On the Quest for the Best Freeze

Predictors of Late Pulmonary Vein Reconnections After Second-Generation Cryoballoon Ablation

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Background—The second-generation cryoballoon is effective in achieving acute pulmonary vein isolation (PVI) and favorable clinical outcome. To date, no data are available on factors affecting late PV reconnection after second-generation cryoballoon ablation.

Methods and Results—A total of 29 consecutive patients (25 male, 86.2%; mean age 57.8±13.8 years) underwent a repeat procedure, after a mean 11.6±4.5 months (range, 3.5–19.7 months), after index ablation using the 28-mm second-generation cryoballoon. All repeat ablations were performed using a 3-dimensional electroanatomical mapping system. Among all 115 PVs, including 1 left common ostiums (LCOs), 25 (21.7%) showed a PV reconnection in 20 patients (1.25 per patient). Persistent PVI could be documented in 90 of 115 PVs (78.2%). In 9 of 29 patients (31%), all PVs were electrically isolated. In the multivariable analysis, time to PVI (P=0.03) and failure to achieve −40°C within 60 s (P=0.05) independently predicted late PV reconnection. At receiver-operator curve analysis, time to PVI <60 s identified the absence of PV reconnection (sensitivity, 86.7%; specificity, 86.2%; positive predictive value, 59.1%; and negative predictive value, 96.4%; area under the curve, 0.85; confidence interval, 0.73–0.97; P<0.001).

Conclusions—The rate of late PV reconnection after second-generation cryoballoon ablation is low (1.25 PVs/patient). Faster time to isolation and achievement of −40°C within 60 s independently predict durable PVI. In addition, 60-s cutoff for time to PVI indicates persistent isolation with 96.4% negative predictive value. These parameters might guide the operator whether to perform further applications to ensure a long-lasting PVI. (Circ Arrhythm Electrophysiol. 2015;8:1359-1365. DOI: 10.1161/CIRCEP.115.002966.)

Key Words: atrial fibrillation ■ cryoballoon ablation ■ pulmonary vein isolation ■ pulmonary vein reconnection ■ second-generation cryoballoon

Pulmonary vein isolation (PVI) represents the cornerstone treatment for atrial fibrillation (AF).1 Data available in the literature indicate that second-generation cryoballoon (CB-Adv; Arctic Front Advance, Medtronic, MN) is a safe and effective tool in achieving both acute PVI and favorable clinical outcome.2-4 Despite encouraging results, arrhythmic recurrences after the index procedure remain relatively frequent which, in most of cases, might be related to PV reconnections, potentially reflecting the lack of efficacy in achieving transmurality and homogeneous long-lasting lesions.2-7

To date, little information is available about occurrence of late PV reconnection after CB-Adv ablation.6 Although, recently published data indicates that roughly 90% of PVs are still isolated 3 months after CB-Adv ablation,2 to the best of our knowledge, predictors of late PV reconnections after CB-Adv ablation for the treatment of AF have not been identified yet.

Methods

Aim of the Study

The aim of the study was to assess predictors of late PV reconnections after PVI initially achieved using CB-Adv. Electric reconnection rate and gap localization were also taken into consideration as an end point.

Study Population

In this study population, all index CB-Adv procedures were performed as from October 2012 (Table 1). All patients having undergone a repeat procedure for atrial tachyarrhythmia (ATa) recurrence after PVI...
WHAT IS KNOWN

- Second-generation cryoballoon is highly effective in achieving pulmonary vein (PV) isolation and favorable clinical outcome.
- Data on late PV reconnections after second-generation cryoballoon ablation are sparse.

WHAT THE STUDY ADDS

- The rate of late PV reconnection after second-generation cryoballoon ablation is low (1.25 PVs/patient).
- Time to isolation and achievement of −40°C within 60 s are independent predictors of durable PV isolation.
- A cut-off of 60 s for time to PV isolation indicates persistent isolation with 96.4% negative predictive value.

initially achieved with CB-Adv were consecutively included in this study and clinically followed-up according with our standard clinical practice (Table 2). Exclusion criteria were long-standing persistent AF, the presence of an intracavitary thrombus, uncontrolled heart failure, moderate or severe valvular disease, previous PVI procedure, and Contraindications to general anesthesia. The study was approved by the institutional ethics committee on human research of our Institution.

Preprocedural Management

All patients provided written informed consent to the procedure. Structural heart disease was defined as: coronary artery disease, impaired left ventricular ejection fraction <40%, LV hypertrophy >15 mm, valvular insufficiency >2 of 4, significant valvular stenosis, and previous valve replacements. All antiarrhythmic drugs were discontinued at least 3 days before ablation, except amiodarone, which was interrupted 1 month before. For patients under novel anticoagulant agents, our practice is to stop anticoagulation as follows: (1) the last dose of dabigatran was given the morning 1 day before the procedure; (2) and the last dose of rivaroxaban was given the evening 2 days before. For warfarin, uninterrupted administration is performed. No patient was receiving apixaban. A transthoracic echocardiogram was performed within 1 week before ablation. To exclude the presence of intracavitary thrombi, all patients underwent transesophageal echocardiography, the day before the procedure. All patients underwent a preprocedural computed tomographic scan to assess detailed LA and PV anatomy.

Cryoballoon Ablation as Index Procedure

Our standard ablation procedure has been previously reported in detail. All CB-Adv ablation were performed under general anesthesia. Briefly, after obtaining LA access, through a steerable 15 Fr sheath (FlexCath Advance, Medtronic), inner lumen mapping catheter (MC; Achieve, Medtronic) was advanced in each PV ostium. A 28-mm CB-Adv (Arctic Front Advance, Medtronic) was advanced inflated and positioned in each PV ostium. Optimal vessel occlusion was considered as achieved when selective contrast injection showed total contrast retention with no backflow to the atrium. Once occlusion was documented, cryothermal energy was started. Cryoenergy applications lasted at least 180 s. PV activity was recorded with the MC at a proximal site in the ostium before ablation in each vein. During ablation, if PV potentials were visible during energy delivery, time to isolation was recorded when PV potentials completely disappeared or were dissociated from LA activity. Durable PVI was assessed at least 20 minutes after cryoenergy application. To avoid phrenic nerve palsy, a decapolar catheter was inserted in the superior vena cava and diaphragmatic stimulation was achieved by pacing the ipsilateral phrenic nerve with a 1200-ms cycle and a 20-mA output. During the whole procedure, activated clotting time was maintained >250 s by supplementing heparin infusion as required. Total procedure duration was considered as from having obtained femoral venous access to catheter removal.

Repeat Ablation Procedure

A repeat ablation procedure using an RF irrigated-tip CF catheter was offered to all patients experiencing ATa recurrences, except to those who became responsive to previously ineffective drugs or with short-lasting arrhythmic episodes. All patients agreed to undergo a repeat ablation. Briefly, after double-transseptal puncture, 3-dimensional LA reconstruction geometry was performed with CARTO3 (Biosense-Webster). The circular mapping catheter was positioned in each proximal PV ostium to assess potential reconnection and to facilitate localization of conduction gaps. Late PV reconnection was defined as an LA–PV electric reconduction observed at the time of

| Table 1. Clinical Characteristics of the Entire Cohort Having Undergone Cryoballoon Ablation |
|----------------------------------|------------------|------------------|------------------|------------------|
| Age, y                          | 60.5±9.5         | 61.3±12.7        | 59.7±10.2        | 0.45             |
| Male, n (%)                     | 169 (80)         | 139 (80)         | 32 (78)          | 0.66             |
| LA dimensions, mm               | 45.9±4.2         | 46.7±5.1         | 45.3±7.8         | 0.16             |
| CHA2DS2-Vasc score, n           | 1.3±1.2          | 1.2±0.5          | 1.3±1.7          | 0.51             |
| Paroxysmal AF, n (%)            | 175 (83)         | 142 (83)         | 33 (81)          | 0.65             |
| Time to PVI, s                  | 52.3±15.1        | 40.2±18.7        | 65.7±25.3        | <0.001           |
| Nadir temperature, °C           | −50.6±7.5        | −53.5±5.8        | −49.3±9.7        | <0.001           |
| Mean temperature at 60 s, °C    | −43.7±10.5       | −46.3±5.2        | −39.5±6.8        | <0.001           |
| Mean total number of freezes, n | 1.5±0.9          | 1.3±0.5          | 1.4±0.8          | 0.31             |
| Mean LSPV freeze duration, s    | 280±144          | 279±130          | 299±115          | 0.36             |
| Mean LIPV freeze duration, s    | 303±141          | 286±139          | 311±141          | 0.29             |
| Mean RIPV freeze duration, s    | 292±146          | 289±143          | 306±145          | 0.49             |
| Mean RSPV freeze duration, s    | 269±122          | 255±126          | 284±130          | 0.19             |

Data are expressed in mean±SD or number and percentage as appropriate. AF indicates atrial fibrillation; LA, left atrium; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PV, pulmonary vein isolation; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.
the repeat procedure. The location of gaps along previously deployed circumferential lesions was defined as the site of late PV reconnection in 4 different anatomic regions of the PV antrum: antero-superior, antero-inferior, postero-inferior, and postero-superior. Once localized, irrigated RF applications were applied on the conduction gaps until documented isolation, which was also evaluated after 30 minutes. Contact-force data were continuously monitored throughout the entire procedure, with the aim to achieve at least 10 g (mean) with a vector perpendicular to the tissue and with an upper limit of 50 g. Patients experiencing PV reconnection underwent re-PVI. In case of atrial tachycardia, the 3D electroanatomical mapping system allowed to identify the underlying mechanism. After atrial tachycardia termination, if necessary, reisolation of the PVs was also performed in sinus rhythm.

**Follow-Up**

After discharge, patients were scheduled for follow-up visits with baseline ECG and 24-hour Holter recordings at 1, 3, 6, and 12 months. Any symptoms after ablation were deemed as deserving a Holter monitoring. All reports of Holter or ECG recordings having been performed in referring centers were sent to our center for confirmation of the diagnosis of ATa recurrence. Furthermore, telephone calls were performed during the follow-up. All documented ATa episodes >30 s after the index procedure, with standard ECG or 24-hour ECG Holter monitoring and during both planned and symptom-driven consultation, were considered as a recurrence.

**Statistical Analysis**

Categorical variables are expressed as absolute and relative frequencies, whereas continuous variables are expressed as mean±SD. Comparisons of continuous variables were done with a Student t test and binomial variables with $\chi^2$ or Fisher test as appropriate. Factors predicting PV reconnections were identified by univariate and multivariable analyses using the Cox proportional hazards regression model. To avoid overfitting of the model, the convention of limiting the number of independent variables entered was followed. In our analysis, independent variables for entry into the model were selected according to their weight on univariate testing ($P$ values and shorter 95% confidence intervals); consequently, 2 variables were eligible for this analysis: time to PVI and achievement of $-40^\circ$C within 60 s (nollyes=0/1). Receiver-operator characteristic (ROC) curve was constructed to evaluate the performance of time to PVI in predicting arrhythmia recurrence. Procedural parameters were analyzed using generalized estimated equations methods (logit models, Table 3) or robust sandwich covariance estimators (Cox models, Table 4) to account for multiple observations per patient (ie, 4 PVs). A 2-tailed probability value of <0.05 was deemed significant. Statistical analyses were conducted using the SPSS software (SPSS v22, Chicago, IL).

**Results**

**Study Population**

Among a total of 212 patients having undergone CB-Adv ablation from October 2012 to December 2013, 171 did not show arrhythmic episodes during the follow-up, whereas 41 continued to experience arrhythmic recurrences (Table 1). Nadir and mean temperature at 60 s during cryoenergy application were significantly higher in those experiencing arrhythmic recurrences when compared with those who did not (Table 1). In addition, time to isolation was significantly shorter in patients who did not experience ATa recurrences (Table 1). No other differences could be observed between the groups (Table 1). A repeat ablation procedure was only offered to patients

### Table 1. Index Procedure Characteristics According to PV Isolation Persistency

<table>
<thead>
<tr>
<th></th>
<th>CB-AdvA (n=90)</th>
<th>Late PVI (n=25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of applications, n</td>
<td>1.3±0.6</td>
<td>1.5±0.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Single freeze, n</td>
<td>64 (71.1)</td>
<td>14 (56)</td>
<td>0.22</td>
</tr>
<tr>
<td>Nadir temperature, °C</td>
<td>−51.5±4.7</td>
<td>−48.7±4.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Time to PVI, s</td>
<td>42.3±27.2</td>
<td>71.4±18.8</td>
<td>0.05</td>
</tr>
<tr>
<td>−40°C in 60 s, n</td>
<td>68 (75.5)</td>
<td>5 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean occlusion grade, n</td>
<td>3.8±0.4</td>
<td>3.7±0.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Real-time PVI, n (%)</td>
<td>65 (72.2)</td>
<td>16 (64)</td>
<td>0.48</td>
</tr>
<tr>
<td>Rewarming time, s</td>
<td>30.6±3.8</td>
<td>28.9±4.8</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are expressed in mean±SD or absolute number (percentage). CB-AdvA indicates second-generation cryoballoon ablation; PVI, pulmonary vein isolation; and PVR, pulmonary vein reconnection.
experiencing ATa recurrences, except to those responsive to previously ineffective drugs or with short-lasting arrhythmic episodes. Among 41 patients having arrhythmia recurrences, 29 (25 male, 86.2%; mean age 57.8±13.8 years) underwent a repeat ablation, after a mean 11.6±4.5 months (range, 3.5–19.7 months) after index PVI procedure carried out with CB-Adv technology for paroxysmal and early persistent AF (PAF and earlyPersAF). Table 2 shows baseline clinical characteristics of the study population. At the preprocedural computed tomographic scan, a discrete LCOs could be observed just in 1 patient, whereas a distinct 4-PV pattern was present in the remaining 28 patients (96.5%).

Index Ablation Procedural Characteristics
Among all 115 identified PVs, including LCOs, acute isolation was achieved in 105 veins (91.3%) during the first freeze. PV potentials during cryoapplications could be observed in 81 PVs (70.4%): 21 of 28 left superior pulmonary veins (LSPVs; 75%), 19 of 28 left inferior PVs (LIPVs; 67.8%), 22 of 29 right superior PVs (75.8%), and 19 of 29 right inferior PVs (RIPVs; 65.5%). After a single application, PVI was achieved in 27 of 28 LSPVs (96.4%), 26 of 28 left inferior PVs (92.8%), right superior PVs 25 of 29 (86.2%), and 27 of 29 right inferior PVs (93.1%). Additional cryoballoon applications were necessary to achieve PVI in the remaining cases. At the end of the procedure, all veins were isolated with 1.4±0.6 mean number of freeze–thaw cycles. All cryoapplications were performed with the large 28-mm balloon allowing successful isolation in all veins without the need of additional focal catheter applications.

Late PV Reconnection After CB-Adv Ablation
Among all 115 PVs, including 1 LCOs, 25 (21.7%) showed a late PV reconnection in 20 patients (1.25 per patient), at the time of repeat ablation procedure (Figure 1). Overall, persistent PVI could be documented in 90 of 115 PVs (78.2%; Figure 2). In 9 of 29 patients (31%), persistent isolation could be demonstrated in all PVs, whereas PV reconnection could be documented in 20 of 29 patients (69%). In addition, none of the patients exhibited reconnection in all 4 veins. According to the PV location, different rates of persistent isolation could be documented: 26 LSPVs (92.9%), 22 left inferior PVs (78.6%), 21 right superior PV (72.4%), and 21 right inferior PVs (72.4%). In the patient with LCOs, a conduction gap could be observed in the inferior aspect of the vein (Figure 3, blue star). Among all 25 reconnection veins, 16 (64%) were in right-sided PVs, whereas 9 (36%) were in left-sided PVs (P=0.17). Only 2 of 25 (8%) reconnections were located in the LSPV, therefore, representing the less frequent site of conduction gap. Of 25 PV reconnections, a single freeze was applied at the time of index procedure in 14 of 25 PVs (56%), whereas the remaining 11 of 25 veins (44%) received a bonus freeze (P=0.23). Of note, only 1 patient experienced a transient phrenic nerve palsy during right superior PV treatment, determining a premature freeze termination (total application time was 120 s). At the time of repeat procedure, both right-sided PVs were persistently isolated. Spatial distribution of late conduction gaps per PV region is shown in Figure 3.

Predictors of Late PV Reconnections
Late PV reconnection occurrence was associated with warmer nadir temperature (−48.7±4.7 versus −51.5±4.7°C; P=0.009), longer time to isolation (71.4±18.8 versus 42.3±27.2 s; P=0.001), and failure to achieve −40°C within the first 60 s of application (20/25, 80% versus 22/90, 24.4%; P<0.001) during the index procedure (Table 3). However, no difference could be observed in mean rewarming time among veins showing or not PV reconnections (P=0.08). No statistically significant difference could be also observed in the other procedural aspects such as mean number of application, total duration of application (single versus bonus freeze), real-time PVI recording, and degree of occlusion (Table 3). In the univariate analysis, time to PVI, −40°C achievement within 60 s and nadir temperature were significantly associated with LA–PV reconnection (Table 4). Multivariable analysis confirmed time to PVI and failure to achieve −40°C within 60 s as independent predictors of late PV reconnections (Table 4). ROC curve was constructed from time to PVI (Figure 4). Predictive performance increased with faster time to isolation showing an area under the curve of 0.83 (confidence interval, 0.734–0.937; P<0.01). A time to PVI <60 s presented 86.7% sensitivity and 86.2% specificity, with a 59.1% of positive predictive value and 96.4% negative predictive value.
Repeat Procedure Electrophysiological Findings
A total of 29 patients underwent a redo procedure, which was performed with an RF irrigated-tip catheter guided by CF monitoring using a 3D electroanatomical mapping system. The repeat procedure was performed because of AF recurrence in 25 of 29 patients (86.2%), whereas a regular atrial tachycardia was documented in 4 of 29 patients (13.8%; Figure 5). Atrial tachycardias presented as roof-dependent left flutter in 1 patient, mitral-isthmus–dependent flutter in another 1 and 2 of 5 showed PV reconnections in the left inferior PV and right inferior PV, respectively. Re-PVIs and substrate ablations were successfully performed in all patients. A mean number of 3.0±1.6 RF applications was needed to achieve PV reisolation. Cryolesions were located at the PV antrum and point-by-point RF applications focused at the gaps without the need to ablate the whole quadrant. Among 7 patients receiving additional RF applications (Figure 5), 4 were treated with a cavotricuspid line, 2 with a roof line, and 1 with a mitral isthmus line. None of the patients died or experienced cerebrovascular events in the periprocedural period. After a mean follow-up of 10.5±6.1 months, 5 of 29 (17.2%) continued to experience symptomatic AF episodes. None of those presenting with atrial tachycardia experienced further arrhythmic recurrences.

Discussion
To the best of our knowledge, this is the first study reporting predictors of late PV reconnection after CB-Adv ablation. The main findings of our study are (1) PV reconnection rate is 22% (1.25 PVs/patient); (2) time to isolation and −40°C achievement within 60 s are independent predictors of PV reconnections; and (3) 60-s cut-off for time to PVI indicates persistent isolation with 96.4% negative predictive value.

Recovered PV Conduction After PVI
Although recent developments in catheter design aiming at ablation lesion improvement, the incidence of clinical recurrences after PVI is still not negligible. Recovery of conduction has proven to be the cause of the vast majority of ATa recurrences after PVI and conduction gaps ablation represents the cornerstone in the management of patients undergoing a repeat procedure. In our study, electric conduction gaps could be identified in 68.9% of patients in at least 1 PV. In addition, the rate of persistent PVI is considerably high as observed in our series (78.3%), and this finding is in line with recently published data, reporting 77% to 91% rate of durable PVI roughly 6 and 3 months after initial CB-Adv ablation, respectively. The low incidence of late reconnections after CB ablation, as observed in our study, might be because of the novel catheter design, which results in a larger and more uniform zone of freezing on the balloon surface. This technology might offer better catheter stability in particular LA structures, such as the appendage–LSPV ridge, if compared with a focal RF catheter. In fact when using cryoenergy, the balloon adheres to the atrial wall when reaching lower temperatures,
thus resulting in a better catheter–tissue contact and leading to more transmural lesions in such critical anatomic regions. The latter may also explain the lower reconnection rate in LSPV after CB ablation when compared with the point-by-point RF approach.

Predictors of Late PV Reconnections

Cryoballoon temperature is automatically monitored overtime during freezing. It gives reliable information about balloon–tissue contact, explaining the association of low temperatures with ablation efficiency.13,14 As demonstrated in our series, a late PV reconnection was more frequent in those veins with a warmer nadir temperature and a delayed time to isolation. Interestingly, these findings are in agreement with previous studies, showing that a minimal temperature ≤51°C predicted successful isolation and no acute resumption of PV conduction.13,15 However, the multivariable analysis showed that time to PVI and failure to achieve −40°C within the first minute of cryoenergy application are independent predictors of late PV reconnections. In addition, a faster time to PVI is usually achieved with the CB-Adv when compared with its predecessor.3 As observed in our series, a longer time to isolation was associated with an increased incidence of late reconnection. Conversely, a shorter time to isolation and a lower nadir temperature seem to be more frequently observed in patients who do not experience arrhythmic recurrences after ablation, as occurred in our cohort. This seems to be in agreement with previously published observations describing that a longer time to effect is associated with acute PV reconnection and clinical arrhythmic recurrences.5,15 Of note, according to our data, if isolation is achieved within 60 s, a late PV reconnection might be ruled out with a 96.4% negative predictive value. For the first time, this finding shows a direct link between fast isolation times (ie, <1 minute) and durable PV isolation. Moreover, as demonstrated in this study for the first time, the achievement of −40°C within 60 s significantly predicted long-term persistency of PVI. This new parameter might be a reliable indicator of the correlation between the slope of the freezing curve and the durability of isolation. The abovementioned cut-off was selected for various reasons. First, lesion formation with cryoenergy is based around the generation of hypothermia at the catheter–tissue interface. 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 cryolesion.16 In addition, full-flow cryorefrigerant is usually achieved within 1 minute, and at that time the slope of the curve starts to plateau. Therefore, during hypothermia the catheter adheres to the tissue affording greater stability, therefore, eliminating the brushing effect that occurs during beat-to-beat rocking heart motions and with respiratory variations.17

Limitations

The study was a nonprospective, nonrandomized, single-center trial conducted in a relatively limited number of patients. Future larger studies with longer follow-up are needed to confirm these data. A further limitation of this study consists in the fact that only patients with documented ATa recurrences after the index procedures have been included. Therefore, the rate of late PV recovery in our patient cohort might represent an overestimation of the real incidence of late PV reconnections in individuals having undergone CB-Adv ablation. The parameter failure to achieve −40° within 60 s has been derived from a retrospective analysis of the data. For this reason, a prospective study is necessary to confirm its usefulness. Nor systematical esophageal probe neither esophagastroduodenoscopy were used, thus the incidence of esophageal lesions after ablation might have been underestimated.18 Finally, diaphragmatic electromyography (compound motor action potentials) is valuable in predicting and potentially preventing phrenic nerve palsy during cryoballoon ablation.19 However, compound motor action potentials has not been performed in this study. Some observations might be relevant for further statistical analysis. Despite independent variables for entry into the multivariable model have been selected according to their weight on univariate testing to avoid potential overfitting, we cannot exclude that nadir temperature might be an...
independent predictor as well. Further prospective and larger studies are needed to assess this issue.

Conclusions

The rate of late PV reconnection after CB-Adv ablation is low (1.25 PVs/patient). Faster time to isolation and achievement of −40°C within 60 s independently predicted durable PVI. In addition, 60-s cut-off for time to PVI indicates persistent isolation with 96.4% negative predictive value. These parameters may not only be a marker of an effective ablation, but they can also guide the operator whether to perform further applications to ensure a long-lasting PVI.

Disclosures

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References


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