Comparison of Empiric Isolation and Conventional Isolation of Superior Vena Cava in Addition to Pulmonary Vein Isolation on the Outcome of Paroxysmal Atrial Fibrillation Ablation
A Meta-Analysis
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Summary
Radiofrequency catheter ablation (RFCA) in the treatment of AF is currently based on pulmonary vein isolation (PVI). Some studies have investigated the efficacy of empiric SVC isolation (SVCI) in addition to conventional PVI in order to improve success rates and reduce recurrence rates. However, the results of the studies have given conflicting data.

We performed a meta-analysis to evaluate the efficacy and safety of the empiric SVCI compared with conventional SVCI for paroxysmal atrial fibrillation (PAF) ablation.

We searched MEDLINE, EMBASE, the Web of Science, and the Cochrane Database from the period January 1986 to August 2016 and identified qualified studies. The primary clinical outcome was the recurrence rate of atrial tachyarhythmias, and the secondary clinical outcomes were procedure time, fluoroscopy time, and complications.

We identified 3 randomized controlled trials (RCTs) and one nonrandomized, observational study (nROS) involving 245 patients with empiric SVCI and 269 patients with conventional SVCI. The empiric SVCI group had a lower recurrence rate of atrial tachyarhythmia after a single procedure compared with the conventional SVCI group (16.7% versus 29.4%, OR: 0.48, 95%CI: 0.31 to 0.74, \( P = 0.0009 \)). There was no significant difference in fluoroscopic time (\( P = 0.22 \)), procedure time (\( P = 0.32 \)), or clinical complications (\( P = 0.33 \)) between the two groups.

Empiric SVCI is more effective than conventional SVCI in terms of the long-term outcomes of PAF patients after a single PVI procedure, with the same fluoroscopic time, procedure time, and clinical complications. (Int Heart J 2017; 58: 1-6)

Key words: Arrhythmia, Pulmonary vein, Atrial fibrillation, Meta

Radiofrequency catheter ablation (RFCA) is an effective treatment option for patients with atrial fibrillation (AF). At present, RFCA in the treatment of AF is based on pulmonary vein isolation (PVI), whether it is segmental PVI or circumferential PVI. \(^1\) AF can be also initiated by nonpulmonary vein ectopic beats as in the superior vena cava (SVC), coronary sinus ostium, left atrial posterior wall, crista terminalis, and ligament of Marshall. \(^3\) Despite initial positive results of the PVI strategy, RFCA that targeted the pulmonary vein alone showed a significant recurrence rate after the first procedure with the reconnection of the pulmonary vein or with the emergence of non-PV ectopic foci including the SVC. \(^3\) Some researchers have investigated the efficacy of empiric SVC isolation (SVCI) in addition to conventional SVCI (performing SVCI only for patients who have triggers in the SVC) in order to improve success rates and reduce recurrence rates in patients with AF. \(^7\) However, some studies also have provided conflicting data indicating that there was no statistical significance for these two strategies after the initial AF ablation. \(^10,11\) Therefore, we believed a meta-analysis of published data was needed to assess the efficacy of empiric isolation and conventional isolation of SVC in patients with paroxysmal AF (PAF).

METHODS

Literature search: We searched MEDLINE, EMBASE, the Web of Science, and the Cochrane Database to identify all the studies in patients with AF using the terms “ablation”, “atrial
fibrillation” and “superior vena cava”. Two investigators (Li and Jiang) independently screened all titles and abstracts to identify studies for further assessment. All studies were limited to English language publications from January 1989 to August 2016. The major inclusion criteria were: 1) clinical trials published in peer-reviewed journals with full available text in English; 2) comparison of empiric SVCI and conventional SVCI (performing SVCI only for patients who have triggers in the SVC) plus PVI on long-term control of PAF; and 3) evaluating recurrent AF as an outcome after the first procedure. The major reasons for exclusion of a study were: 1) duplicate data; 2) data published in the form of abstracts without peer-reviewed publication of manuscripts; 3) patients underwent repeated ablation because of recurrent atrial tachyarrhythmias; and 4) studies in which only incomplete data could be extracted.

Data collection and quality assessment: Two researchers independently reviewed all potential eligible studies using predefined criteria. Both randomized controlled trials (RCTs) and nonrandomized, observational studies (nROs) comparing the efficacy of empiric SVCI and conventional SVCI plus PVI on long-term control of AF were included in the analysis. Baseline characteristics of patients were extracted as well as data about each trial’s intervention and outcomes assessed. The quality of each study was assessed by evaluating specific elements of each study design using the Jadad quality scale and Newcastle-Ottawa scale for RCTs and nROs, respectively.12,13

Statistical analysis: Statistical analyses were performed using the Review Manager (RevMan, version 5.3, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The efficacy and safety of empiric SVCI and conventional SVCI plus PVI were presented as the odds ratio (OR) with 95% confidence intervals (CIs), and weighted mean differences (WMD) and 95% CIs were calculated to compare the procedure time and fluoroscopic time between the two groups. Heterogeneity was evaluated with Cochran’s Q statistic and qualified by the I² statistic. As there was a significant heterogeneity with P < 0.1, the random-effects model was used; otherwise, the fixed effects model was used. Publication bias was evaluated by means of funnel plots. The results were considered statistically significant if P < 0.05. Sensitivity analyses were undertaken by omitting one study at a time to examine the influence of one study on the overall summary estimate.

Results

Eligible studies: We initially identified 865 potentially relevant studies according to our search strategy. As illustrated with the flow diagram (Figure 1), first, we excluded 849 papers on the basis of screening the titles and abstracts and then excluded an additional 12 articles after a detailed evaluation. In the end, 3 RCTs7,10,11 and 1 nROS fulfilled all the inclusion criteria.8 Of these, two RCTs10,11 studied PAF by comparing PVI plus SVCI versus PVI alone. One RCT7 studied all types of AF by comparing PVI plus SVCI versus PVI alone. The nROS8 studied PAF by comparing PVI plus SVCI versus PVI with as-needed SVCI (SVCI was applied only if SVC-triggered AF or rapid SVC activity was observed during the procedure) (Figure 1). The qualities of the RCTs and nROS were high. The characteristics of the 4 studies are shown in Table I.

Baseline characteristics of the 4 studies: The total sample size was 514 patients in this meta-analysis, with 269 in the conventional SVCI group and 245 empirical SVCI group. There were no significant differences in mean age, gender ratio, mean LVEF, or left atrium diameter between the two groups. The baseline characteristics of the patients enrolled are summarized

![Figure 1. Flow diagram of the study selection process. AF indicates atrial fibrillation; RCT, randomized controlled trial; and nROS, nonrandomized observational study.](image-url)
Primary clinical outcome: We found a statistically lower recurrence rate of atrial tachyarrhythmias after a single procedure in the empiric SVCI group compared with the conventional SVCI group of PAF (16.7% versus 29.4%, OR: 0.48, 95%CI: 0.31 to 0.74, Z = 3.33, P = 0.0009). Because the heterogeneity was nonsignificant (chi² = 2.17, df = 3, I² = 0%, P = 0.54), we chose the fixed effects model instead of the random-effects model to complete the merge analyses (Figure 2). Sensitivity analysis confirmed the overall differences in the recurrence rate in the empiric SVCI group compared with the conventional SVCI group, with P values of 0.007, 0.001, 0.05, and 0.0004 after exclusion of the Corrado, et al.,7 Da, et al.,11 Ejima, et al.,8 and Wang, et al.,10 studies, respectively.

Secondary clinical outcomes: At the end of the procedure, all pulmonary veins were successfully completed in both groups. By obtaining the results from the eligible trials, we found that there was no significant difference in fluoroscopic time (WMD = −4.24, 95%CI: −11.06 to 2.59, Z = 1.22, P = 0.22, I² = 97%; Figure 3) or procedure time (WMD = −9.2412, 95%CI: −27.27 to 9.02, Z = 0.99, P = 0.32, I² = 82%; Figure 4) between the empiric SVCI group and conventional SVCI group.

There was no significant difference in clinical complications between the empiric SVCI group and conventional SVCI group (3.8% versus 2.0%, OR: 1.84, 95%CI: 0.53 to 6.40, Z = 0.96, P = 0.33, I² = 0%; Figure 5). The complications included 1 case of pulmonary stenosis (conventional SVCI group), 1 case of transient ischaemic attack, 2 cases of phrenic nerve injury (both in empiric SVCI group, 1 with transient phrenic nerve palsy and 1 with phrenic nerve injury with partial recovery), 3 cases of femoral artery pseudo-aneurysm, 1 case of thrombotic events, 1 case of cardiac tamponade, and 2 cases of gastric hypomotility.

Publication bias: For the analysis of recurrence rate, the funnel plots including all studies concerning PAF patients (Figure 6) showed no significant publication bias.
Discussion

We performed this meta-analysis of 3 RCTs and 1 nROS with 514 patients to investigate the efficacy of empiric SVCI and conventional SVCI in addition to PVI on the outcome of PAF ablation. The results showed there was a statistical benefit to empiric SVCI compared to conventional SVCI in the long-term outcomes of PAF patients after a single PVI procedure. The addition of SVCI following PVI did not significantly increase the fluoroscopic time or procedure time.

The cornerstone of AF ablation is electrical PVI with the left atrium. Ablation of the pulmonary vein vestibular area can terminate AF because the left atrial ectopic beats mostly originate in the pulmonary vein vestibular area.\(^1\)\(^,\)\(^2\) The success rate of catheter ablation in patients with PAF and without significant structural heart disease was the highest.\(^3\) Recent studies have also supported catheter ablation in patients with persistent AF and cardiac dysfunction.\(^4\) AF can be also initiated by non-pulmonary vein ectopic beats such as in the superior vena cava (SVC), coronary sinus ostium, left atrial posterior wall, crista terminalis, and ligament of Marshall.\(^5\) The SVC is thought to be the most common source of ectopies. Among them, 26% to 30% of nonpulmonary venous foci had originated from the SVC.\(^6\) The SVC is often an important target for the ablation of AF.\(^7\) Catheter ablation of persistent AF is more challenging, and ablation results are often unsatisfactory and are less favo-
rable than prognostic relevance. To improve outcomes, ablation strategies targeting nonpulmonary venous foci are often added to PVI. The arrhythmogenic focus from the SVC was found to be relatively far from the SVC–RA junction. The electrical isolation of arrhythmogenic SVC foci and RA is a fundamental strategy for ablation of AF.

In the past, ablation was performed in SVC with the confirmation of ectopic beats originating from the SVC. A recent method is electrical SVC from the RA. Two randomized prospective studies revealed no significant difference in the atrial arrhythmias occurring between the PVI group and PVI plus SVCI group in PAF patients. On the other hand, other studies found a lower recurrence rate after a single procedure in PAF patients that underwent an empiric SVCI strategy compared to the conventional SVC group. In the observational study by Ejima, 9% of the patients in the conventional SVC group actually had SVC, and after integrating all 4 studies, 2.97% of patients in the conventional SVC group actually had SVC. Arruda evaluated the feasibility of empiric SVC as an adjunct to PVI in patients with all types of AF. They also found empirical SVCI was incorporated as an adjunct to PVI in patients presenting for AF ablation, accounting for a higher long-term success rate. However, in their study, they did not provide any specific data on the recurrence rate of each subgroup or the time of fluoroscopy and procedure, so it could not be included in our meta-analysis.

Some studies reported different incidences of SVC triggers for AF patients. Incidences of the SVC as a site of triggers for AF of 3.7%, 6%, 11%, and 12% have been reported. The debate surrounding the need to perform SVC routinely in every AF patient has yet to be resolved. The incidence of SVC trigger seems to have a close relationship to the efficacy of empiric SVC as an adjunct to PVI in patients with AF. Wang reported an incidence of 3.7% for the SVC as a site of trigger for AF, did not find any significant difference in the outcome of PAF ablation treated with SVC or not. Some studies have reported the benefit of empiric SVC plus PVI in PAF ablation, describing a relatively higher incidence of the SVC as a site of triggers for AF. Recently, a prospective, randomized design, and double-blinded to follow-up research revealed no additional clinical effects of SVC on the long-term follow-up (15 months). SVC may be useful in only a subset of AF patients with demonstrated SVC triggers initiating AF. Therefore, the need to conduct a meta-analysis of published data appears timely and to assess the efficacy of empiric isolation and conventional isolation of SVC in patients with AF. After the meta-analysis, we showed that there was an improved clinical outcome of empiric SVC compared with conventional SVC in addition to PVI in PAF patients. According to the secondary clinical outcomes, there were no statistical differences in the fluoroscopic time or procedure time between empiric SVC and conventional SVC in PAF patients. Nevertheless, we still cannot make any conclusions with regards to the efficacy of empiric SVC compared with conventional SVC in persistent and permanent AF.

RFCA has evolved as an important therapeutic option for curing AF, but AF recurrence after ablation remains a problem in a substantial number of patients. Although many patients with late recurrence after PAF ablation had reconnected PVs, a smaller percentage of patients undergoing repeat procedures for AF recurrence were found to have non-PV foci that may not have been identified or targeted during the initial procedure. About 4% to 42% of patients having repeat ablation procedures for paroxysmal AF need ablation of non-PV foci during the follow-up procedure. In these patients, the roles of non-PV triggers and atrial substrate may be important in maintaining AF.

In order to understand these conclusions, the following aspects should be emphasized. First, the incidence of SVC triggers for AF patients was very important to the AF recurrence rate in this meta-analysis. Studies with negative conclusions seem to have a lower incidence of SVC trigger (3.7%), while studies with positive conclusions seem to have a higher incidence of SVC trigger (9%). The different inducing maneuvers would result in a different incidence of SVC triggers. Only 7% of SVC foci were spontaneously observed, while 93% of the firings were discovered following isoproterenol infusion or immediately after cardioversion. This suggests that most triggers arising from the SVC could be missed without the use of provocative maneuvers. Second, the number of study patients in positive studies (308 patients) was larger than that in negative studies (206 patients), which was also important to the AF recurrence rate. Furthermore, because the largest number of patients was referenced from the observational study of Ejima, the empiric SVC group might have selection bias. Sensitivity analysis showed the Ejima study had a great influence on the difference in the recurrence rate, which has a P value of 0.05 after exclusion of this study. Third, although a circumferential PVI strategy was employed by all 4 studies, the Corrado study used 8-mm ablation catheters while the others used 3.5-mm cooled-tip catheters. In conclusion, more RCTs with a larger series of patients and homogeneity of PVI procedure are urgently needed to confirm the efficacy of empiric SVC in the future.

RFCA application for the SVC has potential risks for developing several complications, namely 1) SVC stenosis, 2) sinus node injury, and 3) right phrenic nerve injury. Among the patients in this meta-analysis, there were 11 (2.1%) cases of complications. The relatively severe complications included pulmonary stenosis, phrenic nerve injury, thrombotic events, and cardiac tamponade.

Limitations: The limitations of this study include: 1) we found a relatively small number of randomized trials eligible for this analysis. 2) The total sample size was not sufficient, and this could have a potential impact on the analysis result. 3) Only one study evaluated all types of AF patients, while the other studies evaluated PAF patients. So it was impossible to make meta-analysis for persistent and permanent AF. 4) The procedure time and fluoroscopy time showed remarkable heterogeneity.

Conclusions: The present analysis suggests that there was a statistical benefit to empiric SVC compared to conventional SVC in the long-term outcomes of PAF patients after a single PVI procedure. The addition of SVC following PVI did not significantly increase complications, fluoroscopic time, or procedure time.

**DISCLOSURE**

**Declarations of interest:** The authors have no conflict of interest.
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