VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2024, Vol. 31, No. 5, 665–674
DOI: 10.5603/cj.95969

ISSN 1897–5593
eISSN 1898–018X

Cryoballoon ablation without use of contrast for the treatment of paroxysmal atrial fibrillation

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Abstract

Background: *Cryoballoon ablation (CBA) for atrial fibrillation (AF) is usually preceded by demonstrating pulmonary vein (PV) occlusion using contrast. The aim of the study was to determine efficacy and safety of a simplified protocol for CBA performed without demonstrating PV occlusion and compare achieved results with conventional CBA.*

Methods: *Paroxysmal AF patients undergoing a first-time CBA were prospectively included. In the non-contrast (NC) group CBA was performed using standardized protocol without demonstrating PV occlusion. In the conventional contrast (CC) group ablations were performed after confirmation of PV occlusion.*

Results: *The NC and CC groups comprised 51 and 22 patients, respectively. PVI according to the group assignment was achieved in 34 (67%) and 21 (95.5%) patients from the NC and CC groups, respectively ($p < 0.001$). In the NC group, 184 (90%) out of 204 veins were isolated without venography. There were no differences between the NC and CC groups in terms of procedure duration (89.7 ± 22.6 vs. 90.0 ± 20.6 min; $p = 0.7$) and fluoroscopy time (15.3 ± 6.3 vs. 15 ± 4.5 min; $p = 0.8$). In the NC group, the use of contrast was significantly lower compared to the CC group (4.9 ± 10.1 vs. 19.4 ± 8.6 mL, $p < 0.001$). There were no serious adverse events in both groups. A 1-year freedom from AF was achieved in 73.5% and 71.5% of patients from the NC and CC groups, respectively ($p = 1$).*

Conclusions: *Cryoballoon ablation without demonstrating vein occlusion with contrast is safe and feasible. Proposed simplified approach enables isolation of the vast majority of pulmonary veins with a significant reduction in the amount of contrast used.* (Cardiol J 2024; 31, 5: 665–674)

Keywords: atrial fibrillation, cryoballoon ablation, pulmonary vein isolation

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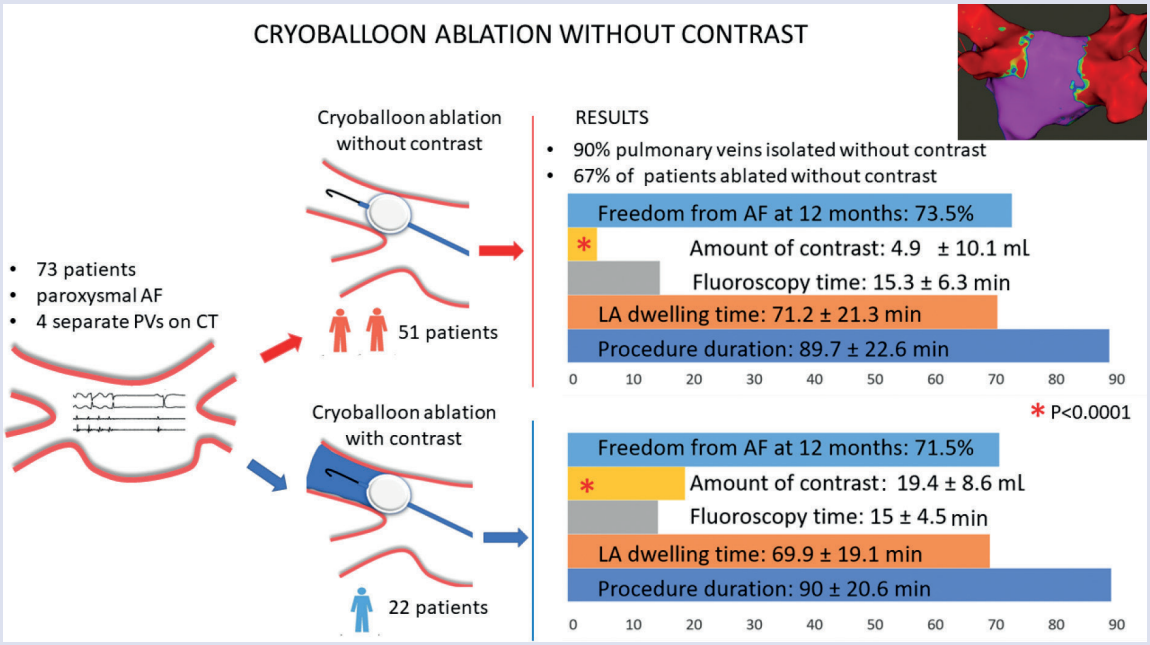
Received: 16.06.2023 Accepted: 23.12.2023 Early publication date: 29.01.2024

Graphical abstract



Introduction

Pulmonary vein isolation (PVI) using cryoballoon ablation (CBA) is a well-established method for the treatment of atrial fibrillation (AF) [1–3]. In terms of efficacy and safety, CBA is not inferior to radiofrequency (RF) ablation [4, 5]. Moreover, it is faster than RF ablation [4], but its drawbacks are the need for higher doses of radiation [4–6] and the need to use iodine contrast during the procedure [2]. It can be of particular importance in patients with renal and thyroid dysfunction, and with allergies to contrast, as well as for diabetic patients. As a rule, cryoenergy delivery is preceded by demonstrating pulmonary vein (PV) occlusion, which is confirmed by injecting contrast through the inner lumen of the balloon catheter after the vein is blocked with a balloon [7]. Research on CBA without the use of contrast is sparse.

Therefore, the aim of the study was to determine the efficacy and safety of a simplified protocol for CBA performed without demonstrating PV occlusion by venography and compare achieved results with those observed in patients undergoing conventional CBA.

Methods

This was a dual-center, prospective, nonrandomized study (NCT04344743). The study cohort consisted of consecutive patients undergoing a first-time CBA from August 2020 to July 2021. Inclusion criteria were as follows: paroxysmal AF, age 18 to 85 years, four separate PVs visualised in computed tomography, left ventricular ejection fraction greater than 45% and a left atrial diameter in the long axis projection of less than 55 mm.

Exclusion criteria included: documented typical atrial flutter, thrombus in the left atrium, glomerular filtration rate of less than 45 mL/min, common trunk of PVs and pregnancy.

In the non-contrast (NC) group CBA was performed using standardized protocol without demonstrating PV occlusion by venography prior cryoapplication. A similar protocol was used in the conventional contrast (CC) group, where ablations were performed after confirmation of complete vein occlusion by venography. Each patient provided a written informed consent to the study protocol, which had been approved by the Institutional Ethics Committee.

Procedural details

Briefly, intracardiac bipolar electrograms filtered using a 30 to 500 Hz band-pass, along with 12-lead electrocardiography (ECG) were recorded at 1 kHz sampling. Catheters were inserted through a right femoral vein. A quadripolar catheter was positioned in the coronary sinus and was used for

recording and pacing. If necessary, the catheter was placed in the right ventricle. During isolation of right PVs, the quadripolar catheter was positioned in the superior vena cava for the high-output (10–25 mA; 1000–1200 ms) right phrenic nerve pacing. Intravenous heparin was administered before transseptal puncture, followed by additional doses to achieve activated clotting time above 300 seconds.

All ablations were performed using a 28-mm cryoballoon catheter (Arctic Front Advance, Medtronic, Inc, Minneapolis, MN) inserted through a 12F steerable sheath (FlexCath; Medtronic). A multipolar mapping catheter (Achieve™, Medtronic) was introduced for mapping of PVs before and after the ablation.

In the NC group cryoapplications were initially delivered without previous venography confirming vein occlusion. In the case of PV isolation failure after a total of 5 minutes of cryoenergy delivery further attempts to isolate the vein were preceded by venography. In both groups, PVI was confirmed using a diagnostic circular catheter, demonstrating entrance and exit block.

The duration of cryoenergy delivery was dependent on the time to vein isolation. In cases of early isolation (less than 60 s) cryoapplications lasted 180 seconds and were prolonged to 240 seconds if isolation occurred later than 60 seconds from the onset of cryoenergy delivery. In cases of very early isolation (less than 30 s) or very low temperatures (less than –50°C), on the discretion of the operator cryoapplication duration could be shortened to 120 seconds from the moment of vein isolation (time to vein isolation + 120 s). To prevent distal cryoapplications, the forward push of the cryoballoon was allowed after the initiation of cryoapplication when the balloon reached its largest diameter. This was especially true when the veins were of a large diameter, the balloon was ostially placed before cryoapplication, and there was a suspicion of a peri-balloon leak. Pull down manoeuvre was allowed after 60 seconds of cryoapplication.

Cryo-applications were discontinued when there were indications that they would be ineffective or associated with an increased risk i.e., in cases where: after 60 seconds the –30°C was not reached, after 120 seconds a vein was not isolated, if temperature reached –50°C after 30 seconds of cryoapplication, if temperature reached –60°C, if phrenic nerve injury occurred or when symptoms suggesting its imminent occurrence were noticed.

Veins with no recordable PV potentials were isolated with one application lasting 240 seconds with a target temperature equal or less than –35°C. Exit and entrance block were verified at least 10 minutes after the final cryoapplication.

Periprocedural and postprocedural management

In order to include into the study only patients with a typical PV anatomy, all patients had computed tomography with the use of contrast before the procedure. Oral anticoagulation was usually stopped on the morning of ablation. It was then resumed in the evening the same day and continued for at least 3 months after the ablation. Antiarrhythmic therapy was stopped during the first 2 months after ablation. Long-term follow-up included symptom assessment based on a standardized form, ECG and 24-hour Holter ECG assessment at 3, 6, 9 and 12 months after ablation. The procedure was considered effective if the patient did not report symptoms typical of AF and no episodes of AF or atrial flutter lasting longer than 30 seconds were recorded, except for the first 3 months of blanking period after ablation. Patients with recurrent symptomatic arrhythmia refractory to antiarrhythmic therapy were referred for re-ablation using the three-dimensional mapping system (Fig. 1).

Procedural endpoints and study outcome measures

Demonstrating entrance and exit block was a procedural endpoint during isolation of individual veins. However, if in the NC group this endpoint was not achieved within the scheduled timeframe, further attempts to isolate the vein were preceded by venography, but patients were kept in the NC group for statistical analyses.

The primary study endpoint was isolation of all PVs according to the original group assignment, and the procedure was considered efficacious in a given patient if this primary endpoint was met. The secondary endpoints in both groups were number of PVs isolated according to the originally assumed protocol, the number and rate of patients with stable sinus rhythm at 1 year follow-up, the amount of contrast used during the procedure, fluoroscopy time and radiation dose exposure during the procedure, left atrial dwelling time, presence of complications.

Statistics

Statistical analyses were performed using Statistica 5.0 (StatSoft Inc., Tulsa, USA). Descriptive

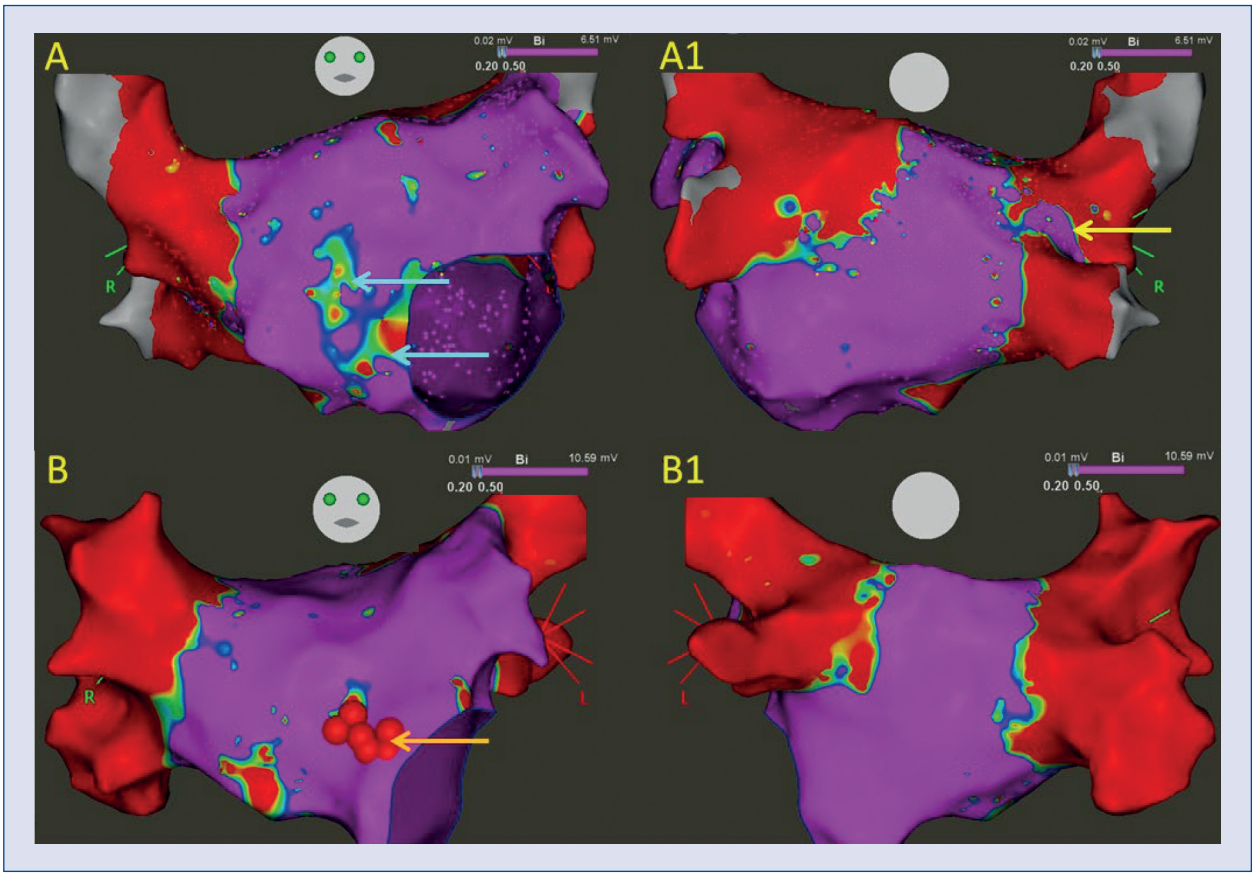


Figure 1. High-density left atrial voltage maps in patients after cryoballoon ablation without contrast; **A, A1.** The map in a patient with atrial fibrillation recurrence 15 months after the index procedure. On panel A1 reconnection area at the posterior carina between right pulmonary veins is indicated by the yellow arrow. After ablation at the spot and in the area shown by blue arrows on panel A, atrial fibrillation was no longer inducible; **B, B1.** The map in a patient with frequent atrial premature contractions 10 months after the index procedure. During an electrophysiological study, complete isolation of pulmonary veins was confirmed. The ectopy originated from the spot indicated by the orange arrow on panel B

statistics including mean, standard deviation, number of cases, frequency of occurrence and percentages were used. The Shapiro–Wilk test was used to evaluate whether or not the data were normally distributed. The Student t test for independent variables or the Mann-Whitney U tests were used for comparisons of continuous variables. The Fisher's exact test was used to evaluate whether there is an association between categorical variables. The 0.05 threshold was considered the level of significance. The results are presented according to the patients' primary allocation to the appropriate groups.

Results

The NC and CC groups comprised 51 and 22 patients, respectively. There were no differences between groups regarding baseline demographics, clinical and echocardiographic data (Table 1). Isolation of all 4 PVs without and with venography was possible in 34 (67%) and 21 (95.5%) patients, respectively ($p < 0.001$). In the NC group 184 (90%) of 204 veins were isolated without confirming their occlusion by venography and in the CC group 87 of 88 veins (98.9%) were isolated after confirming vein occlusion ($p < 0.01$). In the NC group, in a majority of cases (59–69%), veins were isolated during the first cryoapplication, which was comparable to the CC group (Table 2). In the NC group twenty veins (6 left superior PVs, 2 left inferior PVs, 5 right superior PVs, 7 right inferior PVs) in 17 patients were not isolated without previous venography within the predefined 5-minute time frame. 19 of these veins were subsequently isolated with the use of contrast. In one patient from the NC group and in one patient from the CC group right inferior PV was not isolated, due to persistent

Table 1. Baseline demographic and echocardiographic data

	NC group (n = 51)	CC group (n = 22)	Significance level (p)
Women/men	33%/18%	14%/8%	0.93
Age	56.8 ± 11.0	61.6 ± 11.0	0.09
Body mass index	28.7 ± 3.8	28.0 ± 4.1	0.65
CHADS-VASc	1.52 ±1.2	1.59 ± 1.4	0.96
HAS-BLED	1 ± 0.9	0.7 ± 0.8	0.19
CHF	0 (0%)	0 (0%)	NA
HA	34 (67%)	13 (59%)	0.83
CAD	2 (4%)	1 (5%)	1
Stroke/TIA	3 (6%)	2 (9%)	0.64
Diabetes mellitus	4 (8%)	1 (5%)	1
LVEF [%]	61.9 ± 4.2	61.8 ± 4.3	0.94
LAA [cm^2]	23.0 ± 4.2	23.4 ± 6.9	0.54
LA [mm]	41.5 ± 4.7	40.9 ± 4.1	0.61

CAD — coronary artery disease; CC — conventional contrast group; CHF — congestive heart failure; HA — arterial hypertension; LA — left atrium; LAA — left atrial area; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; LVEF — left ventricular ejection fraction; NC — non-contrast group; RIPV — right inferior pulmonary vein; RSPV — right superior pulmonary vein; TIA — transient ischemic attack

conduction recurrence (in the NC group) despite using contrast protocol and transient phrenic nerve injury with subsequent early termination of cryoapplication (in the CC group).

There were no serious adverse events in both groups. In particular, there were no cases of tamponade, stroke, transient ischemic attack, major bleeding, vascular access complications requiring interventional treatment or phrenic nerve palsy. In one patient from the CC group transient phrenic nerve injury was observed during right inferior pulmonary vein isolation, which resolved within 5 minutes after the cryo-application was terminated.

There were no differences between the compared groups in terms of procedure duration, left atrial dwelling time, fluoroscopy time and radiation dose exposure. In the NC group, the use of contrast was significantly lower compared to the CC group. The time to isolation and the minimum temperature achieved were comparable in both groups (Table 2). The number of freezes, the rate of veins isolated during first attempt and total freezing time in left inferior pulmonary vein were lower in the CC group. In other veins, these parameters were comparable between the two groups (Table 2).

In the subgroup of the first 25 patients in the NC group, the procedure duration, the left atrial dwelling time and fluoroscopy time were longer, compared to the subgroup of 26 patients who underwent the procedures at the end (Table 3).

Two patients from the NC group and one patient from the CC group were lost to follow-up. In the remaining patients 1-year freedom from AF was achieved in 73.5% of patients (36/49) from the NC group and in 71.5% of patients (15/21) from the CC group (p = 1).

Two patients from the NC group with recurrent symptomatic arrhythmia, who gave consent for repeat procedure, were referred for re-ablation using the CARTO system. Performed high density voltage maps revealed isolated PVs and the arrhythmogenic focus located close to the mitral anulus in one of them. In a second patient PVs were also isolated, with possible breakthrough in the posterior aspect of the carina between right PVs and a moderately extensive low-voltage area in the anterior LA wall (Fig. 1).

Discussion

The results of the present study indicate that CBA without contrast is feasible, safe and quite effective. It can be argued that the achieved results are not optimal due to relatively low rate of patients in the NC group in whom the primary endpoint was met i.e., isolation of all PVs without contrast in the predefined timeframe. However, in this group 90% of PVs were isolated without contrast, without any serious complications. Until recently it was considered that confirmation of vein occlusion by venography is prerequisite to

Table 2. Comparison of the acute results between the non-contrast (NC) group and the conventional contrast (CC) group

	NC group (n = 51)	CC group (n = 22)	Significance level (p)
Procedure duration [min]	89.7 ± 22.6	90.0 ± 20.6	0.65
LA dwelling time [min]	71.2 ±21.3	69.9 ± 19.1	0.81
Fluoroscopy time [min]	15.3 ± 6.3	15 ± 4.5	0.83
Kerma [mGy]	25 ± 17	26 ± 15	0.90
DAP [cGy*cm^2]	815 ± 594	945 ± 529	0.60
Amount of contrast [mL]	4.9 ± 10.1	19.4 ± 8.6	< 0.001
Number of freezes:			
LSPV	1.98 ± 1.60	1.41 ± 1.1	0.10
LIPV	1.52 ± 0.96	1.09 ± 0.42	0.02
RSPV	1.66 ± 1.07	1.68 ± 1.04	0.86
RIPV	1.88 ± 1.64	1.32 ± 1.57	0.30
Vein isolation during the first cryoapplication:			
LSPV	30 (59%)	17 (77%)	0.18
LIPV	35 (69%)	21 (95%)	0.01
RSPV	30 (59%)	12 (55%)	0.79
RIPV	33 (65%)	16 (73%)	0.34
All veins	63%	75%	0.32
Time to isolation			
LSPV [s]	47 ± 34	46 ± 27	0.85
LIPV [s]	37 ± 22	34 ± 17	0.88
RSPV [s]	48 ± 31	44 ± 37	0.43
RIPV [s]	58 ± 30	56 ± 24	0.98
Minimal temperature			
LSPV [°C]	–48.5 ± 4.9	–49.1 ± 4.9	0.34
LIPV [°C]	–43.3 ± 5.3	–44.7 ± 3.9	0.25
RSPV [°C]	–50.3 ± 6.2	–48.8 ± 6.8	0.33
RIPV [°C]	–47.4 ± 5.4	–47.1 ± 4.8	0.85
Total freezing time:			
LSPV [s]	279 ± 185	230 ± 97	0.45
LIPV [s]	227 ± 76	195 ± 65	0.04
RSPV [s]	242 ± 106	268 ± 137	0.44
RIPV [s]	286 ± 215	233 ± 69	0.43
Pulmonary veins without recordable potentials:			
LSPV	4 (7.8%)/[1*]	2 (9.1%)	0.96
LIPV	4 (7.8%)/[1*]	3 (13.6%)	0.87
RSPV	6 (11.8%)/[0*]	4 (18.2%)	0.52
RIPV	6 (11.8%)/[2*]	1 (4.5%)	0.34

*Number of veins in the non-contrast group with no recordable potentials requiring the use of contrast; DAP — dose area product; LA — left atrium; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; RIPV — right inferior pulmonary vein; RSPV — right superior pulmonary vein

obtain successful vein isolation [7]. Achieving full vein occlusion in certain situations, mainly due to anatomical reasons, can be challenging and may require multiple attempts, which may expose the patient to increased doses of contrast and radiation [7, 8]. At the same time, the purpose of ablation is an electrical isolation of PVs. While achieving complete vein occlusion remains the gold standard during CBA, it does not guarantee that cryoapplication will be successful. Moreover, in some cases full vein occlusion requires deep placement of the balloon, which may lead to its stenosis or phrenic

Table 3. Effect of learning curve

	First non-contrast patients (n = 25)	Last non-contrast patients (n = 26)	Significance level (p)
Procedure duration [min]	98.4 ± 22.2	81.3 ± 19.9	0.005
LA dwelling time [min]	80.7 ± 20.2	62.0 ± 18.2	0.001
Fluoroscopy time [min]	17.3 ± 7.2	13.5 ± 4.4	0.02
Kerma [mGy]	28 ± 19	22 ± 15	0.21
DAP [cGy*cm^2]	836 ± 625	792 ± 573	0.79
Amount of contrast [mL]	6.7 ± 10.6	3.2 ± 9.3	0.21

DAP — dose area product; LA — left atrial

nerve palsy [9]. The correct position of the balloon and circular diagnostic catheters at the PV ostia can be roughly determined based on fluoroscopy, and further enhanced by tactile sensations. As a rule, proper wedging of the balloon catheter in the vein orifice requires a fairly strong support which is enhanced by the proper alignment of the catheter and the sheath. In addition, in many cases the displacement of the balloon after several dozen seconds of cryoapplication, usually by pulling it down, causes full sealing of the vein, contributes to further lowering the temperature (Fig. 2) and leads to full electrical isolation of the vein, which are the aims of ablation [2]. Similar minimum temperatures achieved and freezing times in the two groups suggest, that although complete vein occlusion before cryoapplication was not demonstrated, in most cases the occlusion was most likely present from the onset of cryoapplication or occurred during cryoapplication (Fig. 2). The implementation of NC protocol in our study did not result in prolongation of the procedure and the majority of PVs in the NC group were isolated during the first cryoapplication. Also, other assessed parameters i.e., radiation dose, fluoroscopy time, time to vein isolation and minimal temperature achieved were not different between the NC and the CC groups. Total freezing time and number of freezes were also comparable between groups, except for the left inferior PV, where these parameters were greater in the NC group. This difference may be due to selection bias, because in the relatively small CC group, the vast majority of the left inferior PVs were isolated during the first cryo-application.

Another group that used similar protocol to the current one, showed even more favorable results for the NC group in terms of procedure duration, freezing time, radiation dose exposure and use of contrast media [10]. It is difficult to establish where the variations between the studies come from. They may partially result from differences in protocols or workflows. For example, our protocol required switching to confirmation of vein occlusion using contrast if initial attempts to isolate the veins had failed. However, in the present study, it was shown that when using the NC protocol, there was also a learning curve and in the course of subsequent procedures, a reduction in the procedure duration, radiation time and dose and a further reduction in the amount of contrast used were observed.

Other researchers also implemented NC protocols for CBA, however with the use of other measures to assess PV occlusion prior to the cryoapplication, which included transesophageal or intracardiac echocardiography guidance, electroanatomic mapping systems, PV pressure monitoring, cold saline injection with postinjection PV temperature drop [11–17]. Recently a new dielectric imaging system with a tool occlusion software allowing contrast free cryoablations has been introduced with a potential to change our approach to cryoablation [18, 19]. It could be argued that the proposed methods rely on more objective measures than tactile feedback and fluoroscopic position that were relied upon in the present study. However, the fluoroscopic position of the cryoballoon during ablation is an important safety factor [9]. It can almost certainly be assumed that in some cases in the NC group the PVs were not initially fully balloon-sealed prior to cryoapplication (Fig. 2). At the same time, the so-called proximal sealing technique which may involve sealing the PV after freezing to avoid distal cryoapplications is an effective and recommended technique [2, 15]. The proposed approach is simple and cheap as does not require any additional equipment or systems. The present study proves that CBA without contrast can effectively isolate PVs on the first attempt in the majority of cases. Although it was not the

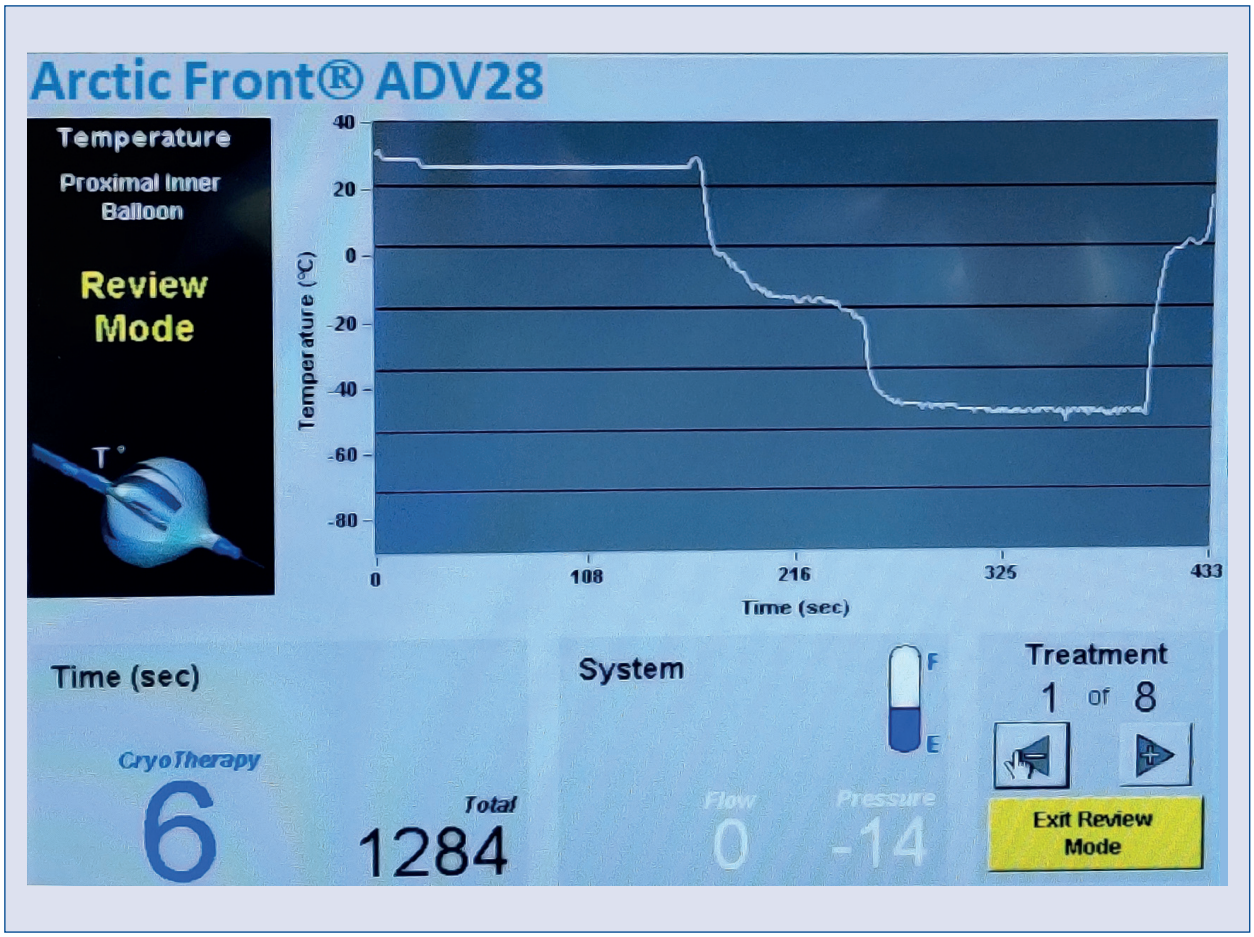


Figure 2. Biphasic temperature drop during cryoballoon ablation without contrast. Biphasic temperature drop during cryoballoon ablation without contrast indicates that the pulmonary vein was most likely not fully balloon-sealed at the beginning of the cryoapplication. Pulmonary vein isolation occurred 3 seconds after the second temperature drop

intention to prove that demonstrating complete vein occlusion during CBA is always redundant, it was shown that it is not always necessary and it can be omitted without exposing the patient to additional risk or significantly worsening the long-term effectiveness of the procedure. Such an approach can be considered especially in the subgroup of patients with impaired renal function and allergy to iodine contrast if, for some reason, the operator and patient prefer balloon cryoablation over RF or pulsed field ablation, or if an allergy to contrast becomes apparent during the procedure itself.

It should be emphasized that no transient phrenic nerve injury was observed during right vein ablation in the NC group. This may be an incidental finding due to the relatively small study group, but it may also be due to a more proximal placement of the balloon during cryoapplications.

The study's observations concerning non-contrast CBA may not be applicable to the new POLARx ablation system (Boston Scientific), which maintains a uniform pressure and size during inflation and cryoablation, contrary to the Arctic Front Advance balloon, which reaches its largest diameter after the start of freezing. As a result, POLARx is a more compliant balloon, at the cost of not being able to maneuver after the start of freezing as recommended by the manufacturer, as it may lead to an automatic termination of the cryoapplication [20]. Such maneuvers were performed during the present study and could allow effective cryoablation even in cases where the PV was not fully sealed before starting cryo-application.

The NC group was too small and the follow-up too short to suggest a change to the NC approach for all cryoballoon ablation procedures. However,

in some cases, especially in clinical situations where administration of contrast is inadvisable, a NC approach can certainly be considered, without fear that it may compromise patient safety or significantly worsen the results.

Limitations of the study

This was a non-randomized study performed at two ablation centers. The population studied was relatively small. It could be argued that the NC patients, in whom PV occlusion was not demonstrated prior to a cryoapplication are more likely to have incomplete ablation. However, long-term results, as well as objective parameters such as time to isolation or nadir temperature, which were not significantly different between the CC and NC groups, argue against such suppositions. All patients had computed tomography with the use of contrast before the procedure. As a result, the potential benefits of NC ablation have been reduced but the current study wanted to ensure that all patients included had a typical anatomy with four separate veins [21]. In clinical practice, such an assessment can be replaced by a transesophageal echocardiography in most cases.

Conclusions

Cryoballoon ablation without demonstrating vein occlusion with contrast is safe and feasible. The proposed simplified approach enables isolation of the vast majority of PVs with a significant reduction in the amount of contrast used.

Acknowledgments: The study was supported by a research grant from Medtronic.

Conflict of interest: Paweł Derejko received consulting fees from Medtronic. Other authors report no competing interests.

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