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ORIGINAL ARTICLE

Ectopies from the superior vena cava after pulmonary vein isolation in patients with atrial fibrillation

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Abstract Episodes of atrial fibrillation (AF) are mainly initiated by triggers from pulmonary veins (PVs). The superior vena cava (SVC) has been identified as a second major substrate of non-PV foci, but the electrophysiologic features of the SVC have not been fully investigated. We hypothesized that SVC ectopies are suppressed by predominant features of PV ectopies and tend to appear after PV isolation (PVI). We evaluated the electrophysiological characteristics and clinical implications of SVC ectopies in patients with AF during catheter ablation using high-dose isoproterenol and the atrial overdrive pacing maneuver. The manifestation patterns and modes of onset (coupling interval and appearance interval) of ectopies from both the PVs and SVC were investigated. 205 patients were enrolled [153 males and 52 females; mean age 64 ± 10 years; paroxysmal in 143 patients (69.8 %), persistent in 40 (19.5 %), and long-standing persistent in 22 patients (10.7 %)]. Before PVI, PV ectopies were detected in 182/205 patients (89 %). SVC ectopies were rarely observed before PVI but were significantly more frequent after the completion of PVI (3/205 vs. 14/205 patients, $p = 0.011$). The coupling interval (CI) and % CI (CI/preceding the A–A interval × 100) of PV ectopies were significantly shorter than those of SVC ectopies (211 ± 78 vs. 282 ± 106 ms, $p = 0.021$, and 34 ± 9 vs. 51 ± 17 %, $p < 0.001$, respectively). The appearance intervals of the PV ectopies were shorter than those of the SVC ectopies (6.3 ± 4.0 vs. 10.7 ± 6.7 s, $p = 0.030$). During repeat procedures, PVs with reconnection to the left atrium were less frequently observed in patients with SVC firing than in patients without SVC firing (1.7 ± 1.5 vs. 2.9 ± 1.1 PVs, $p = 0.029$). We demonstrated that PVI tends to manifest SVC ectopies with less spontaneous activity and that an elimination of predominant ectopies from the PVs may affect appearance of SVC ectopy.

Keywords Atrial fibrillation (AF) · Pulmonary vein (PV) · Superior vena cava (SVC) · Pulmonary vein isolation (PVI) · Non-PV foci

Introduction

Atrial fibrillation (AF) is typically initiated by triggers arising from the pulmonary veins (PVs), and catheter ablation targeting the PVs (PV isolation) is established as the most effective strategy for treating atrial fibrillation (AF) [1–3]. While most patients with AF respond to this procedure, other structures such as the superior vena cava (SVC) are known as "non-PV" foci which account for 6–8 % of all AF triggers [4–9]. One of the most recent studies investigating the clinical aspects of SVC ectopies found an association between the presence of SVC firing and a prior PV isolation (PVI) procedure in patients with AF [10]. We therefore hypothesized that SVC ectopies are suppressed by the predominant features of PV ectopies and tend to appear after PVI.

In this study we sought to validate our hypothesis by evaluating (1) the patterns in which ectopies originating

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from the SVC manifest before and after PVI, (2) the electrophysiological differences between ectopies originating from the SVC and PVs, and (3) association between the results of radiofrequency ablation and appearance of SVC ectopies.

Materials and methods

Two hundred and five consecutive patients (153 males, 52 females, mean age 64 ± 10 years) with symptomatic AF (mean duration 4.5 ± 4.9 years) refractory to 1.1 ± 1.2 antiarrhythmic drug trials were retrospectively enrolled. The study protocol was approved by the institutional review board and informed consent was obtained before the procedure. AF was paroxysmal in 143 patients (69.8 %), persistent in 40 (19.5 %), and long-standing persistent in 22 (10.7 %). Paroxysmal AF was defined as that terminates spontaneously or under anti arrhythmia drugs within 7 days of onset. Persistent AF was defined as that lasting for more than 7 days up to 1 year, and long-standing persistent AF was defined as that lasting for more than 1 year. All antiarrhythmic drugs were discontinued for at least five half-lives before the procedure was performed.

Each patient underwent the electrophysiological study in a fasting, mildly sedated state after giving informed consent. A steerable 20-pole (4 poles for the SVC, 8 poles for the right atrium, and 8 poles for the coronary sinus) mapping catheter (EP Star SAC, Japan Lifeline Co., Ltd) was inserted into the coronary sinus via the right subclavian vein. A 7-F non-irrigated 4-mm-tip quadripolar ablation catheter (Navistar, Biosense Webster) or irrigated 3.5-mm-tip ablation catheter (ThermoCool Navistar, Biosense Webster) was positioned trans-septally at the antrum of the targeted PVs, together with a 10-pole circumferential mapping catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA or EP Star Libero, Japan Lifeline Co., Ltd). Left atrium (LA) angiography was performed in biplane views and displayed during the procedure to show the anatomy of the LA and PVs. The PVs were mapped using circumferential mapping catheters (a 10-pole) of 20, 25, or 30 mm in diameter. The junction of the SVC and the right atrium was determined fluoroscopically using dual projections of SVC angiography. Heparin was administered intravenously at a dose of 100 U/kg body weight after a trans-septal puncture and then continuously infused at rate of 1000 U/h to maintain an activated clotting time of 300–400 s as measured every 30 min. A surface electrocardiogram and bipolar endocardial electrogram were continuously displayed and recorded (CardioLab IT EP Recording System, GE Healthcare, Milwaukee, WI, USA). The intracardiac electrograms were filtered in a range from 30 to 500 Hz. The anticoagulation drug was continued and an trans-esophageal echocardiogram was obtained before ablation in most of the subjects. An enhanced cardiac CT scan was performed before the procedure to assess the PV, SVC-RA junction dimensions, and coronary artery condition.

Detection and induction of ectopies from the thoracic veins

First, the circular mapping catheters were introduced at the left and right superior PV ostium and the ablation catheter was placed at the left inferior PV ostium. The SVC was mapped using a 20-pole coronary sinus catheter and RA-SVC catheter equipped with four proximal poles for recording the SVC electrogram.

The principal of our protocol to identify localization of ectopies is shown in Fig. 1. In cases with sinus rhythm, isoproterenol bolus infusion was administered to provoke ectopies (10–20 μg). If no ectopy was induced with isoproterenol, the subjects underwent burst atrial pacing (15 beats at a 250 ms cycle length, decreased to the shortest cycle length with 1:1 capture) to induce AF followed by electrical cardioversion (CV) to induce ectopies and identify their origin.

If AF continued during the procedure, CV was performed after isoproterenol infusion, and any ectopies during the next 5 min were evaluated.

The origin of the ectopies was determined when local activation (a "spiky" electrogram) could be recorded from the mapping catheter placed at the ostium of the PV, SVC, RA, or CS before activity was recorded from any other site monitored by the intracardiac atrial electrogram. A reversal in the activation sequence on any of the bipolar pairs of the mapping catheter, with the PV or SVC potential preceding the atrial potential, was defined as an ectopy and used as an alternative finding.

If the earliest ectopy was observed in the 4 SVC poles, we placed a circular catheter in the SVC to confirm the reproducibility of the induction and the exact site from which the ectopies originated.

An "AF trigger" was defined as a spontaneous ectopy that triggered atrial tachyarrythmia (either AF or regular atrial tachycardia). An "isolated ectopy" was defined as an ectopy without any subsequent atrial tachyarrhythmia.

Catheter ablation

All of the PVs were completely isolated after the trigger localization. Entrance block was defined as the disappearance of all PV potentials and exit block was confirmed using circumference pacing from circular catheter placed in PVs (4).

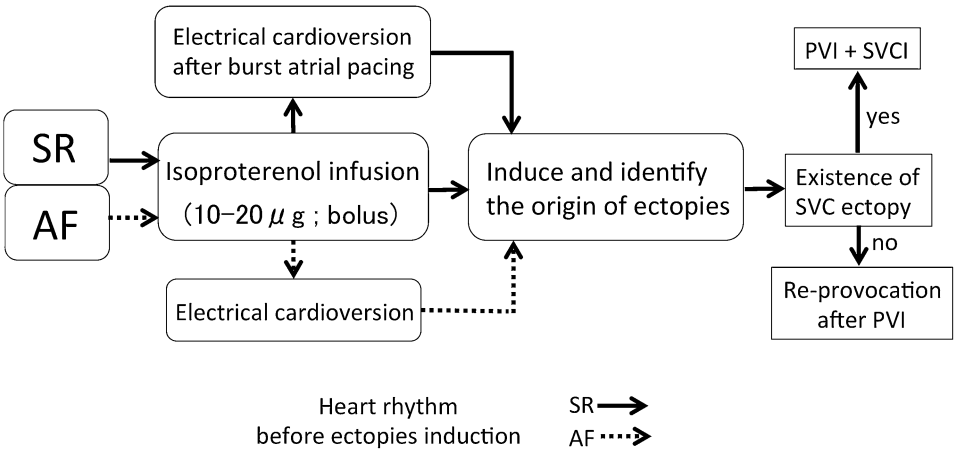

Fig. 1 Principal of our protocol to identify the localization of ectopies. Patients with sinus rhythm without spontaneous ectopy were given bolus injections of isoproterenol to provoke ectopies (10–20 μg). If no ectopy was induced with isoproterenol, AF was induced by burst atrial pacing followed by electrical cardioversion (CV) to induce and identify the origin of ectopies. If AF continued during the procedure, electrical CV was performed following isoproterenol infusion. *SR* sinus rhythm, *AF* atrial fibrillation, *SVC* superior vena cava, *PVI* pulmonary vein isolation; *SVCI* superior vena cava isolation

Ectopy induction after PVI

Once all four PVs were isolated, the appearance of ectopies from other sites was identified, especially those originating from the SVC. The absence of dormant conduction was also evaluated by infusing isoproterenol and administering a bolus injection of adenosine triphosphate. When ectopies from the SVC were detected, the SVC was examined angiographically in biplane views to visualize the SVC-right atrial (RA) junction and then mapped with a 10-pole circumferential mapping catheter (20 mm diameter) for segmental isolation of the vessel.

Post-ablation follow-up

Clinical follow-up visits (after 1 month, and then every 3 months) consisted of 24-h ambulatory monitoring at 3–6 months after ablation. If a patient experienced palpitation, ambulatory monitoring was performed for another 24 h or cardiac events were recorded to determine the cause of the tachycardia. Long-term follow-up information on all of the patients was also obtained from their referring physicians. A recurrence of AF was diagnosed based on the patient symptoms, electrocardiogram recordings, and the results of 24-h ambulatory monitoring. AF recurrence was defined as episodes of atrial tachyarrhythmia lasting more than 30 s after a 3-month blanking period. Repeat ablation procedures were recommended for patients with recurrence. Patients who underwent a second procedure because of recurrent AF were included in the study to investigate how ectopies from thoracic veins would manifest in the future.

Comparison of clinical characteristics between patients with and without SVC ectopies

We divided our patients into two groups, one with SVC ectopies and one without them, to compare the following clinical characteristics: age, gender, body mass index, paroxysmal atrial fibrillation (PAF), AF duration, number of antiarrhythmic drugs, left atrial (LA) diameter, ejection fraction, hypertension.

The manifestation patterns and electrophysiological evaluation of ectopies originating from the PVs and SVC

The manifestation patterns and induciblity of ectopies from thoracic veins were continuously monitored throughout ablation procedures. The electrophysiologic features of the arrhythmias were investigated in patients who manifested ectopies from both the PVs and SVC. The shortest coupling interval (CI, interval from the last sinus beat to the first ectopy at the origin of the ectopy) was measured and the % CI was calculated by the following formula: (CI/preceding A–A interval × 100) [9]. After spontaneous termination of AF or electrical cardioversion, the interval from the termination of the AF to the appearance of the first ectopy was defined as the "appearance interval." In a case with repetitive short duration of AF triggered by ectopies from a particular vein, we calculated a mean value of all appearance intervals. The above three parameters were compared between PV ectopies and SVC ectopies.

Table 1 Clinical characteristics of the patients

Number of patients	205
Age (years)	63.1 ± 10.2
Gender (M/F)	153/52
AF type	
Paroxysmal, *n* (%)	143 (69.8)
Persistent, *n* (%)	40 (19.5)
Long-standing persistent, *n* (%)	22 (10.7)
AF reccurence, *n* (%)	51 (24.9)
Second procedure, *n* (%)	37 (18.1)
Body mass index (kg/m^2)	23.8 ± 3.4
AF duration (years)	4.5 ± 4.8
No. of antiarrhythmic drugs, *n*	1.1 ± 1.2
Left atrial diameter (mm)	38.9 ± 6.7
Ejection fraction (%)	66.5 ± 9.5
Hypertension, *n* (%)	112 (54.6)

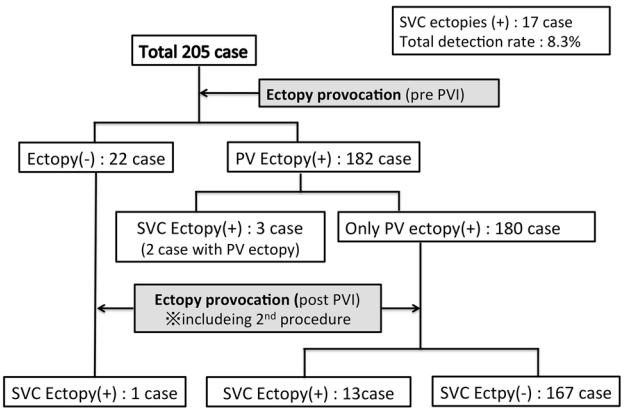

Fig. 2 Flow diagram of patients in the present study. Before PVI, PV ectopies were detected in 182/205 patients (89 %) and SVC ectopies were rarely identified. SVC ectopies appeared with a significantly higher incidence after the completion of PVI. Ultimately we documented SVC ectopies in 17 patients

Statistical analysis

Continuous variables were presented as mean ± SD and analyzed by either the Mann–Whitney *U* test or by Wilcoxon signed-rank test, as appropriate. Proportions were analyzed by the ×2 test with Yates' correction or Fisher's exact test. $p < 0.05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Clinical characteristics

Two hundred and five patients (153 men, 74.6 %) with paroxysmal (143 patients, 69.8 %), persistent (40 patients, 19.5 %) or long-standing persistent (22 patients, 10.7 %) AF were included in the present study. The mean age of the population was 63.1 ± 10.2 years. Thirty-seven patients (18.1 %) underwent a second ablation procedure (Table 1).

Identification of thoracic vein ectopies

Overall, 351 ectopies were identified in 193 (94.2 %) patients (1.8 ectopies per patient) during the provocation procedure. Thirty-seven ectopies failed to meet the strict criteria for localization. No ectopies were observed in 12 patients (Fig. 2). Before PVI, PV ectopies were detected in 182/205 patients (89 %). The PV ectopies were from multiple PVs in 99 of the patients (mean 2.2 ± 0.4 PVs). SVC ectopies were rarely observed before PVI and appeared with a significantly higher incidence after the completion of PVI (3/205 vs. 14/205 patients, $p = 0.011$). Ultimately, 17 patients with SVC ectopies were identified (including 7 patients with SVC ectopies during the second catheter ablation). PV and SVC ectopies were dually observed in 15 patients. "Triggers" (ectopies with AF initiation) were identified in 113/182 of PV ectopies and 10/17 SVC ectopies.

Table 2 Comparison of patients with and without SVC ectopy

	SVC ectopy (+)	SVC ectopy (−)	*p* value
Number of patients	17	188	N/A
Age (years)	61.7 ± 13.5	63.2 ± 9.8	0.879
Female gender (%)	6 (35.3)	47 (25.0)	0.388
Body mass index (kg/m^2)	24.7 ± 3.1	23.7 ± 3.4	0.204
PAF (%)	15 (88.2)	128 (62.4)	0.102
AF duration (years)	6.2 ± 7.6	4.4 ± 4.6	0.592
No. of antiarrhythmic drugs	0.9 ± 1.3	1.1 ± 1.2	0.480
Left atrial diameter (mm)	38.6 ± 7.2	38.9 ± 6.7	0.745
Ejection fraction (%)	67.3 ± 8.2	66.5 ± 9.6	0.651
Hypertension, *n* (%)	11 (64.7)	101 (53.7)	0.454

Clinical characteristics of patients with SVC ectopies

Table 2 shows the clinical characteristics of the patients with and without SVC ectopies. A univariate analysis revealed no clinical parameters indicative of the presence of SVC ectopy.

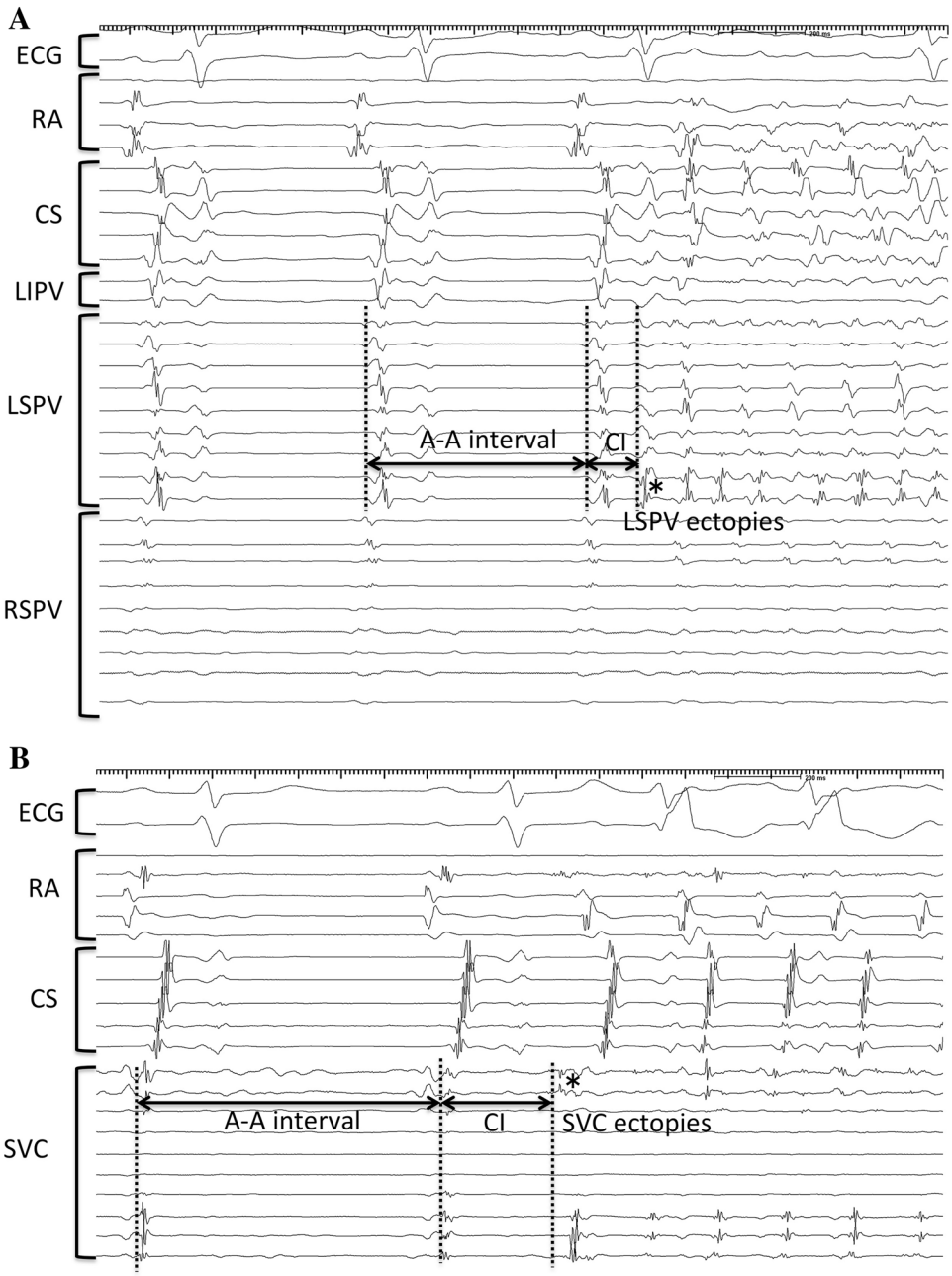

Fig. 3 Simultaneous recordings of both surface and intracardiac electrograms during occurrences of ectopies from pulmonary vein and superior vena cava. Bipolar recordings showing PV (**a**) and SVC ectopies (**b**) triggering atrial fibrillation (AF) in the same patient. Spiky configurations and a significantly faster sequence of ectopy activation from each thoracic vein are seen. Following premature ectopies, the most frequent local firings were recorded in either the PVs or SVC. Note that the coupling interval of the PV ectopy (**a**) is much shorter than that of the SVC ectopy (**b**). *CI* coupling interval, *RA* right atrium, *CS* coronary sinus, *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *RSPV* right superior pulmonary vein, *SVC* superior vena cava

Electrophysiological characteristics

Coupling interval and appearance intervals of ectopies from PV and SVC were compared in 15 patients with both thoracic vein ectopies. As shown in Fig. 3a and b, the PV ectopies appeared with a very short CI while the SVC ectopies appeared with a somewhat longer one. The mean CI and % CI of the PV ectopies were significantly shorter than the mean CI and % CI of the SVC ectopies (211 ± 78 vs. 282 ± 106 ms, $p = 0.021$ and 34 ± 9 vs. 51 ± 17 %, $p < 0.001$, respectively Fig. 4a, b). Figure 5 demonstrates the intervals at which the PV ectopies and SVC ectopies appeared (appearing interval). The appearance intervals of the PV ectopies were shorter than those of the SVC ectopies (6.3 ± 4.0 vs. 10.7 ± 6.7 s, $p = 0.030$). Among four patients with the shorter appearance intervals of the SVC ectopies, two patients had these before PVI (Fig. 5, dotted line).

Results of catheter ablation

During the first procedure, all four targeted PVs were successfully isolated from the LA in all patients. A second ablation procedure was required in 34 patients without

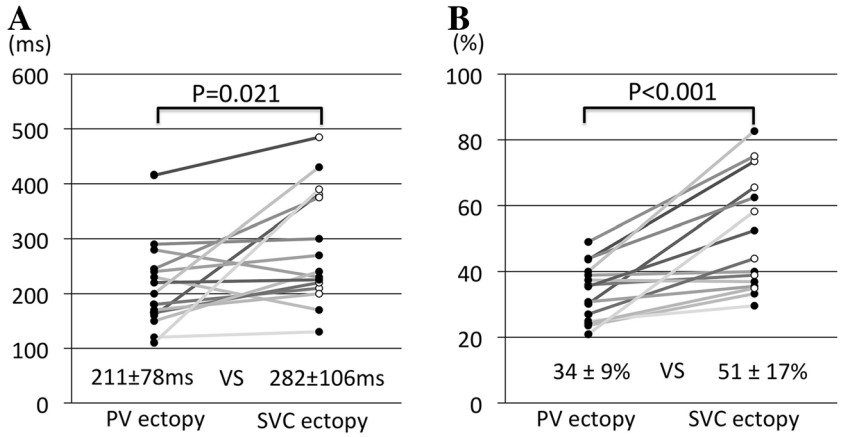

Fig. 4 Comparison of the coupling interval (CI) and % CI ectopy from the pulmonary vein and superior vena cava. **a** The coupling interval (CI) of the PV ectopies is significantly shorter than that of the SVC ectopies (211 ± 78 vs. 282 ± 106 ms, $p = 0.021$). **b** The % CI (CI/preceding A–A interval × 100) is significantly shorter than that of the SVC ectopies (34 ± 9 vs. 51 ± 17 %, $p < 0.001$). The *closed* and *open circle* represent ectopies detected in the first and the second ablation procedure respectively

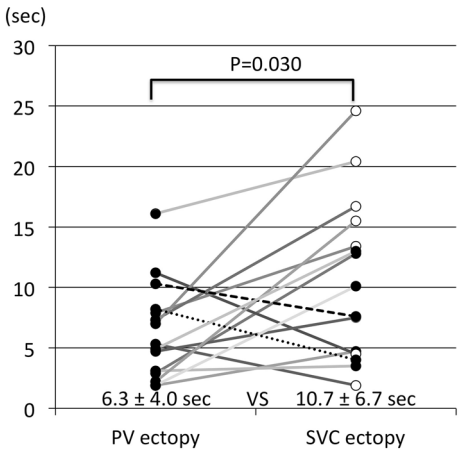

Fig. 5 Comparison of appearance interval between PV and SVC ectopies. The appearance intervals of the PV ectopies were shorter than those of the SVC ectopies (6.3 ± 4.0 vs. 10.7 ± 6.7 s, $p = 0.030$). Among four patients with the shorter appearance intervals of the SVC ectopies, two patients had these before PVI (Fig. 5, *dotted line*). The *closed* and *open circle* represent ectopies detected in the first and the second ablation procedure respectively

SVC ectopies and in 3 patients with SVC ectopies during the previous procedure.

The SVC was successfully isolated in 10 of the patients with SVC ectopies during the first ablation procedure. Among them, the 3 (30 %) patients who underwent a second ablation procedure manifested recurrent AF and SVC-RA reconnection. SVC ectopies were identified for the first time in the second ablation procedure in 7 of the patients and were successfully isolated in every case. During the second procedure, the number of PVs with PV-LA reconnection was less frequently observed in patients with SVC ectopies than in those without them (1.7 ± 1.5 vs. 2.9 ± 1.1 PVs, respectively, $p = 0.029$). The incidence of PV ectopies did not significantly differ between patients with and without SVC ectopies (15/17 vs. 168/188, NS). A complication due to SVC isolation was observed in 1 patient (phrenic nerve injury).

Discussion

In the present study, we demonstrated that PVI tends to manifest SVC ectopies with less spontaneous activity and that an elimination of predominant ectopies from the PVs may affect appearance of SVC ectopy.

Electrophysiologic characteristics of ectopies from PVs and SVC

The electrophysiological features of PV ectopies were found to predominate over those of SVC ectopies, because the CI and appearance interval of PV ectopies were significantly shorter in 15 patients who manifested ectopies from both the PVs and SVC. Interestingly, two out of them with SVC ectopies before PVI showed apparently shorter appearing intervals than those of PV. One previous study supported our results by showing a shorter CI of PV ectopy than that of SVC. The longer effective refractory periods in the SVC or difference of anatomical or electrophysiological properties in SVC may relate to these findings [9]. Although the exact mechanism of inferior property of SVC is unclear, particular anatomical structure or autonomic innervation of thoracic veins may contribute to produce these differences.

The well-recognized effects of PVI as modifier of autonomic nervous system activity may play a role in the

induction of SVC ectopies after PVI [11–13]. We were unable, however, to evaluate the direct effects of PVI on autonomic tone, as our subjects received considerable doses of infused isoproterenol to induce thoracic vein ectopies before the catheter ablation. Catheter ablation to the right upper PV may exert arrhythmogenic effects on the SVC by directly heating the tissue, as the SVC and right upper PV are anatomically close. However, the effects from direct heating seem less likely, given that no SVC ectopies appeared during application to the right upper PV. We therefore suggest that the elimination of predominant PV foci may affect electrophysiologic features of SVC ectoies. Another possible explanation for a trend of SVC appearance after PVI is a poorer reproducibility of the provocation test to induce SVC ecotpies rather than that to PV. Patients with AF recurrence after first session consequently underwent multiple provocation tests through first and second procedures, which could provide more chance to induce SVC ectopies.

Prevalence and predictors of SVC ectopy

Under our provocation protocol we identified SVC ectopies in only 8.3 % of our patients, a percentage similar to what has been demonstrated (from 6 to 10 %) in previous studies. A lower incidence of SVC ectopies suggests that the SVC contributes relatively little as a substrate for AF and that intervention to isolate the SVC in all patients with AF would be excessive. We also recognize that we can better identify non-PV foci during ablation procedures when we know that SVC ectopies tend to appear after PVI. One previous study supported our results by demonstrating a correlation between a higher prevalence of prior ablation procedures and the presence of SVC ectopy [10]. In the present study, we could partly account for the possible electrophysiological mechanism to explain the sequential appearing pattern of ectopies from PV and SVC.

Some investigations of the clinical aspects of SVC ectopies demonstrated the following as predictors of SVC foci: female gender [14], the concurrence of a smaller LA size and spontaneous common AFL [15], a history of repeat ablation procedures, and lower BMI values [10]. None of the clinical characteristics were predictive of the presence of SVC ectopy in the presence study. This discrepancy may be linked to the restricted number of patients included in these studies or to the different protocols used to induce ectopy during catheter ablation.

Clinical impact of SVC foci identification and its elimination

Among the 37 patients undergoing a second ablation procedure in the present study, SVC ectopies were less likely to be induced in patients with multiple PV-LA reconnection. A similar phenomenon has been already reported by Inada, et al. They described that PV-LA re-connection was less frequently observed among the patients with SVC firing during the repeat procedures, suggesting that both PV and non-PV foci should be carefully mapped in patients with fewer PV-LA re-conductions [10].

Limitations of this study

The present study has several limitations. First, this study was performed in a retrospective manner using only a small number of patients. A prospective study with a larger number of patients would provide a more detailed analysis of the predominant characteristics of PV ectopies rather than SVC ectopies. Second, the predominant theory does not necessarily convincingly explain the appearance of SVC ectopies after PVI. We speculate, for example, that these ectopies may be elicited by modification of autonomic nervous activity or tissue damage of the SVC during ablation to the right upper PV. The findings from our study were not sufficient to exclude these alternate explanations. Third, approximately 40 % of the ectopies arising from thoracic PVs showed no discernible action as "triggers" for atrial tachyarrythmias. SVC isolation based on non-trigger ectopies was not always essential or critical to eliminate substrates for AF. Fourth, we could not record the electrograms directly from the right lower PV because of limited number of catheters in the LA. Several ectopies from this PV might be possibly judged as "non-localized" origin. However, it may not affect largely our results because the number of ectopies which did not meet the criteria for localization were small (37 out of 205 patients).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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