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Cryoballoon pulmonary vein isolation – predictors of long-term effectiveness and periprocedural complications.

Izolacja ujść żył płucnych metodą krioablacji balonowej – czynniki predykcyjne skuteczności długoterminowej oraz powikłań okołozabiegowych.

Praca doktorska

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Pracę wykonano w Klinice Kardiologii, Elektrokardiologii Interwencyjnej oraz Nadciśnienia Tętniczego UJCM w Krakowie

Kierownik jednostki: Prof. dr hab. n. med. Marek Rajzer

Kraków, 2021

Składam serdeczne podziękowania
Panu Profesorowi Markowi Jastrzębskiemu,
Pani Profesor Danucie Czarneckiej,
Panu Profesorowi Markowi Rajzerowi,
a także wszystkim współpracownikom z
I Kliniki Kardiologii i Elektrokardiologii
Interwencyjnej oraz Nadciśnienia Tętniczego
Uniwersytetu Jagiellońskiego Collegium Medicum
za pomoc w powstaniu tej pracy.

Pracę dedykuję Żonie Marcie

i całemu Zespołowi Pracowni Elektrofizjologii NSSU

SPIS TREŚCI

I. WYKAZ PUBLIKACJI STANOWIĄCYCH ROZPRAWĄ DOKTORSKĄ

Niniejszą rozprawę doktorską pt.: „Izolacja ujść żył płucnych metodą krioablacji balonowej – czynniki predykcyjne skuteczności długoterminowej oraz powikłań okołozabiegowych" stanowi cykl 3 oryginalnych prac oraz pracy poglądowej powiązanych tematycznie, opublikowanych w międzynarodowych recenzowanych czasopismach naukowych znajdujących się na listach MNiSW, indeksowanych w bazie PubMed oraz znajdujących się na Liście Filadelfijskiej (Journal Citation Reports - JCR).

Łączny wskaźnik oddziaływania: 5,478

Łączna liczba punktów MNiSW: 190

1

Autorzy: Grzegorz Kiełbasa, Marek Jastrzębski.

Tytuł: Cryoballoon pulmonary vein isolation as a standard approach for interventional treatment of atrial fibrillation. A review and a practical guide to an effective and safe procedure.

Czasopismo: Advances in Interventional Cardiology (2020) 16: 359.

DOI: 10.5114/aic.2020.101760

IF = 1.347

MEiN = 40

2

Autorzy: Marek Jastrzębski, Grzegorz Kiełbasa, Kamil Fijorek, Adam Bednarski, Aleksander Kusiak, Tomasz Sondej, Agnieszka Bednarek, Pawel Lis, Agnieszka Olszanecka, Marek Rajzer.

Tytuł: Outcomes of atrial fibrillation ablation program based on single-shot techniques.

Czasopismo: Advances in Interventional Cardiology (2020) 16: 466.

DOI: 10.5114/aic.2020.101773

IF = 1.347

MEiN = 40

3

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Tytuł: Comparison of six risk scores for prediction of atrial fibrillation recurrence after pulmonary vein isolation and development of a simplified method, the 0-1-2 PL score.

Czasopismo: Journal of Arrhythmia (2021)

DOI: 10.1002/joa3.12557

IF = 1.11

MEiN = 40

4

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Tytuł: Patent foramen ovale and left atrial appendage flow velocity predict atrial fibrillation recurrence post cryoballoon ablation

Czasopismo: Kardiologia Polska (2021)

DOI: doi: 10.33963/KP.a2021.0004

IF = 1.674

MEiN = 70

II. WSTĘP

Migotanie przedsionków (AF) jest najczęściej występującą tachyarytmią. Poza objawami w postaci odczucia niemiarowej pracy serca, ograniczenia tolerancji wysiłku czy zawrotów głowy, znaczenie kliniczne AF wynika z zaburzonego przepływu krwi w przedsionkach serca - co skutkuje zwiększonym prawdopodobieństwem powstawania skrzepów, które dostając się do krążenia systemowego mogą prowadzić do udaru/zatorów obwodowych. U podłoża patogenezy AF znajdują się zaburzenia depo- i/lub repolaryzacji - najczęściej w obrębie proksymalnych odcinków żył płucnych (PVs). Skutkują one wyzwalaniem salw ektopowych pobudzeń, które doprowadzają do zawiązywania się mnogich pętli reentry w obrębie przedsionków, a z czasem do ich wtórnego remodelingu anatomicznego i elektrycznego powodując utrwalenie się arytmii [1]. Naturalna historia rozwoju AF obejmuje samoograniczające się napady, które z biegiem czasu trwają coraz dłużej wymagając ostatecznie przerywania poprzez kardiowersję farmakologiczną lub elektryczną. Przy znacznym zaawansowaniu remodelingu miokardium przedsionków migotanie przestaje być podatne na interwencje - przechodząc w stadium utrwalone.

Wprowadzenie zabiegu przezskórnej ablacji ujść PVs prądem o wysokiej częstotliwości (RF) umożliwiło zastosowanie interwencji, która poprzez wytworzenie blizny, przerywa przewodzenie ektopii z żył płucnych do lewego przedsionka. Dalszy rozwój technologiczny umożliwił zastąpienie ablacji metodą punkt-po-punkcie poprzez techniki z zastosowaniem pojedynczej aplikacji (*'single-shot'*) obejmującej jednoczasowo cały obwód danej żyły - cewników wieloelektrodowych (PVAC) oraz kriobalonów napełnianych ciekłym azotem (CB) [2,3]. Zabieg wykonany na wczesnym etapie choroby ogranicza remodeling miokardium, a tym samym znacząco zmniejsza prawdopodobieństwo utrwalenia się arytmii.

W literaturze od lat trwa dyskusja na temat wyższości którejś z technik (ablacja RF vs. CB) - jak dotąd jednak nie ma jednoznacznych dowodów naukowych przemawiających na korzyść jednej z nich [4,5]. Podobna skuteczność odległa i brak większych różnic w czasie trwania zabiegu/fluoroskopii pochodzą jednak z obserwacji z ośrodków, w której operatorzy pierwotnie wykonywali PVI poprzez punktową ablację RF, a następnie przy użyciu CB/PVAC. W literaturze brakuje danych dotyczących PVI wykonywanych przez operatorów od początku przeprowadzających zabiegi z użyciem technik z zastosowaniem pojedynczej aplikacji. Zagadnienie to staje się szczególnie istotne w sytuacji, gdy popularyzacja techniki CB prowadzi do podejmowania tego typu zabiegów przez ośrodki/osoby bez wcześniejszego doświadczenia z techniką RF punkt-po-punkcie. Potencjalna przewaga CB nad ablacją metodą punkt-po-punkcie dotyczy przede wszystkim bardziej stromej krzywej uczenia, pozwalającej osiągnąć przez operatora biegłość i satysfakcjonujące rezultaty dużo wcześniej. Zabieg z użyciem CB w rękach doświadczonego ablacjonisty trwa krócej niż godzinę, czas fluoroskopii nie przekracza kilkunastu minut, a poważne powikłania zdarzają się rzadko. Technika wykonania zabiegu bazuje na opisach/wskazówkach biegłych operatorów oraz doświadczeniach danego ośrodka [6].

Długoterminowa skuteczność PVI nie przekracza 75% - bez względu na zastosowaną technikę. W ostatnich latach powstał szereg modeli oceniających ryzyko nawrotu AF po PVI [7,8]. Do klasycznych czynników ryzyka zwiększających prawdopodobieństwo nieskuteczności zabiegu należą: czas trwania AF, rozmiar lewego przedsionka, frakcja wyrzutowa lewej komory, wiek, obecność nadwagi/otyłości oraz chorób współistniejących. Złożoność większości modeli znacząco ogranicza zastosowanie praktyczne. Dodatkowo zawarte w niektórych skalach czynniki pozabiegowe uniemożliwiają zastosowanie ich jako narzędzi pomocnych w kwalifikacji pacjenta do przeprowadzenia procedury.

Ze względu na znaczny odsetek nawrotów AF po pierwszej PVI część pacjentów poddawana jest ponownej interwencji inwazyjnej. Dostępne dane wskazują na względnie korzystne rokowanie pacjentów, u których obie procedury wykonano za pomocą CB, oraz w grupie, w której pierwszy zabieg przeprowadzony został punktową ablacją RF, a drugi z użyciem CB [9,10]. Brakuje danych odnośnie stosowania sekwencyjnie dwóch różnych technik z zastosowaniem pojedynczej aplikacji - CB i PVAC.

Echokardiografia przezklatkowa i przezprzełykowa, umożliwiają wgląd w strukturę i ocenę funkcji lewego przedsionka - jamy serca bezpośrednio "dotkniętej" migotaniem przedsionków. Parametry echokardiograficzne dostarczają informacji dotyczących zaawansowania zmian anatomicznych i/lub czynnościowych lewego przedsionka. Użyteczność wskaźników echokardiograficznych w stratyfikacji ryzyka nawrotu AF została udokumentowana [11,12], nadal daleko jest jednak do pełnego zrozumienia ich użyteczności klinicznej, przede wszystkim w homogennych grupach pacjentów poddawanych PVI z użyciem CB.

W niniejszej pracy doktorskiej zbadano skuteczność krioablacji balonowej jako preferencyjnej techniki izolacji ujść żył płucnych, częstość powikłań okołozabiegowych oraz czynniki wpływające na ryzyko nawrotu migotania przedsionków po zabiegu.

III. CELE PRACY

Celem pracy było określenie skuteczności i czynników wpływających na ryzyko nawrotu migotania przedsionków po krioablacji balonowej jako preferencyjnej techniki izolacji ujść żył płucnych.

Cele szczegółowe pracy:

1. Podsumowanie aktualnej wiedzy na temat krioablacji balonowej ze szczególnym uwzględnieniem praktycznych aspektów dotyczących wykonania zabiegu - przedstawionych w formie *hands-on*.
2. Przedstawienie skuteczności długoterminowej oraz powikłań okołozabiegowych krioablacji balonowej ujść żył płucnych oraz analiza najważniejszych czynników klinicznych mających wpływ na nawrót arytmii.
3. Ocena możliwości sekwencyjnego wykorzystania dwóch technik *'single-shot'* z zastosowaniem pojedynczej aplikacji - kriobalonów i cewników wieloelektrodowych - u pacjentów z nawrotem migotania przedsionków.
4. Porównanie skali oceniających prawdopodobieństwo nawrotu migotania przedsionków po krioablacji balonowej ujść żył płucnych oraz zaproponowanie uproszczonego modelu opartego o uniwersalne zmienne predykcyjne.
5. Identyfikacja parametrów echokardiograficznych mających związek z nawrotem napadów migotania przedsionków po krioablacji balonowej ujść żył płucnych.

IV. Metodologia

Badania miały charakter retrospektywnej analizy zabiegów izolacji ujść żył płucnych wykonanych w latach 2009–2019. Do badań włączano pacjentów skierowanych do szpitala z powodu rozpoznanego objawowego migotania przedsionków. Analizie poddano dokumentację szpitalną, opisy zabiegowe, zapisy z systemu elektrofizjologicznego, obrazy z fluoroskopii z położeniem elektrod oraz nagrania badań echokardiograficznych.

W celu optymalizacji homogenności grupy - w zależności od celu danej publikacji część pacjentów ulegała wykluczeniu z badanej populacji (napadowe vs. przetrwałe migotanie przedsionków, brak danych z echokardiografii, ograniczenie grupy jedynie do modelu kriobalonów CB2 - szczegóły w metodyce odpowiednich tekstów).

Informacje na temat utrzymania rezultatu zabiegu uzyskano z dokumentacji medycznej z poradni przyszpitalnej - w której odbywają się rutynowe kontrole pacjentów po izolacji ujść żył płucnych co najmniej 1 raz w roku. Obecność bezobjawowych napadów migotania przedsionków okresowo wykluczano wykonując kontrolne 24-godzinne monitorowanie EKG metodą Holtera.

Szczegółowa metodyka każdego z badań znajduje się w sekcji „Methods" w załączonych publikacjach.

V. Teksty opublikowanych prac naukowych będących podstawą pracy doktorskiej

Review paper

Cryoballoon pulmonary vein isolation as a standard approach for interventional treatment of atrial fibrillation. A review and a practical guide to an effective and safe procedure

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Adv Interv Cardiol 2020; 16, 4 (62): 359–375
DOI: https://doi.org/10.5114/aic.2020.101760

A b s t r a c t

Since the cryoballoon was introduced into clinical practice, approximately half a million patients have undergone a pulmonary vein isolation (PVI) using this tool throughout the world. This single-shot technique makes the pulmonary vein isolation procedure easier and has the potential to expand access to the interventional treatment of atrial fibrillation (AF), eventually leading to a reduction of the AF-related disease burden. Several studies and metanalyses have assessed the acute and long-term efficacy of cryoballoon-based PVI. The reported success rate of PV isolation during the procedure is about 98%. Despite this, the long-term effectiveness of the procedure (AF free survival) assessed at 1 year after the ablation is in the range of 70–82%. The AF-free survival rate significantly depends on the clinical characteristics of the studied group and the presence of risk factors, especially the type of AF (paroxysmal vs. persistent), LA size and the presence of heart failure. For a safe and effective procedure the electrophysiologist should be aware of all minute details of the procedure including several tricks developed by the most experienced operators and the pre-procedural and post-procedural management recommendations. Detailed knowledge of complications of cryoballoon (CB)-based ablation is mandatory. This review concentrates on the practical aspects and recommendations for a cryoballoon ablation procedure. The review is based on the authors' experience, including 800 procedures performed over 11 years with a low complication rate, and is presented within the context of the literature.

Key words: atrial fibrillation, cryoballoon, ablation, outcome, complications.

Introduction

There has been substantial progress in the diagnosis and treatment of atrial fibrillation (AF) over the last two decades. During that time catheter-based pulmonary vein (PV) isolation became the most effective method of AF treatment. However, since AF is the most common sustained arrhythmia and a significant cause of morbidity and mortality generating high costs for healthcare, there was a need for a more streamlined, more standardized procedure and with a steeper learning curve than the classic point-by-point radiofrequency (RF) catheter based PV isolation procedure. That demand was met by the development of several single-shot techniques [1]. The most successful of these was the cryoballoon (CB) ablation method, with already over half a million of patients having undergone that procedure. The less commonly used single-shot tools are the 'hot balloon' and the pulmonary vein ablation catheter (PVAC). Single-shot techniques make the PV isolation procedure easier and have the potential to expand access to the interventional treatment of AF, eventually leading to a reduction of the AF-related disease burden. Clinical equivalency, in terms of clinical outcome, between CB ablation and RF ablation was documented by the 'Fire and Ice' trial and other studies [2]. In this article we will review and summarize the current knowledge regarding outcomes of cryoballoon ablation and provide a practical, 'hands-on' review of the technique on the basis of the literature and our experience with over 800 cryoballoon procedures performed during the last 11 years.

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Received: 23.11.2020, **accepted:** 23.11.2020.

Cryo – an old new energy source

The physical mechanism responsible for inducing freezing in tissues is based on the Joule-Thomson effect: the temperature decline of an expanding gas when it is forced to pass through a valve where it loses pressure. An important milestone in the practical application of cryoenergy was the invention of a closed cryoprobe with continuous flow of liquid nitrous oxide by New York City neurosurgeon Irving Cooper in 1961. The first cardiac application of such a cryoprobe, by John Gallagher at Duke University in the USA, was for intraoperative ablation of accessory pathways and the atrioventricular node in 1977. The introduction of steerable percutaneous cryocatheters (2001) and cryoballoons (2006) made cryoenergy available for all interventional electrophysiologists.

The aim of cryoablation is to selectively destroy the targeted tissue in a chosen area using low temperature. The main mechanisms of low temperature induced cellular damage result from a combination of direct cellular failure related to the harmful effects of ice crystal formation during hypothermia and ischemic cell death attributable to microcirculatory damage and the following vascular stasis during thawing. The current understanding of this complex mechanism divides it into the following stages: (1) freeze and thaw, (2) hemorrhage and inflammation, and (3) replacement fibrosis. In the first phase hypothermia leads to stiffening of cardiac myocytes, destruction of ion pumps and the intracellular pH becomes more acidic. Persistence of these changes depends on the minimal achieved temperature and the duration of cryoapplication – the shorter the exposure to hypothermic conditions, the more rapidly cells recover. This property of cryoenergy has very important clinical implications – it permit the functional assessment of the chosen ablation areas (cryomapping) without permanent cellular injury. Continuation of freezing results in formation of ice crystals (a hallmark of irreversible tissue destruction), firstly in the extracellular matrix and later intracellularly. The density of ice crystals and their dimension depend on distance to the cryocatheter, the achieved local temperature and the rate of cooling. Intracellular ice crystals cause progressive damage of intracellular organelles when extracellular crystals cause the extracellular space to become hypertonic, subsequently leading to cell shrinkage and rendering the intracellular space hyperosmotic and acidic. It finally results in damage of enzymes, protein impairment and ultimately rupture of the cell membrane. Freezing also negatively affects microcirculation which leads to (A) hyperemia, (B) interstitial edema and (C) microthrombosis, which eventually leads to tissue ischemia. After freezing is completed, the tissue slowly, passively returns to the temperature of the body – known as the thawing effect. In this phase of cryoablation, intracellular crystals are fused into larger masses, further extending the cellular damage. In the second phase water migrates out of the endothelial cells to re-establish the osmotic equilibrium that was interrupted earlier. This causes a further increase of intracellular osmotic pressure and can lead to further cell membrane failure. Over time a restoration of microcirculation to the previously frozen area occurs, resulting in edema and further ischemic necrosis. In the last stage, which occurs weeks after the procedure, the final lesion is created due to fibrosis and apoptosis of cells close to the borders of frozen tissue.

Size of final lesions is related to minimum achieved temperature, probe size and contact area with target tissue, duration of application(s), number of repeated freeze/thaw cycles, rate of freezing, contact pressure and the local blood flow. The safety profile of this technique is well documented. The unique feature of cryoenergy-based ablation is cryomapping: in the temperature range of 0 to –30°C conduction in the cardiac tissues reversibly slows down and is eventually blocked while permanent lesions are created when the temperatures drops below –60 to –80°C. In contrast to the RF energy, the cryothermal energy application results in discrete homogeneous lesions that are clearly demarcated, with compact areas of fibrotic tissue, and a preserved tissue matrix with alive endothelial cell layers.

Cryoballoon technology

The Arctic Front system (Medtronic, Minneapolis, MN, USA) consists of the CryoConsole that provides the coolant and the electronic control systems, a 15F steerable sheath (FlexCath) and the 10.5-F balloon catheters available in two sizes (23 mm and 28 mm). The first generation of cryoballoon (CB1) was introduced in Europe in 2006 and in the USA in 2011. The CB1 had four cooling jets with a distance of 7 mm to the balloon tip, resulting in a limited equatorial freezing region that might result in an ineffective circular lesion around the PVs. The second-generation cryoballoon (CB2), approved by the FDA in 2012, was produced on a similar platform as its predecessor, but with a shorter distance from the refrigerating jets to the balloon tip (2.5 mm), and the number of refrigerant jet ports has been doubled. With these improvements, the CB-2 can create a wider and more homogeneous lesion, extending from the equator up to the distal tip. These modifications led to better short-term and long-term success rates in terms of freedom from AF. A central lumen present in these balloon catheters permits introduction of a guidewire for positioning or introduction of a special circular diagnostic mapping catheter for monitoring of PV potentials and positioning as well as the injection of contrast. To facilitate PV potential recording, the third generation cryoballoon (CB-3) was released in 2015 with a 40% shorter tip compared to its predecessor – but because of technical issues with the temperature probe and some dislodgement issues it was withdrawn from the market. The above-mentioned issues were solved and the fourth generation CB (CB-4) was released in October 2018.

A competing cryoballoon system, the POLAR X (Boston Scientific, Marlborough, MA, USA), was recently released. It was very similar in design and working principles to the Arctic Front system although minor improvements/modifications were claimed: 1) a more uniform pressure inside the cryoballoon during inflation and the ablation phase potentially protecting from dislodgment/pop-out caused by the balloon expansion, 2) a tighter bend radius (155°) of the steerable sheath that can improve cryoballoon positioning and access to the inferior pulmonary veins, 3) more versatile cryoconsole that allows optional phrenic nerve and esophageal temperature monitoring, automation of patient data collection and retrieval and ability to program customized ablation quality indicators and timers, and 4) the cryoconsole allows single operator technique since the physician handling the cryoballoon can inflate, ablate, mark isolation, and stop therapy by using a foot pedal. However, the larger outer sheath diameter of the POLAR X than the ArcticFront (15.9 vs. 15 Fr) is potentially disadvantageous.

Pre-procedural considerations and patient management

Indications

European Guidelines 2020 concerning management of patients with atrial fibrillation recommend performing PVI in patients with symptoms after ineffectiveness or intolerance of pharmacological treatment with at least one antiarrhythmic drug from class I or III. This is a class I recommendation for patients with paroxysmal and persistent AF regardless of the presence of major risk factors for recurrence of AF. These guidelines also recommend performing PV isolation already after failed β-blocker treatment (IIa) or as a first-step treatment for patients with paroxysmal (IIa) and persistent (IIb) AF, considering in the decision process the patient's preferences, potential benefits, and risks. Importantly, PV isolation is recommended as a first-line therapy to reverse LV dysfunction in AF patients when tachycardia-induced cardiomyopathy is highly probable (class I) and also as a strategy to avoid pacemaker implantation (IIa) in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion (i.e. sick sinus syndrome).

The main goals and benefits of PV isolation are the reduction of arrhythmia-related symptoms and improvement in quality of life. Among asymptomatic patients PV isolation could by conducted after detailed discussion and consideration of the pros and cons, as there are no randomized trials to ensure mortality benefits in AF patients without heart failure. However, pathophysiological reasoning and some studies point to decreased mortality, stroke and heart failure rates after AF ablation [3–5].

Risk of AF recurrence after ablation

To facilitate patient counselling and selection for CB ablation several risk scales that assess the risk of AF recurrence after CB ablation were proposed [6]. The major risk factors connected with AF recurrence include persistent AF type, obesity, enlargement of the left atrium and reduced ejection fraction of the left ventricle. These risk scores have some limitations. Firstly, they are difficult to use in clinical practice because of a lot of included components, sometimes based on hard to obtain data. Secondly, application of these risk scores in different populations provided divergent results, probably due to the inclusion of a number of risk factors that were not universal but population/operator/center dependent. To address these limitations our center developed a simplified tool based on only two universally validated, easily available and strong risk factors: AF type and left atrial (LA) size > 45 mm – named the "0-1-2 PL score". This score had higher predictive power, as assessed by area under the curve, than other much more complicated scores that were validated on non-Polish populations (in press).

Anticoagulation

Patients with risk factors for stroke should take adequate anticoagulation for at least 3 weeks directly before the procedure (class I) – alternatively, transesophageal echocardiography could be performed to exclude the presence of thrombi in the LA (IIa). The 2020 ESC guidelines recommend not interrupting the oral anticoagulant therapy before ablation – as such a strategy was used in trials that compared warfarin with novel anticoagulants. However, other recent guidelines (2017 HRS/EHRA Calkins *et al.*) considered that it is reasonable to hold one to two doses of novel oral anticoagulant prior to AF ablation with re-initiation after ablation. We believe that it is unreasonable to perform ablation on an active oral anticoagulant without immediate access to a reversible agent and that the local anticoagulant strategy should be monitored with local outcomes/complication rather than blindly rely on data from trials performed in different centers/populations. In our center we follow the strategy of postponing the morning dose of any oral anticoagulant, with the re-initiation on the same day, 6 h after the vascular sheaths are removed/hemostasis achieved. No periprocedural strokes were observed in our center over several years when such a strategy of minimal interruption was followed.

The cryoballoon ablation procedure

Access

Femoral access is obtained in a typical fashion. To minimize the local trauma and the risk of arterial puncture we probe for the femoral vein by aspiration during injection of local anesthesia via a thin needle (outer diameter 0.8 mm). This method can precisely pinpoint the location and depth of the femoral vein as the thin needle does not obliterate the vein lumen when puncturing the vein wall. In difficult cases ultrasound is used to visualize the femoral vein and Valsalva maneuvers to increase the size of the vein. We perform three venous punctures: one for the transseptal sheath and two to introduce the His catheter and steerable coronary sinus (CS) diagnostic multipolar catheter. Diagnostic catheters facilitate transseptal puncture by providing anatomical landmarks and are subsequently used for pacing maneuvers to confirm PV isolation, for ventricular pacing during bradycardia and for phrenic nerve pacing.

Transseptal puncture is performed using the electrophysiological approach, SL-1 sheath and the Brockenbrough (BRK-1) needle. The whole assembly/needle tip should be oriented medially and posteriorly. The orientation of the transseptal needle is adjusted according to the coronary sinus catheter/mitral annulus position by keeping the needle indicator pointing at the 4 o'clock (usually) to even at the 8 o'clock direction (in severely rotated hearts). For this the right anterior oblique view can be used as it helps to locate the dilator tip posterior to the site of the His catheter and posterior and parallel to the CS catheter. In the left anterior oblique (LAO) view the tip of the dilator should be well above the CS catheter. Contrast injection (the septal staining technique) is occasionally used to visualize the interatrial septum. In difficult cases, the interatrial septum should be visualized with intracardiac or transesophageal echocardiography to increase the safety of the puncture – guided then by the tenting sign. For fossa ovalis localization the whole assembly is slowly withdrawn under fluoroscopy in the LAO 30° projection until two jumps of the catheter tip are observed, one from the superior vena cava to the right atrium (often very minimal in LAO) and the other (usually very obvious) into the fossa ovalis. We do not follow the recommendations for low fossa ovalis puncture as in our experience it makes access to the PV more difficult. The interatrial septum is then punctured by advancing the needle. At this point, the blood is withdrawn for initial confirmation of LA access. We do not use pressure monitors but rely on fluoroscopic visualization of contrast injected through the needle to confirm access to the LA. In case of doubt/poor visibility, coronary angioplasty or another 0.014" guidewire can be introduced through the needle and positioned in one of the PVs to confirm that the appropriate structure was accessed. The introducer together with the SL-1 sheath is then inserted over the needle into the LA. After this the SL-1 sheath is immediately replaced with a stiff 0.035" guide wire, positioned in one of the left-sided PVs. A heparin bolus of 10 000–16 000 U is administered, aiming for an activated clotting time of 350–400 s; this should be performed immediately after puncture or preferably before puncture [7].

Sedation and analgesia

Shortly before the procedure intravenous acetaminophen (1000 mg) is administered to reduce the need for opioids. During the procedure, after the transseptal puncture, intravenous boluses of midazolam (2.5 mg) and fentanyl (0.05 mg) are used for pain/anxiety control. The procedure is usually well tolerated.

Engagement and occlusion of the veins

Engagement of the left-sided PVs is performed in LAO 30–40° while right-sided PVs are engaged and ablated in the postero-anterior view and occasionally in the shallow RAO view. We use the dedicated intraluminal circular mapping catheter (Achieve catheter) to intubate all PVs starting with the left superior or the left inferior vein. The inferior PVs are located posterior and inferior to the superior PVs; therefore, once a superior or an inferior vein is intubated this directs the rotation and flexing of the Flexcath sheath to intubate the other. To prevent LA trauma/perforation by the stiff tip of the CB catheter or the Flexcath sheath the soft-tipped mapping catheter should always be exposed to lead the CB catheter. For *de novo* PV isolation procedure we do not recommend any preprocedural visualization of the LA anatomy or intraprocedural visualization of the veins using angiography as this is very rarely useful and has unproven outcome benefits. In the vast majority of cases veins have a typical anatomical position and can be accessed using simple maneuvers. Moreover, PVs are visualized anyway during contrast injection for determination of the balloon occlusion grade. In difficult cases, when one of the veins cannot be intubated or there is a need to confirm the presence of common trunk or an additional vein is suspected, the LA angiography can be performed by a fast injection of 50 ml of contrast into the LA during fast ventricular pacing (250 bpm; to slow atrial emptying) – Figure 1.

Once the mapping catheter is inside the target vein, the markers on the cryoballoon body are used to position it outside of the Flexcath sheath (the second white band indicates that the cryoballoon is out of the sheath). Balloon inflation should be performed outside of the vein – in the PV antrum or LA. An antral level of isolation likely reduces collateral damage by maximizing the distance between the balloon and the phrenic nerve, the esophagus and the lungs. It is extremely important to provide adequate forward pressure to the balloon/sheath to ensure the best possible contact of the balloon with the PV antrum. Often appropriate Flexcath rotation/flexion or some 'tricks' (see below) are necessary for this. Good contact ensures rapid isolation and probably prevents re-conduction. Initial confirmation of a good contact relies on the assessment of the occlusion grade with contrast injection via the balloon catheter lumen into the occluded vein. There should be no contrast leak into the LA or a very minimal leak that will close once the balloon slightly expands during freezing.

It might be tempting to position the balloon deeper, not in the antrum but in the proximal part of the PV, as this provides a more stable position, a perfect occlusion and a fast isolation. However, it is a very dangerous approach and cannot be pursued, and once such a position is identified, the balloon should be immediately deflated and repositioned. In large diameter superior veins it is especially easy to inadvertently position the balloon too deep. To ensure an antral position the ‘proximal seal’ technique should be routinely used (Figure 2). This technique is based on withdrawing the cryoballoon slightly to create a temporary contrast leak, as this will either visualize the PV ostium or will visualize the more proximal part of the vein, indicating that that the balloon, after withdrawal, was still inside the vein. In such cases a popular trick that increase the balloon diameter and stiffness and prevents it from jumping inside the PV during forward pressure is to initiate the ablation/freeze a few seconds before advancing the balloon.

For good vein occlusion and balloon contact with the antrum the proper alignment of the axes of the mapping catheter, the Flexcath sheath and the PV antrum is probably the decisive factor. Therefore, if a good occlusion cannot be initially achieved, then the vein should be intubated several times as different branches are then often engaged with the mapping catheter and the orientation of the Flexcath sheath, with regard to the antrum, as well as the sheath and catheter rotation/flexion changes. Although most of the support for the balloon is provided by the Flexcath sheath, the mapping catheter often also provides a desirable stabilization – but only when positioned deep inside the vein. Unfortunately, this prevents real-time monitoring of the PV isolation process, as in a deep position the catheter does not record PV potentials. Therefore, the deep mapping catheter position facilitating stabilization versus the shallow position facilitating PV potential recording should be balanced. We initially aim for recording of PV potentials, as this provides the ultimate information that the balloon was in good circumferential contact with the tissue and also because such technique facilitates avoidance of a too deep position of the balloon. Therefore, once the occlusion is achieved the circular mapping catheter should be withdrawn and rotated (‘back-flipped’) so that it rests on the balloon and records PV potentials – Figure 3. Only when this repeatedly results in instability/leak/balloon displacement should a deeper positioning of the mapping catheter be allowed. In such cases instead of the real-time PV potentials monitoring, other methods for confirmation of PV isolation should be used (see below).

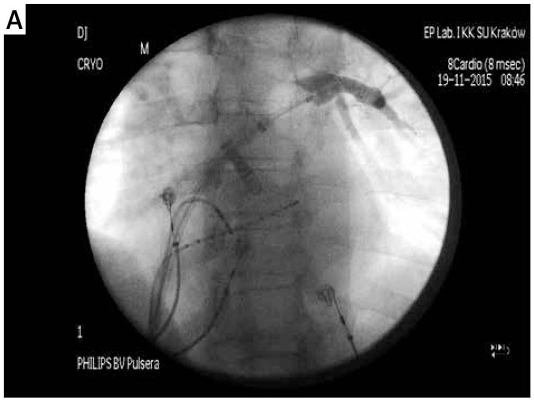
Assessment of the freeze quality and freeze dosing

Assessment of proper positioning of the balloon continues during the freeze application by processing of the real time data from the cryoconsole (temperature drop) and the circular catheter (disappearance of PV potentials, “time to isolation”). Too fast temperature drop (colder than –40°C at 30 s) and too deep nadir temperature (colder than –56°C at any time) indicates a dangerously deep position of the balloon and the freeze should be aborted. As a rule, in such cases a more proximal position with proper temperature behavior can be obtained. Too slow temperature drop resulting in too high temperature at 1 min (warmer than –35°C) should also prompt abortion of the freeze as the balloon is probably in poor contact with the antrum. The thaw time also indicates good vs. poor contact, and shallow vs. deep balloon position. These phenomena and the proper temperature behavior pattern are illustrated in Figure 4.

Short time to isolation is considered the best predictor of a durable lesion and another indicator of a proper balloon position. Time to isolation below < 40 s is a very good sign, and likely a single, short (120–150 s) freeze per such vein might be enough. Time to isolation < 60 s is probably acceptable, while a longer time to isolation or lack of isolation at the end of cryoapplication requires a second freeze – after some change of the balloon position/alignment. The thaw time/rate also informs about the balloon position within the antrum/vein (Figure 4) and is a marker of a durable lesion. However, most likely none of the predictors is good enough to allow the operator to be absolutely certain than the vein was permanently

Figure 1. Left inferior pulmonary vein could not be localized and the angiography of left atrium was performed with 50 ml of contrast injected via the Flexcath sheath during fast ventricular pacing (to slow atrial empting); this visualized left common trunk and confirmed absence of a separate inferior pulmonary vein

A



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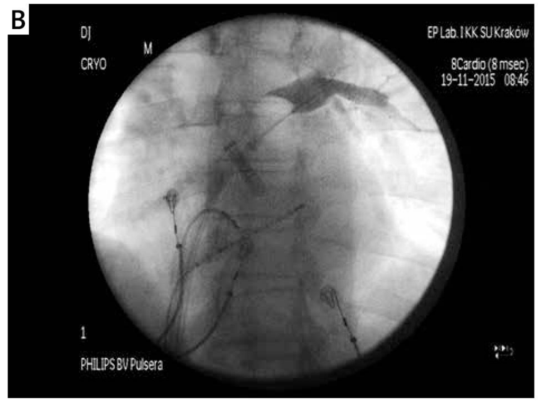

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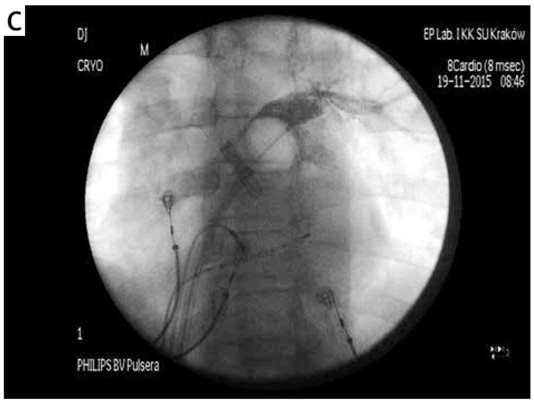

Figure 2. Proximal seal technique. **A** – A good vein occlusion indicated by the contrast retention during an apparently proximal balloon position. However, instead of initiating the freeze application, the balloon was slightly pulled back to create a temporary contrast leak. **B** – During balloon withdrawal instead of a contrast leak to the left atrium – a more proximal part of the left superior pulmonary vein was visualized indicating that the balloon was almost completely inside the vein. **C** – The balloon was pulled back more until the created contrast leak delineated the antrum and indicted the proper proximal position of the balloon

isolated; therefore, other factors should be considered for individualized cryoenergy dosing. Recommended freeze time per vein and per application evolved over the years. Despite multiple studies comparing various fixed and titrated dosing protocols, this part of the procedure is still far from evidence-based standardization. In 2009 we used 3 freezes of 4–5 min duration per vein; nowadays, often a single 120–180 s application is considered enough. Our standard protocol is a single 240-second freeze per vein for left-sided PVs and a single 180-second application per vein for right-sided PVs. These times are often modified and additional freezes are often added according to the time to isolation, achieved temperature drop, phrenic nerve behavior and the perceived arrhythmogenic potential of a particular vein – Figure 5. When dozing the freeze time, several simple rules should be considered. 1). Fast temperature drop and a quick isolation is not equivalent to slow temperature drop and late vein isolation, even if similar temperatures are reached. Slow temperature drop probably indicates a small area of balloon contact with the antrum and/or constant rewarming and the lesion might not be permanent. 2). Increasing freeze time in cases with slow temperature drop will increase the risk of collateral damage, as with the increased duration of the freeze the depth of ice penetration into the nearby tissues grows. 3). Bonus freeze is usually not necessary when the initial freeze had very good parameters (time to isolation < 40 s and the temperature at 1 min below –40°C), 4). Evidently poor freeze parameters: time to isolation > 90 s or temperature at 1 min warmer than 35°C indicate the need for another freeze. 5). Shorter freeze time and no-bonus freeze policy decreases left atrial dwell time, while too short freeze time (< 180 s or even below 240 s for left sided veins) is related to a smaller lesion and a higher risk of re-conduction.

Additional positioning techniques

Several 'tricks' have been proposed to improve the acute results of the cryoballoon based PVI. The most common trick used to facilitate the occlusion of the inferior PVs is the hockey stick technique – for this the Flexcath sheath should be maximally bent and pushed up to provide support for the balloon from the superior position in the left atrium (Figures 3 and 6); the mapping catheter/guidewire should be placed in the most inferior (caudal) branch of the PV, resulting in a hockey stick figure on the fluoroscopy. If despite the hockey stick technique there is still a poor occlusion/temperature or the vein is not isolated at 40–60 s the pull-down maneuver can be used. It is based on the assumption that the superior part of the balloon, frozen to the superior aspect of the inferior vein, stabilizes the cathe-

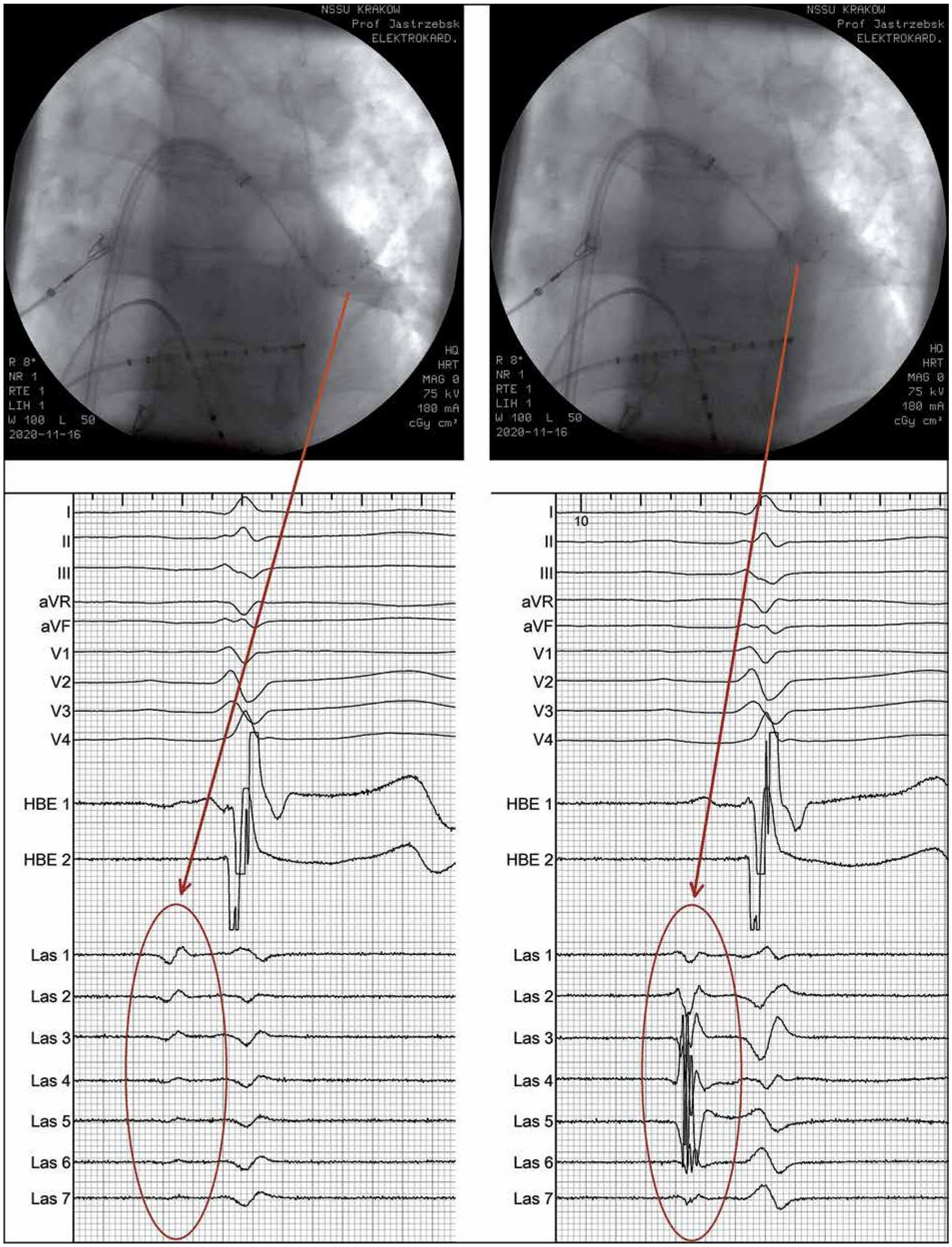

Figure 3. Left inferior pulmonary vein is occluded with the cryoballoon. Distal position of the circular mapping catheter results in lack of pulmonary vein potentials (circle, left panels). After rotation with pulling of the circular mapping catheter it backflips and rests on the balloon where ample pulmonary vein potentials are recorded (right panels)

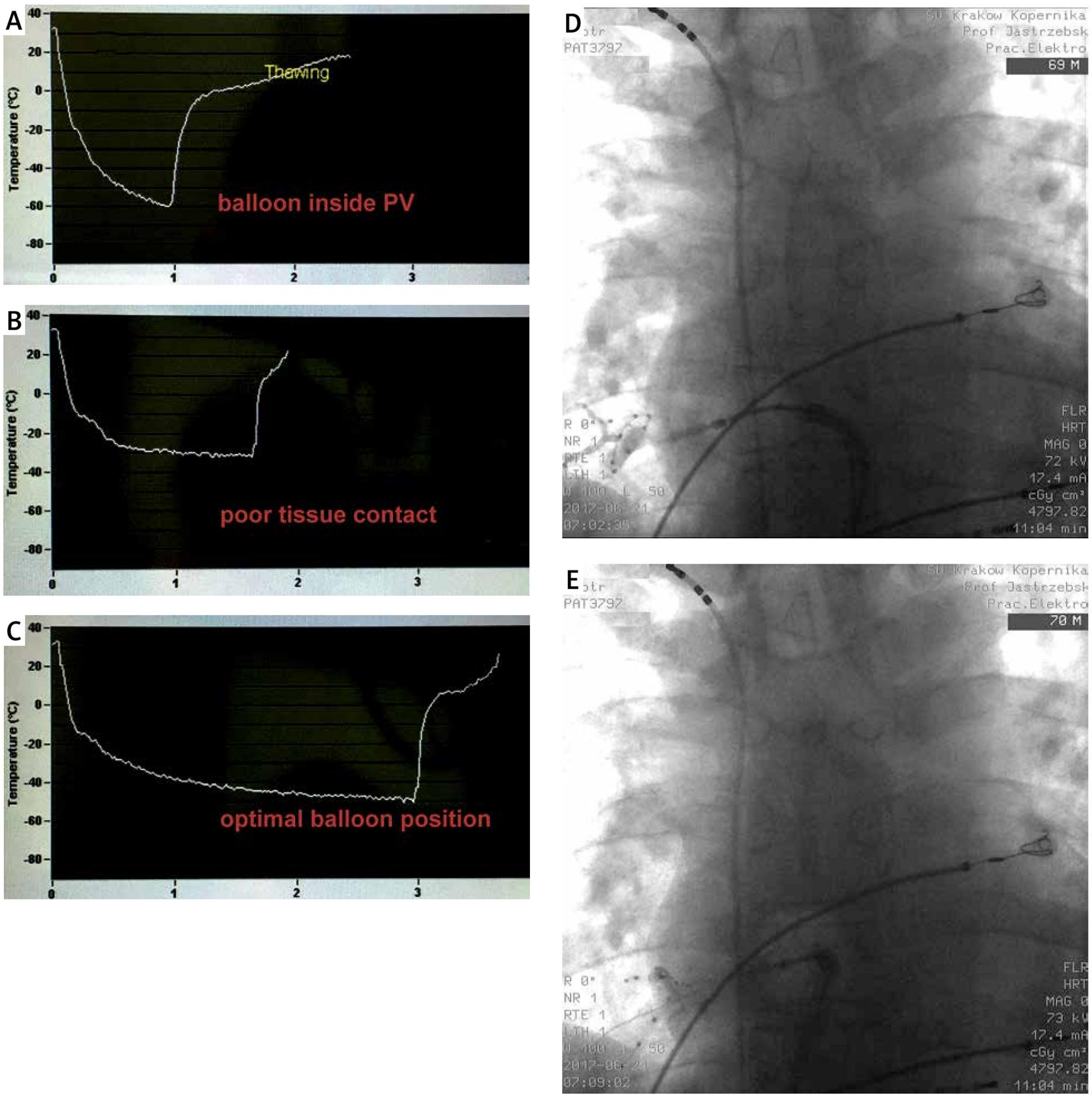

Figure 4. Temperature behaviour patterns observed in the same patient during three separate freeze applications in the right inferior pulmonary vein. The first freeze (**A**) illustrates rapid temperature drop exceeding –40°C at 30 s. This had prompted to stop the application at 1 min when the temperature dropped to –60°C. Such rapid temperature drop was caused by positioning the balloon inside the pulmonary vein (**D**). Note very slow re-warming resulting in a long thaw time. After the balloon was repositioned to a more proximal position (**E**), the next freeze resulted in a very sluggish temperature drop that plateaued around –30°C (**B**). That indicated a poor tissue contact and prompted to stop the freeze to prevent local oedema/temporary lesion; that freeze should have been stopped earlier – already at 1 min. The third freeze was performed with the balloon in the same proximal/antral position as before (**E**), albeit with a more forward pressure and strong counterclockwise rotation of the Flexcath sheath; this resulted in the optimal balloon position and a good tissue contact – as indicated by the proper temperature behaviour; the freeze was completed after 3 min

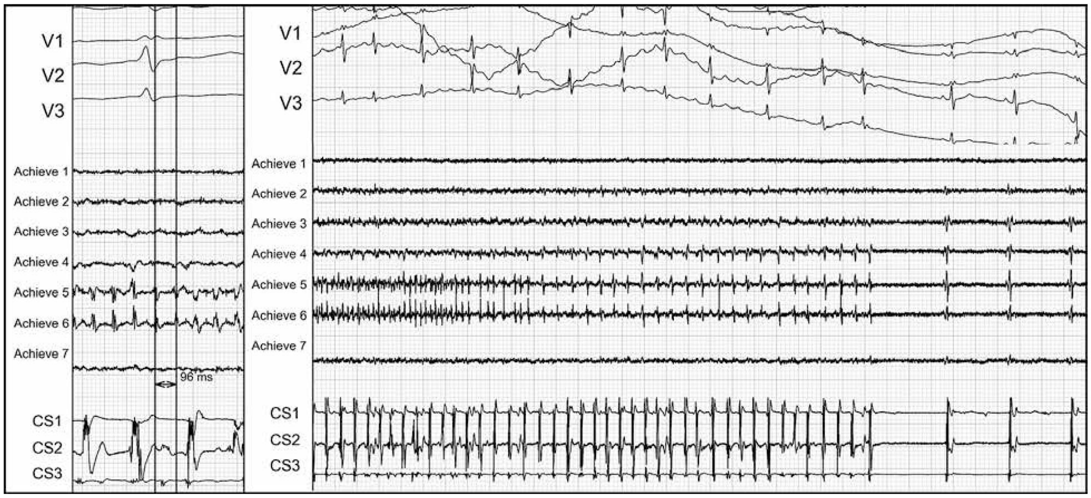

Figure 5. Electrical activity in the left superior pulmonary vein very suggestive that this vein was the culprit vein for paroxysms of atrial fibrillation. Left panel: the spontaneous activity in that vein was much faster than in the rest of the left atrium: cycle of 90–100 ms versus 250 ms in the coronary sinus (CS). Right panel: during freeze application the spontaneous activity in the vein slowed down and the sinus rhythm was restored. In our opinion such a vein deserves a bonus freeze regardless if the initial freeze resulted in a fast isolation or not

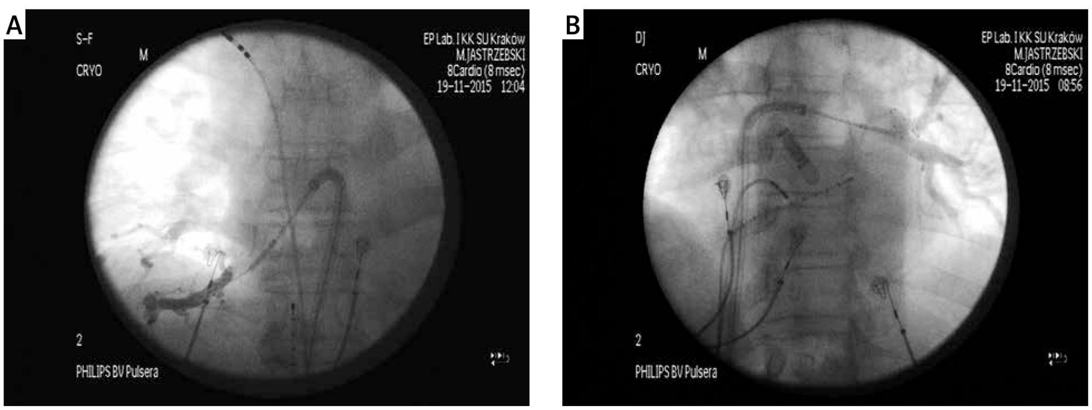

Figure 6. When direct approach to the occlusion of the inferior pulmonary veins fails, the hockey stick technique should be tried. This relies on the strong flexing of the Flexcath sheath to provide support for the balloon from the superior position; it is advised to intubate the most inferior (caudal) branch of the pulmonary vein to facilitate this approach. The resulting hockey stick figure on the fluoroscopy can be appreciated on the upper panel in case of an inferior pulmonary vein occlusion and in the lower panel in a case of a superior pulmonary vein occlusion

ter and pulling the catheter will occlude the vein by closing the inferior gap. This maneuver is very effective in the acute setting. Often the isolation occurs within a few seconds after pulling the catheter and the temperature curve will show an additional small but abrupt decrease. However, the usefulness of the pull-down technique is debatable. Some argue that after 40–60 s the balloon is already covered with an ice layer and cannot provide a good tissue contact at the gap; consequently the isolation will be temporary and the lesion not transmural. We do not share that opinion. The pull-down maneuver has several beneficial effects: 1) it increases the contact area of the cryoballoon at its inferior perimeter, 2) increases contact pressure on local tissues which decreases warming effects of local blood flow, 3) closes the gap preventing warming effects of PV blood flow. These mechanisms profoundly impact heat transmission (subtraction) and lesion size. We are not aware of any studies showing worse outcomes in patients treated with the pull-down technique or supporting the

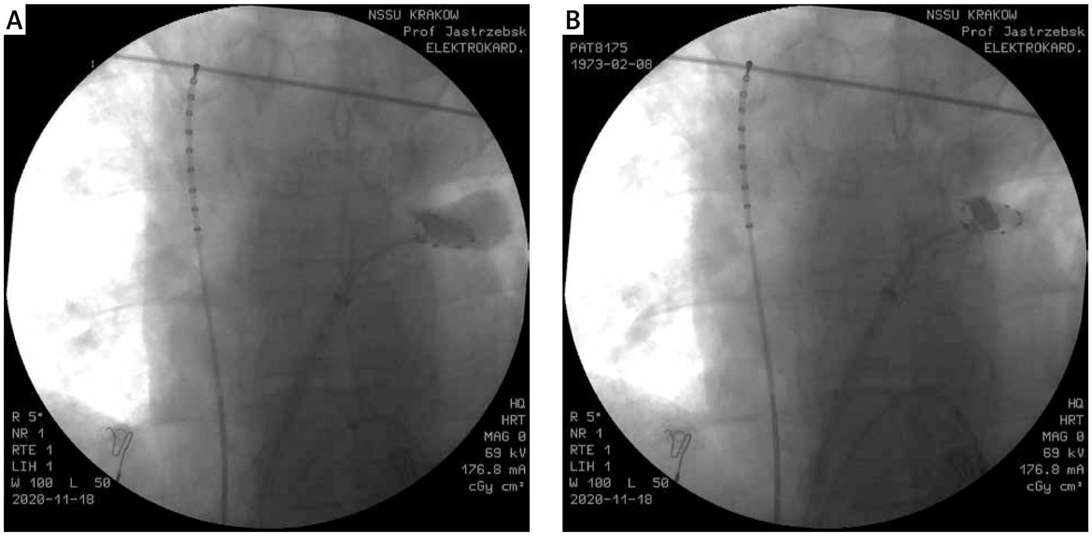

Figure 7. Despite automatic deflation of the balloon by the cryoconsole and rewarming to 36°C and, the catheter should not be repositioned because it is still frozen to the pulmonary vein – as evidenced by the residual ice plug in the proximal part of the vein. In the left panel the ice completely occludes the vein as evidenced by contrast retention. On the right panel with fluoroscopic image obtained some 20 s later, the contrast completely leaked into the left atrium but the circular mapping catheter is still firmly frozen to the vein

speculation that the veins isolated with the pull-down technique are not permanently isolated; on the contrary, there are studies showing that the pull-down maneuver results in permanent isolation of PVs [8, 9]. Moreover, the reasoning that an ice layer prevents cryoenergy transmission seems faulty; thermal conductivity of ice is good. The best evidence comes from the cryoablation itself – damage to the phrenic nerve or other adjacent structures occurs despite the lack of a direct contact with the balloon, low temperatures reach the phrenic nerve via other frozen tissues – composed mainly of water – i.e. via an ice layer. We use the pull-down technique also in cases without contrast leak, as in such cases it can also result in sudden isolation of the vein, through the above-mentioned mechanisms no. 1 and 2. Occasionally the gap or narrow area of contact between the balloon and the PV antrum is at the superior perimeter of the balloon and instead of the pull-down, a push-up maneuver will lead to the increased contact surface area and increased tissue compression resulting in fast PV isolation. The overlapping freeze/lesion technique is an alternative and complementary technique to the pull-down/push-up maneuvers. It is applicable especially to cases with a large diameter antrum of a common trunk that cannot be proximally occluded with the 28 mm balloon. The overlapping freeze applications are performed using the Flexcath sheath to obtain a firm contact of the balloon with different parts of the antral perimeter during the subsequent freezes. This technique seems inferior to the pull-down maneuver as an incomplete PV occlusion results in an unbroken blood flow in the vein and tissue warming – including at the area of balloon contact.

Thawing and balloon deflation

After completion of the desired freeze time the balloon is automatically deflated when the temperature reaches 20°C. However, often the balloon is still frozen to the PV/antrum – as demonstrated in Figure 7. Repositioning the balloon immediately after deflation might damage the PV wall; it is recommended to wait until the ice cap melts completely. However, often it does not contain contrast and is, therefore, not visible; gentle pulling can be used to ensure that the catheter in not adhered to tissue but moves freely. Very slow thawing should raise the suspicion that the balloon was inside the PV, while very fast thawing indicates that the surface area of balloon contact with the antrum was small and perhaps a bonus freeze with slightly different position should be made even if the PV isolation was achieved. When it is planned to occlude another vein the balloon should be retracted into the sheath; for this the balloon should be first inflated and deflated while advancing the push button on the catheter handle that extends the balloon to maximum length.

Electrophysiological assessment of pulmonary vein isolation

Regardless of the energy source used for ablation, demonstration of PV isolation is obligatory. Real-time

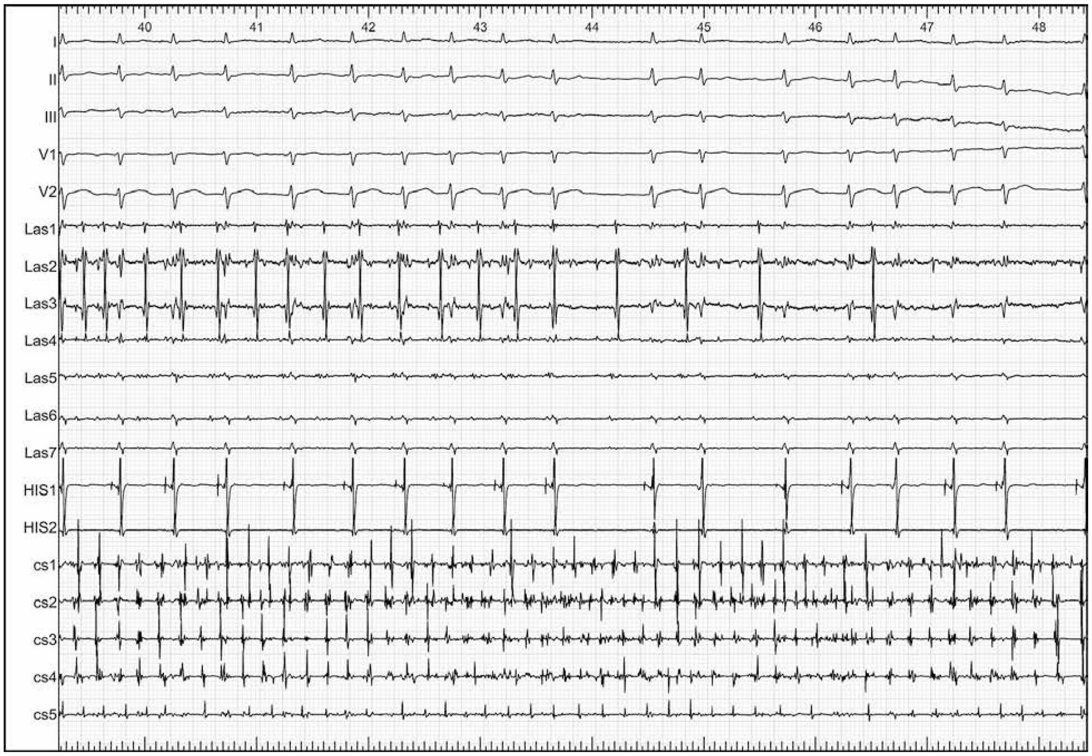

Figure 8. Cryoballoon based isolation of the left inferior pulmonary vein during a re-do procedure in a patient after remote point-by-point RF pulmonary vein isolation. Real time recording of the pulmonary vein potentials allow easy differentiation of PV potentials and far-field potentials

monitoring of PV potentials and rapid PV isolation observed in the majority of cases makes this task easy during CB ablation (Figure 8). This method leaves little doubt what the PV potential and the far-field potential are, and when block occurs, therefore, additional maneuvers are rarely necessary to confirm PV isolation.

However, when the real-time recording of PV potentials is not feasible, alternative methods have to be used. An elegant proof that the vein was isolated is the observation of a spontaneous PV electrical activity dissociated from the atrial activity (Figure 9). However, this is a relatively uncommon phenomenon. Constant pacing from the circular mapping catheter during freezing enables one to demonstrate the exit block as it will manifest itself with delayed activation and then loss of synchronized atrial activation while PV capture is ensured by the stable position of the frozen catheter. Pacing inside the PV with 5 V output after the ablation and at the site of recorded suspicious potentials also differentiates local potentials from far-field potentials that are usually not captured with moderate/low output. Alternatively, the template method can be used by obtaining a proximal recording of the PV potentials before the freeze and comparing it with the recordings from the same position obtained after the freeze. In the case of doubt, if the remaining potentials are far-field or PV potentials classic electrophysiological maneuvers should be performed using the coronary sinus catheter and the His bundle catheter for right atrial, CS and left appendage pacing for differentiation.

Extended use of cryoballoon catheter for ablation/isolation of non-PV targets

Pulmonary vein isolation is the cornerstone of the AF ablation procedure, but outcome benefits of ablation of other targets are less well documented or controversial. However, in selected patients ablation of non-PV sites might be critical to achieve a good outcome. Cryoballoon can be used (off-label) to isolate the superior vena cava and the persistent left superior vena cava using a similar approach as with pulmonary veins [10]. Extreme caution should be used in such cases as the risks of such use of the cryoballoon are not defined and vein stenosis and damage to left the phrenic nerve, the sinus node or other structures are quite possible. The left atrial appendage can also be the source of AF triggers, and CB based isolation of the left atrial appendage was reported to improve the outcome [11]. Potentially, CB based ablation might be a better option for such procedures than the point-by

Figure 9. Electrical isolation of the left inferior pulmonary vein was diagnosed by observation of an exit block – there was a spontaneous slow electrical activity in the pulmonary vein (Las2 - Las4) that was dissociated from the regular electrical atrial activity and the sinus rhythm, evident in the coronary sinus recordings (CS1-CS2) and the surface ECG leads (III, aVR, aVF, V1), respectively

point RF technique. However, undefined risk of damage to the right phrenic nerve, coronary arteries, appendage perforation and mechanical dysfunction of the isolated appendage, with related thromboembolic risk, makes this procedure controversial and justified only in highly selected cases with evident triggers in that structure. It was recently shown that the cryoballoon can be used for isolation of the posterior wall and the creation of a roof line [12]. Such a procedure is technically challenging, time consuming and potentially related to the increased risk of damage to the esophagus and creation of an atrio-esophageal fistula. Until further studies characterize the outcome benefits and safety of such an approach it cannot be recommend for routine use.

Post-procedural management

Immediately after the procedure we routinely perform a short echocardiographic study, still in the electrophysiological laboratory, to exclude pericardial effusion. If there is substantial effusion, regardless of symptoms, pericardiocentesis is not deferred but immediately performed. Post-procedural groin management depends on the results of the echocardiographic examination. If there is any trace of pericardial effusion, or the transseptal puncture was troublesome, protamine is administered, the sheaths are removed and a figure-of-eight suture is used to stop the bleeding. If the result of the echocardiographic examination is normal then the sheaths are left and removed on the ward after 5 h. Oral anticoagulation is either normally continued or if the morning dose was skipped then it is administered 5 h after obtaining groin hemostasis. Long-term anticoagulation is always continued for 2 months, regardless of the presence of risk factors for stroke, although probably one month should suffice as the healing process is at that time already completed. Necessity of a long-term continuation of anticoagulation should be determined on the basis of the patient's stroke risk profile and not on the apparent success or failure of the ablation procedure. Preprocedural antiarrhythmic drugs are usually continued for 3 months of the so-called blanking period. In patients with long-term persistent atrial fibrillation and/or heart failure, occasionally amiodarone is continued for 6 months to facilitate atrial remodeling. Monitoring for AF recurrence is based on symptoms, periodic ECG monitoring, Holter ECG monitoring (every 6–12 months) and occasionally by implantable ECG recorders – Figure 10 [13]. It is well documented that the success rate defined according to the guidelines-recommended detection of a 30-second long AF episode depends on the intensity of ECG monitoring – to the point when after the implantation of the continuous ECG recorder it loses its original sense and other measures of success have to be applied (AF burden rather than the 30-second AF episode detection). However, since the procedure is mainly performed for control of symptoms, extensive search for asymptomatic episodes of AF has undefined practical value.

Acute and long-term outcome

Several studies and metanalyses have assessed the acute and long-term efficacy of cryoballoon-based PVI. The reported success rate of PV isolation during the procedure is about 98% [14, 15]. Despite this, the long-term effectiveness of the procedure (AF free survival) assessed at one year after the ablation is in the range of 70–82%. The AF-free survival rate significantly depends on the clinical characteristics of the studied group and the presence of risk factors, especially the type of AF – paroxysmal vs.

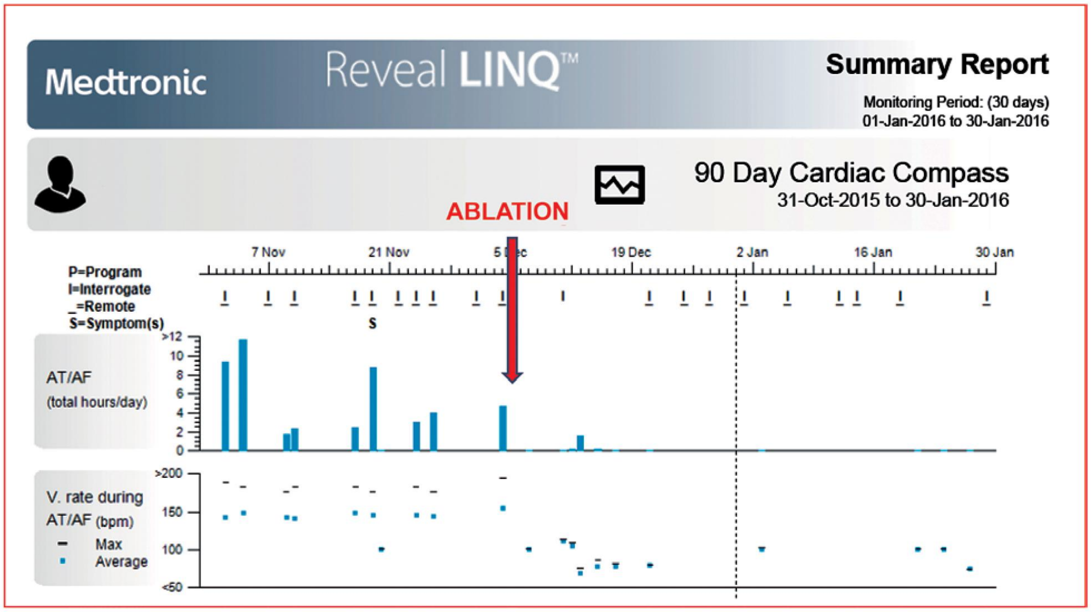

Figure 10. Implantable ECG recorder enables to monitor effect of cryoballoon ablation in a much more accurate fashion than the periodic ECG monitoring. Several AF episodes (blue bars) were confirmed before the pulmonary vein isolation (red arrow); while after the procedure there was only one AF episode – during the healing phase/blanking period. That confirmed the good result of the procedure

persistent, LA size and the presence of heart failure [15, 16]. Patients with persistent AF have a poorer long-term outcome than patients with paroxysmal AF – 55–72% vs. 75–81% respectively [15, 17, 18]. Patients with heart failure probably have the greatest survival benefit from AF ablation (CASTLE-AF trial) despite the significantly lower AF-free survival after ablation than patients with preserved left ventricular function [19–22]. In our center we observed similar efficacy of ablation with almost 80% of patients without recurrence at 1 year. Type of AF and LA size were the strongest predictors of failure in our population [23].

Both CB and RF ablation techniques are considered as standard methods with similar outcomes. However, based on the largest comparison of both techniques – the "Fire and Ice study" – patients after CB ablation had significantly fewer all-cause re-hospitalizations, cardiovascular re-hospitalizations, re-ablations, and direct current cardioversions after the index procedure [2, 16, 24, 25]. In our opinion there are several important advantages of CB ablation making it the preferred approach. During CB ablation a more stable position of the catheter can be achieved, which is less sensitive for beat-to-beat heart and respiratory motions. With CB there is better control over application, which translates to more predictable, more continuous and homogeneous lesions, that are less arrhythmogenic. The rate of secondary, iatrogenic LA arrhythmias after cryoballoon ablation is markedly lower than after the point-by-point RF technique (very high for inexperienced operators, non-negligible for experienced operators). The PV re-connection rate after CB ablation is dramatically lower than after RF ablation. The most striking difference that makes the CB ablation the method of choice for many operators is the speed of PV isolation; it usually takes less than 1 min from the balloon apposition in the antrum to the electrophysiologically confirmed PV isolation, and this translates into a much shorter LA dwell time, usually < 30 min. In contrast to RF ablation there is usually little doubt whether PV was isolated or not. General anesthesia during ablation is not necessary as the procedure is less painful than the RF ablation.

Adverse events and prevention of phrenic nerve injury

Prospective, registry-based data show that approximately 4–14% of patients undergoing AF catheter ablation experience complications, 2–3% of which are serious/potentially life-threatening. The frequency of complications after CB ablation is similar, however, it differs to some extent between studies – Table I [26–30]. Based on the large clinical trials, in which mainly experienced high-volume centers take part, major complications occur in approximately 4.0% of patients; this is similar to data coming from our center. Complications occur mostly within the first 24 h after the ablation. The spectrum of complications includes hematoma and/or

Table I. Frequency of major complications after cryoballoon ablation

Parameter	Andrade [26] 2019 (*n* = 231)	Hoffmann [27] 2019 (*n* = 2329)	Rottner [28] 2018 (*n* = 563)	Kuck [29] 2016 (*n* = 374)	Luik [30] 2015 (*n* = 156)	Jastrzebski [23] 2020 (*n* = 589)
Death	0	2 (0.09)	1 (0.18)	0	0	0
Pericardial effusion needed treatment	1 (0.43)	6 (0.27)	0	1 (0.27)	2 (1.28)	5 (0.85)
Pericarditis	3 (1.29)	4 (0.18)	N/D	N/D	N/D	1 (0.17)
Stroke	1 (0.43)	4 (0.18)	1 (0.18)	2 (0.54)	0	1 (0.17)
Transient ischemic attack	2 (0.86)	0	1 (0.18)	0	0	1 (0.17)
Major groin complication	1 (0.43)	10 (0.9)	3 (0.54)	7 (1.89)	6 (3.84)	9 (1.53)
Persistent* phrenic nerve palsy	3 (1.29)	22 (0.99)	15 (2.7)	10 (2.7)	5 (3.2)	7 (1.17)
Permanent phrenic nerve palsy	0	8 (0.36)	3 (0.54)	1 (0.27)	0	1 (0.17)
Atrioesophageal fistula	0	0	0	0	0	0
Pulmonary vein stenosis	0	0	0	0	0	0
ASD requiring intervention	N/D	N/D	N/D	N/D	N/D	8 (1.36)

*Numbers in parentheses denote percentage; *persistent indicates present after discharge; ASD – atrial septal defect.*

pseudoaneurysm at the groin access site, cardiac tamponade/pericardial effusion, thromboembolism causing cerebrovascular accidents, phrenic nerve injury/palsy, migraine attacks, silent cerebral lesions, hemoptysis, periesophageal vagal nerve injury/gastroparesis, pericarditis and iatrogenic atrial septal defect.

The periprocedural death rate related to AF ablation is approximately 0.2–0.98%; however, in the majority of CB studies and in our practice no deaths were observed [31]. The most common (1–0.5%) life-threatening complication is tamponade [32]. Pulmonary vein stenosis and atrioesophageal fistula formation are complications occurring mainly after RF ablation, hardly ever after CB ablation [33]. We believe that monitoring temperature in the esophagus, recommended by some to prevent atrioesophageal fistula formation, is not justified. Frequency of this complications after CB based ablation (1 : 10 000) is 10 times lower than after RF ablation (1 : 1000), and likely mostly related to positioning the CB deep within the left inferior PV [34]. Routine prescription of proton pump inhibitors to facilitate healing of esophageal injury/prevent fistula formation, recommended by some, has unproven value. The practice of stopping the freeze when the temperature drops below –56°C, limiting the time and number of freezes and following the proximal seal technique probably further reduces this complication.

The complication most feared by the patients is stroke. Over 11 years of performing this procedure we have observed only one such incident (0.17%), in which symptoms largely resolved during follow-up, and one short-lasting transient ischemic attack; this was much less than the stroke rate reported for the RF-based AF ablation procedures (approx. 1%). However, according to the literature silent cerebral embolization, a phenomenon of unknown clinical significance, occurs in approximately 25% of patients – similarly as in many other cardiac interventions that involve left heart catheterization. Most likely the cerebral embolization is mainly related to air embolism. Great care is mandatory during sheath management; catheter insertion and withdrawal should be slow to avoid air suction via the Flexcath valve, and reinsertion of the CB catheter should be avoided.

Pericarditis develops in a very small percentage of patients after cryoablation ablation – probably due to a larger than usual surface of the transmural lesions. The long-term consequence of subclinical pericarditis (Figure 11), probably an underestimated phenomenon, could be the formation of pericardial adhesions [35]. Hemodynamically important iatrogenic atrial septal defect (ASD) and its consequences after PVI seem to be an underestimated problem as well. There are limited data from the literature regarding this complication [36]; the large diameter of the Flexcath sheath that facilitates this complication is one of the weak sides of the current technology. Apart from many cases of asymptomatic, tiny ASD and a few cases of ASD requiring percutaneous intervention, we have observed a few cases of severe migraine after CB ablation, a complication probably related to iatrogenic ASD. In some patients this was *de novo* migraine, but in most cases it was an exacerbation of the pre-existing migraine that was inactive before the procedure, sometimes for many years. In all our cases migraine subsided within a few months. The estimated incidence of migraine after ablation/transseptal puncture is 1–2% [37].

Palsy of the right phrenic nerve deserves special attention as it remains the Achilles' heel of the cryoballoon technique (Figure 12). It usually occurs during freezing in the right superior PV, less frequently in the right inferior PV. It is the most common intraprocedural complication, occurring in about 8–6% of patients; although it usually resolves within a few minutes it limits further freeze delivery to the right PVs. Persistent palsy (i.e. still present

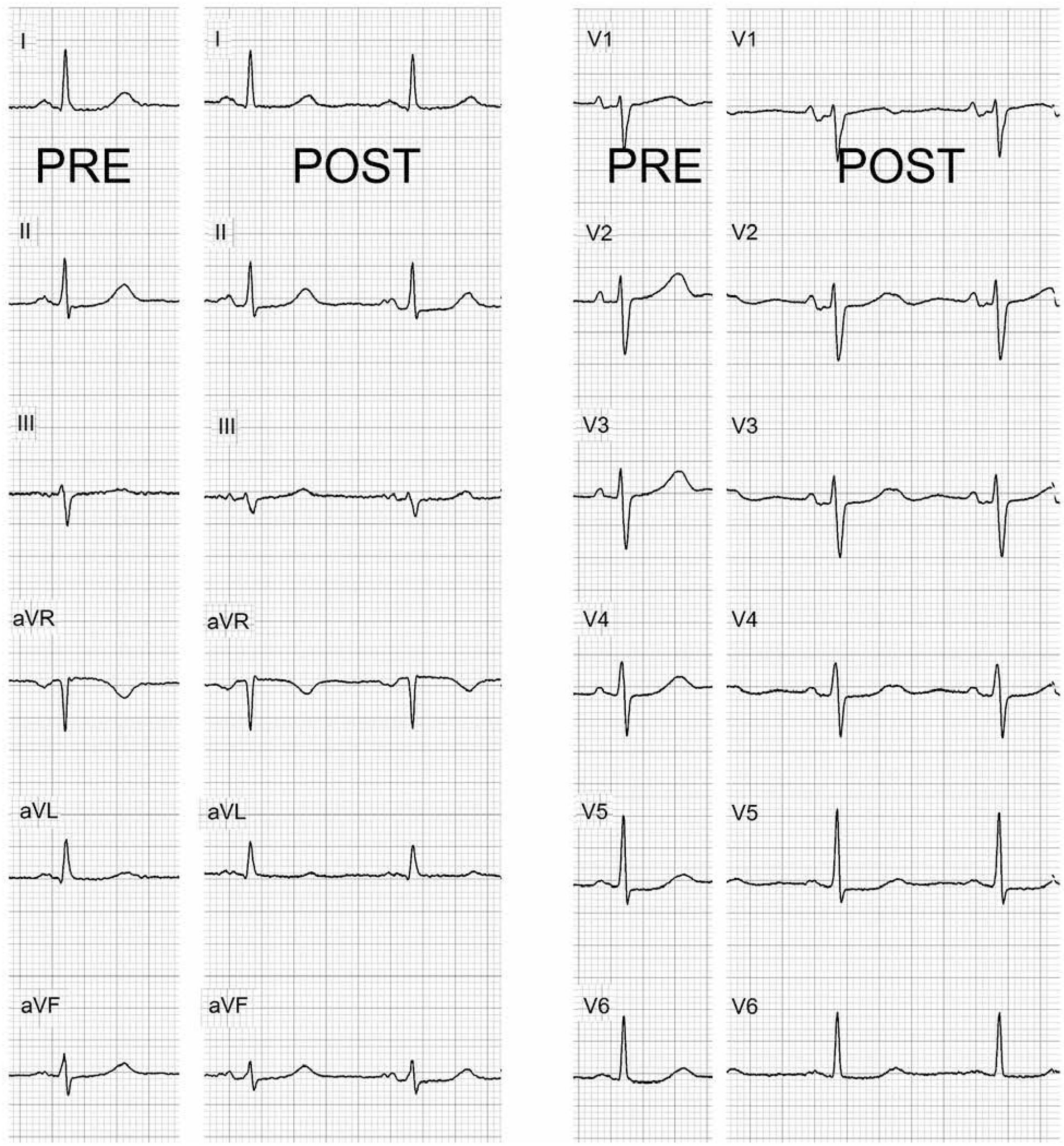

Figure 11. 12-lead ECG recorded at the beginning (panels 'PRE') and at the end (panels 'POST') of an uneventful cryoballoon ablation procedure. After the procedure there is an evident depression of the PR interval in several leads (II, III, aVF, V1-V3) as well PR interval elevation in lead aVR indicating pericardial inflammation due to the transmurality of the cryoablation lesions – or more extensive necrosis/damage to the left atrium. This is a common ECG phenomenon post cryoballoon ablation

at discharge) is present in approximately 1–2% of cases [38]. Steroids might be administered in such cases to limit inflammation. In most of these cases the phrenic nerve regains function within 1 year. Permanent nerve palsy affects approximately 0.2% of cases, fortunately, most of them remain asymptomatic. A chest X-ray is recommended before the discharge in cases where phrenic nerve palsy was observed during the procedure. In some patients phrenic nerve palsy might course under the mask of pneumonia/atelectasis.

Several precautions can limit this complication significantly. During every freeze in the right sided PVs the phrenic nerve activity must be monitored by constant pacing. The left phrenic nerve can be paced by placing the coronary sinus deflectable catheter near the junction of the superior vena cava and the right subclavian

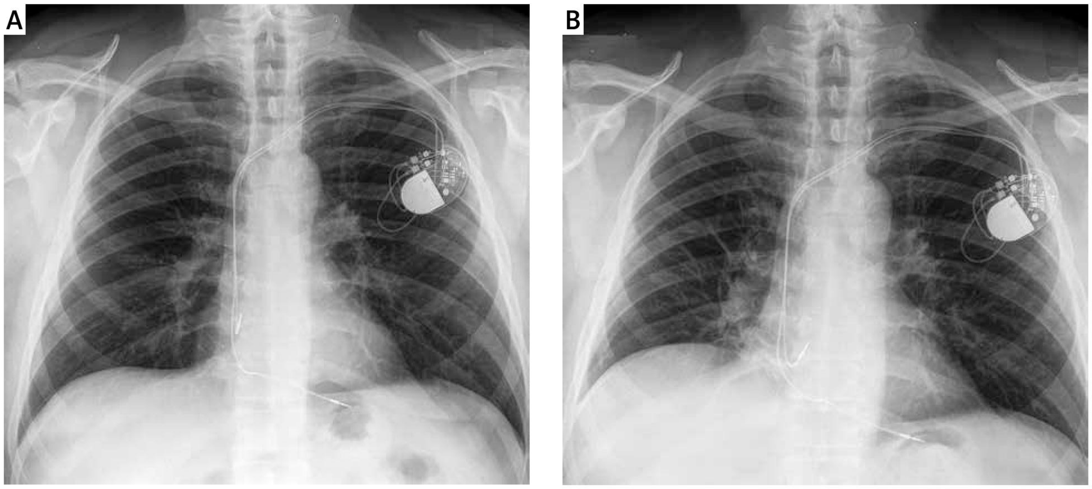

Figure 12. Chest X-ray performed before (upper panel) and after ablation illustrates the most common complication of cryoballoon based pulmonary vein isolation – phrenic nerve palsy. Note the higher position of the right diaphragmatic dome after the procedure

vein. Phrenic nerve function is then monitored by constant palpation of the abdomen. At the first moment when the strength of the diaphragmatic excursion decreases, the balloon should be deflated using the double stop technique (resulting in immediate deflation rather than delayed deflation occurring when the balloon is rewarmed). Some recommend monitoring the diaphragmatic compound motor action potential [39]. This can be easily done by observing ECG with modified lead I: the right-arm electrode is placed above the xiphoid, and the left-arm ECG electrode is placed along the right costal margin. This methods also allows the other members of the team to monitor the nerve function in the electrophysiological laboratory and, according to a few studies, makes it possible to detect the damage to the phrenic nerve at a slightly earlier phase than monitoring mechanical function. We ceased to use this method as in our experience it does not offer any advantage over manual palpation; a noticeable decrease in the potential amplitude seems to be coincident with the decrease in diaphragmatic excursion. Apart from monitoring the nerve function it is important to position the balloon in the PV as proximally as possible, not allowing too low temperatures, and occasionally use the 'pull-back' maneuver.

Conclusions

Cryoballoon technology greatly simplified the contemporary approach to the PV isolation procedure, without compromising outcomes, offering a new hope for patients with AF. For a safe and effective procedure the electrophysiologist/interventionalist should be aware of all minute details of the procedure including several tricks developed by the most experienced operators and the pre-procedural and post-procedural management recommendations. Detailed knowledge of complications of CB-based ablation is mandatory.

Conflict of interest

Dr Jastrzębski – moderate lecture and proctoring fees from Medtronic. Other author declare no conflict of interest.

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Original paper

Outcomes of atrial fibrillation ablation program based on single-shot techniques

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Adv Interv Cardiol 2020; 16, 4 (62): 466–473
DOI: https://doi.org/10.5114/aic.2020.101773

Abstract

Introduction: Single-shot techniques such as cryoballoon and multipolar phased pulmonary vein ablation catheter (PVAC) are an alternative to the point-by-point radiofrequency method for atrial fibrillation (AF) ablation. However, there is a lack of data concerning sequential use of single-shot techniques, that is, for both the index and redo ablation.

Aim: To assess long-term outcomes of the 'single-shot techniques only' AF ablation strategy.

Material and methods: We analyzed all consecutive AF ablations performed over a 10-year period (2009–2019) in a center where a 'single-shot technique only' principle was followed from the start of the AF ablation program. Kaplan-Meier AF-free survival curves were calculated and complications were assessed on the basis of our prospectively maintained database.

Results: A total of 597 patients (62.4 ±12.5 years) with paroxysmal (78.1%) or persistent (21.9%) AF entered the study and 655 AF ablation procedures were performed. In 96.5% of redos (*n* = 58) a different technique (mostly PVAC) was used than for the index ablation (mostly cryoballoon). The Kaplan-Meier estimates of 1, 2 and 5 years freedom from AF were 78.2%, 69.2%, and 56.0%, for the index ablation, and 80.3%, 76.1% and 68.3%, for the redo, respectively. The minor and major complication rates were 8.1%, and 4.0%, respectively.

Conclusions: An AF ablation program based solely on sequential use of two different single-shot techniques for both index and redo procedures is safe and effective. These observations might have important practical implications for new operators/centers starting AF ablation programs and for use of single-shot techniques for redo procedures.

Key words: atrial fibrillation ablation, redo ablation, single-shot technique, pulmonary vein ablation catheter, cryoballoon.

Summary

Long-term effectiveness and safety of an atrial fibrillation (AF) ablation program based on the principle of using only "single-shot" technique is reported. This novel AF ablation strategy was based on sequential use of two different single-shot techniques. Our results include, the first to date, assessment of efficacy of PVAC (pulmonary vein ablation catheter)-based ablation for AF redo procedures and suggest that various single-shot technique types can be successfully combined. These observations might have important practical implications for new operators/centers starting AF ablation programs and for use of single-shot techniques for redo procedures.

Introduction

Pulmonary vein (PV) isolation is a standard treatment option for patients with symptomatic atrial fibrillation (AF). Single-shot ablation techniques such as cryoballoon and multielectrode circular catheter emerged as a practical alternative to the classic point-by-point radiofrequency/3-dimensional system based AF ablation method [1, 2]. Several studies have shown that outcomes of cryoballoon ablation, in terms of freedom from AF and safety profile, are comparable to point-by-point radiofrequency ablation [3, 4]. Data concerning multielectrode phased radiofrequency ablation using pulmonary vein ablation catheter (PVAC, Medtronic) are less robust, although reported outcomes were similar [1]. However,

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Received: 7.10.2020, **accepted:** 26.10.2020.

data concerning these two single-shot techniques came from centers/operators with substantial prior experience with radiofrequency/3-dimensional system based AF ablation. This might affect the single-shot technique outcomes, and the results of these studies might not be fully applicable to new centers or operators who want to rely solely on single-shot techniques. Moreover, there is a scarcity of data concerning the use of single-shot techniques for redo ablation when the index procedure was also performed with a single-shot technique, i.e. sequential use of two single-shot methods. Together these gaps in knowledge might lead to the underutilization of single-shot techniques.

Aim

The aim of this study was to investigate outcomes (AF-free survival, redo rate, redo efficacy and complications) of AF ablation in an electrophysiology laboratory where a 'single-shot technique only' principle was followed at the start of the AF ablation program, both for the index ablation and for all redo procedures.

Material and methods

Study population

This observational study enrolled consecutive patients with symptomatic paroxysmal, persistent and long-standing persistent AF, defined according to the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) guidelines, with a history of failed treatment with one or more antiarrhythmic drugs (class I or III) [5]. On the basis of our prospectively maintained registry of all consecutive PV isolation procedures performed over a 10-year period, from June 2009 to September 2019 (to ensure a minimal follow-up of 6 months) we conducted a study analyzing outcomes of AF ablation after the index and redo single-shot technique based procedures. The study was approved by the institutional ethical committee of the Jagiellonian University (number 1072.6120.70.2020).

Preprocedural management

Transthoracic echocardiography using standard parasternal long and short axis views and apical two- and four-chamber views was performed within 1 week before ablation, enabling assessment of left ventricular ejection fraction and intracavitary dimensions. The anticoagulation strategy evolved during the study period. In the years 2009–2017 patients were anticoagulated with warfarin or acenocoumarol – with low-molecular weight heparin bridging before/after the procedure. Between 2017 and 2019, procedures were generally performed with uninterrupted oral anticoagulation (warfarin/acenocoumarol), while novel oral anticiagulatns were stopped shortly before CB ablation (morning dose skipped). The presence of left atrial thrombi was excluded by transesophageal echocardiography within 24 h before ablation in every patient. To exclude thrombus the left atrial appendage (LAA) was visualized in multiple two-dimensional TEE imaging planes. It was achieved by first developing the mid-esophageal aortic valve short-axis view (30–60°) and then anteflexing the transducer and rotating the multiplane angle from 0° to 180°. Later, a multi-planar LAA reconstruction of 4D volume was prepared.

Ablation procedure

All procedures were performed by one of the two operators (M.J. or T.S.), both without any prior experience with PV isolation using the point-by-point radiofrequency technique. For the first ablation procedure, a cryoballoon was preferably used while for the redo procedures PVAC was favored. All ablation procedures were performed under conscious sedation (fentanyl and midazolam boluses). A single transseptal puncture using a Brockenbrough needle (BRK-1, St. Jude Medical, St Paul, MN, USA) and 8F transseptal sheath (SL-1, St. Jude Medical, St Paul, MN, USA) was performed under fluoroscopy using only contrast injection to confirm left atrial access. No prior PV anatomy assessment was performed; if considered necessary, PV anatomy was assessed with contrast/angiography during the procedure. His bundle catheter and coronary sinus catheter were used to facilitate transseptal puncture and also for phrenic nerve pacing and electrophysiological assessment of PV isolation. During the procedure intravenous heparin was administered to achieve an activated clotting time > 350 s; measurements were performed every 30–40 min.

The 28-mm cryoballoon (Medtronic Cryocath, Minneapolis, MN, USA) was used in all patients. The procedure generally followed published expert consensus recommendations [6]. However, the cryoballoon technique evolved over the 10-year observation period of this study. Notably, the balloon design was changed from cryoballoon type 1 (CB1) to cryoballoon type 2 (CB2) to allow more uniform cooling and freeze protocols were appropriately modified; CB1 was used until November 2012. Optimal vein occlusion with total contrast retention, i.e. no back flow to the atrium, was aimed for; when this was not possible the 'pull-down' maneuver or overlapping applications were used. On the basis of published data freeze time was shortened from 5 mins to 3–4 min for left PVs and to 2–3 min for the right PVs and the number of applications was decreased from 3 per vein to 1–2 per vein. Both the freeze time and number of applications per vein were at the operator's discretion, guided by 'time to effect', minimal achieved temperature, thaw time, grade of the vein occlusion, use of 'pull-down' maneuver, the perceived arrhythmogenic potential of a particular vein, etc. For 226 consecutive patients ablated with CB2 the following information was gathered for better group characterization: number of cryoballoon applications per vein, total time of all cryoballoon applications per vein, minimal temperature achieved at 1 minute in each vein, minimal temperature at the end of cryoballoon application in each vein, PV entrance block time ("time-to-effect") in each vein.

The PVAC is a steerable, 9F, over-the-wire multielectrode circular mapping and ablation catheter that requires a multichannel radiofrequency (RF) generator (GENius; Medtronic, USA) in order to deliver synchronous duty-cycled phased unipolar and bipolar RF energy with its multiple electrodes. Overlapping 60-second RF applications were delivered in each PV. Ablation was mostly performed in a 2 : 1 bipolar/unipolar mode and switched to a 1 : 1 or 4 : 1 mode at the operator's discretion. We followed the ablation technique as described by others [1].

Regardless of the single-shot technique and/or protocol used for the energy application the procedural endpoint both for the index procedure and redo ablation was electrical isolation of all PVs. PV isolation was confirmed with the sudden disappearance of PV potentials or complete dissociation of PV potentials from atrial electrical activity; this was assessed in real time during cryoballoon freeze using an inner lumen circular multielectrode catheter (Promap, ProRhythm Inc., Ronkonkoma, NY, USA or Achieve, Medtronic Minneapolis, MN, USA). Alternatively, when disappearance of PV potentials was not visualized in real time during cryoenergy application, PV ostia were assessed for PV potentials and conduction block after the completion of a freeze-thaw cycle and this was compared with electrical activity at this site before cryoballoon application (template method). In case of recording suspicious electrical activity beyond the ablation line, pacing maneuvers from the coronary sinus, left atrial appendage and right atrium were performed to differentiate far-field signals from PV potentials and also presence of exit block was assessed by pacing from the circular catheter within the PV. Because electrograms cannot be assessed during the delivery of phased RF current the template method combined with diagnostic pacing maneuvers was used during all PVAC-based ablation procedures. At the end of the procedure patients still in atrial fibrillation were electrically cardioverted, and when considered necessary PV isolation was re-assessed.

During ablation in the antra of the right-sided PVs, phrenic nerve function was monitored by continuous phrenic nerve stimulation in the superior vena cava combined with palpation of the upper abdomen in order to assess strength of diaphragmatic contraction. Moreover, in the last 307 patients a rule was adopted to stop cryoapplication when the freezing temperature dropped below –56°C.

Post-ablation management

Sheaths were usually removed 5 h after the procedure or, occasionally, immediately after the ablation, following protamine administration. Oral anticoagulation was started 6 h after sheath removal and continued for at least 3 months, and according to the CHADS2/CHA2DS2-VASc scores thereafter. Preprocedural antiarrhythmic drugs were usually continued for 1–2 months. Some patients with long-persistent AF were treated with amiodarone for 3–6 months.

Follow-up and study endpoints

The analyzed primary endpoint of this study was freedom from AF recurrence. AF recurrence was defined as the first episode of AF lasting > 30 s diagnosed after the blanking period of 3 months. AF had to be documented by electrocardiogram (ECG), Holter monitoring or physician interpreted intracardiac electrogram from the implanted device (event marker data were considered unreliable). All patients were advised to have an ECG performed each time they experienced palpitations. Holter monitoring (24–72 h long) was scheduled after 3 and 6–9 months post-ablation and then advised once a year. Additionally, all patients received a telephone call at the time of conducting this study and were asked about symptoms, results of ECGs and Holter monitoring.

Secondary endpoint of this study was freedom from acute and long-term complications of AF ablation procedures. Acute (i.e. predischarge) complications were monitored and analyzed prospectively in accordance with the HRS/EHRA guidelines, published systematic reviews and other studies focused on specific complications of single-shot methods [7–12]. Long-term complications were determined on the basis of out-patient visits and/or final telephone conversation. Major complications were defined as any life-threatening situation or any adverse event with serious symptoms and/or permanent harm and/or requiring interventional treatment.

Following our strategy for redo procedures, a different single-shot technique was offered to the patients who had documented AF post-index ablation and remained symptomatic despite the reintroduction of β-blockers and/or class I antiarrhythmic drugs. The follow-up and endpoint assessment after a second PV isolation procedure was performed in the same way as after the index ablation.

Statistical analysis

Continuous variables are presented as means and standard deviations or medians and upper-lower quartile for data with non-normal distribution, while categorical variables are presented as numbers and percentages. For normality assessment the Shapiro-Wilk test was applied. The Kaplan-Meier method was used to estimate the survival functions for each endpoint. The log-rank test was used to compare survival distributions. Statistical analysis was performed in R 3.2. *P*-values < 0.05 were considered statistically significant.

Results

Studied cohort and procedural characteristics

We have identified 617 consecutive patients who underwent a single-shot technique based isolation of PVs in our center during the study period; of these, 20 cases were excluded for a number of reasons: prior point-by-point PV ablation in other institution (*n* = 17), lack of follow-up data (*n* = 1), non-AF clinical arrhythmia (*n* = 1) or unrelated death (*n* = 1). Consequently, 597 patients, with a mean age of 57.9 ±10.6 years, were analyzed with regard to both study endpoints. The majority of patients suffered from paroxysmal atrial fibrillation (78.1%), were overweight/obese (83.1%) and had some comorbidities (84%); detailed baseline clinical characteristics of this cohort are presented in Table I. A total of 655 ablation procedures were performed. The median fluoroscopy time was 16.4 (11.2–25.0) min, median dose-area-product, recorded only for the last 267 cases, was 1885 (890–3826) cG × cm². Acute success rate was 98%; in 5 (1.5%) patients one PV could not be isolated, in 2 (0.5%) patients two PVs could not be isolated. Cryoballoon application characteristics (number of applications in each vein, minimal temperature etc.) for 226 non-selected, consecutive patients are presented in Table II.

Table I. Baseline characteristics of the study population (*n* = 597)

Parameter	
Age [years]	57.9 ±10.6
Male gender	390 (65.3%)
BMI [kg/m²]	29.1 ±4.3
AF type:	
Paroxysmal	466 (78.1%)
Persistent	105 (17.6%)
Long-standing persistent	26 (4.3%)
Duration of AF history [months]	36.0 (18.0–72.0)*
Number of failed antiarrhythmic drugs	1.5 ±0.88
Current/past smoker	172 (28.8%)/38 (6.2%)
Comorbidities:	
Hypertension	397 (66.5%)
Diabetes mellitus	76 (12.7%)
Chronic coronary syndrome	60 (10.1%)
Heart failure	27 (4.5%)
Structural heart disease#	51 (8.5%)
Stroke/TIA	59 (9.9%)
CHA_2DS_2-VASc score	1.8 ±1.3
eGFR < 60 ml/min/1.73 m²	63 (10.5%)
Echocardiography:	
Left atrial diameter [mm]	42.8 ±5.7
Left ventricular ejection fraction, %	60.3 ±8.6
Left ventricular end-diastolic dimension [mm]	50.2 ±5.7

**Data presented as median and upper and lower quartile. #Defined as cardiomyopathy or artificial valve or severe valvular disease or left ventricular ejection fraction < 50%. BMI – body mass index, AF – atrial fibrillation, TIA – transient ischemic attack, eGFR – estimated glomerular filtration rate.*

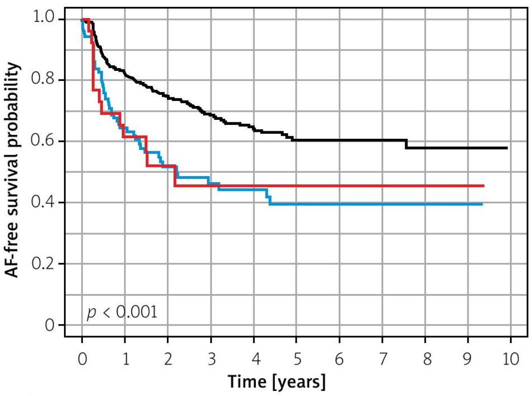
Index procedure outcomes

For the index procedure cryoballoon (*n* = 589), or, much less frequently, PVAC (*n* = 8) ablation was performed. The 10-year observation period resulted in 520 571 patient-days of follow-up. The median number of Holter ECG monitoring per patient was 3 (2–5) days; additionally 36 patients had data available from the implanted device capable of AF detection.

Table II. Characteristics of the cryotherapy dosage protocol (*n* = 226)

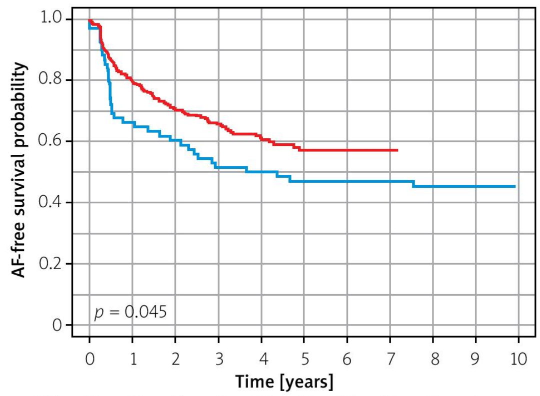
Parameter	Value
Number of cryoballoon applications per vein, *n*:	
LSPV	2.2 ±1.0
LIPV	1.8 ±0.7
RSPV	2.1 ±0.9
RIPV	2.0 ±0.8
Duration of total freezing time per vein [s]:	
LSPV	351.9 ±143.6
LIPV	308.4 ±114.5
RSPV	243.7 ±101.0
RIPV	281.8 ±127.5
Minimal temperature at 1 min [°C]:	
LSPV	41.8 ±4.4
LIPV	39.7 ±3.9
RSPV	43.1 ±4.6
RIPV	40.6 ±4.9
Minimal temperature at the end of application [°C]:	
LSPV	49.0 ±5.3
LIPV	45.2 ±4.9
RSPV	48.9 ±5.1
RIPV	47.0 ±5.7
Time-to-effect (PV entrance block) [s]:	
LSPV (61.1%)*	61.1 ±67.3
LIPV (41.6%)*	42.1 ±42.4
RSPV (47.3%)*	43.4 ±24.8
RIPV (29.6%)*	43.9 ±21.2

*LSPV – left superior pulmonary vein, LIPV – left inferior pulmonary vein, RSPV – right superior pulmonary vein, RIPV – right inferior pulmonary vein, PV – pulmonary vein. *Percentage of patients in whom it was possible to visualize real-time occurrence of pulmonary vein isolation.*



Parox	466	324	203	143	105	71	48	33	13	4
Persist	105	54	31	23	19	13	10	4	1	1
Persist long	26	16	10	3	1	1	1	1	1	1

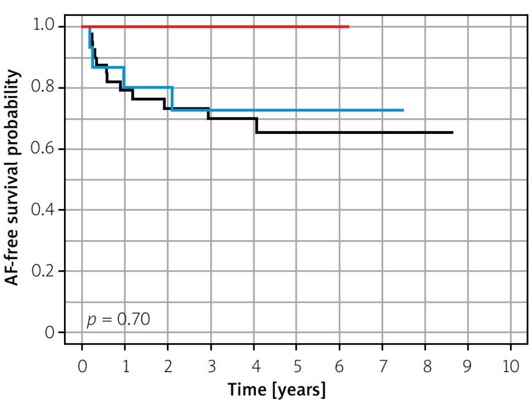
Figure 1. The Kaplan-Meier AF-free survival curve after the index AF ablation with regard to AF type



CB1	68	45	41	35	34	32	32	32	15	6
CB2	529	349	203	134	91	53	27	6		

Figure 2. The Kaplan-Meier AF-free survival curve after the index AF ablation with regard to type of cryoballoon used for ablation. CB1 – cryoballoon type 1; CB2 – cryoballoon type 2

During the blanking period AF was observed in 73 (12.2%) patients. The primary endpoint (AF recurrence, after the 3-month blanking period) was met in 197 (33.0%) patients. The Kaplan-Meier estimates of 1-, 2- and 5-year freedom from AF after the index ablation were: 78.2% (95% CI: 74.9–81.6%), 69.2% (95% CI: 65.3–73.3%), and 56.0% (95% CI: 50.9–61.6%), respectively. Success rate was higher for paroxysmal AF than for persistent/long-standing persistent AF (Figure 1). The first 68 patients were treated with CB1, the rest with CB2. The Kaplan-Meier analysis of survival curves showed a 10% lower long-term success rate when CB1 vs. CB2 was used (Figure 2).



Parox	41	29	23	20	16	14	12	9	4
Persist	15	12	11	9	5	3	1	1	
Persist long	2	2	1	1	1	1	1		

Figure 3. Kaplan-Meier AF-free survival curve after the redo ablation with regard to the AF type

Redo procedure outcomes

A total of 58 redo procedures were performed including 51 PVAC and 7 cryoballoon ablations; in 96.5% of cases a different single-shot technique was used for the second procedure. A median of 2 (1–3) PVs per patient showed reconnection; all PVs were successfully re-isolated. Redo patients were followed for 67.4 months (119 319 patient-days) after the re-ablation. AF recurrence after the 3-month blanking period was observed in 17 (29.3%) patients. Kaplan-Meier estimates of 1-, 2- and 5-year freedom from AF after the redo procedure was 80.3% (95% CI: 70.4–91.4%), 76.1 (95% CI: 65.5–88.4) and 68.3 (95% CI: 56.1–83.0), respectively; there was no difference in success rate between patients with paroxysmal AF vs. persistent/long-standing persistent AF (Figure 3).

Post-ablation non-AF left atrial arrhythmias

In 7 patients atypical atrial flutters were observed, 6 after index ablation and one after re-do ablation. In all but one of these patients concurrent AF recurrence was also noted. Since these arrhythmias are pathophysiologically distinct from AF they were treated with RF catheters rather than single-shot devices.

Complications

There were no deaths or permanent disabilities. In 72 (12.1%) patients some complication occurred, including major complications in 4.0% of patients. Almost all complications occurred after the index ablation. In the redo procedures only one complication was noted –

a persistent phrenic nerve paralysis. The most frequent complications were related to thermal phrenic nerve injury; these were closely followed by vascular access site complications and iatrogenic atrial septal defect requiring intervention (septal occluder implantation in 7 cases and cardiac surgery in 1 case). All complications, except one permanent phrenic nerve palsy, were resolved with appropriate medical treatment. A full list of observed complications is listed in Table III.

Discussion

This study showed the long-term effectiveness and safety of the 'single-shot technique only' ablation strategy for the management of AF in a large representative cohort of patients. The major findings were:

1) the sequential use of two different single-shot techniques is effective, resulting in freedom from AF at 2 years of 74% and 52%, after the index procedure, and 73% and 80% after the redo procedure, for paroxysmal and persistent atrial fibrillation, respectively;
2) the PVAC-based method can be successfully used for redo AF ablation.

AF-free survival after single-shot technique based ablation

With each year of follow-up the percentage of AF-free patients falls, likely reflecting both a suboptimal result of the index ablation and the natural course/progression of the arrhythmia substrate. The reported AF recurrence rate at the second year after a single-shot technique based ablation is around 25–50% with moderate differences between different tools used (PVAC, cryoballoon, hot-balloon) and very comparable with the point-by-point radiofrequency current ablation method [1–3, 8, 13]. Our study provides a similar recurrence rate after a single procedure over the 10 years of follow-up (Kaplan-Meier survival curve in Figure 1). The novelty of our results lies in adding a new piece of data to the concept that the single-shot technique approach is completely equivalent and alternative to the classic point-by-point radiofrequency method, since in the current study such ablation outcomes were achieved using solely single-shot techniques and by operators who never used the classic point-by-point radiofrequency, 3D system based ablation method.

Additionally, the current study corroborates the data regarding higher efficacy of CB2 vs. CB1 [14], and expands it with very long-term follow-up data that show 10% absolute difference in AF recurrence rates after 5–6 years (Figure 2).

Overall, 9.7% of patients underwent a redo during the study period; this constituted 29.4% of all patients with AF recurrence. The redo rate in our study was slightly lower than in most cryoballoon ablation studies that reported a 11.8–19.1 re-ablation rate [15–18], albeit similar to the rate of 7.8% obtained from the analysis of Swedish catheter ablation registry and the Atrial Fibrillation Ablation Long-Term registry of the European Heart Rhythm Association [4]. Our novel strategy for redo ablations, based on the principle that a different single-shot technique should be preferred for the second procedure, was effective, as freedom from AF after the second procedure was high (Figure 2). Such a strategy was employed based on the intuitive rationale that a failure of one single-shot technique based procedure might indicate that the left atrial anatomy was not suitable for the index single-shot technique and that using a different single-shot method has a higher chances of overcoming this limitation than using the same tools again. For example, a too large antrum might facilitate poor contact at some parts of the balloon perimeter and hence gaps that could be easily closed with PVAC using overlapping circular lesions while

Table III. Complications of single-shot technique based ablation observed in the current study

Complications	*n* (%)
Major:	
Death related to the procedure	0
Atrioesophageal fistula	0
Symptomatic pulmonary vein stenosis	0
Stroke	1 (0.17)
Transient ischemic attack	1 (0.17)
Tamponade/pericardiocentesis	5 (0.84)
Tamponade requiring surgery	0
Persistent phrenic nerve injury§	7 (1.17)
Permanent phrenic nerve injury	1 (0.17)
ASD requiring intervention	8 (1.34)
Bleeding requiring blood transfusion	1 (0.17)
Minor:	
Vascular access site complications*	9 (1.51)
Pericardial effusion	4 (0.67)
Pericarditis	1 (0.17)
Transient phrenic nerve injury#	10 (1.67)
Migraine/headaches	6 (1.00)
Hemoptysis	2 (0.33)
Atelectasis/pneumonia	5 (0.84)
Symptomatic gastroparesis	2 (0.33)
Symptomatic inappropriate sinus tachycardia	3 (0.50)
Other	2 (0.33)

*ASD – atrial septal defect, §present after discharge, *including large hematoma, arterio-venous fistula and pseudoaneurysm treated conservatively, and deep vein thrombosis; #resolved before discharge.*

the balloon might fail again; a small antrum might not allow stabilization of the 28 mm balloon, or the PV take-off angle or orifice shape might not allow good occlusion to be achieved or might result in off-axis cryoballoon to PV alignment, leading to poor contact of some segments with the balloon. When repeating ablation with balloon the same problems might repeat themselves, while with PVAC such anatomy might not constitute a problem. PVAC-based ablation after cryoballoon ablation for the index procedure was the dominant sequence employed by us. We are not aware of any study reporting outcomes of such an AF ablation strategy.

A limited number of studies have investigated outcomes of cryoballoon ablation for redo after the index procedure was also performed with a cryoballoon. Westra *et al.* studied 40 patients who had both the index and redo procedure performed with a cryoballoon and reported that at 1 year, 70% of patients were free of recurrent AF [16]. Similarly, Shade *et al.* used a cryoballoon for both the index and redo procedure in 47 patients and found that 60% of them had no AF recurrence during a 12-month follow-up period [17]. Cryoballoons were also used for redo procedures after the index ablation was performed with the point-by-point technique with 76.6–43% of patients reported free from AF recurrence after 11–15 months of follow-up [19, 20]. Together, these reports suggest that cryoballoons are useful for re-ablation procedures; our data expand these observations to the other single-shot technique, namely, the PVAC. To the best of our knowledge there are no published data regarding the use of PVAC for redo procedures, suggesting that PVAC might be underused for this application.

Complications of AF ablation based on single-shot techniques

Several studies focusing on major complications of AF ablation using the point-by-point technique have reported complication rates between 3.9% and 4.9% [8, 9]. The major complication rate seen during ablation performed with cryoballoons, PVAC or other single-shot techniques seems to be similar or slightly lower, in the range of 2–6% [4, 8, 12, 18, 21]. Our current study corroborates these observations and expands it to a setting with a more radical use of single-shot techniques. Of note, despite similar percentages, complication profiles of single-shot techniques are slightly different than complications of the point-by-point ablation method, and might, therefore, be more prone to reporting bias. Some complications such as significant iatrogenic atrial septal defect, gastroparesis or migraine headaches (observed together in 2.7% of patients in the current study) are not even mentioned in most papers focusing on complications of atrial fibrillation using the classic point-by-point radiofrequency method. Importantly, the single-shot technique based redo strategy used by us was not related to an increased percentage of complications; on the contrary, there was only a 2% rate of minor complications during redos. This stands in contrast to the point-by-point technique, where redo procedures were shown to be an independent predictor of major complications (odds ratio 3.6) [22].

Limitations

This was a single-center study with a small number of operators and related potential referral and treatment bias. Moreover, the ablation technique evolved and the equipment changed during the study; notably, after the initial 68 cases the CB1 was replaced by CB2, which resulted in a higher success rate. Due to the relatively small size of the CB1 cohort we believe that this was a minor limitation that we addressed in an additional Kaplan-Meier survival analysis. No long-term monitoring was performed in the majority of patients; therefore, the AF recurrence rate might have been underestimated. However, we believe that our monitoring approach reflected real life clinical practice.

Conclusions

This study suggests that a single-shot technique based ablation program results in similar effectiveness in atrial fibrillation ablation both for index and redo procedures and that the use of various single-shot technique types can be combined for a successful AF ablation program. These observations might have important practical implications for new operators/centers starting AF ablation programs and also warrant further studies to investigate the role of single-shot techniques for redo procedures.

Conflict of interest

The authors declare no conflict of interest.

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Received: 3 February 2021 | Revised: 16 April 2021 | Accepted: 1 May 2021
DOI: 10.1002/joa3.12557

ORIGINAL ARTICLE

Journal of Arrhythmia WILEY

Comparison of six risk scores for the prediction of atrial fibrillation recurrence after cryoballoon-based ablation and development of a simplified method, the 0-1-2 PL score

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Abstract

Introduction: There are several prognostic scores for the assessment of risk of atrial fibrillation (AF) recurrence post ablation procedure. However, the use of these complex scores is difficult and the validation on different populations brought divergent results. Our goal was to compare the performance of these risk scores as the basis for the development of a new, simplified score based only on few universally predictive variables.

Methods: All cryoballoon-based AF ablations performed in a single-center over a 10-year period were prospectively analyzed with regard to AF recurrence. This served to analyze the performance of APPLE, CAAP-AF, SCALE-CryoAF, MB-LATER, $CHADS_2$, and CHA_2DS_2-VASc risk scores.

Results: A total of 597 patients, mostly (78.1%) with paroxysmal AF were studied. Analyzed risk scores performed poorer than in the original publications because some risk factors were not predictive of AF recurrence. A simplified score named **0-1-2 PL**, composed of just two universally predictive variables, AF type (1 point for Persistent AF) and LA dimension (1 point for LA size >45 mm) was developed. The 0-1-2 PL score stratified patients into low risk (**0** points), intermediate risk (**1** point), and high risk categories (**2** points) which were related to a 2-year risk of AF recurrence of 21%, 37%, and 55%, respectively. This score had C-statistics (0.620) higher/comparable to other investigated much more complex scores.

Conclusion: The assessment of risk of AF recurrence at the pre-ablation stage can be simplified without compromising accuracy. This could help to popularize risk assessment and standardization of AF management.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; ECG, electrocardiogram; HR, hazard ration; LA, left atrium; LAd, left atrial dimension; LV EF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; NYHA, New York heart association; PCI, percutaneous coronary intervention; PV, pulmonary vein; PVAC, pulmonary vein ablation catheter; TIA, transient ischemic attack.

KEYWORDS
0-1-2 PL score, cryoballoon, atrial fibrillation ablation, atrial fibrillation recurrence, risk score

1 | INTRODUCTION

Pulmonary vein isolation with catheter based ablation was shown to be superior to antiarrhythmic drugs for atrial fibrillation (AF) treatment. Natural progression of the disease and suboptimal results of the index ablation is responsible for AF recurrence that is seen in 15%-50% of patients within the first year, with a steadily increasing percentage of recurrences in the subsequent years. It is well established that the recurrence rate of AF ablation strongly depends on the clinical profile and the stage of left atrial disease. Several predicting scores for the assessment of risk of AF recurrence were developed for better patient selection and appropriate counseling (CAAP-AF, PLAAF, SCALE-CryoAF, BASE-AF2, APPLE, MB-LATER, ALARME, ATLAS, etc).[1-9] However, the use of these scores is, in our experience, rather difficult: several variables have to be remembered, perception of risk strata is not intuitive because the number of assigned points is wide (eg, 0-15 in SCALE-CryoAF) and often varies, even within a particular variable (eg, 0-4 for left atrial size in CAAP-AF). Moreover, some necessary data are difficult to obtain (eg, “abnormal PV anatomy” in PLAAF or indexed left atrial volume in ATLAS). Furthermore, the validation of these scores on different populations brought divergent results.[4,10] This limits the popularity and a “real life” clinical application of these risk scores. A novel prognostic method that would be both universal, ie, based on variables predictive in various populations, and straightforward in use, is needed to help standardize AF management, patient counseling, and popularize pre-procedural risk assessment.

Our goal was to compare risk scores for AF recurrence in patients who underwent first pulmonary vein isolation procedure—as a basis to develop a novel prognostic tool, focusing on universality, and simplicity of application.

2 | METHODS

2.1 | Study population

This study enrolled consecutive patients with symptomatic paroxysmal, persistent, and long-standing persistent AF who underwent pulmonary vein isolation procedure using cryoballoon technique. On the basis of our prospectively maintained registry of all consecutive AF ablation procedures performed over a 10-year period (June 2009-September 2019), we analyzed potential clinical, biochemical, electrocardiographic, and echocardiographic predictors of AF recurrence after the first ablation. The study was approved by the institutional ethical committee and it adheres to the provisions of the Declaration of Helsinki.

2.2 | Ablation procedure

All procedures were performed by two operators (MJ or TS) using 28-mm cryoballoon (CryoCath, Medtronic). All ablation procedures were performed under conscious sedation. Single transseptal puncture using Brockenbrough needle and 8F transseptal sheath was performed under fluoroscopy using only contrast injection to confirm LA access. No prior pulmonary vein anatomy assessment was performed; if considered necessary, pulmonary vein anatomy was assessed with contrast/angiography during the procedure. A His bundle catheter and coronary sinus catheter was used to facilitate the transseptal puncture and also for phrenic nerve pacing and electrophysiological assessment of PV isolation. During the procedure, intravenous heparin was administered to achieve an activated clotting time of >350 s; measurements were performed every 30-40 minutes. The procedure generally followed published expert consensus recommendations and was described by us in detail elsewhere.[11,12] Optimal vein occlusion with total contrast retention, ie, no back flow to the atrium was aimed for; when this was not possible, a "pull-down" maneuver or overlapping applications was used. On the basis of published data, freeze time was shortened from 5 minutes to 3-4 minutes for left pulmonary veins and to 2-3 minutes for the right pulmonary veins and the number of applications was decreased from 3 per vein to 1-2 per vein. Both the freeze time and the number of applications per vein were at the operator's discretion, guided by the “time to effect,” the minimal achieved temperature, thaw time, grade of the vein occlusion, the use of “pull-down” maneuver, the perceived arrhythmogenic potential of a particular vein, etc.

2.3 | Follow-up and study endpoints

The analyzed endpoint of this study was freedom from AF recurrence. AF recurrence was defined as the first episode of AF lasting >30 s diagnosed after the blanking period of 3 months. AF had to be documented by ECG, Holter monitoring or intracardiac electrogram from the implanted device. All patients were advised to obtain an ECG each time they experienced palpitations. Holter monitoring (24-72 hours long) was scheduled after 3 and 6-9 months post-ablation and then advised once a year. Additionally, all patients received a telephone call at the time of conducting this study to ensure the accuracy of gathered data.

2.4 | Analyzed risk scores

The predictive value of several clinically important variables was analyzed including: sex, age, AF type (paroxysmal, persistent, long-standing persistent), stroke/transient ischemic attack, diabetes mellitus, myocardial infarction, percutaneous coronary intervention / coronary artery bypass grafting, congestive heart failure, glomerular filtration rate, QRS duration >120 ms, cigarette smoking status (past, current, never), body mass index, echocardiographic left atrial dimension in parasternal M-mode, left ventricular ejection fraction, left ventricular end diastolic dimension in parasternal M-mode, AF observed within the 3-month blanking period, and presence of structural heart disease.

Some of these variables were used in various combinations and various assigned weights by others to formulate risk scores (Table 1). We analyzed the following risk scores specifically developed for prediction of AF recurrence post ablation: APPLE, CAAP-AF, SCALE-CryoAF, and MB-LATER. Moreover, the predictive value of $CHADS_2$ and CHA_2DS_2-VASc scores, originally developed for the prediction of the risk of stroke, but reported to be useful for predicting AF recurrence,[13] were also analyzed. All scores were calculated as described in the original publications by authors that have introduced these methods.[1-7,14] SCALE-CryoAF was also additionally assessed without the post-procedural data (ie, without points for "early return of atrial fibrillation").

2.5 | Statistical analysis

Continuous variables are presented as means and standard deviations, while categorical variables are presented as numbers and percentages. The Kaplan-Meier method was used to estimate the survival functions for each endpoint. Univariate and multivariate Cox proportional hazard models were used to describe the effect of predictors on survival. All variables believed to be clinically important were pre-specified and entered into multivariate Cox proportional hazard models. Results of Cox models were presented as hazard ratios (HRs) along with tests of significance and 95% confidence intervals (CIs). There were no significant violations of the proportionality assumption that underlies the Cox proportional hazard method. Final risk score model will be based on the smallest number of variables resulting in highest value of the C-statistics. Statistical analysis was performed in R 3.2. *P*-values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

A total of 617 consecutive patients was identified who had undergone catheter-based isolation of the pulmonary veins in our center between the period of 2009 and 2019. Of these, 20 cases were excluded due to prior AF ablation in other institutions (n = 17), due to ablation performed with other technique or other causes (n = 12). Consequently, 588 patients aged 58.1 ± 10.6 years were analyzed with regard to AF recurrence after the first ablation. The 10-year observation period resulted in an average follow-up time of 28.6 months (520 571 patient-days).

Most of the patients had paroxysmal atrial fibrillation (78.1%), were overweight or obese (83.1%), and/or had some comorbidities

TABLE 1 Risk factors included in the scoring systems analyzed in the current study

	APPLE	CAAP-AF	SCALE-CryoAF	MB-LATER	0-1-2 PL	$CHADS_2$	CHA_2DS_2-VASc
Age	1	1-3				1	1-2
Sex		1		1			1
Atrial fibrillation type	1	2	3	1-2	1		
Left atrial dimension	1	1-4	1	1	1		
Early recurrence			4				
Hypertension						1	1
Coronary artery disease		1	3				
Diabetes mellitus						1	1
Chronic kidney disease	1						
Stroke/TIA						2	2
Antiarrhythmic drugs failure		1-2					
Vascular disease							1
Bundle branch block			3	1			
Left ventricular EF	1						
Chronic heart failure						1	1
Structural heart disease[a]			1				

Abbreviations: EF, ejection fraction; TIA, transient ischemic attack.
[a]Including cardiomyopathy and severe valvular disease.

(84%). Detailed baseline clinical characteristics of this cohort are presented in Table 2.

All studied patients underwent cryoballoon (Arctic Front 28 mm, Medtronic)-based ablation. On average, there were 3.7 (±2.3) days of Holter ECG monitoring per patient; additionally, 36 patients had data available from the implanted device capable of AF detection. During the blanking period, AF was observed in 72 (12.2%) patients. AF recurrence, after the 3-month blanking period, was observed in 191 (32.5%) patients.

3.2 | Predictors of AF recurrence

Several variables in univariate analysis showed predictive value (Table 3). Predictors with the highest hazard ratio were: early recurrence, persistent/long-standing persistent AF and left atrial dimension, followed by hypertension, stroke, body mass index, and left ventricular ejection fraction. Kaplan-Meier AF free survival curves with regard to the strongest pre-procedural predictors in univariate analysis are presented in Figure 1 and Figure S1. In multivariate analysis, (Table 4) independent predictors of AF recurrence were left atrial diameter, AF type, stroke, and AF episodes within the blanking period.

3.3 | Comparison of risk scores

All scores were the predictive of AF recurrence (Figure 2), each additional point in a particular score increased risk (HR of 1.17-1.49 per point). $CHADS_2$ and CHA_2DS_2-VASc scores were less predictive than scores specifically designed for AF recurrence prediction. Of these, the SCALE-CryoAF score had the highest predictive value with C-statistics of 0.640 (Table 5). When SCALE-CryoAF was assessed on the basis of pre-procedural data, (ie, without points for AF recurrence during the blanking period) the C-statistics of this score was lower - 0.601. A simplified, novel score named **0-1-2 PL** composed of only two variables, AF type (**P**ersistent vs paroxysmal) and **L**eft atrial dimension >45 mm—and each assigned 1 point was developed and assessed. This score stratified patients into three categories of **0**, **1**

TABLE 2 Baseline patient characteristics (n = 588)

Parameters	
Age (years)	58.1 ± 10.6
Male gender	382 (65.0%)
BMI (kg/m^2)	29.1 ± 4.3
AF type	
Paroxysmal	460 (78.2%)
Persistent	102 (17.3) %
Long-standing persistent	26 (4.4%)
Duration of AF history (months)	59.6 ± 70.3
Number of failed antiarrhythmic drugs	1.5 ± 0.9
Current/past smoker	171 (29.1%)/38 (6.5%)
Comorbidities	
Hypertension	390 (66.4%)
Diabetes mellitus	75 (12.8%)
Coronary heart disease	60 (10.2%)
Heart failure	27 (4.6%)
Structural heart disease[a]	50 (8.5%)
Stroke/TIA	53 (9.0%)
CHA_2DS_2-VASc score	1.8 ± 1.3
eGFR <60 mL/min/1.73m^2	63 (10.7%)
Echocardiography	
Left atrial dimension (mm)	42.8 ± 5.7
Left ventricular ejection fraction (%)	60.4 ± 8.6
Left ventricular end-diastolic dimension (mm)	50.1 ± 5.6

Abbreviations: AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.
[a]Defined as cardiomyopathy or artificial valve or severe valvular disease or left ventricular ejection fraction <50%.

TABLE 3 Predictors of AF recurrence in univariate analysis

Predictor	HR	CI	*P*-value	C-statistics
Male sex	0.91	0.68; 1.21	.506	0.505
Age per 10 years	1.16	1.01; 1.34	.033	0.525
BMI per 10	1.44	1.05; 1.97	.025	0.550
Current smoker	1.06	0.77; 1.45	.730	0.512
Past smoker	0.90	0.47; 1.71	.737	0.512
Hypertension	1.42	1.04; 1.94	.029	0.533
Stroke	1.56	1.04; 2.33	.032	0.521
Diabetes mellitus	1.47	1.00; 2.16	.050	0.521
Myocardial infarction	1.37	0.78; 2.41	.272	0.510
PCI / CABG	1.19	0.74; 1.91	.479	0.506
NYHA class >2	1.76	0.98; 3.15	.060	0.517
Structural heart disease	1.22	0.74; 2.01	.434	0.508
eGFR <60	1.24	0.79; 1.93	.350	0.507
AF during blanking	3.05	2.19; 4.24	.000	0.585
Persistent AF	2.02	1.45; 2.80	.000	0.578
Long persistent AF	2.27	1.28; 4.03	.005	0.578
LAd per 10 mm	1.66	1.36; 2.03	.000	0.622
LV EF per 10%	0.98	0.97; 1.00	.018	0.552
LVEDd per 10 mm	1.25	0.97; 1.62	.080	0.531
MI per 1 grade	1.29	1.08; 1.54	.004	0.559
QRS>120 ms	1.12	0.65; 1.92	.694	0.498

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; LAd, left atrial dimension; LV EF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; MI, mitral insufficiency; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

or **2** points, each corresponding to a distinctly different risk strata in Kaplan-Meier analysis (Figure 3). The C-statistics of 0-1-2 PL score was higher/comparable to C-statistics of any other score based on pre-ablation data (Table 5).

The data that support the findings of this study are available from the corresponding author on reasonable request.

4 | DISCUSSION

In this study, we analyzed the predictors of AF recurrence post pulmonary vein isolation in a sizable cohort of patients with a long follow-up. The main findings of our study were that for the pre-ablation assessment of risk of AF recurrence, the novel 0-1-2 PL score

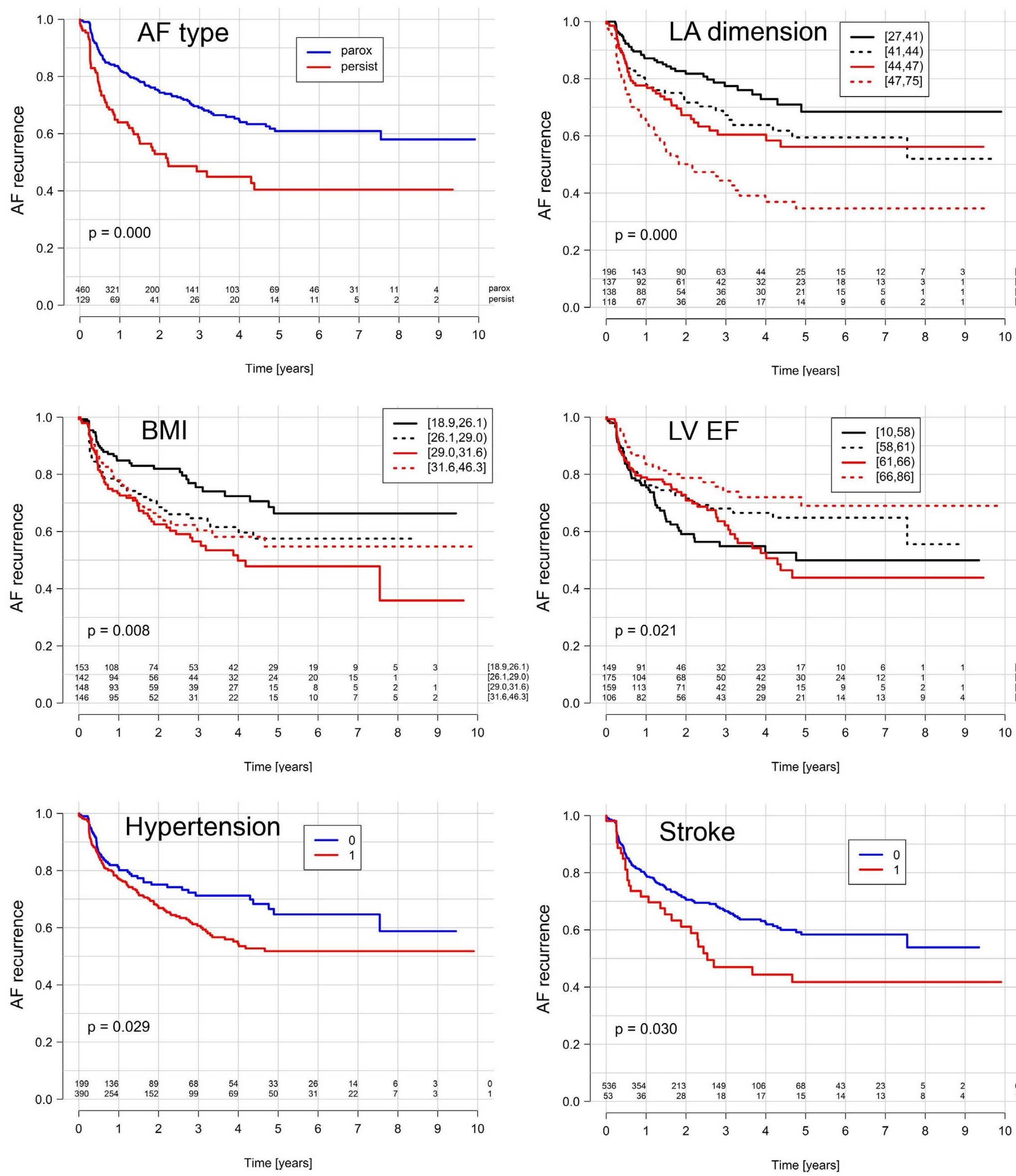

FIGURE 1 The Kaplan-Meier AF-free survival curve after AF ablation with regard to the strongest preprocedural predictors in univariate analysis. AF, atrial fibrillation; LA, left atrium; BMI, body mass index; LV EF, left ventricular ejection fraction

performed better than SCALE Cryo-AF, APPLE, CAAP-AF, MB-LATER, $CHADS_2$ and CHA_2DS_2-VASc scores. When post-ablation data were employed, the SCALE Cryo-AF was the best method to predict AF recurrence, followed closely by the much simpler 0-1-2 PL score.

Studies that analyzed the predictors of AF recurrence provided divergent results with regard to several variables. For example, smoking status reported by Canpolat et al as an important predictor of AF recurrence was found to be nonsignificant by Bavishi et al,[8,10] and also by us in the current study; most of the components of the PLAAF score were nonsignificant in other studies.[10] These contradictory results are reflected in the choice of variables included in various risk scores, eg, in the CAAP-AF and PLAAF, female sex was related to an increased risk of AF recurrence while in the MB-LATER, it was the male sex that was related to increased risk.[4-6] Table 2 shows that variables used in one risk score are seldom used by other scores. For example, chronic kidney disease used in APPLE is not used by SCALE Cryo-AF, CAAP-AF or MB-LATER.[1,2,4,6] While QRS duration >120 ms, exploited by MB-LATER and SCALE Cryo-AF, is ignored by other scores. This raises the question if variables used in these risk scores are the universal predictors of risk of AF recurrence or rather subject to some local bias, methodological nuances, length of follow-up, population differences, AF ablation technique or even chance findings. The lack of universality of these variables probably explains the weaker performance of risk scores when original studies, that introduced these scores, are compared with independent validation studies that analyzed these scores later. For example, the MB-LATER boasted area under the curve in receiving operator characteristic analysis of 0.782 while in another large study, on different population it was only 0.575, (similar to our result for this score).[4,10] This obvious limitation of the risk scores, uncertainty which one should be used and a broad spectrum of variables that have to be assessed/obtained together with a plethora of corresponding non-intuitive risk strata lowers the popularity and clinical application of these methods. Moreover, some of these scores use variables that are obtainable only after the ablation procedure (eg, occurrence of AF during 3-month post-ablation blanking period included in SCALE-CryoAF) limiting their use of the pre-ablation stage for patient selection, counseling or the modification of ablation technique.

TABLE 4 Predictors of AF recurrence in multivariate analysis

Predictor	HR	CI	*P*-value	C-statistics
Age per 10 years	1.24	1.07; 1.44	.004	0.650[a]
LA diameter per 10 mm	1.64	1.30; 2.05	.000	-
Stroke/TIA	1.94	1.28; 2.95	.002	-
Persistent AF	1.86	1.33; 2.60	.000	-
Long persistent AF	2.48	1.39; 4.43	.002	-

[a]C-statistics value for the whole model.

4.1 | Development and performance of 0-1-2 PL score

The above considerations have directed us to develop a prediction model that would be simple in application (maximum of 2-3 variables), easy to remember (only 0/1 point per variable), and based on factors that are both universal (widely accepted and validated by several studies) and easily available before ablation. There is high consistency of data with regard to the type of AF, left atrial size, and reduced left ventricular ejection fraction as potent risk factors which suggests that these might be universal predictors, less influenced by local population, ablation technique or length of follow-up. The success rate of patients with persistent atrial fibrillation in the present study was very similar like in other recent studies that investigated the usefulness of cryoballoon ablation in such patients.[15,16] Since the left atrial dimension and AF type were the only variables that were included in all other AF recurrence risk scores, had the highest C-statistics in univariate analysis, and inclusion of other variables (age, stroke) increased C-statistics only marginally, we decided to base the novel risk score on just these two variables. A cut-off point of 45 mm for the left atrial dimension was selected on the basis of Kaplan-Meir analysis. This value was between the cut-off of 43 mm used by APPLE and SCALE-CryoAF scores and 47 mm used by MB-LATER.[1,4] To underline the simplicity of application, we named this novel method 0-1-2 PL score for the two variables (**P** for Persistent AF and **L** for Left atrial dimension >45 mm) and for the three risk strata into which it categorizes patients: **0**, **1** and **2**. Kaplan-Meir analysis confirmed that this score stratified patients into low risk category (0 points), intermediate risk category (1 point, ie, either persistent AF present or LA was >45 mm), and high risk category (2 points); see Figure 3. These categories were related to a 2-year risk of AF recurrence of 21%, 37%, and 55%, respectively, which correspond well with the current clinical perception of low, intermediate, and high risk of AF recurrence post pulmonary vein isolation. Interestingly, the C-statistics of the 0-1-2 PL score (Table 5) was higher than C-statistics of any other scores based on pre-ablation data including the scores that exploited the same variables: a left atrial dimension and AF type. We believe that this supports our concept that some variables are not universal risk factors and that incorporating them into a risk score not only increases the score complexity but also can lower the accuracy when the score is used by others. Although the SCALE-CryoAF score had higher C-statistics than the 0-1-2 PL score, it included "early AF recurrence"—a variable closely connected to what this score intends to predict. AF recurrence during the first three months is partially the same as AF recurrence during later periods as the 3-month cut-off is arbitrary, and probably too long when cryoablation outcomes are assessed.[17] Therefore, this variable can be considered a kind of predicting recurrence on the basis of recurrence, a kind of glimpse into the future to predict future. Since the main application of scores is balancing indications and expected outcomes for pre-ablation counseling, patient selection, and choice of ablation strategy (more extensive ablation), we have concentrated on scores that can be used at the pre-ablation stage. Although SCALE-CryoAF uses one post-ablation risk factor, it was suggested in the original publication that this score can still be also applied at the pre-ablation stage by calculating the score without the "early return of atrial fibrillation" variable.[1] However, the predictive power of such a new prognostic model was not provided by its authors. In our current assessment, the C-statistics of SCALE-CryoAF when eliminated of this potent risk factor was not impressive, lower than predictive power of the straightforward 0-1-2 PL score.

4.2 | Limitations

This was a single-center observational study with related potential referral and treatment bias and ablation method was limited to the cryoballoon technique. It is necessary to validate our results with multicenter data analysis including patients treated with radiofrequency current ablation. However, since the 0-1-2 PL score was based on

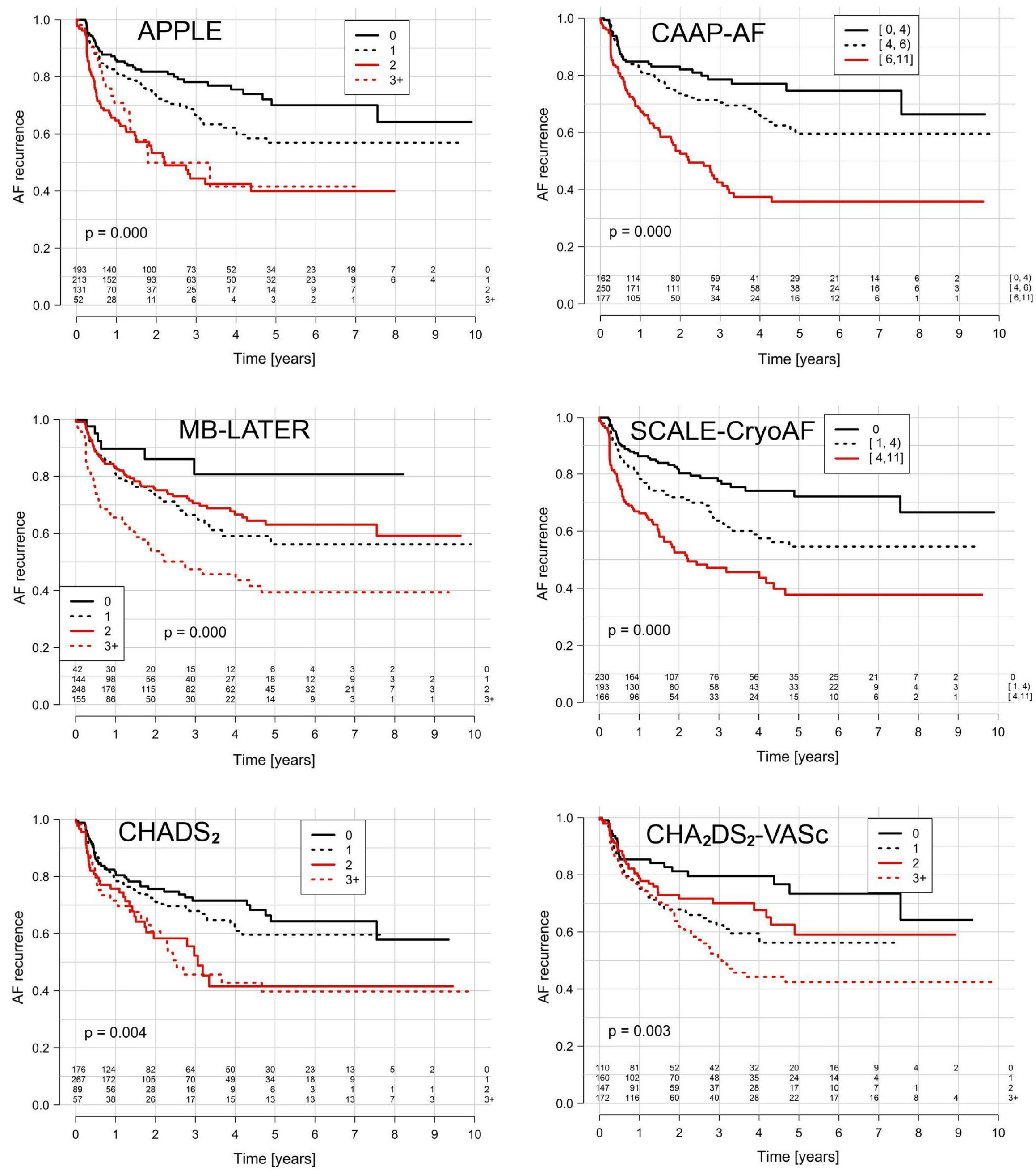

FIGURE 2 The Kaplan-Meier AF-free survival curves after AF ablation with regard to the results of risk scores. AF, atrial fibrillation

TABLE 5 Predictive value of risk scores for AF recurrence

Predictor	HR	CI	P-value	C-statistics
APPLE[a]	1.44	1.26; 1.66	.000	0.611
CAAP-AF[a]	1.27	1.18; 1.37	.000	0.624
MB-LATER[a]	1.49	1.29; 1.72	.000	0.603
SCALECryoAF[a]	1.24	1.17; 1.31	.000	0.640
SCALECryoAF[a,b]	1.17	1.09; 1.25	.000	0.601
$CHADS_2$[a]	1.26	1.11; 1.44	.000	0.559
CHA_2DS_2-VASc[a]	1.17	1.06; 1.30	.002	0.551
0-1-2 PL score = 1	1.96	1.43; 2.69	.000	0.620
0-1-2 PL score = 2	2.99	2.03; 4.41	.000	0.620

[a]HR per one assigned point.

[b]Assessed on the basis of preprocedural data, ie, without "early return of atrial fibrillation".

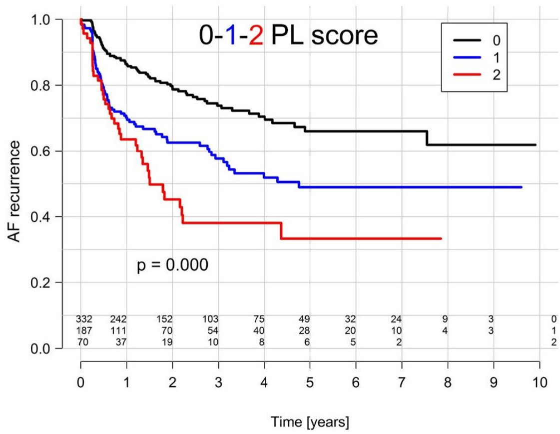

FIGURE 3 The Kaplan-Meier AF-free survival curves after AF ablation with regard to the number of points in the 0-1-2 PL score. AF, atrial fibrillation

variables that are known to perform well in various settings/studies, and the ablation endpoint was universal (PVI isolation) it is unlikely that the results in other centers/populations would be much different.

Since arrhythmia recurrences can be asymptomatic and periodic ECG monitoring is far from perfect, undoubtedly we missed some episodes of asymptomatic AF. However, since AF ablation is performed mainly for symptom control and asymptomatic episodes are likely to be distributed equally in all three score strata, this should not influence the clinical application of the 0-1-2- PL score nor the conclusions of our study.

5 | CONCLUSIONS

This study suggests that despite the significant differences between risk scores in terms of the choice of risk factors and the relative weights assigned to them, their performance for pre-ablation risk assessment is quite similar and weaker than originally reported. It seems that the assessment of risk of AF recurrence at the pre-ablation stage can be simplified by the novel 0-1-2 PL score instead of more complex methods. This would help in popularizing pre-ablation risk assessment as well as facilitate the standardization of AF management.

CONFLICT OF INTEREST

Dr Jastrzebski declares consulting fees from Medtronic; other authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Jastrzębski M, Kiełbasa G, Fijorek K, et al. Comparison of six risk scores for the prediction of atrial fibrillation recurrence after cryoballoon-based ablation and development of a simplified method, the 0-1-2 PL score. *J Arrhythmia*. 2021;00:1–9. https://doi.org/10.1002/joa3.12557

KARDIOLOGIA POLSKA
Polish Heart Journal
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957
Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon
ISSN 0022–9032
e-ISSN 1897–4279

Patent foramen ovale and left atrial appendage flow velocity predict atrial fibrillation recurrence post cryoballoon ablation

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Article type: Original article

Received: March 3, 2021

Accepted: May 2, 2021

Published online: May 13, 2021

Patent foramen ovale and left atrial appendage flow velocity predict atrial fibrillation recurrence post cryoballoon ablation

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Short title: TEE-derived predictors of AF recurrence

Conflict of interest: none declared.

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What's new?

This is the first study that reported the prognostic value of patent foramen ovale for predicting atrial fibrillation recurrence after ablation. Presence of patent foramen ovale doubles the risk of unfavourable long-term results of pulmonary vein isolation with cryoballoon ablation.

In the largest study to date we showed also relationship between the left atrial appendage flow velocity and atrial fibrillation recurrence in patients after cryoballoon ablation procedure. Consequently, this study corroborated the data that indicated that left atrial appendage flow velocity is an independent and important predictor of atrial fibrillation recurrence.

Abstract

Background: Transesophageal echocardiography (TEE) allows detailed characterization of atrial fibrillation (AF) substrate and could be valuable for predicting pulmonary vein isolation (PVI) procedure outcomes.

Aims: We aimed to assess the value of TEE-derived left atrial (LA) and LA appendage (LAA) features as prognostic markers for AF recurrence after cryoballoon-based ablation.

Methods: Patients were enrolled using prospective database of consecutive PVI procedures performed over a 7-year period. Following TEE-derived parameters were investigated: LAA emptying flow velocity (LAA-FV), presence of patent foramen ovale (PFO), LA spontaneous echo contrast and mitral regurgitation. Diagnosis of AF recurrence was based on scheduled and symptoms triggered ECG monitoring. Cox's regression model and Kaplan-Meier survival curves were applied for statistical analysis.

Results: A total of 417 consecutive patients who underwent their first PVI using cryoballoon were analysed (mean age: 59 years). AF recurrence was noted in 25.7 % of patients (median follow-up of 24 months). Four TEE-derived variables had predictive value for AF recurrence: LAA-FV < 45 cm/s, presence of PFO at resting state, LA spontaneous echo contrast and mitral regurgitation. In the multivariable model, apart from the transthoracic echocardiography-derived LA size, two TEE-derived features (LAA-FV <45 cm/s and presence of PFO) remained as independent predictors.

Conclusions. This study proposed a novel TEE-derived AF recurrence risk factor - presence of PFO and confirmed the prognostic value of LAA flow velocity in patients undergoing cryoballoon-based AF ablation. These risk factors could be useful in global assessment of AF recurrence risk and potentially helpful in planning the ablation strategy.

Key words: atrial fibrillation recurrence; cryoballoon ablation; patent foramen ovale; left atrial appendage flow velocity

Introduction

Atrial fibrillation (AF) ablation is the most commonly performed interventional procedure for arrhythmia treatment. Despite significant progress and development of multiple AF ablation techniques, the long-term AF recurrence rate remains high. The assessment of the risk factors for AF recurrence is important both for patient selection/counselling and understanding the reasons behind the failure of this treatment modality.

The most recognized and validated risk factors for AF recurrence include the type of AF (paroxysmal vs persistent), left atrium (LA) enlargement, impaired systolic function of the left ventricle and comorbidities such as obesity, hypertension, diabetes mellitus or obstructive sleep apnea [1–3]. Transesophageal echocardiography (TEE) can potentially provide a more accurate risk assessment as it allows the characterization of the AF substrate, i.e. the aspects of morphology and function of the LA and LA appendage (LAA) which are unobtainable in the transthoracic echocardiography (TTE). Several studies have shown that features obtained from the TEE have independent prognostic value [4–11].

In this study, we aimed to investigate the value of TEE derived parameters, concentrating on LA and LAA size and function as prognostic markers of long-term outcomes after a cryoballoon-based pulmonary vein isolation (PVI) procedure.

Methods.

Study population

This retrospective analysis was based on our prospectively maintained registry of all consecutive AF ablation procedures performed in patients with symptomatic AF over a 10-year period (June 2009–September 2019). We screened 617 patients; subjects with persistent AF (n = 122), paroxysmal AF with arrhythmia episode during TEE examination (7), incomplete data (n = 20), ablation performed with radiofrequency current technique (n = 8) or with cryoballoon type 1 (n = 26) or re-do procedures (n = 17) were excluded. Consequently, the studied group included 417 patients with paroxysmal AF who underwent their first PVI ablation procedure using cryoballoon type 2 (Arctic Front Advance, Medtronic Inc., Minneapolis, MN, USA).The study flow-chart was presented in Figure 1. The study was approved by the institutional ethical committee.

Echocardiographic examination

Each patient underwent a TTE study to obtain the standard dimensions and parameters. In the next step TEE examination using a Vivid 9 (GE Healthcare, Horten, Norway) device with a 4D

TEE probe on the day the AF ablation was scheduled to assess LA and LAA. To exclude any thrombus, LAA was visualized in the mid-esophageal aortic valve short-axis view (30-60^0). Then, the probe was flexed anteriorly and rotated from an angle of 0º to 180º; placing the pulsed-wave sample-volume in the proximal one-third segment of the LAA, and the flow velocities were recorded. The mean value of the LAA late diastolic emptying flow velocity from three consecutive cardiac cycles during regular sinus rhythm was recorded for further analysis. TEE was also used for the detection of LA spontaneous echo contrast. Possible leakage through interatrial septum was tested with Doppler echocardiography both at rest and after the injection of an intravenous contrast (9 ml of 5% dextrose solution shaken with 1 ml of ambient air) and Valsalva maneuver. Figure 2 presents examples of investigated features in TEE examination.

Ablation procedure

All PVI procedures were performed under conscious sedation using a 28-mm cryoballoon. No prior pulmonary vein anatomy assessment was performed; if considered necessary, pulmonary vein anatomy was assessed with contrast/angiography during the procedure. A His bundle catheter and coronary sinus catheter were used to facilitate the transseptal puncture and also for phrenic nerve pacing and electrophysiological assessment of PV isolation. Transseptal puncture was used as an access method to the left atrium in all included patients, including patients with patent foramen ovale (PFO). No attempts to cross PFO with guidewire or ablation catheter was made. Such strategy was based on the considerations that PFO is situated more superior and anterior in comparison to the ideal access site made with the use transseptal puncture. As a result the trans-PFO access may limit the access to pulmonary veins and hinder the successful creation of permanent lesions around PVs' ostia. Our approach/strategy of cryoballoon-based PVI was described in detail elsewhere [12–13] and generally followed the expert consensus recommendations [14]. The procedural endpoint was the electrical isolation of all PVs.

Follow-up and the study endpoint

The analysed endpoint of this study was freedom from AF recurrence. AF recurrence was defined as the first episode of AF lasting >30 seconds diagnosed after the blanking period of 3 months. Atrial fibrillation had to be documented by ECG, Holter monitoring or intracardiac electrogram from the implanted device. Holter monitoring (24–72 hours long) was scheduled after 3 and 6–9 months post-ablation and then advised once a year. Moreover, all patients were advised to obtain an ECG each time they experienced palpitations. Data regarding the primary endpoint were obtained prospectively during the scheduled follow-up visits. However, additionally, all patients received a telephone call at the time of conducting this study to ensure the accuracy of the database with regard to the study endpoint. Antiarrhythmic drugs were discontinued either immediately post-ablation or at the latest after the 3-month blanking period.

Statistical analysis

Continuous variables are presented as means and standard deviations or medians with quartiles (Q_1, Q_3) while categorical variables are presented as numbers and percentages. In order to confirm the normal distribution Shapiro-Wilk test was used. Comparisons between groups were performed using Student's t-test for independent variables (continuous variables) and the chi-square test (proportions). Freedom from AF (time to first AF re-occurrence) after the ablation was assessed with the use of Kaplan-Meier curve. Survival distribution between groups was compared using log-rank test. The cut-off point of LAA flow velocity value was calculated based on ROC-curve using post-hoc data. Univariable and multivariable survival analyses were performed used to describe the effect of predictors of AF-free survival. All variables believed to be clinically important were pre-specified and entered into the multivariable Cox regression model. Subsequently, the Wald statistic values were used for stepwise elimination of insignificant variables. The results of Cox models were presented as hazard ratios (HRs) along with tests of significance and 95% confidence intervals (CIs). There were no significant violations of the proportionality assumption that underlies the Cox proportional hazard method. Statistical analysis was performed in Statistica Software version 13.1 (TIBCO Software Inc. Palo Alto, CA, USA). P <0.05 were considered statistically significant.

Results

Patient characteristic and follow-up

The studied group consisted of 417 patients aged 59 [11] years [mean (SD)], most of them with at least one comorbidity (71.7%) and unsuccessful treatment with at least one (38.9%), two (27.1%) or more (11.4%) antiarrhythmic drugs. Detailed baseline clinical and echocardiographic characteristics of this group are presented in Table 1 and Table 2, respectively.

The 7-year observation period resulted in a median follow-up time of 24 months (Q_1–Q_3, 15.5–45.6) — in total 11 056 patient-months. On average, there were 84 hours of Holter ECG monitoring per patient during the observational period. Additionally, 36 patients had data available from the implanted device capable of AF detection (22 implantable loop recorders and 14 pacemakers). AF recurrence after the blanking period was observed in 107 (25.7%) patients with a median of 225 days (Q_1–Q_3, 115–550) without AF post ablation.

Clinical and echocardiographic predictors of AF recurrence

We investigated several clinical and echocardiographic features as potential pre-procedural predictors of AF recurrence. Five non-TEE variables in univariable Cox's regression model showed predictive value: the presence of hypertension and diabetes mellitus, BMI, age and LA enlargement more than 40 mm — which was the strongest predictor (Table 3). Four TEE-derived variables were predictive of AF recurrence: LAA flow velocity <45 cm/s, the presence of PFO at resting state, LA spontaneous echo contrast and mitral regurgitation of any degree (Table 3).

Kaplan-Meier AF free survival curves with regard to the pre-procedural predictors from TEE are presented in Figure 3. These factors predicted a 16% to 20% absolute difference in the study endpoint at the end of the 4th year. Multivariable survival analysis that included all variables from the univariable analysis showed that two of the TEE-derived variables (LAA flow velocity <45 cm/s and presence of PFO) were independent predictors (Table 3), with a *P* for the whole model of <0.001. The cut-off point of LAA flow velocity value was determined by the ROC-curve analysis.

Additionally, the relation of LAA flow velocity to other TEE-derived parameters was assessed by between group comparison (Table 4); the presence of LA spontaneous echo contrast and mitral regurgitation was strongly related to the LAA flow velocity value.

Discussion

The major finding of our study is that LAA flow velocity and the presence of PFO were independent predictors of AF recurrence in a sizable and homogeneous cohort of patients with paroxysmal AF who underwent cryoballoon-based PVI. To the best of our knowledge, this is the first study that reported the relation between PFO and the risk of AF recurrence and the largest study to date showing the relation of LAA flow velocity and arrhythmia recurrence in patients after cryoballoon ablation.

Patent foramen ovale

We found that PFO is an independent risk factor of AF recurrence with a prognostic impact similar to LA size (HR of 1.79 vs 1.88, respectively). The relation between PFO and AF recurrence post ablation is a novel finding and still not fully understood. However, it is tempting to speculate that there is a causative relationship.

One study found that patients with PFO have "atrial latent vulnerability" to develop tachyarrhythmias due to shorter refractoriness and more frequent arrhythmia inducibility during electrophysiological testing [15]. Moreover, we hypothesize that PFO may also act as AF trigger — mechanically inducing premature atrial depolarizations.

The increased prevalence of PFO among patients with a migraine headache is well-documented [16]. One of the postulated mechanisms of this relation evokes the impact of circulating platelet aggregates, serotonin and other chemicals – which in normal situations are "detoxified" in their first passage through the lungs. Similar mechanism can be operative in the pathogenesis of AF occurrence/recurrence as it is possible that influx of venous blood into the LA in patients with PFO delivers to LA biologically active substances that may predispose to AF initiation or progression of atrial myopathy. Indeed, in a recent work Daher et al. found an increased prevalence of PFO reaching 57% in AF patients referred for PVI [17].

It is also possible that PFO is secondary to LA dilatation. Malcoaptation of the edges of the fossa ovale and interatrial shunting may be a consequence of stretching of the interatrial septum — being a part of the process of atrial enlargement [18]. Consequently, PFO could be a marker of structural changes in LA, i.e. a culprit rather than a causative factor. However, this seems a less likely explanation as PFO was found in the current study to be an independent risk factor alongside the LA size.

LAA flow velocity

LAA flow velocity was validated as an indicator of LA contractile and reservoir function [19]. The relationship between reduced LAA flow velocity and increased risk of AF recurrence after PVI has previously been reported by a number of studies — summarized in Table 5 [6–11]. However, most of these studies were based on small cohorts and only one study investigated patients who underwent cryoballoon-based ablation [6]. Gerede et al. studied 51 patients who underwent cryoballoon ablation and found that LAA flow velocity was an independent risk factor of AF; our results corroborate this with an analysis based on a group almost 10 times the size than in the previously studied population. Furthermore, in our study, all patients during TEE were in sinus rhythm, in contrast to some other reports. This seems important since including patients with persistent AF or patients with AF episodes during TEE, and analyzing them together with patients in sinus rhythm results in a serious methodological limitation, as during AF the LAA flow velocity is temporarily decreased.

The LAA flow velocity cut-off point among most studies was similar; any small differences between studies were probably caused by dissimilarities in studied populations and methodology. Our population was relatively healthy, most commonly with hypertension as the only important comorbidity. In the largest LAA flow velocity study to date, a cut-off of 40 cm/s was proposed — a value slightly lower than in our study (45 cm/s). This could be attributable to the inclusion of patients with persistent AF in that study, as velocity cut-off for persistent AF patients is much lower [9].

Presence of LA spontaneous echo contrast

LA remodelling related to AF progression manifests in decreased LA contractility development of LA spontaneous echo contrast that can be considered as a final result of LA remodelling, fibrosis, dilation, and decreased hemodynamic function [20]. The presence of LA spontaneous echo contrast as an important independent risk factor of AF recurrence in similar populations was reported by Gerede et al. [6]. However, in our research, this factor was not an independent factor — because it was strongly related with LAA flow velocity (Table 4).

Clinical implications

AF recurrence is reported to occur in 10–50% of patients post-cryoballoon ablation. Although several risk factors for AF recurrence were proposed, pre-procedural risk assessment is still far from perfect. A few reports pointed out that other features concerning LA and LAA size and function — like morphological type of LAA, LA strains and LA pressure, might offer better risk assessment than the standard clinical and TTE-derived measures [4, 21–23].

This study demonstrated that two TEE-derived measures are independent predictors for AF recurrence and potentially could be helpful to distinguish patients with paroxysmal AF who would have a preferable outcome by cryoballoon ablation from those who would not, and could improve the clinical decision-making in these patients. Moreover, it seems justified to speculate that patients with the presence of the above risk markers might benefit from more extensive cryoballoon-based LA ablation (roof and posterior wall lines, LAA appendage isolation, etc.) [24–26] in order to reduce the AF recurrence.

Low LAA flow velocity probably reflects functional atrial remodelling or LAA remodelling related to increased arrhythmogenicity. This seems similar to the observation that the left ventricular ejection fraction predicts occurrence of ventricular tachyarrhythmias. Since LAA flow velocity remained an independent factor after adjustment for a very potent risk factor - LA size, this suggests that LAA function deterioration may precede LA dilatation and may occur in the early stages of LA remodelling while the presence of PFO may reflect particular structural atrial remodelling that takes place before global dilatation is observed.

Limitations

This was a single-centre observational study with related potential referral and treatment bias. It is necessary to validate our results with multicentre data analysis. Since arrhythmia recurrences can be asymptomatic and periodic ECG monitoring is far from perfect, undoubtedly some episodes of asymptomatic AF were missed. However, asymptomatic episodes were likely distributed equally in both groups — with and without recognized AF limiting the impact of missed AF episodes on the obtained results.

It is possible that we underestimated the true prevalence of PFO. One study showed that TEE is less sensitive in detection of PFO than gentle attempts to cross the interatrial septum with the use of steerable catheter during the PVI procedure [17]. However, the prognostic importance of small PFO that does not manifest in TEE during Valsalva manouver might be different from importance of a more "manifest" PFO — as investigated in our population.

The cut-off point of LAA flow velocity was estimated on the basis of post hoc data analysis, potentially leading to the bias of the test validity. However, this type of bias has higher impact on the test performance in studies with small sample size or low prevalence of the analyzed effect [26].

Conclusions

This study proposed a novel TEE-derived AF recurrence risk factor - presence of patent foramen ovale and confirmed the prognostic value of left atrium appendage late diastolic emptying flow velocity during sinus rhythm in patients undergoing cryoballoon-based AF ablation. These risk factors could be useful in global assessment of AF recurrence risk and potentially helpful in planning the ablation procedure strategy.

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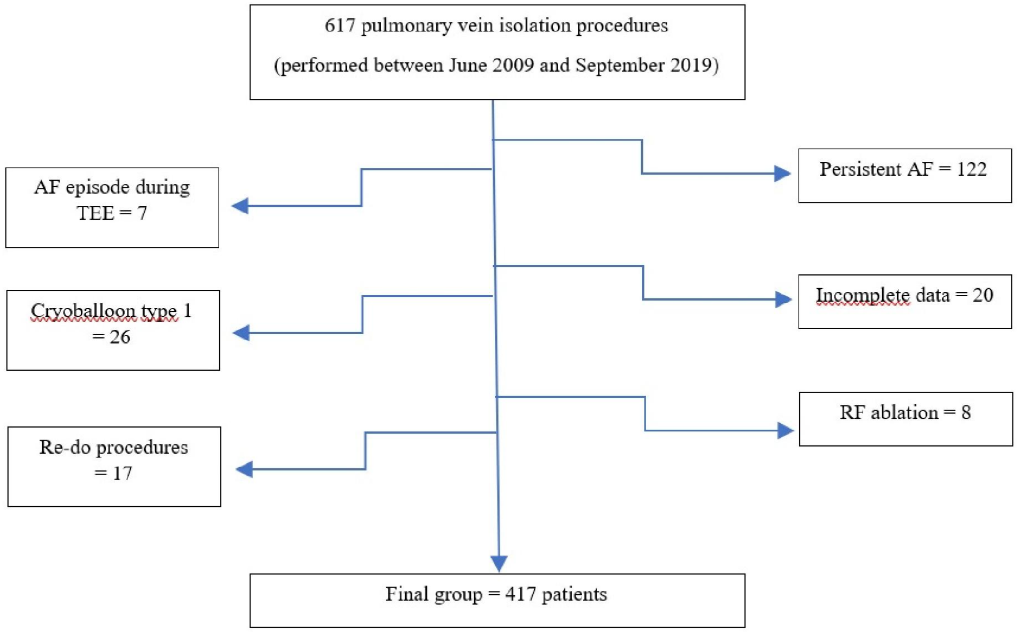

Figure 1. Study flow-chart illustrating reasons for exclusion from the study. Abbreviations: AF, atrial fibrillation; TEE, transesophageal echocardiography; RF, radiofrequency ablation

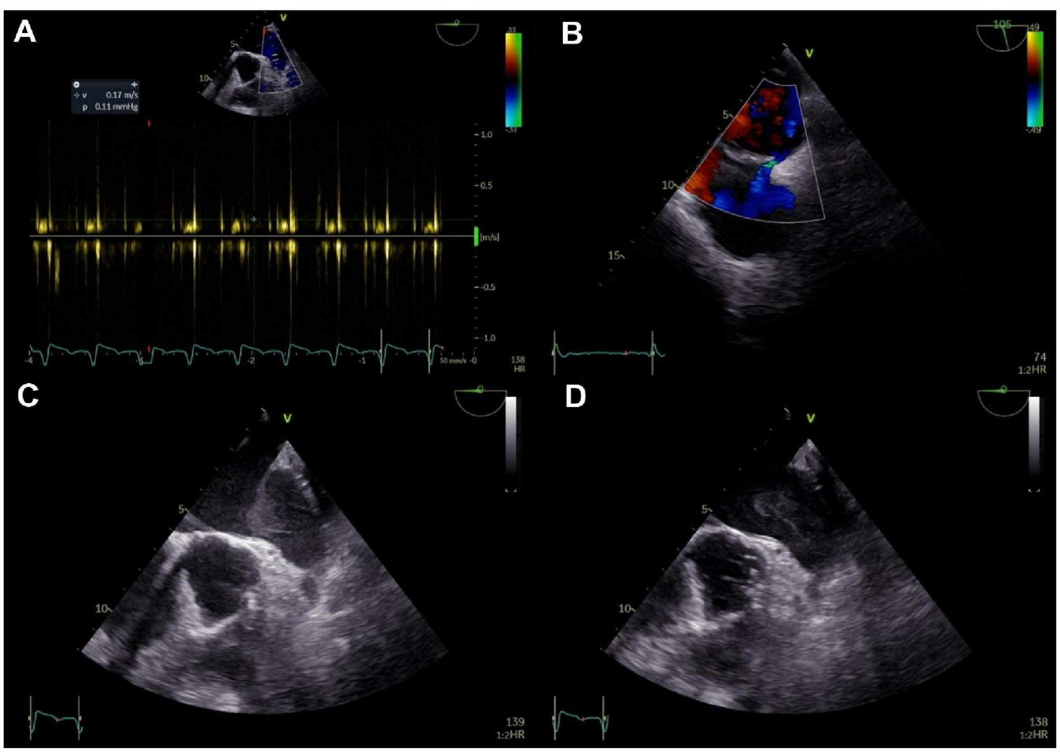

Table 1. Baseline characteristics of the study population (n = 417)

Parameters	Whole group (n = 417)	No AF recurrence (n = 310)	AF recurrence (n = 107)	*P*
Age, year, mean (SD)	59 (11)	58 (11)	61 (9)	**0.03**
Male gender	253 (60.7%)	194 (62.6%)	59 (55.4%)	0.49
BMI[a], kg/m^2	28.8 (25.9–31.5)	28.4 (25.7–31.5)	29.5 (27–32)	**0.03**
AF history[a], months	48 (24–72)	36 (24–77)	60 (24–72)	0.28
AA drugs use >2	41 (11.3%)	30 (9.7%)	17 (15.9%)	0.08
Current/past smoker	124 (29.7%) / 25 (6.0%)	90 (29.0%) / 20 (6.5%)	34 (31.8%) / 5 (4.7%)	0.72
CHA_2DS_2-VASc score[a]	2 (1–3)	2 (1–3)	2 (1–3)	**0.01**
Comorbidities				
Hypertension	277 (66.4%)	198 (63.9%)	79 (73.8%)	0.06
Diabetes mellitus	55 (13.2%)	35 (11.3%)	20 (18.7%)	0.051
Chronic coronary syndrome	34 (8.2%)	26 (8.4%)	8 (7.5%)	0.77
Heart failure	13 (3.1%)	8 (2.6%)	5 (4.7%)	0.28
Structural heart disease[b]	30 (7.2%)	21 (6.8%)	9 (8.4%)	0.57
Stroke/TIA	19 (4.6%)	11 (3.6%)	8 (7.48%)	0.09
eGFR <60, l/min/1.73 m^2	49 (11.8%)	35 (11.3%)	14 (13.1%)	0.62

[a]Data presented as median with quartiles (Q_1, Q_3).

[b]Defined as cardiomyopathy or artificial valve or severe valvular disease or left ventricular ejection fraction <50%.

Abbreviations: AA, antiarrhythmic; AF, atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack

Table 3. Predictors of atrial fibrillation recurrence in univariable and multivariable survival analysis

Predictor	**Univariable analysis HR (95% CI)**	***P***	**Multivariable analysis HR (95% CI)**	***P***
Male sex	0.77 (0.52; 1.12)	0.17	—	
BMI per 1 kg/m^2	1.05 (1.01; 1.09)	**0.03**	—	
Age per 10 years	1.31(1.08; 1.6)	**0.006**	—	
Hypertension	1.58 (1.02; 2.43)	**0.04**	—	
Diabetes mellitus	1.75 (1.08; 2.85)	**0.02**	—	
Stroke/TIA in history	1.84 (0.89; 3.77)	0.1	—	
Chronic coronary syndrome	0.95 (0.46; 1.95)	0.89	—	
Structural heart disease	1.38 (0.7; 2.74)	0.35	—	
Heart Failure NYHA class ≥ II	1.84 (0.75; 4.52)	0.18	—	
Current smoker	1.12 (0.74; 1.68)	0.6	—	
eGFR <60 l/min/1.73 m^2	1.24 (0.71; 2.17)	0.46	—	
LA dimension >40 mm	1.97 (1.29; 3.01)	**0.002**	1.88 (1.23; 2.87)	**0.004**
LV ejection fraction per 10%	0.8 (0.63; 1.02)	0.07	—	
LVEDD per 10 mm	1.19 (0.84; 1.69)	0.32	—	
LA spontaneous contrast	1.69 (1.05; 2.73)	**0.03**	—	
LAA-FV <45 cm/s	1.73 (1.14; 2.65)	**0.01**	1.63 (1.06; 2.49)	**0.02**
Patent FO (at rest)	1.88 (1.07; 3.31)	**0.03**	—	
Patent FO (Valsalva)[a]	2.02 (0.64; 6.36)	0.23	1.79 (1.02; 3.15)	**0.04**
Any mitral regurgitation	1.55 (1.05; 2.28)	**0.03**	—	

[a]Transition of contrast micro-bubbles through foramen ovale during Valsalva maneuver.

Abbreviations: NYHA, New York Heart Association; HR, hazard ratio; CI, confidence interval other abbreviations — see Table 1 and 2

Table 4. Comparison between patients with left atrial flow velocity <45 cm/s and ≥45 cm/s

	LAA-FV <45 cm/s (n = 89)	**LAA-FV ≥45 cm/s (n = 328)**	***P***
LA spontaneous echo contrast	37 (41.6)	18 (5.5)	**<0.001**
Patent FO (at rest)	8 (9.0)	26 (7.9)	0.75
Patent FO (Valsalva)[a]	3 (3.4)	16 (4.9)	0.77
Any mitral regurgitation	59 (66.3)	156 (47.6)	**0.002**

Data are presented as number (percentage) of patients.

[a]Transition of contrast micro-bubbles through foramen ovale during Valsalva maneuver.

Abbreviations — see Table 1 and 2

Table 5. Left atrial appendage late diastolic emptying flow velocity value as a risk factor for atrial fibrillation (AF) recurrence

Study	n	AF type	HR (CI) recurrence	LAA-FV (cm/s)	Ablation method	Follow-up, months
Kiełbasa 2021	**417**	Parox	1.63 (1.06; 2.49)	≥45	**CB**	24
Gerede 2016 [6]	51	Parox	1.13 (1.11; 1.23)	≥30	CB	12
Fukushima 2014 [7]	105	Parox	2.69 (1.14; 6.32)	≥64.9	RF	19
Kanda 2015 [8]	53	Persist	3.24 (1.24; 8.48)	>28	RF	12
Ma 2016 [9]	55	Persist	1.23 (1.06; 1.47)	>8	RF	12
Ma 2016 [9]	65	Parox	1.14 (1.02; 1.27)	>32	RF	12
He 2018 [10]	80	Parox	1.1 (1.01; 1.19)	≥39.2	RF	12
Kim 2019 [11]	2352	Parox and Persist	2.35 (1.97; 2.79)	>40	RF	51

Abbreviations: parox, paroxysmal; persist, persistent; CB, cryoballoon ablation; RF, radiofrequency ablation; other abbreviations – *see* Table 2

VI. Wyniki

Publikacja 1

W pierwszym opublikowanym artykule z cyklu - pracy poglądowej, przedstawiono obecny stan wiedzy na temat izolacji ujść żył płucnych (PVI). Szczególną uwagę poświęcono praktycznym aspektom bezpiecznego wykonania krioablacji balonowej (CB), koncentrując się na technice zabiegu. Krok po kroku opisano przebieg procedury, uwzględniając sytuacje szczególne, problemy, które mogą wystąpić oraz proponując możliwości ich rozwiązania - bazując na własnym doświadczeniu ośrodka, w którym wykonano w ostatnich 11 latach ponad 800 zabiegów PVI. Porównano CB i ablację RF - aspekt samego zabiegu oraz skuteczności długoterminowej. Obszerną część tekstu poświęcono możliwym powikłaniom zabiegu - rodzajowi, działaniom mającym na celu zapobieganie im, częstości występowania, koniecznym interwencjom, gdy wystąpią oraz trwałości na przestrzeni czasu. Przedstawiono najważniejsze czynniki wpływające na ryzyko nawrotu migotania przedsionków - w pierwszej kolejności typ arytmii (napadowe vs. przetrwałe), wielkość lewego przedsionka oraz obecność niewydolności serca. Doświadczenia własne skonfrontowano z danymi z literatury, przede wszystkich z cyklem publikacji FIRE AND ICE, oraz innymi publikacjami typu *state of the art* doświadczonych ośrodków/operatorów.

Publikacja 2

Przedstawiono skuteczność długoterminową PVI ośrodka, w którym od początku zabiegi wykonywano technikami pojedynczej aplikacji (CB oraz PVAC). Roczny, dwuletni oraz pięcioletni okres bez nawrotu AF zaobserwowano u (odpowiednio): 78.2%, 69.2% oraz 56.0% z 597 pacjentów. Przeanalizowano efektywność reablacji z użyciem innej techniki z zastosowaniem pojedynczej aplikacji (w przypadku pierwotnej aplikacji wykonanej z zastosowaniem CB reablacja odbywała się z użyciem PVAC - i odwrotnie; w 2 przypadkach z 58 reablacji użyto tej samej techniki) - w 80.3% uzyskano roczny brak nawrotu AF, w 76.1% dwuletni oraz w 68.3% pięcioletni. Powikłania PVI wystąpiły u 12,1% pacjentów - z czego u mniej niż 1/3 klasyfikowane jako poważne - w postaci tamponady (0,84%), udaru (0,17%), porażenia nerwu przeponowego (1,34%) oraz wytworzenia jatrogennego ASD wymagającego interwencji (1,51%).

Publikacja 3

W grupie pacjentów po PVI wykonanej jedynie przy użyciu CB zbadano niezależne klasyczne czynniki ryzyka związane z długoterminowym brakiem skuteczności zabiegu, do których zaliczono: wymiar lewego przedsionka (dla każdych kolejnych 10mm: HR = 1,64 (1,30; 2,05), p < 0,001), przetrwały typ AF (HR = 1,86 (1,33; 2,6), p < 0,001), wiek (dla każdych 10 kolejnych lat: HR = 1,24 (1,07; 1,44), p = 0,004) oraz udar w historii medycznej (HR = 1,94 (1,28; 2,95), p = 0,002). W badanej populacji porównano opublikowane uprzednio skale oceniające ryzyko nawrotu migotania przedsionków (SCALE Cryo-AF, APPLE, CAAP-AF, MB-LATER, $CHADS_2$ and CHA_2DS_2-VASc) - uzyskując najlepszą wartość predykcyjną dla skali SCALE Cryo-AF (C-statistic = 0,602 dla zmiennych jedynie prezabiegowych oraz = 0,638 uwzględniając zmienne pozabiegowe). Stworzono autorską skalę nawrotu AF : **0-1-2 PL Score** - wyróżniającą się prostotą - zawierającą jedynie dwie zmienne: powiększenie **L**ewego przedsionka oraz **P**rzetrwały typ migotania przedsionków; oraz wysoką wartością C-statistic = 0,620 przy uwzględnieniu jedynie czynników prezabiegowych. Stworzona skala klasyfikuje pacjentów do grup niskiego (0 punktów), pośredniego (1 punkt) oraz wysokiego (2 punkty) ryzyka nawrotu AF. Uzyskana punktacja związana jest z 21% (0 punktów), 37% (1 punkt) lub 55% (2 punkty) 2-letnim ryzykiem pozabiegowego nawrotu AF.

Publikacja 4

W wyselekcjonowanej grupie pacjentów z napadowym migotaniem przedsionków, u których wykonano PVI jedynie przy użyciu 2-giej generacji kriobalonów, przeanalizowano dane z echokardiografii przezklatowej oraz przezprzełykowej w aspekcie nawrotu migotania przedsionków po zabiegu. W analizie wieloczynnikowej regresji logistycznej ustalono związek nawrotu AF z powiększeniem lewego przedsionka >40 mm (HR = 1.88 (1.23; 2.87), p = 0.004), obecnością przetrwałego drożnego *foramen ovale* (PFO) (HR = 1.79 (1.02; 3.15), p = 0.04) oraz prędkością wypływu z uszka lewego przedsionka <45cm/s (HR = 1.63 (1.06; 2.49), p = 0.02). Nasze badanie jest pierwszym przedstawiającym związek pomiędzy długoterminową nieskutecznością krioablacji balonowej a obecnością PFO oraz największym, z w pełni homogenną grupą pacjentów, potwierdzającym związek z zredukowaną prędkością wypływu z uszka lewego przedsionka.

VII. WNIOSKI

Informacje zawarte w ***Publikacji 1*** stanowią użyteczne klinicznie kompendium - zarówno dla ablacjonistów wykonujących zabiegi izolacji ujść żył płucnych (PVI) jak również dla lekarzy uczestniczących w kwalifikacji pacjentów do ablacji oraz sprawujących opiekę pozabiegową. Przedstawienie własnego *state of the art* - jako jednego z nielicznych doświadczonych polskich ośrodków, który od początku wykonuje PVI metodami pojedynczej aplikacji - jest elementem popularyzacji krioablacji (CB) jako metody z wyrobu w leczeniu pacjentów z objawowym migotaniem przedsionków. Porównanie skuteczności oraz powikłań okołozabiegowych ablacji RF oraz CB dodatkowo ugruntowuje pozycję CB jako metody co najmniej równie skutecznej i bezpiecznej jak klasyczna ablacja RF.

Przedstawione w ***Publikacji 2*** wyniki długoterminowej skuteczności PVI wykonywanej metodami pojedynczej aplikacji ukazują daleko satysfakcjonujący efekt CB - eliminację napadów AF w okresie 5-letnim u ponad połowy pacjentów. Obserwowany odsetek istotnych powikłań oraz przede wszystkim brak zgonu przyczynowo związanego z zabiegiem stawia CB w gronie procedur względnie bezpiecznych, szczególnie po wstępnym okresie zbierania doświadczenia przez ośrodek. W artykule dodatkowo po raz pierwszy potwierdzono użyteczność sekwencyjnego wykorzystania dwóch różnych metod ablacji z pojedynczą aplikacją (CB i PVAC) jako metody wyjściowej oraz użytej podczas reablacji.

W badaniu opisanym w ***Publikacji 3*** potwierdzono znaczenie rozmiaru lewego przedsionka oraz typu migotania przedsionków (napadowe/przetrwałe) w aspekcie nawrotu AF po CB. Autorska skala 0-1-2 PL Score - zawierająca tylko te dwa czynniki, posada najwyższą wartość predykcyjną nawrotu AF spośród wszystkich opublikowanych skali, a jej prostota i oparcie o czynniki predykcyjne sprawdzające się we wszystkich ośrodkach umożliwia szerokie zastosowanie kliniczne i być może będzie punktem wyjścia do standaryzacji oceny rokowania w ablacji migotania przedsionków.

Publikacja 4 potwierdziła użyteczność parametrów echokardiograficznych jako czynników predykcyjnych nawrotu AF w grupie pacjentów z napadowym typem arytmii poddanych CB. Potwierdzono związek nawrotu AF z zredukowaną prędkością wypływu z uszka lewego przedsionka oraz obecnością przetrwałego *foramen ovale*. Otrzymane wyniki uzupełniają wiedzą dotyczącą przedzabiegowej stratyfikacji ryzyka długoterminowej nieskuteczności krioablacji balonowej.

Ze względu na rozpowszechnienie migotania przedsionków krioablacja balonowa ujść żył płucnych być może będzie w najbliższych latach najczęściej wykonywaną procedurą elektrofizjologiczną. Dalszy rozwój wiedzy związany z szerokorozumianą tematyką krioablacji balonowej jest więc kluczowy dla ciągłej poprawy rokowania pacjentów poddawanych tym zabiegom.

Cykl publikacji będących podstawą rozprawy doktorskiej:

- potwierdził skuteczność długoterminową i bezpieczeństwo krioablacji balonowej,
- podkreślił znaczenie typowych klasycznych czynników ryzyka w pozabiegowym nawrocie migotania przedsionków - ujętych w autorską skalę O-1-2 PL SCORE,
- dostarczył nowych informacji odnośnie strategii zabiegu (podwójne, sekwencyjne zastosowanie różnych technik 'single-shot') oraz echokardiograficznych parametrów związanych z długoterminową nieskutecznością krioablacji balonowej, które mogą być przydatne w codziennej praktyce klinicznej.

VIII. STRESZCZENIE

Tematyka migotania przedsionków (AF), ze względu na epidemiologię oraz znaczenie kliniczne, pozostaje w ostatnich latach jednym z głównych obiektów zainteresowań zarówno naukowców jak i klinicystów. U podłoża patogenezy AF znajdują się zaburzenia depo- i/lub repolaryzacji - najczęściej w obrębie proksymalnych odcinków żył płucnych (PVs), które skutkują wyzwalaniem salw ektopowych pobudzeń. Powtarzające się bodźcowanie elektryczne lewego przedsionka prowadzi do zawiązywania mnogich pętli reentry, a z czasem do wtórnego remodelingu anatomicznego i elektrycznego powodując utrwalenie się arytmii.

Wprowadzenie zabiegu przezskórnej ablacji ujść PVs umożliwiło wytworzenie izolacji elektrycznej lewego przedsionka. Zabieg wykonany na wczesnym etapie choroby ogranicza remodeling miokardium, a tym samym znacząco zmniejsza prawdopodobieństwo utrwalenia się arytmii. Wraz z rozwojem technologicznym ablacja punktowa w coraz większej ilości ośrodków wypierana jest przez techniki z zastosowaniem pojedynczej aplikacji obejmującej jednoczasowo cały obwód danej żyły - głównie kriobalonów napełnianych ciekłym azotem (CB).

W niniejszej pracy doktorskiej zbadano skuteczność krioablacji balonowej jako preferencyjnej techniki izolacji ujść żył płucnych (PVI), częstość powikłań okołozabiegowych oraz czynniki wpływające na ryzyko nawrotu migotania przedsionków po zabiegu

Celem pierwszej pracy z cyklu było podsumowanie aktualnej wiedzy na temat praktycznych aspektów krioablacji balonowej z przedstawieniem w formie *state of the art*. Szczególną uwagę poświęcono praktycznym aspektom bezpiecznego wykonania CB koncentrując się na technice zabiegu. Najważniejsze informacje zawarte w opracowaniu obejmują:

1) Zbyt szybki spadek temperatury (poniżej −40°C po 30 s) oraz zbyt niska temperatura minimalna (< −56°C) oznacza zbyt głębokie położenie kriobalonu - wymagające przerwania krioaplikacji.

2) Najbardziej wiarygodny punkt końcowy każdej aplikacji mający znaczenie rokownicze dotyczy osiągnięcia izolacji danej żyły płucnej w czasie krótszym niż 40s.

3) Po zakończonej procedurze konieczne jest wykonanie przeglądowego badania echokardiograficznego w celu wykluczenia krwawienia do worka osierdziowego. W razie

obecności niewielkiej ilości płynu / trudnego nakłucia transseptalnego należy podać siarczan protaminy i usunąć założone koszulki naczyniowe.

4) Najważniejszymi klasycznymi czynnikami ryzyka nawrotu migotania przedsionków po PVI są: przetrwały typ migotania przedsionków, powiększenie lewego przedsionka oraz obecność niewydolności serca.

5) PVI wykonywane z zastosowaniem krioablacji balonowej jest co najmniej równie skuteczne i bezpiecznie jak przy użyciu klasycznej punktowej ablacji RF.

Informacje zawarte w artykule stanowią użyteczne klinicznie kompendium - zarówno dla ablacjonistów wykonujących zabiegi izolacji ujść żył płucnych jak również dla lekarzy uczestniczących w kwalifikacji pacjentów do ablacji oraz sprawujących opiekę pozabiegową.

W drugim artykule przedstawiono skuteczność długoterminową PVI wykonywaną w ośrodku, który od początku używa jedynie technik typu *single-shot*. Ponadto oceniono możliwości sekwencyjnego wykorzystania dwóch technik z zastosowaniem pojedynczej aplikacji - kriobalonów i cewników wieloelektrodowych - u pacjentów z nawrotem migotania przedsionków po pierwszym zabiegu. Do badania włączono 597 pacjentów (655 zabiegów ablacji - w tym 58 reablacji z powodu nawrotu AF). Roczny, dwuletni oraz pięcioletni okres bez nawrotu AF po pierwszej PVI zaobserwowano u (odpowiednio): 78.2%, 69.2% oraz 56.0% z 597 pacjentów. Dla reablacji wykonanej z użyciem innej techniki z zastosowaniem pojedynczej aplikacji (w przypadku pierwotnej aplikacji wykonanej z zastosowaniem CB reablacja odbywała się z użyciem PVAC - i odwrotnie; w 2 przypadkach z 58 reablacji użyto dwukrotnie krioablacji) - w 80.3% uzyskano roczny brak nawrotu AF, w 76.1% dwuletni oraz w 68.3% pięcioletni. Powikłania PVI wystąpiły u 12,1% pacjentów - z czego u mniej niż 1/3 klasyfikowane jako poważne - w postaci tamponady (0,84%), udaru (0,17%), porażenia nerwu przeponowego (1,34%) oraz wytworzenia jatrogennego ASD wymagającego interwencji (1,51%). Brak nawrotu AF w okresie 5-letnim u ponad połowy pacjentów pokazuje satysfakcjonujący długoterminowy efekt zabiegu - dodatkowo optymalizowany poprzez wykonaną reablację inną techniką z zastosowaniem pojedynczej aplikacji. Obserwowany odsetek istotnych powikłań oraz przede wszystkim brak zgonu przyczynowo związanego z zabiegiem stawia CB w gronie procedur względnie bezpiecznych, szczególnie po wstępnym okresie zbierania doświadczenia przez ośrodek.

Celem trzeciej pracy było porównanie opublikowanych skali oceniających prawdopodobieństwo nawrotu migotania przedsionków po krioablacji balonowej ujść żył płucnych oraz zaproponowanie nowego użytecznego klinicznie modelu. Do badania włączono 588 pacjentów, u których wykonano PVI jedynie metodą krioablacji balonowej. Za niezależne klasyczne czynniki ryzyka związane z długoterminowym brakiem skuteczności zabiegu, do których zaliczono: wymiar lewego przedsionka (dla każdych kolejnych 10mm: HR = 1,64 (1,30; 2,05), p < 0,001), przetrwały typ AF (HR = 1,86 (1,33; 2,6), p < 0,001), wiek (dla każdych 10 kolejnych lat: HR = 1,24 (1,07; 1,44), p = 0,004) oraz udar w historii medycznej (HR = 1,94 (1,28; 2,95), p = 0,002). W badanej populacji pacjentów po CB porównano skale oceniające ryzyko nawrotu migotania przedsionków: SCALE Cryo-AF, APPLE, CAAP-AF, MB-LATER, $CHADS_2$ and CHA_2DS_2-VASc. Uzyskano najlepszą wartość predykcyjną dla skali SCALE Cryo-AF (C-statistic = 0,602 dla zmiennych jedynie prezabiegowych oraz = 0,638 uwzględniając zmienne pozabiegowe). Z uwagi na złożoność powyższych modeli zaproponowano autorską skalę nawrotu AF **: 0-1-2 PL Score**. Wyróżnia się ona prostotą - zawiera jedynie dwie zmienne: powiększenie **L**ewego przedsionka oraz **P**rzetrwały typ migotania przedsionków; oraz wysoką wartością C-statistic = 0,617 przy uwzględnieniu jedynie czynników prezabiegowych. Stworzona skala klasyfikuje pacjentów do grup niskiego (0 punktów), pośredniego (1 punkt) oraz wysokiego (2 punkty) ryzyka nawrotu AF. Uzyskana punktacja związana jest z 21% (0 punktów), 37% (1 punkt) lub 55% (2 punkty) 2-letnim ryzykiem pozabiegowego nawrotu AF. Łatwość zastosowania oraz podkreślenie najważniejszych czynników wpływających na rokowanie pacjenta dotyczące nawrotu AF po CB umożliwia rzeczywiste zastosowanie kliniczne zaproponowanej skali.

W ostatniej pracy z cyklu przenalizowano przedzabiegowe badania echokardiograficzne pacjentów (przezklatkowe oraz przezprzełykowe) w aspekcie identyfikacji parametrów mających związek z nawrotem napadów migotania przedsionków po krioablacji balonowej ujść żył płucnych. Do badania włączono 417 pacjentów jedynie z napadowym typem arytmii, u których PVI wykonana była przy użyciu drugiej generacji kriobalonów. W analizie wieloczynnikowej regresji logistycznej ustalono związek nawrotu AF z powiększeniem lewego przedsionka >40 mm (HR = 1.88 (1.23; 2.87), p = 0.004), obecnością przetrwałego drożnego *foramen ovale* (PFO) (HR = 1.79 (1.02; 3.15), p = 0.04) oraz prędkością wypływu z uszka lewego przedsionka <45cm/s (HR = 1.63 (1.06; 2.49), p = 0.02). Związek z PFO z nawrotem

AF po CB został opisany w literaturze po raz pierwszy; zależność z prędkością wypływu z uszka lewego przedsionka przedstawiona została dotychczas jedynie w jednym niewielkim badaniu. Otrzymane wyniki uzupełniają wiedzą dotyczącą przedzabiegowej stratyfikacji ryzyka długoterminowej nieskuteczności krioablacji balonowej.

Cykl publikacji będących podstawą rozprawy doktorskiej potwierdził skuteczność długoterminową i bezpieczeństwo krioablacji balonowej. Otrzymane rezultaty podkreśliły znaczenie typowych klasycznych czynników ryzyka w pozabiegowym nawrocie migotania przedsionków, jak również dostarczył nowych informacji odnośnie echokardiograficznych parametrów związanych z długoterminową nieskutecznością krioablacji balonowej, które mogą być przydatne w codziennej praktyce klinicznej.

IX. SUMMARY

The topic of atrial fibrillation (AF), due to its epidemiology and clinical significance, has remained one of the main subjects of interest for both scientists and clinicians in recent years. The pathogenesis of AF is based on depo- and / or repolarization disorders - most often in the proximal parts of pulmonary veins (PVs), what leads to release of ectopic beats/bursts. Repeated electrical stimulation of the left atrium leads to creation of multiple reentry loops, and over time to secondary anatomical and electrical remodeling, causing the arrhythmia to persist.

The introduction of percutaneous ablation of the PVs ostia made it possible to create electrical insulation of the left atrium. The procedure performed at an early stage of the disease reduces the remodeling of the myocardium, and thus significantly reduces the probability of arrhythmia persistence. With technological development, point RF ablation in more centres is being replaced by techniques with the use of a single application covering the entire circumference of a chosen vein at the same time - mainly cryoballons filled with liquid nitrogen (CB).

In this PhD thesis, the effectiveness of cryoballoon ablation as a preferential technique of isolation of the pulmonary vein ostia (PVI), the incidence of periprocedural complications and factors influencing the risk of recurrence of atrial fibrillation after procedure were investigated.

The aim of the first study in the series was to summarize the current knowledge on balloon cryoablation with the presentation of the local *state of the art*. Particular attention was paid to the practical aspects of safe CB performance, focusing on the technique of the procedure. The most important information contained in the study includes:

1) Too rapid temperature drop (below −40°C after 30 s) and too low minimum temperature (< −56°C) means too deeper position of the cryoballon and requires interruption of the cryoapplication.

2) The most reliable endpoint of any application with prognostic significance is achieving isolation of a chosen pulmonary vein in less than 40 seconds.

3) After the procedure is completed, it is necessary to perform a review echocardiographic examination to exclude bleeding into the pericardium. In the event of a small amount of fluid / difficult transseptal puncture, ones should administer protamine sulphate and remove the vascular sheaths.

4) The most important classical risk factors for recurrent of atrial fibrillation after PVI are persistent atrial fibrillation, left atrial enlargement and the presence of heart failure.

5) PVI performed with cryoballoon ablation is at least as effective and safe as with classical point RF ablation.

The information contained in the article is a clinically useful compendium - both for ablationists who perform PVI procedures as well as for physicians participating in the qualification of patients for ablation and providing postoperative care.

The second article presents the long-term efficacy of PVI performed in a centre that uses only single-application techniques from the beginning. In addition, the possibility of sequential use of two single-application techniques - cryoballons and multi-electrode catheters - in patients with recurrence of atrial fibrillation after first PVI was assessed. The study included 597 patients (655 ablations - including 58 reablations due to recurrent AF). One-year, two-years, and five-years AF-free periods after the first PVI were observed in 78.2%, 69.2% and 56.0% of 597 patients, respectively. For reablation performed using a different single-application technique (in the case of the index application performed with the use of CB, reablation was performed with the use of PVAC - and vice versa; in 2 of 58 reablations, cryoablation was used twice) - in 80.3% patients there was a 1-year AF-free period, in 76.1% two-year and 68.3% five-year. Complications of PVI occurred in 12.1% of patients - less than 1/3 classified as serious - tamponade (0.84%), stroke (0.17%), phrenic nerve palsy (1.34%) and iatrogenic ASD requiring intervention (1.51%). The lack of recurrence of AF in a 5-year period in more than half of the patients shows a satisfactory long-term effect of the procedure - additionally optimized by reablation with another single-application technique. The observed percentage of significant complications and, above all, no death caused by the procedure, places CB among the relatively safe procedures, especially after the initial period of collecting experience by the centre.

The aim of the third study was to compare the published scales assessing the probability of atrial fibrillation recurrence after cryoablation and to propose a new clinically useful model. The study included 588 patients who had PVI performed only by cryoballoon ablation. The following classic risk factors related to the long-term ineffectiveness of the procedure were confirmed: the size of the left atrium (for each 10 mm: HR = 1.64 (1.30; 2.05), $p < 0.001$), persistent AF type (HR = 1.86 (1.33; 2.6), $p < 0.001$), age (for each 10 years: HR = 1.24 (1.07; 1.44), $p = 0.004$) and history of stroke (HR = 1.94 (1.28; 2.95), $p = 0.002$). In the studied population of patients after CB, the following scales assessing the risk of atrial fibrillation were compared: SCALE Cryo-AF, APPLE, CAAP-AF, MB-LATER, CHADS2 and CHA2DS2-VASc. The best predictive value was obtained for the SCALE Cryo-AF scale (C-statistic = 0.602 for only pre-ablation variables and = 0.638 for whole, also post-procedure variables). Due to the complexity of all above models, the new scale was proposed: 0-1-2 PL Score. It is distinguished by its simplicity - it contains only two variables: **L**eft atrium enlargement and **P**ersistent atrial fibrillation; and relatively high value of C-statistic = 0.617, based on only the pre-ablation factors. The developed scale classifies patients into the groups of low (0 points), intermediate (1 point) and high (2 points) risk of AF recurrence. The score obtained is associated with a 21% (0 points), 37% (1 point) or 55% (2 points) 2-years risk of post-ablation AF recurrence. The ease of use and highlighting the most important factors influencing the patient's prognosis regarding recurrence of AF after CB enables the real clinical application of the proposed scale.

In the last work of the series, pre-ablation patients' echocardiographic examinations (transthoracic and transesophageal) were analyzed in the aspect of identifying parameters related to the recurrence of atrial fibrillation after cryoballoon ablation. The study included 417 patients with only paroxysmal type of arrhythmia, in which PVI was performed using the second generation of cryoballoons. In multivariate logistic regression analysis, we found the relationship between AF recurrence and: left atrial enlargement > 40 mm (HR = 1.88 (1.23; 2.87), $p = 0.004$), presence of persistent patent foramen ovale (PFO) (HR = 1.79 (1.02; 3.15), $p = 0.04$) and the rate of the left atrial appendage emptying flow velocity <45 cm/s (HR = 1.63 (1.06; 2.49), $p = 0.02$). The association of PFO with AF recurrence after CB has been described for the first time in the literature; the relationship with the rate of the left atrial appendage emptying flow velocity has so far been presented only in one small study. The obtained results complement the knowledge concerning the pre-ablation risk stratification of long-term ineffectiveness of cryoballoon ablation.

The series of publications being the basis of the PhD dissertation confirmed the long-term effectiveness and safety of cryoballoon ablation. The obtained results emphasized the importance of typical risk factors in post-ablation atrial fibrillation recurrence, as well as provided new information on echocardiographic parameters related to long-term ineffectiveness of cryoballoon ablation, which may be useful in clinical practice.

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XI. OŚWIADCZENIA WSPÓŁAUTORÓW

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- opracowaniu koncepcji badania
- współuczestnictwie w opracowaniu i analizie wyników
- przygotowaniu manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Grzegorza Kiełbasa jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Grzegorza Kiełbasa polegający na:

- współudziale w zaplanowaniu badania
- przygotowaniu baz zawierających niezbędne dane
- przeglądzie aktualnej literatury
- opracowaniu i analizie wyników
- przygotowaniu manuskryptu pracy

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- współudziale w zaplanowaniu badania
- przygotowaniu baz zawierających niezbędne dane
- przeglądzie aktualnej literatury
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- współuczestnictwie w opracowaniu i analizie wyników
- współprzygotowaniu manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Grzegorza Kiełbasa jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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- współudziale w przygotowaniu baz zawierających niezbędne dane
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- współuczestnictwie w przeprowadzaniu analizy statystycznej
- opracowaniu i analizie wyników
- przygotowaniu manuskryptu pracy

Aleksander Kusiak
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Kraków, 03.06.2021

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OŚWIADCZENIE

Jako współautor pracy:

Jastrzębski M, Kiełbasa G, Fijorek K, Bednarski A, Kusiak A, Sondej T, Bednarek A, Wojciechowska W, Rajzer M. Comparison of six risk scores for the prediction of atrial fibrillation recurrence after cryoballoon-based ablation and development of a simplified method, the 0-1-2 PL score. Journal of Arrhythmia. 2021.

oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji wynosi 5 % i polegał na:

- współuczestnictwie w opracowaniu i analizie wyników
- współprzygotowaniu manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Grzegorza Kiełbasa jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Grzegorza Kiełbasa polegający na:

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- zaplanowaniu badania
- opracowaniu i analizie wyników
- przygotowaniu manuskryptu pracy

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- współuczestnictwie w opracowaniu i analizie wyników
- współprzygotowaniu manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie w/w pracy przez lek. Grzegorza Kiełbasa jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Oświadczam, iż samodzielna i możliwa do wyodrębnienia część ww. pracy wykazuje indywidualny wkład lek. Grzegorza Kiełbasa polegający na:

- współudziale w zaplanowaniu badania
- przygotowaniu baz zawierających niezbędne dane
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- opracowaniu i analizie wyników
- przygotowaniu manuskryptu pracy

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- współudziale w przygotowaniu baz zawierających niezbędne dane
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- redakcji przygotowanego manuskryptu

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- przygotowaniu manuskryptu pracy

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- stworzeniu hipotezy badawczej
- opracowaniu koncepcji badań
- współuczestnictwie w opracowaniu i analizie wyników
- przygotowaniu manuskryptu

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- współudziale w zaplanowaniu badania
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- współuczestnictwie w przeprowadzaniu analizy statystycznej
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Grzegorz Kiełbasa
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