How to Learn Pulmonary Vein Isolation with a Novel Ablation Device: Learning Curve Effects Using the Endoscopic Ablation System

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Learning Curve of Laser Balloon PVI. ***Introduction:*** **Novel ablation devices for pulmonary vein isolation (PVI) need a careful evaluation of its efficacy and safety beyond clinical studies in a real world situation. The endoscopic ablation system (EAS) was recently approved for PVI in Europe. We sought to determine the safety, efficacy, and learning curve effects of EAS-PVI in a large volume single center.**

Methods and Results: **Between June 2010 and March 2013, all EAS guided PVI procedures were analyzed and 150 consecutive patients were divided in tertiles (T). Clinical follow-up of 12 months assessed freedom from atrial fibrillation (AF) using 72 hour-Holter ECG recordings. In total, 497 of 583 PVs (85%) were isolated by visual guidance only. In T 2 and T 3, visually guided PVI rates increased from 73% to 91% ($P < 0.001$). After gap mapping, 96% and 99% of all PVs were isolated in T 1–3, respectively ($P = 0.018$). Total procedure and fluoroscopy time significantly declined over time. All major periprocedural complications occurred in the first T. In 3 patients (2 in 1st and 1 in 2nd T), phrenic nerve palsy was observed (2%). At 12-months follow-up, 103 of 133 patients (77%) remained in stable sinus rhythm without significant differences between Ts.**

Conclusion: **With EAS even first time users may achieve acute PVI in a high number of patients with favorable clinical outcomes after 1 year. Yet, acute procedural efficacy and safety are further improved after passing a learning curve of 50 patients.** *(J Cardiovasc Electrophysiol, Vol. pp. 1-6)*

atrial fibrillation, catheter ablation, endoscopic ablation, laser balloon, learning curve, pulmonary vein isolation

Introduction

In Europe, approximately 85% of all catheter ablation procedures for atrial fibrillation (AF) are carried out with radiofrequency current.[1] With intent to simplify pulmonary vein isolation (PVI) and to improve its clinical outcome, several novel ablation devices have been introduced in the past years.[2-7] The endoscopic ablation system (EAS; HeartLight™, CardioFocus, Marlborough, MA, USA) is a balloon based ablation system and offers the theoretical advantage of optimal tissue contact and precise lesion deployment with little need for extensive catheter manipulations. Recent studies suggested a steep learning curve for EAS with considerable shortening of procedure times after only 15 cases, but did not investigate its influence on safety or efficacy.[8]

When adopting novel technologies, operators and centers need to pass an individual learning curve. Since initially this may be associated with longer procedure times, higher complication rates, and lower clinical success, the time course of learning and the effects of procedural changes are of profound clinical importance. This is particularly true for the large number of low volume centers performing <50 cases per year.[9]

We, therefore, sought to describe the learning curve with EAS implemented into clinical routine at our center with particular interest in procedural characteristics as well as safety and efficacy endpoints.

Methods

Study Population

This study included 150 consecutive patients (aged 18–80 years) with symptomatic drug-refractory paroxysmal or short-lasting persistent (<6 months) AF who had undergone EAS-PVI at our center between June 2010 and March 2013.

Patients were excluded if they had a previous PVI attempt, a left atrium (LA) size >55 mm, or valvular dysfunction > II°.

Before the procedure, transthoracic and transesophageal echocardiography was performed in each patient in order to assess LA size, valve patency, and to rule out LA thrombi.

Two experienced EP physicians (B.S. and K.R.J.C.) performing more than 400 AF ablations per year (including 150 cryoballoon ablations) completed the procedures.

The population was divided into T with equal number of patients (n = 50).

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All patients gave written informed consent before the procedure.

Ablation Protocol

The ablation procedures were performed, as previously described.[10-13] Briefly, procedures were carried out under deep sedation, using boluses of midazolam, and fentanyl as well as continuous infusion of propofol 1% with continuous monitoring of noninvasive blood pressure and oxygen saturation. An esophageal temperature probe (SensiTherm™, St. Jude Medical, Minnetonka, MN, USA) was inserted. If esophageal temperature exceeded 39 °C, energy delivery was terminated and ablation was continued using reduced energy and/or at a more proximal or distal location.

After placing two multipolar catheters in the coronary sinus and at the His bundle, single transseptal puncture was performed using the modified Brockenbrough technique. An 8.5 F sheath (SL1; St. Jude Medical, Minneapolis, MN, USA) was advanced into the LA. Before or immediately after transseptal puncture heparin was administered to maintain activated clotting time between 300 and 350 seconds. Selective pulmonary vein (PV) angiography was performed to identify the PV ostia. A circular mapping catheter (CMC, Biosense Webster Inc., Diamond Bar, CA, USA) was placed at the PV ostium to record PV potentials using a computerized EP-system (Axiom Sensis XP, Siemens, Erlangen, Germany).

The transseptal sheath was then exchanged for a 12F steerable sheath via a guidewire in the left superior PV (LSPV). A second 8F sheath in the femoral vein was exchanged for the long 8.5F transseptal sheath and placed in the superior vena cava carrying a diagnostic catheter to perform phrenic nerve stimulation (20 mA, 2.9 milliseconds) during ablation of the right superior PV (RSPV). If loss or weakening of capture was observed, energy delivery was instantaneously terminated.

EAS Guided PVI

The details of the EAS have been described elsewhere.[14,15] Briefly, the EAS consists of a nonsteerable, compliant balloon catheter with a range of diameters from 9 to 35 mm that is introduced into the LA by a steerable 12F sheath. The balloon is filled and continuously flushed with deuterium (D_2O). Once the balloon has been inflated, a 2F fiber optic endoscope that is positioned within the central catheter shaft enables direct visualization of the PV antrum. A diode laser generator delivers energy at a wavelength of 980 nm via a second fiber.

In all the study population, the same EAS version was employed and the balloon was positioned at each individual PV ostium to perform ablation. After obtaining optimal PV occlusion, ablation lesions were deployed in a contiguous fashion under visual guidance. Particular care was taken to overlap the individual lesions by 30–50% with the aid of the LightTrack™ (CardioFocus) software. Energy was titrated from 5.5 to 12 W (20–30 seconds ablation time) according to the degree of tissue exposure.

The largest inflation size of the balloon still providing optimal PV occlusion was attempted to assure a proximal (antral) ablation lesion deployment.

In all patients PVs were treated in the following sequence: LSPV, left inferior PV (LIPV), RSPV, and right inferior PV (RIPV). If a left common PV (LCPV) was present, it was treated first.

After complete visually guided circular ablation, the PVs were remapped for entrance block using the CMC. In case of ambiguous PV recordings, differential pacing and pacing from the CMC was performed to verify PVI. In case of residual LA to PV conduction, additional ablation was carried out using the laser balloon (LB) according to the activation sequence in the circular mapping catheter as recently described.[11]

Postprocedural Care

After echocardiographic exclusion of pericardial effusion, oral anticoagulation with phenprocoumon or a direct anticoagulant was resumed. Previously ineffective antiarrhythmic drug therapy was discontinued.

Study Endpoints

The primary objective of this study was to assess safety, efficacy, and learning curve effects of circumferential PVI using the novel EAS in a large volume single center.

The acute primary efficacy endpoint was the number of isolated PVs after a single, purely visually guided ablation circle around the individual PV. The secondary acute efficacy endpoint included the number of acutely isolated PVs with EAS at the end of the index ablation.

The chronic primary endpoint was freedom from AF lasting longer than 30 seconds off antiarrhythmic drug 90 and 365 days postablation.

The primary safety endpoint was defined as the occurrence of periprocedural and postprocedural complications, such as major bleeding requiring transfusion, vascular access complications, pericarditis, myocardial infarction, damage of cardiac valves, cardiac tamponade, cerebral vascular accident, phrenic nerve palsy, atrioesophageal fistula, PV stenosis, or death.

Follow-Up

A telephonic follow-up was carried out 30 days after ablation. At 3, 6, and 12 months, patients were scheduled for outpatient visits, including a 72-hour Holter ECG. In case of symptoms suggestive of arrhythmia recurrence, patients were equipped with a transtelephonic ECG monitor.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). P values of <0.05 were considered statistically significant. Continuous variables were summarized using mean and standard deviation or median and interquartile ranges where appropriate. Qualitative variables were summarized using frequencies and percentages. Between groups comparisons were performed using ANOVA (continuous), chi-square (categorical) and nonparametric rank test (Mann–Whitney *U*-test). For *post hoc* analysis, a Bonferroni test (ANOVA) was used.

Results

Patient Characteristics

A total of 150 consecutive patients (60 female; mean age 64 $\pm$ 9 years) were enrolled in the study and divided in T

TABLE 1
Baseline Characteristics of the Study Population

Baseline Characteristics	All n = 150	Tertile 1 n = 50	Tertile 2 n = 50	Tertile 3 n = 50	P Value
Age (years), mean ± SD	64 ± 9	73 ± 9	64 ± 10	62 ± 9	0.140
Male gender, n (%)	90 (60)	27 (54)	36 (72)	27 (54)	0.105
Persistent AF, n (%)	39 (26)	6 (12)	16 (32)	17 (34)	0.021
Years of persistent AF	3.8 ± 3.1	3.7 ± 3.3	3.1 ± 2	4.5 ± 4	0.487
Hypertension, n (%)	100 (67)	31 (62)	30 (60)	39 (78)	0.111
Diabetes, n (%)	18 (12)	4 (29)	4 (30)	10 (31)	0.103
LA (mm), mean ± SD	40 ± 5	39 ± 5**	40 ± 5	42 ± 5*	0.004
LVEF (%), mean ± SD	62 ± 6	63 ± 6	62 ± 6	62 ± 6	0.740
# of AAD, median	1 (0;2)	2 (1;2)	1 (0;1)	0 (0;1)	0.0001

**Bonferroni posttest P < 0.05 versus *.

(Table 1). Ablation procedures were performed between June 2010 and June 2011, July 2011 and May 2012, and June 2012 and March 2013 for T 1–3, respectively.

Patients in T 3 were more likely to have persistent AF (34% vs. 12% in T 1; Table 1) and a larger LA diameter (P = 0.004). The median number of AADs was significantly higher in T 1 (P = 0.001).

Acute Procedural Efficacy

A total of 583 PVs were targeted with the EAS. Twenty-two patients displayed variant PV anatomy with an LCPV (n = 20), right middle PV (RMPV; n = 1), or right common PV (RCPV; n = 1).

After visually guided ablation, 497 of 583 PVs (85%) were isolated (Table 2). The acute visually guided PVI rate significantly increased in T 2 and 3 (91% vs. 73%, P < 0.001; Table 2, Fig. 1). The total number of isolated PVs at the end of the procedure was higher in the latter 2 Ts (99% vs. 96%; P = 0.018; Table 2, Fig. 1).

The mean total number of laser applications per PV did not significantly differ among the Ts (Table 2), but at LSPV a significant decrease of the applications required to achieve PVI was observed in the last patients (33 ± 5 in T 3 vs. 37 ± 12 in T 1; P = 0.016).

Total procedure time significantly declined from 148 ± 36 to 130 ± 24 minutes and 123 ± 35 min in Ts 1–3, respectively (P < 0.001; Table 2, Fig. 2). Similarly, the mean fluoroscopy time significantly decreased over time (15 ± 5 minutes vs. 13 ± 6 minutes vs. 12 ± 7 minutes in Ts 1–3, respectively, P = 0.028; Table 2, Fig. 3).

Procedural Complications

The total complication rate was 7% (11 in 150 patients; Table 3) and was significantly higher in T 1; no complications were observed in T 3. Only 1 pericardial tamponade occurred in T 1. It was drained percutaneously, and the patient's clinical course was uneventful.

In 1 patient from T 1, a transient ischemic attack (TIA) occurred, most likely due to air embolism, but completely resolved during the hospital stay.

Vascular access complications were the most prevalent complication (4%). The incidence tended to decline across the Ts (3 vs. 3 vs. 0). In T 1, 1 patient underwent surgical repair of a femoral venous laceration.

Phrenic nerve palsy was observed in 3 patients (2%; 2 patients from T 1 and 1 in T 2). Phrenic nerve function had recovered in all patients after a 3-months follow-up.

Clinical Outcome

Seventeen patients were lost to follow-up. The median follow-up time was 467 days (Q1–Q3: 375–657 days). At 12-months follow-up, 103 of 133 patients (77%) remained in stable sinus rhythm (75% in T 1 vs. 73% in T 2 vs. 86% in T 3; P = 0.355). Kaplan–Meier analysis with log-rank test did not show any differences in AF free survival between the Ts (Fig. 4; P = 0.304).

In total, 27 patients underwent a repeat procedure 317 ± 192 days after the index procedure (12, 8, and 7 patients from T 1–3, respectively).

Of the 109 previously isolated PVs, electrical reconduction to the LA was observed in 46 PVs (42%). Durable isolation rates showed differences among Ts: 24 of 48 (50%)

TABLE 2
Procedural Data Comparison

Procedural Data	All n = 150	Tertile 1 n = 50	Tertile 2 n = 50	Tertile 3 n = 50	P Value
Procedural time (minutes)	133 ± 33	148 ± 36**	130 ± 24*	123 ± 35*	<0.001
Fluoroscopy time (minutes)	13 ± 6	15 ± 5*	13 ± 6	12 ± 7**	0.028
Applications LSPV	34 ± 8	37 ± 12	32 ± 5	33 ± 5	0.016
Applications LIPV	29 ± 8	28 ± 11	30 ± 6	29 ± 7	0.82
Applications RSPV	32 ± 8	31 ± 8	33 ± 9	32 ± 6	0.37
Applications RIPV	30 ± 9	31 ± 11	33 ± 9	32 ± 6	0.88
LCPV	46 ± 11	53 ± 16	50 ± 13	48 ± 24	0.89
RMPV		13			
RCPV		37			
Visually guided PVI	497/582 (85)	144/195 (74)	177/194 (91)	176/193 (91)	<0.001
PVI after remapping	573/582 (98)	188/195 (96)	193/194 (99)	192/193 (99)	0.018

**Bonferroni posttest P < 0.05 versus *.

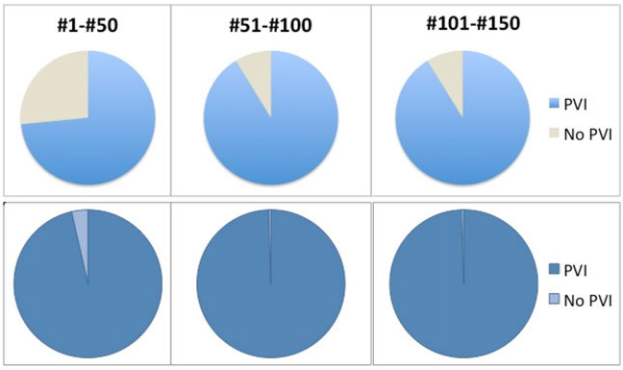

Figure 1. *Visually guided PVI and total PVI in the 3 tertiles. The upper panel shows the fraction of acutely isolated PVs (blue) compared to failed PVI (grey) after purely visually guided PVI in T1–T3. The lower panel shows the PVI rates after gap mapping and ablation using EAS. Dark blue: PVI; light blue: no PVI. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology's website: www.wileyonlinelibrary.com/journal/jce*

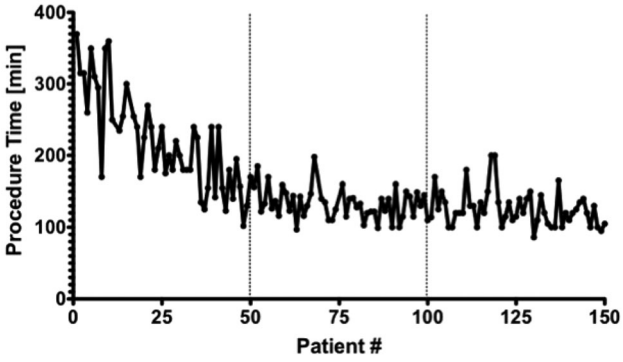

Figure 2. *Learning curve of procedure time.*

PVs in T 1, 19 of 33 (57%) PVs in T 2, and 20 of 28 (71%) PVs in T 3 (P = 0.189).

Discussion

The purpose of this study was to describe the implementation of a novel ablation device into a center's clinical routine with particular emphasis on safety and efficacy.

The major findings were (1) that acute procedural efficacy improved after the first 50 patients but showed only modest improvements thereafter; (2) that the number of safety events significantly decreased even after 100 successfully completed cases; and (3) that mid-term clinical outcome is acceptable for new users and moderately inclines with experience.

Acute Procedural Efficacy

EAS is an anatomical ablation system aiming at PVI by a purely visually guided circular ablation without the need for intracardiac electrograms recorded by a circular mapping catheter. In previous studies, this endpoint was achieved in 68–78% of PVs.[8,16] Subsequent gap mapping and ablation ultimately led to PVI rates of 99%. Both studies reflect early clinical experiences of multiple new users and therefore data is well in line with the results of T 1 presented here.

The development and implementation of standardized ablation strategies to enhance catheter contact and catheter control led to improved procedural results.[11] Second, the deliberate use of higher ablation energies facilitated to achieve acute electrical PVI.[17] Shorter procedure and fluoroscopy times were achieved by obviating the need for gap mapping, which is particularly time consuming with EAS due to the absence of mapping electrodes.[11]

It may be assumed that the EAS learning curve with respect to acute procedural efficacy is completed between 15 and 50 cases. While former studies did not show significant differences for operators having performed more or less than 15 cases,[8] this study clearly does. This is also suggested by the rather horizontal course of the procedure time plot (Fig. 2) as a surrogate for experience.

The determination of a learning curve is clinically relevant since in the United States, 80% of all AF ablation procedures are performed at centers with an annual case volume of 50 ablations.[9] It is evident that under these circumstances the demand for "easy-to-learn" ablation technologies is growing.

Procedural Safety

Parallel to increasing procedural efficacy the number of safety events declined with increasing experience. This was driven by a reduction in vascular access complications and phrenic nerve palsy.

The former may be explained by changes in the periprocedural anticoagulation protocol. In the initial T, oral anticoagulation had been stopped preprocedurally and bridged with low-molecular weight heparin. In the next Ts, the current guideline recommendations were adopted performing ablation under therapeutic INR levels.[17]

Phrenic nerve injuries are a characteristic complication of balloon-based procedures. Due to mechanical distortion of the ostial anatomy the distance between the balloon surface and the phrenic nerve is decreased eventually causing thermal damage.[18] The sizeable nature of the EAS and the flexible positioning of the laser generator allow for more antral energy delivery at reduced risk for nerve damage. Bigger balloon sizes were consistently used with increasing experience leading to considerably lower phrenic nerve palsy rates compared to other balloon devices[19-25] and early EAS experiences.[8,16]

Pericardial tamponade is the most devastating complication of AF ablation.[26,27] Balloon catheters are prone to have a reduced risk for cardiac perforation due to easier navigation properties and lower mechanical force per square due to its larger surface compared to tip catheters. Moreover, steam pops infrequently occur with EAS and have never been observed during cryoballoon ablation.

Clinical Outcome and Chronic PVI

After a follow-up of 12 months, no significant differences in AF free survival were noted. Most strikingly, EAS enables new users to achieve favorable mid-term clinical success rates comparable to experienced centers using RFC ablation.[28]

It is also of note that in the latter 2 Ts, significantly more patients with persistent AF had been treated without decreasing clinical success rates.

Limitations

Learning curve characteristics may depend on the level of experience the operator has with AF ablation in general

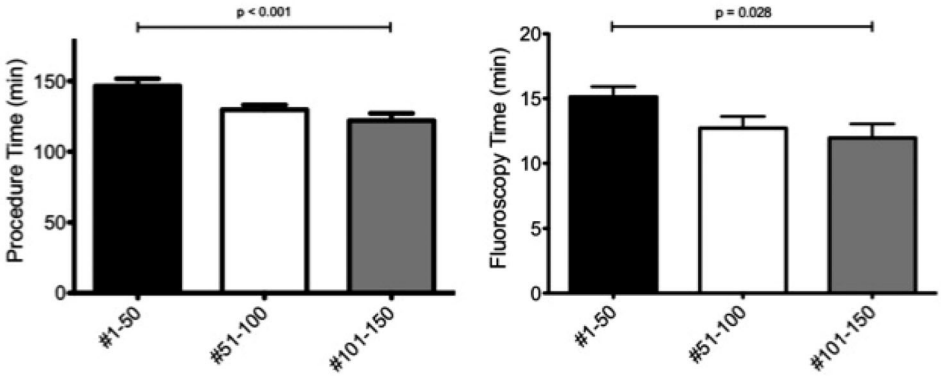

Figure 3. *Procedure and fluoroscopy time analysis.*

TABLE 3
Procedural Data Complications

	Complications				
	All n = 150	**Tertile 1 n = 50**	**Tertile 2 n = 50**	**Tertile 3 n = 50**	**P Value**
Overall, n (%)	11 (7)	7 (14)	4 (8)	0	0.026
Tamponade, n (%)	1 (0.6)	1 (2)	0	0	0.366
TIA, n (%)	1 (0.6)	1 (2)	0	0	0.366
PNP palsy, n (%)	3 (2)	2 (4)	1 (2)	0	0.360
Vascular access, n (%)	6 (4)	3 (6) • 1 femoral vein laceration • 1 groin hematoma • 1 pseudo aneurysm	3 (6) • 3 pseudo aneurysms	0	0.209

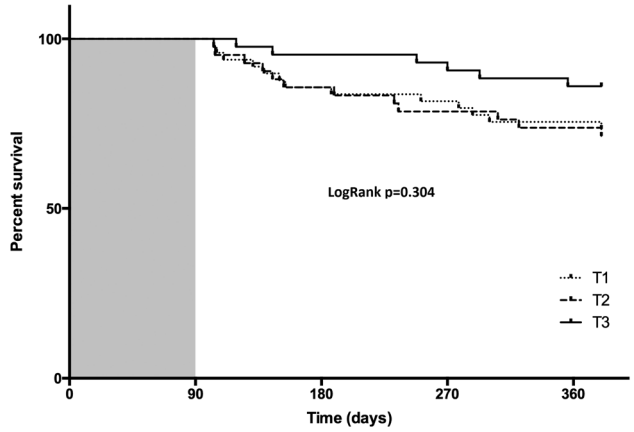

Figure 4. *Kaplan–Meier plot of AF free survival. A blanking period of 90 days was applied.*

and with similar technologies (e.g., balloons). Therefore, the present results may vary for others. Nonetheless, the present data outline the importance of a particular caseload to improve efficacy and decrease complications. Moreover, it signifies the importance for continued real-world investigations after initial feasibility studies to determine the true clinical value of a novel technology.

The value of EAS in patients with persistent AF remains ill defined. Unfortunately, the number of patients in this study is too small to draw final conclusions. Therefore, prospective randomized multicenter studies were designed and are currently ongoing (clinical trials.gov number NCT 01863472).

Conclusions

With EAS, even first time users may achieve acute PVI in a high number of patients with favorable clinical outcomes after 1 year. Yet, procedural efficacy and safety are further improved after passing a learning curve of 50 patients.

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