Pulmonary vein isolation combined with superior vena cava isolation for atrial fibrillation ablation: a prospective randomized study

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Aims Circumferential pulmonary vein isolation (CPVI) is an established strategy for atrial fibrillation (AF) ablation. Superior vena cava (SVC), by harbouring the majority of non-pulmonary vein (PV) foci, is the most common non-PV origin for AF. However, it is unknown whether CPVI combined with SVC isolation (SVCI) could improve clinical results and whether SVCI is technically safe and feasible.

Methods and results A total of 106 cases (58 males, average age 66.0 ± 8.8 years) with paroxysmal AF were included for ablation. They were allocated randomly to two groups: CPVI group (n = 54) and CPVI + SVCI group (n = 52). All cases underwent the procedure successfully. Pulmonary vein isolation was achieved in all cases. The procedural time and fluoroscopic time were comparable between the two groups. The mean ablation time for SVC was 7.8 ± 2.7 min. Superior vena cava isolation was obtained in 50/52 cases. In the remaining two cases, SVCI was not achieved because of obviating diaphragmatic nerve injury. During a mean follow-up of 4 ± 2 months, 12 (22.2%) cases in the CPVI group and 10 (19.2%) cases in the CPVI + SVCI group (n = 52) underwent the procedure successfully. Pulmonary vein isolation was achieved in all cases. The procedural time and fluoroscopic time were comparable between the two groups. The mean ablation time for SVC was 7.8 ± 2.7 min. Superior vena cava isolation was obtained in 50/52 cases. In the remaining two cases, SVCI was not achieved because of obviating diaphragmatic nerve injury. During a mean follow-up of 4 ± 2 months, 12 (22.2%) cases in the CPVI group and 10 (19.2%) cases in the CPVI + SVCI group underwent reablation (P = 0.70). Nine of 12 cases in the CPVI group and 8/10 cases in the CPVI + SVCI group underwent reablation (P = 0.86), and PV reconnection occurred in 7/9 cases in the CPVI group and in 8/8 cases in the CPVI + SVCI group. All PV reconnection was reisolated by gaps ablation. There was no SVC reconnection in the CPVI + SVCI group. In two cases without PV reconnection from the CPVI group, SVC-originated short run of atrial tachycardia was identified and eliminated by the SVCI. At the end of 12 months of follow-up, 50 cases (92.6%) in the CPVI group and 49 (94.2%) in the CPVI + SVCI group were free of ATa recurrence (P = 0.73).

Conclusion In our series of paroxysmal AF patients, empirically adding SVCI to CPVI did not significantly reduce the AF recurrence after ablation. Superior vena cava isolation may be useful, however, in selected patients in whom the SVC is identified as a trigger for AF. However, because of the preliminary property of the study and its relatively small sample size, the impact of SVCI on clinical results should be evaluated in a large series of patients.

Introduction

Ectopic foci arising from pulmonary veins (PVs) are the predominant sources for the initiation and maintenance of atrial fibrillation (AF) in a vast majority of cases.1,2 Pulmonary vein isolation has therefore become the main strategy for treating this frustrating arrhythmia.3,4 The main approach for PV isolation is circumferential PV isolation (CPVI), which is performed at the PV antrum to encircle PV foci.5,6 However, further studies demonstrate that ectopic foci also exist in the non-PVs areas in 10–20% of the cases with paroxysmal AF7–10 such as superior vena cava (SVC), coronary sinus (CS), inferior vena cava, ligament of Marshall, and so on. Especially, SVC by harbouring 26–30% of the non-PV foci becomes the most common non-PV origin for AF.7 This prospective study is carried out to explore whether SVC isolation (SVCI) is feasible and safe and to evaluate the effectiveness of adjunctive SVCI for AF therapy.

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Methods

Patients’ population
From June 2006 to October 2006, altogether 106 cases (58 males, average age 66.0 ± 8.8 years) with drug-refractory paroxysmal AF were included consecutively for catheter ablation. Atrial fibrillation was refractory to 2.1 ± 1.1 anti-arrhythmic drugs prior to ablation. By transthoracic echocardiography, the mean left atrium (LA) diameter was 36.8 ± 2.6 mm (range 29–40 mm) and the mean left ventricular ejection fraction was 54 ± 8.1% (range 51–60%). Transoesophageal echocardiography was performed to exclude thrombi in the LA. A total of 22 cases had hypertension, one with coronary artery disease, one with hypertrophic cardiomyopathy, and seven with diabetes mellitus.

They were allocated randomly to two groups: CPVI group (n = 54) and CPVI + SVCI group (n = 52). Randomization was generated by a computer after enrolment, but prior to electrophysiological study and catheter ablation. Cases were blinded to their group assignment. The baseline demographic data of the two groups were well balanced (Table 1). All cases provided written informed consent.

Electrophysiological study
Prior to ablation, all cases were kept on oral anticoagulation with warfarin for 1 month, and the drug was withdrawn 3 days before ablation. Low-molecular-weight heparin was injected subcutaneously twice a day and was withdrawn 12 h prior to ablation. All anti-arrhythmic drugs except amiodarone were discontinued for at least five half-lives. The procedure was performed under conscious sedation with a continuous infusion of propofol. One decapolar mapping catheter (Biosense Webster, Diamond Bar, CA) was positioned in the CS via left or right subclavian vein access. Two L1-type Swartz sheathes (St Jude Medical, Minneapolis, MN) were advanced in the SVC via right femoral vein and were advanced in the LA via a Swartz sheath. The geometry of LA was reconstructed, and each ostium of the PVs was tagged on LA geometry. The ipsilateral left and right PVs were encircled in one lesion line by CPVI. Radiofrequency (RF) energy was delivered at 43°C, 35 W, 0.5 cm away from the PV ostia at the anterior wall, and it was reduced to 43°C, 30 W, 1 cm away from the PV ostia at the posterior wall, with a saline irrigation speed of 20 mL/min. Each lesion was ablated continuously until the local potential amplitude decreased by >80% or RF energy deliveries exceeded 40 s. The endpoint of CPVI was PV isolation, which was confirmed by Lasso mapping, showing the disappearance of all PVPs or the dissociation of PVPs with left atrial activity.

Superior vena cava isolation
After the completion of CPVI, mapping and ablation catheters were withdrawn back into the RA. The geometry of RA was reconstructed, and the SVC–RA junction was tagged on the geometry based on the SVC angiography. Sites at the posterolateral wall of the SVC with positive diaphragmatic stimulation by high output pacing (30 mA) were also tagged on the geometry. In such sites, ablation was avoided to prevent phrenic nerve injury. Ablation settings were identical to those in CPVI. Two strategies were applied for SVCI: segmental or circumferential ablation. Segmental ablation was defined as targeting the earliest RA–SVC conduction when the RA–SVC conduction sequence could be discerned in regular atrial rhythm. Circumferential ablation was defined as connecting ablation lesions one by one to form a whole lesion line when the RA–SVC conduction sequence could not be discerned due to an irregular atrial rhythm. Initial segmental ablation was changed to circumferential ablation when SVC could not be isolated by ablation >50% of the SVC circumference. Initial circumferential ablation was judged as ‘segmental’ when SVC could be isolated by ablation <50% of the SVC circumference. Superior vena cava isolation was characterized as disappearance of SVC potentials or dissociation of SVC potentials with right atrial activity.

Post-ablation management and follow-up
All cases were kept on anticoagulation treatment with low-molecular-weight heparin injection for 3–5 days and then with warfarin for 3 months to maintain an international normalized ratio range of 2–3. Class III anti-arrhythmic drug with amiodarone, 200–400 mg/day, was administered in all cases for 1 month after the ablation and was withdrawn 1 month later in cases without AF recurrence, but was continued otherwise. Surface ECGs were performed and repeated 1 day, 1 week, 2, 3, 6, 9, and 12 months post-procedure. Monthly telephone inquiry blinded to patient assignment was made to evaluate the severity of symptoms, and cases were asked to record ECG when having symptoms indicating AF. Holter recording was performed for 24 h at 2-month intervals post-procedure to document any form of atrial arrhythmias. Electrocardiograms and Holters were analysed by reviewers blinded to patient assignment.

The first 1 month after ablation was set as the blanking period, and the whole follow-up duration was 12 months. After the blanking period, trobucurides and Holters were analysed by reviewers blinded to patient assignment.
period, any episode of symptomatic or asymptomatic atrial tachyarrhythmias (ATa) with ECG and Holter recording that lasted over 30 s was considered as a recurrence. Reablation was performed at least 1 month after the initial procedure. Spiral computed tomography (CT) was performed at 3 months after the procedure to assess the PV or SVC stenosis.

Statistical analysis
Continuous variables were expressed as mean ± SD and categorical variables as counts or proportions (%). Two-tailed unpaired t-test for continuous variables of normal distribution or non-parameter test for inhomogeneity of variance and continuous variables of normal distribution or non-parameter test for categorical variables were applied to compare the parameters between the two groups. A value of $P < 0.05$ was considered statistically significant. The Kaplan–Meier survival analysis was also performed to compare the AF-free survival between two groups.

Results
The circumferential pulmonary vein isolation procedural parameters
All cases underwent the procedure successfully. Pulmonary vein isolation was achieved in all cases. There was no statistically significant difference on the procedural time, left and right PVs isolation time, and fluoroscopic time between the two groups (Table 2).

Superior vena cava isolation
The mean ablation time for SVCI was 7.8 ± 2.7 min, and the mean numbers of RF energy delivery were 6 ± 2 times. Superior vena cava was isolated successfully in 50/52 cases. Segmental ablation was performed in 39/50 cases, SVCI was achieved by ablating 3 ± 1 segments at the RA–SVC junction, including 54 segments at the septal aspect of SVC, 41 segments at the posterior wall, 11 segments at the anterior wall, and 13 segments at the lateral wall. Circumferential SVC ablation was performed in 11/50 cases, and 9 SVCs were isolated. In the remaining two cases, SVC was not achieved due to diaphragmatic stimulation by pacing from the postero-lateral wall of RA.

Follow-up data after initial ablation
During a mean follow-up of 4.6 ± 2.3 months post-ablation, 12 (22.2%) cases in the CPVI group had ATa recurrence, including AF in 8 cases, left atrial tachycardia in 3 cases, and AF concomitant with cavo-tricuspid isthmus-dependent flutter in 1 case. During a mean follow-up of 4.0 ± 2.2 months post-ablation, 10 (19.2%) cases in the CPVI + SVC group had ATa recurrence, including AF in 8 cases and left atrial tachycardia in 2 cases. Atrial tachyarrhythmias recurrence proportion between two groups is comparable ($P = 0.70$). In both groups, recurrent ATas were refractory to at least three anti-arrhythmic drugs such as propafenone, amiodarone, and verapamil.

Results from reablation procedure
Nine (16.7%) of 12 cases in the CPVI group and 8/10 cases (15.4%) in the CPVI + SVC group underwent reablation procedure due to drug-refractory ATa ($P = 0.86$), including 14 cases with AF (7 cases from the CPVI group and 7 cases from the CPVI + SVC group), 2 cases with left atrial tachycardia (1 case from the CPVI group and the other from the CPVI + SVC group), and 1 case with AF and typical atrial flutter (from the CPVI group). Pulmonary vein reconnection occurred in 7/9 cases in the CPVI group and in 8/8 cases in the CPVI + SVC group, which was summarized in Table 3. During the second ablation procedure, all PV reconnection was reisolated by closing gaps along initial ablation lines.

There was no SVC reconnection in 8/8 redo cases in the CPVI + SVC groups. Superior vena cava-originated extrasystole and short run of ATa were identified spontaneously or by rapid proximal CS pacing (cycle length 250–180 ms) in two cases without PV reconnection in the CPVI group and were eliminated successfully by SVCI (Figure 1). Typical atrial flutter was terminated by cavo-tricuspid isthmus ablation in one case. In one case from the CPVI + SVC group, left atrial tachycardia was caused by the conduction gap along left PV ablation line and was terminated when closing the gap. In the other case in

Table 2 The procedural parameters between two groups during initial ablation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPVI (n=54)</th>
<th>CPVI + SVC (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total procedural time (min)</td>
<td>182.7±17.7</td>
<td>185.7±19.3</td>
<td>0.40</td>
</tr>
<tr>
<td>LPVs isolation time (min)</td>
<td>46.3±10.5</td>
<td>44.8±13.0</td>
<td>0.50</td>
</tr>
<tr>
<td>RPVs isolation time (min)</td>
<td>33.7±6.8</td>
<td>31.7±7.4</td>
<td>0.15</td>
</tr>
<tr>
<td>SVC time (min)</td>
<td>–</td>
<td>7.8±2.7</td>
<td>–</td>
</tr>
<tr>
<td>Fluoroscopic time (min)</td>
<td>16.4±2.7</td>
<td>17.6±3.6</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or counts (%). LPVs, left-sided pulmonary veins; RPVs, right-sided pulmonary veins; SVC, superior vena cava isolation.

Table 3 Results of circular mapping by Lasso during reablation procedure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPVI (n=54)</th>
<th>CPVI + SVC (n=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with ATa recurrence, n (%)</td>
<td>12 (22.2)</td>
<td>10 (19.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Reablation cases, n (%)</td>
<td>9/54 (16.7)</td>
<td>8/52 (15.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Proportion of PV reconnection in reablation cases, n (%)</td>
<td>7 (77.8)</td>
<td>8 (100)</td>
<td>0.16</td>
</tr>
<tr>
<td>LSPV</td>
<td>7 (77.8)</td>
<td>7 (87.5)</td>
<td>0.60</td>
</tr>
<tr>
<td>LIPV</td>
<td>6 (66.7)</td>
<td>8 (100)</td>
<td>0.07</td>
</tr>
<tr>
<td>RSPV</td>
<td>6 (66.7)</td>
<td>4 (50)</td>
<td>0.49</td>
</tr>
<tr>
<td>RIPV</td>
<td>7 (77.8)</td>
<td>4 (50)</td>
<td>0.23</td>
</tr>
<tr>
<td>Proportion of SVC reconnection</td>
<td>–</td>
<td>0</td>
<td>–</td>
</tr>
</tbody>
</table>

ATa, atrial tachyarrhythmias; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; SVC, superior vena cava.
relapsed in one case in the CPVI group and in one case in the CPVI + SVCI group.

Surface electrocardiograms and Holter documentation during the whole follow-up period

After the first procedure, both groups had 42 cases free of ATa recurrence. Among them, surface ECGs at scheduled time were recorded in 39 cases from the CPVI group and in 40 cases from the CPVI + SVCI group. Holter monitoring was performed every 2 months in 35 cases from the CPVI group and in 34 cases from the CPVI + SVCI group. Atrial tachyarrhythmias recurred in the remaining 12 cases from the CPVI group, which was proved by symptomatic ECG recording in 8 cases, by routine ECG examination in 1 case, and by Holter monitoring in 3 cases. Surface ECGs at scheduled time and 2-month interval Holter monitoring were performed in 7/9 reablation cases after the second procedure; the remaining five cases recorded their ECGs or Holter occasionally. Atrial tachyarrhythmias recurred in the remaining 10 cases in the CPVI + SVCI group, which was proved by symptomatic ECG recording in 8 cases and by Holter monitoring in 2 cases. Surface ECGs at scheduled time and regular Holter monitoring were performed in 7/8 reablation cases, whereas surface ECGs were recorded irregularly in the remaining three cases with ATa recurrence.

Follow-up data after reablation

After the initial ablation procedure, there was no statistically significant difference on AF-free survival between the two groups (Figure 2, log rank test, \( P = 0.75 \)). Cases with AF and/or ATa recurrence, who underwent second ablation, were viewed as recurrences. When taking the reablation cases into consideration, at the end of 12 months of follow-up, 50 cases (92.6%) in the CPVI group and 49 (94.2%) in the CPVI + SVCI group were free of ATa recurrence (\( P = 0.73 \)), including 3 (5.6%) cases in the CPVI group and 2 (3.8%) cases in the CPVI + SVCI group taking anti-arrhythmic drugs.

Figure 1  Episode of atrial tachycardia triggered by ectopic foci in superior vena cava and eliminated by superior vena cava isolation. Panels A and D: tracings were lead I, V1, Lasso 1–2 to 9–10 within superior vena cava ostium, coronary sinus distal to proximal, Ablation (ABL) distal to proximal. A, right atrium; SVCP, superior vena cava potential. Note that in panel A, episode of atrial tachycardia was initiated by extrasystole from superior vena cava (superior vena cava potential preceded to A wave). In panel D, fibrillitative rhythm persisted within superior vena cava, while atrium restored sinus rhythm by superior vena cava isolation. Panels B and C showed the postero-anterior view and left anterior oblique view of right atrium and ablation lesion at the septal and posterior wall of superior vena cava. White dots represented the ostia of superior vena cava, purple dot represented the beginning of ablation, red dots represented the ablation lesions, and green dots represented superior vena cava isolation by ablation.

Figure 2 Kaplan-Meier curve of freedom from recurrent atrial tachyarrhythmias for both groups. Green line, circumferential pulmonary vein isolation + superior vena cava isolation group; blue line, circumferential pulmonary vein isolation group. Log rank test, \( P = 0.75 \).
Complications
Femoral artery pseudo-aneurysm occurred in one case in the CPVI group and two cases in the CPVI + SVC group. Major stroke was developed in one case with left limb hemiplegia 12 h post-ablation (ACT of 300–340 s was maintained during the procedure). All complications were treated with conservative therapy. There was no PV or SVC stenosis identified by CT scan 3 months post-ablation. There was no sinoatrial node or phrenic nerve injury.

Discussion
To the best of our knowledge, this is the first randomized prospective study evaluating SVCI as an adjunctive strategy for treating paroxysmal AF. The main finding of the study is that CPVI combined with SVCI contributed little to the success rate during initial ablation for paroxysmal AF and that SVCI is necessary to eliminate non-PV-originated AF in some of redo cases.

The circumferential pulmonary vein isolation procedure
It is established that PVs’ firing is the dominant source for AF initiation and maintenance. Further studies have demonstrated that the anisotropic arrangement of myocardial sleeve around ostia of PVs provides the substrate for micro-re-entry and fibrillatory conduction. The procedure of CPVI is designed to isolate PVs’ foci as well as to modify LA substrate and has become the main ablation strategy for AF treatment, especially for the treatment of paroxysmal AF. Several investigators have reported a high success rate of 90–95% for AF elimination after one or two ablation procedures. In cases with ATa recurrence, PV reconnection is the main finding during reablation procedures. Our study again has replicated the high success rate of CPVI for paroxysmal AF elimination.

Arrhythmias originating from superior vena cava
The proximal SVC is derived from the embryonic sinus venosus (right sinus horn). Histological findings show that atrial myocardial sleeves extend into SVC for 2–5 cm. Because the embryological sinus precursor comprises all the pacemaker sites, myocardial sleeves in the SVC harbour ectopic pacing cells that can depolarize by means of accelerated automaticity or after depolarization, providing the substrate for atrial arrhythmias, such as atrial tachycardia or AF. Tsai et al. observed that spontaneous bursts of ectopic beats originated from SVC-initiated AF in 8 (6%) of 130 cases. Lin et al. reported SVC-originated AF in 27 (37%) of 68 cases with non-PV-originated AF. Lee et al. reported that AF was originated from non-PV foci in 94/293 cases, and 38/94 cases had AF originating from SVC. A recent study by Arruda et al. found that SVC foci were present in 24 (12%) of 190 cases, but their study did not show that SVC that in addition to PV antrum isolation could improve the success rate of AF ablation. However, their study is not a randomized and controlled one, and SVCI is only achieved in 82% of the cases; therefore, it is difficult to evaluate the true contribution of adjunctive SVCI to the effectiveness of AF ablation. In our study, only 2 (3.7%) of 54 cases exhibited SVC-originated AF during reablation. The prevalence of SVC-originated AF in our study was much lower when compared with the foregoing studies. Probably, it could be explained by the different induction algorithms applied in each one of the studies. We observed spontaneous or CS pacing-induced ectopic beats in our study, whereas in the other studies, more aggressive induction was applied, such as infusion of isoproterenol in addition to burst atrial pacing.

Superior vena cava isolation procedure
One autopsy study of the SVC–RA junction showed that myocardial sleeves extended from RA to SVC in 38/50 SCS and that RA–SVC myocardial connection was discontinuous most commonly or circumferential in fewer cases, with the mean thickness of 1.2 ± 1.0 mm and a mean length of 13.7 ± 13.9 mm. Superior vena cava–right atrium connection is most commonly located at the septum and myocardial sleeve is thinner at the posterior wall. On the basis of these findings, SVCI could be obtained by segmental ablation. In our study, segmental ablation was performed in 39/50 cases, with the mean procedural time of 7.8 ± 2.7 min and mean numbers of 3 ± 1 segments of RA–SVC junction. Circumferential SVCI was performed in only 11/50 cases. Empirically, SVCI was commenced at the septal aspect of SVC and subsequently at posterior wall or anterior wall. We performed high output pacing (30 mA) before ablating the postero-lateral wall of SVC, and sites with positive diaphragmatic stimulation were not ablated to minimize the risk of diaphragmatic nerve injury. In two cases, SVCI was not achieved due to diaphragmatic stimulation by pacing from the postero-lateral wall of RA. We have not experienced sinoatrial node injury in this study, although sinus pause or severe sinus bradycardia has been reported by several investigators.

Possible explanation of the comparable results from two groups
It is established that PV reconnection is the main cause for ATa recurrence after initial CPVI procedure. Ouyang et al. reported that PV conduction recovery accounted for >80% of the ATa recurrence in reablation cases. Even in cases with prior surgical Maze procedure, PV reconnection still was the dominant cause for recurrent ATa. In our study, PV reconnection occurred in 88% of cases who underwent second ablation, and by reisolation of all PVs, AF could be cured in 15/17 cases. Superior vena cava is the main source for non-PV AF, however, the prevalence of AF with an SVC origin is much lower than that with a PV origin. In contrast, our randomized study was a preliminary one and only 106 cases were included. Due to the low prevalence of SVC-originated AF and the relatively small sample size, SVCI contributed insignificantly to the clinical results.

Limitations
This study has two major limitations: 1. At the time the study was initiated, little literature was available about the exact prevalence of AF originating from SVC, although it was already clear that AF was initiated by PV foci in >90% of the cases and that AF could be eliminated in 70–90% of cases by CPVI. Considering the unknown prevalence of SVC-originated AF, it might be difficult to estimate the...
number of patients required to be enrolled. Therefore, this was a preliminary study and patient enrolment was open. Owing to the relatively small sample size and the short follow-up period of the study, we have not observed the statistically significant difference regarding the success rate between two groups. The exact role of SVCI on long-term clinical results should be evaluated in large volume, long follow-up period studies. 2. The success rate of ablation might be overestimated as ATa recurrence was mainly judged upon symptoms. Frequent ECG examination, 24 h Holter monitoring every 2 months, and monthly telephone inquiry did not exclude asymptomatic or short episode of ATa.

Conclusions
In our series of paroxysmal AF patients, adjunctive SVCI does not significantly improve the success rate of ablation, although SVCI is necessary for eliminating SVC-originated AF. Superior vena cava isolation is technically safe and feasible. Owing to the relatively small sample size, the impact of SVCI on clinical results should be evaluated in a large series of patients.

Conflict of interest: none declared.

References