological events.

Limitations of the present study include the non-randomized nature, the small sample size (limited power), and the medium-term FU duration. In addition, no neurocognitive function tests or cerebral brain imaging were performed to rule out silent cerebral embolism caused by the procedure itself or by paradoxical embolism via IASD.

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6 CONCLUSIONS

Based on our results detailed above, we have drawn the following main conclusions:

1. The second-generation cryoballoon and the contact force sensing radiofrequency catheter ablation techniques have similar safety profiles and a comparable single procedure success rate over a two-year follow-up period.
2. After cryoballoon ablation, late reconnection of the inferior pulmonary veins was predominantly confirmed, which correlated with the minimum balloon temperature indicating balloon-tissue contact. Following radiofrequency ablation, pulmonary vein reconnection was mostly detected in the anterior-inferior segments of the left pulmonary veins and in the inferior and inferoposterior parts of the right inferior pulmonary vein, with the lowest force-time integral values in the anterior part of the left pulmonary veins.
3. Iatrogenic atrial septal defect is a moderately common phenomenon in the early postprocedural period following atrial fibrillation ablation. Based on our prospective study, the ablation technique did not influence iatrogenic atrial septal defect incidence at three-month follow-up with transoesophageal echocardiography.
4. During radiofrequency ablation, the single or double transseptal puncture technique did not significantly affect the presence of iatrogenic atrial septal defect.
5. Iatrogenic atrial septal defects demonstrated a high spontaneous closure rate in the first year after the procedure.

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7 SUMMARY

Pulmonary vein isolation using either radiofrequency or cryoballoon ablation has emerged as a widely used treatment modality in patients with paroxysmal atrial fibrillation. In our first single-center study, we followed 98 patients with symptomatic, drug-refractory paroxysmal atrial fibrillation who underwent pulmonary vein isolation for the first time between September 2012 and December 2013 at the Gottsegen National Cardiovascular Center using the second-generation cryoballoon catheter or the contact force sensing radiofrequency catheter. Both ablation techniques were found to be safe, with the cryoballoon procedure being significantly shorter. Late pulmonary vein reconnection patterns around the pulmonary veins show variations after different ablation methods. At the 24-month follow-up, the clinical success rate was comparable between the two ablation techniques. Therefore, in patients with paroxysmal atrial fibrillation, both ablation techniques can be widely used with safety and high clinical efficacy.

Secondly, we prospectively investigated the incidence of iatrogenic atrial septal defects and cerebrovascular events associated with transseptal puncture during atrial fibrillation ablation. Our study included 94 patients with paroxysmal atrial fibrillation who underwent cryoballoon or radiofrequency ablation (single or double transseptal puncture) for the first time between July 2014 and September 2016. Transesophageal echocardiography was performed to confirm atrial septal defect before the procedure and assess iatrogenic atrial septal defect at the 3- and 12-month follow-up. This study was the first to make the following findings. The incidence of iatrogenic atrial septal defects was moderately high 3 months after atrial fibrillation ablation, but the ablation technique did not significantly affect its incidence. After radiofrequency ablation, the iatrogenic atrial septal defect incidence was not influenced by the single or double transseptal puncture technique. Finally, iatrogenic atrial septal defects showed a high spontaneous closure rate at 12-months in both ablation groups.

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