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Vagal Modification Can Also Help Prevent Late Recurrence of Atrial Fibrillation After Segmental Pulmonary Vein Isolation

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Background: The relationship between vagal modification and paroxysmal atrial fibrillation (PAF) recurrence after segmental pulmonary vein (PV) isolation (S-PVI) was investigated.
Methods and Results: S-PVI was performed in 77 PAF patients using a multielectrode basket or circular catheter to achieve electrical disconnection of all 4 PVs independent of eliminating vagal reflexes. Serial Holter-recordings were obtained at baseline, immediately and 1, 3, 6, and 12 months after S-PVI to analyze the heart rate variability. Fifty-one patients were free from symptomatic PAF (Group A) and 26 had late PAF recurrences (Group B) at 12-month follow-up. Immediately after S-PVI, the root mean square of the successive differences (rMSSD) and high-frequency (HF) power, which reflected parasympathetic nervous activity, were significantly lower in Group A than in Group B (rMSSD: 33.6±26.0 vs 60.6±23.2 ms, $P<0.05$; ln HF: 8.73±0.84 vs 9.31±0.95 ms^2, $P<0.05$). There were no significant differences in the average heart rate or ratio of the low-frequency to HF powers between the 2 groups. By multivariate analysis, only the HF immediately after S-PVI was an independent predictor of PAF recurrence (hazard ratio 1.707, 95% confidence interval 1.057–2.756, $P<0.05$).
Conclusions: Vagal modification after S-PVI could also help prevent late recurrence of PAF. (*Circ J* 2009; **73:** 632–638)

Key Words: Atrial fibrillation; Autonomic nervous system; Heart rate variability; Radiofrequency catheter ablation

Segmental catheter ablation (SCA) of the pulmonary veins (PVs) is an effective technique for curing paroxysmal atrial fibrillation (PAF).[1–4] It has been reported that adding an ablation aimed at vagal denervation that is adequate for eliminating the vagal reflexes[5] or targeting ganglionated plexi in the left atrium (LA)[6] may reduce atrial fibrillation (AF) recurrence. Those reports suggest that modification of autonomic nervous function may prevent PAF recurrence. SCA alone has induced an immediate decrease in the autonomic nervous function,[7] but the relationship between modification of autonomic nervous function and PAF recurrence after SCA remains unknown. This study was undertaken to reveal that relationship by analyzing heart rate variability (HRV).

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Methods

Patient Characteristics

The study population consisted of 97 patients (74 men, 58±12 years) with symptomatic PAF refractory to 2±1 class I or class III antiarrhythmic drugs (not including amiodarone). The mean PAF history was 4±4 years (0–17). The mean echocardiographic dimension of the LA was 35±5 mm (25–46) and mean left ventricular ejection fraction 68±9% (50–89%). Three patients had a history of an old myocardial infarction (MI) and 3 had had prior embolic episodes. The exclusion criteria were sick sinus syndrome, diabetes mellitus, thyroid dysfunction, recent MI (<6 months), history of a prior thoracotomy, β-blocker therapy, and a pacing rhythm. Each patient gave written informed consent, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the study.

Electrophysiologic Study

A 7-French decapolar catheter with 1-5-1-mm interelectrode spacing between each electrode pair (St Jude Medical, AF Division, Minnetonka, MN, USA) was placed in the coronary sinus via the subclavian vein. The transseptal procedure was performed with intracardiac echocardiography guidance recorded with a 9-French transducer catheter (Boston Scientific, Natick, MA, USA) operating at 9 MHz. Catheterization into the LA was performed with a 1-puncture and 2-sheath technique (1 sheath (8-French, St Jude Medical, AF Division) for an ablation catheter and another (8.5-French, Soft Tip EP Sheath™, EP Technologies, Boston Scientific Corporation/San Jose, CA, USA) for a mapping catheter). After the transseptal procedure, sys-

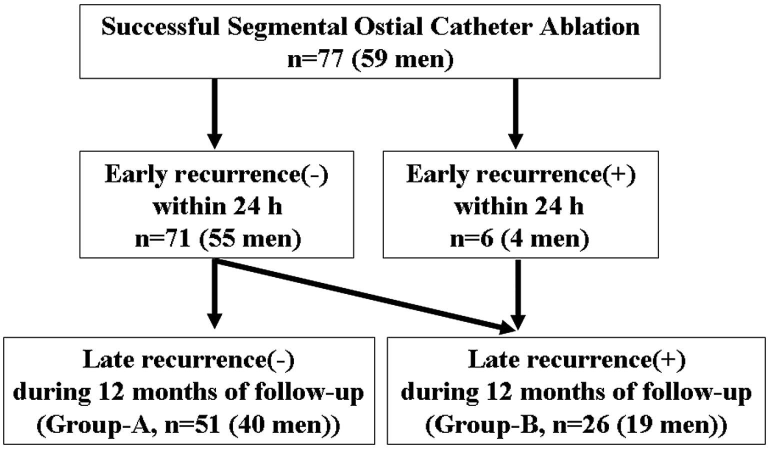

Figure 1. Clinical outcome after segmental ostial catheter ablation in the 77 patients with paroxysmal atrial fibrillation.

Table 1. Clinical Characteristics of the 2 Groups

	Late recurrence		P value
	No Group A (n=51)	Yes Group B (n=26)	
Age, years	58±12	60±11	0.52
Sex, M/F	40/11	19/7	0.60
Duration of PAF, years	4±4	3±3	0.64
Ineffective AADs, n	2±1	2±1	0.42
SHD, n	2	1	0.99
LAd, mm	34±4	35±5	0.49
LVEF, %	68±8	67±10	0.62

PAF, paroxysmal atrial fibrillation; AAD, antiarrhythmic drug; SHD, structural heart disease; LAd, left atrial dimension; LVEF, left ventricular ejection fraction.

Table 2. Comparison of HR and HRV Before Ablation in the 2 Groups

	Late recurrence		P value
	No Group A	Yes Group B	
Minimum HR, beats/min	46.0±6.9	48.3±7.6	0.32
Average HR, beats/min	67.2±11.9	69.3±8.1	0.55
Maximum HR, beats/min	118.9±21.7	115.3±21.0	0.61
PACs, %	3.2±4.1	3.4±3.4	0.83
ASDNN, ms	61.6±14.2	63.6±30.2	0.76
SDANN, ms	126.6±29.2	119.9±50.8	0.58
SDNN, ms	152.0±32.7	150.8±72.3	0.94
rMSSD, ms	59.0±26.7	59.2±41.1	0.99
ln LF, ms^2	8.99±0.52	8.79±0.42	0.21
ln HF, ms^2	9.36±0.56	9.06±0.51	0.10
LF/HF	0.72±0.23	0.78±0.19	0.42

HR, heart rate; HRV, HR variability; PAC, premature atrial contraction; ASDNN, mean of the standard deviation of all NN intervals for all 5-min segments; SDANN, standard deviation of the average of the NN intervals in all 5-min segments; SDNN, standard deviation of all NN intervals; rMSSD, root mean square successive differences; ln, natural logarithm; LF, low-frequency power; HF, high-frequency power; LF/HF, ratio of LF to HF.

temic anticoagulation was achieved with intravenous heparin to maintain an activated clotting time >250 s. Selective angiography of the PVs was performed in all patients.

PV Mapping With Multielectrode Basket Catheter (MBC)

In all cases, PV mapping and SCA were performed by the same technique as we previously reported.[7] All 4 PVs were targeted for this SCA technique according to the evidence reported in previous studies.[8,9] When the right inferior PV was difficult to cannulate with a MBC, it was isolated with a circular catheter as previously reported.[1] A 31-mm MBC (Constellation™, EP Technologies, Boston Scientific Corporation), which comprised 8 splines (A–H) with 8 1-mm electrodes with 2-mm spacing, was deployed within the target PV coaxially to its long axis and with its most proximal electrodes positioned at the LA–PV junction. PV mapping was performed using a computerized 3-dimensional (D) mapping system (QMS2™) with MBC. QMS recordings were obtained during sinus rhythm (right PVs) or distal coronary sinus pacing (left PVs). In the analysis of the QMS2™ recordings, an animation of the 3-D potential map was used to reveal the electrical connections between the LA and PVs. The onset of a centrifugal activation toward the distal PVs observed at the LA–PV junction was identified as a prior electrical connection.

SCA

SCA was performed at the LA–PV junction, targeting the preferential electrical connection identified by the QMS mapping. Radiofrequency (RF) energy was delivered with a target temperature of 55°C and maximum power output of 40 W for 60 s (EPT-1000TC generator, EP Technologies, Boston Scientific Corporation), using an 8-mm tip catheter (Blazer II 5770T, EP Technologies, Boston Scientific Corporation) with the guidance of a navigation system (Astronomer™; EP Technologies, Boston Scientific Corporation) associated with the MBC. Successful SCA was defined as either the abolition or dissociation of the distal PV potentials independent of the elimination of vagal reflexes. After successful SCA, induction of spontaneous AF was attempted with burst atrial pacing and an isoproterenol infusion. When spontaneous AF remained inducible, isolation of the superior vena cava (SVC) for the SVC triggers, or focal ablation targeting the other triggers, was performed as we previously reported.[10,11] Those procedures were repeated until non-inducibility of spontaneous AF was confirmed.

Analysis of HRV

Serial 24-h Holter recordings were obtained at baseline, immediately after and at 1, 3, 6, and 12 months after SCA to analyze the HRV. After an automatic analysis, the data file was visually reviewed and edited by an experienced technician. The heart rate (HR) and time- and frequency-domain

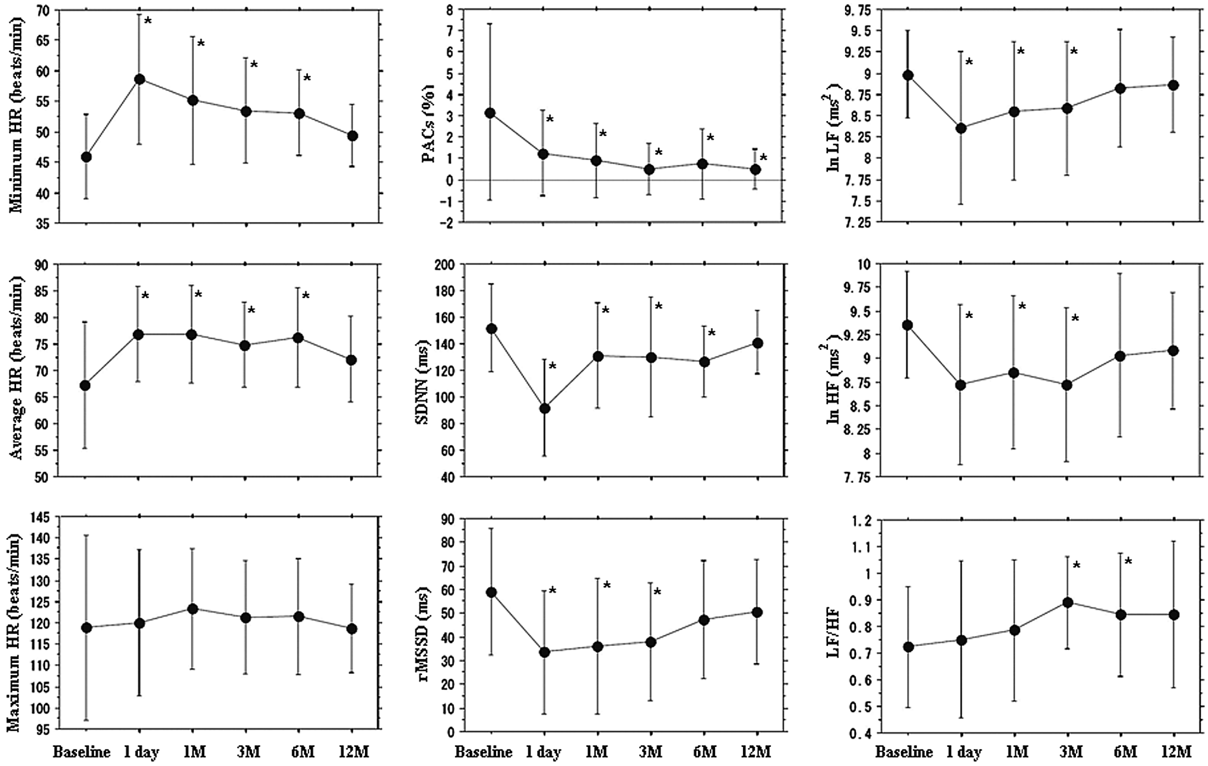

Figure 2. Serial changes in heart rate (HR), percentages of premature atrial contractions (PACs), and heart variability before, immediately (1 day), 1 month (1M), 3 months (3M), 6 months (6M), and 12 months (12M) after segmental ostial catheter ablation (SCA) in Group A patients. *P<0.05 vs before ablation. LF, low-frequency; HF, high-frequency; LF/HF, ratio of the LF to HF powers; rMSSD, root mean square of the successive differences; SDNN, standard deviation of all NN intervals.

HRV were analyzed from the Holter recordings using an analysis program (Philips Zymed Holter 2010 Plus). Supraventricular premature beats, AF, ventricular premature beats, electrical noise, and other aberrant ECG signals were excluded from the HRV analysis. The underlying rhythm was carefully analyzed, and only artifact-free episodes of sinus rhythm were included in further analyses. HRV was used as an indicator of autonomic activity in accordance with the guidelines for standardization.[12] The time-domain measures of the HRV included the standard deviation (SD) of all NN intervals (SDNN), SD of the averages of the NN intervals in all 5-min segments (SDANN), mean of the SD of all NN intervals for all 5-min segments (ASDNN), and root mean square successive differences (rMSSD). The frequency-domain measures of the HRV included the low-frequency (LF: 0.04–0.15 Hz) power, high-frequency (HF: 0.15–0.40 Hz) power, and ratio of the LF to HF powers (LF/HF). The frequency-domain HRV was calculated by a fast Fourier transform for each 5-min segment of data. All values of the frequency-domain HRV were expressed as the average of all 5-min segments of the 24-h recordings and were logarithmically transformed to avoid the undue influence of extreme values. The rMSSD and HF were used to reflect parasympathetic nervous activity, and the LF/HF was used to reflect sympathetic nervous activity.

Follow-up

During the follow-up period, none of the patients was administered antiarrhythmic drugs. Clinical follow up was performed at 2 weeks, 1 month and every month until 12 months after the procedure, using 24-h Holter and cardiac recordings. All patients who reported symptoms were given an event monitor to document the cause of the symptoms. Enhanced electron beam tomography was performed in all the patients at 3 and 6 months after the procedure for the detection of PV stenosis.

Statistical Analysis

All values are expressed as the mean ± SD. The frequency-domain measurements of the HRV (LF and HF) were expressed in squared milliseconds. Comparisons of continuous variables were analyzed using the Student's t-test. Categorical variables expressed as numbers and percentages in different groups were compared with a chi-square test. Multivariate Cox regression analysis was performed to determine the independent predictors of AF recurrence. Statistical significance was considered to be present for P<0.05.

Results

Catheter Ablation

In all the study patients, successful SCA of all 4 PVs was achieved. In 34 right inferior PVs in which QMS mapping was not available, successful SCA was achieved with a circular catheter. In 20 patients, spontaneous AF was induced after successful SCA and additional SVC isolation and/or focal ablation targeting the triggers was performed. All 20 cases were excluded from the analysis because any additional ablation might have affected autonomic nervous function. The average total procedure and fluoroscopy times was 209±51 min and 87±22 min, respectively. The

Table 3. Comparison of the Changes in HR and HRV Before and After Ablation in Group A

	Baseline	1 day	1 month	3 months	6 months	12 months
Minimum HR, beats/min	46.0±6.9	58.6±10.7*	55.2±10.5*	53.5±8.6*	53.1±7.0*	49.3±5.1
Average HR, beats/min	67.2±11.9	76.9±8.9*	76.9±9.2*	74.9±7.9*	76.2±9.4*	72.1±8.1
Maximum HR, beats/min	118.9±21.7	120.0±17.1	123.3±14.1	121.3±13.3	121.5±13.7	118.7±10.5
PACs, %	3.2±4.1	1.2±2.0*	0.9±1.7*	0.5±1.2*	0.7±1.7*	0.5±0.9*
ASDNN, ms	61.6±14.2	37.2±20.0*	50.3±30.0	45.4±26.4*	44.0±15.5*	48.3±12.3*
SDANN, ms	126.6±29.2	79.1±29.1*	107.3±27.0*	113.7±38.6	111.0±24.4*	128.9±21.7
SDNN, ms	152.0±32.7	92.0±36.0*	131.0±39.6*	130.0±45.4*	126.8±26.7*	140.9±23.7
rMSSD, ms	59.0±26.7	33.6±26.0*	36.0±28.6*	37.9±24.8*	47.4±24.9	50.7±22.0
ln LF, ms^2	8.99±0.52	8.36±0.90*	8.56±0.82*	8.59±0.79*	8.82±0.69	8.87±0.56
ln HF, ms^2	9.36±0.56	8.73±0.84*	8.85±0.80*	8.72±0.81*	9.03±0.87	9.08±0.61
LF/HF	0.72±0.23	0.75±0.29	0.79±0.27	0.89±0.17*	0.84±0.23*	0.84±0.28

*P<0.05 vs before ablation.
Abbreviations as in Table 2.

average total RF duration needed to complete the SCA was 70±23 min for 66±18 RF applications. During SCA of the left PVs, transient AV block was elicited in 3 patients. During SCA of the right PVs, sinus bradycardia with hypotension was elicited in 2 patients.

Clinical Outcomes

Six patients had early PAF recurrence within 24 h of SCA and all of them also had late PAF recurrences. Of the 77 patients, 51 were free from symptomatic PAF without any antiarrhythmic drugs (Group A) and 26 had a late PAF recurrence (Group B) at 12 months follow-up (**Figure 1**). There were no significant differences between the 2 groups in their clinical characteristics and HRV parameters before the ablation (**Tables 1,2**). There were no significant differences between the 2 groups in the total number of RF applications (66±16 vs 67±21, P=0.85), total RF energy delivery (68,127±26,054 vs 69,864±32,541 J, P=0.82) or extent of the targeted regions (69±13 vs 70±11% of the circumference, P=0.71).

HR and HRV Changes

In Group A, the minimum and average HR increased immediately after SCA and remained elevated for 6 months. The time- and frequency-domain HRV parameters, including the SDNN, rMSSD and HF, decreased immediately after SCA and remained attenuated for 3–6 months. The LF/HF did not change significantly immediately after SCA, but increased 3 months later. The percentage of premature atrial contractions (PACs) out of the total beats in the Holter recordings had an acute reduction immediately after SCA and a subsequent gradual decrease throughout the entire observation period (**Figure 2**, **Table 3**). In Group B, the minimum and average HR also increased immediately after the SCA, but all the time- and frequency-domain HRV parameters, excepting the SDANN and SDNN, did not change significantly (**Tables 2,4**). Because 21 of 26 (76.9%) Group B patients underwent another ablation procedure (n=18) and/or took antiarrhythmic drugs or β-blockers (n=10) because of PAF recurrence, subsequent Holter recordings after those interventions were excluded from the HRV analyses of those patients.

Comparisons of the HR and HRV in the 2 groups immediately after SCA are shown in **Table 4**. The rMSSD and HF, which reflect parasympathetic nervous activity, were significantly lower in Group A than in Group B (rMSSD: 33.6±26.0 vs 60.6±23.2 ms, P<0.05; ln HF: 8.73±0.84 vs

Table 4. Comparison of HR and HRV Immediately After SCA

	Late recurrence		P value
	No Group A (n=51)	Yes Group B (n=26)	
Minimum HR, beats/min	58.6±10.7	55.8±7.4	0.25
Average HR, beats/min	76.9±8.9	78.7±8.1	0.40
Maximum HR, beats/min	120.0±17.1	123.2±17.7	0.46
PACs, %	1.2±2.0	2.5±3.2	0.049
ASDNN, ms	37.2±20.0	50.1±26.1	0.02
SDANN, ms	79.1±29.1	83.0±21.8	0.56
SDNN, ms	92.0±36.0	111.2±39.2	0.046
rMSSD, ms	33.6±26.0	60.6±23.2	0.0001
ln LF, ms^2	8.36±0.90	8.68±0.95	0.16
ln HF, ms^2	8.73±0.84	9.31±0.95	0.009
LF/HF	0.75±0.29	0.63±0.23	0.09

Abbreviations as in Table 2.

Table 5. Results of Cox Regression Analysis in 77 PAF Patients

Covariates	Coefficient	P value	Hazard ratio	95%CI
Age, years	–0.019	0.38	0.981	0.940–1.024
Sex (1/0=M/F)	0.067	0.91	1.069	0.358–3.194
Duration of PAF	–0.009	0.89	0.991	0.877–1.120
SHD (0/1=no/yes)	–1.188	0.29	0.305	0.034–2.741
LAD	0.041	0.45	1.042	0.936–1.159
LVEF	–0.015	0.65	0.985	0.925–1.050
Average HR	0.017	0.59	1.017	0.956–1.082
ln HF	0.535	0.03	1.707	1.057–2.756
LF/HF	–1.536	0.13	0.215	0.029–1.587
No. of RF lesions	0.010	0.45	1.010	0.984–1.037

CI, confidence interval; RF, radiofrequency. Other abbreviations as in Tables 1,2.

$9.31\pm0.95\,ms^2$, $P<0.05$). The percentage of PACs out of the total beats in the Holter recordings was significantly lower in Group A than in Group B (PACs: 1.2 ± 2.0 vs $2.5\pm3.2\%$, $P<0.05$). There was a significant correlation between the HF and percentage of PACs immediately after SCA ($r=0.525$, $P<0.0001$). There were no significant differences between the 2 groups in the minimum, average or maximum HR and LF/HF.

Repeat Procedures

In total, 18 (69%) of 26 Group B patients underwent a second procedure, and 17 (94%) of them exhibited the recovery of the electrical connections between the LA and PVs in 11 left superior PVs, 12 right superior PVs, 11 left inferior PVs, and 6 right inferior PVs. In all of those PVs, a successful electrical disconnection could be achieved by the same technique used in the first procedure.

Predictors of AF Recurrence

After 12 months of follow-up since the first SCA procedure, 66% of the patients were free from symptomatic AF. By multivariate Cox regression analysis, only the HF immediately after SCA was an independent predictor of PAF recurrence (**Table 5**).

Discussion

Major Findings

Vagal modification varied among the patients after SCA, the end point of which was PV electrical disconnection independent of whether or not the vagal reflexes were completely eliminated. Parasympathetic nervous activity after SCA was significantly lower in the patients without PAF recurrence than in the patients with PAF recurrence, and that remained attenuated for 3–6 months in the patients without PAF recurrence. Most of time-domain HRV parameters (ASDNN, SDNN, and rMSSD) after SCA tended to be lower in the patients without PAF recurrence than in the patients with PAF recurrence. This study demonstrated that further vagal modification and HRV attenuation after SCA resulted in greater suppression of PAF recurrence. The study results also suggest that the HF alone could be a valid predictor of PAF recurrence after SCA.

Parasympathetic Attenuation and AF Recurrence After SCA

An anatomical study has recently demonstrated that the adrenergic and cholinergic nerve densities are highest in the LA within 5 mm of the LA–PV junction and are not homogeneous around the PV ostium, independent of the distribution of the myocardial fibers.[13] Therefore, in the present study vagal modification might have varied among the patients after SCA in which RF energy was delivered segmentally around the PVs, targeting the myocardial connection between the LA and PVs.

The main cause of AF recurrence after SCA is the fairly high occurrence of recovery of the electrical connections between the LA and PVs,[1,14–16] which was also observed in this study. On the other hand, it has been recently reported that there are no statistically significant differences in the persistence of PV disconnections in the patients with and without recurrence after an AF ablation procedure,[17] although that was not demonstrated in the present study. One possibility that may explain the results of these 2 studies is that recovery of the electrical connections happens to occur in the arrhythmogenic PVs in the patients with AF recurrence, whereas it does not occur in the arrhythmogenic PVs in the patients without AF recurrence. However, it would be reasonable to consider the possibility of another mechanism in the prevention of AF recurrence after PV ablation. In the present study, there was a significant difference in the parasympathetic nervous activity of the 2 groups after SCA. These findings suggest that parasympathetic attenuation after SCA might play a role in preventing PAF recurrence. Why would vagal modification after SCA prevent late recurrence of PAF? The occurrence of PAF greatly depends on variations in autonomic tone, according to studies using HRV.[18] A shift toward vagal predominance was observed essentially in patients with PAF triggered by PV foci.[19] AF is easily initiated and maintained by parasympathetic stimulation, even in structurally normal hearts, and transvascular atrial parasympathetic nervous system modification by RF catheter ablation abolishes vagally mediated AF in mongrel dogs.[20] Parasympathetic stimulation dramatically shortens the atrial effective refractory period and decreases the wavelength of atrial reentrant circuits that play an important role in the initiation and perpetuation of AF.[21–23] Therefore, vagal denervation may suppress the initiation and perpetuation of AF whether the mechanism of AF is mediated via the PVs or not. Although in the present study, it was in fact unclear whether or not the PACs originated from the PVs with the conduction recovery, greater vagal denervation resulted in a greater suppression of PACs after SCA in the patients without PAF recurrence as compared with those with PAF recurrence. On the other hand, the results of previous reports,[5,24] as well as this study, suggest that vagal denervation after catheter ablation may be a transient phenomenon. Pappone et al proposed that transient vagal denervation effects might contribute to the prevention of AF recurrence by reversing AF-induced atrial electroanatomic remodeling.[5] In the clinical setting, it may be challenging to demonstrate atrial electroanatomic reverse remodeling after SCA using signal-averaged ECG or echocardiography because healing of the LA tissue damaged by RF ablation may occur simultaneously. However, their proposal is the most reasonable explanation of the mechanism so far. Therefore, we think that suppression of PAF triggers by vagal denervation early after SCA might have allowed atrial reverse remodeling, resulting in long-term prevention of PAF recurrence.

Clinical Implications

It has been reported that elimination of all evoked vagal reflexes during circumferential PV ablation resulted in further vagal denervation and contributed to a reduction in AF recurrence.[5] The present study demonstrated that significant vagal denervation also occurred for 3–6 months after standard SCA and it could be helpful for preventing late recurrence of PAF, suggesting that additional RF applications to eliminate vagal reflexes for vagal denervation after SCA may reduce the incidence of late recurrence of PAF. When vagal modification after SCA is limited in the patients with PAF recurrence, adjunctive vagal denervation in the redo-session may be recommended to prevent late recurrence of PAF.

In fact, some doctors have abandoned SCA because extensive LA catheter ablation (LACA) encircling the PVs has been demonstrated as a more effective technique for curing PAF than SCA.[25,26] However, it is still controversial whether SCA or LACA is superior, for the following reasons: (1) SCA is an easier technique for achieving PV electrical disconnection than LACA, (2) it was recently reported that there is no superiority of LACA over SCA for the treatment of AF in terms of efficacy and safety,[27,28] and (3) LACA can have some life-threatening complications such as atrio-esophageal fistula[29] or congestive heart failure associated with LA edema.[30,31] Therefore, we believe that our study provides some important evidence for an advance in the catheter ablation of AF.

Study Limitations

We did not investigate the difference in vagal modification between patients with and without vagal reflexes during SCA, because coronary sinus pacing during SCA in the left PVs might have masked some vagal reflexes. However, Hsieh et al reported that regardless of the appearance of vagal reflexes during PV ablation, the HRV parameters described above showed similar changes.[32] Therefore, we believe that the appearance of vagal reflexes did not significantly change the results of this study.

Recent reports have revealed by the use of transtelephonic and long-term Holter monitoring that asymptomatic AF recurrence after AF ablation occurs more often than might be expected and thus freedom from AF after AF ablation may be overestimated.[33,34] In this study, asymptomatic PAF recurrences might have been missed and the cure rate might have been overestimated because intermittent Holter recordings alone were performed as clinical follow up.

Conclusions

Parasympathetic nervous activity after SCA was significantly lower in the patients without PAF recurrence than in those with PAF recurrence. This study suggests that vagal modification during SCA could also help prevent late recurrence of PAF.

Disclosure

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