THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Long-term Outcomes of Cryoballoon-based Empirical Superior Vena Cava Isolation in Addition to Pulmonary Vein Isolation in Persistent Atrial Fibrillation

ORIGINAL INVESTIGATION

ABSTRACT

Background: Superior vena cava (SVC) is atrial fibrillation (AF)'s most common non-pulmonary vein (PV) foci. Studies reported conflictory results when SVC isolation (SVCi) was combined with PVi and long-term outcomes were lacking. Therefore, we aimed to evaluate the long-term efficacy and safety of empirical SVCi as an adjunct to cryoballoon-based PV isolation (PVi) in persistent AF ablation.

Methods: A total of 40 consecutive persistent AF patients (60.6 ± 8.2 years, 52.5% females) who underwent SVCi in addition to PVi compared with a propensity score matched cohort of 40 persistent AF patients (58.6 ± 8.7 years, 50% female) in whom PVi-only was performed. Second-generation cryoballoon (CB2) was used in all procedures. Atrial tachyarrhythmia (ATa) recurrence was defined as the detection of AF, atrial flutter, or atrial tachycardia (≥30 s) after a 3-month blanking period.

Results: Pulmonary veins and SVC were successfully isolated in all patients. At a mean of 46.7 ± 7.8 months follow-up, 22 (55%) patients in the PVi-only group, and 27 (67.5%) patients in the PVi + SVCi group were free of ATa after the index procedure (P = .359). Phrenic nerve injury (PNI) was detected in 2 (5%) patients in the PVi-only group (during right PVi) and 2 (5%) patients in the PVi + SVCi group (during SVCi) (P = 1.00). Cox regression analysis revealed that early recurrence was the only predictor of recurrence (hazard ratio 4.88, 95% confidence interval 1.59-14.96; P = .005).

Conclusion: Long-term results of our small sample-sized study revealed that CB-based PVi + SVCi was associated with outcomes similar to the PVi-only strategy in patients with persistent AF. Although complication rates were similar between the groups, close follow-up of diaphragmatic movement is crucial to prevent PNI during SVCi.

Keywords: Non-pulmonary vein trigger, superior vena cava, atrial fibrillation, cryoballoon

INTRODUCTION

Pulmonary vein isolation (PVi) is the cornerstone of catheter-based atrial fibrillation (AF) ablation therapy since PVs have been reported as the most common triggering source for AF.[1] Although procedural success rates of PVi have been increased by various technological developments, a significant amount of patients show recurrences at long-term follow-up.[2] Thus, additional ablation is necessary for selected patients, particularly in non-paroxysmal AF.[3] While the most commonly encountered reason for recurrences was PV reconnection,[4,5] non-PV ectopic foci, including the superior vena cava (SVC), should also be suspected in the case of silent PVs.[6] But, the identification of the arrhythmogenicity of non-PV triggers is not always easy. SVCi using radiofrequency is the established strategy.[7-9] Previous studies showed controversial results regarding empirical SVCi in addition to PVi.[8,9] Despite the safety and efficacy of cryoballoon (CB) for SVCi,[10-17] data is scarce regarding the long-term outcomes of SVCi as an adjunct to PVi. Therefore, we aimed to assess the long-term outcomes of empirical SVCi as an adjunct to PVi using the second-generation CB technique among patients with persistent AF.

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Received: January 29, 2024
Accepted: May 7, 2024
Available Online Date: June 3, 2024

Cite this article as: Canpolat U, Yorgun H, Aytemir K. Long-term outcomes of cryoballoon-based empirical superior vena cava isolation in addition to pulmonary vein isolation in persistent atrial fibrillation. *Anatol J Cardiol*. 2024;28(9):437-445.

DOI:10.14744/AnatolJCardiol.2024.4092

METHODS

Study Population

In this prospective and observational study, we consecutively enrolled symptomatic persistent AF patients who underwent catheter ablation using second-generation CB between January 2016 and December 2018. The study was designed to compare the long-term efficacy and safety of 2 different ablation strategies: PVi-only (group I) vs. PVi plus empirical SVCi (group II) using the CB technique. For group I, we conducted a retrospective, propensity-score matched cohort analysis in whom only CB-based PVi was performed. Group II consisted of consecutive persistent AF patients who underwent empirical SVCi as an adjunct to PVi between January 2016 and December 2018. The definition of early persistent and persistent AF followed the latest updated AF guidelines.[1,18]

Medical history and details of patients' characteristics including CHA_2DS_2-VASc score were taken from the hospital database. Uncontrolled thyroid dysfunction, the left atrium (LA) thrombus, severe valvular disease, pre-procedural significant coronary artery disease, myocardial infarction or cardiac surgery in the previous 3 months, previous atrial tachyarrhythmia (ATa) ablation history, pregnancy, posteroanterior LA diameter of >55 mm, ablation of other non-PV triggers besides SVCi during the procedure and life-expectancy <12 months were the main exclusion criteria for patient enrollment. Informed consent was obtained from each patient before the procedure. The study complied with the principles outlined in the Declaration of Helsinki and was approved by the Institutional Ethics Committee (document number: B.10.4.İSM.4.06.00.15-12587).

Pre-procedural Management

Transthoracic echocardiography (TTE) was performed in all patients to evaluate the ventricular functions, valvular disease, and LA diameter. Cardiac computed tomography angiography was performed for the assessment of LA and PV anatomy. Transesophageal echocardiography (TEE) was performed before the procedure to exclude the LA thrombus. All procedures were performed with uninterrupted oral anticoagulation (OAC) with warfarin if the international normalized ratio (INR) was 2.0-2.5 or novel oral anticoagulants (NOACs), which were ceased 24-48 hours before the procedure according to the glomerular filtration rate. Electrical cardioversion to obtain sinus rhythm during the procedure was attempted the day before the CB ablation. If sinus rhythm had not been obtained the day before the procedure, electrical cardioversion was repeated just after PVi and before the SVCi procedure.

Pulmonary Vein Isolation

Our ablation procedure was mentioned in detail elsewhere.[2] The ablation procedure was performed under conscious sedation using boluses of midazolam and fentanyl. In all patients, invasive arterial blood pressure, ECG, and oxygen saturation were continuously monitored. After femoral vein punctures, a 6 F steerable decapolar catheter was placed into the coronary sinus. The transseptal puncture was performed using the modified Brockenbrough technique (BRK-0/1, St. Jude Medical) under fluoroscopic guidance. After a transseptal puncture, unfractionated heparin was given to maintain an activated clotting time of ≥300 seconds. The steerable sheath (FlexCath Advance, Medtronic CryoCath, Minneapolis, Minn, USA) was placed into the LA. A Second-generation 28 mm CB catheter (Arctic Front Advance™, Medtronic, Minneapolis, Minn, USA) was used for PVi. The inner lumen circular mapping catheter (Achieve™, Medtronic, Minneapolis, Minn, USA) was used both for maneuvering the CB into the PVs and assessment of PV signals. The duration of each freezing cycle was 180-240 seconds for each targeted PV. After 1 application, an additional bonus freeze of 180-240 second duration was applied in case of the disappearance of the PV potentials >60 seconds during the first cycle. The right phrenic nerve was constantly paced from the SVC during freezing at the right-sided PVs with a 2000 ms cycle and a 12-mA output to detect phrenic nerve palsy (PNP). Intermittent fluoroscopy and direct palpation of the right diaphragmatic excursion were performed during phrenic nerve stimulation.

Successful PVi was defined as the elimination (or dissociation) of all the PV potentials recorded by the inner lumen circular mapping catheter. The cooling temperatures, as well as time to PV signal isolation, were recorded during the procedure. Electrical PVi was confirmed by entrance and exit block pacing maneuvers by CS electrode and circular mapping catheter stimulation, respectively.

Superior Vena Cava Isolation

After isolation of all PVs, steerable sheath and CB were withdrawn into the right atrium (RA) under fluoroscopic guidance. After placing the Achieve catheter into the SVC, the CB was inflated in the RA and positioned at the RA–SVC junction. After contrast injection, occlusion was confirmed by the retention of contrast media in the SVC without backflow into the RA (Figure 1, Supplementary Video 1). Achieve catheter was flipped back to acquire real-time SVC signal during ablation. The duration of the CB freeze was 90 seconds. If SVCi was not achieved in 60 seconds, CB was deflated and positioned again. If the SVC is not isolated after 2 complete 90 second applications, the procedure is terminated. The right phrenic nerve was constantly paced from the circular mapping catheter with a 2000 millisecond cycle length and a 12 mA output (Supplementary Video 1). If there is no capture

HIGHLIGHTS

- Our study is one of the few studies with long-term follow-up data that reports the safety and efficacy of empirical SVCi in addition to PVi using the second-generation CB in persistent AF patients.
- Our findings indicate that empirical isolation of SVC as an adjunct to PVi using CB did not improve freedom from ATa compared to PVi alone in patients with persistent AF at long-term follow-up.
- Early recurrence was the only independent predictor of ATa recurrence at long-term follow-up.
- Moreover, the complication rates including PN injury were similar between study groups.

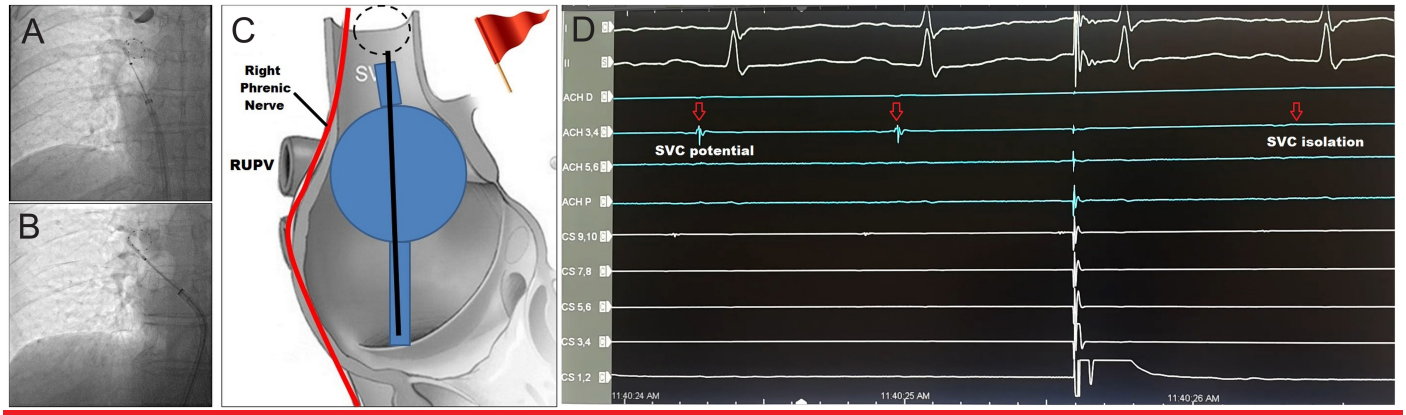


Figure 1. After placing the Achieve catheter into the superior vena cava (SVC), the cryoballoon catheter was inflated in the right atrium (RA) and positioned at the RA–SVC junction. After contrast injection, occlusion was confirmed by the retention of contrast media in the SVC without backflow into the RA. According to the morphology of the SVC–RA junction, an additional maneuver may be required for complete occlusion of the SVC (A and B). There is a close relationship between SVC, right upper pulmonary vein (RUPV), and right phrenic nerve (RPN) (C). D shows electrical isolation of the SVC at 12 seconds while pacing the RPN via a decapolar catheter.

of PN with the Achieve catheter, the quadripolar catheter is placed in the subclavian vein for continuous pacing of the PN during CB application. Phrenic nerve capture was assessed by tactile feedback obtained from the patient's abdomen and intermittent fluoroscopy. We also observed the neck and face of the patient to avoid extreme engorgement of veins due to occlusion of SVC besides close follow-up for any symptom during cryo energy application.[19]

Successful electrical SVCi was defined as either the disappearance of the SVC potentials recorded by the circular mapping catheter or the dissociation of SVC electrical activity from RA (Supplementary Video 2). Time to isolation, the temperature at isolation, nadir temperature, and total freezing time were recorded for all SVCi procedures. To avoid sinus node injury, the SVCi was performed in sinus rhythm rather than in AF rhythm for all patients. Sinus node activity and P-wave morphology were continuously monitored throughout the procedure. The CB application was interrupted immediately in cases of sinus arrest, severe bradycardia (<40 bpm), any episodic acceleration and deceleration of the sinus rate during ablation (gradually shortened P-P interval followed by prolongation of P-P interval), the shortening of P-R interval (suggesting low-atrial or junctional rhythm), or observation of regularly irregular atrial rhythm.

All the sheaths were removed at the end of the procedure. The figure-of-eight suture technique was used for the 15 F venous sheath as described before.[20,21]

Post-procedural Management and Follow-up

Transthoracic echocardiography was performed in all patients after the procedure to rule out pericardial effusion. Oral anticoagulation was started 4-6 hours after the procedure. Routine follow-up visits were scheduled at 3, 6, and 12 months and every 6-12 months thereafter or earlier if patients had symptoms consistent with recurrent ATa or procedure-related complications. In addition to physical examination, 12-lead ECG and TTE were also done at each follow-up visit. A 24-hour Holter ECG was recorded in the 3rd month after the procedure, usually on anti-arrhythmic drugs (AAD). In the absence of documented arrhythmia and/or symptoms consistent with recurrent ATa, all AADs were discontinued. Additional 24-hour Holter ECG was scheduled at the sixth month and every 1 year thereafter or earlier in case of arrhythmic symptoms. Additionally, telephone calls were made at the end of the follow-up period before the analysis. Patients remained on the AAD regimen that was prescribed before the ablation in the first 3 months after ablation. The need for life-long OAC was assessed based on the CHA2DS2-VASc score at the 3rd-month visit in all patients.

Study Endpoints

Procedural success was defined as the electrical isolation of all PVs and SVCs. The blanking period was defined for the first 3 months after the AF ablation. ATa recurrence was defined as the detection of AF, atrial flutter, or atrial tachycardia (≥30 s) evaluated with ECG and Holter recording. Any recurrence within the first 3 months of ablation was defined as early recurrence, whereas recurrence >3 months was defined as recurrence. Freedom from ATa recurrence at the last follow-up visit was the primary endpoint of the study. Safety measures such as complications during the index hospitalization, bleeding events, transient ischemic attack, stroke, and death were also recorded throughout the follow-up.

Statistical Analysis

To estimate the propensity score, we used logistic regression including the following covariates: age, gender, body mass index, history of coronary artery disease, diabetes mellitus, dyslipidemia, previous history of transient ischemic attack (TIA)/stroke, hypertension, heart failure, smoking, glomerular filtration rate, AF subtypes, duration of AF, CHA_2DS_2-VASc score, left ventricular ejection fraction, LA diameter, number of failed AADs, and cardiovascular medications. Based on their propensity score, the patients who underwent SVCi plus PVi and PVi-only were matched on a 1:1 basis with the nearest neighbor algorithm

without replacement using a caliper width 1/5 logit of the standard deviation (SD). Matching was done using the nearest neighbor method using a one-to-one (1:1) ratio using the R extension pack (R version 2.15.0). The selection process used a *P*-value cutoff of 0.05 for a characteristic to enter and remain in the model. Analyses were conducted in the matched cohorts.

Continuous variables are presented as mean values ± SD or median (25%-75% percentiles), whereas categorical ones are presented as number (n) and percentage (%). The Kolmogorov–Smirnov criterion was used for the assessment of normality. Comparisons between baseline characteristics were performed by independent Student's *t*-test, Mann–Whitney *U*-rank-sum, Fisher's exact, or χ^2 tests where appropriate. Cox proportional hazards regression was used to test the effect of the explanatory variables on AF recurrence, adjusted for other variables. Parameters that are found to be univariately associated with the outcome and those that show an association with the outcome with $P < .1$ are included in the multivariable Cox regression analysis. Time to recurrence of AF was plotted using Kaplan–Meier analysis for patients with AF due to study groups (SVCi plus PVi vs. PVi-only) separately (with a blanking period of 3 months following CB applied). AF-free survival distributions were compared between the treatment groups through the log-rank test. A 2-tailed *P*-value <.05 was considered statistically significant. All analyses were performed, using the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc 11.4.2 (MedCalc Software, Mariakerke, Belgium).

We did not use any artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work.

RESULTS

Patient Characteristics

Among 43 patients with persistent AF in whom PVi + SVCi was attempted, SVCi could not be achieved in 3 (7%) patients and was excluded from the final analysis. The reason for SVCi failure was anatomical and technical reasons (28 mm size of the CB prevented good occlusion of SVC-RA junction). Finally, a total of 80 patients with persistent AF who underwent PVi-only (group I, n = 40, age 60.6 ± 8.2 years, 52.5% female) or PVi + SVCi (group II, n = 40, age 58.6 ± 8.7 years, 50% female) were enrolled. Both groups included similar rates of early persistent and persistent AF patients ($P = .31$). The mean LA diameter (44.3 ± 4.6 mm vs. 42.7 ± 4.1 mm, $P = .1$) and median duration of AF history were (36 vs. 24 months, $P = .351$) similar between groups. The baseline demographic and clinical characteristics of the study groups are represented in Table 1.

Table 1. Baseline Characteristics of the Study Groups (n = 80)

Parameters	Group I (PVI Only) (n = 40)	Group II (PVI + SVCI) (n = 40)	*P*
Age (years)	60.6 ± 8.2	58.6 ± 8.7	.294
Sex (female)	21 (52.5%)	20 (50.0%)	1.000
BMI (kg/m^2)	29.0 ± 5.6	28.1 ± 4.5	.421
History of CAD[a]	22 (55.0%)	19 (47.5%)	.655
Diabetes mellitus	7 (17.5%)	9 (22.5%)	.781
Dyslipidemia[b]	16 (40.0%)	9 (22.5%)	.147
Previous TIA/CVA	0 (0.0%)	2 (5.0%)	.494
Hypertension	23 (57.5%)	17 (42.5%)	.263
Congestive heart failure	2 (5.0%)	4 (10.0%)	.675
Alcohol intake[c]	7 (17.5%)	9 (22.5%)	.781
Current smoking history	7 (17.5%)	9 (22.5%)	.781
CHA_2DS_2-VASc score	1.93 ± 0.52	2.05 ± 0.36	.217
AF type			
Early persistent	27 (67.5%)	32 (80.0%)	.310
Persistent	13 (32.5%)	8 (20.0%)	
Duration of AF history (months)	36 (25-60)	24 (18-46)	.351
LA diameter (mm)	44.3 ± 4.6	42.7 ± 4.1	.100
LVEF (%)	59.6 ± 7.6	58.9 ± 10.6	.757
Serum creatinine (mg/dL)	0.99 ± 0.23	0.82 ± 0.22	.127
No. failed antiarrhythmics	1.80 ± 0.46	1.75 ± 0.36	.574
Antiarrhythmic medications			
Beta-blockers	28 (70.0%)	20 (50.0%)	.110
Amiodarone	24 (60.0%)	21 (52.5%)	.652
Propafenone	16 (40.0%)	15 (37.5%)	1.000
Sotalol	4 (10.0%)	2 (5.0%)	.675
Antiplatelet and anticoagulants			
Aspirin	7 (17.5%)	4 (10.0%)	.518
Clopidogrel	1 (2.5%)	1 (2.5%)	1.000
Warfarin	6 (15.0%)	5 (12.5%)	.745
NOAC	25 (62.5%)	21 (52.5%)	.365
No OAC	9 (22.5%)	14 (35.0%)	.216

Data are median (25%-75% percentiles), means ± SD, or n (%). AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; EHRA:, European heart rhythm association; LA, left atrium; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; SD, standard deviation.
[a]Defined as a previous history of ischemic heart disease.
[b]Dyslipidemia is defined as total cholesterol ≥200 mg/dL or treatment with a lipid-lowering agent.
[c]Alcohol intake is defined as having up to 1 drink per day for women and up to 2 drinks per day for men in which heavy drinkers and abusers were excluded.

Procedural Characteristics

Pulmonary vein isolation and SVCi were performed using a 28 mm CB in all patients. The total procedural time was 61.8 ± 10.2 minutes and 59.7 ± 9.5 minutes, and the total fluoroscopy time was 10.7 ± 2.8 minutes and 10.7 ± 3.0 minutes in group I and group II, respectively ($P > .05$). The mean number of CB applications per PV, nadir temperature, time to isolation, and temperature at isolation were similar between groups. Acute procedural success rates for PVi were 100% in both groups I and II. Cryoballoon for SVCi was applied for a median 1 (1-2) cycle, time to isolation was a median of 38.5 (22-75) s, and median temperature at isolation was −30°C (−23°C to −40°C) in patients who underwent SVCi. Detailed procedural characteristics are shown in Table 2.

Table 2. Procedural and Ablation Characteristics of the Study Groups (n = 80)

Parameters	Group I (PVI-only) (n = 40)	Group II (PVI + SVCI) (n = 40)	*P*
Total procedure time (minutes)	61.8 ± 10.2	59.7 ± 9.5	.343
Fluoroscopy time (minutes)	10.7 ± 2.8	10.7 ± 3.0	.893
CB model			
Second generation	40 (100.0%)	40 (100.0%)	1.000
Mean number of freeze–thaw cycles	1.49 ± 0.28	1.35 ± 0.28	.034
Total number of PVs	152	154	.356
Number of PVs per patient	3.8 ± 0.4	3.9 ± 0.5	.617
Pulmonary vein variants			
Left common ostium	8 (20.0%)	9 (22.5%)	.784
Right middle vein	2 (5.0%)	0 (0.0%)	.494
Left superior PV			
Cryoapplication duration per vein, seconds	240 (180-240)	240 (180-240)	.762
Cryoapplication frequency per vein	2 (1-2)	2 (1-2)	.006
Temperature at isolation (°C)	34 (26-38)	34 (21-42)	.340
Nadir temperature (°C)	49.5 (42-53)	48 (44-54)	.634
Time-to-isolation (seconds)	41.5 (31-72)	40 (30-76)	.543
Left inferior PV			
Cryoapplication duration per vein, sec	240 (180-240)	240 (180-240)	.467
Cryoapplication frequency per vein	2 (1-2)	1 (1-2)	.003
Temperature at isolation (°C)	28.5 (22-36)	31 (21-39)	.536
Nadir temperature (°C)	43.5 (38-47)	41 (37-46)	.378
Time-to-isolation (s)	38.5 (21-90)	34 (23-66)	.487
Right superior PV			
Cryoapplication duration per vein (seconds)	180 (180-240)	180 (180-240)	.631
Cryoapplication frequency per vein	1 (1-2)	1 (1-2)	.582
Temperature at isolation (°C)	30.5 (21-36)	29 (19-38)	.541
Nadir temperature (°C)	46 (41-55)	46.5 (40-52)	.259
Time-to-isolation (seconds)	37 (23-45)	30 (20-62)	.271
Right inferior PV			
Cryoapplication duration per vein (seconds)	180 (180-240)	180 (180-240)	.066
Cryoapplication frequency per vein	1 (1-2)	1 (1-2)	1.000
Temperature at isolation (°C)	29 (18-35)	31 (25-36)	.212
Nadir temperature (°C)	41.5 (36-48)	45 (40-52)	.069
Time-to-isolation (seconds)	38.5 (21-65)	34 (28-58)	.774
Superior vena cava			
Time-to-isolation (seconds)	–	38.5 (22-75)	NA
Temperature at isolation (°C)	–	30 (23-40)	NA
Nadir temperature (°C)	–	43.5 (38-48)	NA
Total freezing time (seconds)	–	135 (110-160)	NA
Complications			
Femoral hematoma	1 (2.5%)	0 (0.0%)	1.000
Femoral pseudoaneurysm	0 (0.0%)	1 (2.5%)	1.000
Right phrenic nerve palsy			
During Right PVi	2 (5.0%)	0 (0.0%)	1.000
During SVCi	0 (0.0%)	2 (5.0%)	
Follow-up			
Duration of follow-up (months)	47.1 ± 6.7 (42-55)	46.2 ± 7.9 (34-54)	.594
Recurrence time (months)	43 (12-37)	42 (16-48)	.199
Early recurrence	8 (20%)	5 (12.5%)	.546

(*Continued*)

Table 2. Procedural and Ablation Characteristics of the Study Groups (n = 80) (Continued)

Parameters	Group I (PVI-only) (n = 40)	Group II (PVI + SVCI) (n = 40)	*P*
Recurrence after index procedure	18 (45%)	13 (32.5%)	.359
Medical therapy	11 (61.1%)	7 (53.8%)	
Re-do CBA	1 (5.6%)	2 (15.4%)	.658
Re-do RF ablation	6 (33.3%)	4 (30.8%)	
Mean number of catheter ablation	1.1 ± 0.44 (1-2)	1.08 ± 0.27 (1-2)	.760
ATa-free survival after redo-ablation(s)	28 (70%)	31 (77.5%)	.446

Data are median (25%-75% percentiles), means ± SD, or n (%). AF, atrial fibrillation; CB, cryoballoon; NA, not applicable; PV, pulmonary vein; PVi, pulmonary vein isolation; SVCi, superior vena cava isolation.

Procedural Safety Outcomes

Vascular access site complications including hematoma and pseudoaneurysm were similar between groups. Right-sided PNP developed in 2 patients (5%) during right PVi in group I and 2 patients (5%) during SVCi in group II (*P* = 1.00) which resolved spontaneously during the procedure. There was no sinus node injury (sinus arrest, pause, exit block) or inappropriate sinus tachycardia in any of the SVCi patients at immediate and long-term follow-up. Mean heart rates were similar before SVCi, just after SVCi, and at long-term follow-up among SVCi patients. Detailed procedural complications are demonstrated in Table 2.

Procedural Efficacy Outcomes

The mean follow-up duration was 47.1 ± 6.7 (42-55) months in group I and 46.2 ± 7.9 (34-54) months in group II (*P* = .594). Early recurrence was observed in 8 (20%) patients in group I and 5 (12.5%) patients in group II (*P* = .546). In the whole study population, ATa recurrence after index CB ablation procedure was observed in 31/80 (38.8%) patients [18 (45%) in group I vs. 13 (32.5%) in group II, *P* = .359]. Kaplan–Meier survival analysis showed that 70% (n = 28) of the patients in group I and 77.5% (n = 31) of the patients in group II were free of ATa after multiple ablation procedures during the long-term follow-up (*P* = .446) (Figure 2).

All the recurrences were AF episodes in both study groups. Seven patients in group I and 6 patients in group II underwent re-do catheter ablation. No SVC reconnection was observed in any of those patients. PV reconnection was observed and re-isolated in 10/13 patients, PVs were silent, and posterior wall isolation was performed in the remaining 3/13 patients during re-do ablation procedures.

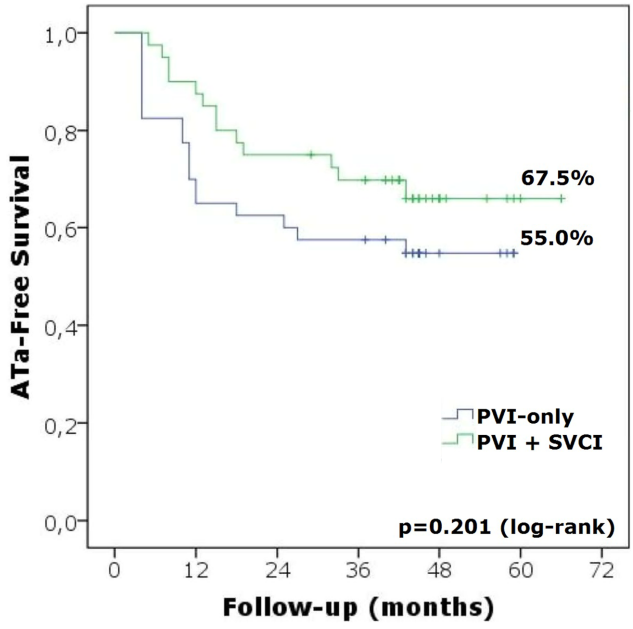
Predictors of Recurrence

Univariate Cox proportional hazard regression analysis showed that nadir temperature for LSPV [hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.99-1.15; *P* = .079], the temperature at isolation for LIPV (HR 0.94, 95% CI 0.88-1.01; *P* = .066), and early recurrence (HR 6.90, 95% CI 3.28-14.5; *P* < .001) were predictors of ATa recurrence. Multivariate Cox proportional hazard regression analysis revealed that only early recurrence (HR 4.88, 95% CI 1.59-14.96; *P* = .005) was a significant predictor for late recurrence after the procedure (Table 3).

DISCUSSION

To the best of our knowledge, our study is one of the few studies with long-term follow-up data that reports the safety and efficacy of empirical SVCi in addition to PVi using the second-generation CB in persistent AF patients. Our findings indicate that empirical isolation of SVC as an adjunct to PVi using CB did not improve freedom from ATa compared to PVi alone in patients with persistent AF at long-term follow-up. Early recurrence was found as the only independent predictor of ATa recurrence at long-term follow-up. Moreover, the complication rates including PN injury were similar between study groups.

Pulmonary veins are the main AF trigger sites in patients with paroxysmal and non-paroxysmal AF.[22] Thus, the PVi is the basis for all ablation procedures in the treatment of all AF subtypes. However, long-term success rates after PVi only strategy in non-paroxysmal AF as compared to paroxysmal AF are still insufficient which provoked operators for



	0	12	24	36	48	60
PVI-only	40	28	25	23	6	
PVI+SVCI	40	36	30	27	9	2

Figure 2. Kaplan–Meier survival analysis of atrial tachyarrhythmia-free survival in persistent AF patients during follow-up based on ablation strategy as pulmonary vein isolation-only vs. pulmonary vein isolation + superior vena cava isolation.

Table 3. Univariate and Multivariate Cox Proportional Hazard Regression Results of the Atrial Tachyarrhythmia Recurrence After Cryoballoon-Based Atrial Fibrillation Ablation

	Univariate Model			Multivariate Model		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (years)	1.02	0.98-1.07	.279			
BMI (kg/m^2)	1.03	0.96-1.09	.429			
Hypertension	1.73	0.84-3.56	.138			
Diabetes mellitus	0.54	0.19-1.53	.243			
Congestive heart failure	0.92	0.22-3.85	.908			
LA diameter (mm)	1.35	0.62-2.93	.447			
CHA_2DS_2-VASc score	1.32	0.59-2.96	.502			
Nadir temperature for LSPV	1.07	0.99-1.15	.079	1.05	0.96-1.15	.277
Temperature at isolation for LIPV	0.94	0.88-1.01	.066	0.96	0.89-1.02	.190
Time-to-isolation for LIPV	0.98	0.95-1.01	.168			
Time-to-isolation for RIPV	0.98	0.94-1.02	.330			
PVi only strategy	1.58	0.77-3.22	.211			
Early recurrence	6.90	3.28-14.5	<.001	4.88	1.59-14.96	**.005**

AF recurrence after the blanking period is the dependent variable. AF, Atrial fibrillation; ATa, atrial tachyarrhythmia; BMI, body mass index; CB, cryoballoon; CI, confidence interval; HR,: hazard ratio; LA, left atrium; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; PVi p vein isolation; RIPV, right inferior pulmonary vein.

adjunctive ablation approaches besides PVi.[1] To now, it is unclear for whom and how additional ablation approaches including atrial substrate modification, fibrosis-based ablation, rotor ablation, or non-PV triggers elimination should be performed besides PVi.[1]

Although the PVs and PV antrum have a critical role in AF, non-PV foci have also been identified as important sources of AF.[6] Among one of the most common non-PV AF sources, the SVC has atrial muscular sleeves extending up to a short distance from the right atrium.[23] and plays a role not only as a trigger but also as a driver for AF like the PVs.[24,25] Previous reports have shown that the prevalence of SVC foci-initiating AF ranges between 11% and 13% among paroxysmal AF patients.[26,27] In the study presented by Santangeli et al,[22] non-PV triggers were found in 11% of the patients which was similar among the different types of AF. Although isolation of all the PVs is the preferred approach during AF ablation independent from their arrhythmogenicity, it is controversial whether a non-PV trigger ablation including empirical SVCi as an adjunct to PVi increases the efficacy of AF ablation. Only 2 randomized studies were presented, which have been criticized for various drawbacks and contradictory results.[8,9] In a previous study by Wang et al,[9] empirical SVCi in addition to PVI did not have a significant reduction in ATa recurrence in patients with paroxysmal AF. Similarly, a meta-analysis evaluating the role of empirical SVCi in addition to PVI revealed no beneficial effect of SVCi to PVI-alone strategy in a total of 526 patients.[28] The addition of empirical SVCi at repeat PVi ablation for the recurrence of ATa also revealed no improvement in outcome compared to a PVi-only approach.[17] However, several recent studies yielded favorable outcomes after empirical SVCi.

The main concern regarding empirical ablation of non-PV triggers is mainly related to the inherent electrophysiological properties of the focus causing arrhythmia development. Previously, Higuchi et al[24] demonstrated that long SVC sleeves (>30 mm) and large SVC potentials (>1 mV) were the main factors related to its arrhythmogenicity. As SVCi has various risks of complications, the appropriate selection of patients for non-PV trigger isolation has paramount importance. The feasibility of SVCi in addition to PVi using RF ablation has long been evaluated.[7] Moreover, CB was also shown to be an effective tool for SVCi.[10,11,29] SVCi using CB after PVi may cause earlier isolation due to the proximity of SVC and right superior PV which can create a collateral effect resulting in the conduction delay of SVC potentials.[30] In paroxysmal AF patients with a documented trigger site for AF, Chang et al[31] demonstrated that 73% of the patients remained free of AF for 5 years after a single catheter ablation procedure of SVCi. On the other hand, a comparison of empirical SVCi to SVC-triggered AF in addition to PVi in patients with paroxysmal AF yielded better ATa recurrence in the empirical SVCi group during a mean follow-up of 27 $\pm$ 12 months.[32] In a very recent study by Zhang et al,[33] empiric SVCi during the re-do procedure improved freedom from ATa compared to the conventional SVCi group (patients with either triggered or rapid SVC activity) during 19 $\pm$ 10 months follow-up. Similarly, the mechanisms of recurrent ATa after second-generation CB were evaluated in a recent study, which revealed upper PV reconnection as well as arrhythmogenic SVC as a non-PV focus were the responsible structures for ATa recurrence.[34] Beyond these studies, our study has a longer follow-up duration with freedom from ATa rate of 55% in the PVi-only group vs. 67.5% in the PVi plus SVCi group. Although there was a non-significant difference for ATa recurrence between study groups at long-term follow-up, it might be due to (a) a small sample size, (b) the progression of the disease over time, and (c) the necessity of an additional non-PV trigger ablation or substrate modification beyond SVCi during index procedure. Further large-scale studies are needed to incorporate the empirical SVCi approach without assessing the

arrhythmogenic per-patient basis -similar to the current PVi approach- to the standard AF ablation procedure.

Although the number of complications specific to SVCi was rare in the current study, both phrenic nerve injury and sinus node dysfunction should be kept in mind and the operators should be careful about these complications both during the procedure and follow-up.[35]

Our study findings expand the literature in terms of longer follow-up with SVCi besides PVi using CB in persistent AF. Using the second-generation CB, SVCi can be accomplished in around 38.5 (22-75) seconds with a high safety profile. As the SVC caliper is larger than PVs, the flip-back maneuver of the circular mapping catheter enables easy SVC signal recording after the engagement of the inflated CB to the RA−-SVC junction. Moreover, a circular mapping catheter can be used to pace the right phrenic nerve during the procedure. Short application duration for SVCi seems to be the main advantage of CB in patients undergoing AF ablation in whom SVC is planned to be isolated.

Our study has several limitations. Firstly, this is a small-scale retrospective analysis in a subset of persistent AF patients which limits the generalizability of our findings. Secondly, ATa recurrence was assessed by 24-hour Holter recording, which might cause an underestimation of true ATa incidence compared to implantable loop recorders.

In conclusion, empirical SVCi besides PVi has similar long-term outcomes in terms of safety and efficacy compared to the PVi-only strategy in patients with persistent AF. Non-PV triggers other than SVC and the atrial substrate should also be kept in mind in such patients. Future large-scale randomized studies evaluating the role of routine implementation of SVCi into persistent AF ablation procedures are needed.

Ethics Committee Approval: EPC document number: B.10.4.İSM.4.06.00.15-12587 (December 12, 2014).

Informed Consent: Written informed consent was obtained from each patient before the procedure.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – U.C., H.Y., K.A.; Design – U.C., H.Y., K.A.; Supervision – K.A.; Resources – U.C., H.Y.; Materials – U.C., H.Y.; Data Collection and/or Processing – U.C., H.Y.; Analysis and/or Interpretation – U.C., H.Y.; Literature Search – U.C., H.Y.; Writing – U.C., H.Y.; Critical Review – U.C., H.Y., K.A.

Declaration of Interests: U.C.: Proctoring for Biotronik and Medtronic, K.A., and H.Y.: Proctoring and lecturer for Biosense Webster, Abbott, and Medtronic.

Funding: The authors declared that this study has received no financial support.

Video 1: After contrast injection, occlusion of the superior vena cava (SVC) was confirmed by the retention of contrast media in the SVC without backflow into the right atrium (RA). The right phrenic nerve capture is performed via an Achieve catheter in the current patient.

Video 2: Electrical isolation of the superior vena cava (SVC) and capturing the right phrenic nerve via a decapolar catheter located at the right subclavian vein level.

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