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Original article

Mechanism, underlying substrate and predictors of atrial tachycardia following atrial fibrillation ablation using the second-generation cryoballoon☆

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ABSTRACT

Background: Data regarding atrial tachycardia (AT) following second-generation cryoballoon ablation (CBA) of atrial fibrillation (AF) are limited.
Aim: To describe the incidence, mechanisms, and clinical predictors of ATs following CBA.
Methods and results: In this retrospective single-center study 238 patients undergoing CBA for treatment of paroxysmal (91/238; 38.2%) or persistent AF were analyzed. During a mean follow-up of 11.9 ± 5.5 months recurrence of AF occurred in 49/238 patients (20.6%) and AT in 27/238 (11.3%). Twenty-six patients with AT and 14 with AF only underwent a redo ablation. The prevailing mechanism of AT was macroreentry [typical atrial flutter (AFL) (n = 10), left atrial macroreentry (n = 14), focal left-AT (n = 2)]. Non-cavotricuspid-isthmus-dependent macroreentry right-AT was mapped and ablated in 3 patients after initial AFL ablation. In a multivariate regression model, persistent type of AF (HR = 3.3; CI = 1.2–9.4), cardiomyopathy (HR = 3.5; CI = 1.5–8.4), treatment with beta-blockers (HR = 0.3; CI = 0.1–0.6), and pulmonary vein-abnormality (HR = 4.6; CI = 2.1–10.4) were independent predictors of AT. Substrate analysis revealed a significantly higher number of low voltage areas in the left atrium in patients with left-AT in comparison to patients with AF recurrence only (2.0; IQR=2.0−4.0 vs. 0.5; IQR = 0.0–2.25; $p = 0.005$).
Conclusion: In this study, AT after CBA occurred in 11.3% of patients with macroreentry being the prevalent mechanism. All patients with left-AT presented with low voltage areas in the left atrium, suggesting a more progressive underlying fibrotic disease in these patients.
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Introduction

Second-generation cryoballoon based ablation (CBA, Arctic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) for pulmonary vein isolation (PVI) has demonstrated high procedural success rates and a promising clinical outcome for patients with paroxysmal (PAF) and persistent atrial fibrillation (PersAF) [1–4]. The "Fire And Ice" trial proved non-inferiority of CBA to radiofrequency-based (RFA) PVI with regard to efficacy and safety for the treatment of patients with PAF [5,6]. Atrial tachycardia (AT) after PVI is often more symptomatic than AF itself due to the potential to develop faster ventricular rates [7–9]. These arrhythmias are generally refractory to drug therapy and often require repeat ablation [10]. The incidence of AT after catheter ablation of AF depends on the ablation strategy used. Besides typical atrial flutter (AFL), a large proportion of ATs after point-by-point RFA are localized in the left atrium (LA) and their mechanism mainly relates to gaps in ablation lines [7,10]. The reported incidence of postablation ATs ranges from 5% to 50% with an increased risk when AF duration is prolonged and additional substrate modification was part of the index ablation procedure [8,9,11]. The

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prevalence of AT in patients after CBA has been described as 2.8% according to the results of a recent meta-analysis [12]. The primary mechanism of AT is supposed to be due to atrio-venous reconnection [13–15], while a macroreentrant mechanism was described in only one study [16].

Only one study described left-AT after second-generation CBA, but in a predominant PAF cohort and without analysis of the underlying substrate [16]. The objectives of this study were therefore to determine the incidence, mechanisms, underlying substrate, and clinical predictors of ATs after CBA in a predominantly PersAF cohort of patients.

Methods

In this retrospective study, patients with symptomatic PAF and PersAF, undergoing PVI using the second-generation cryoballoon between July 2015 and March 2017, were enrolled. Informed consent was obtained from each patient before the procedure. The study complied with the principals outlined in the Declaration of Helsinki and was approved by the local Ethics Committee.

All patients underwent transthoracic echocardiography before ablation to assess structural abnormality, left ventricular ejection fraction (LVEF), LA diameter, and valvular disease. Transesophageal echocardiography was performed to rule out the presence of LA thrombus on the same day or the day before the procedure. No additional pre-procedural imaging was performed. All patients were treated under uninterrupted warfarin with international normalized ratio 2–3. For patients, who took new oral anticoagulants (NOAC), it was discontinued the evening before the ablation procedure.

Cryoballoon ablation procedure

All procedures were performed with the use of analgosedation using midazolam, fentanyl, and propofol [17]. A 10-pole diagnostic catheter (Webster® CS Uni-Directional, Biosense Webster, Inc., Diamond Bar, CA, USA) was positioned within the coronary sinus. A single transseptal puncture was performed using a modified Brockenbrough technique and an 8.5 French transseptal sheath (SL1, St Jude Medical, Inc., St Paul, MN, USA). Heparin was given to maintain an activated clotting time of $\geq$300 s. The transseptal sheath was then exchanged over a guidewire for a 12 French steerable sheath (Flexcath Advance, Medtronic, Inc., Minneapolis, MN, USA). Selective PV angiography was performed to identify all PV ostia. These angiograms were stored and used for further measurement of the PV diameter at the level of the ostia using a specific image management software (Xcelera, Philips, Amsterdam, The Netherlands). PV abnormality was defined as the presence of a left common trunk with a length of $\geq$ 10 mm or presence of a right middle PV. An esophageal temperature probe (Sensitherm, St Jude Medical, Inc.) was inserted and positioned according to the individual cryoballoon position to facilitate esophageal temperature monitoring during energy delivery. The second-generation 28-mm cryoballoon was introduced into the LA and a spiral mapping catheter (20-mm diameter; Achieve, Medtronic, Inc.) was advanced into the target PV to record electrical activity. The cryoballoon was inflated proximal to the PV ostium and pushed against the PV ostium to facilitate complete antral sealing. Contrast medium injected through the central lumen of the cryoballoon was used to verify complete occlusion of the PV ostium. Each freeze-cycle duration lasted 180 s. If time to PVI was longer than 60 s, a 240-s freeze-cycle and one additional 240-s bonus freeze-cycle were applied. For patients demonstrating AF at the time of the procedure, electrical cardioversion was performed after the final freeze-cycle and PVI was re-confirmed in sinus rhythm (SR). During energy delivery along the right PVs, continuous phrenic nerve pacing at maximum output and pulse width (12 mA/2.9 ms) at a cycle length (CL) of 1000 ms was performed, using a diagnostic catheter positioned in the superior vena cava. Phrenic nerve capture was monitored by intermittent fluoroscopy, diaphragmatic electromyography (CMAP) [18], and tactile feedback of diaphragmatic contraction.

Cavotricuspid isthmus (CTI) ablation was performed by open-irrigated radiofrequency catheter (NaviStar ThermoCool, Biosense Webster, Inc.) in case the patient had typical AFL documented in electrocardiography or induced during the procedure.

Anticoagulation was continued for at least three months and after that based on the individual CHA2DS2-VASC score. To prevent early recurrences of AF, patients continued previously ineffective antiarrhythmic medications for at least three months. Following a blanking period of 3 months, patients completed outpatient clinic visits at 3, 6, and 12 months and additional symptom-driven visits. A 24-h Holter electrocardiogram and interrogations of implanted devices, if present, were recorded at each visit.

Mapping and ablation of AT during redo ablation

A 10-pole diagnostic catheter (Webster® CS Uni-Directional, Biosense Webster, Inc.) was positioned within the coronary sinus. If a right atrial (RA) origin of AT was unlikely according to entrainment mapping, double transseptal puncture was performed. A deflectable circular mapping catheter (10-pole Lasso-Nav, 15 mm; Biosense Webster, Inc.) and a 3.5-mm irrigated-tip ablation catheter (SmartTouch ThermoCool F-curve; Biosense Webster, Inc.) were introduced into the LA. Electroanatomical activation mapping (EAM) of the LA/RA was performed using Carto-3 (Biosense Webster, Inc.). Entrainment mapping was used to confirm the consistency of the EAM. Macroreentrant tachycardia was diagnosed when the CL was entirely recorded in the mapped atrium (presence of early-meets-late phenomenon, total activation time >75% of the CL), confirmed by positive entrainment from at least 2 separated segments of the atrium [19]. Focal ectopic activity was defined by a distinct source with centrifugal atrial activation and relatively fast impulse propagation along the atrium (total activation time <75% of the CL) with positive entrainment only in one segment of the atrium, if any [19]. Microreentrant activity was diagnosed when the CL was entirely recorded only in one segment of the atrium (total activation time >75% of the CL, which could be covered by a circular mapping catheter) with centrifugal activation of the rest of the atrium. After validation of the AT mechanism, reisolation of reconnected PVs was performed, if needed. Macroreentrant tachycardias were treated by linear lesions, followed by confirmation of bidirectional block. Focal ectopic and microreentrant activity were treated by focal lesions. Radiofrequency energy was applied at 25–40 W using 'power control' mode using quantification of lesion formation by "ablation index" [20]. The endpoint of the redo procedure was non-inducibility of any sustained AT by programmed and burst atrial pacing, electrical isolation of all PVs and bidirectional block of all performed linear ablations.

The clinical AT recorded at the beginning of the redo procedure was defined as "primary". ATs that appeared as a result of transformation of the primary AT during ablation or induced after termination of any other AT, were defined as "secondary" AT.

Bipolar map analysis

Bipolar maps were created with thresholds between 0.15 mV and 0.5 mV (low voltage zone was defined as contiguous areas of bipolar voltage <0.5 mV). The LA was divided into five segments (posterior wall, inferior LA, mitral isthmus, anterior wall, septum, omitting left atrial appendage) [21].

Statistical analysis

Continuous data are presented as mean ± standard deviation, skewed continuous parameters were expressed as median (interquartile range defined as Q1–Q3). Categorical data were summarized as frequencies and percentages. Comparisons between baseline characteristics were performed by Student's t-test, Mann–Whitney rank-sum, $\chi 2$, or Fisher exact tests where appropriate. To analyze the association of baseline and procedural factors on arrhythmia recurrence, Cox logistic regression analysis was used. Parameters that were found to be univariately significantly associated with arrhythmia recurrence and those that show a slight association with arrhythmia recurrence with $p < 0.20$ were included in the multivariate Cox logistic regression analysis. Statistical analyses were performed using SPSS statistical software (version 22.0; SPSS Inc., Chicago, IL, USA). A 2-tailed $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 238 patients [64.8 ± 11.2 years, 145 (60.9%) male] with PAF (91/238; 38.2%) and PersAF (147/238; 61.8%) undergoing CBA with complete follow-up were included (4/242 patients were excluded due to incomplete follow-up) (Fig. 1). In 14 (5.9%) patients concomitant AFL was documented. Baseline characteristics of the study population are summarized in Table 1. Procedural characteristics of the primary CBA are shown in Table 2. All targeted 952 PVs were isolated in all patients. The touch-up applications were performed for left superior pulmonary vein (LSPV) in 89 (37.4%), left inferior pulmonary vein (LIPV) in 92 (38.7%), right superior pulmonary vein (RSPV) in 53 (22.3%), and right inferior pulmonary vein (RIPV) in 99 (41.6%) patients with no statistically significant difference in number of applications for each PV between the patients with and without ATs recurrence. PV abnormality was seen in 43 patients (18.1%) with a left common ostium in 26 (10.9%) and a right middle PV in 20 (8.4%) patients.

Freedom from any sustained arrhythmia during the 11.9 ± 5.5 months of follow-up was 75.2% (179/238 patients). Recurrence of AF was documented in 49/238 (20.6%) patients, who previously underwent CBA for PAF [13 (14.3%) patients] and PersAF [36 (24%) patients] and sustained regular AT was documented in 27 (11.3%) patients [5 (5.5%) with previous CBA due to PAF and 22 (15%) with PersAF]. Among 49 patients with AF recurrence, 17 (34.7%) patients had concomitant AT and 32 (65.3%) patients had AF only as the recurrent arrhythmia (Fig. 1).

Redo-ablation was performed in 40/59 (67.8%) patients with arrhythmia recurrence (14 patients with AF recurrence only, 10 patients with CTI-dependent AFL, and 16 patients with left-AT). Clinical and procedural characteristics are listed in Table 3. Patients with left AT had longer history of AF (33.6 ± 39.4 months) and bigger LA diameter (45.6 ± 4.5 mm) in comparison with patients with AFL (7.1 ± 7.2 months and 41.6 ± 5.9 mm, correspondingly) and AF-only (15.9 ± 27.6 months and 41.9 ± 7.7 mm, correspondingly), but this difference did not meet statistical significance.

Pulmonary vein reconduction and substrate analysis during redo ablation

Reconduction of at least one PV could be recorded in 24/40 (60.0%) patients as follows: in 7/14 (50.0%) patients with AF recurrence only, in 8/10 (80.0%) with CTI-dependent AFL and 9/16 (56.2%) with left-AT, respectively (Table 3). Reconnection of one PV was observed in 17/40 (42.5%) patients, of two PVs in 4/40 (10%) patients, and of all four PVs in 3/40 (7.5%) patients. The following PVs were reconnected: LSPV in 13/40 (32.5%), LIPV in 6/40 (15.0%), RSPV in 8/40 (20.0%), RIPV in 10/40 (25.0%) patients.

Bipolar voltage mapping of the LA was performed during SR in 4 patients (10%), AF in 12 (30%) patients, and ongoing AT in 24 (60%) patients. Low voltage areas in the LA was more frequently observed in patients with left AT as compared to patients with AFL or AF only recurrence (2.0; IQR 2.0–4.0*† vs. 0.5; IQR 0.0–1.8* vs. 0.5; 0.0–2.25† segments, respectively; $p = 0.003$*/0.005†, Table 3, Fig. 2). CTI ablation converted AFL directly into SR in 5 of 10 patients, into a left AT in 2 of 10 patients, and into a right AT in the remaining 3 patients. Voltage mapping of the RA revealed low voltage areas in the RA posterior wall in all three patients that converted to a right atrial tachycardia. All ATs terminated during ablation (Fig. 3).

Mechanisms of AT

All 26 patients undergoing redo ablation for AT, presented with ongoing AT during the procedure. After verification of the

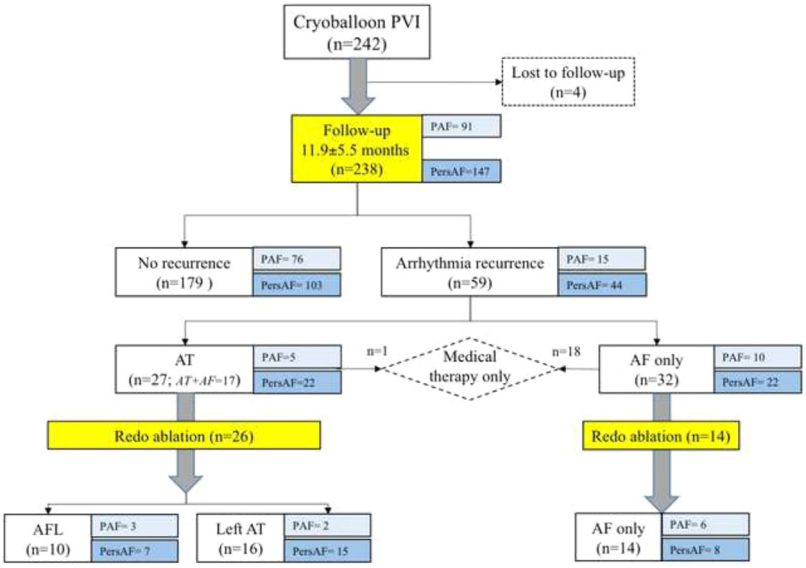

Fig. 1. Study flowchart with numbers of patients.
AT, atrial tachycardia; AF, atrial fibrillation; AFL, typical atrial flutter; PAF, paroxysmal atrial fibrillation; PersAF, persistent atrial fibrillation; PVI, pulmonary vein isolation.

Table 1
Patient characteristics.

Parameter	AT (n = 27)	Non AT (n = 211)	p
Demographics			
Age (years)	63.1 ± 12.1	65.0 ± 11.0	0.457
Male gender, n (%)	15 (55.6)	130 (61.6)	0.544
BMI	26.1 (25.1–28.7)	28.4 (25.3–31.2)	0.058
Medical history			
Persistent AF, n (%)	22 (81.5)	125 (59.2)	0.025
CHA2DS2VASc	2.4 ± 1.2	2.5 ± 1.6	0.882
EHRA Score	2.6 ± 0.7	2.5 ± 0.7	0.641
Mean duration of AF, months	6.0 (3.0–24.0)	7.0 (3.0–24.0)	0.786
Hypertension, n (%)	19 (70.4)	155 (73.5)	0.733
Diabetes mellitus, n (%)	6 (22.2)	28 (13.3)	0.211
Previous MI, n (%)	3 (11.1)	21 (10.0)	0.742
Previous PCI, n (%)	6 (22.2)	46 (21.8)	0.960
CABG operation, n (%)	2 (7.4)	7 (3.3)	0.271
Other heart operation, n (%)	1 (3.7)	8 (3.8)	1.000
Cardiomyopathy, n (%)	10 (37.0)	37 (17.5)	0.017
Valvular heart disease, n (%)	1 (3.7)	9 (4.3)	1.000
Echo parameters			
LA diameter, mm	45.0 (39.0–48.0)	40.0 (36.0–44.0)	0.008
LVEF (%)	53.0 (45.0–55.0)	55.0 (50.0–56.0)	0.036
PV anatomy			
LSPV diameter, mm	16.0 (14.0–19.0)	16.0 (13.0–17.0)	0.167
LIPV diameter, mm	14.0 (13.0–16.0)	13.0 (12.0–15.0)	0.125
RSPV diameter, mm	15.0 (12.0–16.0)	15.0 (13.0–17.0)	0.955
RIPV diameter, mm	14.0 (12.0–16.0)	12.0 (11.0–15.0)	0.055
PV abnormality, n (%)	11 (40.7)	32 (15.2)	0.001
LCPV, n (%)	7 (25.9)	19 (9)	0.008
RMPV, n (%)	5 (18.5)	15 (7.1)	0.06
Therapy during follow-up			
Treatment with ß-Blocker, n (%)	15 (59.3)	170 (80.6)	0.012
Class I AAD (Flecainide, Propafenone), n (%)	10 (37.0)	92 (43.6)	0.516
Class III AAD (Amiodarone, Sotalol), n (%)	8 (29.6)	46 (21.8)	0.360
Recurrence in Blanking period, n (%)	13 (48.1)	20 (9.5)	<0.001

AAD, antiarrhythmic drugs; AT, atrial tachycardia; AF, atrial fibrillation; BMI, body mass index; CABG, coronary bypass grafting operation; CMP, cardiomyopathy; EHRA Score, European Heart Rhythm Association score; LA, left atrium; LCPV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIPV, right inferior pulmonary vein; RMPV, right middle pulmonary vein; RSPV, right superior pulmonary vein.
The continuous variables are presented as mean ± SD or as median (interquartile range defined as Q1–Q3), if skewed. Categorical data were summarized as frequencies and percentages.

Table 2
Procedural parameters of second-generation cryoballoon ablation.

Parameter	AT (n = 27)	Non AT (n = 211)	p
Total procedure time, min	148.3 ± 32.6	132.9 ± 30.3	0.014
Fluoroscopy time, min	23.1 (16.0–26.2)	22.3 (15.4–24.2)	0.482
Fluoroscopy dose, cGy*cm2	39.1 (25.7–123.0)	40.0 (22.0–123.0)	0.653
Initial sinus rhythm, n (%)	9 (33.3)	107 (50.7)	0.089
Freezes in LSPV, times	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.757
Freezes in LIPV, times	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.870
Freezes in RSPV, times	1.0 (1.0–2.0)	1.0 (1.0–1.0)	0.354
Freezes in RIPV, times	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.450
LSPV freeze duration, seconds	240.0 (180.0–360.0)	240.0 (180.0–360.0)	0.981
LIPV freeze duration, seconds	240.0 (180.0–369.0)	240.0 (180.0–381.0)	0.903
RSPV freeze duration, seconds	235.0 (180.0–300.0)	180.0 (180.0–240.0)	0.409
RIPV freeze duration, seconds	240.0 (180.0–420.0)	240.0 (180.0–420.0)	0.882
Minimum temperature in LSPV, °C	−47.1 ± 5.3	−48.4 ± 5.7	0.306
Minimum temperature in LIPV, °C	−45.6 ± 6.3	−45.3 ± 6.2	0.832
Minimum temperature in RSPV, °C	−48.6 ± 6.9	−49.2 ± 5.8	0.650
Minimum temperature in RIPV, °C	−46.4 ± 6.3	−46.2 ± 6.2	0.854
Total number of applications, n	5.0 (4.0–7.0)	6.0 (5.0–6.0)	0.821
Total duration of application, seconds	1113.1 ± 323.5	1120.0 ± 275.9	0.674
Balloon temperature <−60 °C, n (%)	2 (7.4)	22 (10.4)	0.624
Cardioversion during procedure, n (%)	15 (55.6)	89 (42.2)	0.187
Additional CTI during the procedure, n (%)	2 (7.4)	12 (5.7)	0.664

AT, atrial tachycardia; AF, atrial fibrillation; CTI, cavotricuspid isthmus; LA, left atrium; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIPV, right inferior pulmonary vein; RMPV, right middle pulmonary vein; RSPV, right superior pulmonary vein.
The continuous variables are presented as mean ± SD or as median (interquartile range defined as Q1–Q3), if skewed. Categorical data were summarized as frequencies and percentages.

Table 3
Clinical and procedural parameters in patients, who underwent REDO ablation, according to the mechanism of the recurrence (left AT vs. right AT vs. AF only recurrence).

Parameter	Patients with left AT (n = 16)	Patients with AFL (n = 10)	Patients with AF only (n = 14)	*p*-value *left AT vs AFL/ †left AT vs AF only/ §AFL vs AF only
Demographics				
Age (years)	67.7 ± ±8.2	56.1±14.7	65.6 ± 9.8	0.036*/0.525†/0.180§
Male gender, n (%)	9 (56.2)	8 (80.0)	9 (64.3)	0.069*/0.299†/0.653§
BMI	28.6 ± 8.9	25.6 ± 5.2	28.7 ± 4.9	1.000*/0.355†/0.371§
Medical history				
Persistent AF, n (%)	14 (87.5)	7 (70.0)	8 (57.1)	0.271*/0.101†/0.678§
CHA2DS2VASc	2.7 ± 1.2	1.3 ± 1.9	2.6 ± 1.5	0.135*/0.886†/0.285§
EHRA Score	3 (2–3)	2 (2–3)	3 (2–3)	0.068*/0.951†/0.074§
Mean duration of AF (months)	**33.6 ± 39.4**	**7.1 ± 7.2**	15.9 ± 27.6	0.041*/0.179†/0.437§
Hypertension, n (%)	12 (75.0)	6 (60.0)	13 (92.9)	0.420*/0.336†/0.122§
Diabetes mellitus, n (%)	4 (25.0)	2 (20.0)	1 (7.1)	0.786*/0.336†/0.550§
Previous MI, n (%)	1 (6.2)	2 (20.0)	3 (11.5)	0.286*/0.586†/1.000§
Previous PCI, n (%)	3 (18.3)	2 (20.0)	4 (28.6)	0.937*/0.675†/1.000§
CABG operation, n (%)	1 (6.2)	1 (10.0)	1 (7.1)	0.727*/1.000†/1.000§
Other heart operation, n (%)	1 (6.2)	0 (0)	0 (0)	0.420*/1.000†/NA
Cardiomyopathy, n (%)	7 (43.8)	2 (20.0)	**1 (7.1)**	0.216*/0.036†/0.550§
Valvular heart disease, n (%)	1 (6.2)	0 (0)	0 (0)	0.420*/1.000†/NA
Echo parameters				
LA diameter (mm)	45.6 ± 4.5	41.6 ± 5.9	41.9 ± 7.7	0.077*/0.179†/0.886§
LVEF (%)	50.2 ± 6.6	49.8 ± 10.7	52.2 ± 6.6	0.660*/0.448†/0.886§
Procedural parameters				
Total procedure time (min)	1423 ± 29.7	**156.8 ± 37.9**	**124.1 ± 30.7**	0.310*/0.085†/**0.036§**
Fluoroscopy time (min)	21.2 ± 8.9	24.8 ± 11.7	21.8 ± 10.5	0.484*/0.790†/0.341§
Fluoro Dose, cGy*cm2	62.8±63.6	78.6±46.1	46.9±43.7	0.286*/0.355†/0.084§
Initial sinus rhythm, n (%)	4 (25.0)	5 (50.0)	8 (57.1)	0.192*/0.135†/1.000§
Freezes in LSPV (times)	1 (1-2)	1 (1-2)	1 (1–2)	0.856*/0.854†/9.31§
Freezes in LIPV (times)	1 (1-2)	1 (1-2)	1.5 (1–2)	0.737*/0.400†/0.709§
Freezes in RSPV (times)	1 (1-1.8)	1 (1-2)	1 (1–1.3)	0.776*/0.886†/0.666§
Freezes in RIPV (times)	1 (1-2)	1 (1-2)	1.5 (1-2)	0.737*/0.294†/0.546§
LSPV freeze duration (seconds)	289.9 ± 137.0	298.6 ± 169.6	267.8 ± 92.1	0.856*/0.951†/0.886§
LIPV freeze duration (seconds)	270.9 ± 103.6	288.0 ± 119.3	280.9 ± 111.7	0.897*/0.697†/0.931§
RSPV freeze duration (seconds)	242.1 ± 120.0	269.5 ± 163.2	232.6 ± 94.6	0.586*/0.728†/0.371§
RIPV freeze duration (seconds)	254.9 ± 87.2	318.0 ± 129.8	360.4 ± 189.6	0.336*/0.120†/0.752§
Minimum temperature in LSPV (°C)	−47.7 ± 5.6	−46.1 ± 5.2	−47.7 ± 5.9	0.452*/0.918†/0.403§
Minimum temperature in LIPV (°C)	−44.9 ± 5.7	−45.0 ± 5.4	−44.4 ± 4.4	0.897*/0.854†/0.709
Minimum temperature in RSPV (°C)	−50.0 ± 6.7	−46.8 ± 7.3	−51.8 ± 5.0	0.363*/0.552†/0.096§
Minimum temperature in RIPV (°C)	−46.4±6.4	−46.4±6.8	−45.8±4.5	0.737*/0.637†/0.796§
Total number of applications (n)	5.4 ± 1.5	5.7 ± 1.5	5.7 ± 1.3	0.623*/0.525†/0.886§
Total duration of application (seconds)	1057.8 ± 331.5	1174.1 ± 318.1	1141.6 ± 314.2	0.310*/0.224†/0.752§
Balloon temperature <−60 °C, n (%)	1 (6.2)	0 (0)	0 (0)	0.420*/1.000†/NA
Cardioversion during procedure, n (%)	10 (62.5)	5 (50.0)	4 (28.6)	0.530*/0.081†/0.403§
Additional CTI during the procedure, n (%)	2 (12.5)	0 (0)	1 (7.1)	0.508*/1.000†/1.000§
PV anatomy				
LSPV diameter (mm)	15.9 ± 3.7	18.7 ± 4.7	16.8 ± 4.0	0.027*/0.580†/0.074§
LIPV diameter (mm)	14.5 ± 2.7	14.3 ± 2.6	13.9 ± 2.6	0.856*/0.498†/0.752§
RSPV diameter (mm)	15.0 ± 3.2	14.4 ± 4.1	15.0 ± 4.4	0.568*/0.822†/0.796§
RIPV diameter (mm)	13.8 ± 3.5	14.1 ± 3.2	13.2 ± 2.9	0.484*/0.580†/0.371§
PV abnormality, n (%)	5 (31.2)	6 (60.0)	5 (35.7)	0.228*/1.000†/0.408§
LCPV, n (%)	3 (18.8)	4 (40.0)	2 (14.3)	0.369*/1.000†/0.192§
RMPV, n (%)	3 (18.8)	2 (20.0)	3 (21.4)	1.000*/1.000†/1.000§
Therapy in the follow-up				
Treatment with beta-blocker, n (%)	9 (56.2)	6 (60.0)	13 (92.9)	0.851*/0.039†/0.122§
Class I AAD (Flecainide/ Propafenone), n (%)	7 (43.8)	3 (30.0)	8 (57.1)	0.683*/0.464†/0.240§
Class III AAD (Amiodarone, Sotalol), n (%)	3 (18.8)	4 (40.0)	0 (0)	0.369*/0.228†/0.020§
LA substrate after CBA				
Patients with PV reconnection	9 (56.2)	8 (80.0)	7 (50.0)	0.336*/0.790†/0.235§
Number of PV reconnections, n	0.8 ± 1.0	1.3 ± 1.2	0.8 ± 1.1	0.220*/0.854†/0.192§
Presence of low voltage area in the LA, n (%)	16 (100)	4 (40.0)	7 (50.0)	0.001*/0.002†/0.697§
Number of low voltage areas in the LA, n	2.0 (2.0–4.0)	0.5 (0–1.8)	0.5 (0–2.25)	0.003*/0.005†/0.815§
Low voltage area in the LA post wall, n (%)	13 (81.3)	3 (30.0)	6 (42.9)	0.015*/0.057†/0.678§
Low voltage area in the inferior LA, n (%)	4 (25.0)	0 (0)	0 (0)	0.136*/0.103†/NA
Low voltage area in the LA mitral isthmus, n (%)	5 (31.2)	0 (0)	2 (14.3)	0.121*/0.399†/0.493§
Low voltage area in the LA anterior wall, n (%)	11 (68.8)	2 (20.0)	3 (21.4)	0.041*/0.014†/1.000§
Low voltage area in the LA septum, n (%)	9 (56.2)	2 (20.0)	4 (15.4)	0.109*/0.159†/1.000§

AAD, antiarrhythmic drugs; AT, atrial tachycardia; AF, atrial fibrillation; BMI, body mass index; CABG, coronary bypass grafting operation; CBA, second-generation cryoballoon ablation; CMP, cardiomyopathy; EHRA Score, European Heart Rhythm Association score; LA, left atrium; LCPV, left common pulmonary vein; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIPV, right inferior pulmonary vein; RMPV, right middle pulmonary vein; RSPV, right superior pulmonary vein.
The continuous variables are presented as mean ± SD or as median (interquartile range defined as Q1–Q3), if skewed. Categorical data were summarized as frequencies and percentages.

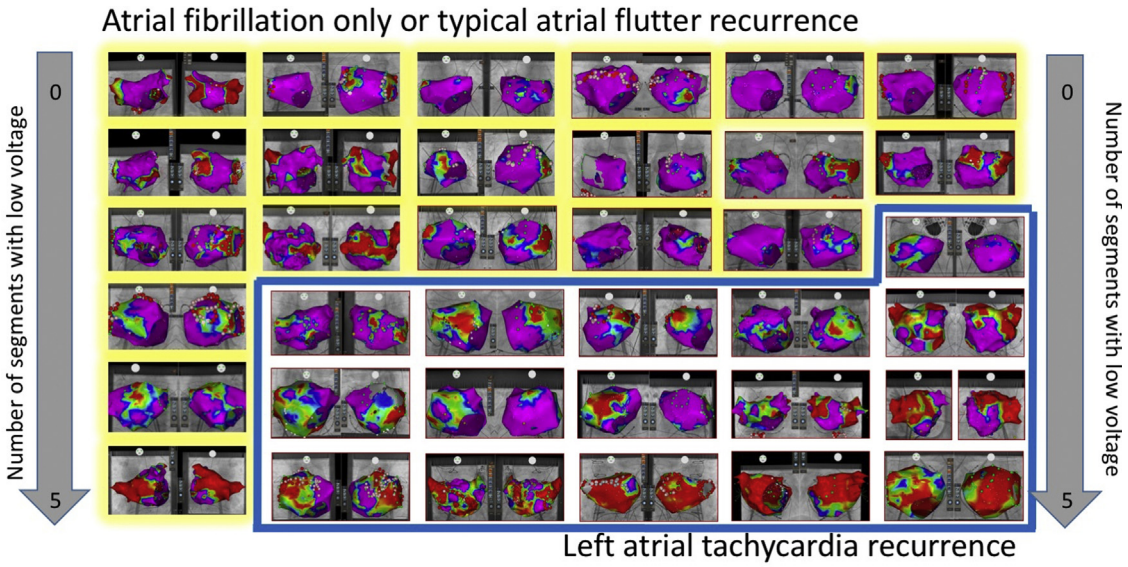

Fig. 2. Bipolar voltage maps of the LA (scale range from 0.15 to 0.5 mV) of 16 patients with left atrial tachycardia recurrence (encountered in the blue line), 14 patients with AF only and 6 patients typical atrial flutter + AF recurrence are schematically presented. The area of low voltage beyond the pulmonary vein antra (number of the segments) is increasing from the top to the bottom. Note that most of the patients with left AT had large low voltage area in the LA, whereas most of the patients with AF only or typical atrial flutter recurrence had moderate or small low voltage area.
AT, atrial tachycardia; AF, atrial fibrillation; LA, left atrium.

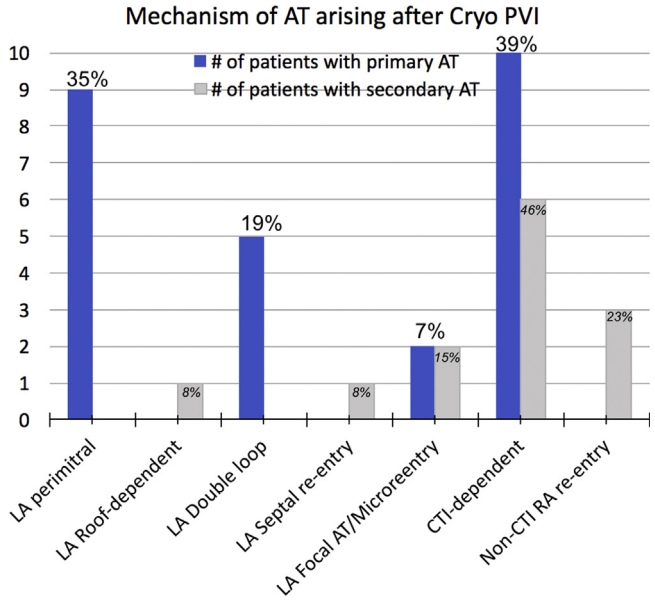

Fig. 3. Electrocardiograms and bipolar voltage maps of the RA (scale range from 0.15 to 0.5 mV) and activation maps of 3 patients with non-CTI-dependent reentry right AT (A, B, C) and 2 patients with typical atrial flutter (D, E). The low voltage area at the posterior wall of the RA is superimposed to the anterior part of the right pulmonary veins (LA is shown as transparent marine-green counter, PV antra marked with the green points). This low voltage area corresponds to the slow conduction zone of non-CTI-dependent RA reentry as well as some cases of typical atrial flutter, which was confirmed by concealed entrainment. Intracaval linear ablation across the low voltage area at the posterior wall of the RA terminated the AT in all 3 cases of the non-CTI-dependent AT.
AT, atrial tachycardia; CTI, cava-tricuspid-isthmus; LA, left atrium; PV, pulmonary vein; RA, right atrium.

mechanism of the initial AT, termination of the AT and conversion to SR was observed in 13 (50%) patients during RFA and transformation to secondary AT, that was subsequently ablated, occurred in 13 (50%) patients (Fig. 4). All ATs terminated during ablation. No patient required direct current cardioversion. No sustained AT was inducible by programmed stimulation or burst pacing at the end of the redo procedure.

Right atrial tachycardias

CTI-dependent AT was diagnosed in 10/26 (38.5%; 4.2% of the total patient population) patients as initial AT and in 6/26 (23.1%) as secondary AT. None of these 10 patients had previous CTI ablation. In 3 (11.5%) patients CTI ablation led to transformation to non-CTI-dependent reentry in the RA (upper loop-reentry) (Fig. 3). Voltage map showed the presence of low voltage area in the RA posterior wall opposite to the right PVs in all of these patients. Placement of an intercaval line in the RA successfully terminated the AT in all 3 cases. No focal ectopic or microreentrant mechanism was detected in the RA.

Left atrial tachycardias

In 16/26 (61.5%; 6.7% of the total patient population) patients a LA origin of the AT was diagnosed (Fig. 5). EAM and entrainment confirmed a macroreentrant mechanism of primary left AT in 14/26 (53.8%) patients. Primary perimitral reentry was diagnosed in 9/26 (34.6%) patients and primary double-loop reentry in the LA (perimitral and roof-dependent reentry) in 5/26 (19.2%) patients. Roof-dependent AT was mapped in one patient (3.8%) as secondary AT (as the result of transformation of perimitral reentry after anterior line ablation) and LA septal reentry was mapped in one patient (3.8%) as secondary AT. LA focal AT occurred in two (7.2%) patients as the primary AT (posterior wall, LA septum), and in one (3.8%) patient as a secondary AT (LA septum). Microreentry was mapped in one (3.8%) patient as a secondary AT localized in the LA ridge. No case of PV-associated AT was observed in our patient population. Voltage mapping analysis revealed the presence of low voltage areas in different segments of the LA in all patients with left-AT (Fig. 5).

Three patients experienced recurrence of AT (perimitral AT after initial perimitral AT ablation, perimitral after initial double-loop reentry AT ablation, and recurrence of AFL after initial CTI-ablation) during follow-up (14, 12, and 7 months after previous AT ablation) and were successfully reablated during the third procedure.

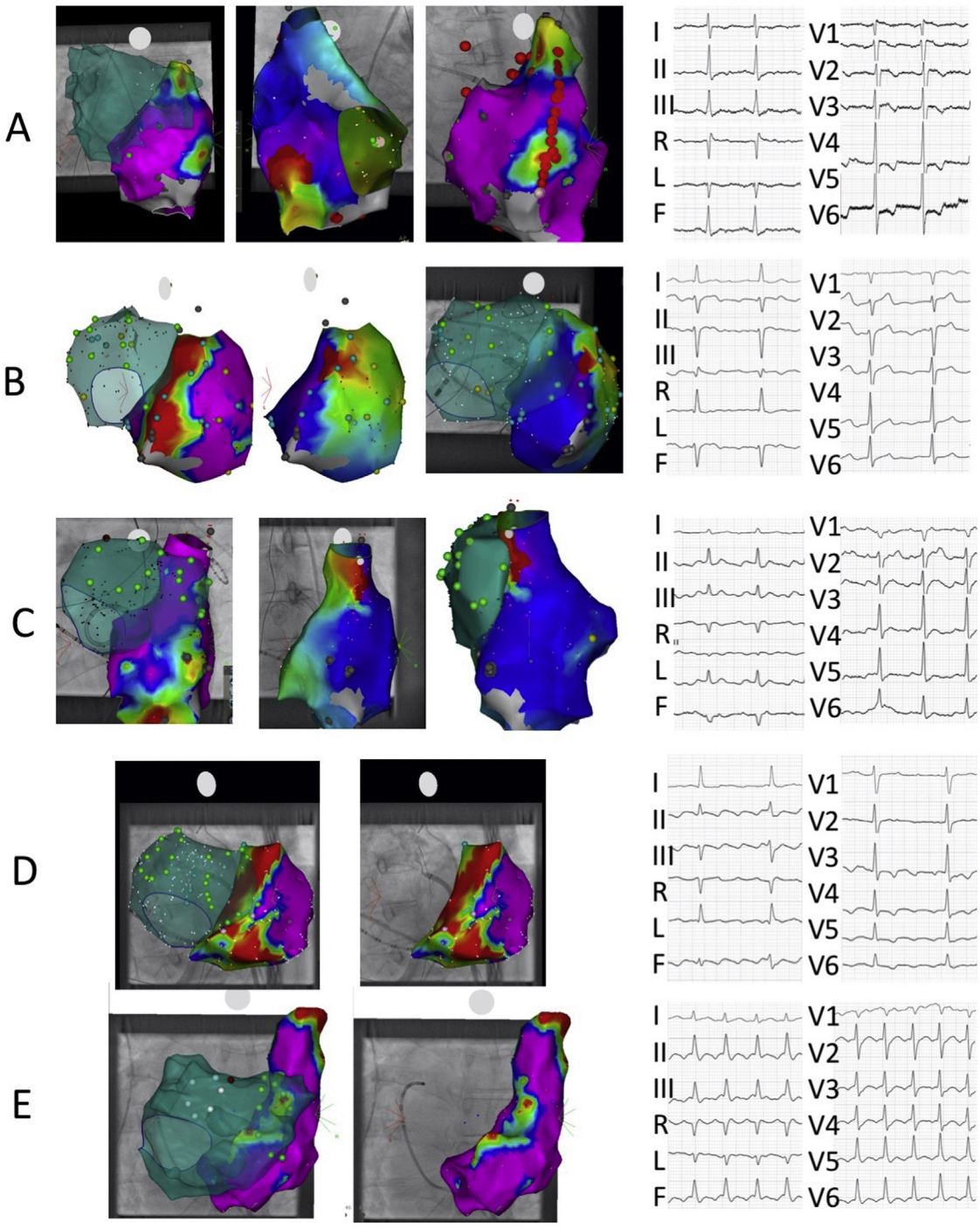

Fig. 4. Mechanisms of AT, arising after Cryo PVI. Primary AT is defined as the clinical AT, which was initially mapped during redo-ablation. Secondary AT is the AT, that occurred during the redo-ablation as the result of transformation of primary or any other AT during its ablation.
AT, atrial tachycardia; Double loop, simultaneous perimitral and roof-dependent reentry in the left atrium; LA, left atrium; PVI, pulmonary vein isolation; CTI, cava-tricuspid-isthmus; RA, right atrium.

Predictors of AT recurrence

Univariate analysis revealed the following predictors of AT after CBA: persistent type of AF, any type of cardiomyopathy, LA diameter, LVEF, PV abnormality, diameter of the right inferior PV, duration of CBA, eschewal of beta-blockers during follow-up (Tables 1 and 2). After multivariate adjustment persistent type of AF (HR = 3.3; CI = 1.2–9.4; $p = 0.022$), any type of cardiomyopathy (HR = 3.5; CI = 1.5,8.4; $p < 0.0001$), PV abnormality (HR = 4.6; CI = 2.1–10.4; $p = 0.022$) and eschewal of beta-blockers in follow-up (HR = 0.3; CI = 0.1–0.6; $p = 0.001$) remained as independent predictors of AT.

Discussion

The main findings of the study are: (I) A significant number of patients undergoing second-generation CBA for predominantly PersAF developed AT during follow-up (11.3%). (II) Macroreentry

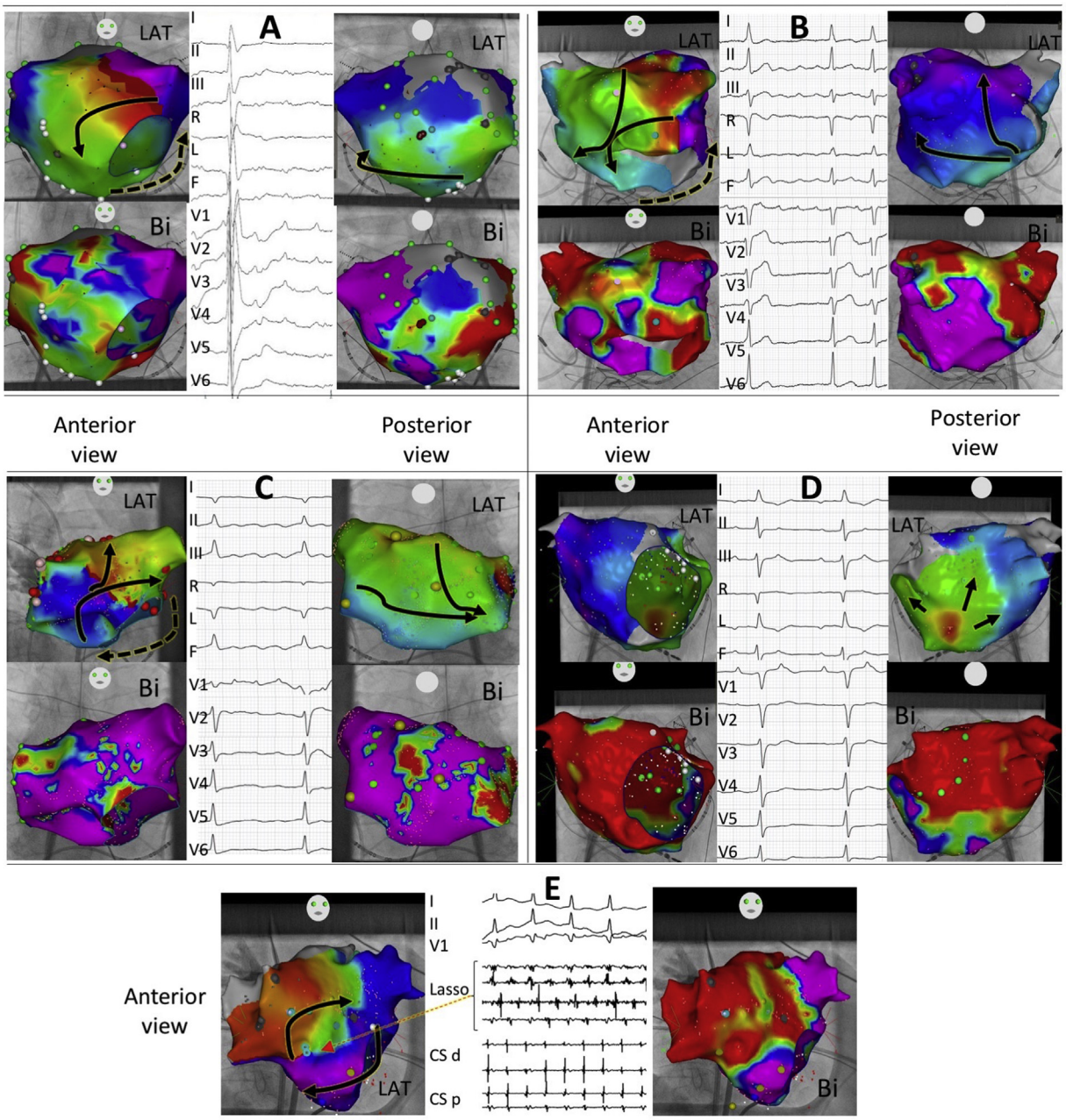

Fig. 5. Activation maps (LAT), bipolar voltage maps (Bi) of the LA (scale range from 0.15 to 0.5 mV) and electrocardiograms of 5 patients with LA atrial tachycardias. (A) Counterclockwise perimitral reentry. (B) Double-loop reentry (counterclockwise perimitral and roof-dependent reentry). (C) Double-loop reentry (clockwise perimitral and roof-dependent reentry). (D) Focal atrial tachycardia from the LA posterior wall. (E) LA septal reentry (note the activation gradient of intracardiac electrograms from the Lasso-catheter, positioned at the LA septum). All mechanisms of AT depicted on the activation maps were confirmed by entrainment.
AT, atrial tachycardia; LA, left atrium; LAT, local activation time.

AT was the prevailing mechanism. (III) Neither macroreentry nor focal AT were related to PV reconnection or originated inside the PVs. (IV) All patients with right ATs revealed low voltage areas in the posterior wall of the RA.

PVI remains the ablation strategy of choice for the treatment of AF [10,22]. Long-term outcomes following radiofrequency based circumferential PVI are excellent in patients with paroxysmal AF and moderate in patients with nonparoxysmal AF [23,24]. Nevertheless, AF recurrence and especially newly developed postprocedural ATs may occur after initial PVI in a significant portion of patients (11–44%) [10]. The mechanisms of ATs following PVI were carefully described in several studies [7–9,11,25]. After the pivotal randomized "Fire And Ice" trial demonstrating non-inferiority of the second-generation CBA compared to RFA with regard to efficacy and safety for treatment of patients with PAF, the number of CBA increased dramatically [5,6]. AT may also occur following CBA. However, data regarding the exact incidence, predictors, and clinical relevance of ATs after CBA are sparse.

Previous studies with postprocedural AT: Cryoballoon ablation

Currently there are four studies reporting on the prevalence and mechanisms of ATs after CBA. Only one of them evaluated left-AT occurring exclusively after second-generation CBA in patients with PAF and PersAF, but without description of RA tachycardias [16]. The prevalence of ATs in our study (11.3%) is higher than reported in previous studies (Hermida et al. (9.2%), Mikhaylov et al. (8%), Akerström et al. (6%), and Juliá et al. (3%) [13–16]. Mikhaylov and

Juliá reported exclusively cases of focal AT in the LA related to PV reconnections, whereas Akerström and Hermida described left macroreentrant ATs and focal ATs related to PV reconnection. In our study macroreentry was the prevalent mechanism of left-AT (87.5%) and right-AT (100%) after CBA. Neither focal ectopic AT nor microreentry AT were related to PV reconnections in our study population, whereas most of the focal AT in previous studies were attributed to reconnected PV activity [13–16].

CTI-dependent AFL was observed in previous studies as the only mechanism of right-AT after CBA [13–15]. Basically right atriotomy for cardiac surgery, previous RA ablations, or fibrotic processes may lead to the development of slow-conduction zones in the RA, maintaining atypical right AFL [26]. Our study is the first one to describe a non-CTI-dependent macroreentrant mechanism (upper-loop-reentry) in the RA in patients after CBA. These findings are associated with the presence of low voltage areas at the posterior wall of the RA opposite to the right PVs that can be a substrate for slow impulse conduction.

Potential explanations for discrepancies in prevalence and mechanisms of AT might relate to the heterogeneity of study populations, with a higher prevalence of PersAF (61.8%) in our study compared to the study by Mikhaylov, Akerström, Juliá (PAF-only patients), and Hermida (44% of PersAF patients). Advancement of remodeling of the atrial myocardium may be more prominent in persAF, and thus result in the fibrotic changes of the atrial myocardium and provide the substrate for macroreentry (Fig. 2). Furthermore, the use of the 28-mm second-generation cryoballoon only in our study might influence results, while Mikhaylov and Hermida used a 23-mm cryoballoon for 22.8% and 8.0% of cases, respectively. Mikhaylov et al. and Akerström et al. used the first-generation cryoballoon while Juliá et al. reported the use of both generations of the cryoballoon. It is also noticeable, that 65.5% of the patients in our study had antiarrhythmic medication after CBA, which increase the atrial refractoriness and promote the occurrence of macroreentry. This could also potentially explain the high incidence of macroreentry AT in our patient population.

Previous studies with postprocedural AT: radiofrequency ablation

Several studies have been published, describing the mechanisms of ATs following point-by-point RFA. Direct comparison of RFA vs. CBA in the studies by Akerström et al., Juliá et al. and a recent meta-analysis by Cardoso et al. showed a higher prevalence of AT after RFA in comparison to CBA (6.7% vs. 2.8%) [12,14,15]. This was explained by higher catheter stability of CBA going along with more homogeneous lesions with fewer applications, whereas the point-by-point RFA might have a higher likelihood of remaining gaps in ablation lines, which may eventually lead to focal or reentry AT, especially related to PV reconnections. The results of our study showed a significant prevalence of AT (11.3% of the total study population; left-AT in 6.7%), comparable with the prevalence after RFA.

The mechanism of AT depends on the design of the PVI: The most common mechanism of AT after segmental or circumferential PVI is focal activity from the reconnected PV [8]. ATs following wide antral circumferential ablation (WACA) PVI have a macroreentrant mechanism, which can involve the reconnected PV antrum or not (roof-dependent AT, perimitral AT) [25]. Overall, the incidence of non-PV-dependent macroreentry AT is higher, when linear ablations in the LA were initially performed [11].

Substrate of AT

To our knowledge, this is the first study, where analysis of voltage maps was systematically performed for patients with AT, who underwent redo procedures after CBA. Voltage mapping of both atria revealed the presence of low voltage areas that play a key role as slow conduction isthmus of the macroreentry circuit. All patients with left-AT had low voltage substrate in at least one segment of the LA (median 2.0; IQR 2.0–4.0 segments), whereas this was observed in only half of patients with AF-only (median 0.5; IQR 0.0–2.25 segments) and in 40% of the patients with AFL recurrence (median 0.5; IQR 0.0–1.8 segments) (Fig. 2, Table 3). Interestingly, the earliest activation site of focal left-AT was mapped in the border zone between low voltage and normal voltage areas in all cases (Fig. 5).

Three patients with RA upper-loop-reentry had corresponding low voltage areas in the posterior wall of the RA opposite to the right PVs with slow impulse conduction in this segment (Fig. 3). Placement of an intercaval line in the RA successfully terminated the AT in all three cases. One can speculate about the nature of the observed low voltage areas in the RA: It could be the result of myofibrotic displacement, especially in patients with PersAF or it may be also the result of collateral damage during CBA of the right PVs. Further studies are needed to define the role of the 28-mm CBA in the development of low voltage areas.

Predictors of AT recurrence

Mikhaylov et al. reported beta-blocker therapy, presence of AT before ablation, and additional right PV as predictors of AT after CBA [13]. An additional right middle PV was associated with development of AT, but did not meet statistical significance in the study by Juliá et al. [15]. According to Hermida et al. LVEF was the only predictor of AT following CBA, and was not mentioned in other studies [16]. The results of our study indicate persistent type of AF, cardiomyopathy, PV abnormality (such as left common trunk or right middle PV), and eschewal of beta-blocker therapy during follow-up as predictors of AT development. One can speculate that in patients with persistent type of AF and cardiomyopathy myofibrotic replacement is more prominent, promoting sustained reentry in the atrium. In contrast to Mikhaylov et al. the results of our study showed that beta-blocker therapy during the follow-up period is associated with lower incidence of AT [13].

Limitations

Limitations of this study relate to the single center, nonrandomized study design. Although our study presents the largest patient population until today, this series included only a small number of patients with AT. Bipolar voltage maps were conducted during ongoing AF or AT in 90% of cases and only in 4 (10%) cases during SR, which could have led to overestimation of the low voltage area. Moreover, a prospective study is needed to define the role of CBA for the development of substrate for AT.

Despite reliable follow-up with 24-h Holter monitoring and/or device interrogations (if present) at 3, 6, and 12 months, some cases of AT could have been missed due to discontinuous rhythm monitoring. For patients with known AF recurrence only we did not routinely perform AT induction before reisolation of the PVs during redo ablation due to lack of clinical relevance.

Conclusion

The results of our study indicate that the incidence of AT after CBA is relatively high (11.3%) with macroreentry being the prevalent mechanism. Persistent AF, abnormality of the PVs, cardiomyopathy of any cause, and eschewal of beta-blocker therapy were identified as independent predictors of AT recurrence. Substrate analysis revealed presence of low voltage areas in the LA in all patients with left-AT and low voltage areas in the

posterior wall of the RA as part of the reentry circuit in all patients with right atrial non-CTI-dependent reentry AT.

Disclosures

E. Lyan received travel grants and Speaker's Bureau Honoraria from Biosense Webster (modest), Medtronic (modest). R. Tilz received travel grants and Speaker's Bureau Honoraria from Biosense Webster (modest). C.H. Heeger received travel grants by Medtronic Inc. (modest). C. Eitel CE received presentation fees (modest) from Bayer, Biosense Webster, Impulse Dynamic, St. Jude Medical/Abbott, Pfizer, Liva Nova, Zoll, Boston Scientific, Novartis, Daiichi Sankyo, AstraZeneca and travel grants (modest) from St. Jude Medical, Biotronik, and Medtronic.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2019.02.006.

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