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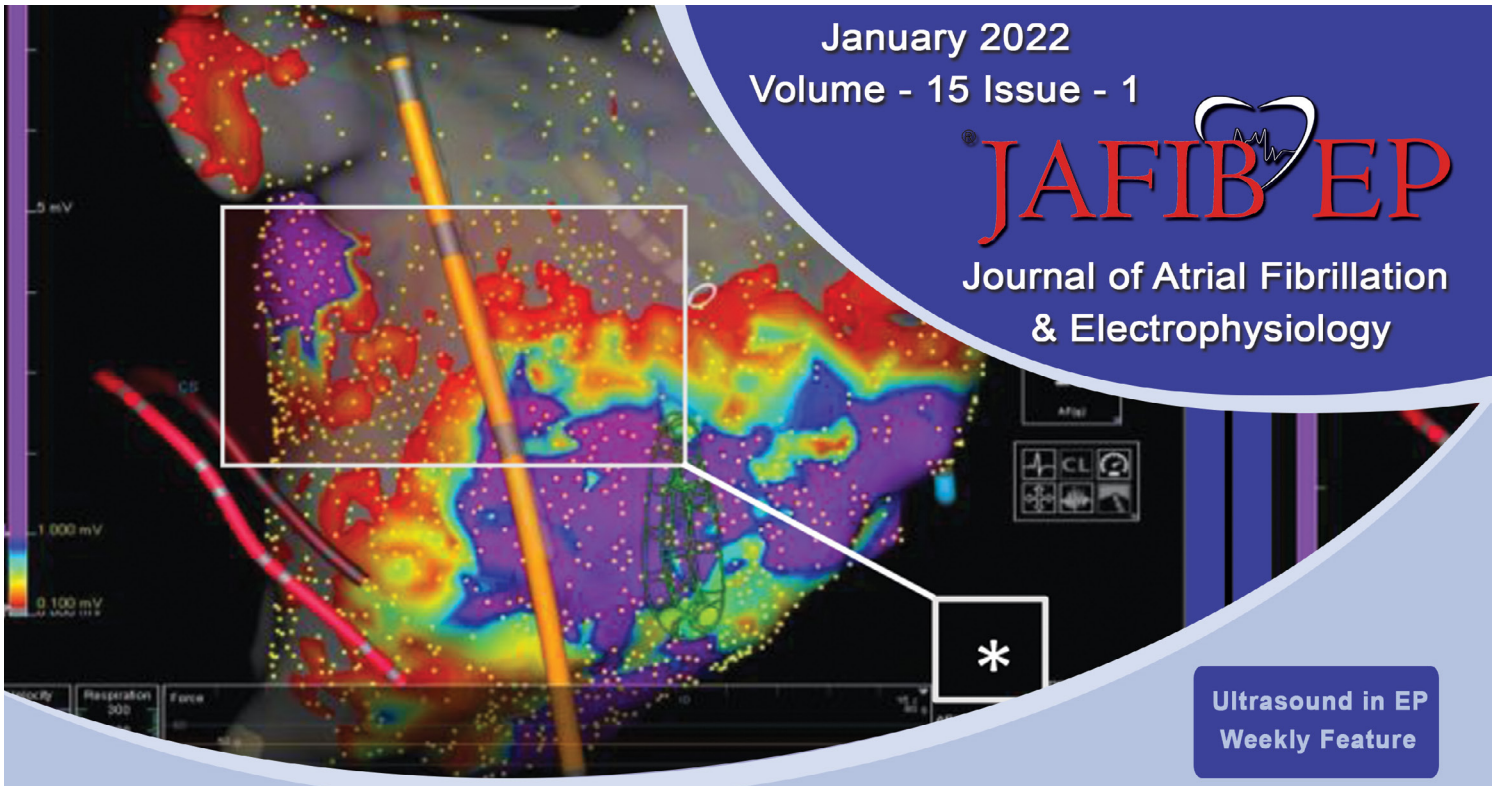

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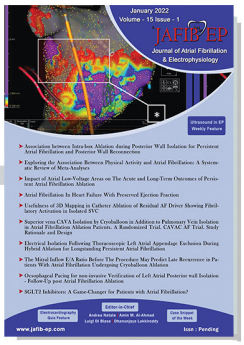

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Welcome to the Journal of Atrial Fibrillation & Electrophysiology

Journal of Atrial Fibrillation & Electrophysiology

January - 2022

Issue 1

Volume 15

Dear Colleagues

As we usher in a new year, I am delighted to announce some important changes to the Journal of Atrial Fibrillation (JAFIB). First and foremost, the journal has been renamed as Journal of Atrial Fibrillation and Electrophysiology (JAFIB-EP). This change reflects the true nature of the work being published in JAFIB-EP that covers a broader range of arrhythmia issues, but also reflects the importance of atrial fibrillation and the beginnings of our journal.

In addition to the change in name, we are delighted to announce new sections that will be published periodically by the journal. A section on"Imaging in Electrophysiology,"-headed by Dr. Mansour Razminia, will bring cases that demonstratethe utility of intracardiac ultrasound, transesophageal echo, electro anatomical mapping and other modalities to illustrate important teaching points that are valuable to the clinician. Drs. Sergio Pinski and Adrian Baranchuk will head a second section, "Electrocardiography Corner," that showcases ECG and EGM pearls and pitfalls. A thirdsection, "Robotics in Electrophysiology," will lay outinteresting cases that are done using a robotic navigation system and will be headed by Drs. Peter Weiss and Tamas Szili-Torok.

Importantly, the new journal will be PubMED indexed and will continue to bring out high quality publications completely free of charge. JAFIB-EP is the only online open access journal that is run by physicians for physicians with no charge for publication or subscription. Please register yourself on the website to be on the subscription mailing list. We continue to believe that the important science in our field should be shared widely across the world without the traditional cost structure of many journals in our discipline.

This is the journal that will continue with the tradition of high-quality publications. In this issue,we will see important contributions on ablation techniques in the left atrium and the superior vena cava for triggers as well as the impact of low-voltage areas, echocardiographic findings, and differences in mapping systems.

We hope that you find the issue as stimulating and informative as we do, and we hope that you continue to consider the journal for your publications. We are confident that together we can continue the mission of helping all arrhythmia patients globally.

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Best warm wishes
Andrea Natale

Andrea Natale
MD, FACC, FESC, FHRS
Editor-in-Chief
Journal of Atrial Fibrillation & Electrophysiology

JAFIB EP

Original Research

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Oesophageal Pacing for non-invasive Verification of Left Atrial Posterior wall Isolation - Follow-Up post Atrial Fibrillation Ablation

Nitin Chandra Mohan[1], *Guy A Haywood*[1]

[1]University Hospitals Plymouth NHS Trust, United Kingdom. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Abstract

Background: Left atrial posterior wall isolation (LAPWI) has been proved to be beneficial in long standing persistent atrial fibrillation (AF). This study aims to assess the accuracy of oesophageal pacing catheters to detect reconnection at a time point during long-term follow-up remote from the isolation procedure.

Method: This is a prospective study and includes patients who underwent ablation therapy (catheter or hybrid) for long standing persistent AF, where LAPWI was judged to have been achieved based on surgical or catheter ablation criteria. Patients underwent oesophageal pacing and recording at an interval greater than 6 weeks following initial ablation. Subsequent to this, all patients underwent a left atrial electrophysiology (EP) study to confirm or refute findings from the oesophageal study.

Results: In 20 out of 21 patients studied, the oesophageal catheter study correlated with the invasive EP study. The negative predictive value of this test is 95.00 % (95% CI of 74.29% to 99.92%), where a negative result is being unable to capture the atrial rhythm by oesophageal pacing indicating that the LAPW remains isolated. The positive predictive value is 100%, where a positive finding indicates being able to capture the atrial rhythm by oesophageal pacing indicating that the LAPW has reconnected.

Conclusions: We were able to demonstrate that oesophageal pacing catheters can successfully be used for verification of LAPWI. This is important in assessment of the long-term efficacy of LAPWI and also in informing operators of the durability of the results they are achieving by either catheter or surgical ablation.

Introduction

Pulmonary vein isolation (PVI) is the cornerstone for managing patients with paroxysmal atrial fibrillation (AF)[1]. However, in individuals with non-paroxysmal AF, additional lesion sets in the left atrial posterior wall (LAPW) may be required to prevent recurrences. The LAPW shares a common embryological origin with the pulmonary vein and has electrophysiological characteristics that give rise to its arrhythmogenic potential[2]. LAPW isolation can be achieved through additional lesion sets on top of PVI, such as adding 'roof lines' between right and left superior pulmonary veins (PV) and 'floor lines' between the right and left inferior PVs. These lesion sets are based on the main principle of the modified Cox-Maze surgical technique[3]. Besides catheter ablation, LAPW isolation can also be achieved by thoracoscopic surgical ablation (SA), or a combination hybrid approach. Ablation procedures do come with risks, some of which are serious. These include stroke, fatality and cardiac tamponade[4]. The oesophagus runs a variable course in the posterior aspect of the left atrium (LA)[5]. Given the close anatomical relationship between the two structures, there is a small risk of atrio- oesophageal fistula from ablation procedures, which is often fatal[4]. Safety mechanisms such as specialized oesophageal temperature probes have been developed for use during ablation procedures to reduce the risk of atrio-oesophageal fistula[6]. However, they cannot measure every point within the oesophagus and so can never provide complete safety.

In our initial feasibility study, 7, we were able to establish that an oesophageal pacing catheter can be used to confirm or refute LAPW isolation with a sensitivity of 100% and specificity of 95% during an invasive isolation procedure. In this study, we aim to prospectively assess the positive and negative predictive value of using oesophageal pacing to detect reconnection at a time point during long-term follow-up after the isolation procedure, without the need for any hospital admission. The verification of isolation was then compared to a subsequent gold standard invasive electrophysiological (EP) study.

Key Words

Atrial fibrillation; Posterior-wall isolation; Oesophageal pacing.

Corresponding Author
Guy A Haywood,
Cardiology department, University Hospitals Plymouth NHS trust, Derriford road, PL6 8DH, United Kingdom

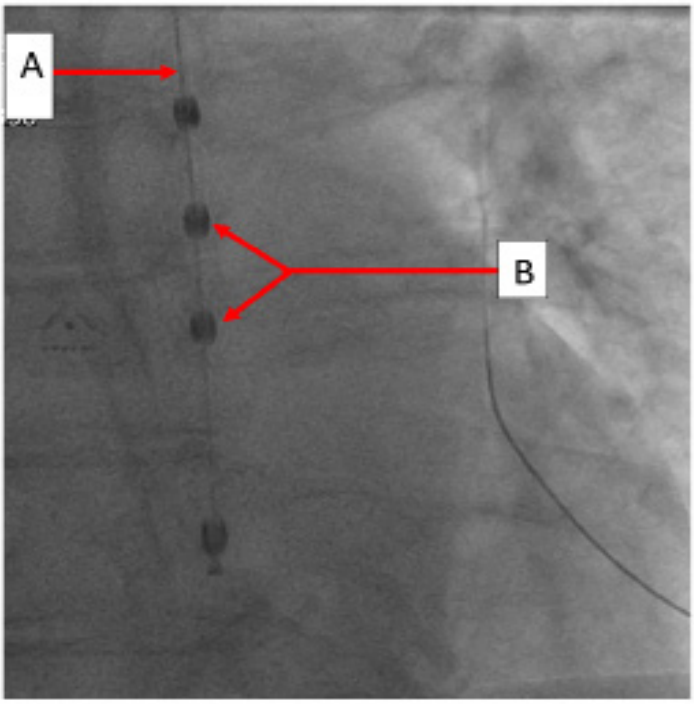

Figure 1: A: Antero-posterior fluoroscopic projection of the oesophageal catheter ('Box Check' Oesophageal catheter, Dot Medical Limited, U.K.), which is positioned posterior to the left atrial wall. B: Oesophageal pacing is performed through the middle poles of the catheter

2. Method

2.1 Study Cohort and recruitment

This a prospective study of patients who were recruited from the electrophysiological service at the South West Cardiothoracic Centre, University Hospitals Plymouth, United Kingdom between 2014 and 2019. The inclusion criteria for this study are patients who underwent ablation therapy (catheter, surgical or hybrid) for symptomatic, drug-refractory persistent AF aiming to achieve LAPW isolation. The decision regarding a catheter or staged hybrid ablation approach was based on the multi-disciplinary team and patient discussions. Patients underwent oesophageal pacing and recording at an interval greater than 3 months (ranging from 5 months to 120 months) following surgical or catheter ablation where LAPW isolation was judged to have been achieved based on surgical or catheter ablation criteria. Subsequently, all patients underwent a further left atrial EP study at which the predicted result from the oesophageal study was either confirmed or refuted.

Ethical approval was granted for all the participants of this study by the Devon and Cornwall Research Ethics Committee prior to the recruitment stage. Informed consent was obtained from all the patients prior to the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2 Procedures

2.2.1 Oesophageal Pacing and Recording

The quadra-polar oesophageal catheter ('Box Check' Oesophageal catheter, Dot Medical Limited, U.K. – Figure 1) is placed while the patient is laid supine on the fluoroscopy table (with or without mild sedation depending on patient preference). The catheter itself is 75 centimetres long and 2.3 millimetres in diameter with an inter-electrode distance of 10 millimetres. In patients in sinus rhythm, the only preparation required is the attachment of a bedside electrocardiogram monitor. The oesophageal pacing catheter is passed through the left or right nostril depending on patient preference, prior success with naso-gastric tubes, or presence of a deviated septum. On passing the catheter through the nasopharynx, the patients are advised to swallow. The 2 middle pacing electrodes on the 'BoxCheck' catheter are positioned immediately behind the isolated region of the LAPW using fluoroscopy to check for correct positioning (see section 4.1). The pacing was performed in a bipolar fashion and the pulse width was set at 10 milliseconds. The amplitude was initially set at 5mA, and increased up to 20mA (at a rate above sinus) until there was either capture of the atrial rhythm or 20mA was reached without capture. If capture of the atrium was not achieved at 20mA, the study predicted that isolation of the left atrium with bidirectional block across the ablation lines enclosing the left atrial posterior wall would be found at the subsequent invasive EP study.

2.2.2 Endocardial instrumentation at the subsequent invasive EP study

Access to the left atrium was gained via atrial trans-septal puncture using fluoroscopic guidance. Patients were heparinised during the procedure, aiming to achieve an activated clotting time greater than 300 seconds. An SL-1 sheath (Abbott Inc., St. Paul, Minnesota, USA) was passed through the aperture created by the trans-septal puncture and an A Focus 2 mapping catheter was placed on the left atrial posterior wall to sense and pace.

2.2.3 Endocardial electrophysiological mapping and ablation

Patients received direct current cardioversion to achieve sinus rhythm if they were in AF. This permitted pace capture and mapping in sinus rhythm. We used the Abbott Inc. Precision mapping system and the AFOCUS II catheter (Abbott Inc. Medical, St. Paul, Minnesota, USA) to create a three- dimensional voltage map of the left atrium. Our standard settings were between 0.1mV - 0.13 mV (grey colour scale) to 0.5mV (purple colour scale). Healthy tissues were denoted by areas of higher voltage, and scar tissue was marked by areas of low electrical amplitude (e.g., surgical ablation areas). Electrical isolation was checked by placing the AFOCUS II catheter (Abbott Inc. Medical, St. Paul, Minnesota) in the LAPW and PV. An EP study was then performed assessing for entry (absence of sinus beats conducted inside the box lesion) and exit blocks (absence of capture of the atrium by pacing above the sinus rate) at several points within the ablation 'box' of the LAPW (10mA@2ms).

3. Results

3.1 Patient cohort

A total of 21 patients (Table 1) were studied. 4 patients had undergone catheter only ablation, 16 patients had undergone hybrid ablation procedures and 1 patient was studied 120 months post concomitant surgical ablation. Of the patients who had hybrid ablation, 9 patients had undergone both surgical and catheter ablation prior to

Table 1: Summary of findings from Oesophageal pacing study compared with an invasive EP study

Patient details				Ablation Strategy aiming to achieve LAPW isolation	Findings from Oesophageal Pacing study		Findings from invasive EP study subsequent to the oesophageal study		Oesophageal study consistent with restudy EPS?	Complications	Comments
Age	Sex	BMI	LA size (mm)		LAPW Capture @ 20 mA	LAPW isolation status	LAPW isolation status	LAPW established with RF			
76	M	26	47	Catheter	No	Isolated	Isolated	Already established	Yes	No	
76	F	22	42	Catheter	Yes	Not isolated	Not isolated	Yes	Yes	No	
78	M	24	48	Catheter	Yes	Not isolated	Not isolated	Yes	Yes	No	
75	M	26	39	Catheter	Yes	Not isolated	Not isolated	Yes	Yes	No	
[52]	M	33	39	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
73	M	30	58	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
74	M	22	48	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
72	M	28	41	Hybrid	Yes	Not isolated	Isolated	Already established	no	No	Oesophagus close to right veins - narrow area of isolation at this site. When correctly positioned oesophageal pacing failed to capture at 25mA.
69	M	34	59	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
59	M	31	55	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
57	M	33	40	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
73	M	26	32	Hybrid	Yes	Not isolated	Not isolated	No	Yes	No	PVI procedures x2 prior to Hybrid AF ablation. CTI line only added at 2nd stage catheter ablation
72	M	27	48	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
68	M	32	50	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
59	M	32	47	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
72	M	26	52	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
62	M	26	42	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
68	M	25	50	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
73	M	24	49	Hybrid	Yes	Not isolated	Not isolated	Yes	Yes	No	
68	M	26	40	Hybrid	No	Isolated	Isolated	Already established	Yes	No	
83	M	25	51	Surgical Concomitant	No	Isolated	Isolated	Already established	Yes	No	

the oesophageal pacing study, and 7 patients had just undergone the initial surgical stage at the time of the oesophageal pacing study.

Following invasive left atrial EP studies, 10 patients had achieved LAPW isolation from their index procedure/s and 11 patients had breakthrough lines from their original LAPW isolation procedure requiring further ablation. Out of the 11 patients that needed further ablation, LAPW isolation was subsequently achieved in 10 patients through radiofrequency catheter ablation.

3.2 Oesophageal recording and pacing

In 20 out of 21 patients, findings from the oesophageal catheter study correlated with the invasive EP study. In one patient, we were able to capture at 20mA despite having evidence of LAPW isolation at the subsequent invasive study. On review of this case, we noted that the oesophagus was anatomically positioned close to the right pulmonary veins and this particular zone had a narrow area of isolation between the roof and floor lines. The oesophageal pacing catheter was reintroduced during the invasive study to understand the mismatch in predicted result and actual result of the isolation procedure. When correctly positioned with the central 2 electrodes of the oesophageal pacing catheter behind the narrow-isolated area of the LAPW, oesophageal pacing failed to capture at 20mA (Figure 2).

3.3 Comparison between Oesophageal and Invasive Electrophysiological study

There was one false negative in the study, where it was possible to pace the LAPW despite LAPW isolation. With this in mind, the results from this study gives a negative predictive value of 90.00 % (95% CI of 57.95% to 98.33%). A true negative result is defined as the inability to pace the left atrium in patients with LAPW isolation. The positive predictive value is 100%, where a true positive finding indicates the ability to pace the left atrium in the absence of LAPW isolation. The sensitivity is 91.67% (95% C.I. 61.52% to 99.79%) and specificity is 100% (95% CI of 66.37% to 100%). This analysis has been illustrated in table 2.

Table 2: Sensitivity and specificity analysis of oesophageal pacing catheters in being able to predict LAPWI

True Negative (LA non-capture in the setting of LAPWI)	9
False negative	1
True Positive (LA capture in the setting of electrical reconnection)	11
False positive	0
Sensitivity	91.67%
Specificity	100%

Key
LA – Left Atrium, LAPWI - Left Atrial Posterior Wall isolation

3.4 Complications

No complications were observed in our current patient cohort. No patients complained of residual effects of the oesophageal study.

4. Discussion

The posterior wall of the left atrium is located between the left and right pulmonary veins. In essence, it should be thought of as an extension of PV from an anatomical, embryological and electrophysiological standpoint[8]. Persistent pulmonary vein isolation remains difficult to achieve. Reconnection rates have sometimes been reported to be as high as >70%[9]. This is more so the case in patients with longstanding persistent AF with larger atria, and therefore additional ablative lesions are advocated in such patients[10]. STAR AF 2 trial showed no advantage in the use of additional lesion sets in conjunction to PVI. However, the lesion sets used to achieve left atrial posterior wall isolation were not tested in STAR AF2[11].

Studies to date have provided evidence that LAPW isolation gives additional value to PVI in certain groups of patients with atrial fibrillation [12 - 19]. Kim et al., in their randomized trial of 120 patients with long-standing persistent AF, have shown that AF recurrence rate in one year was significantly lower in those with LAPW isolation compared to PVI alone (16.7% vs. 36.7%)[14]. Other noteworthy randomized studies looking at patients with long standing persistent AF include CASA-AF[15] and CONVERGE[16] trials. The CONVERGE trial compared LAPW isolation to PVI with or without a roof line and also showed that LAPW isolation was more effective than PVI in preventing AF recurrences and reducing symptom burden from AF. However, interpreting the results from such trials are limited by uncertainty over whether the LAPW remains isolated during long term follow up. Reconnection across the wide area circumferential ablation (WACA) lines performed with radiofrequency ablation remains at a minimum of approximately 20% of cases even in the hands of experienced operators using contact-force sensing catheters and guided by Ablation-index (PRAISE Study)[17]. It is likely that reconnection across the roof or floor line occurs at least as common, and if so the clinical benefit from adding LAPW isolation to PVI may have been underestimated.

There are several means to pace the heart temporarily. Transcutaneous pacing offers a quick and non-invasive means to treat severe-symptomatic or haemodynamically unstable bradyarrhythmias. This is achieved by delivering pulses of electricity to the precordium usually through self-adhesive pads. The main disadvantage of transcutaneous pacing is that it can cause painful stimulation of the cutaneous nerves and skeletal muscles[20]. Transvenous pacing offers a durable solution to those who need temporary pacing for longer periods of time. Following venous access (usually via subclavian vein, internal jugular vein or femoral vein), a pacing electrode catheter is placed in the right ventricle with the goal of restoring effective cardiac depolarization. This method however, carries a low probability of developing serious complications such as vascular injuries, septal / right-ventricular free wall perforation, and eventually cardiac tamponade[21].

Transoesophageal pacing is another form of temporary pacing and has the potential to replace invasive pacing in many circumstances[22,23]. It can be a very useful in measuring electrophysiological properties in a non-invasive fashion. Historically, oesophageal pacing was also used for sinus node evaluation, atrio ventricular node conduction delay, and assessment of paroxysmal supra ventricular tachycardia[24]. However, this has been largely replaced by invasive electrophysiological studies. In a pediatric setting, it can be used for emergency pacing[25,26]; but in adults, this is superseded by intravenous temporary pacing wires. More recently, oesophageal catheters have been implicated in ambulatory monitoring due to the superior monitoring of atrial activity in comparison to a 12-lead electrocardiogram[27]. The theoretical adverse effects of oesophageal pacing include dyspepsia, discomfort/ nausea during insertion, and soft tissue injury. There have been no reports of serious / long-term complications in this pacing modality.

In our latest study, we were able to show the effectiveness of oesophageal pacing catheters in confirming or refuting the preservation of LAPW isolation during long term follow-up using a very simple protocol. Findings from the oesophageal study correlated with invasive EP study in 20 out of 21 patients. One patient had a false negative result from oesophageal pacing (no exit block despite LAPW isolation). The sensitivity and specificity for the oesophageal pacing and recording procedure in assessing reconnection from LAPW isolation in the long term is 92% and 100% respectively. These results are promising; however, a larger multicentre study is still required to prove the general applicability of the technique. While an invasive EP procedure remains 'gold standard' in determining LAPW isolation, there are inevitable risks associated with this procedure, such as stroke and cardiac tamponade. Oesophageal pacing and recording offers a safe and quick way of identifying LAPW isolation without the need for general anaesthesia.

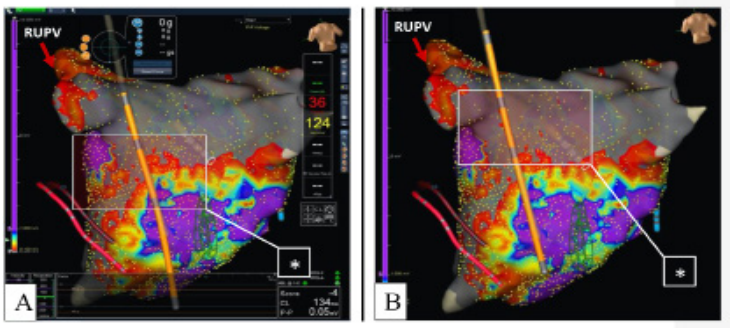

Figure 2: A: Precision map (Abbott Inc., St. Paul, Minnesota, USA) of the left atrial chamber with the 2 middle pacing electrodes (Asterix) of the oesophageal catheter advanced too far, resulting in capture of the atrium with pacing at 20mA. B: Oesophageal pacing is performed through the middle electrodes of the catheter with the catheter positioned correctly with no capture at 20mA.

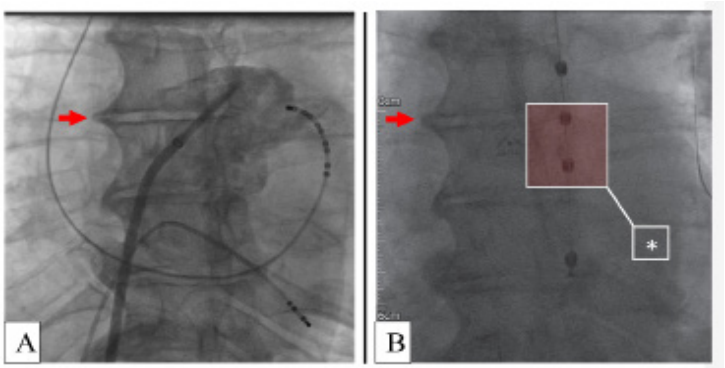

Figure 3: A: Antero-posterior (AP) projection illustrating the roof of the left atrium in line with the sharp osteophyte on the mid thoracic intervertebral disc (Arrow) in the index ablation procedure. B – Roof level osteophyte marker used for correct positioning of middle 2 electrodes (Asterix) on oesophageal pacing catheter to verify electrical isolation during long term follow-up

It could be argued that operators performing LAPW isolation should assess the long-term efficacy of the procedures they perform using such a technique. This could then feedback beneficially in achieving optimal outcomes from their work and demonstrate that an appropriate percentage of durable LAPW isolation is being achieved by the operator compared to their peers. This would apply both to catheter and intra-operative surgical AF ablation. It could also be of importance in judging the efficacy of different modalities in achieving durable isolation lines. This could be of especial importance in understanding the results of clinical trials where head-to-head comparisons of such techniques have been made, such as the CASA-AF study[15]. Oesophageal pacing could be of particular use in patients who need follow-up assessment after an apparently successful LAPW isolation ablation procedure due to AF recurrence. Knowing that the previously established LAPW isolation is intact or has reconnected may alter the methodological and mapping approach to any subsequent ablation procedures.

4.1 Tips to improve diagnostic accuracy of oesophageal pacing catheter

The optimal position of the two central electrodes in the oesophageal catheter used for pacing and recording could be documented for future reference during the initial LAPW isolation procedure (if fluoroscopy is used at the time of the initial procedure). The oesophageal catheter can also be positioned in relationship to the inter-vertebral discs and vertebral osteophytes seen fluoroscopically to be in the area isolated at the index LAPWI procedure (Figure 3). In patients who have undergone prior coronary artery bypass grafting and a catheter LAPW isolation procedure, the location of the isolation zone could be documented with reference to sternotomy wires, left atrial appendage occlusion clips or bypass graft clips seen on fluoroscopy at the time of the catheter ablation. Following concomitant or standalone surgical AF ablation, knowledge of the type of ablation device used and the cardiac silhouette may help guide correct placement of the oesophageal catheter. Left atrial appendage clips, if present, are particularly helpful in indicating the level of the area of isolation. It is worth noting if the course of oesophagus is unusually far out of line with the left atrium, as may occur where procedures such as lobectomy have been performed previously, further assessment with oesophageal catheters may not be advocated in such patients. Finally, we feel that the oesophageal pacing study should be contra-indicated in patients with intrinsic oesophageal diseases such as Barrett's oesophagus or strictures, in order to avoid the chances of false positives.

5. Limitations

This is a small, single centre, prospective trial. Larger multicentre studies are needed to confirm the positive and negative predictive values of oesophageal catheter studies in multiple operators' hands. This technique was found to be inaccurate in one patient where the oesophageal position coincided with a particularly narrow distance between the roof and floor lines. In our previous study[7], one patient had Barrett's oesophagus which also impeded the diagnostic ability of the oesophageal pacing catheter, possibly as a result of oesophageal scarring.

In catheter ablation, LAPW isolation can be achieved by a single circle[28] enclosing the four pulmonary veins and the LAPW, or by wide area circumferential ablation (WACA) of the pulmonary veins, following which the roof and floor lines are added[14]. The oesophageal catheter is accurate in identifying electrical isolation in areas between the roof line, floor line, and the posterior aspect of the WACA. However, this technique is not able to identify reconnection across the anterior aspects of the PVI WACA lines. The oesophageal pacing technique is not suitable for assessing reconnection at the cavo tricuspid isthmus and mitral isthmus lines.

6. Conclusion

We have demonstrated in a prospective fashion that, in patients who have previously undergone a LAPW isolation procedure, oesophageal pacing catheters can successfully identify reconnection across LAPW ablation lines or, conversely, confirm preserved LAPW isolation. This technique can negate the need for an invasive EP study, which is more expensive, requires hospital admission, and is less safe.

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The Mitral Inflow E/A Ratio Before The Procedure May Predict Late Recurrence in Patients With Atrial Fibrillation Undergoing Cryoballoon Ablation

Taner Ulus[1], Ahmet Serdar Yilmaz[1], Emre Şener[1], Halit Emre Yalvaç[1], Ezgi Çamlı[1], Fatih Enes Durmaz[1], Yüksel Çavuşoğlu[1]

[1]Department of Cardiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

Abstract

Aim: High recurrence rates after catheter ablation for atrial fibrillation (AF) is a major problem. Many predictors for recurrence after AF ablation have been described. Left ventricular diastolic dysfunction (LV DD) is directly related to most of such predictors. Some studies investigating the relationship between LV DD and late recurrence after AF ablation have found conflicting results. The mitral inflow E/A ratio is a simple and practical method commonly used to evaluate LV DD. We aimed to determine whether the E/A ratio before the procedure was predictive for late recurrence in patients with AF undergoing cryoballoon ablation.

Methods: A total of 99 patients undergoing AF ablation for the first time using second-generation cryoballoon were included. Only patients with paroxysmal AF and sinus rhythm the day before the procedure, and pre-procedural pro-B natriuretic peptide levels within normal limits were included. The patients who developed recurrence and those who did not were compared in terms of basal characteristics and procedural features. Any atrial tachyarrhythmia episode longer than 30 s after the blanking period was defined as late recurrence.

Results: The patients [age: 58 (50-62) years, 53.5% female] were followed up for a median of 45.0 (15.0-63.0) months and late recurrence developed in 25 (25.2%) patients. The E/A ratio was lower in patients with late recurrence than in those without it [0.5 (0.4-1.2) vs 1.4 (0.6-1.7), respectively, p=0.001]. A multivariate analysis showed that female gender (HR: 4.44, 95%CI: 1.31-15.05, p=0.017), early recurrence (HR: 7.35, 95% CI: 2.28-23.71, p=0.001), and E/A ratio (HR: 0.28, 95%CI: 0.11-0.68, p=0.005) were independent predictors for late recurrence.

Conclusions: Female gender, early recurrence, and E/A ratio are independent predictors of late recurrence in patients with AF undergoing cryoballoon ablation. Measuring the E/A ratio in patients with sinus rhythm before AF ablation may help to predict future recurrences.

Introduction

Antral pulmonary vein isolation (PVI) is a mainstay for catheter ablation of atrial fibrillation (AF) [1]. However, high recurrence rates after catheter ablation for AF are a major problem. Previous studies have identified some predictors associated with recurrence such as female gender, obesity, AF duration, early recurrence, elevated CHA_2DS_2-Vasc score, and left atrial (LA) diameter [2-6]. The left ventricular (LV) diastolic dysfunction (DD) is related to most of the above predictors, and it has been shown that DD increases the risk of AF development [7].

Some investigators also investigated whether a relationship between DD and long-term recurrence after catheter ablation for AF, but they found conflicting results. Some of them found the relationship between DD and late recurrence[8] while others did not show such association [9]. These studies had relatively short follow-up duration and they did not have a standard ablation protocol. Some patients were taken to PVI only, while additional linear lesions were added in localizations such as the LA roof, LA isthmus, and cavotricuspid isthmus in others [8,9]. These issues are likely to have affected the results of such studies. The mitral inflow E/A ratio is a simple and practical indicator of DD [9]. Cryoballoon (CB) is a widely used option for catheter ablation of AF, and it has similar efficacy and safety outcomes compared to radiofrequency ablation [1]. In this study, we aimed to investigate whether the mitral inflow E/A ratio before the procedure was predictive for late recurrence in patients with AF undergoing pulmonary vein isolation (PVI) with cryoballoon.

Key Words

Atrial Fibrillation, Cryoballoon Ablation, Recurrence.

Corresponding Author
Taner Ulus,
Department of Cardiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey. Email Id: tanerulusbuca@gmail.com

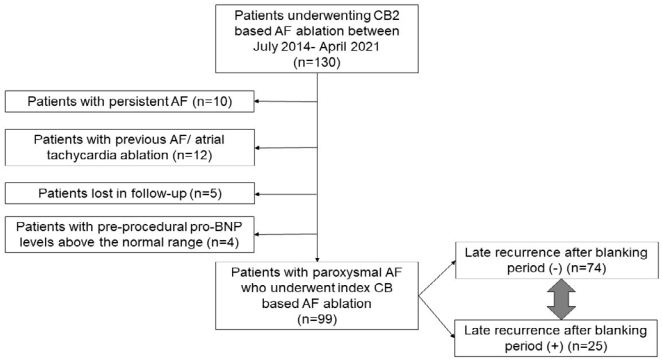

Figure 1: Flow chart of the study. AF: Atrial fibrillation, pro-BNP: pro-B natriuretic peptide, CB: Cryoballoon, CB2: Second-generation cryoballoon.

Methods

Study population

Among 130 patients undergoing PVI for AF using second-generation cryoballoon (CB2) at Eskisehir Osmangazi University hospital between July 2014 and April 2021, a total of 99 patients with paroxysmal AF undergoing ablation for the first time were included in the study. To measure the mitral inflow E/A ratio, only patients with paroxysmal AF and sinus rhythm the day before the procedure were included. Paroxysmal AF was defined by current guidelines [10]. In addition, pre-procedural pro-B natriuretic peptide (pro-BNP) levels of all patients included in the study were within normal limits. Patients with moderate/ severe valve disease, recent decompensated heart failure (HF) attack, pseudonormal or restrictive LV filling pattern, acute myocardial ischemia, cardiac surgery within 3 months before ablation, LA thrombus, posteroanterior LA diameter >45 mm, active hyperthyroidism, pregnancy or serious comorbidities were excluded. Figure 1 shows the flow chart of the study protocol.

Detailed medical history including cardiovascular diseases, cardiovascular risk factors, and medications was recorded. The CHA_2DS_2-Vasc score was calculated and the duration of AF before ablation was recorded. Pro-BNP levels were studied one day before catheter ablation. The study was performed according to the Declaration of Helsinki principles and the local ethics committee approved the study.

Pre-procedural work-up

Transthoracic echocardiography was done to assess LV ejection fraction (LVEF), valvular pathologies, intracavitary dimensions, and LV mass index. To evaluate LV diastolic functions, the sample volume was positioned at the mitral leaflet tips in the apical four-chamber view. Transmitral early and late diastolic peak flow velocities (E wave and A wave, respectively), deceleration time of E wave (DT), and isovolumic relaxation time (IVRT) were recorded using pulse wave Doppler. The E/A ratio was calculated. All measurements were made in sinus rhythm the day before the procedure in accordance with the recommendations [11,12]. All patients underwent pre-procedural multidetector computed tomography to evaluate LA and PV anatomy. If the patients were taking warfarin and the international normalized ratio was <2.5 before the procedure, ablation was performed without discontinuing warfarin. New oral anticoagulants were interrupted 24 h before the procedure. Antiarrhythmic drugs were ceased at least 5 days before the procedure. Transesophageal echocardiography was performed within 24 hours before catheter ablation to exclude the presence of LA thrombus in all patients.

Procedural Aspects

All procedures were performed conscious sedation with dexmedetomidine infusion or midazolam and fentanyl boluses. Details of the procedure have been described previously [13]. One arterial and

Table 1: Baseline characteristics and procedural features of all patients, those with and without late recurrence

	Total (n=99)	Late recurrence (-) (n=74)	Late recurrence (+) (n=25)	P value
Age (years)	58.0 (50.0 – 62.0)	58.0 (47.7 - 62.0)	58.0 (54.0 - 66.0)	0.329
Female gender (n,%)	53 (53.5)	35 (47.3)	18 (72.0)	0.032
Body mass index (kg/m²)	27.7 (25.7 - 29.9)	27.2 (25.7 - 29.5)	28.6 (27.3 – 31.0)	0.149
Hypertension (n,%)	53 (53.5)	35 (47.3)	18 (72.0)	0.032
Diabetes mellitus (n,%)	23 (23.2)	15 (20.3)	8 (32.0)	0.230
CAD (n,%)	9 (9.1)	5 (6.8)	4 (16)	0.224
HF with reduced EF (n,%)	2 (2.0)	1 (1.4)	1 (4.0)	0.443
Current smoking (n,%)	7 (7.1)	6 (8.1)	1 (4.0)	0.675
Alcohol intake (n,%)	2 (2.0)	1 (1.4)	1 (4.0)	0.443
CHA_2DS_2-VASc score	1.0 (1.0 – 2.0)	1.0 (0 - 2.0)	2.0 (1.0 - 3.0)	0.013
AF duration (months)	23.6 ± 8.9	22.3 ± 8.3	27.8 ± 9.4	0.007
Beta blocker (n,%)	56 (56.6)	42 (56.8)	14 (56.0)	0.947
RAAS blocker (n,%)	45 (45.5)	30 (40.5)	15 (60.0)	0.091
Statin (n,%)	10 (10.1)	7 (9.5)	3 (12.0)	0.710
Propafenone (n,%)	26 (26.3)	19 (25.7)	7 (28.0)	0.819
Amiodarone (n,%)	15 (15.2)	9 (12.2)	6 (24.0)	0.197
Hemoglobin (g/dl)	13.6 (12.6 – 14.6)	13.6 (12.6-14.7)	13.2 (11.9-14.2)	0.085
eGFR (ml/dk/1.73 m²)	88.9 ± 19.3	90.2 ± 19.6	85.3 ± 18.4	0.272
pro-BNP (pg/ml)	286.0 (186.0 - 366.0)	281.0 (185.0 - 363.7)	295.0 (185.5 - 417.5)	0.635
Left atrial diameter (mm)	37.8 ± 3.9	37.5 ± 3.8	38.6 ± 4.0	0.231
LV EF (%)	60.0 (60.0-65.0)	60.0 (60.0-65.0)	60.0 (60.0-65.0)	0.861
LV mass index (g/m2)	84.0 (71.0 - 94.0)	82.0 (70.0 - 92.2)	85.0 (72.0 - 104.5)	0.176
E/A ratio	1.2 (0.5 – 1.6)	1.4 (0.6-1.7)	0.5 (0.4-1.2)	0.001
DT (msec)	190.0 (170.0 – 230.0)	180.0 (170.0 – 230.0)	230.0 (170.0 - 242.5)	0.079
IVRT (msec)	90.0 (75.0 – 110.0)	85.0 (70.0 – 110.0)	103.0 (90.0 – 111.5)	0.016
Early recurrence (n,%)	8 (8.1)	3 (4.1)	5 (20.0)	0.023
Common trunk PV (n,%)	32 (32.3)	21 (28.4)	11 (44.0)	0.149
Accessory PV (n,%)	12 (12.1)	9 (12.2)	3 (12.0)	1.000
Procedure time (min)	80.8 ± 18.5	79.2 ± 18.4	85.5 ± 18.2	0.143
Fluoroscopy time (min)	21.3 ± 6.5	20.7 ± 6.7	23.0 ± 5.6	0.120
Follow-up (months)	45.0 (15.0 – 63.0)	42.5 (12.7 – 62.2)	52.0 (22.0 – 65.5)	0.373

AF: Atrial fibrillation, BNP: B natriuretic peptide, CAD: Coronary artery disease, eGFR: Estimated glomerular filtration rate, DT: Deceleration time, EF: Ejection fraction, HF: Heart failure, IVRT: Isovolumic relaxation time, LV: Left ventricle, PV: Pulmonary vein, RAAS: Renin-angiotensin-aldosteron system.

Table 2: Cox regression analysis to identify predictors of late recurrence after catheter ablation for AF

	Univariate			Multivariate		
	Beta	HR (95% CI)	P value	Beta	HR (95% CI)	P value
Female gender	0.917	2.50 (1.04-5.99)	0.040	1.491	4.44 (1.31-15.05)	0.017
Hypertension	0.886	2.42 (1.01-5.81)	0.047	0.895	2.44 (0.77-7.77)	0.129
CHA_2DS_2-VASc score	0.409	1.50 (1.13-1.99)	0.004	-0.16	0.85 (0.55-1.30)	0.459
AF duration	0.052	1.05 (1.01-1.09)	0.012	0.036	1.03 (0.97-1.10)	0.287
Early recurrence	1.418	4.12 (1.54-11.02)	0.005	1.995	7.35 (2.28-23.71)	0.001
E/A ratio	-1.277	0.27 (0.12-0.62)	0.002	-1.26	0.28 (0.11-0.68)	0.005

AF: Atrial fibrillation, HR: Hazard ratio.

two venous sheaths were inserted from the right inguinal region. A 6F steerable decapolar catheter (St. Jude MedicalTM) and a 6F pigtail catheter (AlvisionTM) were positioned in the coronary sinus and aortic root, respectively. Single transseptal (TS) puncture was performed by modified Brockenbrough technique using a TS needle (BRK-1TM, St. Jude Medical) and an 8F TS sheath was placed in the LA. Then, a bolus of 100 U/kg unfractionated heparin bolus was administered immediately and the activated clotting time was maintained for 300-350 s with repeated bolus administrations. The TS sheath was exchanged with a 15F steerable sheath (FlexCath Advance, Medtronic Inc., Minneapolis, MN, USA) over the wire. A 28-mm CB2 catheter (Arctic Front AdvanceTM, Medtronic) was used for PVI. A circular mapping catheter (Achieve™, Medtronic, Minneapolis, MN, USA) was inserted through the lumen of the CB catheter to record PV potentials and to maneuver the balloon. After confirming complete occlusion of the PV by application of 50% diluted contrast agent, a freezing cycle of 180-240 s was applied for each PV. An additional bonus freeze of 120 s was performed if PVI was not obtained within 60 s or early PV reconnection occurred [14]. The right phrenic nerve was paced with a 1500/2000 ms cycle and a 12/15-mA output while freezing the right-sided PVs to avoid phrenic nerve paralysis. The phrenic nerve stimulation was monitored by intermittent fluoroscopy and direct palpation of the right hemi-diaphragmatic contraction. Acute procedural success was defined as the disappearance or dissociation of all visible PV potentials. Entrance and exit blocks were tested by pacing through the coronary sinus and circular catheter PV, respectively.

Follow-up

Transthoracic echocardiography was repeated immediately after the procedure. If no pericardial effusion was observed on echocardiography, oral anticoagulation was restarted on the evening of the procedure and continued for at least 3 months. Antiarrhythmic drugs were also continued for at least 3 months after the procedure. Routine follow-up visits were programmed at 1, 3, 6, and 12 months after ablation and every one year thereafter. If the patients had any complaints compatible with atrial tachyarrhythmia (ATa) or procedure-related complications, they were evaluated earlier. Follow-up visits are composed of the evaluation of arrhythmia-related complaints, physical examination, 12-lead electrocardiogram (ECG), and 24-h Holter ECG monitoring. Any ATa episode (AF, atrial flutter or atrial tachycardia) longer than 30 s was defined as recurrence. The first 3-month period after ablation was considered as the blanking period. Recurrences within and after the blanking period were defined as 'early recurrence' and 'late recurrence', respectively [13].

Statistical analysis

A one-sample Shapiro-Wilk test was used to determine whether continuous variables were normally distributed. Normally and skewed distributed continuous variables were presented as mean±standard deviation and the median (25th, 75th percentiles), respectively, and they were compared between the groups using the Student's t-test and Mann-Whitney U test, respectively. Categorical variables were presented as frequencies and percentages and were compared using the chi-square test. The Cox proportional hazards model was used to find the predictors of long-term ATa recurrence. Variables with a P-value of <0.05 in univariate analysis were included in multivariate analysis. ATa-free survival was estimated by the Kaplan-Meier method and compared by log-rank test. An optimal cut-off value of the mitral inflow E/A ratio to predict the long-term recurrence was determined by the receiver-operating characteristic curve analysis. Statistical analyses were performed using statistical software (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp., USA), and a two-tailed P-value of <0.05 was considered statistically significant.

Results

All patients underwent only PVI using CB2. No additional ablation was performed in the patients. The age of the patients was 58 (60-62) years and 53 (53.5%) were female. Fifty-three patients (53.5%) were hypertensive and 23 (23.2%) had diabetes mellitus. The median CHA_2DS_2-Vasc score was 1.0 (1.0-2.0). The baseline characteristics of the study population were summarized in Table 1.

Procedural findings and complications

Total procedural and fluoroscopic time were 80.8±18.5 min and 21.3±6.5 min, respectively. Common trunk PV was observed in 32 patients (32.0%) (30 left common and 2 right common) (Table 1).

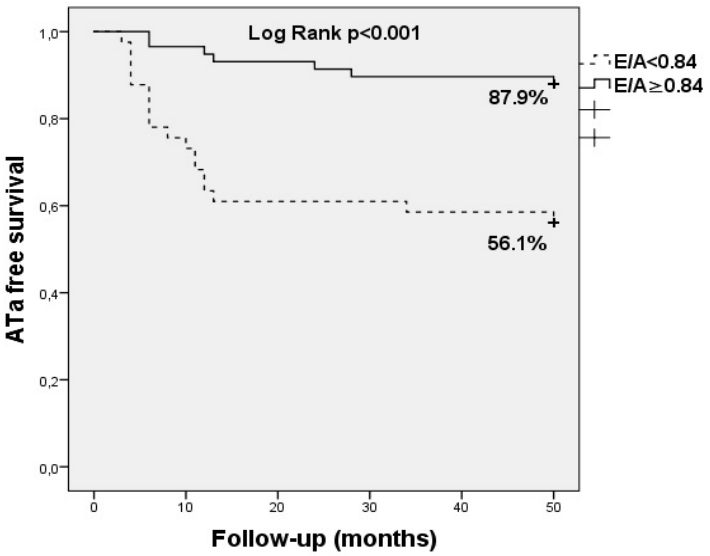

Figure 2: Kaplan-Meier survival curve showing the comparison of ATa free survival rates according to cut-off mitral inflow E/A ratio of 0.84 after AF ablation. AF: Atrial fibrillation, ATa: Atrial tachyarrhythmia.

A total of 394 PV including common trunks were detected, of which 389 (98.7%) were successfully isolated. Freezing numbers were 2.0 (1.0 – 3.0) for the left superior PV, 2.0 (1.0 – 2.0) for the left inferior PV, 2.0 (1.0 – 2.0) for the right superior PV, 1.0 (1.0 – 2.0) for the right inferior PV, 3.0 (2.0 – 3.0) for the left common trunk, 1.5 (0.7 – 2.0) for the right common trunk.

As procedural complications, cardiac tamponade requiring pericardiocentesis was seen in 2 patients; while diaphragm paralysis occurred in 1 patient during cryoablation at the right superior PV. Groin complications were observed in 2 patients; the patient with femoral hematoma was followed up medically and the other with femoral arteriovenous fistula underwent surgical repair. Atrio-esophageal fistula, PV stenosis, cardiac embolism, or procedure-related deaths were not observed in any of the patients.

Follow-up data

The median follow-up duration was 45.0 (15.0-63.0) months. Early recurrence was developed in 8 (8.1%) patients. Of these, 3 spontaneously reverted to sinus rhythm, 4 achieved sinus rhythm with pharmacological cardioversion, and 1 with electrical cardioversion. Late ATa recurrence was observed in 25 (25.3%) patients in the long-term follow-up. Of these, 17 were followed-up medically, RF ablation was performed in 7 patients, and 1 underwent second cryoablation with CB2. Among 8 patients who underwent a second procedure, typical atrial flutter was observed in 4 patients, PV reconnection was found in 2 patients, and atrial tachycardia (one roof dependent and one right atrial tachycardia) was detected in 2 patients.

Predictors of long-term recurrence after cryoballoon ablation

When the patients were compared according to the development of ATa recurrence after the blanking period, female gender (72.0% vs 47.3%), hypertension (72.0% vs 47.3%), and the frequency of early recurrence (20.0% vs 4.1%) were found to be higher in patients who develop ATa recurrence after blanking period than in those who did not develop (p =0.032, 0.032 and 0.023, respectively). The CHA2DS2-Vasc score was higher [2.0 (1.0-3.0) vs 1.0 (0-2.0)], AF duration was longer (27.8 ± 9.4 vs 22.3 ± 8.3 months), the mitral inflow E/A ratio was lower [0.5 (0.4-1.2) vs 1.4 (0.6-1.7)], and IVRT was longer [103.0 (90.0-111.5) vs 85.0 (70.0-110.0) ms] in patients with long-term recurrence than in those without it (p=0.013, 0.007, 0.001 and 0.016, respectively). The patients' baseline characteristics and procedural findings according to the presence of late ATa recurrence are given in Table 1.

The total procedure time, fluoroscopy time, and PV anatomic features were similar between the groups (p>0.05 for all) (Table 1). There was no significant difference between the groups regarding freezing numbers and freezing durations for each PV (p>0.05).

The results of Cox regression analysis to determine predictors of long-term ATa recurrence are given in Table 2. In the univariate analysis, female gender (HR: 2.50, 95% CI: 1.04-5.99, p=0.04), AF duration (HR: 1.05, 95% CI: 1.01-1.09, p=0.012), hypertension (HR: 2.42, 95% CI: 1.01-5.81, p=0.047), early recurrence (HR: 4.12, 95% CI: 1.54-11.02, p=0.005), the CHA_2DS_2-Vasc score (HR: 1.50, 95% CI: 1.13-1.99, p=0.004) and the mitral inflow E/A ratio (HR: 0.27, 95% CI: 0.12-0.62, p=0.002) were significantly associated with long-term recurrence. The multivariate analysis showed that female gender (HR: 4.44, 95% CI: 1.31-15.05, p=0.017), early recurrence (HR:7.35, 95 % CI: 2.28-23.71, p=0.001) and E/A ratio (HR: 0.28, 95 % CI: 0.11-0.68, p=0.005) were independent predictors of late ATa recurrence.

Receiver operating characteristic analysis showed that the optimal cut-off level of the E/A ratio was 0.84 (Sensitivity: 72%, specificity: 70%). Kaplan-Meier curves comparing ATa free survival according to cutoff E/A ratio of 0.84 after AF ablation are presented in Figure 2. Any ATa free survival rate was significantly lower in patients with E/A ratio <0.84 than in those with ≥0.84 (56.1% vs 87.9%, log-rank p<0.001).

Discussion

In this study, we investigated whether the mitral inflow E/A ratio was a predictor of ATa recurrence in patients with paroxysmal AF who underwent PVI using CB2 during median 45 months follow-up. Our main findings were: 1) Clinical success without ATa recurrence was 74.7% at long-term follow-up. 2) Female gender, hypertension, the median CHA_2DS_2-Vasc score, AF duration, the presence of early recurrence, and E/A ratio were significantly associated with late ATa recurrence after the blanking period. 3) Female gender, early recurrence, and E/A ratio were independent predictors of late recurrence.

Diastolic dysfunction is a condition that develops as a result of abnormalities in LV relaxation and compliance during diastole [12]. As a result, the LA pressure increases to ensure adequate filling of the LV and atrial wall tension increases. Enlargement of the LA and PVs due to increased wall stretch may induce ectopic firing from PVs. Another mechanism is stretch-induced atrial remodeling, which consists of changes such as Ca^{+2} channel downregulation, myocytolysis, and atrial fibrosis. All of the factors mentioned above may contribute to the development of AF in DD [12,15-17].

The transmitral flow velocity measurements including E wave, A wave, E/A ratio, DT, and IVRT are practical and useful tools to assess diastolic functions. Impaired LV relaxation with normal LA and LV pressures is an early form of DD. At this stage, the E/A ratio is <1, DT is >240 ms, and IVRT is >110 ms [12]. In our study, we used the E/A ratio to evaluate LV DD. We did not include patients with recent decompensated HF attacks or pre-procedural pro-BNP levels above the normal range. Again, we did not include patients with the pseudonormal DD pattern or restrictive type DD by excluding patients with pre-procedural pro-BNP levels above the normal range or DT<160 and IVRT<60 msec [12,18]. For this reason, we think that the low E/A ratio in our study reflects the early stage of DD.

We showed that the E/A ratio before the procedure was an independent predictor of long-term ATa recurrence after AF ablation. Some studies have investigated the relationship between DD and late recurrence and they found different results. Kosiuk et al. showed that preprocedural E/A ratio was associated with early recurrence after AF ablation, but not with late recurrence [9]. Kim et al and Li et al found that DD, as measured by the E/e' ratio was an independent predictor of late recurrence [19,20]. However, a standard ablation method was not

used in any of these studies. Some patients underwent PVI, while others underwent linear ablation of the LA or cavotricuspid isthmus. The lack of a standard ablation procedure is likely to have affected the results of such studies. However, we performed a standard procedure in all patients, PVI with CB2. In addition, the follow-up period of the patients was relatively longer than the others. In patients who will undergo AF ablation, the E/A ratio can be measured before the procedure to predict long-term recurrences. Closer follow-up against the possibility of recurrence and more strict control of modifiable risk factors to reduce recurrence may be considered in patients with a low E/A ratio.

The CB2 has been shown to have favorable clinical outcomes compared to first-generation one, probably due to extensive wide-area circumferential antral lesion creation [13,21]. We also found that female gender and early recurrence were independent predictors of long-term recurrence in the study. Our results were compatible with previous studies [2,4]. The frequency of hypertension, the median CHA_2DS_2-Vasc score, and AF duration were significantly higher in patients with late recurrence, but they were not independent predictors. The LA diameter is similar between the groups in our study. The exclusion of patients with persistent AF and LA diameter >45 mm, and the low number of patients may have been responsible for this result.

Limitations

This study had some limitations. First, the study was single-center and the number of patients was small. Second, the study was of a retrospective design, and E/e'was not included in the analyses because mitral annular diastolic peak velocities (e') were not recorded in most patients. Third, regular follow-up was based on clinical examination, ECG, and 24-h Holter monitoring, and some asymptomatic nonsustained ATa episodes may have been overlooked. Fourth, our study results cannot be applied to all patients undergoing AF ablation. However, our results suggest that a low E/A ratio may be an independent predictor for late recurrence after AF ablation in patients with DD in the early stage. Fifth, we did not define whether atrial substrate existed with methods such as magnetic resonance imaging in our patients. Sixth, we did not include LA volume measurements in the analyses. Finally, the study had no follow-up data on diastolic functions after AF ablation.

Conclusion

The mitral inflow E/A ratio, female gender, and early recurrence are independent predictors of late ATa recurrence in patients with AF undergoing PVI with cryoballoon. Measuring the E/A ratio in patients with sinus rhythm before AF ablation may help to identify patients who may develop recurrence in the future. In this regard, there is a need for further studies with a larger number of patients, including other parameters showing diastolic functions, and in which the standard ablation method is applied in all patients.

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Superior vena CAVA Isolation by Cryoballoon in Addition to Pulmonary Vein Isolation in Atrial Fibrillation Ablation Patients. A Randomized Trial. CAVAC AF Trial. Study Rationale and Design

Castro-Urda V[1], Segura-Dominguez M[1], Jiménez-Sánchez D[1], Vela-Martín P[1], García-Izquierdo E[1], Aguilera-Agudo C[1], Veloza-Urrea D[1], Morillo-Diaz J[1], Pham-Trung C[1], Hernández-Terciado F[1], De Castro Campos D[1], Chichakli Cela M[1], Mingo-Santos S[2], García Rodriguez D[1], Toquero-Ramos J[1] and Fernández-Lozano I[1]

[1]Electrophysiology Unit. Cardiology Service. Hospital Puerta de Hierro. Majadahonda (Madrid). Spain.
[2]Cardiac Imaging Unit. Cardiology Service. Hospital Puerta de Hierro. Majadahonda (Madrid). Spain.

Abstract

Background: Superior vena cava (SVC) has been considered a specific trigger in atrial fibrillation (AF) development. Cryoballoon SVC isolation seems feasible and safe, and has never been compared in addition to pulmonary vein isolation (PVI) to PVI alone.

Methods and results: A unicenter randomized trial, comparing two ablation procedures is proposed. Cryoballoon SVC isolation in addition to PVI is compared to PVI alone in paroxysmal or non-longstanding persistent AF patients. Patients from 18-80 years old are included. Patients are excluded if there is a previous AF ablation procedure, transvenous pacemaker or defibrillator (ICD) implanted, severe mitral valve disease, left atrium (LA) anteroposterior diameter > 55mm or LA indexed volume > 48ml/m² in an echocardiogram performed in the last year, left ventricular ejection fraction (LVEF) < 35%, hypertrophic or restrictive cardiomyopathy.

All patients are provided an Alivecor® Kardia Mobile device to record an electrocardiogram (ECG) every day and in case of clinical symptoms to monitor recurrences.

The primary efficacy end point is defined as any AF/atrial flutter/atrial tachycardia recurrence, with a minimal duration of 30 seconds, registered with surface ECG, Holter ECG or Kardia mobile registry during a 12 months follow up period.

Conclusion: Our study will provide data about the efficacy of SVC isolation in addition to PVI compared to PVI alone in a randomized way, in paroxysmal and non long standing persistent AF patients.

Introduction

Pulmonary vein isolation (PVI) is the most important aspect of atrial fibrillation (AF) ablation procedure. Ectopic beats originating in PV can promote AF episodes.[1,2]. Different types of energy are used in AF ablation procedures, where radiofrequency and cryoablation predominate. Both techniques have been considered equivalent regarding efficacy and safety, although procedure time and technical requirements are different[3,4]. In spite of technical improvements, experience and better tools during recent years, AF ablation success rate still is suboptimal, especially regarding persistent AF[5].

Key Words

Superior vena cava isolation, Pulmonary vein isolation, Cryoballoon ablation, Atrial fibrillation

Corresponding Author
Víctor Castro Urda,
Manuel de Falla, 1. 28232. Majadahonda (Madrid). SPAIN

Other ablation targets have been proposed in addition to PVI, like left atrial lines, scar homogeneization, rotors, vein of marshall ablation, appendage isolation or extrapulmonary foci[6,7]. In general, ablation of these targets have failed in achieving greater success rate in AF ablation procedures.

Superior vena cava (SVC) has been considered a specific trigger in AF development and it is implicated in about 30% of extrapulmonary foci according to different studies [8,9,10]. It has also been involved in the maintenance and as a substrate in AF episodes[11]. SVC isolation has been considered a different target in AF ablation procedures in order to improve success rates. At present, all the available scientific evidence regarding SVC isolation refers to radiofrequency ablation procedures. Initially, only if it was demonstrated that it behaved as an AF trigger, SVC was isolated. Later on, empirical SVC isolation has been proposed in addition to PVI in AF ablation procedures. Three randomized studies and two meta analysis suggest that SVC empirical isolation in addition to PVI, confer some benefit in AF ablation[12,13,14,15,16]. This benefit seems

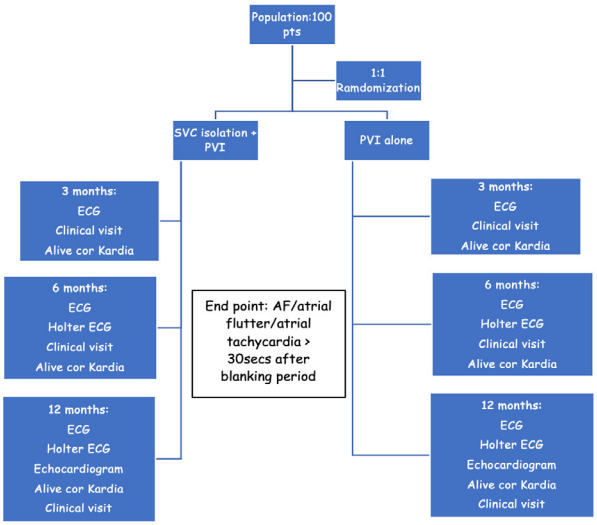

Figure 1: **Flowchart of the trial**

to be obtained only in paroxysmal AF and not in persistent forms. No significant differences were found regarding procedures times, fluoroscopy time and complications.

SVC isolation using Cryoballoon is feasible, according to a recent study, in which a third generation balloon was used. 30 patients were included, achieving a 89% isolation success rate and one transient phrenic paralysis was reported[17].

However, as far as we know, the evidence regarding empirical SVC isolation using cryoballoon in addition to PVI compared to PVI procedure is lacking.

Methods

This is a unicenter randomized trial, comparing the rhythm control effectiveness of 2 ablation procedures: Cryoablation PVI alone or combined to SVC isolation in paroxysmal or persistent AF patients.

The trial was approved by the institutional review boards of the center. All patients provide written informed consent.

Study Population

Patients are eligible if they are between 18-80 years old and have paroxysmal or short duration persistent (less than 1 year) AF and are scheduled for an Cryoballoon AF ablation procedure.

Exclusion criteria are shown in table.

Randomization

Patients are randomly assigned in a 1:1 ratio to either PVI alone or PVI associated to SVC isolation. Randomization is performed using the method of permuted block randomization. The randomization outcome is communicated to the operator. Patients are blinded to randomization outcome, as are the investigators evaluating adverse events and electrocardiographic data. All investigators are blinded to interim analyses.

Study size and duration

100 patients are planned to be included, randomized in a 1:1 ratio. Follow up duration is 12 months. 47 patients are necessary in each branch assuming an alfa error of 5% and statistic power of 80%, to obtain a hazard ratio of 0:54 (data obtained from previous RF meta analysis data)[15]. 6 patients will be included in addition, in case of loss of follow up and to increase statistic power of the study. (Figure)

Patients follow up schedule

After ablation procedure three clinical visits are scheduled.

3 months (first visit after ablation). Clinical visit and electrocardiogram (ECG).

6 months. Clinical visit, ECG and 24h Holter recording.

12 months (final visit). Clinical visit, ECG, 24 h Holter recording and echocardiogram.

Unscheduled visits can be performed during follow up, in case of recurrences of symptoms to modify pharmacologic treatment or to schedule redo procedures. (Figure)

All patients are provided an Alivecor® Kardia Mobile device to record an electrocardiogram everyday, and in case of clinical symptoms. All tracings are downloaded in a smartphone and forwarded to an email address that is check in a daily basis by a trained nurse and three electrophysiologists as backup. (MSD, VCU, DJS, EGI). A good monitoring adherence is defined by a threshold of ≥ 80% monitored days.

Patients will be contacted in case of absence of tracing sending to increase compliance rate.

Table 1: **Study exclusion criteria.**

Exclusion criteria
Age < 18 or > 80 years.
Previous AF ablation procedure.
Pregnancy or probability of it.
Life expectancy < 1 year.
Unavailability to understand or consent to participate in the study.
Reversible AF causes suspected.
Transvenous Pacemaker or ICD previously implanted
Permanent AF or long persistent duration (> 1 year).
Severe mitral valve disease.
Left atrium (LA) anteroposterior diameter > 55mm or LA indexed volume > 48ml/m2 in an echocardiogram performed in the last year.
Left ventricular ejection fraction (LVEF) < 35%.
Hypertrophic or Restrictive cardiomyopathy.
Contraindication to the use of antiarrhythmic drugs.
Left appendage thrombus presence in transesophageal echocardiogram at the moment of the procedure.
Any contraindication to anticoagulant therapy.
No "smartphone" available.
To be participating in another clinical trial.

Study end points

The primary efficacy end point is defined as any AF/atrial flutter/atrial tachycardia recurrence, with a minimal duration of 30 seconds, registered with surface ECG, Holter ECG or Alivecor® Kardia mobile registry during a 12 months follow up period. All the recurrences in the first three months after ablation are considered in the blanking period and are not considered an end point.

The primary safety endpoint is the presence of any procedure related complications during follow up specially phrenic nerve paralysis and sinus node disfunction.

The secondary end points are atrial fibrillation burden (time in atrial fibrillation divided by monitoring time), total mortality, cardiovascular admission rate, stroke, pacemaker implantation rate, AAD necessity after three months, electrical cardioversion, redo procedures, left atrium remodeling (change in left atrial diameter and indexed volume), left ventricular ejection fraction after 12 months follow up, early recurrence of atrial arrhythmias (ERAF) defined as those occurring during the blanking period after ablation, % monitoring adherence, procedural and fluoroscopy time and number of cryoballoon applications.

Age, sex, AF classification, cardiopathy, Hypertension, diabetes, smoking status, AF evolution time, LA diameter and volume, AAD previous use, sleep apnea disorder, renal insufficiency are included as variables to predict ablation success.

Ablation procedure

All cryoablation procedures are performed in a fasting state and under deep sedation. A transesophageal echocardiogram is performed in every patient, previous to vein access, in order to exclude left appendage thrombi. After transseptal puncture bolus heparin (100mg/kg weight) and infusion is administrated to obtain ACT 300-350 seconds.

All procedures are performed with third generation Medtronic Artic Front AdvanceTM Cryoablation Catheter. Pulmonary vein (PV) potentials are recorded with Achieve AdvanceTM circular mapping catheter. According to the protocol in our center, one 180 seconds application is performed if time to isolation is less than 60 seconds, and one 240 seconds application is performed if time to isolation is between 60-100 seconds. If there is no isolation after 100 seconds of application, this is stopped and the balloon is repositioned. No bonus applications are given. In case of lack of pulmonary vein signals, a 180 or 240 seconds application is given depending on the achieved temperature. Phrenic nerve function is monitored during right veins applications with a catheter located in the right subclavian vein. After last application, entrance and exit isolation is checked in all veins. In case of AF rhythm during procedure, and no RS conversion during applications, a biphasic cardioversion is performed before moving catheters to the right side.

In patients assigned to SVC isolation, this is guided by the presence of SVC signals. Time of application is the time necessary to SVC isolation plus 60 seconds. If no isolation occurred after 100 seconds, application is stopped and the balloon is repositioned. Phrenic nerve function is strictly monitored with a pacing catheter located in right subclavian vein and heart rate is monitored in order to exclude sinus node dysfunction. In case of absence of SVC potentials, the patient will be excluded, and ordinary visits are scheduled according to the protocol of the center. In patients assigned to control group, procedure is finished after checking the presence of SVC signals.

Procedures will be performed with no anticoagulation suspension and patients will maintain anticoagulation at least two months after procedure. The decision to keep on anticoagulation after this period is based on the CHA_2DS_2VASc score. Proton pump inhibitors are prescribed during 15 days to avoid oesophageal complications.

After procedure, a 3 months blanking period is stablished, in which antiarrhythmic drugs (AAD) are prescribed in absence of contraindications.

AAD are recommended to be suspended at 3 month clinical visit although they can be maintained or restarted, during follow up, as at the discretion of the treating physician.

During the blanking period, repeated ablation is allowed but would not reset the blanking period.

Ethics and security aspects

The study is conducted in accordance with the guidelines set out in the Standards of Good Clinical Practice (CPMP/ICH/135/95) and the international ethical recommendations contained in the lasted revision of the Declaration of Helsinki and in the Belmont report. The ethics committee of the Hospital Universitario Puerta de Hierro Majadahonda (Madrid. Spain) has approved the protocol. All study data will be recorded, stored, and processed anonymously. All participants will be informed to the fullest extent possible about the study, in a language and terms that are understandable. All participants sign an informed consent at enrolment including the name, and date personally by the subject, and by the person who carry out the informed consent communication.

Statistics

Shapiro Wilks and Kolmogorov Smirnov test are used to test for normality. Continuous data are described as mean ± SD if normally distributed and as median (interquartile range) for no normal data. Categorical variables are described as counts and percent. Student t test (Mann-Whitney U test if normality not satisfied) and chi-square test are used to compare groups.

Recurrence free survival is compared by the log-rank test, and Kaplan-Meier curves are generated. Event free duration is defined as time from procedure to occurrence of outcome event (arrhythmia recurrence after blanking period). For patients who are event free at the end of follow up, time to event is censored. Death from any cause within the study period is considered for mortality analysis.

Univariate and multivariate Cox proportional hazard models will be used for identifying significant predictors of AF recurrence. Hazard ratios and 95% confidence intervals (Cis) from the Cox model are reported in the results.

All enrolled patients who undergo the index procedure constitute

the intent to treat population and are the subject for safety and efficacy analyses.

All test are 2 sided, and a p value < 0.05 is considered statistically significant. Analyses are performed using IBM Statistics SPSS 25 version.

Discussion

CAVAC AF is a randomized single blind study that compares PVI associated to SVC isolation to PVI alone, in patients with paroxysmal or nnon-longstanding persistent AF. It differs to previous literature in the technique that is employed. All procedures are performed with third generation Medtronic Artic Front AdvanceTM Cryoablation Catheter.

Cryoballoon therapy to treat AF has been shown to be a safe procedure in real world, across a broad cohort of patients with AF [18]. Serious procedure and device related adverse event rates were only 4,7% and 2% in this registry. Cryoballoon has a better learning curve compared to radiofrequency, and shortens procedure time while fluoroscopy and clinical outcomes are comparable[19]. This reason makes cryoballoon therapy a very attractive technique to treat AF patients.

PVI has shown suboptimal outcomes in patients with AF, especially in those with persistent form. Adjunctive strategies employed to ablate non PV triggers have shown favorable although non reproducible outcomes[20].

Cryoballoon SVC isolation has been shown to be a simple, safe and efficacy procedure [17]. According to Campal et al, over 30 patients, success rate was almost 90% and no permanent complications were reported. Only two transient complications occurred (one phrenic nerve paralysis and one sinus node injury).

Atrial fibrillation episodes can often be asymptomatic, even after catheter ablation, creating a disconnect between symptoms and actual arrhythmia burden which may alter clinical management [21]. Outcome after ablation depends on the time of monitoring. The more time of monitoring the less efficacy results are reported. Therefore, a strict system of monitoring seems necessary in atrial fibrillation ablation trials at this moment.

Recent technological advancements have facilitated ambulatory electrocardiogram monitoring in the outpatient environment providing continuous, high resolution ECG data streams ranging from days to months at a time.

The likelihood of AF recurrence detection, after ablation or cardioversion, was 56% significantly greater in patients randomized to AliveCor® Kardia daily monitoring compared to usual care[22], demonstrating that this strategy of monitoring is mostly beneficial for prompt detection of recurrence after ablation.

Limitations

The trial´s main limitation is represented by the small number of patients included. Nonetheless, study size has been calculated to obtain significant differences between groups.

Regarding monitoring adherence after ablation, a high level of ECG compliance is necessary to detect AF recurrences. A good adherence is defined by a threshold of ≥ 80% monitored days.

Another limitation is the single blinded design, therefore an investigational bias can occur to modify procedural aspects in the SVC isolation group.

Conclusions

Our study will provide data about the efficacy of SVC isolation in addition to PVI compared to PVI in a randomized way, in paroxysmal and non-longstanding persistent atrial fibrillation patients.

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Atrial Fibrillation In Heart Failure With Preserved Ejection Fraction

Simon W. Rabkin[1], *Hirmand Nouraei*[1]

[1]University of British Columbia Division of Cardiology Vancouver, B.C., Canada

Abstract

Background: Heart failure with preserved ejection (HFpEF) represents nearly half of all patients with heart failure (HF). The objective of this study was to examine the characteristics of patients with atrial fibrillation (AF) and HFpEF to determine factors that might explain the adverse prognosis.

Methods and Results: Data were collected on 196 patients with HFpEF in a non-hospitalized setting. Clinical and laboratory variables were collected. Patients with AF were compared to those with sinus rhythm. AF was present in 25% of the study population. Individuals with AF had a significant ($p<0.05$) and three-fold greater B-type natriuretic peptide level than individuals without AF. Individuals with AF had significantly ($p<0.05$) larger left atrial volumes. AF was associated with evidence of significantly ($p<0.05$) worse diastolic function and was also significantly greater prevalence of moderate mitral or tricuspid regurgitation. In multivariate analysis, considering age, left atrial volume index, E/A ratio, E/e' and left ventricular internal diameter (LVID), only age and left atrial volume index were significant ($p<0.05$) independent factors related to the presence of atrial fibrillation in HFpEF.

Conclusions: AF in patients with HFpEF is an indication of more severe or advanced heart failure. Several explanations are possible as unifying cellular pathways that links atrial fibrillation and HFpEF specifically processes leading to increases in atrial and ventricular inflammation and/or fibrosis.

Introduction

Atrial fibrillation (AF) is a well-recognized indicator of increased morbidity and mortality [1,2]. A number of factors such as age, heart failure, diabetes mellitus, previous stroke and hypertension identify individuals at higher risk for an adverse outcome which often is thromboembolism, justifying the need for anticoagulation [3,4]. There are, however, challenges with the definition of some of those factors [5]. The reason for the adverse interaction of heart failure and atrial fibrillation is not completely understood. The type of heart failure in patients with AF is more likely to be heart failure with preserved ejection (HFpEF) rather than heart failure with reduced ejection fraction [6]. HFpEF, which affects nearly half of all patients with heart failure, carries a 50% mortality over 5 years [7–9].

Key Words

Atrial Fibrillation; Heart Failure With Preserved Ejection Fraction, Left Atrial Volume

Corresponding Author
Simon Rabkin,
University of British Columbia
9th Floor 2775 Laurel St. Vancouver, B.C., Canada V5Z 1M9

We and others have demonstrated the importance of the coexistence of AF with HFpEF because the combination is associated with a poor outcome [10]. In 1,744 patients with HFpEF referred for cardiopulmonary stress testing at the Cleveland Clinic, AF was associated with impaired contractile reserve, less peak exercise performance and increased mortality [11]. In the Candesartan in Heart failure-Assessment of moRtality and Morbidity (CHARM) study, AF was associated with greater relative risk of the major outcomes in patients with HFpEF than in patients with HFrEF [12]. In an outcomes registry of patients treated for AF, HFpEF was associated with poor long-term outcomes [6]. In a retrospective study of 8,931 patients, AF was associated with a poorer 5-year survival in those with HFpEF than those with HFrEF and it was independent of age [13]. In 1,765 patients enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, Atrial fibrillation at enrollment was associated with increased risk for cardiovascular events and atrial fibrillation that occurred after randomization was associated with an increased risk of morbidity and mortality, that was not influenced by spironolactone [14].

The objective of this study was to examine the characteristics of patients with AF and HFpEF to determine factors that might explain the adverse prognosis.

Methods

The study population has been previously described [10]. Briefly, it is a retrospective study of 196, consecutive, patients with HFpEF who presented in an ambulatory cardiology clinic setting. The study was approved by our Institutional ethics committee. Each patient chart was carefully reviewed by one data collector. The inclusion criteria were (i) adults over the age of 18, and (ii) HFpEF confirmed on a transthoracic echocardiogram (TTE). HFpEF was defined based on the 2016 European Society of Cardiology criteria that included a left ventricular ejection fraction (LVEF) ≥50% [15]. The exclusion criteria were indeterminate diastolic dysfunction on TTE, previous cardiac surgery or severe valvular heart disease. Patients with valvular heart disease graded as mild or moderate were included.

Demographic data, medical history, cardiovascular risk factors, history of stroke, kidney disease, lung disease, other comorbidities, blood pressure, and laboratory test results were collected. The presence of atrial fibrillation was recorded based on a 12 lead ECG done at or before the most recent clinic visit. Records from the most recent clinic visit were used to obtain the information for each patient. Laboratory data included creatinine level, HbA1c, B-type natriuretic peptide (BNP), and lipid profile. The data on BNP were collected from the last hospital admission or during previous clinic visits when there was exacerbation of symptoms. Echocardiographic data included LVEF, valvular abnormalities, atrial and ventricular chamber sizes. The assessment of LVEF was determined by assessment of left ventricular cavity dimensions applying Simpson's method, in the majority of cases. In the other cases, a visual estimation was made. Visual estimation of LVEF by 2D echo by an experienced reader correlates well with EF determined by quantitative real-time three-dimensional echocardiography [16] The degree of diastolic dysfunction including diastolic parameters followed uniformly agreed upon recommendations [17]. Only patients whose diastolic function could be assessed during TTE were included in the tabular data.

Data analysis

Normally distributed continuous variables were described as mean and standard deviation, and others were expressed as medians and interquartile ranges. Tests of significance used analysis of variance (ANOVA) Kruskal-Wallis method for continuous traits and the Chi-squared test was used for categorical traits. A multivariate regression analysis was performed evaluating the presence or absence of atrial fibrillation using the variables: age, left atrial volume index, E/A ratio, E/e' and left ventricular internal diameter (LVID). All analyses were performed with RStudio version 1.2 (RStudio Inc., United States). A p-value of <0.05 was considered statistically significant.

Results

AF was present in 25% of the study population. Individuals with AF were significantly older that those in sinus rhythm (Table 1). Individuals with AF were less likely to have diabetes mellitus or coronary artery disease. Individuals with AF and those in sinus rhythm had identical left ventricular ejection fraction or identical systolic function. However, those with AF had a three-fold higher BNP level.

Individuals with AF had significantly (p<0.05) larger left atrial volumes. AF was associated with evidence of worse diastolic function as reflected by significantly (p<0.05) higher mitral E/A ratio, elevated left ventricular filling pressure and more moderate or severe diastolic dysfunction (Table 2). Although the type of atrial fibrillation was not collected, the high proportion with mitral E/A ratio data suggests the majority of cases had paroxysmal atrial fibrillation. AF was also significantly associated with a greater prevalence of moderate mitral or tricuspid regurgitation (severe valvular heart disease was an exclusion criterion). A multivariate analysis, performed to distinguish the presence atrial fibrillation, used the variables age, left atrial volume index, E/A ratio, E/e' and left ventricular internal diameter (LVID) and showed that this model was significantly (p=2.6663-05) related to the presence of atrial fibrillation. The multivariate analysis showed that of these variables only age (p=0.029) and left atrial volume index (p=0.00019) were significant independent factors related to the presence of atrial fibrillation.

Discussion

This study demonstrated that AF accompanying HFpEF is more often present in patients with more severe diastolic dysfunction, which was reflected by higher circulating levels of BNP, and echocardiographic evidence of a larger left atrium and moderate or severe diastolic dysfunction. While left atrial size (volume) was larger in patients with AF, it can be questioned whether the loss of coordinated atrial contraction in AF is responsible for the larger left atrial size. However, the presence of indices of elevated left ventricular filling pressure and higher prevalence of moderate and severe diastolic dysfunction suggest that the larger left atrial volume is an indicator of worse left ventricular diastolic dysfunction. In addition, there was a three-fold

Table 1: Study population demographics

	Atrial fibrillation (N=49)	Sinus rhythm (N=147)	p-value
Age (years)	83 (72.5, 87.5)	75 (67, 84)	0.003
Male (%)	33	48	0.043
Hypertension (%)	71	74	0.750
Diabetes (%)	10	29	0.001
Dyslipidemia (%)	41	55	0.066
Coronary artery disease (%)	24	41	0.006
Chronic kidney disease (%)	20	18	0.860
Stroke or transient ischemic attack (%)	12	7	0.340
Lung disease (%)	12	7	0.340
Obstructive sleep apnea (%)	8	7	0.990
Body mass index (kg/m2)	25.9 (22.9, 29.4)	25.6 (23.1, 31.3)	0.510
Systolic blood pressure (mmHg)	130 (120, 140)	135 (122, 145)	0.230
Low-density lipoprotein (mmol/L)	2.04 (1.5, 2.74)	2.02 (1.47, 2.64)	0.760
Serum creatinine (mmol/L)	98 (77, 116.5)	88 (71, 114)	0.090
HbA1c (%)	5.8 (5.6, 6.2)	5.8 (5.6, 6.5)	0.310
B-type natriuretic peptide (pg/ml)+	349 (128, 777)	111 (33, 339)	<0.001
Left ventricular ejection fraction (%)	60 (55, 65)	60 (55, 60)	0.210

+ BNP data were available in 36 individuals with atrial fibrillation and 85 individuals in with normal sinus rhythm group
Data on heart rate was not collected

Table 2: Summary of echocardiographic findings

	Atrial fibrillation (N=49)	Sinus rhythm (N=147)	p-value
Right ventricle diameter (mm)	36 (34, 39)	35 (30, 38)	0.071
Tricuspid annular plane systolic excursion (mm)	21 (20, 27)	23 (19, 26)	0.800
Left atrial volume index (mL/m2)	50 (39, 57)	36.5 (32, 45)	<0.001
Left ventricle end-diastolic diameter index (mm/m2)	26 (24, 29)	26 (23, 29)	0.480
Left ventricle mass index (g/m2)	97 (80, 112)	92 (74, 109)	0.340
Mitral valve E/A ratio+	1.35 (0.95, 1.9)	0.91 (0.7, 1.2)	<0.001
Average E/e' ratio++	15 (11.8, 19.5)	13.9 (10, 16.6)	0.047
Pulmonary artery pressure (mmHg)	34 (26.5, 40)	28 (24, 35)	0.036
Elevated LV filling pressure (%)	84	57	<0.001
Moderate diastolic dysfunction (%)	57	50	<0.001
Severe diastolic dysfunction (%)	16	3	<0.001
Moderate MR (%)	41	23	<0.001
Moderate AS (%)	4	7	0.540
Moderate AR (%)	10	10	0.999
Moderate TR (%)	45	17	<0.001

• + E/A was available in 46 individuals in the atrial fibrillation group and 146 of the individuals in the sinus rhythm group
• ++E/e' was available in all 49 in the atrial fibrillation group and 147 in the sinus rhythm group

level of BNP in the patients with atrial fibrillation compared to those without atrial fibrillation. Whether the rapid ventricular rate that may be associated with AF, is responsible for the adverse outcome when AF coexists with HFpEF is uncertain. There are some data that support this contention [18] while others refute it [19]. The nature of both of those ad hoc analyses requires a prospective clinic trial to answer the question. While our study does not by itself provide incontrovertible evidence for the relationship of HFpEF leading to atrial dilatation and eventual atrial fibrillation, this construct can be supported by other evidence. Left atrial enlargement in HFpEF is associated with alterations in left atrial compliance, reductions in atrial pump function and impairment in atrial contractile reserve [20]. In aged female Fischer F344 rats, a model of HFpEF with left atrial enlargement, there is a high frequency of inducible atrial fibrillation and atrial electrical activation mapping revealed abnormal beta-adrenergic responsiveness and slowed conduction velocity [21]. In addition, in our study left atrial volume was a significant independent factor distinguishing patients with atrial fibrillation compared to those without atrial fibrillation even after considering factors such as age, left ventricular size, and two indices of left ventricular stiffness (the ratios E/A and E/e').

Cellular pathways linking atrial fibrillation and HFpEF

A number of cellular pathways have been proposed to explain HFpEF, including abnormalities of cardiomyocyte relaxation processes that include intracellular calcium kinetics, different autocrine or paracrine factors, endothelial dysfunction, inflammation, dysregulated oxidative and nitrosative stress, dysfunctional nitric oxide and cGMP signaling, titin hypophosphorylation, abnormal metabolism including mitochondrial defects, and abnormalities of small arteries and the microvasculature [22–25].

While we recognize that elevated left ventricular diastolic pressure by passively increasing left atrial pressure may simply distend the atrium leading to atrial fibrillation, we speculate that there are two likely potential unifying molecular and cellular concept to link atrial fibrillation and HFpEF, recognizing that they are speculations and were not addressed directly in our research. Cardiac inflammation and fibrosis are two separate but interwoven processes that might explain AF and HFpEF. Infiltration of immune cells and proteins that mediate the inflammatory response alter atrial electrophysiology and structural substrates increasing vulnerability to AF [26,27]. Cardiac inflammation is evident in animal models of HFpEF. Rabbits fed with a cholesterol-enriched diet develop LVDD with preserved systolic function and evidence of cardiac inflammation and oxidative stress. Increased cardiac expression of mRNA for Nox2, Vcam1, Mmp12, Mmp12/Timp1, Il1b and Col1/Col3 ratios was also higher in these rabbits [28]. Toll-like receptor 9 activation produces cardiac inflammation, and deterioration of diastolic function in the SERCA2a depletion-mediated mouse model of diastolic heart failure [29]. Patients with HFpEF have increased serum levels of pro-inflammatory cytokines such as tumor necrosis factor alpha, interleukin (IL) 12, IL-6, monocyte chemoattractant protein 1, C-X-C motif chemokine 10 [30]. The percentage of peripheral monocytes was not only increased in HFpEF but also correlated with echocardiographic indices of diastolic dysfunction [30]. Inflammation can also activate fibrotic pathways leading to cardiac fibrosis with structural remodelling of the atria [26].

Processes leading to increases in cardiac fibrosis in the atrium and ventricle have the capacity to produce respectively atrial fibrillation and HFpEF. Patients with HFpEF have an increased content of myocardial type I collagen, enhanced collagen cross-linking, and lysyl-oxidase (LOX) expression [31]. The production of increased collagen may either be a primary phenomenon or a response to injury, inflammation or myocardial stress. Such stressors may be from valvular heart disease or hypertension. Cardiomyocyte-specific deletion of STAT3 (STAT3cKO) mice develop more cardiac fibrosis than wild type controls [32]. These mice had increased BNP and echocardiographic indices of increased cardiac stiffness [32]. They also demonstrated reduced levels of protein kinase G [32] that is consistent with the picture of HFpEF [24]. HFpEF is associated with higher levels of syndecan-4 [33]. Activation of syndecan-4, a transmembrane proteoglycan, acting through its cytosolic domain and calcineurin/nuclear factor to activate T-cells induces collagen, osteopontin, and LOX which in turn induces cardiac fibroblasts [34]. Syndecan-4 acting through its extracellular domain facilitates LOX-dependent collagen cross-linking [34].

Despite atrial dilation in both HFpEF and HFrEF, patients with HFpEF manifest changes in atrium that are distinct from patients with HFrEF [35,36]. Putko et al found that left atrial enlargement is different between HFrEF and HFpEF because in the former there is a significant relationship between LVEF or LV mass and LA volume which is not consistently observed with HFpEF [36]. Melenovsky et al assessing the pressure volume relationships in left atrium of patients with HFpEF and HFrEF found that the HFpEF group was characterized by increased left atrial stiffening and greater atrial wall stress [35]. Increased left atrial stiffness is consistent with increased atrial fibrosis. AF is well known to be associated with increased atrial fibrosis [37–39]. Atrial fibrosis has been demonstrated by cardiac MRI in AF [37]. The increase in cardiac fibroblasts enhances the probability of their contact with cardiomyocytes. Cardiomyocytes and fibroblasts can

develop low-resistance electrical junctions that can enhance phase 4 depolarization and promote ectopic impulse formation leading to re-entrant arrhythmias [38].

Aging is associated with an increased incidence of AF [40] as well as an increased incidence of HFpEF [41]. The mechanisms responsible for the increased incidence of AF with aging encompass aging-induced atrial electrical and structural remodelling, disturbed calcium homeostasis, enhanced atrial ectopic activity, impairment of sinus node function, increased atrial effective refractory period (ERP), slowed conduction in different regions of the atrium and increased vulnerability to re-entry arrhythmias [40, 42]. Fundamental to the aging process, however, is increased organ fibrosis which also takes place in the heart [43]. 'Reactive interstitial fibrosis", a term applied to the expansion of the cardiac interstitial in the absence of significant cardiomyocyte loss [44], is evident with aging and has been attributed, in part, to reactive oxygen species, chemokine growth factors such as TGF-β, endothelin-1 and angiotensin II signaling that increase collagen synthesis [43]. Reductions in collagen degradation pathways may be more important than increased de novo synthesis in the pathogenesis of aging-associated fibrosis [43] as aging is associated with down-regulation of matrix mletalloproteinase-2 (MMP-2) mRNA with reduced MMP-2 levels as well as reduced proMMP-1 activity [45].

TGF)-β, may play a critical role in aging-induced myocardial fibrosis as it can induce myofibroblast transdifferentiation, enhance fibroblast matrix protein synthesis, as well as suppressing MMP activity by inducing synthesis of protease inhibitors, such as PAI-1 and TIMPs [43]

Study limitations

The limitations of our study have been previously been discussed [10] but it is worthwhile to restate that retrospective studies have challenges and limitations mainly with missing data for subjects that met the inclusion criteria. However, for the variables included in our study population, less than 1% were missing and required imputation [10]. This was a significant improvement compared to a number of other HFpEF studies [46–48]. Never the less it limits the ability to do propensity matching to compare the different group assessing the impact of variables such as BNP and E/A between groups. Another issue is referral bias which may have affected the composition of the patient population. However, the mean age of the large study population in iPreserve was 72 years [49] compared to 77 years of age in our study, A younger patient population in a clinical trial would be expected because of the need for follow-up. The predominance of women (66% in our study is comparable to 60% in iPreserve [49] and 60% in the CHARM-preserved study [50]. The percentage of hypertension, 73%, in our study compares to 65% in CHARM-preserved [50] and 88.5% in iPreserve [49]. Left ventricular ejection fraction was similar in the studies being 60% in our study and 54% in CHARM -preserved [50] and 60 % in iPreserve [49]. A consideration is that the patients in the study did not have 24-hour ECGs to determine the 'burden' of atrial fibrillation in the atrial fibrillation group and whether there might have been some cases of atrial fibrillation present in the non-atrial fibrillation group. This issue, however, is always present as even a 24-hour ECG is only a brief time in the course of HFpEF condition. An insertable cardiac monitor is even more effective than conventional follow-up for atrial fibrillation detection in patients with cryptogenic stroke [51,52]. We did not calculate the CHAD-VASC score in our patient population as the objective of our study was to examine the relationship between HFpEF and atrial fibrillation and not the stroke risk in the HFpEF population with or without atrial fibrillation. Another limitation of the study is that we did not have other indicators of heart failure to compare the atrial fibrillation and non-atrial fibrillation groups. However, BNP levels were three times higher in the atrial fibrillation compared to the non-atrial fibrillation group. Recognizing that BNP is not a perfect mirror of heart failure, it is note worthy that BNP levels are similarly elevated in HFpEF as HFrEF [53]

Conclusion

The coexistence of AF and HFpEF indicates the severity of the underlying processes that lead to each of these conditions. When AF is present with HFpEF, there is an increased likelihood of more severe heart failure as indicated by higher circulating BNP levels, worse diastolic function, reflected by echocardiographic indices of diastolic dysfunction and most importantly larger left atrial size.

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Impact of Atrial Low-Voltage Areas on The Acute and Long-Term Outcomes of Persistent Atrial Fibrillation Ablation

C. Grebmer[2,], A. Tatzber[2], T. Reents[2], F. Bourier[2], V. Semmler[2], M. Telishevska[2], M. Kottmaier[2], A. Buiatti[2,*], G. Hessling[2], I. Deisenhofer[2], S. Ammar-Busch[1,2]*

[1]Klinikum Coburg, II, Medizinische Klinik, Coburg, Deutschland
[2]Deutsches Herzzentrum München, Klinik für Herz- uns Kreislauferkrankungen, Klinik an der Technischen Universität München, München, Deutschland

Abstract

Background: Ablation in patients with persistent atrial fibrillation is associated with an increased risk of recurrence. One of the reasons for this is extended left atrial scarring, which can be identified as low-voltage areas (LVA) during left atrial mapping. To increase the success of ablation, these areas should be adequately identified to estimate the success of ablation based on a cut-off value. Therefore, this study aimed to show the relationship between left atrial voltage and the risk of recurrence for patients after ablation of persistent atrial fibrillation.

Methods: In this prospective study, 70 patients with persistent AF underwent ablation using a modified stepwise approach. We compared two groups according to the Utah fibrosis criteria: the mild group, with left atrial LVA smaller than 20%, and the severe group, with left atrial LVA of 20% or larger. Both groups were compared based on freedom from any atrial arrhythmia recurrence (>30 secondswith repeated 7-day Holterelectrocardiogram) at 12 months and the use of antiarrhythmic drugs.

Results: All patients with atrial fibrillation converted to sinus rhythm by ablation (n=7) had a scar area smaller than 20%. All patients with LVA of 20% or larger were externally cardioverted to to sinus rhythm at the end of the procedure. LVA of 20% or larger tended to show increased recurrence rates after ablation (p= 0.058), significantly shorter periods before recurrence (p=0.041), and a trend toward even shorter periods before recurrence after repeat ablation (p=0.059).

Conclusion: The extent of left atrial LVA influences the acute and long-term outcomes of persistent atrial fibrillation ablation. Patients with LVA smaller than 20% could benefit from a stepwise approach.

Introduction

For patients with paroxysmal atrial fibrillation (AF), pulmonary vein isolation (PVI) is the therapy of choice because of its high success rate ranging from 60% to 85% and freedom from recurrence within 1year[1]. However, for patients with persistent AF,the success rates in terms of stable restoration of sinus rhythm are reduced to 42% to 60% [2,3]. Furthermore, patients with long standing persistent and persistent AF have significantly lower success rates with PVI and high recurrence rates of AF or any atrial tachycardia (AT) up to 68% within 1year[4,5,6]. Additionally, patient age, comorbidities, genetic predisposition, atrial size, and AF duration also have important roles in the success of PVI[7]. Different ablation techniques have different advantages and disadvantages and are variably applied[8]. Methods such as complex fractionated atrial electrogram ablation, rotor ablation, and linear lesion ablation, which are based on PVI, have not shown clearly superior results compared to PVI during previous studies[8]. However, the "philosopher's stone" for the optimal treatment of persistent AF has not yet been found. Because neither linear lesions nor electrogram-guided ablation in addition to PVI have resulted in significantly better outcomes[8], a combined approach or an individualised approach could be beneficial.

This study proposed a novel predictor of out comes after ablation of persistent AF in patients with left atrial (LA) low-voltage areas and the corresponding clinical implications for the affected patient population.

Key Words

Low-Voltage Area, Atrial Fibrillation, Ablation Of Atrial Fibrillation, Pulmonary Vein Isolation, Subtract Modification.

Corresponding Author
Christian Grebmer,
Department of Electrophysiology, German Heart Center Munich
Munich, Germany

Materials and Methods

Study population

During February 2012 to January 2014, a total of 70 consecutive patients with persistent (49%) or long-term and persistent AF (51%)

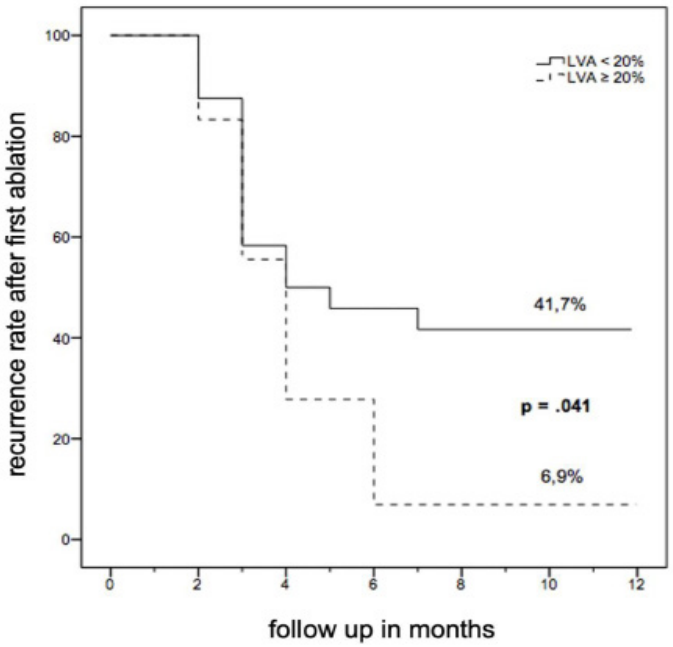

Figure 1: Kaplan Meier curves indicating noatrial fibrillation (AF)/atrial tachycardia (AT) recurrence after single ablation (%) without antiarrhythmic drugs (AAD).LVA, low-voltage area.

were included in a prospective registry study. Follow-up was performed until January 2015. The average age of the patients at the time of intervention was 62.8±9.8 years (minimum, 39.3 years; maximum, 85.7 years). The average body mass index was 27.73±3.90 kg/m^2 (minimum, 19.81 kg/m2; maximum, 38.28 kg/m2). The proportion of male patients was 80.0% (n=56). Persistent AF was defined as AF for more than 7 days with or without prior cardioversion. For long-standing persistent AF, the period was defined as more than 12 months of continuous AF. All patients provided written consent.

Study protocol

All anti arrhythmic drugs except beta-blockers were discontinued for at least 4 weeks before the ablation procedure. Computed tomography or magnetic resonance imaging was performed before the planned procedure to visualize the anatomy of the atria. The LA thrombus was ruled out using computed tomography or transoesophageal echo cardiography as described previously[2].

Examination and ablation procedures

Anticoagulation for at least 4 weeks before ablation was required. Antiplatelet therapy was maintained during the procedure. Continuous novel oral anticoagulants such asrivaroxaban, dabigatran, apixaban, or vitamin K antagonists (phenprocoumon) were used with a target international normalized ratio of 2.0 to 2.8 during the procedure. These oral anticoagulants were continued on the day of the procedure. Periprocedural management and postprocedural management of oral anticoagulation were based on in-house standards.

All patients presented for ablation with ongoing AF. After accessing the left atrium, electroanatomical mapping was performed with a circular steerable mapping catheter (14 Bipole Orbiter® PV;C. R. Bard, Lowell, MA, USA) under the guidance of an electroanatomical mapping system (EnSite Velocity NavX; Abbott Medical Inc., St. Paul, MN,USA). LA maps were recorded in AF. Bipolar endocardial signals were filtered from 30 to 300 Hz. All acquired electromyograms were subsequently visually inspected to ensure homogeneous distribution of measurement points across the LA assuming a minimum map density of 500 points for each LA map. The mapping points were measured after 5 seconds with a stable catheter. A steerable bidirectional sheath (Agillis sheath;Abbott Medical Inc., St. Paul, MN, USA) was used to allow contact with and positioning of the mapping catheter in all positions. The surface colour projection included an interpolation threshold of 8 mm and a minimum colour temperature. The map density was ensured in all parts of the LA. Bipolar endocardial signals with a mean voltage less than 0.1 mV were defined as scarring[3,9,10].

The ablation strategy was performed according to a modified stepwise approach. Circumferential PVI was performed as the first step. After successful PVI, electrogram-guided ablation of sites with voltage between 0.1 and 0.5mV was performed successively in the left atrium, right atrium, and coronary sinus. In case of occurrence of macroreentries, linear lesions were deployed: a roofline was used for roof-dependent atrial flutter; an anterior line was used for perimitralatrial flutter; and a cavotricuspidal line was used for atypical atrial flutter. Localised reentries were ablated focally. Further details of the ablation strategy and its endpoints have been described previously [2,11].

The endpoint of ablation was the conversion to sinus rhythm by ablation, whether via external cardioversion or ablation.Before external cardioversion could be performed,exit and entrance blockage (pulmonary veins) had to be present, blockage across drawn lines had to be confirmed, and local electrograms had to be ablated.

After the procedure, a 3-month course of anticoagulants was prescribed, which was subsequently re-evaluated after 3 months using the CHA_2DS_2 VASc score and continued or discontinued if necessary.

Follow-up

The follow-up duration was 12 months after the first ablation. Atrial arrhythmia (AF or AT) recurrence was evaluated after 3, 6, and 12 months via in-person outpatient visits at the follow-up outpatient clinic or by the patients' general practitioners. During the examinations, the physician evaluated the medical history and focused particular attention on persistent or recurrent palpitations and arrhythmias. A Holter electrocardiogram was performed at each examination for 7 days.

Table 1: Baseline characteristics

	LVA <20% (n=52)	LVA ≥20% (n=18)	P-value
Age (years)	60 (±9.2)	70.7 (±7.0)	<0.001
BMI	27.91 (±4.05)	27.21 (±3.49)	0.520
Male (n)	86.5 % (45)	61.1 % (11)	0.037
Arterialhypertension	61.5 % (32)	83.3 % (15)	0.145
CAD	11.5 % (6)	22.2% (4)	0.268
DM II	17.3% (9)	11.1% (2)	0.716
Pacemaker	13.5 % (7)	27.8 % (5)	0.274

BMI, body mass index; CAD, coronary artery disease; DM II, type 2 diabetes mellitus; LVA, low-voltage area.

Table 2: Procedural data

	LVA <20% (n=52)	LVA ≥20% (n=18)	P-value
Age (years)	60 (±9.2)	70.7 (±7.0)	<0.001
BMI	27.91 (±4.05)	27.21 (±3.49)	0.520
Male (n)	86.5 % (45)	61.1 % (11)	0.037
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BMI, body mass index; CAD, coronary artery disease; DM II, type 2 diabetes mellitus; LVA, low-voltage area.

The first 2 months after ablation have been defined as a blanking period, and recurrences that occurred during that period were not noted. The blanking period was defined by an in-house standard. If relapse occurred after the blanking period, then the time and type of the relapse arrhythmia were evaluated. The number and type of repeat ablation procedures was noted.

Electroanatomical map analysis

After the procedure, the electroanatomical maps that were created were analysed by a second investigator. The total mapped atrial surface area and low-voltage area were measured based on the electrode size and interelectrode spacing of the introduced catheters (field scaling). Two groups of patients were defined: group 1, with a low-voltage areasmaller than 20%, and group 2, with a low-voltage area of 20% or larger.

Statistical data evaluation

The descriptive and inferential statistical data analyses were performed using SPSS Statistics 22 (IBM®) for Mac OSX. The significance level was determined in advance at 5% according to the probability of error; therefore, a result within the framework of the hypothesis-testing tests with p≤0.05 was considered significant.

To describe the characteristic values of metric parameters, mean values and standard deviations as well as minimum and maximum values were determined. Additionally, the median alternative position measurement was used for oblique measurement distribution of a parameter. Descriptive statistics were used to determine the frequencies and their corresponding proportional values for categorical variables. To show the range in which the true value was in the population, the corresponding confidence interval (CI) was determined. For the 5% error probability of the CI, a corresponding two-sided z-value of 1.96 was used, whereby the interval limits were calculated by taking into account the relative frequency of the probability based on the sample value.

As part of the inferential statistical tests, mean value comparisons of metric parameters were performed using the Welch t test for independent samples. The Mann Whitney U test was used as a parameter-free alternative to the test for independent samples in the case of obliquely distributed data. These inferential statistics evaluated the differences between the two samples based on the least ranked data (i.e., an ordinal scale level was assumed).

Results

For all patients with sinus rhythm that could be achieved by ablation (n=7), the scar area was smaller than 20%. In the group with low-voltage areas of 20% or larger(n= 19), sinus rhythm could not be achieved by ablation. The ablation parameters did not differ significantly between groups (p>0.05)(Table 1& 2).

In the present patient population, 66 experienced recurrence during the blanking period. A total of 43 (65.2%) of the 66 patients were affected by relapse of any atrial arrhythmia (AF or AT) for more than 30 seconds when not using anti arrhythmic drugs. Of these 43 patients, 28 patients (58.3%) were in group 1 (28 of 48 in group 1) and 15 patients (83.3%) were in group 2 (15 of 18 in group 2)(p=0.058). The Kaplan Meier curve revealed a significant difference in terms of recurrence rates for AF and AT between the groups withlow-voltage areas smaller than 20% and low-voltage areas of 20% or larger (p=0.04) within 1year (Figure 1).The test of the distribution difference regarding the incidence of recurrence depending on the low-voltage area showed an overall trend toward a higher recurrence rate for patients with low-voltage areas of 20% or larger (x^2 (1)=3.604;p=0.058).

For patients with low-voltage areas smaller than 20%, a longer interval without recurrence can be expected. The median recurrence-free time for low-voltage areas smaller than 20% was 6.96 months (95% CI, 5.72-8.20 months) and that for low-voltage areas of 20% or largerwas 4.36 months (95% CI, 3.14-5.58months).

Repeat ablation

Sixty-six patients completed 12 months of follow-up.Thirty-five patients (53%) required either a single ablation procedure or multiple repeat ablation procedures: 26 (39.4%) required a single ablation procedure, 6 (9.1%) required a second ablation procedure, and 2 (3%)

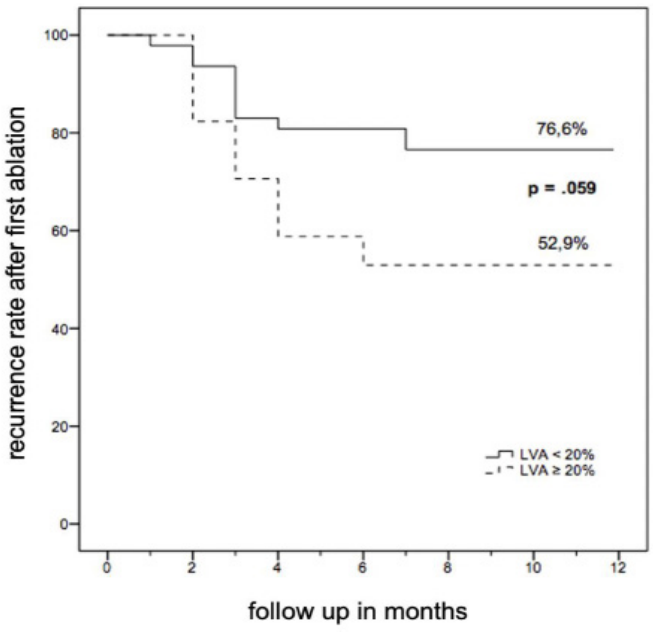

Figure 2: Kaplan Meier curves indicating noatrial fibrillation (AF)/atrial tachycardia (AT) recurrence after repeat ablation. LVA, low-voltage area.

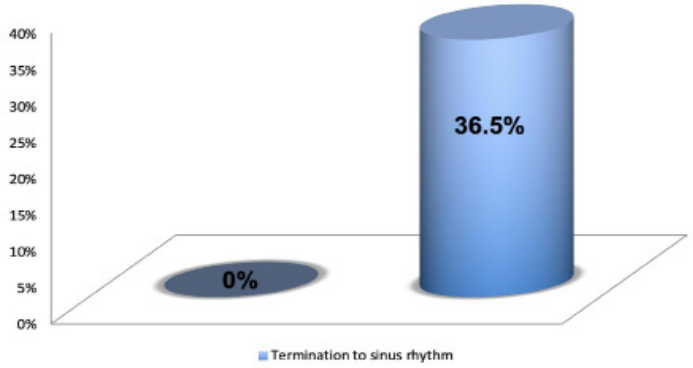

Figure 3: **Acute outcomes after ablation. Periprocedural conversion to sinus rhythm during ablation.**

required a third ablation procedure.

The log-rank comparison (Mantel-Cox) of event distributions showed a trend toward ($\chi^2(1)=3.554$; p=0.059) longer recurrence-free times after repeat ablation for patients with low-voltage areas smaller than 20%. The mean absence of recurrence for low-voltage areas smaller than 20% after repeat ablation was 10.00 months (95% CI, 8.94-11.07 months), and that for low-voltage areas of 20% or larger was 7.88 months (95% CI, 5.76-10.00months) (Figure 2).

Discussion

The main finding of this study was that low-voltage areas of 20% or larger in the LA impact the acute and long-term outcomes of patients with persistent or long-term and persistent AF, as shown by their high rate of recurrence during follow-up. It is of importance that the atrial voltage was measured in AF and not in sinus rhythm, which, according to Qureshi et al., provides significantly better data regarding atrial voltage [10].

The patient population was divided according to the Utah fibrosis classification to analyze the influence of the extension of scar areas. The Utah classification assumes worsening of the prognosis starting from grade 3, resulting in a separation value of 20% for the two patient groups[12].

Voltage maps were recorded in AF, and the mean voltage was evaluated during a period of 5 seconds. This method was described previously [3]. In contrast to the ventricle, where the scar cutoff is clearly defined, scar definition in the atrium has been less well-evaluated. Considering the possible prognostic impact of low-voltage areas, as defined by our study, scarring can be evaluated in AF using a cutoff of 0.1mV.Restoration of sinus rhythm seems to be important to the risk of early recurrence and late recurrence. Depending on which approach is chosen, the risk of provoking AT remains. PVI has been proven to be an effective method of rhythm control in paroxysmal AF [12,13]. For patients with persistent AF, only moderate success can be achieved with PVI alone[2,3,14,15]. During follow-up, only 20% of patients did not experience recurrence 5 years after a single ablation. With multiple ablations, this rate increases to 45% [16,17]. To improve the results of ablation for persistent A Fusing targeted substrate modification, different approaches can be pursued. Relevant strategies include linear lesions, atrial defragmentation, or both in combination [3]. The randomized, multicentre STAR AF II study demonstrated that substrate modification with PVI compared to PVI alone did not result in any benefits for patients who underwent ablation for persistent AF. Atrial arrhythmia without antiarrhythmic drugs after a single procedure was possible after PVI alone for 41%, after PVI with complex fractionated atrial electrogram ablation for 33%, and after PVI with linear lesions for 29%[8]. These results suggest that none of these approaches is optimal. Therefore, there is no clear recommendation regarding substrate ablation. Moreover,it has been suggested that extensive ablation may result in iatrogenically induced arrhythmogenic areas, such as incomplete ablation or incomplete linear blockage[18–20].

A large portion of our study population had long-term and persistent AF, and the ablation outcomes of a modified stepwise approach using two procedures were relatively good for patients with small low-voltage areas. However, the high recurrence ratesof the group with larger low-voltage areas suggest that a different ablation strategy is necessary. Further approaches such as box isolation of low-voltage areas or an individualised approach with limited ablation at the borders of low-voltage areas[21,22,23] have been described. The present results highlight the need to identify critical structures of persistent AF to achieve success through individualised ablation strategies.

Limitations

During our study, we used the automated NavX® cycle length algorithm (NavXsystem automated algorithm of cycle length) to define low-voltage areas. It cannot be excluded that different results might have been achieved with a different mapping system and different automated algorithms. LA scar characterisation by bipolar voltage mapping remains poorly defined. For maps acquired during ongoing AF, a cutoff less than 0.1 mV is considered appropriate for tracing LA scar distribution. However, the extent to which LA scarring can be identified using electroanatomical mapping during AF requires further investigation. The present study shows a statistically significant reduction only in the rate of recurrence. Other results only showed tendencies toward statistical significance. Of course, this is attributable to the very small number of patients.

Current mapping systems can measure atrial voltage even more precisely because of progress in technology and the further development of ablation and mapping catheters.Therefore, evaluations using new technology could be of great relevance to the further development of ablation strategies.

Conclusion

Our study shows that the extent of LA low-voltage areas influences the acute and long-term outcomes of persistent AF ablation. Patients with low-voltage areas of 20% or larger have significantly worse outcomes after single ablation; however, they might benefit from other ablation methods. Patients with low-voltage areas smaller than 20% could benefit from a modified stepwise ablation approach.

Acknowledgments

Authors contributions

Christian Grebmer: main author, drafting article, approval, correspondence, concept and design, statistics.

Sonia Ammar- Busch: senior author, concept and design, fundings critical revision, approval of the article, statistics.

All the other authors: critical revision, data collection, concept and design.

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Exploring the Association Between Physical Activity and Atrial Fibrillation: A Systematic Review of Meta-Analyses

Andreas Müssigbrodt[1,2,], Alireza Sepehri Shamloo[1,*], John Mandrola[3], Jawdat Abdulla[4], Hakeem Ayinde[5], Cristian Ricci[6], Natale Daniele Brunetti[7], Chun Shing Kwok[8,9], Sanghamitra Mohanty[10], Andrea Natale[10], Jedrzej Kosiuk[11], Tiago Luiz Luz Leiria[12], Simon Kircher[1], Nikolaos Dagres[1], Sergio Richter[1], Arash Arya[1], Andreas Bollmann[1], Gerhard Hindricks[1], and Michael Doering[1]*

[1]Department of Electrophysiology, Heart Centre Leipzig at University of Leipzig, Leipzig Heart Institute, Leipzig, Germany
[2]Cardiology Department, CHU Fort de France, Pierre Zobda Quitman Hospital, Martinique, France
[3]Baptist Health Louisville, Louisville, USA
[4]Department for Medicine, Section of Cardiology, Glostrup University Hospital, Copenhagen, Denmark
[5]Division of Cardiology, Section of Electrophysiology, Emory University, Atlanta, USA
[6]Africa Unit for Transdisciplinary Health Research (AUTHeR), North-West University, Potchefstroom Campus, South Africa
[7]Cardiology Department, University of Foggia, Foggia, Italy
[8]School of Primary, Community & Social Care, Keele University, Stoke-on-Trent, UK
[9]Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, UK
[10]Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin, TX, USA
[11]Rhythmology Department, Helios Klinikum Köthen, Köthen, Germany
[12]Cardiology Institute, Porto Alegre, Brazil
*Shared first authorship: Andreas Müssigbrodt and Alireza Sepehri Shamloo contributed equally

Abstract

Background: Numerous studies suggest intensive and prolonged exercise is a risk factor for atrial fibrillation (AF); many other studies have shown that regular exercise can protect against AF in the general population. Meta-analyses of these studies have produced conflicting results. Thus, we performed a systematic review of meta-analyses to understand better the evidence base linking exercise and AF.

Methods: We conducted a systematic review of meta-analyses that evaluated the association between physical activity (PA) and AF. A search of MEDLINE, Scopus, and Google Scholar was performed. The Assessing Methodological Quality of Systematic Reviews 2 (AMSTAR 2) measurement tool was used to evaluate the methodological quality of the included reviews.

Results: A total of twelve meta-analyses met the inclusion criteria. Five meta-analyses reported consistent evidence that the risk of AF was increased among athletes compared to non-athletes. The increased risk of AF ranged from OR 1.64(1.10-2.43) to OR 5.3(3.6-7.9). The results were less consistent among studies of different degrees of PA as three reviews suggest that PA was associated with a reduction in AF, but most studies reported no difference in AF risk. Subgroup analyses suggest that individuals younger than 54-60 years and men were more likely to develop AF with PA.

Conclusion: PA has a dose-dependent J-shape effect on AF risk, with increased risk at very low and very high levels of PA. This effect seems to be gender-specific and more pronounced in younger males.

Key Words

Atrial Fibrillation; Exercise; Sports; Sedentary Lifestyle; Physical Activity; Meta-Analysis; Systematic Review

Corresponding Author
Andreas Müssigbrodt,
Cardiology Department, CHU Fort de France, Pierre Zobda Quitman Hospital, Martinique, France.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults, with an estimated prevalence of 1-2% in the general population[1]. Due to the increasing number of elderly adults and the increasing prevalence of cardiometabolic risk factors associated with AF, an upsurge of AF prevalence has been predicted [2, 3]. A better

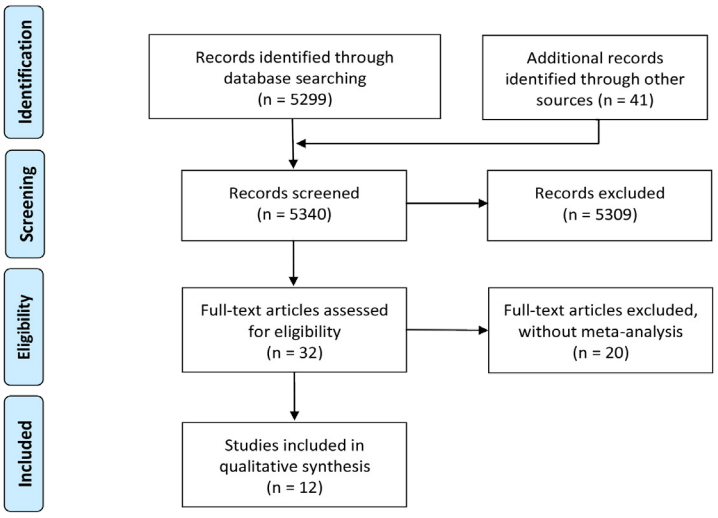

Figure 1: **PRISMA flow chart describing study selection.**

understanding of AF pathophysiology and preventable factors may lead to the development of appropriate preventive programs that could play a significant role in promoting community health and reducing the costs associated with disease management[4,5].

Through its favorable effects on weight, lipids, blood pressure, and cardiorespiratory fitness, physical activity (PA) associates with a lower risk of heart disease.[6] Although numerous studies have suggested that intensive and prolonged exercise as in endurance sports is a risk factor for AF, many other studies have shown that regular exercise can be a protective factor for AF in the general population[7-9]. Over the past two decades, more than 40 studies and twelve meta-analyses have investigated the link between physical exercise and the risk of developing AF. Systematic reviews allow us to enhance our understanding based on accurate, succinct, credible, and comprehensive summaries of the best available evidence on a topic[10]. However, in the case of exercise and AF, the available meta-analyses have produced conflicting results[7,8,11-20]. To improve understanding of this relationship, we performed a systematic review of meta-analyses, evaluating the association between PA and AF from different aspects. In addition, we discussed the possible mechanisms for this association.

2. Methods

2.1 Protocol

We aimed to identify systematic reviews with meta-analysis,which examine the association between PA and AF. This systematic review of meta-analyses was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement[21].

2.2. Eligibility criteria

All studies that evaluated the association between PA and AF, were considered eligible. However, only systematic reviews with meta-analysis were included in the current study. Original papers, case reports, letters, conference abstracts, or comments were not included in this study. There were no restrictions on the definition of PA, which included varying degrees of PA or exercise as well as participants in sports or comparisons of athletes and non-athletes.

2.3. Search

Databases including MEDLINE, Scopus, and Google Scholar, were searched to identify all relevant reviews, without language restriction, published before January 1, 2021. The search terms included the following keywords: ("atrial fibrillation" OR "arrhythmias, cardiac" OR "auricular fibrillation") AND ("physical activity" OR "endurance" OR "exercise" OR "sports" OR "athletes").

2.4. Study selection

Titles and abstracts were screened for the exclusion of unrelated articles. References and citations of included studies were also reviewed for additional reviews that met the inclusion criteria. The selection of studies to be included was independently performed by two reviewers (AM; ASSH).

2.5. Data collection process

Using a data extraction table, the required information from each meta-analysis, including first author's name, publication year, types of included studies, used databases, main inclusion criteria, pooled sample size, age and gender, main findings, and results of subgroup analysis were extracted. In addition, for the results of meta-analyses, the effect estimates (odds ratios, relative risk, hazard ratios) and the number of studies pooled were collected, and any reported measure of statistical heterogeneity. The table was initially completed by one of the first authors (ASSH) and then verified by the other first author to control the accuracy of data entry (AM). After finalizing the first draft of this systematic review of meta-analyses, all corresponding authors (n=11) of the included meta-analyses (n=12) were invited to assess the correctness of the included data and contribute their expert opinion to the manuscript. Seven out of 11 authors accepted the invitation, whereas four authors did not respond. Those seven authors (JA, HA, CR, NDB, MM, CSK, TLLL) revised the entire manuscript and confirmed the authenticity of the final systematic review report after some minor changes.

2.6. Heterogeneity assessment

The heterogeneity between estimates of the AF risks for exposure to a high volume of PA concerning lower PA volume was investigated through Cochrane Q-test and I^2 statistic. Heterogeneity assessment was evaluated by a random effect analysis in which study weights were computed as $wi = 1/(si^2 + t^2)$ where si^2 was the variance estimate from the i-th study, and t^2 was the overall variance. The heterogeneity was investigated for estimates from all meta-analyses as a whole and meta-analyses based on the general population and athletes as well. The sensitivity analysis was conducted in the form of influence analysis, excluding a study at the time. Heterogeneity assessment was reported by forest plot. Heterogeneity assessment, forest plots, and influence analyses were performed using the metan and metaninf function of the STATA software (vers.12). We did not aim to perform an estimate of a meta-analysis of meta-analyses in order to avoid duplication bias.

2.7. Quality assessment

The Assessing Methodological Quality of Systematic Reviews 2 (AMSTAR 2) measurement tool was used to evaluate the

Table 1: Characteristics of include dreviews

Reference	Primary studies (n); Types	Participants (n)	Main Databases	Main inclusioncriteria	Age (A) Gender (G)	Subgroupanalyses	Main aim/question of review
Abdulla [7], 2009	6 Case-control [6]	1550	Medline EMBASE Cochrane	Case--control studies reporting the number of AF or AFlu in athletes compared with controls	A: 51 ± 9 years G: 93% male	N/A	Is the risk of AF higher in athletes than in the general population?
Nielsen [8], 2013	10 Case control [6] Cross-sectional [4]	1550 (onlycase-controls)	Medline EMBASE Cochrane	Case--control studies reporting number of incidental AF or AFlu in athletes compared with non-athletes	A & G: N/A	-Athletes and non-athletes -PA categories	To examine the relationship between PA and risk of new-onset AF or AFlu.
Ofman [11], 2013	4 Prospectivecohort [4]	95526	Medline EMBASE Cochrane	Both prospective cohort and case--control studies examining the relation of regular PA and AF risk	A & G: N/A	N/A	To examine the association between regular physical activity and the risk of AF
Kwok[12], 2014	19 Post hoc RCT [2] Cohort [10] Case-control [7]	511503	Medline EMBASE	1. Studies assessing the link between the history of PA and the subsequent risk of AF 2. Studies assessing outcomes in athletes for PA 3. There was no strict definition of PA	A: Range 41-73 years G: N/A	-Nature of PA -Studies quality	To examine the relationship between AF and the extent of PA
Brunetti[13], 2016	11 Post hoc RCT [1] cohort [5] Case-control [5]	81787	Medline	1. Studies assessing the risk of developing AF in subjects practicing PA or sport activity 2. There was no strict definition of PA	A: Range 43-73 years G: N/A	-Gender -Age groups	To examine the association of age and gender with the Incidence of AF in subjects practicing PA
Mohanty[14], 2016	22 Cohort [12] Case-control [5] Post hoc RCT [1] Cross-sectional [2] Prospective observational [1] Retrospective [1]	656750	Medline Bio Med Centra Cardio source EMBASE clinicaltrials. gov ISI Web of Science	1. Report relation between PA and incidence of AF 2. A case-control or population-based design 3. Specify AF incidence and number of participants for men and women	A & G: N/A	-Athletes and non-athletes -Gender -PA categories	To examine the association of different intensities of PA with the risk of AF in Men and Women
Zhu [15], 2016	13 Post hoc RCT [2] Prospective cohort [10] Case-control [1]	568072	Medline Cochrane Science Direct	Studies estimating the association between PA and developing AF in the general population	A & G: N/A	-PA categories -Region -Gender	To examine the association between PA and incident AF, as well as to determine whether a sex difference existed
Ricci [16], 2018	19 Cohorts [18] Case-control [1]	29855 (all were AF subjects)	Medline EMBASE Cochrane CINAHL	Studies reported relative risk (RR) estimates of the association between PA and AF in the general population	A & G: N/A	-Region -Publication date -Studies quality -Adjustment for CAD RFs	To examine the association between PA volume and AF risk
Ayinde [17], 2018	8 Cohorts [6] Case-control [2]	9113	Medline EMBASE Scopus SPORT Discus	Studies assessed the association between competitive or semi-competitive sports and AF	A & G: N/A	-Studies quality -Age groups	To examine the association between competitive sports sport and AF risk
Li [18] 2018	9 Cohort [3] Case-control [4] Cross-sectional [2]	8901	PubMed Embase Cochrane	1. Case-control or cohort studies that focused on the association of endurance exercise and AF 2. Comparison of athletes group with non-athletes group (control).	A: mean age 39-72.8 years G: N/A	-Gender -Mean age -Study type -Sample size -Sports mode	To quantitatively assess the risk of AF in athletes and the general population
Garlipp [19] 2019	11 Cohort [10] Post hoc RCT [1]	276323	Medline BVS Health Cochrane	All cohort studies, prospective, cross-sectional, observational and randomized clinical trials with patients who performed physical exercises and the development of AF.	A: Range 12-90 years G: N/A	N/A	To analyze the effects of physical activity on the incidence of AF
Mishima [20] 2020	15 Prospective cohort studies	1,464,539	Medline Embase	Prospective cohort studies, with a minimum follow-up of 4 years, reporting the association between PA and incident AF	A: median age 55.3 years G: 51.7 % female	-Gender	to systematically summarize the evidence on the 82 association between PA and risk of AF

AF: Atrial fibrillation; AFlu: Atrial flutter; N/A: Not available; PA: physical activity; CAD RFs: Coronary artery disease risk factors; RCT: Randomized Controlled Trial

Table 2: A summary of main findings of conducted meta-analyses

Reference	Studies and Participants (n)	Effectsize (95% CI)	Narrative findings	Definition forphysical activity
		Studies comparing athletes versus non-athletes		
Abdulla [7], 2009	6 studies 1550	OR=5.29 (3.57 - 7.85)	The risk of AF or atrial flutter was significantly higher in athletes than in controls.	N/A
Nielsen [8], 2013	6 studies 1550	OR=5.3 (3.6- 7.9)	AF increased in athletes compared to non-athletic	N/A
Kwok [12], 2014	6 studies 1973	RR=1.98 (1.00 - 3.94)	The risk of AF was increased in athletes or participants with a history of sports activity (low-quality studies) in comparison with controls	N/A
Ayinde [17], 2018	8 studies 9113	OR=1.64 (1.10 - 2.43)	Athletes have an increased risk of AF compared to the general population. Age appears to modify the risk of AF in athletes	Competitive or semi-competitive sports (no further definition)
Li [18] 2018	9 studies 8901	OR=2.34 (1.04–5.28)	The risk of AF was significantly higher in athletes than in the general population	N/A
		Studies comparing high PA versus low PA		
Ofman [11], 2013	4 studies 95,526	OR=1.08 (0.97-1.21)	AF was not different in maximum versus the minimal amount of PA	Based on cumulative PA per week (4-5 categories)
Nielsen [8], 2013	3 studies N/A	OR=0.92 (0.80 - 1.05)	AF was not different in high PA compared with low PA	N/A
Zhu [15], 2016	10 studies N/A	RR=0.98 (0.90 - 1.06)	Comparing the most physically active vs. the least physically active groups	PA categories
Ricci [16], 2018	19 studies 29,855	RR= 0.97 (0.85 - 1.10)	High PA, in comparison to low PA, did not affect AF risk	Based on MET-h/week <3 (light intensity PA like slow walking) 3–6 (moderate intensity PA like slow cycling) >6 (vigorous-intensity PA like fast running).
Garlipp [19] 2019	11 studies 276,323	RR=0.914 (0.833 - 1.003)	Individuals who exercise are less likely to have AF.	N/A
		Studies comparing high PA versus no PA		
Nielsen [8], 2013	3 studies N/A	OR=0.78 (0.68 - 0.89)	AF reduced in high PA compared with no PA	N/A
Kwok [12], 2014	8 studies 152,925	RR=1.0 (0.82 - 1.22)	Engaging more intensive PA in comparison with controls had no effect on AF risk	N/A
Mohanty[14], 2016	7 studies 93,995	OR=2.47 (1.25 - 3.7)	A sedentary lifestyle compared to moderate or intense activities was RF for AF	Study reports (Based on 3 to 5 PA or exercise levels)
Brunetti[13], 2016	11 studies 81,787	OR=0.92 (0.84 - 1.01)	The risk of AF was not significantly higher in subjects practicing PA than in controls	Nostrictdefinition
Zhu [15], 2016	11 studies N/A	RR=1.07 (0.93 - 1.25)	The risk of AF was not significantly increased in individuals with intensive physical activity (vigorous, high intensity, or heavy workload)	High-intensityexercise>2000 hours
Garlipp [19] 2019	11 studies 276,323	RR=0.914 (0.833 - 1.003)	Individuals who exercise are less likely to have AF.	N/A
		Studies comparing high PA versus moderate PA		
Nielsen [8], 2013	3 studies N/A	OR=1.01 (0.88 - 1.17)	AF was not different in high PA compared with moderate PA	N/A
		Studies comparing high/moderate PA versus low/no PA		
Nielsen [8], 2013	2 studies N/A	OR=0.89 (0.83 - 0.96)	AF reduced in moderate/high PA compared with none/very low PA	N/A
Kwok [12], 2014	4 studies 112,784	RR=0.95 (0.72 - 1.26)	Spending more time on PA in comparison with controls had no effect on AF risk	N/A
Mishima [20] 2020	15 studies 1,464,539	HR 0.94, (0.90-0.97)	PA at guideline-recommended levels and above are associated with a significantly lower AF risk. However, at 2000 MET-minutes per week and beyond, the benefit is less clear	N/A

AF: Atrial fibrillation; CI: confidence interval, N/A: Not available; PA: physical activity; MET-h: Briefly, a metabolic equivalent (MET-h) is defined as an energy expenditure of 1 kcal/kg per h and is roughly equivalent to the energy cost of sitting quietly. OR: odds ratio, RR: risk ratio

methodological quality of the included meta-analysis[22]. The AMSTAR contained 16 items for quality assessment of the reported information. Then studies were classified into four different groups critically low, low, moderate, and high based on the result of quality assessment calculated online via https://amstar.ca/. Quality assessment was performed by two different assessors (AM and ASSH) and a third assessor (CR) for discrepancies.

3. Results

3.1. Selection of meta-analyses

A total of 5340 unique abstracts were retrieved in electronic databases and manual cross-checking of reference lists. From this, 5309 were

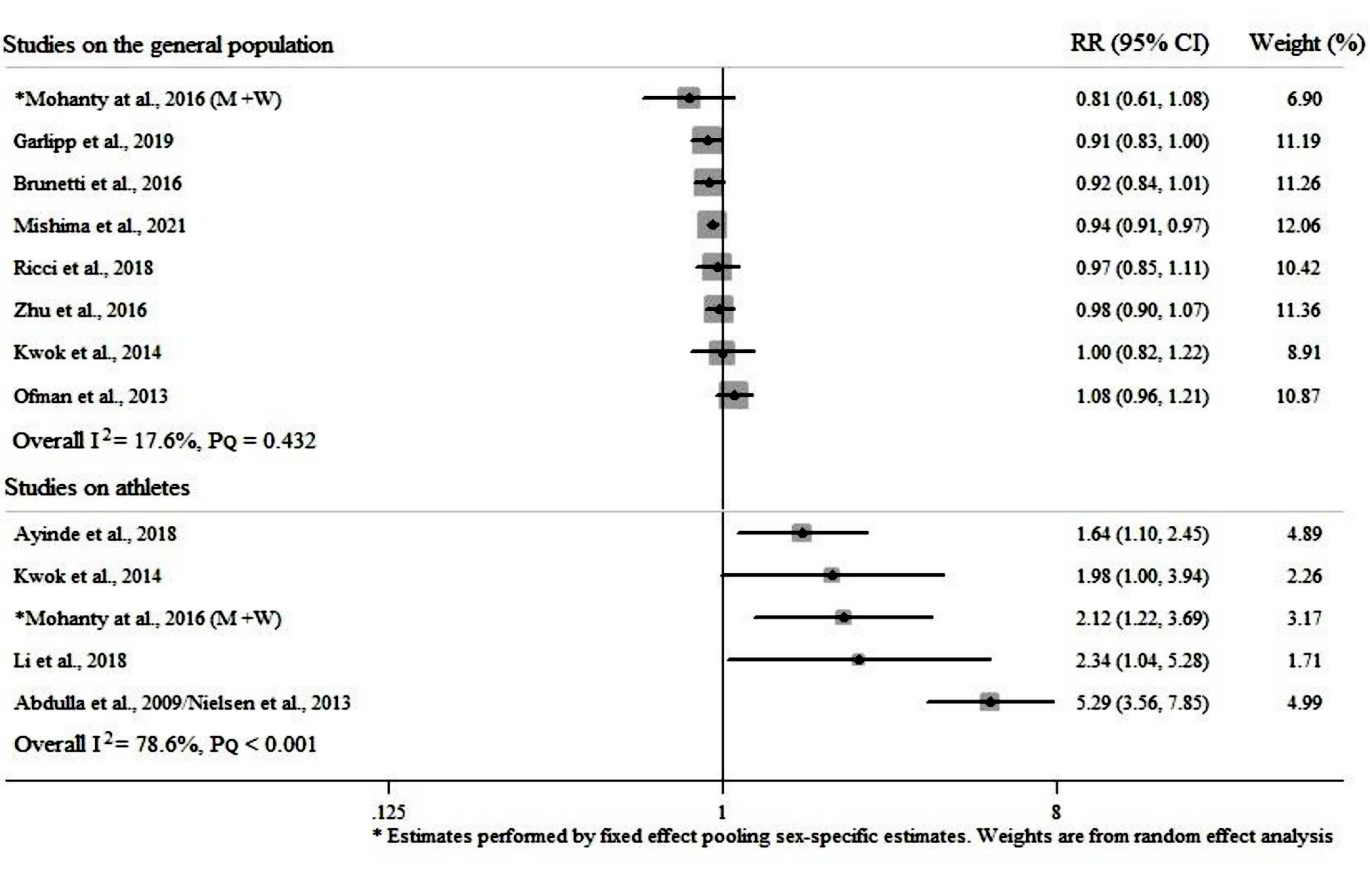

Figure 2: Forest plot of meta-analytical estimates of AF risk for higher vs. lower physical activity volume in athletes and the general population. PQ is the P-value for the Cochrane Q test for heterogeneity

excluded, and the full text of the remaining 32 review articles was studied in detail. Finally, 12 meta-analyses were included in this review (Figure 1).

3.2. Characteristics of included meta-analyses

The included systematic reviews and meta-analyses are summarized in Table 1. The reviews were published over an 11-year period between 2009-2020. The review with the largest pooled sample size was authored by Mishima et al. (n=1,464,539)[20], while the smallest was the first published study by Abdulla et al. (n=1,550)[7]. The pooled gender ratio was reported only in two studies [7,20], and the pooled age was reported by six studies [7,12,13,18-20]. Most of the reviews, included studies of only case-control or cohort/post hoc analysis of randomized controlled trials in design, but two reviews did include cross-sectional studies (Table 1).

Subgroup analyses were performed in most of the studies (11/12). The most common types of subgroup analyses were for PA categories and gender. Ricci et al.[16] performed the greatest variety of subgroup analyses, including region, publication date, studies quality, and adjustments for CAD risk factors (Table 2-3). Most of the conducted meta-analysis compared AF risk in two groups of high PA versus no PA (n=6), or high PA versus low PA (n=6); followed by athletes versus non-athletes (n=5), high/moderate PA versus low/no PA (n=4), and high PA versus moderate PA (n=1) (Table 2).

3.3. Main findings

3.3.1. Studies comparing athletes versus non-athletes

Five meta-analyses assessed the differences in AF risk between athletes and non-athletes [7,8,12,17,18]. These found a significantly higher risk of AF or atrial flutter in athletes compared with non-athletes or controls (odd ratio (OR) range [95% CI] 1.64 [1.10-2.43] - 5.3 [3.6-7.9] and relative risk (RR) range 1.98 [1.00-3.94] [7,8,12,17,18] (Table 2).Results from heterogeneity assessment pointed out a large variability when all studies were considered a whole (I^2 = 88.6%). Nevertheless, a low variability among AF risks estimates from studies conducted on the general population was observed (I^2 = 17.6%). On the other hand, a consistent heterogeneity among AF risks estimates from meta-analyses conducted among athletes was observed (I^2 = 78.6%) (Figure 2). The heterogeneity from meta-analyses conducted among athletes was nullified (I^2 = 0%) in a sensitivity analysis, excluding the study with the highest AF risk[7].

3.3.2. Studies comparing high versus low/no physical activity

Five out of five meta-analyses revealed no difference between low PA and high PA for risk of AF [8,11,15,16,19] (Table 2).

3.3.3. Studies comparing high versus no physical activity

Two different categories of results were found in this group of studies. Three studies found no significant difference in AF risk between high PA and no PA[12,13,15], whereas three others found a protective effect of high PA on AF development[8,14,19] (Table 2).

Table 3: Studies comparing the impact of PA on AF based on different factors

Reference	Subgroups Effectsize (95% CI)		Narrative findings
Genders			
Brunetti[13], 2016	Male OR=7.49 (3.12 - 19.01)	Male and/or female OR=0.89 (0.81– 0.97)	The risk of AF seems higher in male subjects practicing physical exercise
Mohanty[14], 2016	Male Moderate 0.81 (0.26 - 1.003) Intense 3.30 (1.97 - 4.63)	Female Moderate 0.91 (0.78 - 0.98) Intense 0.72 (0.57 - 0.88)	Moderate and intense exercise compared to sedentary were protective factors for AF in women. Although moderate exercise was a protective factor, intense exercise was a risk factor for AF in men.
Mohanty[14], 2016	Male Athletes 3.3 (1.72 - 5.91) Non-athletes 3.4 (1.26 - 5.42)	Female Athletes 0.67 (-0.59 - 1.92) Non-athletes 0.85 (0.51 - 1.21)	Vigorous PA versus leisure-time exercise in man was found to be associated with a significantly high risk of AF in athletes with endurance sports practice
Zhu [15], 2016	Male Total PA RR=1.18 (1.02 - 1.37) Intensive PA RR=1.12 (0.99 - 1.28)	Female Total PA RR=0.92 (0.87 - 0.97) Intensive PA RR=0.92 (0.86 - 0.98)	Association between total PA exposure and the risk of AF Association between total intensive PA exposure (vigorous, high intensity, or heavy workload) and the risk of AF
Li [18] 2018	Male Athletes OR=4.03 (1.73–9.42)		The risk of AF was significantly higher in athletes compared with the general population, especially in male athletes <60 years old.
Mishima[20], 2020	PA above the guideline-recommended level Male HR 0.96 (0.93 – 1.00) Highest PA HR 1.03 (0.94 – 1.12)	PA above the guideline-recommended level Female HR 0.91, (0.88-0.95) Highest PA HR 0.88 (0.83 – 0.92)	PA above the guideline-recommended level was associated with a lower risk of incident AF in women and men. Highest PA was associated with a lower risk of AF in women, but not in men, compared to inactive.
Age			
Brunetti[13], 2016	Younger than 54 years OR=5.30 (3.43 - 8.20)	Olderthan 54 years OR=0.84 (0.76 - 0.92)	A reverse correlation between age and risk of AF seems to be evident
Ayinde[17], 2018	Younger than 54 years OR=1.96 (1.06 - 3.65)	Olderthan 54 years OR=1.41 (0.81 - 2.44)	Age appears to modify the risk of AF in athletes.
Li [18] 2018	Younger than 60 years OR=3.24 (1.23 - 8.55)		The risk of AF was significantly higher in athletes compared with the general population, especially in male athletes <60 years old.
Region			
Zhu [15], 2016	American RR=0.95 (0.86 - 1.06)	Non-American RR=1.05 (0.86 - 1.27)	The impact of total PA on AF risk was not related to the region of studies
Zhu [15], 2016	American RR= 1.02 (0.89 - 1.17)	Non-American RR: 1.23 (0.68 - 2.21)	Impact of Intensive PA (vigorous, high intensity, or heavy workload) on AF risk was not related to the region of studies
Ricci [16], 2018	American RR=1.24 (0.97 - 1.60)	Non-American Europe RR=0.86 (0.71 - 1.04) Australia and New Zealand RR=0.80 (0.62 - 1.03)	The impact of PA on AF risk was not related to the region of studies
Publicationrelatedissues			
Kwok[12], 2014	Low risk of bias OR=0.80 (0.52 - 1.24)	High risk of bias OR= 1.12 (0.94 - 1.32)	The impact of any PA or leisure-time activity on AF risk was not related to the bias risk of the studies
Kwok[12], 2014	Low risk of bias RR=1.04 (0.87 - 1.24)	High risk of bias OR=1.04 (0.73 - 1.49)	The impact of intensive PA on AF risk was not related to the bias risk of the studies
Ricci [16], 2018	NOS1>6 RR= 1.06 (0.92 - 1.22)	NOS≤6 RR= 0.87 (0.66 - 1.14)	The impact of PA on AF risk was not related to the quality score of studies
Ayinde[17], 2018	NOS ≥ 6 OR=2.23 (1.45 - 3.41)	NOS < 6 OR=1.22 (0.81 - 1.83)	The impact of PA on AF risk was related to the quality score of studies
Ricci [16], 2018	After median RR= 1.02 (0.66 - 1.57)	Before median RR= 0.96 (0.85 - 1.08)	The impact of PA on AF risk was not related to the publication date of studies
Li [18] 2018	Case control group OR=5.10 (3.07–8.46)		In the subgroup analysis based on study type, a significant risk was found in the case control group
Sample size			
Li [18], 2018	sample sizes <300 OR=4.91 (3.08 - 7.84)		Based on the sample sizes, the group with sample sizes <300 demonstrated significant results
Mode of sport			
Li [18], 2018	Single typesports OR=3.97 (1.16 - 13.62		In the subgroup analysis based on sports mode, a significantly increased risk was found in the group with a single type

1: NOS: Newcastle Ottawa Quality

3.3.4. Studies comparing high/moderate versus low/no physical activity

In this category, although Nielsen et al. and Mishima et al. reported a reduction in AF with moderate/high PA compared to none/very low PA[8,20]; the review by Kwok et al. showed no significant difference between any physical activity or leisure-time activity and risk of AF (RR 0.95 [0.72-1.26])[12] (Table 2).

3.3.5. Studies comparing high versus moderate physical activity

The only conducted meta-analysis on this issue revealed that AF risk was not significantly different for individuals with high levels of PA versus moderate levels of PA (OR 1.01 [0.99-1.17]) [8] (Table 2).

3.4. Subgroup analyses

3.4.1. Gender and Age Subgroups

Subgroup analysis based on gender suggests that men have a greater risk of AF with PA[13-15,18]. Mishima et al. reported that PA above the guideline-recommended level was associated with a lower risk of AF in women, but not in men[20]. In two meta-analyses, a subgroup analysis of patients younger and older than 54 years was performed [13,17], and

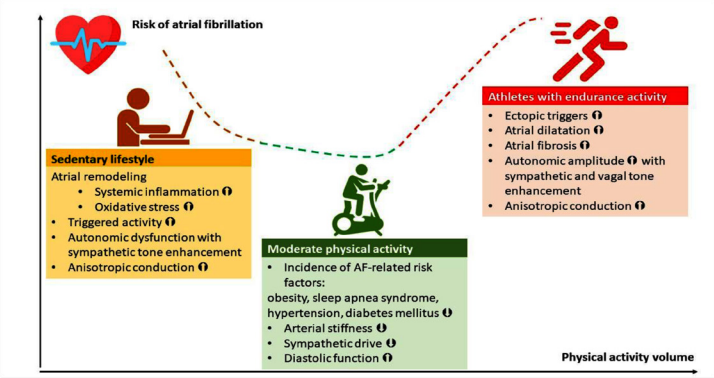

Figure 3: **Different possible mechanisms through which physical activity may contribute to atrial fibrillation.**

individuals younger than 54 years in both studies reported a higher risk of AF. In contrast, individuals older than 54 years showed no association between PA and AF[17] or a protective effect of exercise [13] (Table 3). Li et al. showed that AF risk was significantly higher in male athletes <60 years old the general population[18].

3.4.2. Geographic regions

Two meta-analyses reported that the influence of American and non-American studies on PA on AF risk, and the studies conclude that the impact of PA on AF risk was not significantly affected by the region where the study took place[15,16] (Table 3).

3.4.3. Publication related issues

In two studies, the impact of "included studies quality" was assessed[16,17], while in two meta-analyses, the effect of publication bias was investigated[16,20]. These studies revealed that neither publication bias nor quality scores were associated with the impact of PA on AF risk. In another study, the effect of the publication date of studies was assessed, which showed no significant impact too[16] (Table 3). The impact of sample size and mode of sport on the risk of AF was also reported by Li et al.[18]

3.4.4. Levels of Activity

Ricci et al.[16] performed the only meta-analysis linking exercise dose to the risk of AF. They showed that in individuals with PA at volumes of 5–20 metabolic equivalents per week (MET-h/week), PA was associated with a significant reduction of AF risk (RR for 19 MET-h/week=0.92 (0.87 - 0.98). By comparison, PA volumes exceeding 20 MET-h/week were unrelated to AF risk (RR for 21 MET-h/week=0.95 (0.88 - 1.02).

3.4.5. Sports mode

In the subgroup analysis based on sports mode - performed by Li et al. [18], a significantly increased risk was found in the group with a single type of sport (OR=3.97, 95% CI=1.16–13.62, $P_{heterogeneity}$=.018, I^2=70.4%)

3.5. Quality assessment

The overall quality of the included studies using the AMSTAR-2 tool was evaluated and reported in Table 4.

4. Discussion

4.1. Main findings

The main findings of this systematic review can be summarized as follows: First, there is consistent evidence from few reviews that athletes are at greater risk of AF than non-athletes. Second, in a general population with both genders, there is evidence that high or moderate PA compared to low or no PA is associated with a lower risk of AF. Third, the literature suggests that men are more likely to develop AF with PA compared to women. Finally, patients younger than 54-60 years appear to have a greater risk of AF with increased levels of PA.

4.2. Overview of the results of twelve different meta-analyses

Abdulla and Nielsen published the first meta-analysis of 6 case-control studies in 2009 [7]. They then published another meta-analysis in 2013, which now included prospective comparative data on the intensity of PA in populations with and without AF [8]. Despite the addition of newer studies, they still found an increased risk of AF in athletes than non-athletes or the general population. Nevertheless, a new observation from the three prospective studies was that moderate/high habitual PA was associated with a significantly reduced risk of AF compared with none or very low-intensity PAOR=0.89[8].

Also, in 2013, Ofman et al. published a meta-analysis with the opposite result: "Our data do not support a statistically significant association between regular PA and increased incidence of atrial fibrillation" [11]. The reason for the disparate findings was likely that Ofman et al. evaluated the relation between increased level of PA and AF among non-athletes, while Nielsen et al. conclusion was mainly based on the comparison between athletes and non-athletes.

In 2014, Kwok et al. performed a larger meta-analysis of 19 studies including ≈ 511k individuals and confirmed the findings of Ofman et al. that there was no association between higher levels of PA and AF [12]. Further more, due to the larger size of the study, Kwok et al., were able to conduct subgroup analyses based on the effect of vigorous PA, level of PA.

The meta-analysis by Brunetti et al. from 2016 also confirmed previous findings that found no significant associations between PA and increased risk of AF[13]. Brunetti et al. even noted a trend towards a lower risk of AF, though the strength of this finding was limited by high heterogeneity [13].The heterogeneity might be due to gender and age; they argued that AF development risk seemed to be increased in studies enrolling younger and male subjects[13].

The gender-dependency of AF hypothesis was then re-assessed by Zhu et al. and Mohanty et al. Zhuet al. showed that increased PA exposure was associated with an increased risk of AF in males, with a significantly reduced risk of AF in women [15]. Similarly, Mohanty et al., found intensive PA associated with an increased risk of AF in men and a decreased risk of AF in women [15].

Mohanty et al. also observed that a sedentary life style significantly increases the risk of AF while a moderate amount of PA reduces the risk of AF[14]. Ricci et al. described a J-shaped relation between PA volume and AF risk, where PA at volumes of 5 to 20 MET-h/week

Table 4: Evaluation of quality of included studies using the AMSTAR-2 tool

Reference	Components of PICO[1]	Registered protocol	Eligibility criteria	Search strategy	Duplicatedstudyselection	Duplicateddataextraction	Excludedstudieslist	Includedstudiesdescription
Abdulla (7), 2009	☺	☹	☺	😐	☺	☺	☹	😐
Nielsen (8), 2013	☺	☹	☺	☺	☺	☺	☹	☹
Ofman(11), 2013	☺	☹	☺	😐	☺	☺	☹	☺
Kwok(12), 2014	☺	☹	☺	☹	☺	☺	☹	☺
Brunetti(13), 2016	☺	☹	☺	☹	☺	☺	☹	☹
Mohanty(14), 2016	☺	☹	☺	☺	☺	☺	☹	☺
Zhu (15), 2016	☺	☹	☺	😐	☺	☹	☹	☺
Ricci (16), 2018	☺	☹	☺	😐	☺	☹	☹	☺
Ayinde(17), 2018	☺	☹	☺	😐	☹	☺	☹	😐
Li (18), 2018	☺	☹	☺	☺	☹	☹	☹	☺
Garlipp(19), 2019	☺	☹	☺	☺	☺	☺	☹	☺
Mishima(20), 2020	☺	☺	☺	☺	☹	☺	☹	☺

1. **PICO:** Patient, intervention, comparison, outcome

☺Yes 😐Partial Yes ☹ No/Unclear

was associated with a reduced AF risk, whereas both, sedentary lifestyle and intensive PA of more than 20 MET-h/week, showed no protective effect on AF risk and no difference in direct comparison.

Two different meta-analyses by Ayinde et al.[17]. and Li et al.[18], both conducted in 2018, reconfirmed the early findings from Abdulla and Nielsen, and showed that athletes have an increased risk of AF compared to the general population. Subgroup analysis by Ayinde et al.[17] demonstrated an increased risk for adults younger than 54 years. Li et al. similarly reported an increased risk for men younger than 60 years.

Garlipp et al.[19] included studies with athletes and studies with the general population in their meta-analysis. The combined analysis of the studies did not suggest a significant increase in AF in subjects submitted to exercise (RR = 0.914, 95% CI = 0.833 – 1.003, heterogeneity: $p < 0.001$). Garlipp et al. concluded that individuals who exercise are less likely to have AF.

In 2020, Mishima et al.[20] published a meta-analysis with the most participants so far. It included 1,464,539 individuals. According to their results, individuals achieving the guideline-recommended level of PA (450 MET-minutes per week)had a significantly lower risk of AF (HR 0.94, 95% CI 0.90-0.97, p=0.001). Dose-response analysis showed that PA levels up to 1900 MET minutes per week were associated with a lower risk of AF, with less certainty beyond that level.

The publication of 12 meta-analyses on AF and PA in the last 12 years demonstrates a strong interest in the topic. Individual meta-analyses led to different, apparently contrary conclusions. Our interpretation of the existing body of evidence refers to a dose-response association between PA dose and AF risk. Whereas moderate PA seems to have a protective effect, it seems that no PA and vigorous exercise may increase the risk for AF. The next question is whether the pathophysiology supports the epidemiologic observations.

4.3. Potential mechanisms for altered risk of AF with physical activity

4.3.1. Athletes are more at risk of AF than non-athletes

AF pathophysiologyis characterized by Coumel's triangle consisting of focal triggers, arrhythmogenic substrate created by e.g. increased left atrial size with anisotropy and fibrosis, and additional factors as autonomic imbalance or disturbed electrolyte homeostasis[23-25].

Typical, non-athletic patients with AF are overweight elderly patients with arterial hypertension. Athletes with AF exhibit a different phenotype. So even though similar pathophysiology may exist in both non-athletic patients and athletes with AF, other mechanisms or a different degree of influence of the above-mentioned factors seems likely (Figure 3).

Athletes show specific characteristics that may favor the development of AF. These characteristics mainly occur in endurance athletes, which seem to be more prone to AF than athletes from non-endurance sports [26]. In addition, athletes exhibit an increased autonomic influence by both antipodes of the autonomous nervous system, the vagal and the adrenergic system[27].

Strong support of an exercise-induced model of AF came from Guasch et al., who compared exercised rats with sedentary control rats. Training caused enhanced atrial fibrosis, increased AF vulnerability, and vagal tone. Detraining reversed AF vulnerability and vagal tone[28]. Studying human subjects, Wilhelm et al. reported that vagal activity, p-wave duration, premature atrial contractions, and LA volume were associated with lifetime training hours in a study with runners[29].

Wijffels et al. observed in goats that atrial refractory period shortening (electrical remodeling) by pacing occurred directly, where as persistent AF occurred after two weeks. The authors hypothesized, therefore, that persistent AF needed a "second factor" [30]. A potential "second factor" could be an atrial structural disease such as tissue fibrosis [31].

Findings of direct histological substrate characterization in patients with AF have also confirmed atrial substrates' presence, mainly fibrosis, in the development and progression of AF[32].

Another risk factor for AF is arterial hypertension[33]. Arterial hypertension leads to impaired diastolic function by cardiac remodeling and associates with an enhanced risk of AF [33-35]. Thus, arterial hypertension induced and/or enhanced by exercise may also increase the probability of developing AF in athletes. However, as only a minority

Table 4: Evaluation of quality of included studies using the AMSTAR-2 tool (continued)

Reference	UseRoBassessmenttechniques	Report on the funding source for the included studies	Appropriate meta-analysis method	Assessment ofRoBimpact	Attention to RoB in interpreting/discussing the results	Heterogeneityexplanation	Publicationbiasassessment	Conflict of interest or Funding report
Abdulla (7), 2009	☹	☹	☺	☹	☹	☺	☹	☺
Nielsen (8), 2013	☹	☹	☺	☹	☹	☺	☺	☺
Ofman(11), 2013	☺	☹	☺	☺	☺	☺	☺	☺
Kwok(12), 2014	☺	☹	☺	☹	☹	☺	☺	☺
Brunetti(13), 2016	☹	☹	☺	☹	☺	☺	☹	☺
Mohanty(14), 2016	☺	☹	☺	☺	☹	☺	☺	☺
Zhu (15), 2016	☺	☹	☺	☺	☺	☺	☹	☺
Ricci (16), 2018	☺	☹	☺	☺	☺	☺	☺	☺
Ayinde(17), 2018	☺	☹	☺	☺	☺	☺	☺	☺
Li (18), 2018	☺	☺	☺	☺	☺	☺	☺	☺
Garlipp(19), 2019	☹	☹	☺	☹	☹	☺	☹	☺
Mishima(20), 2020	☺	☹	☺	☺	☹	☺	☺	☺

1.**RoB:** risk of bias

☺Yes ☺Partial Yes ☹ No/Unclear

of athletes develop AF, it is still unknown, which specific factors most likely determine the AF risk. In addition, genome-wide association studies in the general population described common variants in specific genomic regions related to AF[36]. Nonetheless, no typical mutation has been reported in athletes with AF.

4.3.2. In the general population, moderate physical activity seems to be protective against AF

Regular PA by physical work, moderate leisure-time sports, or daily commuting by walking or using a bicycle has many positive effects on physical and mental health. It increases general fitness, helps to maintain average weight, blood pressure,and blood sugar [26]. In addition, regular PA has positive effects on mood and mental health. It may balance the negative effects of the increasingly sedentary lifestyle in industrialized countries, and there is evidence that it increases life expectancy.

As regular PA counteracts risk factors for AF as overweight, arterial hypertension, and diabetes mellitus, it is not surprising that a sedentary lifestyle is associated with an increased prevalence of AF. In contrast, regular physical work seems to reduce the risk for AF.

Still though, our review cannot answer the often-asked: What distinguishes athletic activities that seem to increase the risk for AF from daily life physical activities that decrease the risk? It seems logical that PA volume and intensity are increased in athletes, compared to "normal" physical in the general population. Another factor might be the increased vagal and adrenergic activity in athletes, compared to the general population. Thus, the dose response relation between PA volume and AF risk appears to follow a J- or U-shaped curve. PA at the bottom of the curve with volumes of 5 to 20 MET-h/week may result in a reduced risk for AF, whereas lower and higher volumes of PA may lead to an increased risk for AF[16].

4.3.3. In the male gender, physical activity seems to act as a risk factor for AF development, while in females as a protective factor

Male gender has been found as a risk factor for AF in athletes [37]. At similar amounts of exercise, males showed - compared to females - a more pronounced atrial remodeling and an impaired diastolic function. In addition, arterial hypertension at rest and during exercise and an increased sympathetic tone in males might increase the AF susceptibility [37]. Another reason may be the taller stature of males that associates with increased LA size as an independent risk factor for AF [38,39]. However, Myrstad et al. observed that intensive endurance exercise might also increase AF's risk among athletic females [40].

4.3.4 Physical activity in individuals younger than 54-60 years old is associated with a higher risk of AF

We do not know yet why PA in individuals younger than 54-60 years is associated with a higher risk of AF. We hypothesize that this finding is caused by the effect of several competing, age-dependent risk factors and protective factors. Nevertheless, we can assume that exercise volume and intensity might be greater in younger individuals than in older individuals with the corresponding increased effects on the autonomous nervous system. Perhaps the susceptibility of the autonomous nervous system by intensive exercise decreases with advanced age? Perhaps intensive exercise makes AF occur earlier in people with a predisposition for the development of AF?

As advanced age on its own also is a risk factor for AF, the risk modifying effect of exercise seems to become less important or may even reduce the risk for AF in individuals older than 54-60 years.

4.3.5 Previous literature

Valenzuela et al.[41] first published a meta-analyses review to summarize the evidence on the association between PA/sports practice and AF risk. The authors included 11 meta-analyses in their research. We suggest a slightly different interpretation of the existing body of evidence than the interpretation of Valenzuela et al.. In their summary, they stated that"according to the meta-analytical evidence that is currently available, overall PA does not appear to influence the risk of AF, but sports practice, particularly in endurance events, can increase AF risk." In contrast to Valenzuela, we interpret the existing body of evidence that moderate PA compared to no PA is associated with a lower risk of AF in a general population. Whereas gender and age were not analyzed by Valenzuela et al., our results suggest that males and patients younger than 54-60 years are more likely to develop AF with increased levels of PA. As Valenzuela et al. we can confirm that athletes are at greater risk of AF compared to non-athletes. An essential aspect of our manuscript is that most of the authors of the included meta-analyses agreed to contribute and approved the results.

5. Limitations

Publication bias in the included papers of the conducted meta-analyses was a significant limitation to conclude the association between AF and PA. Possibly, negative or neutral studies were less likely to be published. Furthermore, grey literature often is not considered. Heterogeneity was the other limitation of the included studies in the meta-analyses, which was reported to be significant in most of them. Different study designs, different definitions for PA intensity and duration, different methods of AF diagnosis seem to be the potential causes of heterogeneity, and only some studies' reasons for the heterogeneity were determined.

Moreover, in case-control studies on athletes with cases and controls belonging to two different populations, the logistic analysis often lacked to be adjusted for confounding factors. Another limitation would be that many studies, e.g., on athletes, did not report the exposure to PA in terms of MET/h-week so that these could not be included in dose-response analysis. Furthermore, a critical limitation of exercise studies showing gender-specific effects is that the intensity of PA is not standardized in any of them. Possibly, what is a high PA for women, could be moderate PA for men. Specific studies with objectively assessed measures of PA (training schedules, accelerometry) should therefore be performed in the future. Finally, the difference between AF risks concerning PA from meta-analyses conducted in athletes and the general population is affected by the different study designs. In particular, estimates from retrospective case control studies conducted in athletes may have overestimated the effect of PA on the AF risk compared to the findings of prospective cohort studies conducted on the general population. However, the magnitude of the AF risk difference between athletes and the general population suggests the concrete existence of a possible association between AF risk and the volume of PA.

6. Conclusions

Our review suggests that athletes have an increased risk of AF compared to the general population. In the general population, PA has a dose dependent, J-shaped effect on AF risk, with increased risk at very low and very high levels of PA. This effect seems to be gender-specific and more pronounced in younger males. Population groups with a higher risk of AF may benefit from opportunistic screening for AF, especially with cardiac symptoms. Moderate physical activity seems to reduce the risk for AF.

Authorship and Contributorship

All authors mentioned earlier substantially contributed to the conception or design of the work (AM, ASS), or the acquisition, analysis, or interpretation of data (AM, ASS, JM, JA, HA, CR, NDB, CSK, SM, AN, JK, TLLL, SK, ND, SR, AA, AB, GH, MD). Furthermore, all above named authors contributed either to the drafting of the work (AM, ASS) or revised it critically (JM, JA, HA, CR, NDB, CSK, SM, AN, JK, TLLL, SK, ND, SR, AA, AB, GH, MD). All authors finally approved this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (AM, ASS, JM, JA, HA, CR, NDB, CSK, SM, AN, JK, TLLL, SK, ND, SR, AA, AB, GH, MD).

Joint first authorship

Andreas Müssigbrodt and Alireza Sepehri Shamloo contributed equally to this work and shared their firstauthorship.

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Association between Intra-box Ablation during Posterior Wall Isolation for Persistent Atrial Fibrillation and Posterior Wall Reconnection

Sayuri Tokioka[1]; Seiji Fukamizu[1]; Takashi Kimura[1]; Masao Takahashi[1]; Takeshi Kitamura[1]; Rintaro Hojo[1]

[1]Department of Cardiology, Tokyo Metropolitan Hiroo Hospital, Tokyo, Japan

Abstract

Background: Posterior wall isolation (PWI) combined with pulmonary vein isolation (PVI) has been proven effective for persistent atrial fibrillation (AF). Intra-box ablation, defined as application in the "box" area during PWI in this study, is sometimes necessary when linear ablation of the roof and bottom fails to achieve complete isolation. This study aimed to investigate the factors of patients requiring intra-box ablation and to evaluate the effect of intra-box ablation on clinical outcomes.

Methods: This is an observational study including patients who underwent PVI and PWI for persistent AF in the first procedure from June 2017 and March 2020, at the Tokyo Metropolitan Hiroo Hospital. When linear ablation of the roof and bottom failed to complete PWI, intra-box ablation was added. Six months after the procedure, patients undertook follow-up electrophysiological study and additional ablation as the second procedure. Findings of the left atrium (LA) mapping and ablation in the first procedure and posterior wall (PW) reconnection in the second procedure were evaluated. Patient characteristics and outcomes were compared between patients with and without intra-box ablation.

Results: Of the 93 patients included in this study, successful PWI was achieved in 91 (mean age, 67.5±9.8 years; male, 75.3%), and intra-box ablation was needed in 59 (63.4%). Shorter PW activation time (40.3±10.4 vs 51.3±15.2, p=0.026) and larger upward conduction patterns in the PW were significant association with the necessity of intra-box ablation. More PW reconnection in the second procedure was observed in patients with intra-box ablation than in those without intra-box ablation (21/28,75.0% vs 8/20, 40.0%; p=0.020).

Conclusion: We showed that the requirement of intra-box ablation was related to lower durability of PW. Findings of LA mapping suggested the possibility that PW conduction velocity and patterns was one of the mechanisms of failure of linear PWI.

Introduction

Pulmonary vein isolation (PVI) is a standard strategy of catheter ablation for atrial fibrillation (AF). However, it is less effective for persistent AF than for paroxysmal AF [1]. The posterior wall (PW), with its complex structure of varied wall thickness and mixed fibers, is known to play an important role in AF [2,3]. Previous meta-analyses showed that less AF recurrence was observed in patients with both of PVI and posterior wall isolation (PWI) than in those with PVI only [4,5].

However, PW reconnection is a problem and the effectiveness of the hybrid of endocardial and epicardial ablation has been reported [6-9]. Epicardial procedure involves some risks, such as cardiac tamponade and pericarditis, and should be limited to refractory AF cases. Improving the PWI technique from the endocardial approach is needed to reduce refractory AF. Linear ablation of roof and bottom is one of the strategies for PWI. After failing to achieve complete PWI by linear ablation, the application in "box" area, which is defined as intra-box ablation in this study, is sometimes required. The characteristics of patients who need intra-box ablation and the impacts of intra-box ablation on clinical outcome remain unknown.

Hence, this study is aimed to investigate the characteristics of patients with intra-box ablation and to evaluate the effect of intra-box ablation on AF recurrence.

Key Words

Atrial Fibrillation, Box Isolation

Corresponding Author
Sayuri Tokioka,
Tokyo Metropolitan Hiroo Hospital
2-34-10 Ebisu, Shibuya-ku, Tokyo, Japan

Material and methods

Study population

This was a single-center observational study. Patients who underwent PVI and PWI for persistent AF in the first procedure between June

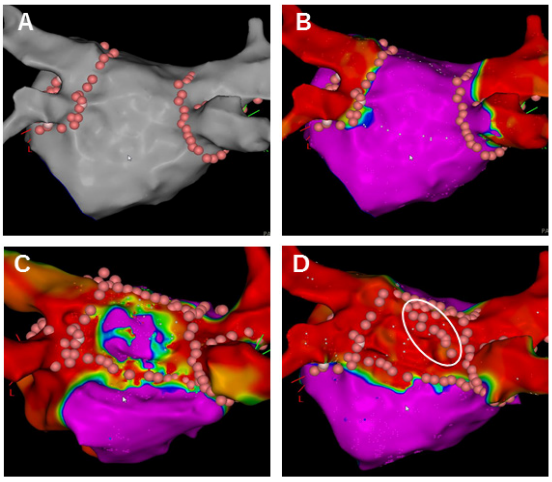

Figure 1: An example of PVI and PWI.

These figures show the procedure of PVI and PWI. A) First, PVI is performed. B) After PVI, LA mapping during RA pacing is performed to confirm PVI. This map is analyzed after the procedure. C) Linear ablation for PWI is performed. When compete PWI is not achieved, posterior wall mapping is performed. D) In this case, intra-box ablations (in white circle) are required to achieve complete PWI. After PWI, posterior wall mapping is performed again to confirm endpoints.
PVI, pulmonary vein isolation; PWI, posterior wall isolation; LA, left atrium; RA, right atrium.

2017 and March 2020 at the Tokyo Metropolitan Hiroo Hospital were included in this study. Patients who previously experienced catheter ablation for AF, atrial flutter or atrial tachycardia were excluded. Patients who required additional ablation other than PVI and PWI during the first procedure, for example, mitral isthmus ablation and complex atrial fractionated electrograms, were also excluded.

Protocol for catheter ablation

Anti-arrhythmic drugs (AADs) were discontinued for ≥5 half-lives prior to ablation. Oral anticoagulant therapy was initiated at least 1 month prior to the procedure.

In the first procedure, the protocol was as follows: the first circumferential PVI and ablation of the carina were performed (Fig.1 A); Left atrium (LA) mapping during right atrium (RA) pacing was conducted to confirm PVI (Fig.1 B); roof and bottom linear ablation was performed for PWI (Fig.1 C); and lastly, when linear ablation failed to complete PWI, intra-box ablation was added (Fig.1 D).

The electrophysiological study and ablation were performed under deep sedation, using an intravenous administration of propofol. A 20-polar superior vena cava (SVC)-RA-coronary sinus (CS) electrode catheter (BeeAT, Japan Lifeline, Tokyo, Japan or Inquiry, Abbott, Abbott Park, Illi, USA) was inserted via the right subclavian vein into the coronary sinus. The PVs and LA were mapped using a multielectrode mapping catheter (PentaRay, Biosense Webster, Diamond Bar, CA, USA) and a three-dimensional anatomical mapping system (CARTO, Biosense Webster). A 3.5-mm irrigated-tip catheter (ThermoCool Smart touch SF, Navistar, BiosenseWebster) was used for ablation. PVI was performed using a circular mapping catheter (Lasso, Biosense Webster) placed within the ipsilateral ostia of the superior and inferior PVs. The endpoint of PVI was the achievement of a bidirectional conduction block between the LA and PVs. After PVI, cardioversion was delivered to restore sinus rhythm. LA mapping was conducted by multielectrode catheter (PentaRay, Biosense Webster) during high RA pacing (basic cycle length, 600 msec), and then PWI was conducted.

During PWI, the PentaRay was placed at the PW to record its electrical potential. Roof line and bottom line ablation were conducted to achieve PWI. After linear ablation, LA mapping was conducted to confirm isolation of the PW. The area under 0.05 mV was defined as the scar area. The endpoint of PWI was defined as the absence of electrical activity in PW, and the inability to conduct from posterior wall to LA, which was confirmed by 5 mA output pacing from PentaRay at PW. Automaticity and local capture recorded by the PentaRay in the PW were also supportive findings of complete PWI. When PWI was incomplete after linear ablation, PW mapping was performed to search for the gap. In case the propagation map showed excitement traversing the gap to the PW, the gap was ablated. When the gap ablation failed to complete PWI or the gap was unclear, applications in the "box" area, which were defined as intra-box ablation, were conducted. The intra-box area was defined as the area surrounded by the roof and bottom line with a margin of 4-mm. The area with electrical activity was ablated. In this case, the endpoint was the absence of electrical activity captured by high output pacing with 20 mA; if pacing was captured, ablation was added until pacing was not captured.

Radiofrequency (RF) energy was applied point-by-point, and the setting differed per term as Table 1 shows.

The esophageal temperature was monitored using CIRC-S-CATH (CIRCA Scientific, Englewood, CO, USA), and application was abandoned when the temperature was over 41°C.

After confirming the achievement of endpoints, we administered a bolus injection of 20 mg of adenosine triphosphate (ATP) to exclude ATP-provoked dormant conduction of PVs and PW. Catheter ablation was performed to eliminate the presence of reconnection and/or dormant conduction.

LA mapping analysis

LA mapping was performed after PVI and before PWI during RA pacing by a SVC-RA-CS electrode catheter in most patients, and LA mapping data were analyzed after the procedure. LA mapping was abandoned in cases of ongoing AF after cardioversion and the inability to stabilize RA pacing. Box area was defined as the area surrounded by PVI, roof, and bottom lines. Voltage was measured in the para-line area, which was defined as the area of the roof and bottom line with a

Table 1: Radiofrequency energy settings

	PVI except for posterior PVs	posterior PVs	PWI roof line	PWI bottom line
from Jun 2017 to Mar 2018	30 W, 30 sec	25 W, 30 sec	30 W, 30 sec	25 W, 30 sec
From Mar 2018 to Jan 2020	40 W, AI 500	30W, AI 450	40 W, AI 500	30W, AI 450
From Feb 2020 to Mar 2020	50 W, AI 500	50 W, AI 400	40 W, AI 500	30W, AI 450

AI, ablation index; PVs, pulmonary veins; PVI, pulmonary vein isolation; PWI, posterior wall isolation; sec, seconds.

Table 2: Comparison of patient characteristics between intra-box ablation and non-intra-box ablation groups

	Intra-box n=57	non-Intra-box n=34	p value
Age [year]	65.8±10.2	68.9±9.1	0.13
Sex (male)	40 (75.4%)	25 (73.5%)	0.83
AF duration [months]	35.6±42.6	26.6±29.0	0.30
Heart failure	14 (24.6%)	7 (20.6%)	0.19
Hypertension	35 (61.4%)	19 (55.9%)	0.27
Diabetes mellitus	5 (8.8%)	3 (8.8%)	0.99
Stroke	5 (8.8%)	4 (11.8%)	0.64
BNP [pg/]	295.0±360.1	263.7±239.3	0.82
Ejection fraction [%]	55.6±10.6	57.4±11.1	0.60
Left atrial diameter* [mm]	42.0±7.3	42.8±6.8	0.59
Left atrial volume** [ml]	144.0±47.0	156.7±44.3	0.22

AF, atrial fibrillation; BNP, brain natrium peptide; PW, posterior wall; PV, pulmonary vein.
* Left atrial diameter was measured by transthoracic echocardiography.
** Left atrial volume was measured by computed tomography scan.

margin of 4-mm above and below, and the intra-box area was defined as the "box" area excluding the para-line area. Total activation time of the box area were measured. Activation time reflects how much time the excitement takes to propagate to the whole PW.

CARTO version 7's propagation map and vector map were used to observe the conduction pattern of the PW. The cycle length of the vector map was set to the LA activation time in the propagation map. The excitatory wave front is highlighted in the propagation map; the vector map follows the propagation path of an excitatory wave front.

Follow-up

After undergoing PVI and posterior isolation, patients were discharged from the hospital with a prescription for oral anticoagulants. The use of AADs could be discontinued three months after ablation, at the physician's discretion. The rhythm and presence of arrhythmias were evaluated based on the patient's symptoms and a resting 12-lead electrocardiogram, which was recorded during regular visits to our outpatient clinic. To detect AF recurrence and atrial tachyarrhythmia, we performed a 24-h Holter monitoring at 1, 3, and 6 months after the first procedure. AF recurrence was defined as AF and other atrial tachyarrhythmias documented lasting longer than 30 seconds regardless of AADs usage. The blanking period was three months, and AF recurrence was evaluated until 6 months after the first procedure.

Patients underwent a follow-up electrophysiological study and additional ablation for PV reconnection, PW reconnection, and/or non-pulmonary vein foci, if present as the second procedure, 6 months after the first procedure, regardless of AF recurrence. All patients were eligible for the second procedure except for those who rejected it. PV and PW reconnection were evaluated by LA mapping and catheters positioned in the PW and PVs, respectively. When there was PV and/or PW reconnection, applications for gaps were conducted after sites of gaps were searched by using propagation map. After applications for gaps failed to achieve PW re-isolation, intra-box ablation was added. Procedural endpoints were same as the first procedure.

Outcomes

Primary outcomes were findings of LA mapping after PVI before PWI in the first procedure, such as PW voltage, activation time, and propagation/vector map pattern, abundant applications because of esophageal temperature rise, and reconnection of PW in the second procedure. Secondary outcomes were reconnection of PVs in the second procedure and AF recurrence at six months after the first procedure.

Outcomes and patient characteristics were compared between patients with intra-box ablation and without intra-box ablation (intra-box group vs non-intra-box group).

Statistical analysis

Normal continuous and categorical data are presented as the mean ± standard deviation and numbers and percentages, respectively. Non-normally distributed data are summarized as median and interquartile ranges. For statistical test, categorical variables were analyzed using the chi-squared test, where appropriate, with Fisher's exact test and trend test otherwise used. Continuous variables were compared using Student's t-test and Mann-Whitney's U test, as appropriate for the data distribution. The level of significance was set at $p<0.05$.

All analyses were performed using Stata/IC 16.1 (StataCorp LCC, Texas, USA).

Ethics

The study design and procedures were approved by the institutional review board of Tokyo Metropolitan Hiroo Hospital. All patients provided written informed consent before undergoing both the first and the second procedures. The ethical problems with performing the second procedure for all patients were discussed and overcome based on previous reports [10-12] including our data [13,14].

Results

Patient characteristics

Altogether, 93 patients underwent PVI and PWI for persistent AF. Figure 2 shows the procedure for patient selection.

Ninety-one patients remained (mean age, 67.5±9.8 years; male, 75.3%) for statistical analysis after two patients were excluded because of unsuccessful PWI. Intra-box ablation was needed in 57 of the 91

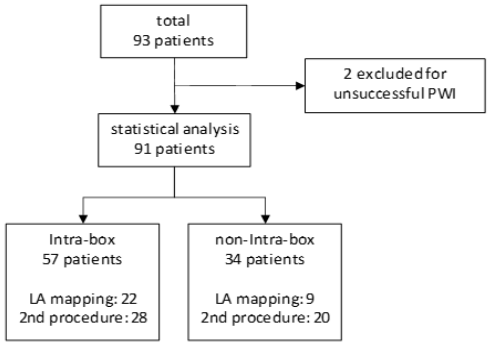

Figure 2: Flow chart of patient selection

LA, left atrium; PVI, pulmonary vein isolation; PWI, posterior wall isolation.

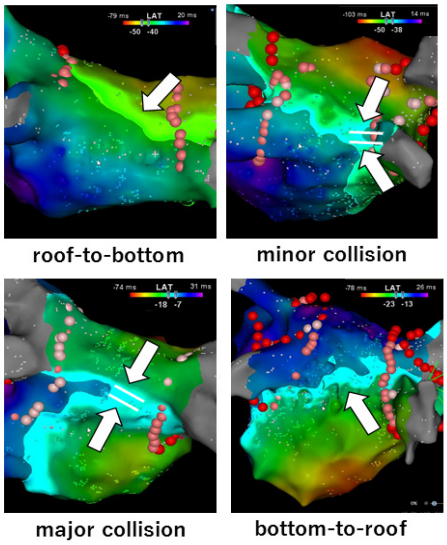

Figure 3: The posterior wall conduction patterns.

These figures show activation maps of four posterior wall conduction patterns. Roof-to-bottom pattern, the excitement wave front enters the posterior wall (PW) from the right of the roof line and proceeds to the bottom; minor collision pattern, the excitement wave front enters the PW from the right of the roof line and proceeds to the bottom, and another excitement wave front enters from the right of the bottom and collides at the lower right of the PW; major collision pattern, the excitement wave front enters from the roof and from the bottom colliding in the middle of the PW; and bottom-to-roof pattern, the excitement wave front enters the PW from the bottom and proceeds to the roof, often with low voltage in the anterior wall.

patients (62.6%) to achieve complete PWI. Patient characteristics with and without intra-box ablation are compared in Table 2. There was no difference in patient characteristics between the two groups.

There was no major complication, such as cardiac tamponade and esophageal fistula, although minor complications were reported in 3 patients (hematoma at puncture site in 2 and asymptomatic PV stenosis in 1).

Findings of LA mapping and ablation in the first procedure

LA mapping after PVI and before PWI during high RA pacing was performed in 31 patients. In the LA map, 879±308 points were collected. The comparison between the intra-box group and non-intra-box group is shown in Table 3. PW activation time was significantly shorter in the intra-box group than in the non-intra-box group (40.3±10.4 ms vs 51.3±15.2, p=0.026), although there was no significant difference in two groups.

The propagation maps of posterior wall revealed that there are four patterns (Figure 3, Supplemental videos): the roof-to-bottom pattern, the minor collision pattern, the major collision pattern, and the bottom-to-roof pattern.

The proportion of the upward (from bottom to roof) conduction to that of downward (from roof to bottom) were large in the following order: bottom-to-roof, major collision, minor collision, and roof-to-bottom. More patients with a larger proportion of upward conduction needed intra-box ablation and this trend was statistically significant (4/4, 100% with the bottom-to-roof pattern; 4/4, 100% with the major collision pattern; 9/14, 64.2% with the minor collision pattern; 5/9, 55.6% in the roof-to-bottom pattern; p for trend =0.049).

During the procedure, more patients in intra-box ablation group abandoned applications because of esophageal temperature rise, however there was no significant difference (31/57, 68.9% vs 14/34, 31.1%; p=0.19).

Findings of the second procedure

Forty-eight of 91 patients (56.5%) underwent the second procedure. Among them, 28 patients were in the intra-box group and 20 patients were in the non-intra-box group. More PW reconnection was observed in patients with intra-box ablation than those without intra-box ablation (21/28,75.0% vs 8/20, 40.0%; p=0.020). There was no significant difference in PV reconnection (10/28, 35.7% vs 4/20, 20.0%; p=0.31).

Among patients with PW reconnection, gap of roof line was observed in 16 patients (55.2%) and gaps of bottom line was in 13 (44.8%). Gap ablation was success in 14 patients (48.3%) and the rest of them needed intra-box ablation. There was no significant difference between intra-box group and non-intra-box group.

Follow-up

AF recurrence at six months after the procedure was observed more frequently in patients with intra-box ablation (9/57, 15.7% vs 3/31, 9.7%; p=0.14), although there was no significant difference. AADs were continued until 6 months after the procedure in 14 of 91 patients (15.4%).

Discussion

Main findings

This observational study is novel for evaluating the characteristics and clinical effect of intra-box ablation during PWI for persistent AF. It showed that short PW activation time and conduction patterns were related to the necessity of intra-box ablation and that intra-box ablation was related to more reconnection of PW.

Achievement of complete PWI and lesion transmurality

PWI is reportedly effective for persistent AF when combined with PVI [4,5]. The one of the major strategies of PWI is linear ablation, although various strategies have been used [15]. The successful rate of PWI varies between reports, ranging from 36.8% to 96% [7,16-18]. It can be difficult to achieve PWI, especially by linear ablation only. Here, 63.4% of patients required intra-box ablation to complete PWI.

Table 3: Findings of LA mapping after PVI before PWI

	Intra-box n=22	Non-intra-box n=9	p value
Max voltage, intra-box [mV]	5.1±2.0	5.0±2.0	0.96
Median voltage, intra-box [mV]	1.4±0.70	1.7±1.5	0.51
Max voltage, para-line [mV]	4.6±2.1	5.7±2.3	0.24
Median voltage, para-line [mV]	1.1±0.60	1.3±0.73	0.39
PW area [cm²]	12.5±2.7	13.5±2.0	0.35
PW activation time [ms]	40.3±10.4	51.3±15.2	0.026

LA, left atrium; PVI, pulmonary vein isolation; PW, posterior wall; PWI, posterior wall isolation.

The main reason may be the inability to create a transmural lesion by linear ablation. Some studies evaluating the combination of endocardial and epicardial mapping provide direct evidence of a nonuniform lesion [8, 9, 19]. A previous study showed that 38% of lines, including the roof line and bottom line, required epicardial ablation to create a transmural lesion and that the existence of conduction abnormalities in the epicardium was suggested [8]. Another study of endocardial and epicardial mapping reported end-epi dissociation not only in voltage, but also in propagation [9].

One of the possible causes of non-transmural lesions is the position of the esophagus; hence, ablation should be abandoned because of esophageal temperature rise, thereby avoiding esophageal injury, particularly for the bottom line. Ablation was abandoned in 49.5% of patients in this population.

The endocardial and epicardial ablation hybrid may be effective for creating a transmural lesion; however, it is unclear whether this hybrid is more effective than endocardial ablation only [7]. Although hybrid ablation is reportedly effective and feasible [6-8], it should not be the standard strategy for the first procedure for safety reasons. Thus, improving endocardial ablation strategy is crucial.

Intra-box ablation appeared to be a risk factor for PW reconnection in this study. The necessity of intra-box ablation may reflect the inability of the transmural linear lesion or the connection between the endocardium and epicardium. Clinicians should confirm that PWI is achieved by the pacing maneuver and mapping especially in patients with intra-box ablation, given the higher rate of PW reconnection.

The relationship between conduction pattern in the PW and intra-box ablation

The PW has a complex structure with varied thickness of the septopulmonary bundle (SPB), and the right side of the SPB has abrupt changes in muscle thickness and fiber direction [20-22]. The conduction abnormality on the left and right boundaries of SBP was reported to provide a substrate for AF [20].

According to the observation of propagation and vector maps, we classified the PW conduction pattern into four patterns: roof-to-bottom, minor collision, major collision, and bottom-to-roof. The main difference among these patterns was the proportion of upward to downward conduction in the PW. The proportion of upward conduction is larger in the order of bottom-to-roof, major collision, minor collision, and roof-to-bottom and the former two patterns were observed in the intra-box ablation group, which means it may be more difficult to achieve PWI by linear ablation only in cases with a larger proportion of upward conduction in the PW. Although this study evaluated the posterior voltage in the first procedure and PW gaps in the second procedure, the mechanism remained unclear.

Limitations

This was an observational study with a small number of patients. In particular, LA mapping analysis was performed only under RA pacing in a limited number of patients; LA mapping data should be evaluated in a larger number of patients during pacing from several sites to confirm its relationship with intra-box ablation. The half of the patients rejected the second procedures, and it may have caused selection bias that more patients with palpitation and/or AF recurrence tended to undertake the procedure. Under the situation, actual PW durability may be higher. Moreover, this study is underpowered for AF recurrence and its design failed to evaluate long-term AF recurrence because second procedure was conducted 6 months after the first procedure.

This study could not provide solutions to increase the success rate of linear ablation and reduce intra-box ablation. Further study to compare endocardial PWI strategies is needed to improve PWI.

Besides these limitations, this study is novel as it showed the clinical impact of intra-box ablation and new insight on the PW conduction pattern.

Conclusion

In summary, this observational study firstly evaluated the intra-box ablation during PWI and showed that intra-box ablation during PWI was associated with lower durability of PW. PW activation time and conduction patterns were related to the necessity of intra-box ablation.

Supplemental videos

Videos show activation maps with vector maps of four posterior wall conduction patterns: roof-to-bottom, major collision, minor collision, and roof-to-bottom.

Video 1, roof-to-bottom pattern; **Video 2**, minor collision pattern; **Video 3**, major collision patten; **Video 4**, bottom-to-roof pattern.

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Case Report

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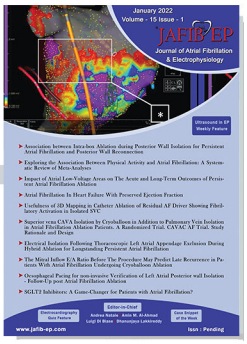

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Electrical Isolation Following Thoracoscopic Left Atrial Appendage Exclusion During Hybrid Ablation for Longstanding Persistent Atrial Fibrillation

Syed M. Ali Hassan[1], Sarah Paleczny[1], Bobby Yanagawa[2], Benedict Glover[3], Gianluigi Bisleri[2]

[1]Division of Cardiac Surgery, Queen's University, Kingston, ON, Canada
[2]Division of Cardiac Surgery, University of Toronto, Toronto, ON, Canada
[3]Division of Cardiology, University of Toronto, Toronto, ON, Canada

Abstract

Left atrial appendage (LAA) exclusion with the use of the AtriClip (AtriCure, Inc., OH, USA) device has been shown to be a safe, effective, and durable strategy predominantly to reduce the lifelong risk of thromboembolism and stroke in patients with atrial fibrillation (AF). We present a case showing electrical isolation of the LAA after its exclusion with the AtriClip device during hybrid ablation for the treatment of longstanding persistent AF. Our case demonstrates the effectiveness of the AtriClip device in not only mechanically occluding the LAA but also electrically isolating it, thereby addressing an electrical driver of AF in addition to reducing its thromboembolic sequelae.

Introduction

The left atrial appendage (LAA) is a known risk of ischemic stroke in atrial fibrillation (AF); however, it is also responsible for ectopic foci in 27% of AF patients presenting for repeat ablation procedures and LAA electrical isolation can reduce AF recurrence rates [1]. LAA exclusion with the use of the AtriClip (AtriCure, Inc., OH, USA) device has already been proven to be a safe, effective, and durable strategy predominantly to reduce the lifelong risk of thromboembolism and stroke [2-5]. We present a case demonstrating a secondary benefit of LAA exclusion with the AtriClip device in achieving electrical isolation of the LAA, thereby treating a potential trigger and driver of long standing persistent atrial fibrillation (LsPAF) as well.

Case Report

A 59-year-old man presented with 10 years of LsPAF refractory to anti-arrhythmic drugs and 2 unsuccessful cardioversions. He was in NYHA III with severe limitations to his daily activities. A pre-operative transthoracic echocardiogram (TTE) showed left atrial volume index of 33 ml/m^2, left atrial antero-posterior diameter of 4.7 cm, left ventricular ejection fraction of 56%, and no evidence of valvular disease.

Key Words

Left Atrial Appendage; Exclusion; Electrical Isolation; Atrial Fibrillation

Corresponding Author
Gianluigi Bisleri,
Division of Cardiac Surgery
St. Michael's Hospital- Bond 8, 30 Bond Street, Toronto, ON, Canada, M5B1W8.

Technique

Hybrid ablation for LsPAF and epicardial left atrial appendage exclusion was performed by right and left thoracoscopy, respectively [6,7]. Briefly, the patient was placed in a 30-degree left lateral decubitus position and, following right lung deflation, three 10 mm trocars were placed in the 3rd, 4th and 5th right intercostal spaces. Pericardiotomy was performed 3 cm anterior and parallel to the phrenic nerve at the level of the SVC to the junction of the IVC and the transverse and oblique sinuses were accessed with blunt dissection. During surgical dissection, simultaneous endovascular access was obtained for insertion of endocardial mapping catheters.

A baseline endocardial map was created using the EnSite Precision mapping system (Abbott) after removal of all surgical instruments to avoid the risk of electrical interference. The baseline voltage map provided an initial assessment of the atrial substrate indicating the voltage conductance at each anatomical location in the left atrium including the left atrial appendage (LAA). The threshold for high voltage was set at >0.5 mV and a color-coded voltage map was generated.

After endocardial mapping, a baseline epicardial voltage map was generated via a 15mm Advisor circular loop mapping catheter (Abbott) inserted through the thoracoscopic surgical port and applied to the posterior epicardial surfaces. Following this, epicardial box ablation was performed via the Fusion 150 device (Fusion, AtriCure, OH, under Health Canada Special Access Program) positioned around the pulmonary veins for a total of 18 mins. Endocardial mapping did not show any surgical gaps, and so there was no need for left-

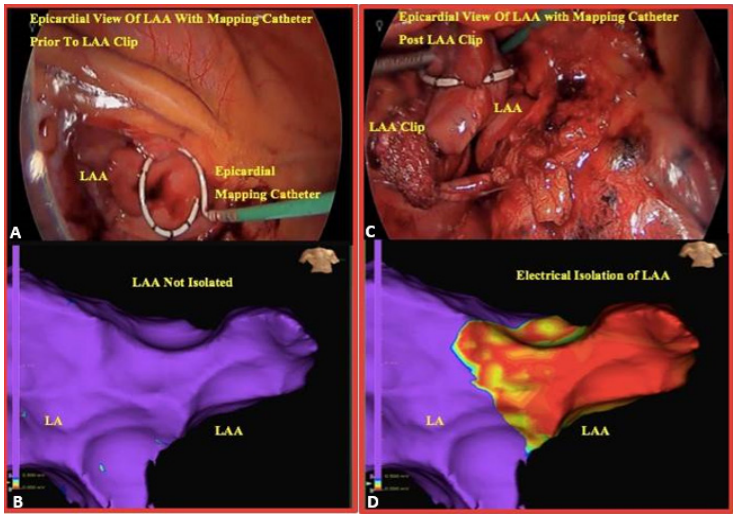

Figure 1: **A) Baseline epicardial mapping of the LAA showing B) electrical activity (purple; voltage > 0.5mV). C) Epicardial mapping after AtriClip LAA exclusion D) showing complete electrical isolation (red).**

sided endocardial ablation. Entrance and exit block were successfully achieved. The rhythm spontaneously converted from atrial fibrillation to typical atrial flutter, and ablation was performed in the right atrium endocardially at the level of the cavotricuspid isthmus and conversion to normal sinus rhythm was achieved.

After completion of the ablation and right sided closure, epicardial mapping of the LAA was performed via a left thoracoscopic approach showing electrical activity (Video 1; Fig. 1 A, B). LAA exclusion was then performed with the AtriClip device as we have described before [7]. In this case, a size 50 AtriClip was successfully deployed. Left sided closure was then meticulously performed to avoid complications such as lung hernia [8]. Post-exclusion epicardial mapping via a loop catheter showed complete electrical isolation of the LAA (Video 1; Fig 1 C, D). There were no post-operative complications, and the patient had an uneventful stay at the hospital and was discharged on post-operative day 2 in sinus rhythm. At 1-year follow-up the patient was doing well and in sinus rhythm on antiarrhythmic drugs.

Discussion

Atrial fibrillation is independently associated with a 1.5- to 4-fold increased risk of mortality [9]. The addition of LAA exclusion to catheter ablation has been shown to improve freedom from AF at 1 year compared to no LAA exclusion [10]. While the more commonly reported extra pulmonary vein sites of AF initiation and maintenance are the superior vena cava, ligament of Marshall, coronary sinus, crista terminalis, and left atrial posterior wall, the LAA is an underreported but important site of AF drivers that can potentially sustain LsPAF [1]. Electrical isolation of the LAA has been demonstrated to occur immediately following LAA ligation and is postulated to be due to ligation induced ischemic necrosis[11] The AtriClip device has been shown to be successful in achieving LAA occlusion in 97.8% of patients [4] and thus represents a readily available and safe treatment strategy for effective LAA exclusion. Our case demonstrates the effectiveness of the AtriClip device in not only mechanically occluding the LAA but also electrically isolating it, thereby addressing both a driver of AF as well as its thromboembolic sequelae.

Click for Video :

Intraoperative video showing LAA exclusion with the AtriClip and pre- and post-epicardial mapping of the LAA via left thoracoscopy.

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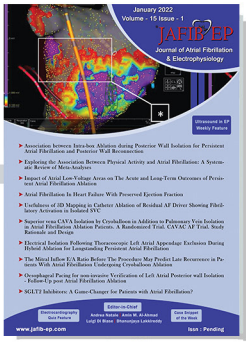

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Usefulness of 3D Mapping in Catheter Ablation of Residual AF Driver Showing Fibrillatory Activation in Isolated SVC

Yuta Sakaguchi[1], Daisuke Izumi[1], Yasuhiro Ikami[1], Kenichi Iijima[1], Tohru Minamino[1], Takayuki Inomata[1]

[1]Department of Cardiovascular Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, JAPAN

Abstract

Ectopic potentials in the SVC can act not only as a trigger but also as a driver of AF. These potentials may be refractory to conventional pulmonary vein isolation for AF. In the present case, the atrium resumed a sinus rhythm spontaneously on the completion of SVC isolation and AF could no longer be induced. However, there was residual fibrillatory activity in the SVC. These findings suggest that residual activity in the SVC worked as a driver of AF. SVC reconnection is commonly reported, with a prevalence of 70%. Thus, we decided to eliminate residual fibrillatory activity in the SVC to prevent recurrence of AF after the third catheter ablation session. In the presence of a fibrillatory pattern, conventional activation mapping techniques cannot map residual SVC activity; however, ICL mapping using the CARTO system can identify the target site of ablation in the isolated SVC.

Introduction

Atrial fibrillation (AF) is a commonly observed arrhythmia that often causes clinical complications such as heart failure and embolic stroke. Initiation and perpetuation of AF can be linked to interaction between triggers and the arrhythmogenic substrate. The triggers can be premature atrial beats or a rapidly firing focus that act to initiate AF, and the arrhythmogenic substrate perpetuates AF through its electrophysiological, mechanical, and anatomical characteristics [1]. AF triggers have been shown to originate mainly from the pulmonary veins (PVs) [2], and PV isolation has been performed worldwide as a standard therapy [3]. In addition, numerous studies have suggested that premature beats from non-PV foci such as the superior vena cava (SVC), coronary sinus, Marshall ligament, crista terminalis, and left atrial posterior free wall could also be triggers of AF [4]. Concomitant ablation of these non-PV foci with PV isolation has been reported to reduce the recurrence rate of AF [5].

Residual potentials, which are often based on automaticity or triggered activity, are frequently observed in isolated PVs [6]. Of the two types of residual potentials, non-fibrillatory discrete potentials and fibrillatory potentials, the latter are considered to be more closely associated with recurrence of AF after PV isolation [6]. Residual potentials also can be observed in the isolated SVC following circumferential SVC isolation [7-8]. Several recent studies have observed that potential in the SVC acts not only as an AF trigger but also as a driver [7-8]. In patients who have residual "fibrillatory" potential in the SVC, ablation of the residual potential in addition to the SVC isolation may improve the maintenance of sinus rhythm [7]. However, the strategy is unclear for identifying the target site for ablation of residual fibrillatory activation in the isolated SVC.

Nademanee et al. were the first to propose that targeting sites with complex fractionated atrial electrograms (CFAE) could be an effective primary strategy for AF ablation [9]. One of the clinically implementable advantages of CFAE-guided ablation is its ability to identify the ablation target, even in the case of fibrillatory activity such as sustained AF, thus overcoming the disadvantage of conventional activation mapping based on a constant cycle length and activation pattern. Dedicated CFAE software implemented in the CARTO system enables visualization of CFAE for localization of candidate ablation sites in AF ablation [10]. However, the CFAE module has not been verified for application to residual fibrillatory activity in the isolated SVC.

We report a case of paroxysmal AF in which residual fibrillatory activation in the isolated SVC was deemed the driver of AF, and the CFAE module in CARTO accurately identified the target ablation site in the SVC.

Key Words

Atrial Fibrillation, Three-Dimensional Mapping, Catheter Ablation, Superior Vena Cava, Interval Confidence Level, Complex Fractionated Atrial Electrogram

Corresponding Author
Kenichi Iijima,
Department of Cardiovascular Medicine
Niigata University Graduate School of Medical and Dental Sciences
1-757 Asahimachi Chuou-ku, Niigata 951-8510, JAPAN

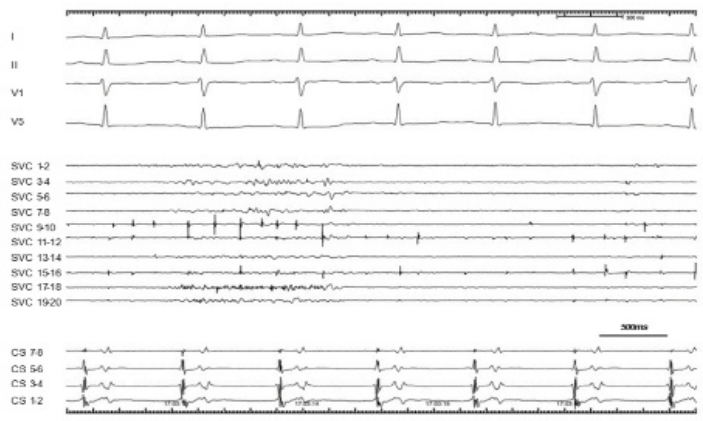

Figure 1: **Fibrillatory activation in the superior vena cava (SVC).**

The atrium resumed sinus rhythm spontaneously after re-isolation of the SVC; however, fibrillatory activation was still observed in the isolated SVC.
SVC = superior vena cava; CS = coronary sinus

Case Report

A 44-year-old female with a 3-year history of palpitations due to paroxysmal AF was admitted to our hospital for a third session of catheter ablation. General examinations including echocardiography and cardiac computed tomography detected no structural heart disease. Left atrial diameter was 31 mm. In the first session, she underwent PV isolation (PVI) with a cryoballoon catheter (Arctic Front Advance, Medtronic, Minneapolis, MN) and inferior vena cava–tricuspid annulus isthmus line ablation using an irrigated tip catheter (Flexability, Abbott, Minneapolis, MN). However, her symptoms and AF recurred even with beta-blockers, and she underwent a second session. We confirmed recurrence of electrical connection between the left atrium and the left PVs that were isolated in the first session, and then performed re-PVI with a radiofrequency catheter (Thermocool ST SF, Biosense Webster, Inc, Diamond Bar, CA) as well as additional empiric SVC isolation. In these two sessions we confirmed that there were no non-PV foci even after intravenous infusion of 10 μg of isoproterenol; however, the patient suffered recurrent palpitations and AF at 6 months after the second session, and a third session was scheduled.

In the third session, we confirmed that there was no PV reconnection under guidance of the CARTO cardiac mapping system (Biosense Webster, Inc, Diamond Bar, CA). SVC reconnection was confirmed by AF initiated by premature atrial complexes from the SVC after the intravenous infusion of 10 μg of isoproterenol. Accordingly, we attempted to re-isolate the SVC using an irrigation catheter. Prior to the ablation, we mapped the phrenic nerve area with pacing from the ablation catheter at the output of 10V and the duration of 2ms, and the targeted area with high ICL in the SVC had sufficient distance from phrenic nerve area. During re-isolation of the SVC, the patient's cardiac rhythm restored sinus rhythm spontaneously upon completion of re-isolation of the SVC, regardless of the residual fibrillatory activation in the SVC (Figure 1). We thought that the residual fibrillatory activation could be presumed as the driver of the patient's AF because her AF was not maintained after SVC re-isolation and her AF would recur easily when SVC reconnection occurred in the future. Thus, we decided to eliminate the residual fibrillatory activation in the SVC. After identifying the ablation target site, we performed CFAE mapping by revisiting the interval confidence level (ICL) using the CFAE module of CARTO (Figure 2) because conventional activation mapping cannot be applied to fibrillatory activation. The ICL map revealed high ICL in the anterior aspect of the SVC. Radiofrequency application with output of 25 W to this site successfully terminated the residual fibrillatory activation in the SVC (Figure 3). No other SVC potential was observed after the ablation, and fibrillatory activation was no longer inducible in either the entire atrium or the SVC. At one year after the last ablation session, the patient has experienced none of further palpitations, episodes of AF, and symptom suggesting SVC stenosis due to the ablation.

Discussion

We present a case of paroxysmal AF in which residual fibrillatory activation in the isolated SVC could be deemed the driver of AF, and its precise location in the SVC was successfully identified using the CFAE module of the CARTO system.

The present patient required no less than three sessions of ablation for paroxysmal AF in a structurally normal heart. Predictors of late recurrence of AF are reported to include hypertension, LA size, LA volume, atrial tissue fibrosis, ablation strategies, and natriuretic peptides [11]. However, most cases of paroxysmal AF can be cured without multiple sessions, and the present case had none of the predictors of AF recurrence listed above. In such as the present case, the presence of hidden AF triggers or drivers at an unusual site (such as the SVC) may need to be considered Eliminating these hidden causes may be the only way to free the patient from AF.

It is well known that ectopic beats originating from the SVC can initiate AF. It has been also reported that SVC tachycardia can be a driver of AF [7-8]. In the present case, the atrium resumed a sinus rhythm spontaneously upon completion of the SVC isolation and AF could no longer be induced. However, there was residual fibrillatory activity in the SVC. These findings suggest that fibrillatory activity in the SVC had acted not only as a trigger but also as a driver of AF. Furthermore, SVC electrical reconnection after circumferential isolation is considered to

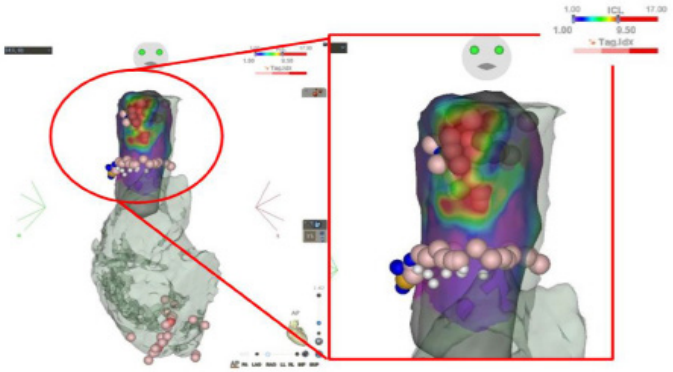

Figure 2: **Interval confidence level (ICL) map in the superior vena cava (SVC) with the CARTO system**

The complex fractionated atrial electrogram (CFAE) module of the CARTO system reveals that the anterior aspect of the SVC demonstrates CFAE with high ICL values. Areas of ICL > 9.5 are indicated in red.

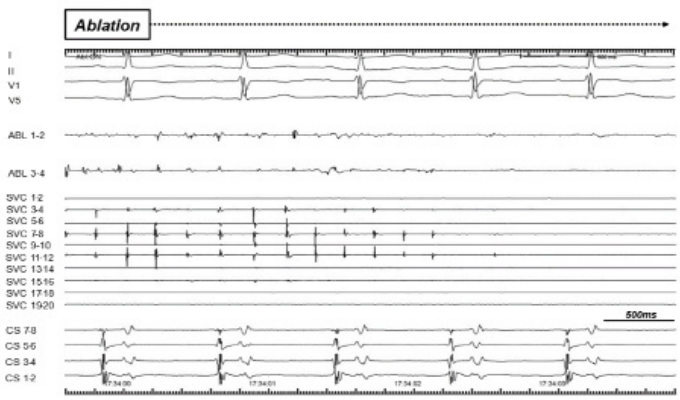

Figure 3: **Ablation of fibrillatory activation in the superior vena cava (SVC).**

In an area with high ICL values, fragmented continuous potentials were recorded at distal pairs of electrodes of the ablation catheter. The application of 25 W radio frequency to this site terminated the fibrillatory activation in 3 seconds.
ABL = ablation; SVC = superior vena cava; CS = coronary sinus.

be relatively common: Miyazaki et al. reported that it is observed in as many as 74% of patients undergoing repeated AF ablation [12]. Even in the present case, SVC electrical reconnection was confirmed in the last session. Thus, elimination of the SVC activity was deemed essential to cure AF in the present case.

In previous reports [7-8], organized potentials or tachycardia that were presumed to be drivers of AF were observed in the isolated SVC. In these cases, the ablation target site could be identified relatively easily with a conventional activation mapping technique with and/or without a 3D mapping system. However, in the present case, the residual potential showed fibrillatory activity without repeatability in its cycle length and activation pattern. Thus, the conventional activation mapping technique could not be applied for ablation of the residual potential in our case.

Nademanee et al. reported that targeting CFAE could be an effective primary strategy for AF ablation [9], based on the hypothesis that CFAE areas are critical sites for AF perpetuation and can serve as target sites for AF ablation. The strongest advantage of CFAE ablation is that it enables operators to identify the therapeutic target even under the condition of fibrillatory activity. The CFAE module in the CARTO system can localize CFAE visually, and guides the operator to the candidate sites for ablation [10].

However, it is also reported that the efficacy of CFAE-based ablation in the atrium was limited [13]. The iatrogenic area of arrhythmogenesis caused by extensive ablation and the low selectivity in targeting of an individual patient's specific arrhythmic substrate were mentioned as the reasons for the lack of benefit associated with additional ablation. In the present case, the residual fibrillatory activities was localized and anchored at the anterior aspect of SVC, and these activities were termination after ablation to the limited areas with high ICL. We speculated that the efficacy of CFAE mapping in the SVC of the present case was based on the stability and localization of the targeted fibrillatory activities.

ICL is a unique parameter of the CARTO system. It is a measure of the interval of each component of fragmented potentials according to the parameter setting. In ICL mode, the number of components of fragmented potentials matching the parameter setting is counted as the ICL, and the total number of ICLs is calculated at each point. A high ICL value indicates a high density of components of fragmented potentials at the site of interest [14-15]. It has been suggested that CFAE could be produced by multiple rotors serving as an AF driver [16]. In the present study, we targeted SVC sites in which CFAE was expressed as high ICL values. Ablation of these sites successfully terminated the residual fibrillatory activity that had acted as the driver of AF in the present case.

SVC stenosis by the circumferential isolation has been reported in few cases and is considered to be relatively rare [17], however, its potential risk should be considered. It was reported that the SVC stenosis occurred by the widespread ablation to the entire circumference of the SVC-right atrium junction, presumably through spread of interstitial edema through the contiguous tissue space [18]. The high ICL area in this case was limited at the anterior aspect of the SVC, and there was no notable anatomical structure. Therefore, we considered the ablation on the area was of low risk of SVC stenosis.

Conclusion

Ectopic activity from the SVC may act as a trigger and drive AF in cases of ablation-refractory AF. In the situation that residual SVC activity shows a fibrillatory pattern, which prevents use of the conventional activation mapping technique, the ICL map of the CARTO system can identify the target site of ablation in the isolated SVC.

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Letter To Editor

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SGLT2 Inhibitors: A Game-Changer for Patients with Atrial Fibrillation?

Alireza Oraii [1], Jeff S. Healey [1,2], Arjun K. Pandey [3], William F. McIntyre [1,2]

[1] Population Health Research Institute
[2] Division of Cardiology, Department of Medicine, McMaster University
[3] Michael G. DeGroote School of Medicine, McMaster University

Dear Editor,

We read with great interest the recently published article by Haloot et al. [1] assessing the effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on the risk of adverse cardiovascular events in patients with atrial fibrillation (AF). This interesting observational study used data from a large multi-center dataset of electronic health records to provide valuable insight into the cardiovascular benefits of SGLT2 inhibitors in an AF population. Their findings suggest that AF patients treated with an SGLT2 inhibitor, compared to an untreated propensity-matched control group, live longer, are less likely to require cardioversion, and are at increased risk of ischemic stroke.

Despite these important findings, the authors could not investigate cardiovascular deaths due to the lack of cause-specific mortality data. However, we wonder about the effect of SGLT2 inhibitors on hospitalization for heart failure (HF). HF is the leading cause of death in patients with AF and accounts for the majority of cardiovascular mortality [2]. Our recent systematic review and meta-analysis showed that SGLT2 inhibitors maintain their efficacy in reducing cardiovascular death or HF hospitalization in patients with AF (hazard ratio 0.70, 95% confidence interval 0.57 – 0.85, p-for-interaction=1.00), similar to those in sinus rhythm [3]. However, these data were derived from the subgroup analysis of phase 3 SGLT2 inhibitor randomized controlled trials, and a consistent signal in a large observational series would strengthen this finding. Furthermore, we recently showed that a large proportion of AF patients are not eligible to receive an SGLT2 inhibitor based on the current approved indications, and these ineligible patients still have a substantial rate of cardiovascular death (approximately 1.5 events/100 person-years) and hospitalization for HF (approximately 1.9 events/100 person-years) [4]. An analysis testing the effect of SGLT2 inhibitors on HF hospitalization in those without a prior HF diagnosis would provide further insight into the effect of SGLT2 inhibitors in primary prevention of HF and HF-related outcomes in patients with AF.

Overall, SGLT2 inhibitors are a promising therapeutic agent for patients with AF both in those with eligibility indications like diabetes mellitus or HF, but also potentially in those without these comorbidities as well. Information from well-conducted observational studies can help guide future randomized studies testing the efficacy of SGLT2 inhibitors in patients with AF.

Sincerely,
Alireza Oraii, MD
Jeff S. Healey, MD MSc
Arjun K. Pandey, BHSc
William F. McIntyre MD PhD

Key Words

Atrial fibrillation; Heart Failure; Sodium-Glucose Transporter 2 Inhibitors.

Corresponding Author
William F. McIntyre,
Population Health Research Institute
237 Barton St East DBVSRI C3-13A Hamilton ON, Canada L8L 2X2.

Disclosures

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Dr. Dhanunjaya Lakkireddy, MD, F.A.C.C, FHRS

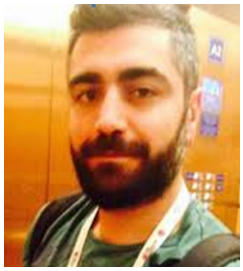
A board certified electrophysiology expert and practices at Mid-America Cardiology and The University of Kansas Hospital Clinics in Kansas City, KS, USA

Dr. Dogac Oksen, MD

Dogac Oksen, MD is clinical cardiologist and investigator, currently working at Istanbul University Institute of Cardiology, Istanbul, Turkey. He has achieved Doctor of Medicine degree at Cerrahpasa Medical Faculty. His scientific focuses are interventional cardiology, arrhythmia cardiac electrophysiology and catheter based treatment of arrhythmias

Dr. Mattias Duytschaever, MD

Department of Cardiology, Sint-Jan Hospital Bruges; Ruddershove 10, 8000 Bruges, Belgium

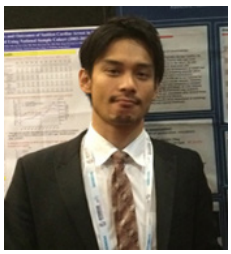


Dr. Tolga Aksu, FESC, FEHRA

He is an Associate Professor of Cardiology. He is working Department of Cardiology and Director of Clinical Electrophysiology at the Kocaeli Derince Education and Research Hospital in Turkey. Dr. Aksu clinically interested in invasive electrophysiology, device implantation and catheter ablation therapies. Special interest areas are Atrial fibrillation and cardioneuroablation. Dr. Aksu has published more than 100 national and international scientific publications. Also, He is in Editorial Board of some international academical journals.

Dr. George Louridas, MD

Emeritus Professor of Cardiology, Aristotle University, Thessaloniki Greece, Director of Cardiac Catheterization Laboratory, AHEPA Hospital (1983-2006), Director of Department of Cardiology, AHEPA Hospital (1996-2006).



Dr. Kyoichiro Yazaki, MD

Affiliation: Ogikubo Hospital, Department of Cardiology,Cardiovascular Center, Tokyo, Japan.
Clinical research of electrophysiology, catheter ablation, and Device therapy are of my interests

Dr. Ashraf Alqaqa, MD, FACC

Dr. Farhad Farokhi received his medical degree from the Kansas City University of Medicine & Biosciences. He finished his internal medicine residency at the Grandview Hospital in Dayton, OH. He currently holds board certification in Cardiovascular Disease and Clinical Cardiac Electrophysiology from the American Osteopathic Board of Internal Medicine, Internal Medicine from the American Osteopathic Board of Internal Medicine, and Echocardiography from the American Society of Echocardiography. Dr. Farokhi's clinical interests include Atrial Fibrillation, Catheter Ablation, Ventricular Arrhythmia, and Left Atrial Appendage Closure (LARIAT).

Dr. Hickey

Dr. Hickey is an Associate Professor of Nursing at Columbia University Medical Center and holds a joint appointment in the Division of Cardiology (electrophysiology) as both a family and adult nurse practitioner. Her interdisciplinary research, clinical practice and scholarship is focused in the areas of cardiac genetics, the clinical care of those with chronic cardiac conditions and arrhythmias, and the prevention of sudden cardiac death. Her current grant awards include a R01 from the National Institute of Nursing Research (iHEART) focusing on arrhythmia telehealth monitoring in those with atrial fibrillation, her newly awarded (multiple-PI) P30 award with Dr. Suzanne Bakken is focusing on improving symptom self-management for underserved populations with or at risk for chronic health conditions.

Dr. Andres Enriquez, MD

Dr. Enriquez received his medical degree from the Universidad de Concepcion, in Chile. He specialized in Internal Medicine, Cardiology and Cardiac Electrophysiology at Pontificia Universidad Catolica de Chile in Santiago.

Between 2013 and 2015 he moved to Canada to continue his electrophysiology training at Queen's University, Kingston, Ontario.

He currently resides in Philadelphia with her wife Karen and is a second-year fellow in the Advanced Clinical Electrophysiology program at the Hospital of the University of Pennsylvania, under the mentorship of Dr. Francis Marchlinski.

Dr. Enriquez interests include electrocardiology, clinical electorphysiology catheter ablation and cardiac devices.

Dr. Ryan Dean White. MD

Dr. Ryan Dean White, MD, medical degree from the University of Missouri and currently training in internal medicine at Indiana University School of Medicine in Indianapolis, Indiana.

Dr. James R Edgerton, MD, FACC, FACS, FHRS

The Heart Hospital

Dr. Jackson J. Liang, MD

Clinical Cardiac Electrophysiology Fellow
Hospital of the University of Pennsylvania

Dr. Gianluca Rigatelli, MD, PhD, EBIR, FACP, FACC, FESC, FSCAI, Vice-Director

Cardiovascular Diagnosis and Endoluminal Interventions
Director, Section of Adult Congenital Heart Interventions
Rovigo General Hospital, Viale Tre Martiri
45100 Rovigo, Italy