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Optimizing ablation duration using dormant conduction to reveal incomplete isolation with the second generation cryoballoon: A randomized controlled trial

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Abstract

Introduction: Efficacy of cryoballoon ablation depends on balloon-tissue contact and ablation duration. Prolonged duration may increase extracardiac complications. The aim of this study is to determine the optimal additional ablation duration after acute pulmonary vein isolation (PVI).

Methods: Consecutive patients with paroxysmal AF were randomized to three groups according to additional ablation duration (90, 120, or 150 seconds) after acute PVI (time-to-isolation). Primary outcome was reconnection/dormant conduction (DC) after a 30 minutes waiting period. If present, additional 240 seconds ablations were performed. Ablations without time-to-isolation <90 seconds, esophageal temperature <18°C or decreased phrenic nerve capture were aborted. Patients were followed with 24-hour Holter monitoring at 3, 6, and 12 months.

Results: Seventy-five study patients (60 ± 11 years, 48 male) were included. Reconnection/DC per vein significantly decreased (22%, 6% and 4%) while aborted ablations remained stable (respectively 4, 5, and 7%) among the 90, 120, and 150 seconds groups. A shorter cryo-application time, longer time-to-isolation, higher balloon temperature and unsuccessful ablations predicted reconnection/DC. Freedom of atrial fibrillation was, respectively, 52, 56, and 72% in 90, 120, and 150 seconds groups ($P = 0.27$), while repeated procedures significantly decreased from 36% to 4% ($P = 0.041$) in the longer duration group compared to shorter duration group (150 seconds vs 90 seconds group). In multivariate Cox-regression only reconnection/DC predicted recurrence.

Conclusion: Prolonging ablation duration after time-to-isolation significantly decreased reconnection/DC and repeated procedures, while recurrences and complications rates were similar. In a time-to-isolation approach, an additional ablation of 150 seconds ablation is the most appropriate.

KEYWORDS
atrial fibrillation, cryoballoon ablation, dormant conduction, pulmonary vein isolation, time-to-isolation

1 | INTRODUCTION

Cryoballoon ablation is an effective single-shot technique for the treatment of paroxysmal atrial fibrillation (AF) and is noninferior to radiofrequency catheter ablation.[1] Several ablation protocols for cryoballoon ablation have been proposed.[2,3] Optimizing the ablation duration to obtain durable ablation lesions without causing extracardiac complications is crucial.

It has been shown that time to pulmonary vein (PV) isolation (time-to-isolation) is related to balloon-tissue contact, with a shorter time-to-isolation indicating a better contact.[4] It can be expected that with a fixed ablation duration, a better balloon-tissue contact will lead to an earlier lesion transmurality and a potentially higher risk for extracardiac complications. It may be beneficial to adapt the application duration according to the time-to-isolation.

The most common extracardiac complications related to cryoballoon ablation are right phrenic nerve palsy (7-8%) and esophageal ulceration (12%).[5,6] Right phrenic nerve palsy can be permanent and may lead to significant dyspnea.[7] A rare, but severe complication is the development of an atrio-esophageal fistula, which can be fatal.[8] Optimizing the ablation duration may prevent these complications.

After ablation, testing for dormant conduction (DC) with adenosine can be used to reveal incomplete pulmonary vein isolation (PVI).[9,10] The absence of reconnection/DC after 30 minutes waiting period may be considered as parameter for durable PVI and is therefore selected as a clinical outcome parameter. The primary objective of this randomized clinical trial was to determine the optimal additional ablation after time-to-isolation with absence of reconnection/DC as the primary endpoint.

2 | METHODS

2.1 | Study population

Patients eligible for a first cryoballoon ablation of paroxysmal AF were prospectively included between May 2014 and October 2016 and 1:1:1 randomized to an additional ablation of 90, 120, or 150 seconds (s) after time-to-isolation (Figure 1). Eligibility was determined with a preprocedural CT-scan (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) and defined as no PV diameter >26 mm. Patients with previous catheter or surgical AF ablation or persistent AF were excluded. Study patients gave written informed consent for participation in the study and were blinded to group allocation. Data were collected using the departmental Cardiology Information System (EPD-Vision). The study was approved by the institutional ethical review board and registered at the Dutch national trial register (NL47833.058.14).

2.2 | Ablation procedure

Antiarrhythmic drugs (AAD) except amiodarone were discontinued five-half-lives before ablation. In all patients, a single ablation with the 28 mm second-generation cryoballoon (Arctic Front Advance, Medtronic Inc., Minneapolis, MN) was initially performed. The 23 mm balloon was only used as bail-out in veins with a maximal diameter ≤20 mm when PV occlusion could not be obtained. Total ablation duration for the right superior PV was limited to 180 seconds to prevent phrenic nerve palsy. Time-to-isolation was defined as the time from the start of ablation to the disappearance of PV potentials, registered with a 20 mm intraluminal

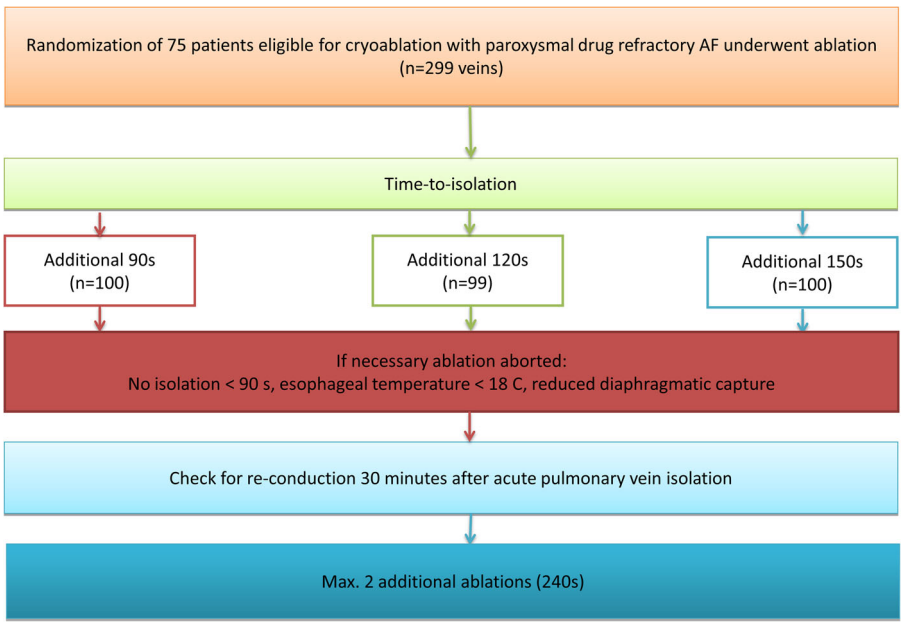

FIGURE 1 Study protocol. Seventy-five patients were enrolled and 1:1:1 randomized into three groups of, respectively, 90, 120, and 150 additional ablation time after reaching isolation of the pulmonary vein. Additional ablations were applied in case of reconnection/dormant conduction. Ablations were aborted if no isolation occurred within 90 seconds, in case of reduced phrenic nerve capture or endoluminal esophageal temperature below 18°C

circumferential mapping catheter (Achieve, Medtronic, Minneapolis, MN). If time-to-isolation was not achieved within 90 seconds, ablation was aborted ("unsuccessful ablation") and the balloon repositioned. If time-to-isolation could not be determined, time-to-isolation was set to 90 seconds to calculate ablation duration. Thirty minutes after ablation, PV isolation was confirmed and adenosine was infused to identify DC. Initial adenosine dose was 18 mg and increased to a maximum of 30 mg to obtain ≥1 sinus beat with blocked AV-conduction. In case of DC, a maximum of two additional ablations with a fixed 240 seconds duration were performed to abolish DC. During ablation of the right veins, absence of phrenic nerve palsy was confirmed by pacing the phrenic nerve from the superior caval vein at 20 mA/2 ms with manual verification of diaphragmatic movement. A nasal temperature probe (Sensitherm, St. Jude Medical, Saint Paul, MN) was used to monitor endoluminal esophageal temperature. Ablation was discontinued immediately ("aborted ablation") using the "double-stop technique" if a reduced diaphragmatic movement or an esophageal temperature <18°C was reached. Repeated ablations were always performed by point-by-point ablation using a Lasso and Thermocool Smarttouch SF Catheter (CARTO, Biosense Webster Inc., Diamand Bar, CA) or the Advisor circular mapping and Tacticath catheters (Ensite, Abbott, St. Paul, MN).

2.3 | Follow-up

Patients were followed 3, 6, and 12 months after ablation with a 24 hours Holter and exercise test. AAD were restarted after the ablation and maintained until the first follow-up at 3 months after ablation. Success was defined as the absence of any recording of AF/atrial tachycardia on ECG or recording of >30 seconds on a 24 hours Holter registration off AAD after a blanking period of 3 months.

3 | STATISTICAL ANALYSIS

Sample size for the prospective randomized groups was calculated based on the incidence of DC in our hospital with the first generation balloon (42%, expected to be comparable with the additional 90 seconds group) and second generation balloon (5%, expected to be comparable with the additional 150 seconds group). For the additional 120 seconds group an expected incidence of 21% was used. A Cochran-Armitage test for linearity was performed to obtain a sample size for the three groups using STATA software, V.12 (Stata Corp, College Station, TX). With $\alpha = 0.05$ the necessary total sample size was 66 patients to detect a significant trend in DC with 80% power. The group size was therefore set at a total sample size of 75 patients. Baseline characteristics were compared between the randomized groups using one-way analysis of variance for continuous variables and χ^2 tests or Fisher's exact test for categorical variables. Predictors for reconnection/DC were tested using multivariate regression analysis. Multivariate Cox-regression was used to identify predictors for recurrence. Variables with a $P < 0.1$ in univariate analyses were entered in the multivariate analysis using the enter method. The log-rank test was used to test differences for AF recurrences. A $P < 0.05$ was considered statistically significant. SPSS (version 23, SPSS Inc., Chicago, IL) was used.

4 | RESULTS

4.1 | Baseline characteristics

Table 1 shows the baseline clinical characteristics of the 75 randomized patients. There were no significant differences in age, sex, and comorbidities between the 90, 120, and 150 seconds groups. All patients had a normal ejection fraction and the mean left atrial diameter was 40 ± 5 mm.

4.2 | Procedural details

The mean procedure time and mean ablation duration for all groups were, respectively, 126 ± 31 and 17 ± 5 minutes and no significant differences were seen between the three groups ($P = 0.053$ and $P = 0.132$, respectively; Table 2). The mean cryoapplication duration

TABLE 1 Baseline characteristics

	90 s (n = 25)	120 s (n = 25)	150 s (n = 25)	*P* value
Age, y	61 ± 11	59 ± 11	60 ± 11	0.857
Male sex	15 (60)	15 (60)	18 (72)	0.594
AF duration, mo	51 [37–112]	24 [12–54]	41 [18–69]	0.066
CHA_2DS_2-VASc score	1.6 ± 1.4	1.1 ± 1.0	1.4 ± 1.1	0.380
LA diameter, mm	39 ± 6	38 ± 5	40 ± 5	0.542
Body mass index, kg/m^2	25.5 ± 3.5	25.0 ± 3.9	25.7 ± 3.4	0.847
AAD at baseline	21 (84)	19 (76)	20 (80)	0.329
Hypertension	11 (44)	7 (28)	14 (56)	0.133
Dyslipidemia	12 (48)	5 (20)	8 (32)	0.109
Diabetes	1 (4)	1 (4)	1 (4)	1.000
Coronary artery disease	1 (4)	2 (8)	1 (4)	0.768
Structural heart disease	4 (16)	4 (16)	1 (4)	0.372

Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; LA, left atrial.
Values are reported as the mean ± standard deviation, median (interquartile range), or n (%).

TABLE 2 Procedural details

	90 s (n = 25)	120 s (n = 25)	150 s (n = 25)	*P* value
Procedure time, min	138 ± 32	118 ± 26	126 ± 31	0.053
Total cryoapplication time, min	18 ± 6	15 ± 4	17 ± 4	0.132
Balloon size (28 mm)	24 (96)	23 (92)	23 (92)	1.000
Balloon size (23 mm)	1 (4)	1 (4)	2 (8)	1.000
Balloon size (23 and 28 mm)	0	1 (4)	0	1.000
Fluoroscopy time, min	24 ± 11	19 ± 9	23 ± 12	0.296
Dose-area product, mSV	2.4 ± 1.5	1.9 ± 1.0	2.8 ± 2.1	0.184
Cavotricuspid isthmus ablation	7(28)	4(16)	4(16)	0.472
Mean time-to-isolation, s	51 ± 25	49 ± 26	52 ± 27	0.641
Mean cryo-application time, s	146 ± 28	167 ± 30	192 ± 34	<0.001
Warming time, s	40 ± 18	41 ± 20	39 ± 19	0.836
Min. balloon temperature , °C	−43 ± 7	−45 ± 7	−45 ± 7	0.038
Min. esophageal temperature, °C	34 ± 5	32 ± 6	33 ± 6	0.249

Values are reported as the mean ± standard deviation or n (%).

was significantly different among the groups (146 ± 28, 167 ± 30, and 192 ± 34 seconds, respectively; $P < 0.001$). The mean number of cryoapplications per patient was 6 ± 2 ($P = 0.339$). Time-to-isolation could be determined for 262 veins (88%). In the remaining veins the disappearance of PV potentials were unclear. Analyses on the differences in biophysical data of the cryoballoon, on the incidence of reconnection and DC and on the predictors of reconnection/DC with exclusion of these pulmonary veins did not influence the results (online supplement). There were no significant differences in time-to-isolation between the four pulmonary veins. In addition, there were no differences in time-to-isolation, minimum balloon temperature, warming time, and minimum esophageal temperature between the three groups. Single-shot isolation was achieved in respectively 81, 79, and 72% of the PVs in the 90, 120, and 150 seconds ($P = 0.254$). There were no significant differences in single-shot isolation rates between the PVs (76% for the left superior PV, 81% for the left inferior PV, 82% for the right superior PV, and 72% for the right inferior PV; $P = 0.465$).

4.3 | PV reconnection/DC

The numbers of patients and PVs with reconnection/DC are specified in Table 3. A significant decrease in reconnection/DC and a corresponding decrease in the number of additional cryo-applications was shown with increasing ablation durations. The procedural duration was also prolonged by the additional applications to abolish dormant conduction and an additional waiting-period of 30 minutes.

4.4 | Predictors of PV reconnection/DC

In multivariate analysis, a shorter cryoapplication time, longer time-to-isolation, a higher nadir balloon temperature and more unsuccessful ablations were associated with a higher incidence of PV reconnection/DC (Table 4). Warming time was not a significant predictor in multivariate analysis.

5 | OUTCOME

During a follow up of 1-year, the single-procedure success rate off AAD was 60% in the total group (68% on/off AAD). Median time to recurrence was 7 (IQR^{5-13}) months. The single-procedure success rates off AAD in the 90, 120 and 150 seconds groups were respectively 52%, 56% and 72% ($P = 0.27$) after 1 year. Total AF-free single-procedure success on/off AAD was, respectively, 56, 72, and 77% ($P = 0.384$). During follow-up a repeated procedure was performed in 15 patients (20%). During the repeated procedure, PV reconnections were observed in 14 patients (19%) and additional ablations were performed in 9 (12%) patients (four superior vena cava, three mitral isthmus line, one posterior left atrial box lesion, one posterior line, and one left atrium anterior wall ablation). During these repeated procedures 53% of the left superior veins were reconnected, 53% of the left inferior veins, 40% of the right superior veins and 20% of the right inferior veins ($P = 0.217$). The rate of repeated procedures significantly decreased with increasing additional ablation time: 36% in the 90 seconds group, 20% in the 120 seconds group, and 4% in the 150 seconds group ($P = 0.041$).

TABLE 3 Incidence of reconnection/DC per patient and per vein.

	90 s (n = 25/100)	120 s (n = 25/99)	150 s (n = 25/100)	*P* value
Reconnection	8 (32)	3 (12)	0	0.005
Reconnection, per vein	9 (9)	3 (3)	0 (0)	0.003
DC	9 (36)	3 (12)	4 (16)	0.085
DC, per vein	15 (15)	3 (3)	4 (4)	0.002
Reconnection/DC	16 (64)	6 (24)	4 (16)	0.001
Reconnection/DC, per vein	22 (22)	6 (6)	4 (4)	0.001

Abbreviation: DC, dormant conduction.
Values are reported as the mean ± standard deviation or n (%).

TABLE 4 Univariate and multivariate regression analyses of the predictors of reconnection/DC in the pulmonary veins

	Univariate		Multivariate	
Variables	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Cryoapplication time (s)	0.991 (0.982-0.999)	0.035	0.975 (0.962-0.988)	<0.001
Time-to-isolation (s)	1.012 (0.999-0.1025)	0.079	1.027 (1.009-1.046)	0.004
Warming time (s)	0.947 (0.955-0.994)	0.011		0.500
Nadir balloon temperature (°C)	1.139 (1.070-1.212)	<0.001	1.163 (1.068-1.266)	0.001
Number of unsuccessful ablations	1.393 (0.998-1.944)	0.052	1.722 (1.113-2.664)	0.015

5.1 | Predictors of recurrence

In multivariate analysis, only PV reconnection/DC was associated with a higher incidence of AF recurrence (Table 5).

6 | COMPLICATIONS

One patient from the 150 seconds group showed persistent phrenic nerve palsy at discharge that was resolved at 1-year follow up. Two patients had complications related to the vascular femoral access, including one patient with a severe bleeding requiring transfusion. In Figure 2 a "safety profile" is made using the number of reconnection/DC, aborted ablations, phrenic nerve palsy, and repeated procedures.

7 | DISCUSSION

7.1 | Main findings

The major finding of this study is that an additional ablation with 90, 120, or 150 seconds after time-to-isolation showed a stepwise decrease in reconnection/DC. Consequently, additional ablations for the treatment of reconnection/DC decreased similarly while the success rates at 1-year off AAD were not significantly different. During follow-up the rate of repeated procedures decreased with increasing additional ablation. To the best of our knowledge, this is the first trial studying single cryoballoon applications with the ablation duration based on time-to-isolation.

7.2 | Decreasing ablation duration with the second-generation cryoballoon

The second-generation cryoballoon with more injection ports for more homogenous and faster cooling was introduced to achieve more durable PVI. At the cost of a higher success rate, more transient and persistent phrenic nerve palsies were described.[11] Instead of a double 300 seconds fixed ablation duration, a double 240 seconds fixed duration was proposed by the manufacturer. Subsequently, studies showed that a single ablation per vein is sufficient.[12] In addition, shortening the ablation duration from 4 to 3 minutes did not increase AF recurrence.[2,13]

7.3 | Making ablation duration dependent on time-to-isolation

Cryothermal energy delivery does not only depend on ablation duration, but also on adequate balloon-tissue contact.[14] As balloon gas flow is constant, time to PVI is related to balloon-tissue contact, with a shorter time-to-isolation indicating a better contact.[15] Indeed, time-to-isolation predicted durable PVI in several studies with

TABLE 5 Univariate and multivariate cox proportional regression analyses of the predictors of recurrence per patient

	Univariate		Multivariate	
Variables	Hazard ratio (95% confidence interval)	*P* value	Hazard ratio (95% confidence interval)	*P* value
Age		0.397		
Male sex		0.119		
BMI, kg/m²		0.782		
LA diameter, mm		0.819		
AF duration, mo		0.483		
Group		0.152		
Reconnection/DC	4.0 (1.465-10.919)	0.007	4.037 (1.446-11.271)	0.008
CTI ablation		0.084		0.096
Diabetes		0.359		

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CTI, cavotricuspid isthmus; DC, dormant conduction; LA, left atrium.

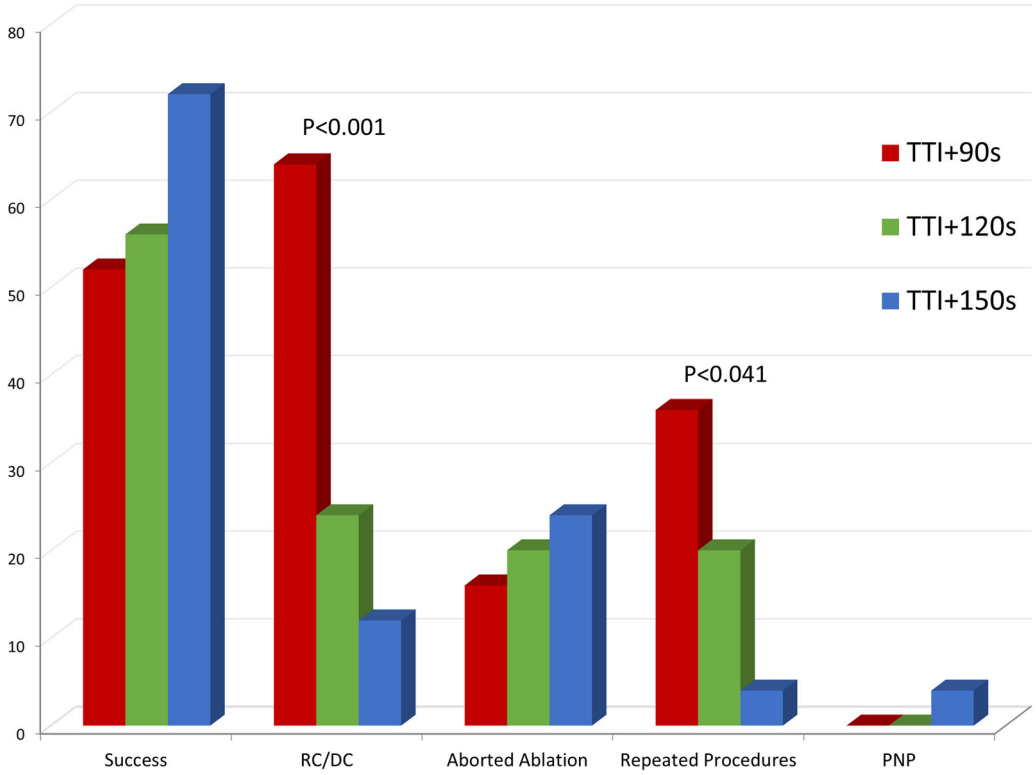

FIGURE 2 Safety profile of the different ablation groups. One-year AF-free survival off antiarrhythmic drugs, percentage of reconnection (RC)/dormant conduction(DC) (per patient), aborted ablations (per patient), phrenic nerve palsy, and repeated procedures across the different groups. There were no significant difference in single-procedure success off AAD, aborted ablations and phrenic nerve palsy (PNP), however significant differences were seen in the percentage of reconnection/dormant conduction ($P < 0.001$) and repeated procedures ($P = 0.041$). PNP, phrenic nerve palsy; RC/DC, reconnection and dormant conduction; TTI, time-to-isolation

significantly lower PV reconnections at 1-year follow up.[4,16] In a canine model, a 60 seconds additional ablation after time-to-isolation showed 100% durable PVI on histology.[17] In addition, extending ablation duration based on a longer time-to-isolation was not associated with durable PVI. Furthermore, a perfect score for the assessment of occlusion was more relevant than total ablation duration in predicting gaps. Therefore, balloon-tissue contact remains the most important factor for durable PVI. Moreover, making ablation dependent on time-to-isolation is feasible, since in a majority of the veins (88%) time-to-isolation could be observed, while other researchers report 72%-81%.[18,19] This percentage may become even higher with the future introduction of the third-generation cryoballoon with a shorter-tip, which facilitates PV electrogram registration.

7.4 | Outcome in time-to-isolation dependent ablation

Two prior studies report on time-to-isolation cryoballoon based ablation. A recent randomized trial by Ferrero-de-Loma-Osorio et al[19] showed in 140 patients that applying 60 seconds additional ablation after time-to-isolation with a second 120 seconds application was similar to a double 180 seconds fixed duration protocol (70.5 vs 74.3% success off AAD at 1 year; $P = 0.61$).[19] In a multicenter trial by Aryana et al[18] an additional ablation of 120 seconds in 355 patients was applied after time-to-isolation, but a second 120 seconds ablation was added when time-to-isolation was >60 seconds. They compared this strategy to conventional ablation performed in 400 pts, which was defined as 2 to 3 applications of 2 to 4 minutes at the discretion of the operator. Outcomes were similar at 83% and 78% at 1-year off AAD ($P = 0.14$).[18] Although we performed no additional ablations in our protocol, our results in the 150 seconds group (72% off AAD at 1 year) are similar to the first study. Interestingly, although we aimed at abolishment of all dormant conducting veins, outcomes were numerically smaller in both the 90 seconds and 120 seconds groups (52% and 56%) compared to the 150 seconds group (72%), suggesting inferiority of this approach. A possible explanation is that during the first incomplete ablation edema occurs,[20] making the second ablation less effective. Indeed, in multivariate analysis we observed that reconnection/DC was the only predictor of recurrence while the number of unsuccessful ablations was a predictor of reconnection/DC. Therefore, a complete lesion formation with a single (durable) freeze may be desirable. In addition, success on AAD was 16% higher than success off AAD in the 120 seconds group, compared to only 4% and 3% difference in the 90 seconds and 150 seconds groups respectively. This may indicate that 120 seconds additional ablation creates enough PV activation delay to maintain sinus rhythm with AAD in this group.

7.5 | Repeat ablation in time-to-isolation dependent ablation

The study of Aryana et al reported 9.9% vs 15.7% reablations in the study and control groups, respectively, with 18.5% vs 5.0% of the veins reconnected.[18] In our study a significant less repeated procedures were required when the additional ablation duration was increased from 90 seconds to 150 seconds (36 vs 4%; $P = 0.041$). As repeated procedures are clinically meaningful, these results suggest that 90 seconds or 120 seconds additional ablation after time-to-isolation is insufficient.

7.6 | Reconnection/dormant conduction in time-to-isolation dependent ablation

Acute PV reconnection is also reported in the trial of Ferrero-de-Loma-Osorio et al[19] In this trial in 140 patients, 3.5 and 2.3% of the veins were acutely reconnected in the study and control groups, respectively ($P = 0.6$).[19] This is comparable to the 4% dormant conduction in our 150 seconds group, while the 90 seconds and 120 seconds groups showed a significant increase in reconnection/DC with decreasing additional ablation.

7.7 | Complications in time-to-isolation dependent ablation

A multicenter comparison of 352 patients undergoing an additional ablation of 120 seconds after time-to-isolation with both a double (152 patients) and single (59 patients) 240 seconds application found 3.7%, 7.9% and 8.5% complications, respectively.[3] However, numbers were mainly driven by remote complications (groin and respiratory tract infections: 0.6%, 1.3%, and 5.1%), while phrenic nerve palsy was present in 2.0%, 5.7%, and 3.4%. In the study of Aryana et al comparing a protocol guided by time-to-isolation (n = 355) vs a conventional group (n = 400), adverse events were similar at 2.0% and 2.7%, with a numerically lower phrenic nerve palsy incidence of 0.6% in the time-to-isolation group vs 1.2 in the control group ($P = 0.33$).[18] The randomized trial of 140 patients reported 8% complications with 3.6% phrenic nerve palsy and no differences between the groups.[19] Our results are comparable to these numbers and were not significantly different between the groups.

8 | LIMITATIONS

This is a small-size single-center randomized study. The study was powered to detect differences in reconnection/DC and not to detect significant differences in complications and recurrence rates. Therefore, a substantial conclusion cannot be drawn regarding outcome and complications. In this study only ablation duration and not contact force and ablation energy were optimized, as contact force cannot be measured by the current technology and ablation energy (balloon gas flow) cannot be adjusted by the operator. Indirect measurements for balloon occlusion, such as fluoroscopic contrast stasis or intracardiac echo doppler measurements were not routinely documented in this study. Due to the small number of patients these factors may have biased the results. In addition, dormant conduction was used to reveal incomplete pulmonary vein isolation, which is only a surrogate for durable PV isolation. In this study the 90 seconds dosing protocol was the least successful with a significant higher number of reconnection/DC. Given the low number of patients in each group, it is possible that there is no significant differences in reconnection/DC between the 120 and 150 seconds group. During follow up only 24-hour Holter monitoring was used, longer rhythm monitoring could have detected more AF-episodes. However, we consequently encouraged patients to seek healthcare support for additional ECG recordings if symptoms occurred.

9 | CONCLUSIONS

An additional ablation with 90, 120, or 150 seconds after time-to-isolation in cryoballoon ablation caused a stepwise decrease in reconnection/DC, a decrease in additional ablations for the treatment of reconnection/DC, while recurrences and complication rates at 1-year were not significantly different. In addition, the rate of repeated procedures during follow-up decreased with increasing additional ablation. Therefore, based on our data selecting an additional ablation of 150 seconds is the most appropriate approach in time-to-isolation based ablation.

CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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