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Towards a tailored cryo-pulmonary vein isolation. Lessons learned from second-generation cryoballoon ablation☆,☆☆

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ABSTRACT

Second–generation cryoballoon ablation has emerged as an effective and practical approach for the treatment of atrial fibrillation. It gained the overall interest of the electrophysiology community due to its excellent success rates, and reproducible clinical outcomes comparable to the point-by-point radiofrequency technique. This technology offers several advantages including a fast learning curve and shorter procedure times making this device widely adopted in many EP-laboratories as an alternative strategy to conventional point-by-point radiofrequency ablation. As compared to its predecessor, the improved technical performances of the second-generation cryoballoon translated into favorable clinical outcomes, which are maintained in long-term follow-up. However, the ideal cryo-application duration and the adequate number of freeze-thaw cycles are not well established and predictors of durable electrical isolation are poorly known. This review provides some practical advices for a successful ablation using the second-generation cryoballoon.

Introduction

In the last 3 decades, we have witnessed the evolution of catheter ablation from an experimental technique to a well-established treatment option for many atrial fibrillation patients [1]. The circumferential electrical isolation of the pulmonary vein (PV) antra represents the cornerstone of any treatment of atrial fibrillation. Traditionally, PV isolation (PVI) by means of radiofrequency (RF) ablation is achieved using a point-by-point technique and 3D navigation, which makes it difficult to create circular and contiguous lesions potentially allowing conduction gap in case of poor catheter-tissue contact and incomplete non-transmural lesions. This approach might also be hampered by a long learning curve, mainly based on the physician dexterity to create contiguous circular lesions. To overcome these issues, recent devices with different designs (i.e. circular catheter, basket shape, balloon-based) and using different energy sources (laser, RF, cryoenergy) [2–4], have been developed aiming specifically for PVI. Among these, the Cryoballoon (CB) is certainly the most appealing for its safety and efficacy profile. The non-compliant, double balloon construction is available in 2 different diameters (23 and 28 mm) and uses nitrous oxide (N2O) as a refrigerant in order to create a circumferential lesion around the PV ostium. The CB was first commercialized in 2006. Although revolutionary, the first-generation device (Arctic Front; Medtronic, MN, USA) was mainly limited by a high rate of incomplete electrical isolation often requiring the need of "touch-up" applications with an additional focal catheter. Conversely, the second-generation device (Arctic Front Advance; Medtronic, MN, USA; CB-Adv) has an optimized catheter design, translating into significant improvements in procedural and clinical outcomes as compared to its predecessor [5], which in turn seduced a growing number of electrophysiologists. The aim of this review is to report the safety and efficacy of second-generation

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CB ablation and to evaluate the most relevant parameters to be considered during a Cryo-AF ablation in order to achieve a durable isolation.

Biophysics of the cryo-lesion

The cryothermal and radiofrequency-induced lesion

Tissue damage using cryoenergy is a complex process and involves 3 main phases: (i). freezing and thawing; (ii). hemorrhage and inflammation; (iii). replacement fibrosis and apoptosis. Resulting cryothermal lesions are well circumscribed, with distinct borders, homogeneous and sharply demarcated with preserved ultrastructural integrity, which may theoretically be less arrhythmogenic than RF lesions considering that border zones are more susceptible to spontaneous depolarization [6].

Comparatively, RF ablation has been shown to disrupt the tissue structure to a greater extent than cryo; heat-based energy tends to denature proteins and negatively impacts collagenous structures. Heat-based energy also creates subsequent edema, which not only impedes further ablation, but also blocks electrical conduction that may give rise to unwanted reversible isolation. As opposed to cryo-lesions, RF lesions contain evident intralesional hemorrhage and ragged lesion edges that are not as well demarcated from normal myocardium. Replacement fibrosis confined to the outer margin of RF lesions but not cryo-lesions suggests a slower postablation healing response to RF energy [9]. Moreover, RF energy has been demonstrated to be 5 times more thrombogenic than cryoablation and that the thrombus volumes are significantly greater with RF compared to cryoablation [7]. The latter phenomenon may be due to a relative endothelial cell preservation following by cryo-induced injury.

Optimal freezing parameters

For cryothermal lesions, cooling first occurs at the point of catheter contact to tissue, and then extends radially into the tissues, establishing a temperature gradient or "dynamic cryomap". The tip also adheres to tissue affording greater stability. This greater stability may lead to a safer programmed electrical stimulation without problems of catheter dislodgement; lower effect of beat-to-beat heart motions and respiratory variations. This advantage is particularly profitable when the ablation target is located at a site where contact is difficult to maintain, e.g. LAA to LSPV ridge. Moreover, a balloon is inherently stable within a vessel that is funnel-shaped, as there is a tendency for the PV antrum to center the balloon, thus offering a large area of circumferential support by essentially holding the balloon in place with adequate forward force.

The characteristics of cryo-lesions depend on many parameters [8]. Larger lesions are generally produced by lower temperatures reached at faster cooling rates. Necrotic injury thresholds for cardiac cells have been reported as −20 °C, and more recently as low as −26 °C with cooling rates such as those found in N_2O-based cryoablation systems [9], which can theoretically reach temperatures colder than −80 °C. A significant dependence of tissue temperatures is linked to the distance from the balloon surface [10]. For the cryoballoon, ablation temperatures, lesion dimensions and ablation success is also strongly dependent on adequate circumferential balloon-tissue contact; ablation gaps can be found where peri–balloon leaks are detected [10].

Longer duration of freezing may also lead to larger lesions, although an important slowing of myocardial ice formation is typically reached within 3 minutes [6,11] resulting in equivalent lesion characteristics when compared to 4 minute ablations [12].

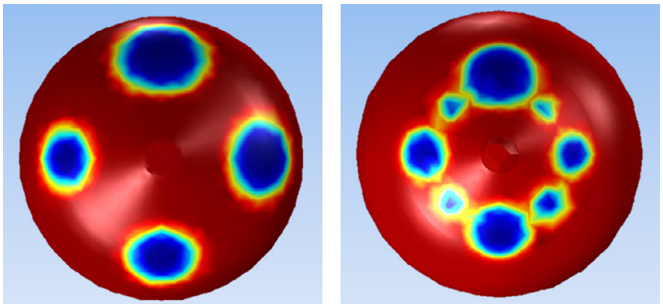

Fig. 1. Representation of the refrigerant distribution (blue to yellow color map) from the CB-1 (left) and CB-Adv (right) on the distal face of the cryoballoon (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A comparison of short and longer ablation times with or CB-Adv cryocatheters has shown no differences in acute isolation, histologic depth, and/or circumferential transmurality between 2- and 4- minute cycle freezes in animal models [13]. On the contrary, 4-min freezes were associated with thicker neointima proliferation leading to PV stricture in 6 out of 30 veins. No stricture occurred in the veins ablated with 2 minutes of freeze cycles.

Research on different cell types has shown that multiple freeze-thaw cycles lead to larger lesions [8], with a greater propensity to kill more cells within the ablation volume [14]. In the case of AF treatment, ablation of relatively thin atrial tissue may not require freeze-thaw cycles, allowing a single ablation to create permanent electrical block.

The increased efficacy and decreased ablation times when using CB-Adv as compared to CB resides in the improved distribution of refrigerant within the balloon. A representation of the different cooling pattern between CB and CB-Adv is shown in Fig. 1. Of note, refrigerant distribution is not only more homogeneous across the distal surface of the balloon, but also creates a wider cooling area, which extends from the balloon's equator to the tip of the catheter [15]. A finite element analysis based on preclinical data shows that circumferential and transmural lethal temperatures can be attained with the CB-Adv within 2 minutes, while more than 3 minutes may be required to accomplish the same results using the CB (Fig. 2). Preclinical data comparing lesions from each catheter generation highlight the benefits of more homogeneous and distal cooling [15], and clinical data strongly rule in favor of CB-Adv in terms of procedural and clinical effectiveness [5,21,23,24,27] (Tables 1 and 2).

Efficacy of second-generation cryoballoon

Initial experiences using CB highlighted shortcomings and challenges related to the catheter design that could affect ablation outcome. Different balloon sizes (23 and 28 mm) or additional focal tip ablation (touch-up), were sometimes needed for completing PVI [20,21], with arrhythmia recurrences after CB ablation more frequently caused by a PV reconnection [16]. The redesign, which increased cooling surface area and homogeneity, led to improved clinical performance. For instance, two studies reported a single-CB Adv procedure AF freedom after 3 years in 60–70% of paroxysmal AF patients [17]. In both studies, such a result rose up to approximately 80% when considering repeat ablations, during which PV re-isolation represented the procedure endpoint in the majority of cases [18]. Of note, the sole use of the bigger device (28 mm) to target all the veins during the same procedure may also bear several advantages. The large balloon allows a wider antral ablation, which is important to limit AF initiation and maintenance. This leads to potential substrate modification of these regions. Based

Table 1
Clinical outcome of Arctic Front (CB1) and Arctic Front Advance (CB2) in various clinical studies.

	STOP AF [51]	CAP AF [52]	STOP AF PAS [53]	CRYO-Japan PMS [54]	FIRE and ICE cryoballoon arm [29]	FIRE and ICE RF arm [29]
Catheter	CB1	CB1	CB2	CB2	CB1 and CB2	Thermocool / thermocool SF, thermocool smarttouch
Number of subjects	163	78	344	616	374	376
Enrollment window	October 2006– June 2008	March 2009 –January 2011	August 2012–October 2014	July 2014–February 2015	January 2012–January 2015	January 2012–January 2015
Freedom from AF recurrence	69.9% @ 12M	65.4% @ 6M	82.2% @ 12M	88.4% @ 6M	65.4% @ 12M	64.1% @ 12M
Persistent phrenic nerve injury	2.5% at 12 months	0.0%	0.9% at 12 months	0.2%	0.3%	0.0%
PV stenosis	3.1%	1.3%	0.6%	0.2%	0.0%	0.0%
Cardiac tamponade / pericardial effusion	0.6%	1.3%	0.9%	1.5%	0.3%	1.3%
Stroke	4.3%	0.0%	0.3%	0.0%	0.5%	0.5%
Death	0.0%	0.0%	0.0%	0.2% (pneumonia)	0.0%	0.0%

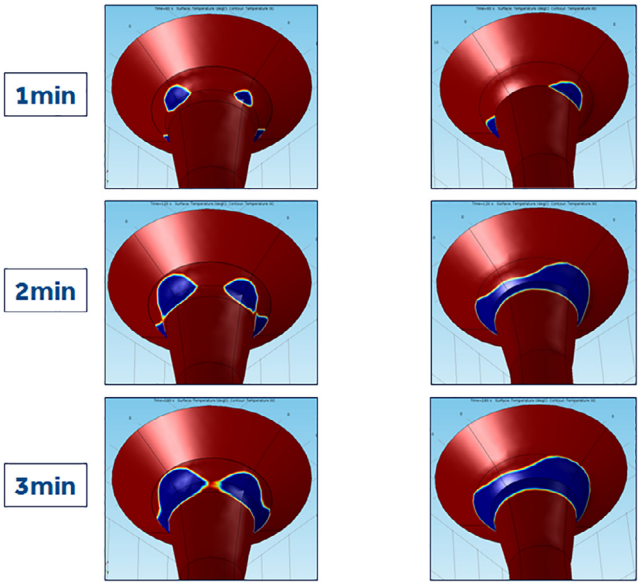

Fig. 2. Finite-element modelling of pulmonary vein transmural temperature during cryoballoon ablation using CB1 (left) and CB-Adv (right) at different ablation time points. Temperatures of less than −25 °C (blue) are shown on the epicardial surface of the PV ostial region (red). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Procedural parameters of Arctic Front (CB1) and Arctic Front Advance (CB2) cryoballoons.

Procedure times (mins; Mean ± SD)	CB1 (STOP-AF)	CB2 (STOP-AF PAS) [53]	*P* value
Total procedure (lab occupancy time)	371 ± 101	233 ± 74	<0.001
LA dwell time	181 ± 75	81 ± 31	<0.001
PV cryoablation	49 ± 19	32 ± 11	<0.001
fluoroscopy	63 ± 32	20 ± 12	<0.001

on technical advantages of the 28-mm CB-Adv in comparison to the first-generation device, and safety concerns regarding the 23-mm catheter due to the potential higher risk of PV stenosis and PNP if deployed too far within the PV, a single big balloon strategy is preferred in most centers for its demonstrated favorable clinical outcomes [19–21].

Despite the use of additional ablation strategies, linear lesions or CFAEs elimination have shown limited value on top of PVI [22]. Furthermore, the encouraging results from these recent experiences in Cryo-PVI in treating paroxysmal AF has allowed expansion of this initial indication, leading to its ancillary adoption even for the persistent form. Initial experiences reported a 60–69% freedom for clinical recurrences at 1 year follow-up [23,24], showing that ablation using CB-Adv is a safe and effective approach in this subset of patients, with the added benefit of shorter procedure times. Moreover, the CB-Adv has been recently used to create a roof line [25] and a posterior box [26], as well as targeting the LAA [27], reporting a better success rate as compared to a PVI-only strategy in PersAF. These novel uses highlight a certain degree of versatility in targeting extra-PV locations with promising results that warrant further investigation.

Recently, a third-generation cryoballoon device has been released. The main difference with the CB-Adv relates to the length of the catheter tip. While it may lead to a higher PVPs visualization rate, it may potentially affect catheter stability in certain anatomies [28]. To date, there is no substantial evidence that it may offer better clinical results as compared to the CB-Adv.

Safety and limitations of the second-generation cryoballoon

This section is available as supplementary online material.

Radiofrequency vs cryo-PVI for atrial fibrillation ablation

The FIRE and ICE trial [29], is the largest prospective randomized multicenter unbiased study to date comparing CB and RF ablation for the treatment of paroxysmal AF (Table 1). Irrigated open-tip catheters with or without CF sensing as well as the CB and CB-Adv were used for PVI, respectively. The study has concluded that both approaches can be considered equivalent from an efficacy and safety perspective. However, procedure and LA dwell times were significantly lower in the CB group, whereas fluoroscopy time was significantly longer when compared to the RF group. Moreover, patients undergoing CB ablation had significantly fewer repeat ablations, cardioversions, all-cause and cardiovascular rehospitalizations during follow-up [29].

At the same time, many other experiences reported no difference between RF and CB ablation in terms of clinical as well as safety outcome in the treatment of both PAF and PersAF [30–33]. The PNP has almost exclusively been reported during CB ablation, being fortunately reversible during the follow-up. The incidence of persistent PNP was 4.5% [34]. One study reported on a higher incidence of persistent iatrogenic septal defects following CB ablation as compared to RF ablation; however, the clinical significance of such events is still uncertain [35].

Additionally, the relative simplicity of CB ablation results in more reproducible and less operator-depended clinical outcomes than RF ablation [36]. Therefore, CB ablation might be particularly

beneficial for centers with less experienced operators and a lower number of catheter ablations per year. However, RF ablation currently allows for individual ablation strategies using more versatile catheters and thus it can be beneficial in searching and treating additional ablation targets beyond the PVs [37].

Freezing duration and dosing strategies

Although it has been proved that CB-Adv ablation is highly effective in achieving both a successful PVI and freedom from arrhythmic recurrences, the ideal freezing duration and the adequate number of freeze-thaw cycles are not well established [5,20,38]. An initial recommendation suggested a 240 seconds (4 minutes) application followed by a "bonus freeze" of the same duration. Current preclinical data suggest that the CB-Adv achieves durable PVI with significantly shorter freeze cycle duration [13,15]. After the first clinical observations that a single 3-minutes freeze cycle allowed roughly 90% of acute PVI [39], a single-freeze approach led to approximately 80% of arrhythmia freedom at 1-year follow-up [23,40–42]. We have recently reported the 2-year efficacy of the single 3-minutes approach demonstrating that arrhythmia freedom was comparable to the conventional 4-minutes plus bonus freeze strategy (77.5% vs 78.8%; $p = 0.82$). A freeze duration reduction may be also associated with a significantly shorter procedure time and lower fluoroscopy exposure, thus providing potential benefits in terms of risk of procedure-related complications. The date available in the literature consistently support a 'single-freeze approach', as the concept of providing an extra application after having already achieved isolation seems to be unnecessary and perhaps potentially dangerous.

Moreover, during 4-minute ablations, additional mean temperature drop from 3 to 4 minutes is roughly $-1/-2$ °C. These findings might be explained by previous experimental observations, reporting that cryoablation lesion size measured by ice grows progressively during the first 3 minutes of freezing in atrial myocardium, and additional 1-minute ablation duration does not determine further benefit as transmural damage is already achieved [12]. Thus, shortening cycle duration might avoid further perhaps unnecessary applications, reducing the risk of neighboring structures damage. Therefore, according to both preclinical and clinical findings gathered from the growing experience in the setting of CB-Adv ablation, the recommendation of performing 4-minute freezes might be obsolete.

Real-time predictors of PVI

PV-specific dose optimization during CB-Adv ablation has gained in clinical interest; the careful analysis of specific parameters during the ongoing lesion, such as time-to-effect, have shown to be important predictors of successful and durable PVI [43,44]. In contrast with a "one-dose-fits-all" approach, this method can be tailored to each PV, potentially reducing ablation time without negatively affecting efficacy. This approach might also predict suboptimal ablations at the beginning of the freeze-thaw cycle, which may warrant abortion of the cryoapplication with subsequent balloon repositioning and further re-ablation. Several studies have reported predictors of successful electrical isolation [43–45].

During CB ablation, the most important maneuver involves PV occlusion with the inflated balloon to achieve continuous circumferential contact. The quality of the occlusion achieved during the procedure is crucial for a successful isolation, and assessment of this contact should help to predict the efficacy of lesion formation. We have recently reported our data regarding potential predictors of persistent PVI following CB-Adv ablation [44]. In a cohort of patients undergoing a repeat ablation because of arrhythmic recurrences, performed at a mean 11.6 ± 4.5 months after the index procedure, persistent PVI could be documented in 90/115 PVs (78.2%). A shorter time-to-isolation (TTI) and a lower nadir temperature seem to be more frequently observed in patients who do not experience arrhythmic recurrences after ablation as reported by previous observations [45,46]. Moreover, if isolation is achieved within 1 minute, a late PV reconnection might be ruled out with a 96.4% negative predictive value demonstrating a direct link between fast isolation times and durable isolation.

Reissmann and colleagues have recently assessed the efficacy of an individual TTI-guided ablation protocol using the CB-Adv in the treatment of paroxysmal and early-persistent AF patients [47]. In this study, when isolation could be verified using a spiral mapping catheter (ILMC; Achieve, Medtronic Inc, MN, USA), freezing was continued for a fixed period of 120 seconds. Conversely, if real-time PV recording was not feasible freeze-cycle duration was set at 240 seconds. All PVs could be isolated with a mean 1.1–1.3 freeze-thaw cycles and the overall success rate of this TTI-guided approach was 72% after 1-year follow-up, which is in line with previous experiences using this method.

Unfortunately, PV potentials may not always be visible, especially when approaching lower PVs. A pull-back maneuver of the MC, after having achieved a satisfactory occlusion, or use of the shorter-tip CB might be effective in increasing the visualization rate. While diagnostic reliability of the MC catheter may be questioned, clinical outcomes following Cryo-PVI using the MC are excellent; therefore there is no proven benefit to recommend the use of a dedicated circular mapping catheter. Furthermore, the use of the novel 25 mm Achieve catheter has been shown to significantly improve real-time recordings during CB ablation when compared to the standard 20 mm MC [48].

Of note, a recent article sought to investigate CB-Adv efficacy based on the attainment of a < -40 °C within the first 60 seconds [49]. Acute isolation of 99% of veins was seen and virtually all veins in which the desired temperature could not be reached during the first freeze and were reengaged with a guidewire led to better temperature recordings during the second application. After a 12-month period this temperature-based approach was comparable to ablation guided by the MC. Moreover, the authors reported a comparable arrhythmia recurrence rate to a similar group of patients matched by propensity-score previously treated with a CB-Adv using a MC.

Other indicators of efficacy may be available only during an ongoing cryoablation indicating the temperature slope during the application. We have demonstrated that achievement of -40 °C within 1 minute independently predicted long-term isolation persistency. In our previous experience, the abovementioned cut-off was selected for various reasons. Progressive cooling below -40 °C results in the formation of intracellular ice crystals, which is the first step in ensuring adherence of the catheter to the tissue during the cryo-lesion [50] and eliminating the "brushing effect" due to cardiac and respiratory movement. In addition, full-flow cryorefrigerant is usually achieved within 1 minute, and at that time the slope of the curve starts to plateau.

These parameters may not only be a marker of an effective ablation, but they can also actively guide the operator throughout the entire procedure by aborting the application and repositioning the CB to achieve better parameters and ensure a better "curve shape" (Fig. 3).

A temperature-guided approach, without the use of a PV mapping catheter, may certainly bear the advantage of being significantly cheaper without sacrificing the clinical outcome [49]. However, it is noteworthy that an EP-guided approach is currently supported by larger clinical evidence (i.e. multicenter analysis, randomized studies) [43,47]. Therefore, using currently available procedural feedback, a multi-parametric approach based on both the *freeze-curve shape* and the time needed to achieve isolation

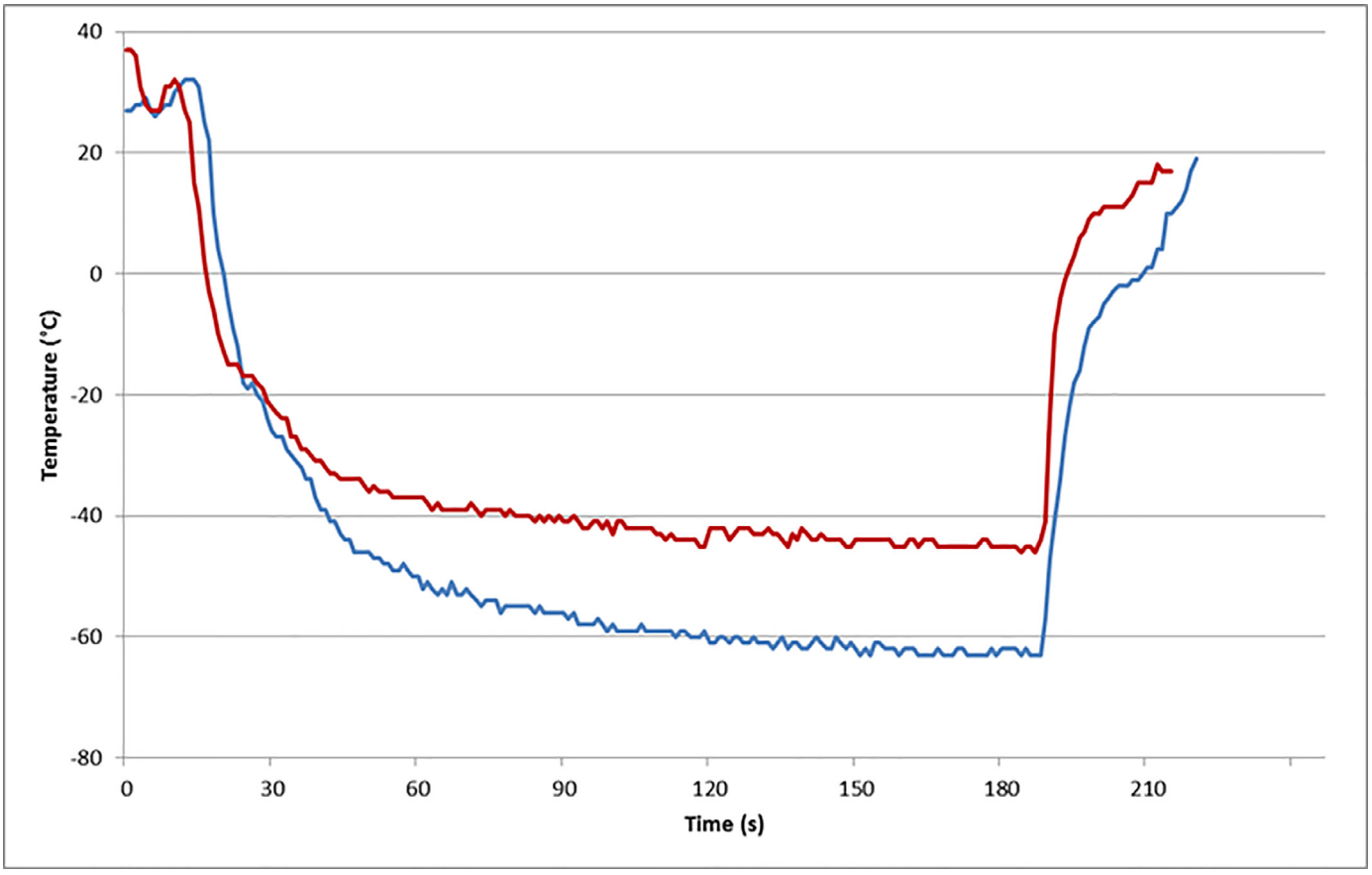

Fig. 3. Example of two different cryoapplications derived from the same patient at the time of CB-Adv ablation procedure. The patient underwent a redo ablation using a 3-D mapping system demonstrating a reconnection in the RIPV (red curve), while the LSPV was persistently isolated 10-months after the index ablation (blue curve). Of note, the LSPV (blue) received a better cryoapplication resulting in a different curve shape as compared to the RIPV (red), showing a lower nadir temperature and −40 °C achievement within the first minute. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

might represent a true tailored strategy when performing a Cryo-AF ablation, aiming at the best clinical result with the lowest risk of complications.

In our laboratory, we follow a TTI-guided approach if PVPs are visible, otherwise we rely on the temperature-curve analysis during the freeze cycle, trying always to avoid second or bonus freeze. In both cases, the first minute of the application is crucial in determining whether the PV will be persistently isolated. During the first minute of application, if PVI or −40 °C is not achieved, we always abort the cycle and try to obtain a better occlusion, as it has been demonstrated in canine model that freeze prolongation do not necessarily determine a better lesion [12].

Conclusions and future perspectives

Second-generation cryoballoon ablation has certainly become a well-established strategy in the treatment of AF because of its highly safe and effective profile.

This technology offers several advantages including a rapid learning curve and shorter procedure times making this device widely adopted in many EP-laboratories.

Given the optimized catheter design, it has been demonstrated that the single freeze per-vein strategy provides a favorable safety profile and clinical outcome, questioning the need of a customarily 'bonus freeze' application.

Furthermore, a shorter freezing time, and a titration of the dosing strategy based on a multiparametric evaluation (temperature- and TTI-guided) may further streamline the approach to Cryo-AF reducing the risk of complications, by ensuring a successful long-term outcome.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tcm.2018.11.009.

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