ORIGINAL SCIENTIFIC PAPER (ZNANSTVENI RAD)

Pulmonary vein isolation by cryoablation on patients with paroxysmal atrial fibrillation

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Abstract

Aim: Atrial fibrillation is just one of many arrhythmias that affects the cardiac rhythm and the heart as a pump which consequently increases the chance of an embolic insult. Due to the electric stimuli that originate from pulmonary vein ostia and their lumen, an isolation procedure is initiated, mostly by cryoablation. The main goals of this study were to investigate the relationship between measured nadir temperatures during cryoablation of each individual pulmonary vein and to compare the success of first-time cryoablation between left and right pulmonary veins.

Participants and methods: The study involved 40 participants who underwent pulmonary vein isolation by cryoablation due to paroxysmal atrial fibrillation, irrespective of gender and age. The procedures were carried out throughout the year 2022 at the University Hospital Centre Zagreb, where the data were collected. All necessary patient data were permanently recorded and saved in a separate cryoconsole used to dictate the entire procedure.

Results: Given the 40 participants in the study, a total of 160 pulmonary veins were analyzed. The t-test shows that the left upper pulmonary vein was the most advantageous vein to isolate, and the lower right pulmonary vein was the least advantageous. p-value analysis has also shown significant differences between left and right pulmonary veins, with that difference being lower in value between the left-sided pulmonary veins. Additionally, the chi-squared test confirmed a statistically significant difference between successful cryoablations of left-sided and right-sided pulmonary veins. This has shown that the left-sided pulmonary veins are easier to isolate on first cryoablation, rather than their right-sided counterparts.

Conclusion: Pulmonary vein isolation by cryoablation is an excellent proof of incorporating fundamental physical principles in medicinal purposes. This study keeps the doors open for further research into optimal approaches in atrial fibrillation treatment. Therefore, comparing our study with recent publications and literature suggests higher success in isolating left pulmonary veins compared to right pulmonary veins.

Keywords: atrial fibrillation; pulmonary vein isolation; cryoablation

Introduction

Atrial fibrillation (AF) is one of the supraventricular tachyarrhythmias characterized by uncoordinated and irregular electrical stimulations which lead to disorganized contractions of the atrium (1). Such arrhythmia poses a significant risk due to the possibility of atrial thrombi formulation, greatly increasing the risk of embolic stroke (2, 3). It is believed that one of the main causes of this cardiac behavior is the abnormal functioning of ectopic foci emitting strong enough electrical impulses that the impulses from the sinoatrial node cannot suppress (3). Such ectopic foci are found in the highest concentration at the junction of the pulmonary veins and the left atrium (4, 5). Namely, the four pulmonary veins that enter the left atrium are made up of several layers; an outer, a middle, and an inner layer.

An exception to this standard structure is a thin layer of endocardium that penetrates the interior of the pulmonary vein even up to several centimeters deep (4, 5). Therefore, the choice of treatment method is the isolation of pulmonary veins through electrophysiological procedures, including cryoablation. Cryoablation involves a procedure in which the tissue of the pulmonary veins is electrically isolated through a cryogenic agent (6). This isolation is achieved by introducing a balloon cryocatheter through the orifice of the pulmonary vein which then changes the tissue due to the action of the cryogenic agent. One of the most crucial steps in cryoablation isolation is adequate occlusion of the pulmonary vein with a balloon cryocatheter, which serves as an indicator of successful isolation (7).

Participants and methods

The study involved 40 patients of various ages who underwent pulmonary vein isolation by cryoablation due to paroxysmal AF. The procedure was performed at University Hospital Centre Zagreb using exclusively the cryoablation system from Boston Scientific during the year 2022. Data were collected using the SMARTFREEZE console from Boston Scientific and analyzed retrospectively. Data on the number of performed cryoablations, pulmonary vein, duration of each cryoablation, minimum cryoablation temperature, time required for isolation according to the cryoconsole recommendation and actual time of cryoablation per vein were collected. Obtained data were analyzed using *Microsoft Excel* and *StatSoft Statistica* softwares and were encrypted for confidentiality. The measured temperature values of each pulmonary vein were compared to the measured temperature values of the other pulmonary veins using a t-test. The difference between the success of isolating left-sided pulmonary veins (LPV) compared to right-sided pulmonary veins (RPV), considering the number of cryoablations required for acute isolation was tested using a chi-square test. All tests were performed at a significance level of $p<0,05$.

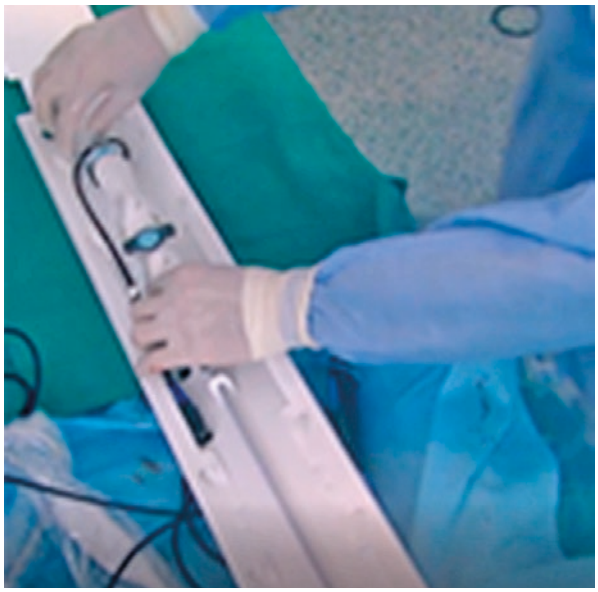

Figure 1. POLARx balloon cryocatheter; credit: adapted from "POLARx Procedure Guide" by Boston Scientific

Results

Arithmetic means of nadir temperatures of left superior pulmonary vein (LSPV), left inferior pulmonary vein (LIPV), right superior pulmonary vein (RSPV) and right inferior pulmonary vein (RIPV) are given in Table 1.

Table 1. Arithmetic means of nadir temperatures for LSPV, LIPV, RSPV, and RIPV in patients undergoing cryoablation at the University Hospital Centre Zagreb during the year 2022.

Pulmonary vein	LSPV	LIPV	RSPV	RIPV
Arithmetic mean	-57,25℃	-55,325℃	-52,05℃	-50,93℃

Data on the achieved nadir temperatures of the pulmonary veins were tested using a t-test which resulted in p-values, thus indicating the statistically significant differences.

LSPV, when compared to all other pulmonary veins, demonstrated the best p-value results, where each comparison of nadir temperatures showed a statistically significant difference between LSPV and the other pulmonary veins. The greatest difference in p-values with LSPV was observed with the RIPV, which was expected, considering that the approach to LSPV is the simplest of all pulmonary veins, while RIPV is the most challenging.

Table 2. p-values obtained by comparing nadir temperatures of LSPV with nadir temperatures of the remaining pulmonary veins (LIPV, RSPV and RIPV) in patients undergoing cryoablation at the University Hospital Centre Zagreb during the year 2022.

	LSPV
LIPV	p=0,03109
RSPV	p=0,00171
RIPV	p<0,001

By comparing the data, the p-values obtained between LIPV and other pulmonary veins indicate a statistically significant difference in achieving the desired temperatures among the compared pulmonary veins. Once again, the greatest statistically significant difference with LIPV is shown with RIPV.

Table 3. p-values obtained by comparing nadir temperatures of LIPV with nadir temperatures of the remaining pulmonary veins (LSPV, RSPV and RIPV) in patients undergoing cryoablation at the University Hospital Centre Zagreb during the year 2022.

	LIPV
LSPV	p=0,03109
RSPV	p=0,03851
RIPV	p=0,00505

Comparing the data of the RSPV with LSPV shows that LSPV remains superior, and there is a significant difference between the two pulmonary veins. However, the p-value between RSPV and LIPV is higher than that of the RSPV and LSPV, despite the former being diagonal to each other. As for the relationship between RSPV and RIPV, it is immediately noticeable that there is no statistically significant difference between these two pulmonary veins.

Table 4. p-values obtained by comparing nadir temperatures of RSPV with nadir temperatures of the remaining pulmonary veins (LSPV, LIPV and RIPV) in patients undergoing cryoablation at the University Hospital Centre Zagreb during the year 2022.

	RSPV
LSPV	p=0,00171
LIPV	p=0,03851
RIPV	p=0,57418

The mean temperature obtained for RIPV is the highest compared to other pulmonary veins. All comparisons with this pulmonary vein show great differences. However, the greatest difference is between the two diagonal values, i.e. LSPV and RIPV.

Table 5. p-values obtained by comparing nadir temperatures of RIPV with nadir temperatures of the remaining pulmonary veins (LSPV, LIPV and RSPV) in patients undergoing cryoablation at the University Hospital Centre Zagreb during the year 2022.

	RIPV
LSPV	p<0,001
LIPV	p=0,00505
RSPV	p=0,57418

We aimed to assess the quality of pulmonary vein cryoablation based on the mean values of achieved nadir temperatures. Better occlusion of the pulmonary vein with a balloon cryocatheter generally indicates lower achieved nadir temperature values, and thus better isolation. However, the tested difference between the success of isolating left-sided pulmonary veins (LPV) compared to right-sided pulmonary veins (RPV), considering the number of cryoablations required for acute isolation, shows a significant difference.

For this analysis, a chi-square test was used. The contigency table with observed frequencies is given in Table 6.

Figure 2. SMARTFREEZE console; credit: adapted from "POLARx Procedure Guide" by Boston Scientific

Figure 3. starting interface of the cryoconsole; credit: adapted from "POLARx Procedure Guide" by Boston Scientific

Table 6. Contingency table of observed frequencies in patients undergoing cryoablation at the University Hospital Centre Zagreb during 2022. The row „LPV" denotes left pulmonary veins, and the row „RPV" denotes right pulmonary veins. The column „+" indicates isolations achieved with the first cryoablation, while the column „-" indicates isolations achieved with multiple cryoablations.

Observed frequency	+	-	Σ
LPV	62 (78%)	18	80
RPV	35 (44%)	45	80
Σ	97	63	160

In Table 6, the number of pulmonary veins isolated by the first cryoablation is presented. Based solely on the observed frequencies, a difference between LPV and RPV can be noticed. The expected results favored LPV due to easier accessibility and smoother placement of the balloon cryocatheter in the LPV lumen, where its task can be performed almost unhindered.

By conducting the chi-square test with observed and expeBy conducting the chi-square test with observed and expected frequencies in the given program, a p-value was obtained (p<0,001), indicating a statistically significant difference in the success of LPV and RPV cryoablations at a significance level of p<0,05.

Discussion and conclusions

Our study aimed to assess the quality of pulmonary vein cryoablation based on the mean values of achieved nadir temperatures by the usage of POLARx cryoballoon. The mean values of nadir temperatures for the respective pulmonary veins are as follows: LSPV achieved the lowest average temperature of all pulmonary veins at -57.25°C; LIPV had a slightly higher average temperature of -55.325°C; RSPV reached values of -52.05°C; RIPV achieved the highest average temperature at -50.93°C.

Comparing the results of our study with the meta-analysis results of Assaf A et al. (9), the following conclusions can be drawn. Their data analysis yielded the following mean values of nadir temperatures: LSPV had a mean value of -59.7°C; LIPV reached the highest value at -55.3°C; RSPV had a lower average temperature than LIPV at -58.7°C; while RIPV achieved nearly identical value to RSPV at -58.5°C. There is evidently a difference between

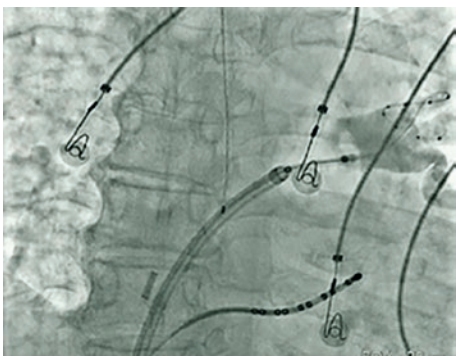

Figure 4. Fluoroscopy of contrast agent injection through the balloon cryocatheter; credit: adapted from "POLARx Procedure Guide" by Boston Scientific

the mean values of nadir temperatures of pulmonary veins in our study and the study by Assaf A et al. However, while in our study there is no statistically significant difference except between RSPV and RIPV, in the study by Assaf A et al., the results are different. By testing their mean values of nadir temperatures, it can be concluded that there is a statistically significant difference only between LIPV and the other pulmonary veins.

While the mean values of nadir temperatures differ between our study and the study by Assaf A et al., this difference decreases concerning the total number of cryoablations. In our study, the mean number of cryoablations for each pulmonary vein was obtained, and subsequently, they were divided into the mean numbers of cryoablations for the left and right sides. Processing the data included in our study yielded the result that LIPV was isolated by the first cryoablation in 92.5% of cases, while LSPV was isolated by the first cryoablation in only 63% of cases. It was expected that the number of cryoablations would be lower for LSPV compared to LIPV because minimal angulation is needed to reach LSPV with the balloon cryocatheter. On the other hand, RSPV was isolated by the first cryoablation in 40% of cases, and RIPV in 50% of cases. Assaf A et al. state in their study that LIPV was isolated by the first cryoablation in 85% of cases, and LSPV in 72% of cases. RSPV was successfully isolated by the first cryoablation in 68% of cases, and RIPV in 70% of cases. Our study and the study by Assaf A et al. completely agree in terms of the number of isolations achieved by the first cryoablation, with the highest number of isolations favoring LIPV and the lowest favoring RSPV.

However, the main goal of our study was to compare the success of isolation by the first or multiple cryoablations between left-sided pulmonary veins (LPV) and right-sided pulmonary veins (RPV). Our study shows that isolation by the first cryoablation was achieved in 78% of cases for LPV. For RPV, a poorer result was expected and obtained, with only 44% of isolations achieved by the first cryoablation. On the other hand, Assaf A et al. compared the results of multiple authors and publications in their meta-analysis. Based on their collected data, it was found that isolation of LPV by the first cryoablation was achieved in 79% of cases, while for RPV, isolation by the first cryoablation was achieved in 69% of cases.

Assaf A et al. have been comparing two different systems in their meta-analysis. Comparison has been made between the POLARx balloon cryocatheter created by Boston Scientific and the Arctic Front Advance Pro balloon cryocatheter (AFA-Pro) created by Medtronic. A similar study (10) has been conducted by Yap SC et al. The aim of their study was to compare the procedural efficacy and biophysical parameters between the two cryoballoon technologies. In the study of Yap SC et al., it is explained that the POLARx cryoballoon has some modifications to their balloon construction which theoretically improves the occlusion of pulmonary veins, supervision of nadir balloon temperature and balloon thawing time.

Yap SC et al. in their results show that patients who underwent pulmonary vein isolation with POLARx cryoballoon (n=57) had longer procedure time (average 81 min) and balloon-in-body time (average 51 min). In their study, total duration of all cryoballoon ablations performed with POLARx was 995s, and with AFA-Pro (n=53) was 912s. POLARx average in LSPV isolation was 209s and 180s for LIPV. On the other hand, RSPV averaged with 240s and RIPV with

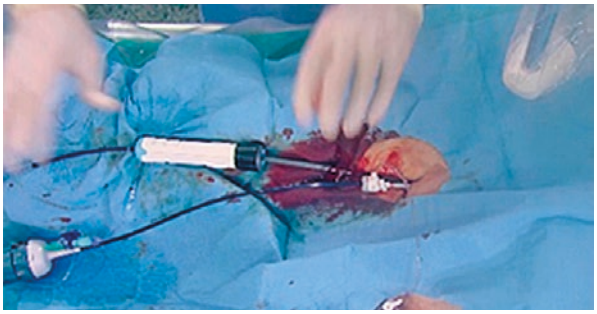

Figure 5. Balloon cryocatheter while the balloon is frozen; credit: adapted from "POLARx Procedure Guide" by Boston Scientific

180s. The protocol usage is mostly defined by the TTI (time to isolation) approximated by the systems in use, depending on the quality of the achieved occlusion. Standard protocols are 180s-long or 240s-long cryoablations if TTI is shorter or longer than 60s. LSPV and RSPV took the longest time for achieving acute isolation, with an important sidenote that 12 (23.1%) of the 57 patients had an anatomical variation to their LPVs (common ostium). Cryoablation with POLARx was also associated with lower nadir temperatures (-55°C) and longer thawing time (16s) in all groups.

In conclusion, our study did not successfully demonstrate a statistically significant difference between all pulmonary veins. Specifically, there is no statistically significant difference between RSPV and RIPV, while that difference has been proven in all other comparisons. However, RSPV seems to be of the highest issue in other studies. On the other hand, the results proved that there is a statistically significant difference in the number of isolations achieved by the first or additional cryoablations between LPV and RPV. ■

References

1. P. Kirchhof, S. Benussi et al.; ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS (2016.); *European Heart Journal*, 37 (38), 2893-2962
2. Michaud GF, Stevenson WG. Atrial Fibrillation. N Engl J Med. 2021; 384:353-361
3. Krmpotić-Nemanić J, Marušić A. i sur.; 2. obnovljeno izd.; Zagreb: Medicinska naklada; 2004. XIV, 664 str.
4. Radaković I. Strategije i tehnike pri ablaciji fibrilacije atrija; diplomski rad; Rijeka: Sveučilište u Rijeci, Medicinski fakultet; 2022.
5. Weiss C, Gocht A, Willems S, Hoffmann M, Risius T, Meinertz T. Impact of the distribution and structure of myocardium in the pulmonary veins for radiofrequency ablation of atrial fibrillation. Pacing Clin Electrophysiol. 2002; 25(9): 1352–1356.
6. Stručić F. Podjela i liječenje različitih oblika supraventrikulske tahikardije; Zagreb: Sveučilište u Zagrebu, Medicinski fakultet; 2017.
7. Jin ES, Wang PJ. Cryoballoon Ablation for Atrial Fibrillation: a Comprehensive Review and Practice Guide. Korean Circ J. 2018; 48(2):114-123
8. Issa ZF, Miller JM, Zipes DP. Clinical Arrhythmology and Electrophysiology: A Companion to Braunwald's Heart Disease. 2nd ed. Philadelphia, PA: Saunders, an imprint of Elsevier Inc; 2012; 336-337
9. Assaf A, Bhagwandien RE, Szili-Torok T, Yap SC. Comparison of the acute outcome of two cryoballoon technologies for pulmonary vein isolation: An updated systematic review and meta-analysis. IJC Heart & Vasculature. 2022; 42:101115
10. Yap SC, Anic A, Breskovic T, et al. Comparison of procedural efficacy and biophysical parameters between two competing cryoballoon technologies for pulmonary vein isolation: Insights from an initial multicenter experience. J Cardiovasc Electrophysiol. 2021;32(3):580-587.