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ATRIAL FIBRILLATION ABLATION USING SECOND-GENERATION CRYOBALLOON. CRYOBALLOON ABLATION

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Abstract

Present study aimed to estimate pulmonary veins ostia cryoablation method and patient treatment results with atrial fibrillation using cryotechnologies, to evaluate the effectiveness of pulmonary vein isolation using cryoablation method and results of atrial fibrillation treatment using cryotechnology in two patient groups with persistent and paroxysmal atrial fibrillation.

Prospective observational cohort study was conducted in National Scientific Center of Surgery after A.N. Syzganov. Totally 240 patients with tachysystolic atrial fibrillation resistance to antiarrhythmic therapy were included in the study. Invasive electrophysiological study and 240 cryoablation interventions were conducted. In this study, the average number of cryoactivities in one pulmonary vein was 1.5±0.5, and the total average number of cryoapplications was 6±2 per patient. Total duration of cryoablation reached 24.8±12.6 min. Every three months, a Holter electrocardiogram was conducted to evaluate freedom from arrhythmias and unscheduled electrocardiogram was performed when suspicious arrhythmia symptoms appeared upon Holter monitor.

Paroxysmal atrial fibrillation was diagnosed in 155 patients; persistent atrial fibrillation - in 85 patients. Repeat left atrium catheter ablation through left atrium linear radiofrequency ablation was performed in the case of clinical manifestations of recurrent atrial fibrillation refractory to antiarrhythmic therapy.

Pulmonary vein catheter isolation using second-generation cryoballoon is a promising method for treating atrial fibrillation, which simplifies ablation in the left atrium. The use of technology makes it possible to achieve 96% left atrium acute electrical isolation.

Keywords. cryoablation, cryoballoon, catheter ablation, atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common type of heart rhythm disorder. It affects 0.5% of the population, and 5% - over the age of 65 years [*Miyasaka Y et al., 2006*]. AF is accompanied by thromboembolism, the development of arrhythmogenic cardiomyopathy, and increased mortality with heart failure [*Lip G 2010]* The most frequently used drugs to rhythm control in AF patients are class I and III antiarrhythmics; unfortunately, they maintain sinus rhythm in only 40% to 50% of patients with persistent AF at 12- to 24-months follow-up [*Calkins H et al., 2012*].

At the end of the 1990's, the concept of trigger factors elimination was introduced, so-called isolation of ectopic areas in pulmonary veins ostia (PVO) by radiofrequency ablation (RFA), which along with the new methods of left atrium (LA) linear RFA, helped to address paroxysmal and persistent AF [*Haissaguerre M et al., 1998*].

Many randomized trials demonstrated the advantage of catheter ablation over drug therapy in sinus rhythm maintenance in patients with AF; according to two trials, 65% to 85% of patients are free from recurrent arrhythmia after ablation

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[*Pappone C et al., 2006; Stabile G et al., 2006*]. However radiofrequency energy has side effects: thrombogenicity, formation of left atrium (LA) and PVO heterogeneity structure lesions, RF energy high-penetrating ability, postablative incisional tachycardia, atrial-esophageal fistulas, and stenoses of PVO [*Rodriguez L et al., 1998*]. Moreover, LA catheter RFA is complex and lengthy, based on sequential applications "point by point" to create solid fault lines [*Haissaguerre M et al., 2004; Stabile G et al., 2006*].

During the last 10 years, cryotechnology has been used extensively in catheter ablation of cardiac arrhythmias. One such technique is catheter ablation with cryoballoon; the point is to achieve PVO electric isolation in a single application. By using an inflatable balloon completely adjacent to PVO, the method simplifies the procedure and achieves PVO isolation instantly [*Van Belle Y et al., 2008*]. In practice, tissue freezing is used to create PVO circular damage. Intracellular ice formation with subsequent thawing causes reliable and safer damage than radiofrequency [*Mikhaylov E et al., 2009*].

The purpose of this work is an assessment of PV isolation using cryoablation method and results of atrial fibrillation treatment using cryotechnology in patients with persistent and paroxysmal AF. Results evaluated PVO electric isolation using second-generation cryoballoon and absence of persistent AF (more than 30 *sec*) in the early postoperative period (6 to 18 *months*).

Material and methods

Prospective observational cohort study was conducted at the period 2014-2017, in the interventional cardiology, arrhythmology, and endovascular surgery department among 240 patients (142 men and 95 women) with tachysystolic AF resistant to antiarrhythmic therapy, whom underwent invasive electrophysiological study (EPS) and cryoablation procedure using cryoballoon catheter second-generation (Arctic Front Advanse, Medtronic). Data were collected prospectively in the Institutional AF Registry. The study protocol was approved by our Institutional Local Research Ethics Committee [June 26, 2016]. All participants in the study received informed consent.

Preoperative procedures: Paroxysmal AF was diagnosed in 155 patients, persistent AF – in 85. Seventy-six patients manifested type I atrial flutter on electrocardiogram (ECG), and 11 patients with AF combined with Wolff–Parkinson–White syndrome and atrioventricular nodal reentrant tachycardia. Antiarrhythmic drug administration was canceled 48 to 72 hours before electrophysiological study (amiodarone was canceled 45 days before procedure). All patients were examined to exclude thrombosis of left atrium appendage – perioperative transesophageal echocardiography was conducted. In 85% of patients, multi-spiral computed tomography was done to study topographic anatomy and size of LA (Fig 1).

All patients were taking anticoagulants for 4 weeks before and 3 months after the procedure under monitoring of international normalized ratio (2.0-3.0). In 225 patients, all 4 pulmonary veins (PVs) were completely isolated; in 14 patients - 3 PVs, in 1–2 left PVs because of phrenic nerve palsy during right inferior PV cryoablation. They further underwent standard RFA. In 76 patients with type I atrial flutter, impulse holding bidirectional block in the cavo tricuspid isthmus of the heart was created.

Operative procedures: In all patients, three standard punctures were performed: one, through the

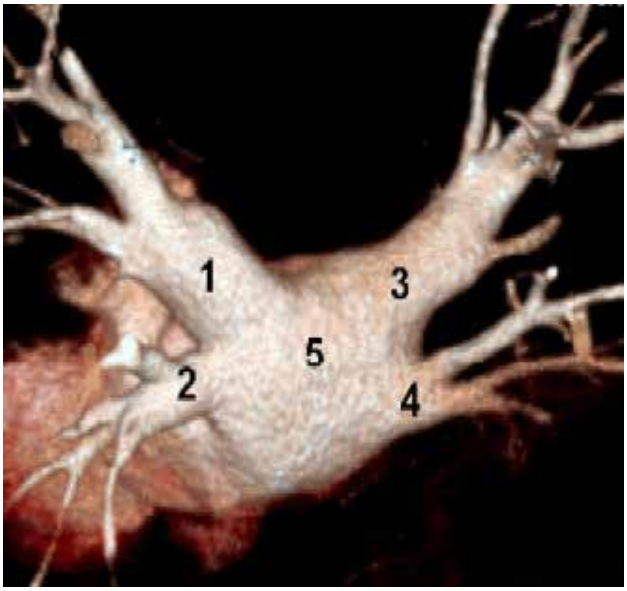

Figure 1. Left atrium and pulmonary veins multispiral computed tomographic (rear view). 1-LSPV, 2 – LIPV, 3- RSPL, 4- RIPV, 5- posterior wall of the left atrium. (LSPV - left superior pulmonary vein; LIPV – left inferior pulmonary vein; RSPV – right superior pulmonary vein; RIPV - right inferior pulmonary vein)

left subclavian and two through the right femoral veins to thread the catheters for cryoballoon ablation. A decapolar electrode was introduced through the left subclavian vein to the coronary sinus. If impracticable, lower access was used through the femoral vein. Transseptal puncture was used to enter the LA through the right atrium (RA), according to standard procedure under fluoroscopic guidance through right femoral vein puncture. Immediately after transseptal puncture, heparin was injected 0.5 *mg per kg* body weight intravenously with subsequent titration to maintain the ACT at >300 *sec*. level. Then, an 8 Fr transseptal puncture introducer was replaced by a 14 Fr cryoballoon delivery catheter. Second-generation cryoballoon set includes Achieve 8-pole mapping catheter, which is delivered to the LA through the inner shaft of the cryoballoon. One more four-pole diagnostic electrode was introduced through the right femoral vein puncture into the right ventricle to pace the RV to control the vasovagal response (bradycardia). That same catheter was placed in the vena cava superior during ablation in the right PVs for phrenic nerve pacing. The Achieve catheter was introduced through the cryoballoon inner shaft; it was placed successively to all PVs to document initial PV electrical potentials and to control PVO electrical isolation during ablation. (Fig. 2).

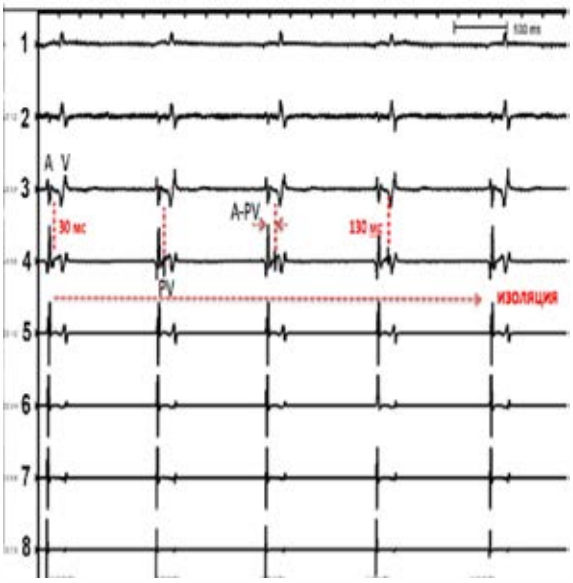

Figure 2. *ECG and endogram record during cryoablation of the pulmonary veins. 1- surface ECG (lead II), endogram: 2-4 the achieve mapping catheter (LS 2-8), 5-8 coronary sinus diagnostic electrode; Potentials: Atriums, Ventricles, PV. A gradual reduction of PV potentials and their complete disappearance has been demonstrated, as PV isolation from LV is achieved. (ECG - electrocardiogram, PV - pulmonary veins, LV – left ventricle)*

Then, the Achieve catheter was placed at one of the largest PV branches. The cryoballoon catheter was conducted so that the distal part was in the ostium of the pulmonary vein. A 28 *mm* diameter balloon was inflated and at the same time pushed towards the PV. The contrast agent was injected through the catheter lume. Once the PV lumen occlusion was achieved, the contrast media was seen to stagnate in the lumen without leaking back to the LA cavity. (Fig. 3).

If the contrast medium was found to leak to the LA past the balloon, the vein obturation was considered incomplete, and the balloon would be repositioned. The ablation started by feeding the cooling agent into the balloon, reaching a temperature of -37 to -60°C. (Fig. 4).

Every application lasted 240 *sec*. After the application was finished, the filling of cooling agents would be discontinued and the balloon deflated. If temperature exceeded 60°C, the filling of cooling agents was stopped; in one vein, the filling was re-

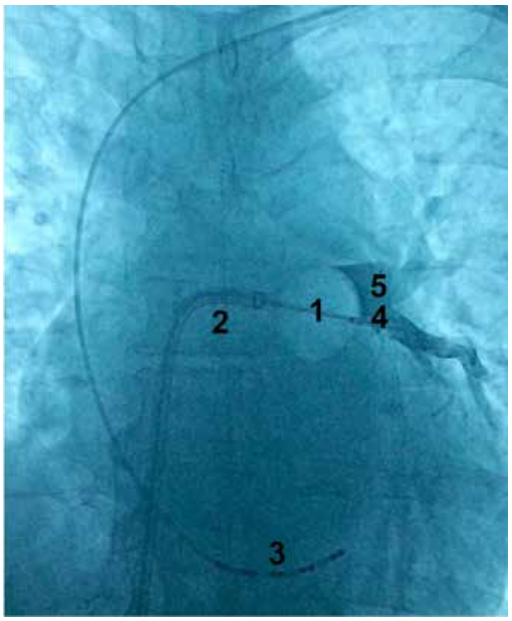

Figure 3. Cryoablation LSPV. Full occlusion the aim veins. 1 - Cryoballoon was inflated in mouth of the LSPV. 2- delivery catheter in LV; 3-10-pole electrode in coronary sinus; 4-8 pole the achieve catheter in LSPV, 5- Contrast agent went stagnant in achieving full lumen of the PV occlusion. (LSPV - left superior pulmonary vein; LV – left ventricle; PV - right inferior pulmonary vein)

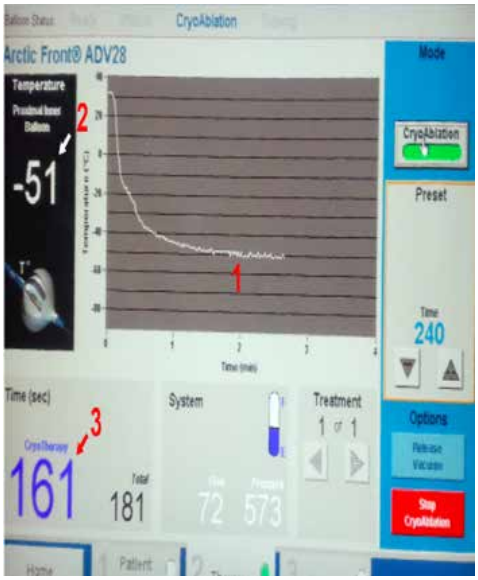

FIGURE 4. Ablation cryoconsole display. 1 - the curve shows temperature achieved cryoballoon with LA and PVO tissue in place of contact, 2 - temperature index, 3 - cryoexposure time indicator. (LA – left atrium; PVO - pulmonary veins ostia).

sumed until 240 *sec*. The PVO cryoablation sequence was as follows: the first was left superior PV (LSPV), and then left inferior PV (LIPV). After the left PVs were completed, we switched to the right PVs. The ablation was started with right inferior (RIPV), after complete isolation RIPV switched to right superior (RSPV), as many studies and our own experience showed, phrenic nerve palsy (PNP) mainly occurs during RSPV cryoablation. So we performed the RSPV cryoaablation in the last turn. In our study, only one of 15 patients had PNP associated with RIPV ablation. A quadripolar diagnostic electrode was repositioned from the right ventricle to the superior vena cava during the right PV ablation, and the right phrenic nerve was stimulated (at 12 *мА*, 2-3 *мс*) with a frequency of 15 *imp/min*. After all PVs have been isolated, an AF induction was attempted. If sinus rhythm did not restore spontaneously upon completion of all four PV isolation, in patients with persistent AF, cardioversion at 300 J was performed to restore the sinus rhythm. Catheters and introducers were removed with careful hemostasis.

Postoperative management and follow-up. Patients would be transferred to the ward and continuously monitored using ECG through the next morning.

Before discharge, ECG was registered daily and 24-hour ECG Holter monitoring was done. After discharge, patients were followed up every 3 months, and in case of any suspicious arrhythmia, ECG and Holter monitoring was performed. Weekly telephone surveys of patients with detailed clinical symptom questioning were conducted. In case of clinical manifestations of recurrent AF refractory to antiarrhythmic therapy, repeat LA catheter ablation with LA linear RFA was performed.

Statistical analysis. All analyses were conducted with SPSS software version 18.0 and MedCalc a Z-statistic, Chi-squared ($\chi 2$), and odds ratio (OR) relative to P-value of <0.05 were used to determine significance. The Student, Fisher criteria and *p* CI were used to compare the reliability of differences between the compared values. *P* less than 0.05 was considered statistically confident. Comparisons of patients' characteristics and outcomes were conducted in the two patient groups with persistent and paroxysmal AF.

RESULTS

Study Population. Totally 240 patients (142 males) with tachysystolic AF resistant to antiarrhythmic therapy (including amiodarone) underwent invasive electrophysiological study and cryoablation procedure. Ages were 29 to 78 years (53.5±24.5 years old) (Table 1).

Estimate of clinical characteristics and possible complications were conducted in the two patient groups with paroxysmal and persistent AF. Both groups were dominated by men (z=3.2, 95% CI 3.0 to 12.9, p value ≤0.05). The patients with persistent AF had longer history of arrhythmia (AF 27±19 month) than those with paroxysmal AF (z=19.9, 95% CI 16.2 to 19.8, p value ≤0.05).

Patients with persistent AF had significantly increased LA, 43±4*mm*, (z=4.6, 95% CI 1.7 to 4.3, p value ≤0.05) and reduced ejection fraction of the LV, 53±9% (z=6.6, 95% CI 4.2 to 7.8, p value ≤0.05) than patients with paroxysmal AF.

Postoperative outcomes: In this study, the average number of cryoactivities in one PV was 1.5 ± 0.5, and total average number of cryoapplications was 6.0 ± 2.0 per patient. Total duration of cryoablation reached 24.8 ± 12.6 min. Patient characteristics of cryoablation are presented in Table 2.

In average follow-up of 11.8±6.8 months,187 (78%) patients remained in sinus rhythm, and 96 (51%) continued taking antiarrhythmics because

Table 1.

Main Characteristics

Characteristic	Paroxysmal AF		Persistence AF		CI	Chi-squared
	n	%	n	%		
Patients, No	155	64.6	85	35.4	15.5;41.8	18.8*
Men, n (%)	88	56.7	54	63.5	10.8;23.6	0.64
Age, years	47.5±15.5		55.5±23.5		3.0;12.9	3.2*
Arrhythmic anamnesis, month	9±5		27±19		16.2;19.8	19.9*
Coronary artery disease	25	16.1	33	38.8	3.2;44.5	3.5
Diabetes,	12	7.7	29	34.1	7.8;47.6	2.9
Hypertension	35	22.6	47	55.3	9.7;57.8	8.7*
LA size, mm	40±3		43±7		1.7;4.3	4.6*
LV Ejection fraction, %	59±5		53±9		4.2;7.8	6.6*
Warfarin, %	88	56.7	57	67.1	6.9;26.6	1.6
Xarelto, %	41	26.4	38	44.7	4.5;39.4	2.8

Notes: *Statistical significance p≤0.05

they have risk factors of arrhythmia recurrence after first ablation.

Sustained AF paroxysms refractory to 3 antiarrhythmic drugs, including amiodarone, were registered in 53 (22%) patients. They underwent another electrophysiological study with a multi-polar Lasso catheter. After PVO electrical conduction was identified, segmental ablation of PVO was completed and linear ablation along the posterior wall and the roof of LA via radiofrequency energy was conducted. Atrial flutter type 1 was registered in 76 of 240 patients; cavotricuspid isthmus RFA was performed. Subsequently, arrhythmias did not recur with patients put on antiarrhythmic medication.

Repeat LA catheter ablation through LA linear RFA was performed in the case of clinical manifestations of recurrent AF refractory to antiarrhythmic therapy in 48 (56.5%) patients with persistence AF, which indicates a direct relationship between refractory and antiarrhythmic therapy and duration of arrhythmia history (OR=5.9, 95% CI 3.3 to 10.6, p value ≤0.05). Later, rhythm disturbances did not recur, with patients on antiarrhythmic drugs. (Table 3).

No inpatient lethal outcomes in patients with AF, both during and after ablation.

Complications: Complications were classified as in-hospital death, nonlethal complications, and PNP.

Nonlethal complications included embolic event, tamponade, femoral/subclavian hematoma, arteriovenous fistula, PV stenosis, PNP, and esophageal injury, which were not in hospital during and after ablation.

Table 2.

Cryoablation data

No	Data	Rate
1	Patients, n (%)	240 (100%)
2	LSPV, number (isol)	212 (82%)
3	LIPV, number (isol)	212 (94%)
4	LPV, number (isol)	28 (62%)
5	RSPV, number (isol)	240 (88%)
6	RIPV, number (isol)	240 (78%)
7	Complete isolation, n (%)	233 (97%)
8	Cardioversions, %	93 (39%)
9	Effects to PV	1.5±0.5
10	Fluoroscopic time (min)	19.5±5.7
11	Duration of the procedure (min)	95±29

Six (7.1%) cases of PNP were seen in the persistent AF patients group, and in 9 (5.8%) paroxysmal AF patients (OR=1.2, 95% CI 0.4 to 3.6, p value ≥0.05) (Table 3). Cardioversion, aimed to restore the sinus rhythm, was attempted mostly in persistent AF, 79 patients (92.9%), than in paroxysmal AF, 14 (9.1%). This indicates a direct relationship between the success rate of restoration of the sinus rhythm and the arrhythmia duration (OR=132, 95% CI 49.0 to 358.7, p value ≤0.05).

Table 3.

Postoperative data

Result	Paroxysmal		Persistence		CI	OR	Z statistic
	n	(%)	n	(%)			
Patients, No	155	64.6	85	35.4	15.5;41.8		18.8*
Hospital stay (days)	7±2		10±3		2.4;6.6		9.2*
Complications	-	-	2	2.3	0.4;196.2	9.3	0.15
Postoperative bleeding	-	-	1	0.2	0.2;137.0	5.5	1.04
Phrenic nerve palsy	9	5.8	6	7.1	0.4;3.6	1.2	0.38
Cardioversion	14	9.1	79	92.9	49.0;358.7	132	9.6*
RFA CTI	28	18.1	48	56.5	3.3;10.6	5.9	5.8*

Notes: *Statistical significance $p \leq 0.05$, CTI - Cavotricuspid isthmus

Discussion

Diagnosis and treatment of patients with cardiovascular disease are a serious problem in the world, which explains why numerous studies have been devoted to it [*Ouyang F et al., 2005; Revishvili A 2012*]. Based on the results of major studies with many patients, freedom of atrial arrhythmia ranges from 59% to 77% [*Neumann T et al., 2008; Kojodjojo P 2010; Kuhne M 2010*]. In these studies, significant efficiency discrepancy could be attributed to differences in ablation protocols, different balloon diameters, different methods for detecting arrhythmia recurrences variability, the presence or absence of a 3-month "blanking" period after ablation during the follow-up.

In recent studies like "Fire & Ice" that compared effectiveness of cryoablation and RFA of PVs, there was no statistically significant difference in ablation results (freedom of arrhythmia at 88% and 92% after a mean of 1.2 procedures with a follow-up period of 33 months). In this large-scale randomized study across Europe, 769 patients from 16 clinics were included [*Kuch K et al., 2016*]. In this study, the primary endpoint by the efficacy criterion was achieved; it was proven that Arctic Front ablation catheters without three-dimensional mapping were noninferior to ThermoCool RFA catheters with three-dimensional mapping ($p = 0.0004$) in terms of reducing frequency of arrhythmia relapses or necessity in antiarrhythmic drug therapy and / or re-ablation. The primary endpoint was also achieved by safety criterion, before the first death time for any reason, before the stroke or transient ischemic attack for any reason, or to serious adverse events due to treatment ($p = 0.24$). Both technologies showed comparably low rates of complications. According to the study results, cryoablation technology provides a shorter duration of procedures (mean value = 124 minutes) compared with RFA (mean = 141 minutes, $p = 0.0001$).

Studies have shown that the recurrence of electrical conduction from PV to LA is the main factor in the AF recurrence after catheter ablation [*Ouyang F et al., 2005; Cherchia G et al., 2009*]. Thirty minutes after cryoablation, 97.2% of PVs remain electrically isolated, in 56-84 days, 88% of PVs remain isolated, and after 144 days, only 46% of PVs remain isolated. Most often, the restoration of electrical conduction is noted in lower PVs and between LAA and left PVs.

In our study, patients who had risks of arrhythmia recurrence took antiarrhythmic therapy. These risks include long arrhythmic history, advanced age, dilated LA, and cardiological comorbidities [*Revishvili A et al., 2012; Bhargava M et al., 2009*].

Unlike traditional radiofrequency, the energy effect of cryoablation damage is characterized by clearly demarcated necrosis line, homogeneous necrosis zone, preserved endocardial layer, and the absence of thrombosis at site of exposure [*Huang S et al., 1987*]. One study showed that cryothermic damage diameter is directly proportional to ablation electrode; however, the depth of damage remains unchanged [*Fujino H et al., 1993*].

The most common complication of PVO cryoablation is right PNP, which develops in 1.7% to 12.0% of patients [*Furnkranz A et al., 2010*]. Close disposition of the right PN to the anterior wall of the right upper PV facilitates this complication. PN paresis risk is higher when the balloon is placed

deep in the PV. Practice shows that using a larger-diameter (28 *mm*) cryoballoon and monitoring phrenic contractions (paced from the superior vena cava) during the ablation can reduce the risk of this complication. In most patients, nerve function is restored in 1 to 12 months. In this study, we observed PNP in 15 (6.25%) out of 240 patients. In 10 patients, phrenic nerve function was restored in 1 day to 1 month, and in 4 patients, in 3 to 6 months. In one patient, it restored in 12 months.

Traditional LA and PVO RFA complications such as PV stenosis, esophageal wall damage, atrial-esophageal fistula formation, and incisional tachycardia after the development of sites of delayed conduction around the injury zone with cryoballoon ablation rarely occur [*Aldhoon B et al., 2013*).

PV cryoballoon isolation is a technique that provides single-shot circular electrical PV isolation for AF treatment. Cryoablation is a safer and easier technique than traditional RFA. Further cryotechnology improvement, such as changing the balloon elasticity and changing the distal part of the balloon, will improve the results of AF cryotherapy.

Conclusions

First, this study was not a randomized controlled study, and the sample size was relatively small. Second, there were no definite criteria for strategy selection, except for operators' experience, skills, and clinical judgments. Third, our study focused only on cryoballoon ablation, and the cost-effectiveness of this approach was not analyzed in the present study.

Pulmonary vein catheter isolation using second-generation cryoballoon is a promising method for treating atrial fibrillation, which simplifies ablation in the left atrium.

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