Is Circumferential Pulmonary Vein Isolation Preferable to Stepwise Segmental Pulmonary Vein Isolation for Patients With Paroxysmal Atrial Fibrillation? — A Randomized Study —

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**Background**
Stepwise segmental pulmonary vein isolation (SPVI) and circumferential pulmonary vein isolation (CPVI) have been developed to treat patients with atrial fibrillation (AF), but the preferable approach for paroxysmal AF (PAF) has not been established.

**Methods and Results**
One hundred and ten patients with symptomatic PAF were randomized into a stepwise SPVI group (n=55) or CPVI group (n=55). Systemic SPVI combined with left atrial linear ablation tailored by inducibility of AF was performed in the stepwise SPVI group. Circumferential linear ablation around the left and right-sided pulmonary veins (PVs) guided by 3-dimensional electroanatomic mapping was performed in the CPVI group. The endpoints of ablation are non-inducibility of AF in the stepwise SPVI group and continuity of circular lesions combined with PV isolation in the CPVI group. After the initial procedures, atrial tachyarrhythmias (ATa) recurred within the first 3 months in 23 of the 55 patients (41.8%) who underwent stepwise SPVI and in 20 of the 55 patients (36.4%) who had CPVI (p=0.69). Repeat procedures were performed in 7 patients from the stepwise SPVI group and 5 from the CPVI group (p=0.76). During the 3–9 months after the last procedure, 46 patients (83.6%) from the CPVI group and 43 (78.2%) from the stepwise SPVI group did not have symptomatic ATa while not taking anti-arrhythmic drugs (p=0.63). Severe subcutaneous hematoma or PV stenosis occurred in 3 patients.

**Conclusions**
The efficacy of stepwise SPVI is comparable to that of CPVI for patients with PAF. (Circ J 2006; 70: 1392–1397)

**Key Words:** Atrial fibrillation; Catheter ablation; Pulmonary vein

During the past decade, a variety of transcatheter ablation strategies targeting the pulmonary veins (PVs) have emerged for the treatment of patients with symptomatic atrial fibrillation (AF). Among them, segmental PV isolation (SPVI) and circumferential PV ablation (CPVA) are 2 approaches gaining more popularity. Several studies have compared the efficacy of these 2 most widely used approaches; however, the conclusions are controversial.

Recently, 2 new ablation approaches based on the traditional SPVI and CPVA have evolved to treat patients with AF. Haissaguerre’s laboratory introduced a stepwise SPVI approach, which is characterized by stepwise left atrial (LA) linear ablation tailored by inducibility of AF after systemic SPVI. Meanwhile, CPVA with the endpoint of PV isolation, so-called circumferential PV isolation (CPVI), has also been developed by another pioneer laboratory. Both of these approaches share high efficacy in treating patients with AF in the literature; however, their relative merits and demerits have not been elucidated.

At present, patients with paroxysmal AF (PAF), particularly those refractory to anti-arrhythmic drugs (AADs), are considered as the ideal candidates for catheter ablation therapy. However, the preferred approach for this subset of patients with AF has not been established. Thus, the aim

| Table 1 Clinical Variables of the Patients With Paroxysmal Atrial Fibrillation |
|---------------------------------|-----------------|-----------------|-----------------|
| CPVI (n=55)                      | Stepwise SPVI (n=55) | p value |
| Age (years)                     | 57.3±9.6         | 58.0±8.1        | 0.68            |
| M/F (n)                         | 38/17            | 35/20           | 0.84            |
| AADs (n)                        | 2±1              | 2±1             | 1.00            |
| History (years)                 | 5.4±3.6          | 4.5±3.1         | 0.16            |
| HTN or SHD % (n)                | 54.5% (19)       | 27.2% (15)      | 0.53            |
| Atrial flutter % (n)            | 10.9% (6)        | 12.7% (7)       | 1.00            |
| LA size (mm)                    | 38.0±4.1         | 37.3±3.9        | 0.36            |
| LVEF (%)                        | 64.1±6.7         | 63.1±5.7        | 0.40            |

CPVI, circumferential pulmonary vein isolation; SPVI, segmental pulmonary vein isolation; AAD, anti-arrhythmic drugs; HTN, hypertension; SHD, structural heart disease; LA, left atrium; LVEF, left ventricular ejection fraction.
of this study was to investigate prospectively the efficacy of these 2 newly developed ablation approaches for patients with PAF.

**Methods**

**Study Population**

This prospective study included 110 consecutive patients who underwent first-time catheter ablation for highly symptomatic PAF. The inclusion criteria were: age 20–80 years, refractory to multiple AADs, New York Heart Association functional class I or II, and at least 9 months follow-up. Exclusion criteria included LA diameter >55 mm, left ventricular ejection fraction <35%, contraindication to anticoagulation, prior AF ablation, and presence of LA thrombus. Additionally, in order to exclude the bias caused by the learning curve, the initial 50 cases undergoing these 2 approaches were not included, and all procedures were performed by 2 investigators with similar experience. The clinical variables of the patients are shown in Table 1. The institutional ethics committee approved the study protocol and all patients gave written informed consent.

**Electrophysiological Study**

The electrophysiological study and ablation procedure were performed under deep sedation with continuous infusion of propofol. A quadripolar catheter was positioned within the coronary sinus (CS) via left subclavian vein entry. One or two 8F long sheath(s) (SL1 and/or SR0, St Jude Medical, USA) were advanced to the LA using a modified Brockenbrough technique. After transseptal catheterization, intravenous heparin was administered to maintain an activated clotting time of 250–350 s. The transseptal sheaths were flushed continuously with saline (20 ml/h) to avoid thrombus formation or air embolism.

**Ablation Protocol**

Patients were prospectively randomized for the 2 ablation strategies: (1) stepwise SPVI (n=55) or (2) CPVI (n=55). Randomization was performed according to a computer-generated randomization scheme. In addition, all patients underwent tricuspid annulus isthmus (TAI) with an endpoint of bidirectional isthmus block.

**Stepwise SPVI** The ablation technique of stepwise SPVI has been described by the Bordeaux group.7–9 Briefly, after attempting to induce AF (see below), systemic SPVI guide by circumferential PV mapping (Lasso™, Biosense-Webster, USA) was performed initially. PV isolation was defined by complete elimination or dissociation of the PV potentials determined with the Lasso catheter. Next, linear ablation along the roof of the LA was performed in patients with persistent or inducible sustained AF (Fig 1). Finally, linear ablation along the mitral annulus isthmus (MAI) was performed in patients with inducible AF refractory to LA roof ablation (Fig 2). For safety reasons, further ablation of the MAI was discontinued if radiofrequency (RF) application lasted $>$30 min. If AF remained inducible after MAI ablation, transthoracic cardioversion was attempted to restore sinus rhythm. Bidirectional block of the LA linear lesions was validated by traditional differential pacing or double potentials. During the procedure, AF was repeatedly induced 5 times by pacing in the CS for 10 s at the shortest cycle length, resulting in 1:1 atrial capture. Induced AF was considered sustainable if it lasted $>$10 min. Ablation was performed using a 4-mm, irrigated-tip catheter (Celsius Thermcool™, Biosense-Webster, USA) with

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Fig 1. Left atrial roofline ablation (A). Before segmental pulmonary vein isolation (SPVI), ongoing atrial fibrillation (AF) was documented. (B) Inducible AF still sustained after systemic SPVI and bidirectional block of the tricuspid annulus. (C) Ongoing AF terminated during roofline ablation. I, aVF and V1, electrocardiogram tracing; CS, coronary sinus recording; PV, pulmonary vein recording; ABL, ablation catheter recording.
target temperature of 43°C, RF energy output of 30 W, saline irrigation speed of 17 ml/min. RF energy was delivered for 30 s at each point. The endpoint of the stepwise SPVI approach is non-inducibility of AF.

**CPVI** The technique of CPVI has been described previously in detail. Briefly, after the PVs were outlined via angiography, the 3-dimensional (D) LA geometry was created using an electroanatomical mapping system (CARTO XP, Biosense-Webster, USA) with a 3.5 mm irrigated tip ablation catheter (Navi-Star, Thermocool™, Biosense-Webster, USA). The ipsilateral PV antrum was then carefully mapped using a combination of venography, electrogram evaluation and the drop-off site of the mapping catheter while dragging it out of the vein. Irrigated RF energy was delivered along the ipsilateral PV antrum using settings similar to those used for SPVI. RF energy was applied for 30 s at each ablation site until the maximal local electrogram amplitude decreased by >70% or <0.1 mV. The endpoint of CPVI is continuity of the circular lesions and PV isolation verified by circumferential PV mapping (Fig. 3). According to the study protocol, no attempt was made to assess the inducibility of AF after achievement of PV isolation in the CPVI group. Cardioversion was performed to restore sinus rhythm at the end of the procedure in patients with sustained AF.

**Post-Ablation Management**

Low-molecular-weight heparin and warfarin were administered during the first 3–5 days after the procedure, but patients were discharged on warfarin alone and the international normalization ratio was maintained between 1.6 and 2.5. Warfarin was withdrawn 3 months later if there were no other indications for anticoagulation treatment. AADs were oral amiodarone or propafenone in the case of a history of dysthyroidism, and were administered routinely for the first 2 months and then withdrawn in the absence of arrhythmia relapse.

**Post-Ablation Follow-up**

All patients were followed up with 12-lead electrocardiography and 24-h Holter recordings at 2 weeks, and then 1, 3, 6, and 9 months after ablation. Also, monthly telephone interviews were conducted for all patients. Any episodes of symptomatic atrial tachyarrhythmia (ATa), regardless of duration, and any episodes of asymptomatic ATa lasting >10 min on Holter recording, were considered as recurrence. An early recurrence was defined as occurring within the first 3 months after the first procedure. Repeat ablation procedures were considered only for recurrent episodes occurring after at least 3 months follow-up from the initial procedure. The same approach as for the initial procedure
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was used for repeat procedures. Successful clinical outcome was defined as the absence of ATa relapse without the use of AADs during the 3–9 months after the last procedure.

Statistical Analysis
Continuous variables are expressed as mean±SD and compared by Student’s t-test. Categorical variables are analyzed by chi-square or Fisher’s exact test. A value of p<0.05 was considered statistically significant. Analyses were performed using the SPSS statistical software (Version 11.5, Chicago, IL, USA).

Results

Patient Characteristics
No significant differences in terms of baseline variables were found between the 2 groups (Table 1).

Procedure Characteristics
Stepwise SPVI Before starting SPVI, spontaneous AF was present in 19 of the 55 patients (34.5%) and sustained AF was induced in the remaining patients. PV isolation and bidirectional blockade of TAI were achieved in all patients, after which AF was persistent or could be induced in 28 patients (50.9%). LA roofline ablation was performed during AF in those patients and resulted in AF termination in 4 patients (14.3%) within 10 min of RF delivery. AF was converted to sinus rhythm by cardioversion in the remaining patients after >10 min of RF ablation. Next, roofline ablation was performed during pacing from the LA appendage and bidirectional block was achieved in 26 patients (92.6%). After roofline ablation, sustained AF could still be induced in 15 patients (27.3%) and MAI ablation was performed during pacing from the distal CS electrode, with bidirectional block was achieved in 12 (80%) of them. Of these 12 patients, 5 needed ablation within the CS. After MAI ablation, inducibility of AF was reduced to 9.0% (5/55).

CPVI Among the 55 patients in the CPVI group, ongoing AF was documented in 20 (36.4%) at the beginning of procedure. CPVI was performed in these patients and resulted in AF termination in 15 of them. Of the remaining 5 patients with sustained AF, 2 terminated spontaneously, and the other 3 were converted to sinus rhythm with direct-current cardioversion. PV isolation and bidirectional block of TAI were achieved in all patients from this group.

Procedural Data
Mean fluoroscopy time (59±16 min vs 30±13 min, p<0.01) and total procedure time were prolonged with the stepwise SPVI approach (219±67 min vs 181±66 min, p=0.003), but the ablation time for stepwise SPVI was comparable to that for CPVI (63±15 min vs 59±9 min, p=0.09).

Follow-up
Early Recurrence of ATa After the first ablation procedure, early (within the first 3 months) recurrence of ATa occurred in 23 patients (41.8%) from the stepwise SPVI group, and in 20 (36.4%) from the CPVI group (p=0.69). The majority of the recurrent ATa (65.2%, 15/23) in stepwise SPVI group was AF alone or AF combined with regular atrial tachycardia (AT), and regular AT alone constituted the rest (34.8%, 8/23). Conversely, the majority (70.0%, 14/20) of the recurrent ATa in the CPVI group was regular AT alone, and AF constituted the minority of cases (30.0%, 6/20).

Delayed Cure Among the 23 patients with early recurrent ATa in the stepwise SPVI group, spontaneous resolu-
tion occurred in 8 (34.8%) during follow-up. Similarly, ATa did not relapse during follow-up in the 8 of 20 patients (40%) with early recurrent ATa in the CPVI group (p=0.76). Of note, most patients with delayed cure were those with recurrent AT alone, including 5 of the 8 patients in the stepwise SPVI group and 6 of the 8 patients in the CPVI group.

Repeat Ablation Seven patients from the stepwise SPVI group and 5 from the CPVI group underwent a repeat procedure within 3–5 months of the initial procedure. During follow-up, recurrent ATa was eliminated in 4 of the 7 patients and 4 of the 5 patients.

Successful Clinical Outcome Late recurrence of AF was detected in 1 patient from the stepwise SPVI group at 5 months after the first procedure and 1 patient from the CPVI group at 6 months after the first procedure. Only 1 episode was detected in the latter case. In summary, during 3–9 months of follow-up after the last procedure, successful clinical outcome was achieved in 46 patients (83.6%) from the CPVI group and in 43 patients (78.2%) from the stepwise SPVI group (p=0.63).

Complications Three patients from the stepwise SPVI group and 4 from the CPVI group developed subcutaneous hematoma and 1 patient from the stepwise SPVI group required a blood transfusion. Asymptomatic right superior PV stenosis was detected in 1 patient each from the stepwise SPVI and CPVI groups.

Discussion

Main Findings

This study was a prospective comparison of the CPVI and stepwise SPVI approaches for treatment of patients with PAF and showed comparable efficacy for the 2 techniques.

Previous Studies

Two other randomized studies have compared SPVI and CPVA for patients with AF. One study by Oral et al3 found that CPVA was superior to SPVI in efficacy for patients with PAF, whereas Karch et al5 in a similar study demonstrated a converse result, demonstrating poorer efficacy for CPVA. However, neither of the studies considered PV isolation as a procedural endpoint for CPVA, namely CPVI which many studies have shown results in higher efficacy for CPVI in the treatment of AF.11–15 Moreover, both those studies used conventional SPVI to isolate the PVs. Compared with them,3,5 the present study has 2 different features: (1) PV isolation, rather than voltage abatement, was the primary endpoint of CPVI and (2) after systemic SPVI, we performed additional LA linear ablation for patients with sustained or inducible AF.

Ablation Approaches

Recent studies indicate that firing foci (eg, from the ligament of Marshall), microreentry, ganglia plexi, and other factors contributing to AF development, could be anchored within the PV antrum.11–13 CPVI approach is designed to produce 2 circular lesion sets along the PV antrum, with the endpoint of PV isolation. As demonstrated by Ouyang et al,6 CPVI alone (without additional LA linear lesions) is very effective in treating PAF, but the approach also has some demerits because of the nature of a predetermined anatomic lesion set. First, different mechanisms may operate in different patients, so 1 approach with fixed lesions may be insufficient or deliver unnecessary ablation in some patients. Second, more aggressive ablation at the posterior LA wall during CPVI will increase the potential risk of esophageal injury.

In theory, stepwise SPVI should overcome the limitations of CPVI. First, the majority of the triggers and drivers that initiate and perpetuate PAF originate from the PVs so traditional SPVI is sufficient for this subset of patients. Second, the non-PV substrate may also be important for some patients and it may be possible to identify those patients by using non-inducibility as the procedural endpoint.20–22 Moreover, as recent studies had shown, traditional SPVI in combination with additional LA linear lesions is more effective in eliminating AF than traditional SPVI alone.23–25 Of the additional LA lesions, roofline and MAI are considered the preferable targets,23 which is why we used stepwise SPVI, rather than traditional SPVI in this study. Another advantage of stepwise SPVI is that the RF energy is delivered at the ostium of the PV, LA roof or MAI, rather than at the posterior wall of LA, thus minimizing the risk of esophageal injury. The clinical follow-up results demonstrated that stepwise SPVA was as effective as CPVI in eliminating AF.

Possible Mechanisms

In contrast to conventional SPVI, which limits ablation to the rim of the PV ostia, stepwise SPVI has 2 major steps: PV isolation with conventional SPVI, and then tailored ablation of the LA substrate by inducibility of AF. Consequently, stepwise SPVI aims to remove not only the PV-dependent mechanisms, but also any modification of the LA substrate. Recent studies have demonstrated that the preferential path and critical isthmus for propagation closely correlates with the muscle fiber orientation or anatomical barriers, which are predominantly localized to the LA roof and mitral annulus.24 In addition, these structures are in a region that demonstrates highly fragmented electrograms or rapid activities, perhaps indicating the presence of substrate capable of sustaining localized reentry or focal firing.24 Thus, ablating those structures tends to compartmentalize the LA, prevent multiple wavelet reentry, or destroys the firing foci and autonomic nerves.

Although stepwise SPVI is different from CPVI from viewpoint of its target, the lesion set of either approach may have interrupted the same mechanism of AF via ablation of different targets. This is because the genesis of AF is complex and multi-factorial, and the lesion set of CPVI overlaps with that of stepwise SPVI.

Ablation Process

One of the advantages of the 3-D mapping system is its real-time navigation ability, which allows the operator to carry out the ablation process with reduced fluoroscopy monitoring. On the other hand, stepwise SPVI requires repeat induction of AF and production of linear lesions, and both of these are time-consuming and sometimes very challenging. This may help explain the much longer fluoroscopy and procedure times in the stepwise SPVI group. The duration of energy application was similar between the 2 approaches because of the extensive ablation.

Safety

The incidence of complications was similar between the
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2 groups of patients. Of note, 7 patients (6.4%) developed a subcutaneous hematoma from the aggressive anticoagulation. In our laboratory, the power discharge was controlled below 30 W and consecutive application was maintained for less than 30 s to minimize the risk of esophageal injury.

**Study Limitations**

There are at least 3 major limitations to this prospective study. First, only efficacy, safety and procedural data were compared, but cost is also an important issue in the choice of ablation approach for patients with PAF. Second, only 41.4% (12/29) of late recurrent cases underwent repeat procedure. This lower proportion of redo cases may influence the assessment of efficacy between the 2 approaches. Third, emerging studies demonstrate that the superior vena cava (SVC) also contributes to the initiation mechanism of PAF in some patients but detailed SVC mapping and isolation was not performed in this study.

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**References**


