

Impact of atrial rhythm on pulmonary vein signals in cryoballoon ablation – Sinus rhythm predicts real-time observation of pulmonary vein isolation

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ABSTRACT

Purpose: Real-time observation of pulmonary vein (PV) potentials with a spiral mapping catheter has emerged as a key electrogram-based procedural parameter to estimate lesion quality and titrate cryoenergy application during PV isolation (PVI) with the cryoballoon. Whether correct PV electrogram interpretation and thus PVI real-time observation rate depends on atrial rhythm during cryoballoon PVI is unknown. We compared observation rates of time-to-PV isolation (TTI) during sinus rhythm (SR group) and during atrial fibrillation (AFib group) in cryoballoon PVI.

Methods: We prospectively included 157 consecutive patients undergoing cryoballoon PVI and compared the incidence of PVI real-time recording of each pulmonary vein during SR and in AFib.

Results: Overall PVI real-time observation rate was 82.1% (491/598 PV) with significantly higher TTI observation rate in the SR group (315/365 PV, 86.3%) compared to the AFib group (176/233 PV, 75.5%; $p < 0.001$). Per vein analysis demonstrated that only TTI observation rate in the left superior pulmonary vein (LSPV) was significantly higher during SR (85/92, 92.4%) compared to AFib (37/54, 68.5%; $p < 0.001$). Regression analysis revealed that atrial rhythm is a strong and independent predictor of PVI real-time observation in the LSPV with an odds ratio of 4.98 (95%-CI: 1.86–13.34, $p = 0.001$) to detect TTI during SR.

Conclusions: Our results demonstrate that correct interpretation of PV electrograms and thus PVI real-time observation is more likely in SR than in AFib. Hence, cardioversion of patients in AFib at the beginning of the procedure should be considered to yield higher PVI real-time observation rates facilitating TTI guided cryoenergy titration.

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1. Introduction

Real-time observation of pulmonary vein (PV) signals with a diagnostic spiral mapping catheter introduced through the cryoballoon inner lumen provides the option to titrate cryoenergy application during cryoballoon pulmonary vein isolation (CB-PVI). As shown by several studies, 3rd generation cryoballoon facilitates real-time observation due to a shorter distal tip compared to the 2nd generation cryoballoon [1–5].

Hence, various dosing strategies taking the individual time-to-PV isolation (TTI) into account have been reported [6–10]. TTI-based ablation protocols with reduction of freeze duration as well as omission of bonus freezes in case of short TTI led to significantly shortened procedures and reduced fluoroscopy times. Remarkably, TTI-based reduction of cryoenergy application down to a minimum of 2-minute freeze duration without further bonus freezes did not translate into higher AF recurrence rates compared to conventional ablation protocols,

underpinning the clinical value of PV signal recording during cryoballoon ablation [9,11].

Pulmonary vein isolation with the cryoballoon leads to progressive left atrium (LA) to PV conduction delay before complete disappearance of PV signals when the PV is isolated (Fig. 1A and B). Typical PV signals are characterized by sharp near-field potentials with rapid upstroke, high amplitude and narrow width. Electrical signals of adjacent cardiac structures such as the left atrial appendage (LAA), the left ventricle or the right atrium often add far-field potentials, which are sometimes hard to separate from PV near-field electrograms (Fig. 1A).

In atrial fibrillation PV potential interpretation can be limited by reduced amplitudes, varying cycle length and lack of temporal separation, e.g. of LAA far-field and PV near-field electrograms [12]. As a result, fibrillatory electrical activation of the atrium compromises the clear differentiation of near- and far-field potentials and (Fig. 1C and D). Hence, one could hypothesize that real-time registration of PV isolation during cryoballoon ablation in atrial fibrillation might be limited as compared to ablation in sinus rhythm. However, impact of atrial rhythm on TTI observation rate has not been reported yet. Hence, the aim of our study was to assess an eventual difference in the real-time PV-isolation

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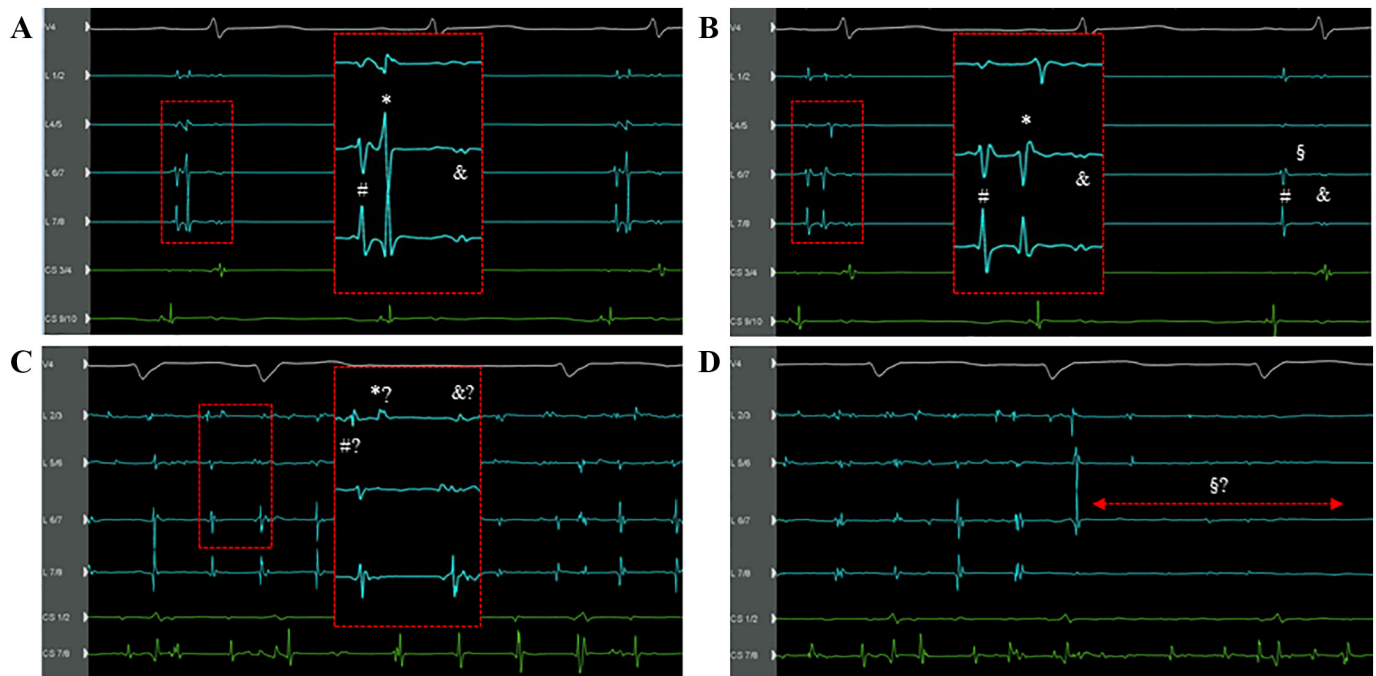


Fig. 1. Surface ECG (□), PV signals recorded by 20 mm spiral mapping catheter (■) and intracardiac ECG of an 8-polar coronary sinus catheter (■). (A) PV electrograms in SR with typical three-component signal consisting of LA far-field (#), sharp PV near-field signal (*) and LV far-field (&). (B) Pulmonary vein isolation using cryoballoon leads to progressive LA to PV conduction delay before complete disappearance of PV signals when the PV is isolated (§). (C) Atrial fibrillation is characterized by chaotic electrical activation of the atrium equalizing typical ECG pattern of near- and far-field potentials (D) complicating real-time observation of pulmonary vein isolation.

observation rate during CB-PVI in atrial fibrillation (AF) as compared to sinus rhythm (SR).

2. Methods

2.1. Study population

We prospectively included 157 consecutive patients undergoing PVI with the 3rd generation cryoballoon in this observational study. Real-time observation of PV isolation during sinus rhythm (SR group) and during atrial fibrillation (AFib group) was recorded for each vein depending on the rhythm during each cryoballoon ablation. The study complies with the Declaration of Helsinki and was approved by our institutional review committee (University Ulm, Germany, ID: 324/16). All patients gave written informed consent to the procedure.

2.2. Periprocedural management

Intracardiac thrombi were ruled out in every patient by transesophageal echocardiography prior to PVI. No additional preprocedural imaging was applied. All patients underwent transthoracic echocardiography to rule out pericardial effusion immediately after the procedure and prior to hospital discharge. Periprocedural anticoagulation was conducted as described before [1].

2.3. Cryoballoon ablation procedure

Cryoballoon ablation procedure has been described in detail before [9]. Briefly, a steerable sheath (Medtronic, Minneapolis, MN, Flexcath Advance) was used to introduce the cryoballoon in the left atrium after single transseptal puncture. After balloon inflation at the PV ostia a 20-mm spiral mapping catheter (Achieve, Medtronic, Minneapolis, MN) was positioned in the PV at the closest achievable proximity to enable real-time observation of PV potentials during PV isolation. PV occlusion was documented by injection of contrast medium.

The TTI was defined as the time of the last recording of a PV potential before sustained isolation. Left common pulmonary veins (LCPV), PVs that were isolated by crosstalk of the ipsilateral PV or PVs that were isolated without using the Achieve catheter as a mapping catheter were excluded from analysis. In all patients individualized TTI-dependent titration of cryoenergy was performed as described earlier [9]. Isolation of all PVs was reassessed at the end of the procedure by documentation of entrance- and exit-block. Phrenic nerve integrity was monitored by stimulation via the diagnostic catheter placed in the superior vena cava and palpation of the right-sided diaphragm and with additional recording of compound motor action potentials (CMAP) of the right sided diaphragm [13,14]. Cryoenergy application was aborted if luminal esophageal temperature (LET) measured by transnasally introduced temperature probe (S-Cath; Circa Scientific Inc., Englewood, CO or Sensitherm, St. Jude Medical, St. Paul, MN) was below 15 °C.

2.4. Statistical analysis

t-Test was used to prove differences of numeric values between the two groups if normal distribution with equal variance was given. Normal distribution was determined by Shapiro-Wilk test and equal variance by Brown-Forsythe test. Numeric variables that were not normally distributed were analyzed by Mann-Whitney rank sum test. Categorical variables were analyzed by Chi square test or Fisher's exact test. A p-value < 0.05 was considered significant. Independency of co-variables potentially influencing TTI observation rate was proven by uni- as well as multivariate logistic regression. Parameters with a p-value of 0.2 or lower in univariate logistic regression were included in multivariate logistic regression. XLStat software (V 2016.02.28430, Addinsoft, New York, NY) was used for statistical operations.

3. Results

A total of 157 patients, 62 females (39.5%), 92 (58.6%) with paroxysmal AFib, mean age of 66.6 ± 10.9 years, mean CHA₂DS₂-VASC-Score of 3.0 ± 1.8 and mean LA diameter of 45.4 ± 6.3 mm were included in this

Table 1
Baseline clinical parameters.

Baseline characteristics	
Patients [n]	157
Gender, female [n (%)]	62 (39.5)
Age (years)	66.7 ± 10.9
Paroxysmal AFib [n (%)]	92 (58.6)
LA diameter (mm)	45.4 ± 6.3
Heart failure [n (%)]	37 (23.6)
Arterial hypertension [n (%)]	121 (77.1)
Diabetes mellitus [n (%)]	26 (16.6)
CHA ₂ DS ₂ -VASC-score	3.0 ± 1.8
Stroke [n (%)]	15 (9.6)

prospective study. Further baseline characteristics are shown in Table 1. Comparison of baseline characteristics with respect to the atrial rhythm during PVI is shown in Supplementary Table 1.

A total of 622 PV including 8 LCPV and 2 right intermediate pulmonary veins were identified in our study group. After exclusion of 8 PV with common ostium (including a common trunc), 10 PV isolated by crosstalk during ablation of the ipsilateral PV, three PV isolated using a stiff wire instead of a spiral mapping catheter, two PV where the Achieve catheter was placed deeply in the PV to increase stability of cryoballoon position and one PV that was not isolated by a 3rd generation cryoballoon, 598 PV were included in our study. While 365 PV (61.0%) were isolated during SR (SR group) 233 (38.9%) PV were isolated during AFib (AFib group). All PV were successfully isolated by 3rd generation cryoballoon without any additional touch-up ablations.

Overall real-time observation rate of PVI was 82.1% (491/598 PV). TTI observation rate in the SR group was 86.3% (315/365 PV), whereas TTI observation rate during AFib was significantly lower (75.5%, 176/233 PV; $p < 0.001$).

Per vein analysis revealed that the higher overall real-time observation rate was mainly driven by a higher real-time observation rate of left superior pulmonary vein (LSPV) during SR (85/92 PV, 92.4%) compared to TTI detection rate during AFib (37/54 PV, 68.5%; $p < 0.001$). Thus, observation rate of TTI is increased by 23.9% when cryoablation of the LSPV is performed during SR. In contrast, TTI observation rate for the LIPV was 83.1% (74/89 PV) in the SR group compared to 81.8% (45/55 PV) in the AFib group ($p = 0.838$). A TTI in the RSPV was observed in 84.2% (80/95

PV) during SR and in 79.3% (46/58 PV) during atrial fibrillation ($p = 0.440$). Also, PVI real-time observation in the RIPV was statistically not different between both study groups (SR group: 84.4% (76/90 PV) vs. AFib group: 74.6% (47/63 PV); $p = 0.131$; Fig. 2).

To dissect the impact of atrial rhythm on additional procedural parameters, we analyzed mean nadir temperature as well as rate of pulmonary vein isolation with first cryoenergy application for both study groups. Similar to LSPV observation rate, we found that LSPV isolation with first freeze occurred significantly more often in the SR group (89.1%) compared to the AFib group (68.5%; $p = 0.004$). No significant procedural differences were found for LIPV, RSPV and RIPV between the SR and the AFib group (Table 2). The same holds true for mean time to PV isolation including all PV, which was 43.4 ± 23.1 s in the SR group compared to 40.8 ± 20.3 s in the AFib group ($p = 0.195$). There was also no significant difference in the TTI of each individual PV (Table 2).

To determine whether atrial rhythm is an independent predictor for TTI observation and to assess influence of other factors, we performed uni- as well as multivariate logistic regression analysis of patient specific conditions such as LA diameter, age, CHA₂DS₂-VASC-Score, type of AF (paroxysmal vs. persistent), comorbidities or the atrial rhythm during PV isolation. Interestingly, we found that atrial rhythm is the strongest independent predictor of TTI detection in the LSPV with an odds ratio of 4.98 (95%-CI: 1.86–13.44, $p = 0.001$) to detect TTI during SR (Table 3). Remarkably, whether the patient had paroxysmal or persistent AF did not have an influence on TTI detection rate rendered by univariate regression analysis ($p = 0.441$).

In summary, TTI detection rate appears to be strongly influenced by the atrial rhythm during cryoballoon PVI. TTI detection rates are much higher during SR as compared to AF, especially in the LSPV. The higher TTI-detection rate during SR also translated significantly into higher one-shot isolation rates of the LSPV.

4. Discussion

The introduction of a spiral mapping catheter (Achieve) that can be advanced through the inner lumen of the cryoballoon catheter to be placed within the PV enabled recording of real-time PV signals during cryoballoon PVI. This offered the opportunity to record the time from beginning of a freeze cycle to sustained PV isolation, the time-to-isolation (TTI), sometimes also referred to as time-to-effect (TTE). TTI

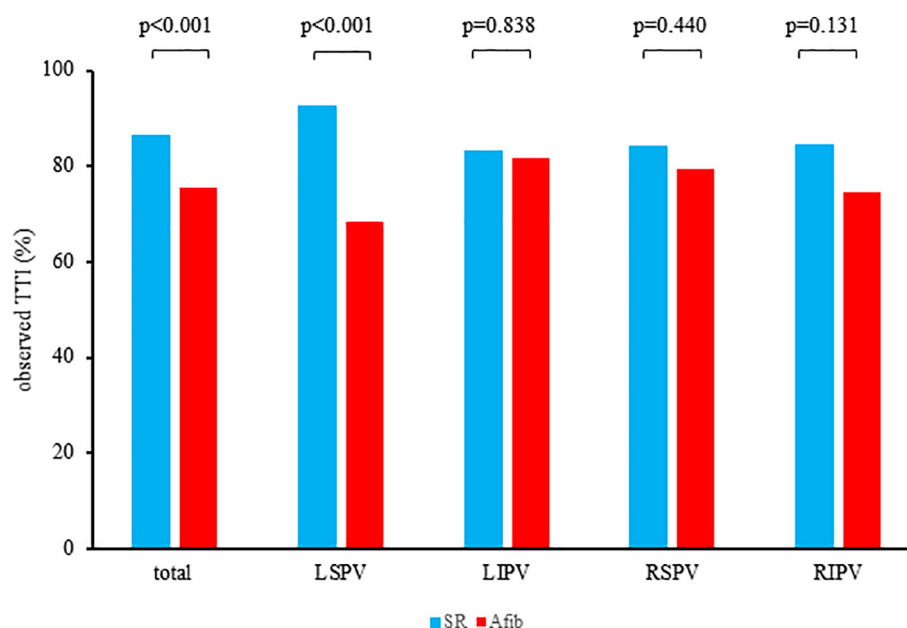


Fig. 2. Overall and per vein incidence of real-time PV observation during sinus rhythm and during atrial fibrillation. The significant higher overall TTI observation rate is mainly driven by distinct differences in LSPV signal interpretation between the SR group and the AFib group.

Table 2
Procedural parameters.

Procedural data	SR	AFib	p-Value
Pulmonary veins [n]	365	233	
PV isolation with 1. Freeze [n (%)]	314 (86.0)	194 (83.2)	0.421
LSPV [n (%)]	82 (89.1)	37 (68.5)	0.004
LIPV [n (%)]	73 (83.0)	52 (89.1)	0.129
RSPV [n (%)]	82 (86.3)	52 (89.7)	0.621
RIPV [n (%)]	77 (82.2)	53 (84.1)	0.829
Mean nadir balloon temperature [°C, SD]	-45.0 ± 6.0	-45.7 ± 6.2	0.195
LSPV [°C, SD]	-46.4 ± 5.7	-47.0 ± 5.4	0.329
LIPV [°C, SD]	-42.5 ± 6.0	-42.3 ± 4.7	0.689
RSPV [°C, SD]	-46.3 ± 6.0	-47.3 ± 6.0	0.399
RIPV [°C, SD]	-44.6 ± 5.6	-46.1 ± 7.2	0.298
Mean TTI all PV [sec., SD]	43.4 ± 23.1	40.8 ± 20.3	0.276
Mean TTI LSPV [n (%)]	51.8 ± 26.2	44.8 ± 22.2	0.245
Mean TTI LIPV [n (%)]	36.6 ± 17.1	36.1 ± 18.65	0.730
Mean TTI RSPV [n (%)]	38.1 ± 20.2	39.5 ± 20.1	0.740
Mean TTI RIPV [n (%)]	46.1 ± 24.4	43.1 ± 22.1	0.505

Bold values signifies if $p < 0.05$.

has emerged as a key procedural parameter to predict long-term procedural outcome.

Moreover, individualized titration of number and length of freeze cycles based on TTI leads to significantly shortened procedure duration and fluoroscopy time underpinning the clinical benefit of a high TTI observation rate enabled by a correct PV electrogram interpretation [6,7,9]. Hence, we here compared TTI observation rate during SR as well as during AFib in patients undergoing PVI with the 3rd generation cryoballoon and found that TTI detection rate during SR is significantly higher than during AFib. Also, per vein analysis revealed numerically higher TTI observation rates for every single PV during SR. However, statistical significance was only reached for the LSPV. Hence, higher overall TTI registration rate during SR is mainly driven by significant differences in TTI observation rate of the LSPV in the SR group compared to the AFib group.

Based on the close anatomical proximity of the left atrial appendage (LAA) and the LSPV, LAA potentials contribute consistently and significantly to ECG recordings in the LSPV as shown by Shah and co-workers [15]. Thus, differentiation between LSPV near-field and LAA far-field may be challenging during PVI especially at the LSPV even if PV and LAA signals are regular, distinct and have a high amplitude as observed in SR. In addition, during AFib no progressive conduction delay as in SR but rather decreasing frequency of observable PV signals can be registered. Possibly due to less abundant far-field signals in the LIPV, RSPV and RIPV as compared to the LSPV it appears that TTI observation is less hampered by AFib in these PVs.

Other factors like left atrial fibrosis might also impact on the ability to detect TTI. We have not recorded voltage maps in our study and thus this information is not available. However, fibrosis is generally

Table 3
Uni- and multivariate logistic regression for TTI detection.

Variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95%-CI)	p-Value	OR (95%-CI)	p-Value
Left atrial diameter	0.94 (0.88–1.01)	0.08	0.95 (0.88–1.03)	0.25
Age	1.00 (0.96–1.04)	0.88		
CHA ₂ DS ₂ -VASC-score	0.90 (0.70–1.15)	0.39		
Persistent AF	1.44 (0.57–3.61)	0.44		
Sex	0.91 (0.37–2.21)	0.83		
Heart failure	0.73 (0.26–2.05)	0.56		
Hypertension	0.81 (0.28–2.35)	0.69		
Diabetes	0.39 (0.14–1.09)	0.07	0.49 (0.16–1.50)	0.21
Coronary vessel disease	0.45 (0.18–1.10)	0.08	0.62 (0.23–1.62)	0.33
Sinus rhythm during PVI	5.58 (2.13–14.59)	<0.001	4.98 (1.86–13.34)	0.001

Parameters with a p-value of 0.2 or lower in univariate logistic regression were included in multivariate logistic regression. Parameters with a p-value <0.05 were considered significant in the multivariate logistic regression.

considered to be more pronounced in persistent AFib as compared to paroxysmal AFib. Nevertheless, in our logistic regression analysis persistent AFib is not associated with a lower TTI detection rate.

Beside patient specific conditions, ongoing technical developments of the procedural equipment used for cryoballoon PVI also influence PV signal interpretation. Recently, several studies demonstrated higher TTI observation rates using the novel 25 mm circular mapping catheter with ten instead of eight mapping electrodes for 2nd generation cryoballoon PVI [16,17]. Whether atrial rhythm impacts TTI observation rate in patients undergoing 3rd generation cryoballoon in combination with this novel circular mapping in combination with the 3rd generation cryoballoon was not subject of this study.

Taken together, our data of significantly lower TTI observations in the LSPV in the AFib group suggests that interference of LSPV near-field potentials and LAA far-field potentials is more pronounced during AFib and finally disables registration of LSPV real-time isolation. Accordingly, lower TTI observation rate in the LSPV translates into decreased incidence of LSPV isolation with the first freeze and consequently into increased number of LSPV freezes in the AFib group compared to the SR group.

These data in mind, one might speculate that electrical cardioversion should be routinely restored before cryoablation in order to facilitate PV signal interpretation and to reduce expendable cryoenergy applications. Whether this approach enables higher TTI detection rate, cannot be answered finally by this observational study. However, as shown by our data, type of AFib does not correlate with TTI detection rate, indicating that PV signal interpretation during cryoballoon PVI is also feasible in patients with persistent AFib and SR during the procedure. Since LSPV is usually the first PV to be isolated and atrial rhythm mainly impacts LSPV TTI detection rate, risk of mechanical AFib reinduction after cardioversion is rather low. Additionally, catheter manipulation between electrical cardioversion and LSPV ablation can be reduced by placing the cryoballoon in the LSPV before cardioversion.

5. Conclusion

We here demonstrate for the first time that atrial rhythm independently predicts TTI detection rate during cryoballoon ablation and incidence of “one-shot-isolation” is significantly higher during SR. Thus, cardioversion before conduction of PV isolation may lead to higher real-time observation rate of pulmonary vein isolation enabling more frequent application of TTI guided cryoballoon ablation.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jjcha.2019.100353>.

Disclosures

T. Dahme received speaker's honoraria and consulting fees from Medtronic. A. Pott is invited fellow of the Boston Scientific EP training program. The other authors have no conflicts to report.

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