

# Frequency Gradient Within Coronary Sinus Predicts the Long-Term Outcome of Persistent Atrial Fibrillation Catheter Ablation

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**Background**—The coronary sinus (CS), as a junction of the atria, contributes to atrial fibrillation (AF) by developing unstable reentry, and isolating the atria by ablation at the CS could terminate AF. The present study evaluated whether AF activities at the CS in a subset of patients contributed to AF maintenance and predicted clinical outcome of ablation.

**Methods and Results**—We studied 122 consecutive patients who had a first-time radiofrequency ablation for persistent AF. Bipolar electrograms were obtained from multiple regions of the left atrium by a Lasso mapping catheter before ablation. Pulmonary vein isolation terminated AF in 12 patients (9.8%). Sequential stepwise ablation was conducted in pulmonary vein isolation nontermination patients and succeeded in 22 patients (18%). In the stepwise termination group, AF frequency in the proximal CS (CSp) was significantly higher ( $10.2 \pm 2.1$  Hz versus  $8.3 \pm 1.8$  Hz,  $P < 0.001$ ), and the ratio of distal CS (CSd) to proximal CS (CSd/CSp ratio,  $56.6\% \pm 10.11\%$  versus  $70.7\% \pm 9.8\%$ ,  $P < 0.001$ ) was significantly lower than that in the nontermination group. The stepwise logistic regression analysis indicated that the CSd/CSp ratio was an independent predictor with an odds ratio of 1.131 (95%CI 1.053–1.214;  $P = 0.001$ ). With a cutoff of 67%, the patients with lower CSd/CSp ratios had significantly better index and long-term outcomes than those with higher ratios during a follow-up of  $46 \pm 18$  months.

**Conclusions**—Rapid repetitive activities in the musculature of the proximal CS may contribute to maintenance of AF after pulmonary vein isolation alone in persistent AF. A cutoff at 67%, of the CSd/CSp frequency ratio might be an indicator to stratify the subset of patients who might benefit from CS ablation. (*J Am Heart Assoc.* 2017;6:e004869. DOI: 10.1161/JAHA.116.004869.)

**Key Words:** ablation • atrial fibrillation • coronary sinus • pulmonary vein isolation • radiofrequency

The electrical activity in the pulmonary vein (PV) has a critical role in initiation and maintenance of atrial fibrillation (AF),<sup>1</sup> and pulmonary vein isolation (PVI) is the hallmark in catheter ablation of AF.<sup>2,3</sup> However, PVI alone appears inefficient in patients with persistent atrial fibrillation (PeAF).<sup>4–6</sup> Therefore, strategies with additional ablation to

modify the substrates in PeAF have been extensively used in clinical practice. However, recently, multiple randomized trials have indicated that less extensive ablation strategy showed a non–statistically significant trend in favor of better outcomes.<sup>7</sup> Meta-analyses have also suggested that additional ablation beyond PVI provided inconsistent benefits.<sup>8</sup> Therefore, to limit the extensive ablation, it is necessary to develop individual-specific tailored ablation strategy.

Most recently, Haïssaguerre and his co-workers revealed that the high gradient between PV activity and left atrial AF circle length might identify the subset of patients with PeAF.<sup>9</sup> Moreover, the focal discharges perpetuating AF have been described within the whole atrium, including the superior vena cava, the vein of Marshall, the coronary sinus, the posterior wall of the left atrium, the roof of the left atrium, and/or the crista terminalis of the right atrium.<sup>10,11</sup> It has been suggested that identifying the pattern of focal discharges or activities will allow development of individual-specific tailored ablation strategies in a subset of patients with PeAF.<sup>12,13</sup>

The muscular sleeve of the coronary sinus, as a major electrical connection between the left and right atria, might contribute to AF.<sup>14,15</sup> Over a decade ago an observation on 9

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paroxysmal AF patients showed that electrical connections between the CS and the left atrium contribute two-thirds of a patient's AF after PVI.<sup>16</sup> Previous studies reported that CS contributed ~25% of patients with atypical flutter after ablation for AF<sup>17</sup> and 35% of AF maintenance after PV isolation.<sup>18</sup> Furthermore, isolation of the CS from the left atrium eliminated micro- and macroentry and increased the success of AF ablation.<sup>19,20</sup> Recently, through a high-volume optical mapping technique, a canine study identified that microentry within the CS drove 88% of pacing- and acetylcholine- induced AF in the study. Further catheter ablation at CS-atrial junctions by isolating the CS from the atria eliminated the sustained AF.<sup>21</sup>

In the current context we hypothesized whether the characteristics of CS activities would help us to identify a subset of patients in whom the electrical activities of CS might play an important role in maintenance of AF and predict the outcome of AF ablation.

## Methods

### Study Population

The study protocol was preapproved by the Research Development and Human Ethics Committee at the First Affiliated Hospital of Dalian Medical University. All patients signed written informed consent before enrolling in the study. Patients with symptomatic refractory PeAF for their first catheter ablation were derived from the First Affiliated Hospital of Dalian Medical University between March 2009 and July 2012. PeAF was defined as sustained >1 week, or sustained <1 week but requiring external cardioversion to recover sinus rhythm (SR) (according to 2007 guideline and 2011 updates).<sup>22-24</sup> Patients were eligible if they had symptomatic, drug-refractory persistent AF, and were undergoing radiofrequency catheter ablation for the first time. Exclusion criteria were as follows: (1) paroxysmal atrial fibrillation; (2) age <18 years or >80 years; (3) left atrium size >60 mm measured on echocardiogram; (4) AF with rheumatic valvular disease; (5) previous AF ablation; and (6) being post-cardiac surgery.

### Electrophysiological Study

The procedures were performed under general anesthesia. The antiarrhythmic medications were discontinued for  $\geq 5$  half-lives before ablation. Oral anticoagulation therapy was given to all patients for  $\geq 1$  month. Left atrial appendage thrombus was ruled out by transesophageal echocardiogram before transseptal puncture. Surface electrocardiogram and bipolar endocardial electrogram morphology (filtered from 30 to 500 Hz) were continuously monitored and stored on a

computer-based digital amplifier/recorder system (GE Healthcare, CardioLab, Milwaukee, WI). The following catheters were introduced through the left femoral vein: (1) a steerable decapolar catheter (St Jude Medical, St. Paul, MN) was positioned within the CS; (2) a 4-pole catheter placed in the right ventricle for protective pacing. The left cardiac catheter was positioned by atrial septal puncture: (1) a 10-pole circumferential catheter (Lasso or Lasso SAS; Biosense Webster, Diamond Bar, CA) was used for PV and left atrial (LA) mapping; and (2) an irrigated 3.5-mm-tip catheter was used for ablation. The Lasso was stabilized with a long sheath (SLO; St Jude Medical, St. Paul, MN). Heparin as bolus and infusion were administered immediately after transseptal puncture to maintain the activated clotting time within a range of 250 to 300 seconds.

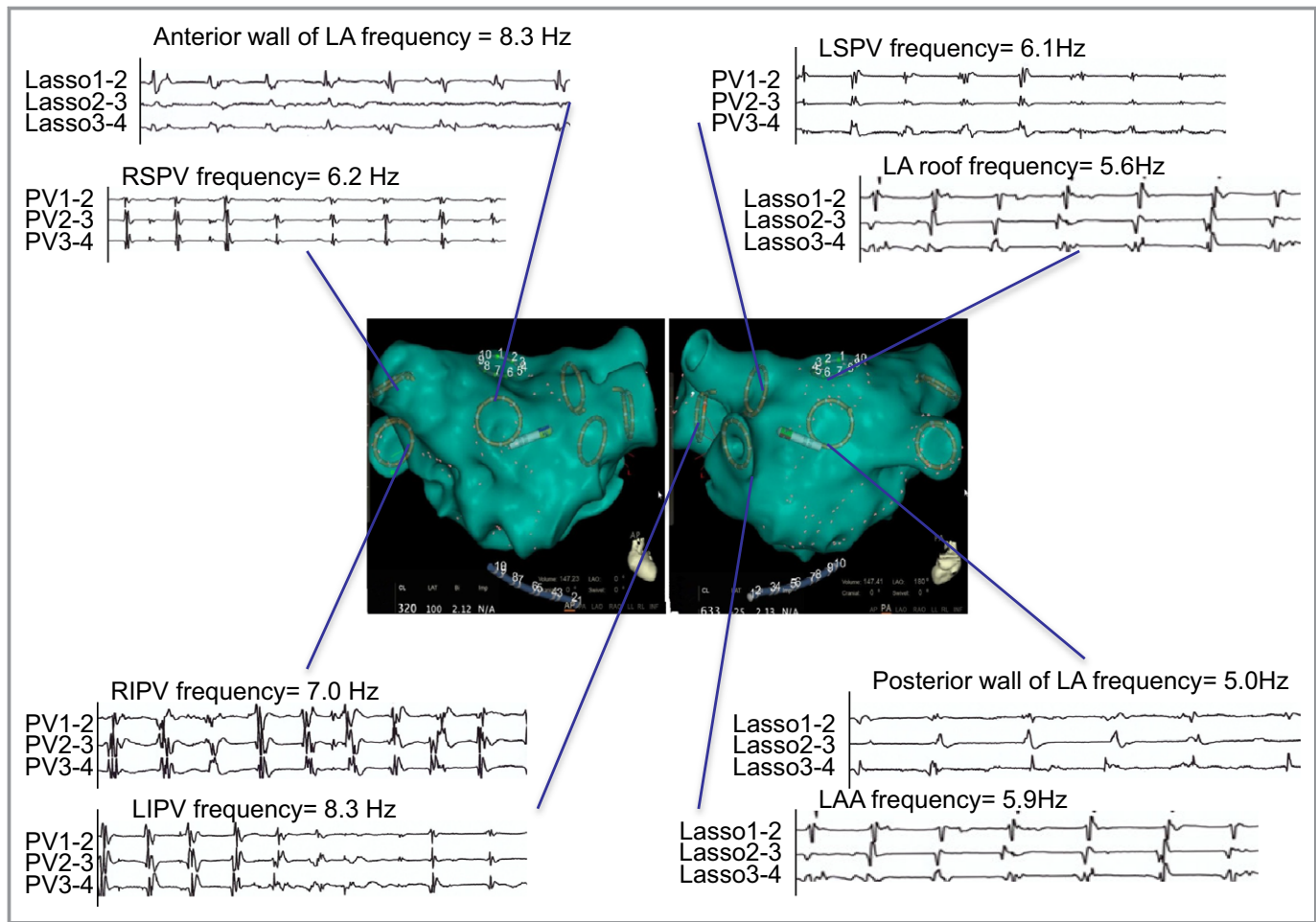
### AF Mapping

A Lasso or Lasso SAS mapping catheter was implemented to obtain bipolar electrograms from PV ostia, the left atrial appendage, the superior vena cava, the roof of left atrium, posterior and anterior parts of left atrium, as well as the crista terminal of the right atrium (Figures 1 and 2) before ablation.

AF activities that were proximal and distal to the CS were recorded with a decapolar catheter inside the CS. The circumferential catheter was sequentially positioned in the 4 PVs near the ostia. One-minute observations were chosen to measure the frequency. The time interval between successive PV signals was measured with electronic calipers at a sweep speed of 100 mm/s.<sup>9</sup> The shortest cycle length within a 1-minute window was recorded. Three 1-minute windows were chosen for each site in every other minute sequentially, and the shortest of 3 windows was considered for analysis. Then the cycle length was converted to frequency as Hz (according to  $\text{Hz}=1/\text{s}$ ). All the data were collected and analyzed by 2 cardiologists who were blinded to the clinical information.

### Catheter Ablation Procedures

All 122 consecutive patients received sequential stepwise ablation as previously described.<sup>25</sup> In brief, in all the patients, (1) PVI was performed using contiguous circumferential lesions guided by the Lasso catheter. The endpoint was abolition or dissociation of the electrical activity within the PVs. If AF remained, (2) ablation lines were created in the LA roof; (3) electrogram-guided ablation was then performed at LA sites involved in the complex electrogram features (complex rapid and fractionated electrograms), and the endpoint of ablation was the transformation of complex fractionated electrograms into discrete electrograms or the elimination of electrograms. (4) The ablation from the endocardium of the CS was performed with endpoint of the



**Figure 1.** Typical CARTO 3D map images and tracings from a patient with sequential stepwise ablation in anteroposterior (AP) and posteroanterior (PA) views. Lasso mapping was implemented to obtain bipolar electrograms from pulmonary vein (PV) ostia, left atrial appendage (LAA), the roof of left atrium, as well as posterior and anterior parts of left atrium. The models of left atria and PVs were created by Lasso catheter in AP (left) and PA (right) positions. LA indicates left atrium; LIPV, left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV.

elimination of electrograms or AF termination. (5) The additional linear LA ablation was performed if the AF transformed into atrial flutter (AFL) guided by excitation mapping. PVI and conduction across all the blocked linear lesions were checked after restoration of SR. If there existed sites with electrical conduction, additional radiofrequency to achieve PVI and complete linear conduction block was undertaken.

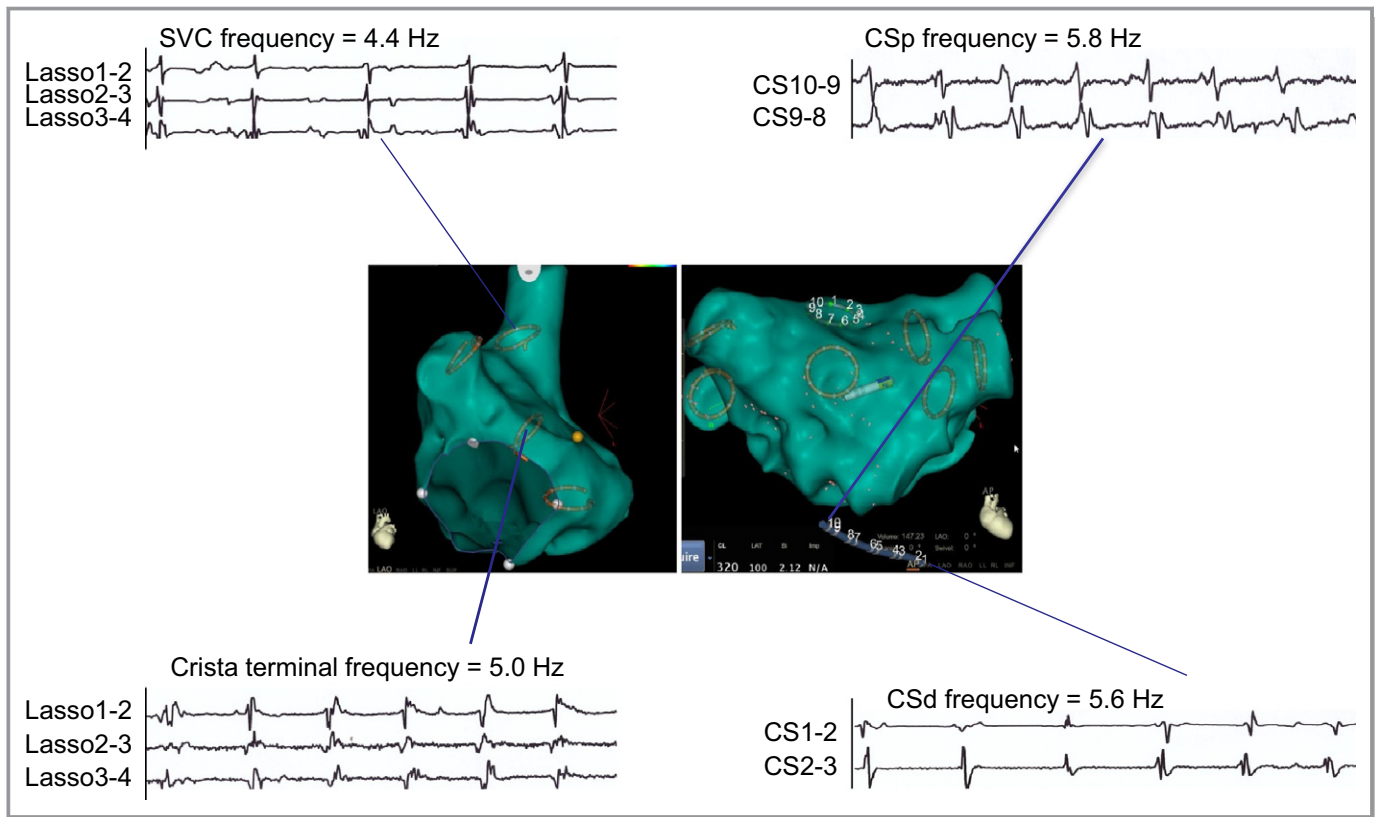
### Termination of AF

The procedural endpoint was termination of AF by catheter ablation either to sustaining AFL or directly to SR (AF termination group). If AF was converted into AFL, further ablation was performed aiming at termination to SR or to any noninductive atrial tachyarrhythmia. If termination was not achieved after the stepwise ablation, electric cardioversion

was performed to restore SR, and the patient was assigned to the AF nontermination group.

### Follow-Up

After ablation, all patients were monitored in hospital for up to 3 days without antiarrhythmic medication except amiodarone. After a 3-month blanking period of ablation, patients were reappraised at 3, 6, 9, and 12 months and every 6 months thereafter, up to 3 years. During the follow-up, questionnaires, 24-hour Holter monitoring, and 12-lead electrocardiographs were used to evaluate whether patients had symptoms and recurrences. The patients who underwent AF recurrence were initially given drug therapy, and additional ablation was performed if medical therapy failed. The repeated additional ablation was the same as the index procedure. A successful clinical outcome was defined as the



**Figure 2.** Typical CARTO 3D map images and tracings from a patient with stepwise ablation in left anterior oblique and anteroposterior (AP) views. Lasso mapping was implemented to obtain bipolar electrograms from the proximal and distal coronary sinus (CS), the superior vena cava (SVC), as well as the crista terminal of the right atrium. The models of right and left atria were created by a Lasso catheter in left anterior oblique 45° (left) and AP (right) positions. CSd and CSp respectively indicate distal and proximal coronary sinus.

absence of AF and a sustained atrial arrhythmia after the last ablation during the follow-up periods.

### Statistical Analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables as counts and percentages. Means were compared using Student t test or the Mann-Whitney test, and categorical values using a chi-squared test or the Fisher exact test. Spearman correlation was used to analyze whether there is a relationship between 2 variables. Diagnostic performance of predictors of AF termination was evaluated by receiver-operator characteristic analysis. The optimal cutpoint was chosen as the combination with the highest sensitivity and specificity. Univariate factors presenting a  $P < 0.1$  were analyzed using stepwise logistic regression to identify independent predictors of clinical success. Candidate covariates for adjustment were age, male sex, LA size, history of AF, hypertension, LV ejection fraction, and diabetes mellitus. Recurrence of AF postablation was analyzed by using the Kaplan-Meier method, and a log-rank test was applied to compare the differences between groups.

All tests were 2-tailed, and statistical significance was assumed for  $P < 0.05$ . Statistical analysis was performed using the software SPSS, 13.0 (IBM, Armonk, NY).

### Results

#### Baseline Patient Characteristics and Outcome of Ablation

A total of 122 patients were studied. The baseline demographic data were shown in Table 1. The average age of patients was  $56.1 \pm 10.3$  years, and 81% of patients were male. The average duration of AF detection was  $31.7 \pm 25.1$  months. Most of baseline characteristics between terminated and nonterminated were comparable. The average ablation times in both termination and nontermination groups were comparable,  $52.8 \pm 16.3$  minutes versus  $56.4 \pm 10.1$  minutes, respectively ( $P = 0.24$ ). AF was terminated in 12 patients (9.8%) by PVI alone. In the remaining 110 patients, 22 were terminated by stepwise ablation. As shown in Table 2, the ablation sites during the stepwise procedure were distributed over multiple regions of atria. All 13 patients with AFL were

**Table 1.** Characteristics of the Study Population

	Terminated		Nonterminated (88 pts)	P Value
	PVI Alone (12 pts)	Sequential (22 pts)		
Age, y	61.00±9.10	55.77±7.48	55.48±10.97	0.190
Male, %	75	77	83	0.707
History of AF, months	28.33±13.09	34.77±27.57	31.43±25.78	0.839
LVEF, %	63.17±3.07	63.23±3.85	64.45±4.84	0.220
LAD, mm	38.67±3.99	39.77±1.60	40.16±3.23	0.375
CHADS2 score	1.00±0.95	1.23±1.02	1.10±0.83	0.810
Hypertension, %	33	27	30	0.934
DM, %	8	9	11	0.919
Structural heart disease, %	17	9	19	0.526
No. of failed AAD	1.67±0.65	1.86±0.64	1.70±0.75	0.515
Amiodarone, %	17	36	34	0.450

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; CHADS2 score, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, previous Stroke, Vascular disease, Age 65 to 74 years, Sex category; DM, diabetes mellitus; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; pts, patients; PV, pulmonary vein; SR, sinus rhythm.

terminated according to the mechanism of AFL. The remainder (88 patients) required electric cardioversion.

### PV Frequency and AF Termination

The AF frequency in whole atria at baseline was mapped before PVI procedure by positioning catheters as illustrated in Figures 1 and 2. As shown in Table 3, AF frequencies at the left atrial appendage, the superior vena cava, the roof, posterior, and anterior of the left atria, and the crista terminal of the right atria, were comparable between the PVI-

terminated and PVI-nonterminated patients. However, the fastest electrical activity among PVs was higher in the terminated than in those not terminated by PVI alone ( $8.4\pm 1.0$  versus  $7.0\pm 0.9$ ,  $P<0.001$ ). In a receiver-operator characteristic analysis, a cutoff value of the PV activity ( $>8.3$  Hz) predicted AF termination with an area under the curve of 0.847 (95%CI 0.720-0.973;  $P<0.001$ ).

The fastest PV activity,  $>8.3$  Hz, predicted AF termination with 42% positive predictive value (sensitivity 67%, specificity 90%, negative predictive value 96%). Using stepwise logistic regression analysis revealed that the fastest electrical activity among PVs was an independent predictor of AF termination by the PVI alone, with an odds ratio (OR) of 0.187 (95%CI 0.070-0.499;  $P=0.001$ ).

**Table 2.** Ablation Performed During Sequential Ablation

Sequential Steps	Terminated (pts)	Nonterminated (pts)
Step 1: PVI	12	110
Step 2: Ablation lines of LA roof	1	109
Step 3: Ablation of fractionated electrograms		
Right superior pulmonary vein antrum	2	107
Interatrial septum	1	106
Step 4: Ablation of the CS	5	101
Step 5: Transform into AFL	13	88
Tricuspid isthmus ablation	6	
Mitral isthmus ablation	2	
LA roof ablation	3	
Interatrial septum ablation	2	
Electrical cardioversion	0	88

AFL indicates atrial flutter; CS, coronary sinus; LA, left atria; PVI, pulmonary vein isolation.

### CS Frequency and AF Termination

In those PVI nonterminated patients, the AF activities inside the CS were recorded with a 10-point catheter (Figure 3). The AF activities at distal (CSd) and proximal (CSp) CS were recorded from points 1 to 2 and 9 to 10 and compared between terminated and nonterminated patients with stepwise ablation. The signals at the middle were similar to the distal and proximal on the record. Compared to the nonterminated, the terminated had a significantly higher AF frequency in the CSp ( $10.2\pm 2.1$  Hz versus  $8.3\pm 1.8$  Hz,  $P<0.001$ ) (Table 3, Figure 4A). By use of a receiver-operator characteristic analysis of the fastest frequency in CSp, a cutoff value of  $>10.0$  Hz predicted AF termination with an area under the curve of 0.769 (95%CI 0.653-0.884;  $P<0.001$ ) (Figure 4B). A frequency  $>10.0$  Hz in CSp predicted AF

**Table 3.** Frequency (Hz) of Atrial Fibrillation

	Terminated		Nonterminated (88 pts)	P Value
	PVI Alone (12 pts)	Sequential (22 pts)		
Superior vena cava	3.95±0.38	4.16±0.93	4.43±1.14	0.293
Left atrial appendage	6.58±1.02	5.97±0.74	6.37±1.02	0.154
Posterior left atrium	4.39±0.67	4.59±1.04	4.68±0.96	0.530
Anterior left atrium	5.38±0.59	5.22±0.76	5.35±0.92	0.742
Roof of left atrial	5.55±1.25	5.73±0.69	6.01±1.28	0.387
Crista terminalis	4.36±0.54	4.82±1.22	4.41±0.87	0.426
LSPV	7.22±1.30	6.81±1.03	6.64±1.01	0.274
LIPV	6.98±0.98	6.73±0.86	6.41±0.93	0.069
RSPV	6.90±1.88	6.75±1.14	6.34±0.90	0.220
RIPV	6.33±1.26	6.11±1.00	5.87±0.86	0.309
PV <sub>max</sub>	8.44±1.01	7.27±0.98	6.94±0.88*	<0.001
CSp	9.12±1.95	10.23±2.13	8.25±1.83 <sup>†</sup>	<0.001
CSd	5.93±1.27	5.70±1.23	5.74±1.10	0.842
CSd/CSp	65.67±8.88	56.55±10.11	70.74±9.78 <sup>†</sup>	<0.001

CSd indicates distal coronary sinus; CSp, proximal coronary sinus; LIPV, left inferior PV; LSPV, left superior pulmonary vein; PV, pulmonary vein; PVI alone, pulmonary vein isolation alone; PV<sub>max</sub>, the fastest frequency among PVs; RIPV, right inferior PV; RSPV, right superior PV.

\**P*<0.05 vs PVI alone.

<sup>†</sup>*P*<0.05 vs sequential.

termination with 54% positive predictive value (sensitivity 64%, specificity 86%, negative predictive value 90%).

Moreover, the CSd/CSp ratio was lower in the termination group than in the nontermination group (57±10% versus 71±10%, *P*<0.001). A cutoff value <67% in the receiver-operator characteristic curve predicted AF termination with an area under the curve of 0.842 (95%CI 0.749-0.936; *P*<0.001) (Figure 4C and 4D). A CSd/CSp ratio <67% predicted AF termination with 53% positive predictive value (sensitivity 86%, specificity 67%, negative predictive value 95%).

Use of stepwise logistical regression analysis revealed that in these PVI-alone nonterminated patients, a CSd/CSp ratio <67% independently predicted AF termination after sequential stepwise ablation with OR of 1.131 (95%CI 1.053-1.214; *P*<0.001), and CSp >10 Hz had an OR of 0.817 (95%CI 0.578-1.156, *P*=0.253).

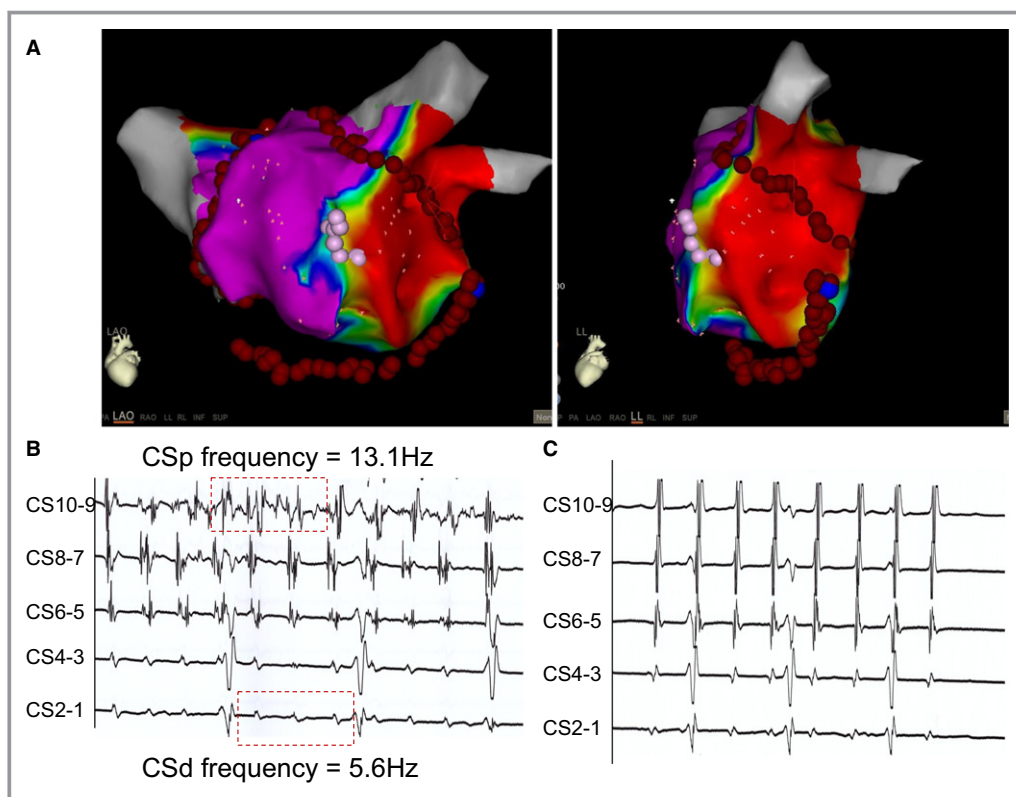
### The CSd/CSp Ratio and Recurrent AF

There were 48 of 110 (44%) patients who had CSd/CSp ratios <67%, and 62 (56%) patients had ratios ≥67%. In recurrent AF, there were 24 patients with PeAF, 10 with paroxysmal AF, and 14 with AFL. Compared to patients with CSd/CSp ratios <67%, those with ≥67% have more recurrence of AF (*P*=0.042) (Table 4). Within this group, 43 of 48 (90%) patients with recurrent AF underwent repeat procedures, and 6 patients

had a third procedure. The success ratio of the AF patients with CSd/CSp ratio <67% and the ratio ≥67% were 69% and 48%, respectively after the index procedure (*P*=0.032). After a mean of 1.4±0.6 procedures per patient and a mean follow-up of 46±18, compared with the group of patients with the ratio ≥67%, SR was maintained in 43 of 48 (90%) patients after the last procedure without antiarrhythmic drugs (90% versus 74%, *P*=0.042), (Table 5). As shown in Figure 5, survival analysis showed that the patients with CSd/CSp ratios <67% had a better long-term outcome than those with the CSd/CSp ratio ≥67% during follow-up of 46±18 months (*P*=0.0375).

### Clinical Predictors of Long-Term Outcomes

With the follow-up of 46±18 (median, 48 months; interquartile range, 30-60 months) months and 1.4±0.6 procedures per patients, SR was maintained in 100 of 122 (82%) patients after the last procedure without antiarrhythmic drugs. Patients free of AF were more likely to have a higher CSp (8.8±2.1 versus 8.04±1.7, *P*=0.097) and significant lower CSd/CSp ratio (67%±11% versus 73%±8%, *P*=0.01), and similar frequency at CSd (5.7±1.1 versus 5.9±1.3, *P*=0.372). As shown in Table 6, there were no significant differences in other characteristics, including age, sex, history of AF, LV ejection fraction, LAD, CHADS2 score, hypertension, diabetes mellitus, structural heart disease, antiarrhythmic drugs,



**Figure 3.** A, The models of the coronary sinus (CS) and left atrium were created by Lasso catheters in the left anterior oblique 45° (left) and left lateral positions. B, The difference of electrical activity within the CS. C, Persistent atrial fibrillation converts to SR after CS potential was ablated. CSp indicates proximal CS; LA, left atrium; SR, sinus rhythm.

amiodarone, ablation duration, procedure steps, and operators between free of AF groups and those with recurrent arrhythmias. In stepwise logistic regression analysis on CSp and CSd/CSp ratio with  $P$  value less than 0.1, CSd/CSp ratio <67% (OR 1.077, 95%CI, 1.013-1.144;  $P=0.017$ ) independently predicted long-term outcomes. And CSp >10 Hz had an OR of 1.021, 95%CI 0.753 to 1.385 ( $P=0.894$ ).

## Discussion

### Main Findings

The major findings are as follows: (1) the CSd/CSp ratio might be an independent predictor of termination rate and long-term success rate of catheter ablation in PeAF; (2) a cutoff of 67% in the CSd/CSp ratio might be helpful to identify a subset of PeAF that is likely prone to terminate with sequential stepwise ablation with CS ablation.

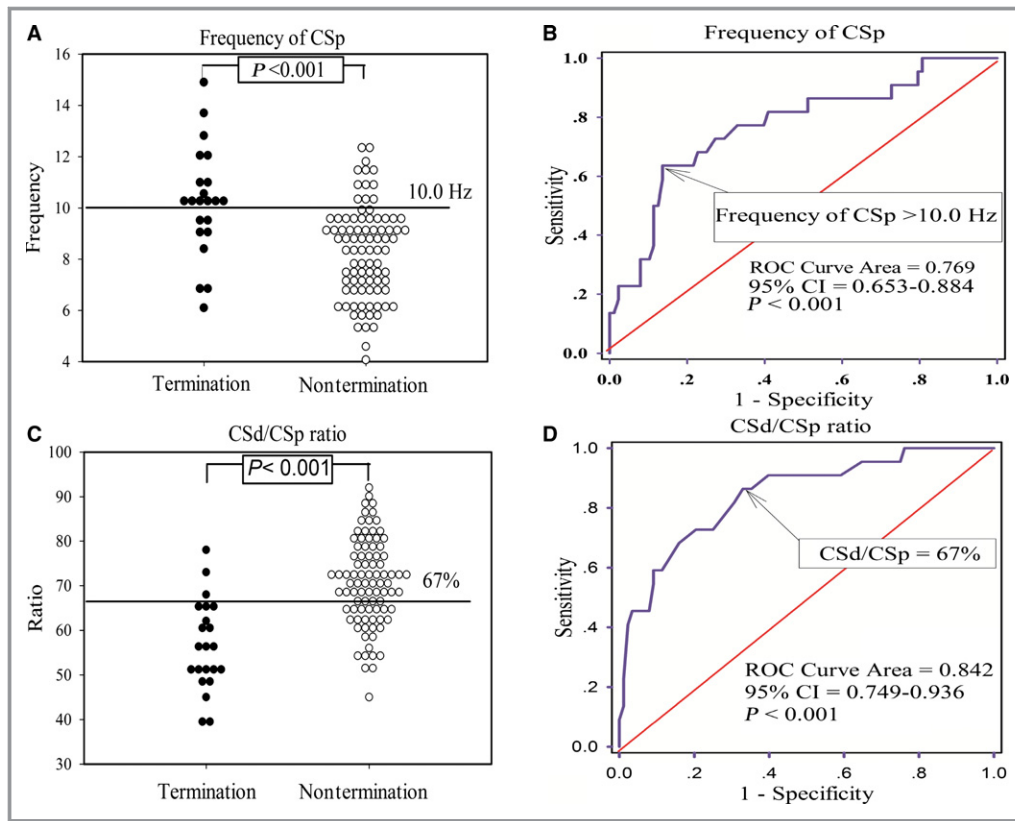
### PV Activity in PeAF

Similar to most recently published results,<sup>9</sup> the present study showed that rapid PV activity might predict the termination of

AF by PVI. Previous reports demonstrated that except in paroxysmal AF, triggers originating in PVs also have critical roles in recurrence of PeAF after catheter ablation. If the triggers were carefully inspected prior to the ablation, a large proportion of them were found to be located in the PVs among patients with PeAF.<sup>4,12,13</sup> Moreover, Verma et al demonstrated that PVI alone can improve the outcome, and about 59% of patients were free from recurrent AF at the end of follow-up,<sup>26</sup> which suggested that pulmonary vein activities play an important role in a certain subset of AF. Therefore, most recently, Pascale et al indicated that the cycle length (CL) gradient between PVs and the LA might identify the subset of patients in whom persistent AF was likely to terminate after PV isolation, which limited substrate ablation to achieve better long-term outcomes.

### High-Frequency Activities at Proximal CS Related to AF Termination

The present study also shows that high AF frequency in CS might play an important role in the subset of PeAF that were not terminated by PVI. In our present study, the highest frequency of AF was used to help distinguish the local



**Figure 4.** Scatterplot showing the (A) frequency in the proximal coronary sinus (CSp) and (C) the distal coronary sinus (CSd) ratio (CSd/CSp ratio) before catheter ablation, Horizontal line indicates optimal diagnostic cutoff value to predict termination of atrial fibrillation. Receiver-operator characteristics (ROC) curve analysis with (B) frequency in the CSp and (D) the ratio of the frequency of CSd/CSp. Arrows shows optimal cutoff point for sensitivity and specificity. CS indicates coronary sinus; PV indicates pulmonary vein.

activation from distant potentials. As previous studies have shown, 2 components could be recorded in CS, in which a high-frequency, higher-amplitude component represents a near-field potential arising from the myocardial cuff of the CS, and a low-frequency, lower-amplitude component represents a far-field potential from the activation of the adjacent LA myocardium.<sup>27-29</sup> The 3-minute sampling in our present study was enough to represent the local activities of AF. The

patterns of AF were more uniform at multiple recording locations than paroxysmal AF, in which temporal variability of AF electrograms assessed by sequential 5-second time segments of 5-minute continuous recordings lacked significant differences in the morphologic and repetitiveness metrics.<sup>30-32</sup> The present study showed that AF activities at CSp showed a close relationship with AF termination, which has been described in a symptomatic drug-refractory AF case by Haïssaguerre’s group in 2004.<sup>33</sup> Further study by catheter

**Table 4.** Comparing the Types of Recurrent Arrhythmia Between Patients With CSd/CSp Ratio <67% and ≥67% After Index Procedure

Type of Recurrent Arrhythmia After the Index Procedure	CSd/CSp Ratio <66.5% Group (n=15)	CSd/CSp Ratio ≥66.5% Group (n=32)	P Value
PeAF, n	8	15	0.680
PaAF, n	6	4	0.078
Atrial flutter, n	1	13	0.042

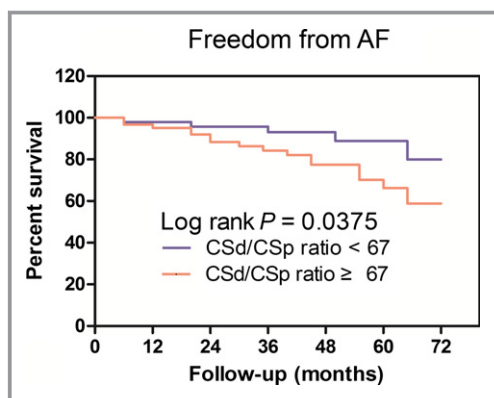
CSd indicates distal coronary sinus; CSp, proximal CS; AF, atrial fibrillation; PaAF, paroxysmal AF; PeAF, persistent AF.

**Table 5.** The Success Ratios Compared Between Patients With CSd/CSp Ratio <67% and ≥67% After the Index, Second, and Multiple Procedures

Procedures	CSd/CSp Ratio <67% Group	CSd/CSp Ratio ≥67% Group	P Value
The index procedure	69	48	0.032
The second operation	53.3	50	0.831
Multiple procedures	89.6	74.2	0.042

CSd indicates distal coronary sinus; CSp, proximal coronary sinus.





**Figure 5.** Kaplan-Meier survival curves plotted to assess clinical outcomes of ablation for persistent atrial fibrillation according to distal frequency/proximal frequency cutoff values. CSd indicates distal coronary sinus; CSp, proximal coronary sinus.

ablation targeting the CS region significantly prolongs fibrillatory cycle length and terminates AF persisting after PV isolation in 35% of patients.<sup>18</sup> However, the anatomy of the CS and its activity are complicated and divergent. Therefore, a

**Table 6.** Univariate Factor Regression Analysis Clinical Predictors

Predictors	Sinus Rhythm	Recurrence	P Value
Age, y	55.53±10.2	58.55±10.48	0.305
Male, %	81.0	81.8	1
History of AF, months	31.8±25.1	31.4±25.5	0.907
LVEF, %	64.2±4.5	63.9±4.6	0.823
LAD, mm	39.9±3.2	40.2±2.9	0.691
CHADS2 score	1.1±0.8	1.2±0.9	0.598
Hypertension, %	30	27.3	1
DM, %	10	13.6	1
Structural heart disease, %	17.0	18.2	1
No. of failed AADs	1.7±0.7	1.8±0.7	0.51
Amiodarone, %	32.0	36.4	1
CSp	8.8±2.1	8.04±1.70	0.097
CSd	5.7±1.1	5.9±1.3	0.372
CSd/CSp	66.3±11.3	73.9±7.4	0.003
PV <sub>max</sub>	7.1±1.0	6.9±0.8	0.313
Ablation duration	55.6±12.5	54.6±13.2	0.758
Procedure steps	4.3±1.3	4.6±1.0	0.118
Operators	1.8±0.8	1.7±0.6	0.715

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation; CSd, distal coronary sinus; CSp, proximal coronary sinus; DM, diabetes mellitus; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PV, pulmonary vein; PV<sub>max</sub>, the fastest frequency among PVs.

repeatable and reliable parameter is needed as a predictor in PeAF ablation.

### The Ratio of CSd/CSp Frequency in PeAF

The present study showed that the frequency gradients between CSd and CSp were most likely correlated to the outcome of AF after stepwise ablation. Previous studies showed that rapid electrical activity within the CS region was related to the initiation and contribution of AF in 35% of the patients in whom AF continued after PVI. Oral et al demonstrated that in a small population with AF ablation, electrical disconnection of the CS from the LA lowered the inducibility of AF after PVI. Further study on a canine AF model also confirmed that isolating the CS from the atria eliminated AF induction.<sup>21</sup> Our present study shows that an increased gradient between CSd and CSp, as in the CSd/CSp ratio, might be an independent predictor for AF termination and long-term outcome. In the present study, by using a cutoff of 67%, low CSd/CSp ratio, was correlated with long-term AF-free survival rate, and less incidence of recurrence of PeAF and AFL after catheter ablation.

However, compared to patients with the CSd/CSp ratio <67%, those with ratios ≥67% have more recurrence of AFL. We may infer that the patients with the ratio <67% will benefit from ablation at the endocardium of CS with long-term freedom from AF. Verma et al<sup>28</sup> demonstrated additional ablations after PVI, such as either linear ablation or ablation of complex fractionated electrograms, did not change the success rate but increased the AFL. Therefore, our present study agreed that a patient-tailored ablation strategy, for example for those with CSd/CSp ratio <67%, might be more efficient and have better long-term benefit.

### Potential Mechanisms of CS Frequency in PeAF

Similar to the PV, CS is complex in structure and electrophysiological character and contains a muscular sleeve.<sup>34,35</sup> The CS musculature provides a connection between right and left atria as well as a part of the interatrial electrical connection.<sup>36</sup> In certain AF patients, rapid repetitive activity in the musculature of the CS may contribute to maintenance of the arrhythmia.<sup>37</sup> Through a canine AF model, Morita et al demonstrated that musculature of the coronary sleeve contributes to unstable reentry and is a source of recurrent AF after PVI, and isolation of the CS musculature from the atria can terminate AF. Therefore, Oral et al<sup>16</sup> put forward the hypothesis that the CS may play a role of the “fifth pulmonary vein.” The characteristics of CS, such as slow conduction and conduction block, promote reentrant tachycardia, and the reentrant circuit is one of the most important mechanisms of AF.

## Study Limitations

There were several limitations to the present study. First, the present results were obtained only in a subset of patients with PeAF. It is unclear whether these findings can be extrapolated to patients with paroxysmal AF. Also, the study retrospectively reviewed cases between March 2009 and July 2012. In the present study, 2 patients with persistent AF within 7 days were converted with electrical cardioversion, but the patients were back to AF 1 day after conversion. Therefore, those 2 cases in the study were defined as PeAF, which does not fit the definition of AF as updated in 2014, in which AF terminated by intervention within 7 days has been changed to paroxysmal AF.<sup>22,23,38</sup> Second, although the association between rapid PV and CS activity and outcome of AF catheter ablation was demonstrated in the present study, further study is needed to investigate the exact role of CS and PVI activity as a predictor to stratify patients for ablation strategy, including ablation at the right atrium or within the CS. Third, in our follow-up protocol, there was limited postablation monitoring postprocedure, which could have missed episodes of AF. Moreover, underlying mechanisms, such as anatomic barriers, neural ganglia distribution, or functional dysfunction, remain to be determined.

## Conclusions

Rapid repetitive activities in the proximal CS may contribute to a subset of cases of AF onset after PVI. A cutoff, 67%, of the CSd/CSp frequency ratio might be an indicator to stratify the subset of patients who might benefit from CS ablation.

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## Disclosures

None.

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