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5-Year Outcome of Pulmonary Vein Isolation by Loss of Pace Capture on the Ablation Line Versus Electrical Circumferential Pulmonary Vein Isolation

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ABSTRACT

OBJECTIVES This study sought to compare long-term arrhythmia-free survival between electrical circumferential pulmonary vein isolation (PVI) and PVI with the endpoint of unexcitability along the ablation line.

BACKGROUND PVI is the standard ablation strategy of paroxysmal atrial fibrillation, although arrhythmia recurrence in long-term follow-up (FU) is high. The endpoint of unexcitability along the ablation line results in decreased arrhythmia recurrence compared to electrical PVI in 1-year FU.

METHODS Seventy-four consecutive patients (age 62.5 ± 10.6 years; 70.3% male) with de novo paroxysmal atrial fibrillation who were initially included in our randomized trial and underwent catheter ablation at our institution were analyzed. Patients who were randomized to either a conventional group (PVI, guided by circumferential catheter signals) or a pace-guided group (PG, anatomical ablation line encircling, ablation until loss of pace capture at 10 V, 2-ms pulse width on the ablation line) underwent long-term FU. The primary endpoint was recurrence of any atrial fibrillation or atrial tachycardia after a blanking period of 3 months.

RESULTS Sixty-nine patients completed a mean FU period of 5.14 ± 0.98 years. Arrhythmia-free survival without antiarrhythmic drug therapy was significantly higher in the PG group (71.05% vs. 25.81%, $p = 0.002$). Furthermore, multiple procedure success (1.29 ± 0.61 procedures in PG vs. 1.97 ± 1.06 procedures in conventional group, $p < 0.001$) was higher in the PG group compared to the conventional group (89.47% vs. 58.06%, $p = 0.005$).

CONCLUSIONS The endpoint of unexcitability along the PVI line improves success rates, resulting in a significant reduction of exposure to invasive procedures in 5-year FU. (J Am Coll Cardiol EP 2017;3:1262–71)

Long-term results describe increasing numbers of patients who benefit from the standard of interventional treatment of pulmonary vein isolation (PVI) in paroxysmal atrial fibrillation (PAF) (1–3). However, arrhythmia recurrence is high, especially during longer follow-up (FU) time (4) and is most often attributed to recovery of conduction between pulmonary veins (PVs) and the left atrium (LA) (5,6).

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One strategy to reduce recovery of PV conduction is to localize excitable tissue along the PVI line using the pace guided (PG) approach, whereby pacing from the ablation catheter's distal electrode pair along the PV ablation line is performed.

At sites where local LA capture at the ablation line is identified, additional ablation can be performed with the goal of unexcitability (UE) of the ablation line. This method has been shown to reduce arrhythmia recurrence in short-term FU, which we could demonstrate in our initial prospective randomized 2-center study (7) and has been shown in other trials (7–10).

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However, there is a paucity of data regarding the potential beneficial long-term effect using an additional endpoint of UE along the ablation line in patients with PAF.

We therefore hypothesized that patients with PAF also benefit from the endpoint of UE in long-term FU from higher single-procedure success and freedom from atrial fibrillation (AF) compared with the standard approach.

METHODS

STUDY POPULATION. A total of 103 patients with symptomatic PAF refractory to antiarrhythmic drugs (at least 1 type I or III antiarrhythmic drug [AAD]) were initially included in the prospective randomized, 2-center trial (University Heart Center Hamburg, Hamburg, Germany, and Brigham and Women's Hospital, Boston, Massachusetts) (7).

From this patient population, 74 consecutive patients who had been referred for their first catheter ablation (CA) to our institution between August 2009 and August 2011 were enrolled in this FU study. The study protocol was approved by the Brigham and Women's Hospital Human Subject Protection Committee and the Ethical Board Committee of the Ethical Committee of the medical Association, Hamburg, Germany. All patients provided written informed consent.

PULMONARY VEIN ISOLATION PROCEDURE. Index ablation procedures have previously been described in detail (7).

Briefly, patients with strictly PAF were eligible for the ablation if effective anticoagulation with vitamin K antagonists (international normalized ratio 2 to 3) for ≥1 month was present and exclusion of LA thrombus by a transesophageal echocardiogram was performed before ablation.

All procedures were guided by a 3-dimensional (3D) mapping system (NavX, St. Jude Medical, St. Paul, Minnesota) with registration of a previously performed imaging study. Surface and intracardiac electrocardiograms (ECGs) were recorded (LabSystem Pro EP recording system, BARD Electrophysiology, Lowell, Massachusetts). Patients were randomized to a conventional group (PVI, guided by circumferential mapping catheter [CMC] signals, using standard techniques) and a pace-guided group (PG) (anatomical ablation line encircling, ablation until loss of pace capture on the ablation line with bipolar pacing at an output of 10 V at 2 ms pulse width) (9) (**Figure 1**).

A 10-pole circumferential PV mapping catheter (Lasso, Biosense Webster, Diamond Bar, California) was placed sequentially at the ostium of 1 of the PVs for mapping and confirmation of PVI. In the PG group the CMC signals were continuously recorded, but blinded to the operator during PVI until atrial tissue on the ablation line was UE to pacing. The presence or absence of local LA capture on the ablation line was monitored according to the atrial signal of the coronary sinus catheter (**Figure 1A**). At sites of local LA capture, additional radiofrequency (RF) energy was delivered until capture was no longer present (**Figure 1B**). The procedural endpoint was confirmation of loss of pace-capture along the entire circumference of the ablation line and bidirectional block, shown by the CMC.

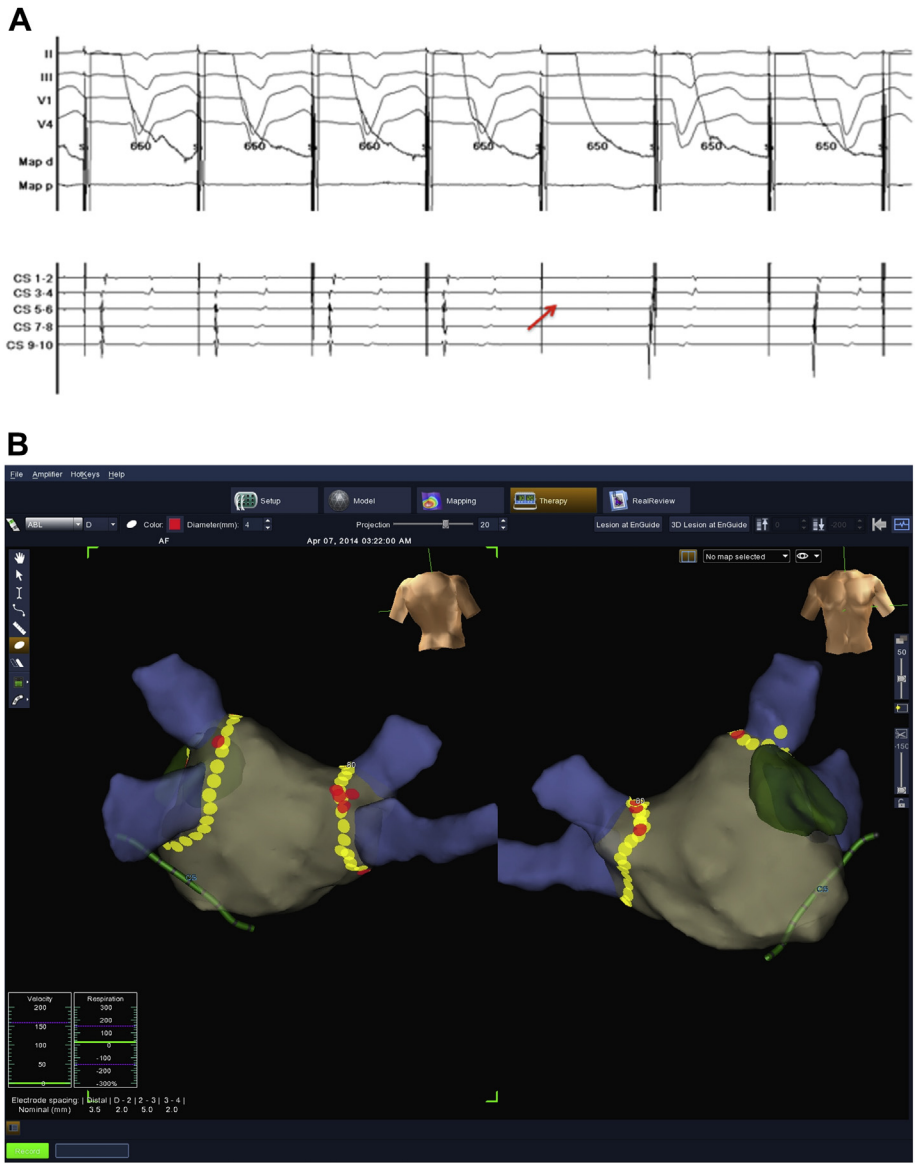
The electrograms from the CMC were then reviewed and electrical isolation of the ipsilateral PVs was assessed with the CMC. In the conventional group, PVI was performed without blinding CMC signals to the operator.

REPEAT PROCEDURES. In case of recurrence of symptomatic AF after a blanking period of 3 months after the index procedure, repeat procedures were performed at our institution using an open-irrigated 3.5-mm tip ablation catheter (without a 3D mapping system until November 2012, then repeat procedures were performed using a 3D mapping system (EnSite NavX (St. Jude Medical, Inc.), CARTO System (Biosense Webster, Inc.), or at other institutions, according to patient's preference. PVI was guided by earliest activation in sinus rhythm using CMC signals. The procedural endpoint was bidirectional block, shown by the CMC. According to the operator's preference, adenosine testing for dormant

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
AT = atrial tachycardia
CF = contact-force
CHA_2DS_2-VASc score = combined stroke risk score: congestive heart failure, hypertension, age >75 years, diabetes, prior stroke/transient ischemic attack, vascular disease
CMC = circumferential mapping catheter
ECG = electrocardiogram
EHRA = European Heart Rhythm Association
FU = follow-up
LA = left atrium
LIPV = left inferior pulmonary vein
LSPV = left superior pulmonary vein
PAF = paroxysmal atrial fibrillation
PG = pace guided
PV = pulmonary vein
PVI = pulmonary vein isolation
RF = radiofrequency
RIPV = right inferior pulmonary vein
RSPV = right superior pulmonary vein
SD = standard deviation
UE = unexcitability

FIGURE 1 Pace Guided Approach



(A) Demonstration of loss of pace capture on the ablation line. Intracardiac tracings during bipolar pacing at 10 Volt/2 ms pulse width with 650 beats/min along the ablation line during ablation. Entrance block and loss of pace capture. **Red arrow** marks loss of pace capture. Circumferential mapping catheter signals are blinded to the operator. CS = coronary sinus. **(B)** Wide circumferential pulmonary vein isolation (3-dimensional mapping: NavX, St. Jude Medical). **Yellow dots** show radiofrequency lesions after circumferential pulmonary vein isolation. During bipolar pacing at 10 Volt/2 ms lesion with capture on the ablation line are identified **(red dots).** Additional energy is applied to these lesions to achieve loss of pace capture.

conduction, ablation of the site of reconnection until achievement of loss of pace capture, or waiting time of 30 min after bidirectional block could be performed in addition to demonstration of bidirectional block. If PVs were found isolated in the repeat procedures, ablation of defragmented signals was performed according to our institutional standards (11). In patients with AF duration of more than 7 days, additional defragmentation was performed.

FOLLOW-UP AND OUTCOMES. Periprocedural, in-hospital complications at first and repeat procedures were analyzed. Minor complications included hematoma at puncture site without surgical intervention,

arteriovenous fistula, aneurysm spurium, and pericardial effusion without intervention. Major complications were defined as hematoma at puncture site with surgical intervention, esophageal-atrial fistula, aspiration pneumonia, pericardial effusion hemorrhage, phrenic nerve palsy, and stroke or transient ischemic attack.

After a 3-month blanking period, patients were followed up in the outpatient clinic with 12-lead ECG and 72-h Holter monitoring or 7-day autotriggered event monitor at 3, 6, and 12 months post-ablation and then at a minimum of a 12-month basis. Twenty-four h Holter monitoring was performed either at their outpatient cardiologist or at our institution, according to patient's preference.

If Holter-ECGs were performed by the referring physicians, the submitted full ECG documentation was analyzed in our clinic to exclude false positive or negative diagnoses of AF episodes.

Clinical FU was available at a minimum of 6 months for every patient. All patients received an additional questionnaire about arrhythmia symptoms and episode duration, last known recurrence dates, and current medications, and were contacted by phone calls if documentation was incomplete or unclear. In case of symptoms suspicious for arrhythmia recurrence without previous documentation, external ECG event recording was performed.

Patients with implanted pacemakers or defibrillators were eligible to be followed by device interrogation. Antiarrhythmic drug treatment was continued at the discretion of the operator, outpatient cardiologist, or patient's decision. Long-term FU data were analyzed in the patients with complete FU only.

Repeat procedures were scheduled if symptomatic AF was documented, or if symptoms were highly suggestive for AF recurrence.

The primary endpoint was recurrence of any AF or atrial tachycardia (AT) after a blanking period of 3 months. Recurrence was defined as recurrence of documented AF/AT >30 s by 12-lead ECG, 12- to 72-h Holter monitoring, transtelephonic monitor recordings, or device interrogation where applicable. Repeat procedures were documented.

Single-procedure success was defined as freedom from recurrence of AF/AT >30 s without treatment with antiarrhythmic drugs (class I/III). Multiple-procedure success was defined as freedom from recurrence of AF/AT >30 s without treatment of antiarrhythmic drugs (class I/III) after a blanking period of 3 months after the last performed CA of AF.

STATISTICAL ANALYSIS. Continuous variables are expressed as the mean ± SD or median (interquartile range) and were compared with Student's *t*-test for normal distribution and Mann-Whitney U test for non-normally distributed variables. Categorical variables are expressed as frequency and percentage and were compared by chi-square test or Fischer exact test for expected frequency of 5 or less. Time to recurrence and event-free survival curves were calculated using the Kaplan Meier estimation method.

Because of the small sample size of patients undergoing repeat procedures, repeat procedures were only analyzed on patient level.

All tests were 2-sided. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using statistical software package GraphPad Prism version 6.0 (GraphPad Software Inc., La Jolla, California).

TABLE 1 Baseline and Procedural Characteristics

	Conventional PVI (n = 35)	Pace-Guided Ablation (n = 39)	p Value
Age, yrs	62.0 ± 10.3	63.1 ± 10.9	0.424
Male	24 (68.6)	28 (71.8)	0.762
CHA_2DS_2-VASc score	1.4 ± 1.0	1.5 ± 0.7	0.022
LV ejection, %	63.2 ± 4.1	63.1 ± 7.0	0.687
Left atrial diameter, mm	43.5 ± 5.8	39.6 ± 7.9	0.766
Sleep apnea	0 (0)	3 (7.7)	0.242
Chronic obstructive lung disease	3 (8.6)	0 (0)	0.101
Diabetes mellitus	3 (8.6)	0 (0)	0.062
Hypertension	12 (34.3)	9 (0)	0.313
History of stroke	1 (2.3)	0 (0)	0.473
Duration of AF, min	17.21 ± 3.61	17.24 ± 4.97	0.479
Procedure time, min	109.7 ± 28.8	157.6 ± 39.4	<0.001
Fluoroscopy time, min	22.8 ± 9.5	23.9 ± 7.0	0.207
Total energy, J	61,780 ± 27,318.8	59,501.9 ± 23,138.6	0.801

Values are mean ± SD or n (%).

AF = atrial fibrillation; CHA_2DS_2-VASc score = combined stroke risk score: congestive heart failure, hypertension, age > 75 years, diabetes, prior stroke/transient ischemic attack, vascular disease; LV = left ventricle; PVI = pulmonary vein isolation.

RESULTS

A total of 74 consecutive patients (age 62.5 ± 10.6 years; 52 of 74 [70.3%] male) were enrolled in the initial study protocol at our institution and eligible for long-term FU. Baseline characteristics are presented in Table 1. Patients in the conventional group had a lower mean combined stroke risk score: congestive heart failure, hypertension, age >75 years, diabetes, prior stroke/transient ischemic attack, vascular disease (CHA_2DS_2-VASc score) (1.4 ± 1.0 vs. 1.5 ± 0.7, p = 0.022); otherwise the groups were comparable.

TABLE 2 Follow-Up Clinical Data

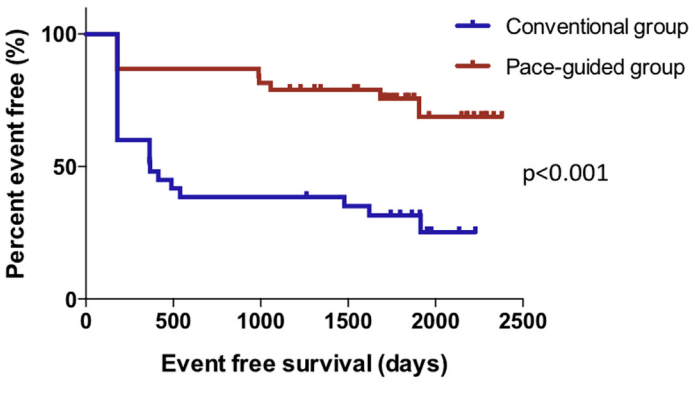
	Conventional PVI (n = 31)	Pace-Guided Ablation (n = 38)	p Value
Median follow-up, days	1,915 ± 364	1,846 ± 352	0.508
Single procedure success, %	8 (25.81)	27 (71.05)	<0.001
Number of total procedures per patient	1.97 ± 1.06 (1-4)	1.29 ± 0.61 (1-2)	<0.001
Multiple procedure success, %	18 (58.06)	34 (89.47)	0.005
EHRA class	1.33 ± 0.67	1.16 ± 0.37	0.162
Antiarrhythmic drugs (Class I, III), %	5 (16.13)	4 (10.53)	0.721
Beta-blocker, %	17 (54.84)	18 (47.37)	0.631

Values are mean ± SD, n (%), or mean ± SD (interquartile range).
EHRA = European Heart Rhythm Association; other abbreviation as in Table 1.

In the PG cohort, all patients had 4 PVs and pulmonary ostia. One patient in the conventional group did have a left common ostium; all other patients in the conventional group had 4 PVs and pulmonary ostia each. In first repeat procedures, 1 patient in the conventional group presented with a left common ostium.

ABLATION PROCEDURE. The endpoint of electrical isolation of all PVs (bidirectional block) was achieved in all patients. The mean procedure duration was 136.0 ± 42.3 min (venous puncture to groin compression) with mean fluoroscopy duration of 23.4 ± 8.2 min and RF application of 2,162.9 ± 893.2 s. Procedure duration was significantly longer in the PG group (157.6 ± 39.4 min vs. 109.7 ± 28.8 min, p < 0.001); fluoroscopy times were not significantly different (23.9 ± 7.0 min vs. 22.8 ± 9.5 min, p = 0.207). Total energy application was comparable among groups (Table 1). In the conventional group, entrance and exit block in the PV, guided by a CMC, was reached in all patients. After achievement of UE in the PG group, left and right vein pairs were isolated in 12 patients. In the remaining 26 patients, isolation of PVs was completed with CMC guidance (mean additional energy, 13,699.9 ± 13,001 J).

FIGURE 2 Kaplan Meier Estimation for Event-Free Survival



Days	500	1000	1500	2000
Conventional group	14	14	11	3
Pace-guided group	38	32	27	10

Numbers at risk

Regarding the primary endpoint, freedom of any atrial tachyarrhythmia without antiarrhythmic drug therapy (Class I/III), a significant difference between the 2 groups could be observed.

ONE-YEAR SUCCESS AND FREEDOM FROM AF. Overall freedom from AF after 18 ± 6 months was 64.86% in our cohort. After this FU interval, freedom from AF was significantly higher in the PG group (p = 0.005); 31 of 38 patients in the PG group (79.49%) versus 17 of 35 patients (48.57%) in the conventional group were event free.

LONG-TERM SUCCESS AND FREEDOM FROM AF. FU of >12 months was available in 69 of 74 patients (93.24%) (5 patients were lost to FU). After a mean FU of 1,915.83 ± 364.60 days (5.25 ± 1.00 years) in the conventional group and 1,846.42 ± 352.14 days (5.05 ± 96 years) in the PG group (p = 0.508), single-procedure success was significantly higher in the PG group versus the conventional group (27 of 31 [71.05%] vs. 8 of 38 [25.81%]; odds ratio [OR]: 7.06; 95% confidence interval [CI]: 2.43 to 20.51; p < 0.001) (Table 2).

Of those patients who were lost to FU, 1 patient died in the conventional group due to a malignancy and severe chronic obstructive lung disease; and in the PG group, 1 patient is in a coma due to complications after a bronchoscopy and 1 patient had a basal ganglia bleeding. None of these events were related to the ablation procedures.

Kaplan Meier analysis for event-free survival did show a significant difference in recurrence of AF (p < 0.001) (Figure 2).

AAD therapy (Class Ic/III) and beta-blocker therapy in FU was not different between the groups. There was also no difference between patients on beta-blocker therapy in the conventional versus the PG group. European Heart Rhythm Association (EHRA) class at FU was comparable between the groups.

After a mean number of 1.29 ± 0.61 (range: 1 to 2) procedures in the PG group versus 1.97 ± 1.06 (range: 1 to 4) in the conventional group (p < 0.001), there was a significant difference in multiple procedure success rate between the 2 groups (34 of 38 [89.47%] patients

TABLE 3 Second Repeat Procedures

	Conventional PVI (n = 2)	Pace-Guided Ablation (n = 2)
Reconnected veins	5 of 8	0 of 8
LSPV	2	0
LIPV	1	0
RSPV	1	0
RIPV	1	0
Defragmentation	2	2

Values are n.

LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; other abbreviation as in Table 1.

in the PG group versus 18 of 31 [58.06%] in the conventional group; OR: 6.14; 95% CI: 1.75 to 21.60; p = 0.005) (Table 2).

Regarding the primary endpoint, freedom from any atrial tachyarrhythmia without AAD therapy (Class I/III), a significant difference between the 2 groups could be observed (p < 0.001) (Figure 2).

REPEAT PROCEDURES AND RECONNECTED VEINS. Time to the first repeat procedure after the index PVI was not significantly different. Of 69 patients, 39 underwent repeat procedures.

The number of patients with PV reconnection at first procedure was significantly higher in the conventional cohort, with 21 (of 31; 67.7%) patients in the conventional cohort versus 15 (of 38; 39.5%) patients in the PG cohort found with PV reconnection (OR: 6.7667; 95% CI: 2.3413 to 19.557; p < 0.001).

In patients undergoing first repeat PVI, 41.67% of PVs (15 of 36 veins) in the PG groups versus 46.98% of PVs (39 of 83 veins) in the conventional group were reconnected. The right superior pulmonary vein (RSPV) (38.45%) in the conventional group and the left superior pulmonary vein (LSPV) and RSPV in the PG group (33.34%, respectively) were the veins reconnected most often.

At second repeat procedures, PV reconnection was present in all patients of the conventional cohort (2 of 2 patients) and none of the patients in the PV group (0 of 2). The number of reconnected veins found in the second repeat procedure was higher in the conventional group with 5 of 8 veins found reconnected in the conventional group versus 0 of 8 veins in the PG group (Table 3).

In first repeat procedures, 1 patient of the conventional cohort had isolated veins and underwent ablation of defragmented signals. Five other patients of the conventional cohort underwent additional defragmentation (Table 4). In second repeat procedures, 1 of 2 patients underwent 3D-guided ablation, all patients underwent defragmentation, none received adenosine, none was tested for UE of the ablated gaps and none underwent waiting time after demonstration of entrance block.

TABLE 4 First Repeat Procedures

	Conventional PVI (n = 21)	Pace-Guided Ablation (n = 9)
Reconnected veins	39	15
LSPV	10 (25.64)	5 (33.34)
LIPV	5 (12.82)	1 (6.67)
RSPV	15 (38.45)	5 (33.34)
RIPV	9 (23.08)	4 (26.67)
Additional defragmentation	5 (23.81)	0 (0.0)
Defragmentation, isolated PVs	1 (4.76)	0 (0.0)
Ablation of gaps until unexcitable	1*	0
Adenosine testing for dormant conduction	1*	1
Waiting time (30 min)	3	4
3D mapping (CARTO, NavX)	6	4

Values are n (%). *Refers to the same patient.

CARTO = CARTO System (Biosense Webster, Inc.); NavX = EnSite Nav (St. Jude Medical, Inc.); PV = pulmonary vein; other abbreviations as in Tables 1 and 3.

In patients with multiple procedures, all veins were found isolated after the first repeat procedure in the PG group and after the second repeat procedure in the conventional group. In those patients undergoing more than 2 repeat procedures, no PV reconnection was found.

ABLATION TECHNIQUES IN REPEAT PROCEDURES. Comparing ablation techniques of first and second repeat procedures, we found no significant difference in the use of 3D mapping systems, use of adenosine, pacing for UE on the site of PV reconnection, or waiting time of 30 min after bidirectional block was achieved.

The different ablation techniques of first repeat procedures are displayed in Table 4.

PROCEDURAL AND IN-HOSPITAL COMPLICATIONS. Overall complication rates, including major and minor complications, were not significantly different at the time of initial procedure with 10.26% (4 of 39) of patients having complications in the PG group and 11.43% of patients (4 of 31) in the conventional group (p = 1.00). No major complication occurred in the conventional group, 1 major complication (hematoma with surgical intervention) was found in the PG group (p = 1.00).

Overall complication rates in first and repeat procedures were not significantly different between groups (complications occurred in 11 of 54 [20.4%] patients in the conventional group and 6 of 50 [12.0%] patients in the PG group, p = 0.5311). In repeat procedures no major complication occurred.

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DISCUSSION

In this single-center long-term FU of a patient cohort included in our previously published randomized study (7) we were able to show that achieving UE along the ablation line significantly improved freedom of AF/AT more than 5.14 ± 0.98 years. In patients with a history of drug-refractory PAF, undergoing PVI pacing along the ablation line aiming for UE of the ablation line results in a better single-procedure and multiple-procedure success rate and less procedures per patient are required to achieve freedom from AF compared to standard PVI with demonstration of bidirectional block alone. These findings verify the important clinical implications of this method and indicate that favorable results can be achieved reducing the necessity for invasive repeat interventions.

The endpoint of an UE ablation line, as independently introduced by Eitel et al. (8) and Steven et al. (2010) (9) is a strategy to improve the outcome of PVI. Loss of bipolar pacing after RF ablation has been found to be associated with the formation of uniform lesions in atrial tissue, pacing at an output of 10 mA at a pulse width of 2 ms (12). To create durable lesions is of major importance to achieve lasting PV-LA conduction block at the index procedure. Several factors such as intra-atrial variability in tissue depth and tissue contact/catheter stability, edema formation and operator competency have been linked to arrhythmia recurrences (10). As mentioned before, delivering additional ablation can improve the durability and transmurality of the index lesion, and result in better long-term outcome (8-10,13-16).

We were able to confirm the findings of the randomized study by Steven et al. (2013) (7) showing that achievement of UE along the ablation line significantly improves short- and long-term freedom from AF/AT. According to our findings of lower numbers of reconnected veins at second repeat procedures, we hypothesize that the endpoint of UE results in more durable lesion formation.

We found a nearly 3-fold difference in recurrence after a single procedure, and after 5 years there still was a significant difference in success rates (34 of 38 [89.47%] in the PG group vs. 18 of 31 [58.06%] in the conventional group, $p = 0.012$).

According to a pilot study by Steven et al. (9), in conventional PVI, 50% of vein pairs revealed sites of capture on the ablation line after PVI was achieved. Based on these results, a 3-fold increase of single-procedure success might seem high; however, we do not exactly know the correlation of PV reconnection invasively documented at a certain time after PVI and symptomatic or asymptomatic AF episodes and especially the impact of an unexcitable PVI line on clinical long-term outcome.

The systematic review and meta-analysis by Nery et al. (17) showed that durable PVI is associated with a lower risk of AF recurrence after CA. However, PV reconnection was also found in arrhythmia-free patients. Furthermore, the association between durable PVI and outcomes was not statistically significant in the pooled analysis of the 7 studies, which exclusively investigated PAF patients. In our cohort, 3.4% of patients had AF episodes with isolated veins at the first repeat procedure (1 of 30 patients).

The above results would imply a smaller difference between success rates in our cohorts, as our cohort consists of patients with PAF. However, in this meta-analysis, no study with PVI plus the additional endpoint of loss of pace capture on the ablation line was included. The rather large difference in recurrence rates between the PG and conventional groups may not only be due to additional beneficial effects of the PG approach.

Applying more energy to the ablation line with creation of larger lesion formation may include ablation of the PV antrum, which may reduce AF recurrence by other mechanisms, for example, non-PV triggers, according to a sub-study of the trial by Narayan et al. (18), comparing treatment of AF with versus without focal impulse and rotor modulation.

AF drivers were shown to be located near the PVs of LA roof in 50% in PAF. PG ablation might thus be more effective, not only because of isolation of PV triggers and creation of durable lesions, but also due to elimination of AF drivers that might maintain AF.

Novel catheters, with combined contact force (CF) and stability measurements may further improve procedural outcome. Using CF guidance has been suggested to create more efficient lesions, probably by improving efficacy of transmural lesion formation (19). The EFFICAS (Efficacy study on atrial fibrillation percutaneous catheter ablation with contact force support) I (20) and II (21) could show correlations between CF parameters and PV durable isolation. Moreover, the use of CF has been shown to result in significant reduction in the prevalence of dormant conduction with improved freedom from recurrent arrhythmias after 1 year (22,23). Meta-analysis of recent research findings in CF-sensing RF ablation revealed improved clinical outcome at 1 year and CF parameters during ablation correlated well with the presence of gaps (24-26). In contrast, the study by Ullah et al. (27) did not show a significant difference in 1-year success rate using CF in ablation of PAF. Although the mean CF between the CF group and control group was not significantly different, the CF

group did show more RF lesions within the defined CF range.

In addition, the ratio of force-time integral and wall thickness has been found to be a strong predictor of gap and dormant conduction formation in PV isolation (28). Besides CF guidance, continuity in deployment of RF lesions along the ablation line is a determinant factor for durable PVI (28). UE along the ablation line might be a surrogate for both good CF while ablating and a continuity of RF lesions along the line. Further studies are needed to evaluate the underlying mechanism.

The use of adenosine to reveal "dormant conduction" within the ablation line appears to be expandable when using the endpoint of UE, as reported by Schaffer et al. (29) in a study of 58 patients. Pacing for UE can identify potential sites of dormant conduction and even sites that would have not been detected by testing with adenosine. However, Kogawa et al. (28) assumed different mechanisms of dormant PV conduction revealed by adenosine test and exit block to the left atrium by pacing from the PV side of the ablation line, suggesting both tests should be performed to reduce PV reconnections.

Other strategies have been used to improve outcomes for patients with PAF, as the use of cryoballoon therapy. Jourda et al. (30) postulated that CF-guided RF and second-generation balloon (CB2) cryotherapy are comparable regarding complications and freedom from AF after 12 months (event-free survival 85.3% in the cryoballoon group vs. 88% in the CF group).

Also, 2 years after the initial procedure in patients with PAF or short-persistent AF undergoing PVI using the 28-mm CB2 2-year single-procedure, clinical success rates of 73% have been reported (31). In a multicenter, randomized trial, Kuck et al. (32) showed a 1-year arrhythmia recurrence rate of 34.6% in the cryoballoon group and 35.9% in the RF group. Cryoballoon ablation was not inferior to RF ablation regarding efficacy (32). None of the "single-shot" devices have been shown to improve long-term outcome compared with PVI using RF energy.

STUDY LIMITATIONS. Whether a longer waiting period at the completion of the procedure would have identified sites where local edema or atrial myocardium stunning may have contributed to the endpoint of UE was not tested in the initial study protocol.

Moreover, outcome after AF ablation is dependent on the quality of clinical FU. In our case, we attempted to maximize detection of arrhythmia recurrences through the use of serial 24-h Holter monitoring and transtelephonic monitor recordings being aware of the inherited limitations of not using continuous monitoring devices.

As FU of patients with PAF (especially detection of silent AF episodes) is always challenging, our study results may underestimate the rate of sub-clinical AF episodes in FU. However, differences of performed repeat procedures and the use of AADs between the conventional and PG group reflect the clinical relevance of the PG approach. Consequently, higher frequency and duration of ECG monitoring in FU might have revealed higher numbers of asymptomatic AF episodes, but this should not have influenced the number of repeat procedures and clinical outcome.

Because of the lower number of patients included in the conventional arm, success rates in this arm could be significantly affected by a few patients having a different outcome. The magnitude in difference between outcomes after 1 procedure may therefore be over-estimated.

We have analyzed patients treated at our institution who were part of a 2-center randomized trial in this extended FU study (7). We assume that, due to similar 1-year success rates between our institution and Brigham and Women's hospital, the chance of a potential ascertainment bias in this extended FU study is low; however, we cannot fully exclude it.

3D mapping systems were not used in every repeat procedure because PV reconnection can, in most cases, be sufficiently identified using a CMC alone. This may have led to a higher total numbers of repeat procedures, as procedural success increases with the use of these systems.

We did not use adenosine or CF in the conventional group, which are now common methods to improve clinical outcomes. At the time of randomization, those methods did not have clinical relevance as they do today. The impact of adenosine testing or combination of adenosine and CF catheters compared to the endpoint of UE remains to be evaluated.

In repeat procedures, UE of the circumferential ablation line was not tested. We have ablated only the sites of PV reconnection to avoid extended ablation.

CONCLUSIONS

The data of this FU study provides evidence that the endpoint of UE is easily applicable and achieves high success rates without depending on adenosine administration, procedure prolonging waiting times, or the necessity to use CF-enabled catheters. Long-term FU data for other approaches aiming for more durable PV isolation are pending.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Arrhythmia recurrence during longer FU in PAF is high and mainly attributed to recovery of conduction between PVs and LA. Approaches to achieve better acute lesion durability, such as the use of adenosine to identify sites of dormant conduction, the use of CF catheters, or "single-shot" devices have shown beneficial short-term success in effective lesion formation, but none of these has been shown to improve long-term outcome. Herein, we propose a therapeutic CA technique to improve clinical long-term outcome of CA by achievement of the endpoint of loss of pace capture on the PV ablation line.

TRANSLATIONAL OUTLOOK: Unexcitablity along the ablation line as endpoint of PVI may represent an easy tool in clinical practice to achieve better long-term outcomes. Further long-term studies are required to determine the efficacy of novel catheter techniques as well as the use of different energy sources or the use of novel catheters in combination with the endpoint of UE are required to find the best strategy for patents with PAF aiming for durable lesions and high arrhythmia-free survival in long-term FU. Furthermore, long-term FU studies to prove the efficacy of translating these techniques into ablation strategies of persistent AF are required.

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