Long-Term Effects of Box Isolation on Sympathovagal Balance in Atrial Fibrillation

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Background: Complete isolation of the posterior left atrium, including all pulmonary veins (box isolation), is a feasible and safe atrial fibrillation (AF) treatment method. Data on long-term effects of box isolation on autonomic function, however, remain limited.

Methods and Results: A total of 92 patients (paroxysmal AF, $n=76$; persistent AF, $n=16$) undergoing box isolation with non-contact mapping were studied. Twenty-four-hours ambulatory electrocardiograms and transthoracic echocardiography were done at baseline and after 2 days, and at 3, 6 and 12 months. Autonomic functions were evaluated by means of heart rate variability (HRV). During a mean follow up of 16 ± 5 months, no AF episodes were detected in 76 patients while AF recurred in 16. Significant long-term HRV attenuations were observed in all patients without AF recurrence, but not in those with AF recurrence. In patients without AF recurrence, the natural logarithm (Ln) high-frequency (HF) decreased significantly from $5.5\pm1.3\text{ ms}^2$ (before) to $4.2\pm0.9\text{ ms}^2$ (after 12 months, $P<0.001$) and the ratio of the low-frequency to HF power increased significantly from 2.4 ± 2.0 (before) to 3.4 ± 2.3 (after 12 months, $P=0.05$). LnHF was significantly lower in patients without than in those with AF recurrence during the 12-month period after ablation. Cardiac function improved significantly in patients without AF recurrence after box isolation.

Conclusions: Changes in the sympathovagal balance with box isolation may contribute to AF prevention. (*Circ J* 2010; **74**: 1096–1103)

Key Words: Atrial fibrillation; Autonomic nervous system; Catheter ablation; Electrophysiology; Heart rate variability

The cardiac autonomic nervous system plays an important role in the initiation and maintenance of atrial tachyarrhythmias,^{1–3} and endocardial and/or epicardial ganglion plexus (GP) ablation including pulmonary vein (PV) denervation enhances the long-term benefit after PV antrum isolation for atrial fibrillation (AF).^{4–8} At the tissue level there were no discrete regions of adrenergic or cholinergic nerve predominance. Instead, both nerve types clustered together to form a single neural plexus, and abrupt increases in stellate ganglion nerve and vagal nerve activities immediately preceded (by <5 s) the onset of paroxysmal AF.¹ Therefore, sympathovagal discharges are common triggers of paroxysmal AF, and extrinsic sympathovagal nerves or operative fat pad ablation reportedly eliminated paroxysmal AF,^{1–5} implying a causal relation between sympathovagal discharges and AF. PV encircling isolation (PVI) is usually effective for vagal AF,^{6–8} and there is evidence that PVs may be prone to vagal nerve activity-induced arrhythmia mechanisms.^{1,2} In particular, PVI and additional endocardial and/or epicardial radiofrequency catheter ablation of selected atrial

sites, in which high-frequency (HF) stimulation induces vagal reflexes, may also prevent AF recurrence.^{4–7} Clinically, re-innervation is evident within 1 month of segmental PVI, whereas there is no evidence of re-innervation for at least 1 year after circumferential PVI.⁸

Furthermore, the PVs and posterior left atrium (LA) demonstrate unique activation and repolarization characteristics in response to autonomic manipulation.^{9–11} Vagal response heterogeneity correlates with the cholinergic fiber distribution pattern in the posterior LA.^{9,10} The unusual autonomic characteristics of the PVs and posterior LA might create the arrhythmogenic substrate necessary for AF to occur.⁹

We recently described an alternative approach involving complete isolation of the posterior LA, including all PVs (box isolation), for treating AF. Our box isolation technique is conducted by means of a non-contact mapping system (NCM) or an electro-anatomical mapping system.^{12,13} Box isolation offers a feasible and safe AF treatment with long-term efficacy. Our results suggest that autonomic denervation by box isolation may cure AF, but data on long-term effects

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of box isolation on autonomic function are still limited. The aim of the present study was therefore to evaluate long-term effects of box isolation on sympathovagal balance using 24-h ambulatory Holter electrocardiograms (ECG).

Methods

Patient Characteristics

We enrolled 110 consecutive patients who underwent catheter ablation for paroxysmal AF (n=91) and persistent AF (n=19), but 18 dropped out of the study. Patients who did not complete the study included 14 with sustained AF before the baseline Holter recordings (paroxysmal AF, n=11; persistent AF, n=3), and 4 with sustained AF during Holter recordings 2 days after ablation (paroxysmal AF, n=3; persistent AF, n=1). If Holter recordings with >20% qualifying AF were excluded from analysis when the blanking period had ended, sustained AF was defined as AF recurrence and Holter recordings were again obtained on another day (within 1 month).

We therefore studied 92 patients who underwent mapping and ablation for paroxysmal AF (n=76) or persistent AF (n=16). When AF was sustained, sinus rhythm was restored by electrical cardioversion before the study. All anti-arrhythmic drugs were discontinued at least 7 days before the study. Absence of structural heart disease was confirmed in 87 patients. Valvular disease was documented in 2 patients, cardiomyopathy in 3 and hypertension in 52. All patients provided informed, written consent before participating in this study.

Electrophysiology

Electrophysiology methods have been described in detail elsewhere.^{12,13} Patients received an oral anticoagulant for at least 1 month before ablation. A trans-esophageal echocardiography was performed in all patients before the procedure. Vascular access was obtained through femoral veins. Two 5-Fr quadripolar electrode catheters (St Jude Medical (SJM), St Paul, MN, USA) were placed in the high right atrium (RA) and coronary sinus. Triple trans-septal punctures were performed, and two 8-Fr SL0 sheaths (SJM) and a 10-Fr SL0 sheath (SJM) were advanced into the LA. After the trans-septal puncture, 100-IU heparin/kg was administered iv and heparinization was continued during the procedure to maintain an activated clotting time >350 s. The ECG and bipolar endocardial electrogram were continuously monitored and the data obtained were stored on a computer-based digital amplifier/recorder system for offline analysis (LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA). The intra-cardiac electrograms were filtered from 30 to 500 Hz and measured at a sweep speed of 200 mm/s. Atrial pacing was performed using a programmed stimulator (SEC-3102, Nihon Kohden, Tokyo, Japan).

A multi-electrode array catheter (EnSite 3000; SJM) was inserted into the LA via a 10-Fr SL0 sheath and the tip of the array was positioned in the LA appendage. A decapolar ring catheter (Lasso, Biosense-Webster, Diamond Bar, CA, USA) was inserted in the LA and used for mapping the PVs. A deflectable, quadripolar 7-Fr ablation catheter (Ablaze Fantasia, Japan Lifeline, Tokyo, Japan) was also inserted into the LA for mapping and ablation. The 3-D geometry was created by maneuvering the Lasso and ablation catheter in the LA and PVs under fluoroscopic and angiographic guidance.

Box Isolation

The details of box isolation have been described elsewhere.^{12,13} Radiofrequency energy was delivered with a power of 30–

40 W. The temperature was limited to 50°C. When radiofrequency energy was delivered at the anterior aspect of the left PVs and the floor line near the esophagus, the power was reduced to 30 W. Radiofrequency energy was delivered for 30 s at each site, and application was prolonged to 60 s when a change in the morphology or sequence of the PV potentials occurred as determined by circumferential mapping. When the floor line crossed close to the esophagus, the ablation was performed at a maximum power of 30 W and a temperature of 45°C for 15 s. Continuous lesions in the anterior portion of the ipsilateral superior and inferior PVs via the carina regions of both PVs were initially created under guidance with the Lasso catheter and NCM, and the LA roof was then ablated by creating a contiguous line of ablation lesions joining the superior PVs. The LA floor was then ablated by creating a contiguous line of ablation lesions joining the inferior PVs, to isolate the posterior LA. During applications, local potential elimination or the formation of double potentials signified the local effectiveness of these ablations. Box isolation was evaluated with NCM after sinus rhythm restoration to allow pacing from the coronary sinus, posterior LA and all PVs. Once residual conduction gaps had been identified, additional radiofrequency applications were carried out until all conduction gaps had been abolished. The conduction block was defined as no wave front propagation across the line, and virtual unipolar electrograms along the line showed two discrete deflections, in reversed polarity, separated by the isoelectric baseline. The box isolation endpoint was defined as all PV isolations indicated by circumferential PV mapping and bidirectional conduction block in the posterior LA, as confirmed by activation maps using NCM during pacing at an output of 5 V, both inside the box isolation area (4 PVs and the posterior LA), and outside of the posterior LA (proximal coronary sinus and sinus rhythm propagation).

After box isolation, atrial tachyarrhythmia inducibility was evaluated on rapid RA pacing performed during RA appendage pacing (20 burst pacing cycle lengths from 250 ms until 2:1 capture were noted). If atrial tachycardia/flutter induction was initially facilitated, this was followed by ablation resulting in termination of these arrhythmias. If the earliest activation site in the LA indicated a positive R wave on the non-contact unipolar electrogram, or if the earliest wave front was sequenced at the RA or coronary sinus proximal site by means of a multi-electrode catheter, it suggested an RA origin and the multi-electrode array was thus moved to the RA.

Holter Recordings and Heart Rate Variability (HRV)

The 24-h ambulatory recordings were performed using a 2-channel bipolar digital recorder (Cardio Memory RAC-3103, Nihon Kohden) and analyzed with a microcomputer and appropriate software (Ambulatory ECG Scanner System DSC-3300 Version 0.1-23, Nihon Kohden). The 24-h Holter ECG were recorded the day before ablation, 2 days after ablation, and again 3, 6 and 12 months after ablation. HRV served as an indicator of autonomic activity in accordance with the guidelines for standardization.¹⁴ AF, ventricular and supraventricular ectopic beats, as well as the preceding and the following RR (NN) interval of each ectopic beat, were excluded from HRV analysis. Only recordings with >80% qualified sinus beats were included in the analysis.¹⁵ The following heart rate (HR) and time-domain HRV parameters were analyzed: maximum HR (beats/min), average HR (beats/min), minimum HR (beats/min), the standard deviation of the NN interval (SDNN; ms), the proportion of adjacent

Table 1. Patient Characteristics

	Long-term AF recurrence		P value
	Group without AF recurrence	Group with AF recurrence	
No. patients	76	16	
Age (years), mean $\pm$ SD	59 $\pm$ 11	64 $\pm$ 9	0.12
Male sex, n (%)	66 (87)	8 (50)	0.009
PAF, n (%)	59 (78)	10 (63)	0.15
AF duration (years), mean $\pm$ SD	6 $\pm$ 5	7 $\pm$ 4	0.88
Failure of anti-arrhythmic drugs (n), mean $\pm$ SD	2 $\pm$ 1	3 $\pm$ 2	0.05
Hypertension, n (%)	41 (54)	11 (69)	0.36
Echocardiography, mean $\pm$ SD			
LAD (mm)	40 $\pm$ 6	42 $\pm$ 8	0.30
LVEF (%)	64 $\pm$ 7	66 $\pm$ 8	0.28

AF, atrial fibrillation; PAF, paroxysmal AF; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

Table 2. Changes in HR and HRV Before vs After Box Isolation

	Baseline	2 days	3 months	6 months	12 months
Group without AF recurrence					
Maximum HR (beats/min)	122 $\pm$ 34	112 $\pm$ 23*	117 $\pm$ 18	113 $\pm$ 15	115 $\pm$ 16
Average HR (beats/min)	67 $\pm$ 13	74 $\pm$ 10*	75 $\pm$ 9*	73 $\pm$ 9*	74 $\pm$ 7*
Minimum HR (beats/min)	46 $\pm$ 9	56 $\pm$ 10*	54 $\pm$ 10*	53 $\pm$ 10*	53 $\pm$ 8*
SDNN (ms)	151 $\pm$ 46	88 $\pm$ 36*	116 $\pm$ 53* [†]	111 $\pm$ 40* [†]	114 $\pm$ 43* [†]
pNN50 (%)	24.7 $\pm$ 27.8	7.5 $\pm$ 10.3*	7.8 $\pm$ 9.6*	7.9 $\pm$ 10.2*	6.0 $\pm$ 7.0*
rMSSD (ms)	60.0 $\pm$ 48.1	28.9 $\pm$ 23.6*	27.0 $\pm$ 17.2*	30.5 $\pm$ 21.7*	26.5 $\pm$ 15.5*
Ln LF (ms ²)	6.12 $\pm$ 1.07	4.31 $\pm$ 1.55*	4.80 $\pm$ 1.16*	5.13 $\pm$ 1.10* [†]	5.20 $\pm$ 1.00* [†]
Ln HF (ms ²)	5.52 $\pm$ 1.24	3.99 $\pm$ 1.38*	4.24 $\pm$ 1.17*	4.33 $\pm$ 1.22*	4.29 $\pm$ 1.00*
LF/HF	2.25 $\pm$ 1.87	2.04 $\pm$ 1.96	2.44 $\pm$ 2.02	2.80 $\pm$ 2.18	3.13 $\pm$ 2.23* [†]
Group with AF recurrence					
Maximum HR (beats/min)	119 $\pm$ 35	127 $\pm$ 41	120 $\pm$ 50	121 $\pm$ 39	120 $\pm$ 32
Average HR (beats/min)	70 $\pm$ 18	80 $\pm$ 24	75 $\pm$ 23	79 $\pm$ 21	76 $\pm$ 18
Minimum HR (beats/min)	55 $\pm$ 12	54 $\pm$ 12	54 $\pm$ 12	54 $\pm$ 14	51 $\pm$ 12
SDNN (ms)	133 $\pm$ 39	90 $\pm$ 53	108 $\pm$ 45	103 $\pm$ 35	97 $\pm$ 38
pNN50 (%)	16.7 $\pm$ 19.5	11.2 $\pm$ 13.1	9.7 $\pm$ 8.4	8.2 $\pm$ 11.4	11.4 $\pm$ 16.3
rMSSD (ms)	41.7 $\pm$ 26.7	38.3 $\pm$ 29.4	36.6 $\pm$ 16.5	32.2 $\pm$ 24.8	39.0 $\pm$ 31.5
Ln LF power (ms ²)	6.10 $\pm$ 0.80	4.53 $\pm$ 1.42 [§]	5.05 $\pm$ 1.28	4.98 $\pm$ 1.40	5.36 $\pm$ 1.19
Ln HF power (ms ²)	5.31 $\pm$ 0.92	4.37 $\pm$ 1.48	4.94 $\pm$ 0.97	4.52 $\pm$ 1.24	5.15 $\pm$ 1.46
LF/HF power	2.26 $\pm$ 1.64	1.54 $\pm$ 1.18	1.39 $\pm$ 0.98	1.63 $\pm$ 1.04	1.48 $\pm$ 0.83

*P<0.05 vs before ablation in the group without AF recurrence. [†]P<0.05 vs 2 days after ablation in the group without AF recurrence. [§]P<0.05 vs before ablation in the group with AF recurrence.

HR, heart rate; HRV, HR variability; SDNN, standard deviation of the average of the NN intervals; pNN50, proportion of adjacent NN intervals differing by >50 ms; rMSSD, root mean square successive differences; Ln, natural logarithm; LF, low frequency; HF, high frequency; LF/HF, ratio of LF to HF. Other abbreviation see in Table 1.

NN intervals differing by >50 ms (pNN50; %) and the root mean square of differences between successive NN intervals (rMSSD; ms). HRV in the frequency domain was analyzed and the following parameters were calculated: low-frequency (LF) components (ms²; 0.04–0.15 Hz), HF components (ms²; 0.16–0.40 Hz), and the LF/HF ratio. The power of each frequency band was logarithmically transformed to avoid the influence of extreme values.

rMSSD and HF reflected parasympathetic nervous activity, LF sympathetic nervous activity, and the LF/HF ratio sympathovagal balance.

Transthoracic Echocardiography

Routine transthoracic echocardiography, including 2-D echocardiography, were done in all patients using a standard

scanner before and 3, 6 and 12 months after box isolation. Transthoracic echocardiography was performed to measure the left atrial diameter (LAD; mm) and left ventricular ejection fraction (LVEF; %).

Post-Ablation Management and Follow up

Patients remained hospitalized under continuous rhythm monitoring for at least 3 days after box isolation. No anti-arrhythmic drugs were prescribed at discharge. Repeat visits were scheduled at 3, 6 and 12 months after ablation. All patients were intensively questioned to identify arrhythmia-related symptoms, and echocardiography, surface ECG and 24-h ambulatory Holter ECG were performed. All patients used a telemetry ECG recorder (Omron HCG-801, Kyoto, Japan) for 6 months to document symptomatic arrhythmias and, if

Figure 1. Before and 2 days (2D), 3 months (3M), 6 months (6M) and 12 months (12M) after box isolation in patients with (dotted line) and without (continuous line) atrial fibrillation (AF) recurrence. * $P < 0.05$ vs before ablation in the group without AF recurrence. HR, heart rate; HRV, HR variability; pNN50, proportion of adjacent NN intervals differing by >50 ms; rMSSD, root mean differences; SDNN, standard deviation of the average of the NN (RR) intervals.

asymptomatic, to record weekly ECG. Any episode of symptomatic or asymptomatic atrial tachyarrhythmia lasting >30 s, and identifiable on the surface ECG, Holter monitoring, or telemetry ECG recorder, was considered to be a recurrence. A 3-month blanking period followed box isolation, during which arrhythmias were excluded.

Statistical Analysis

Data are expressed as mean $\pm$ SD. For categorical variables, the Pearson chi-squared test was performed unless the exact

test was required. The general linear model was applied for analysis of repeated measures, with or without recurrent AF as between-subject factors. Unpaired Student's *t*-test was used to compare patient groups. All tests of significance were 2-sided. $P < 0.05$ was the cut-off for statistical significance.

Results

Catheter Ablation

After box isolation, atrial tachyarrhythmias occurred in 24

patients (26%) (paroxysmal AF, n=18; persistent AF, n=6). Activation using NCM combined with entrainment mapping in these patients demonstrated macro-re-entrant LA flutter utilizing conduction gaps in linear lesions in 8 patients (paroxysmal AF, n=6; persistent AF, n=2; P=0.58). Four of the 6 with paroxysmal AF and both persistent AF patients had concealed entrainment with peri-mitral annulus pacing. Similar findings were obtained in 2 of the 6 patients with paroxysmal LA flutter through one lesion between the right inferior PV gap and the right carina on the right side of both PVs, and in another with a lesion between the left superior PV gap and the left carina on the left side of both PVs. Focal atrial tachycardias originated from the anterior LA wall in 1 patient and RA crista terminalis in 2. These atrial tachyarrhythmias were eliminated by additional applications of ablation targeting the gaps or foci. Cavotricuspid isthmus-dependent atrial flutter was also successfully ablated during the procedure in the remaining 13 patients. If AF was induced after all gaps on the box isolation line (including the carina region), LA and cavotricuspid isthmus-dependent RA flutter had been abolished, sinus rhythm was then restored by transthoracic cardioversion. AF originating from the superior vena cava (SVC) was excluded from analysis because any additional ablation might have affected autonomic nervous function. Herein, we did not perform additional ablation beyond pure box isolation, based on the aforementioned exclusion of patients with LA or RA flutter and focal atrial tachycardia.

Of the 92 patients, during a mean follow up of 16±5 months after box isolation, 76 (83%) were AF-free without anti-arrhythmic drugs while 16 had AF recurrences. All AF recurrence patients were maintained on continuous anticoagulation, and anti-arrhythmic drugs and second ablations at the study endpoint were not required. Eight of 16 AF recurrence patients (paroxysmal AF, n=4; persistent AF, n=4) were re-studied using Holter recordings (>20% qualifying AF). In 5 patients these measurements were performed at 3 months, in 1 at 6 months, and in 2 at 12 months after the procedure. Furthermore, there was no significant difference in long-term arrhythmia elimination ratios between initially enrolled patients (81%) and those who completed the study.

Clinical Characteristics of Patients With vs Without AF Recurrence After Box Isolation

Based on clinical characteristics, the patients were divided into two groups, with and without AF recurrence after box isolation, as shown in Table 1. During a mean follow up of 16±5 months, 76 patients were recurrence free while in 16 AF recurred. The group without AF recurrence had a much higher percentage of men than that with AF recurrence. Moreover, in those without AF recurrence, the number of patients with failed anti-arrhythmic drug treatment and LAD enlargement was smaller than among those with AF recurrence.

Ambulatory Holter ECG Data After Box Isolation

HR and time-domain HRV differed significantly before vs after box isolation during the 12-month follow up in patients without AF recurrence (Table 2; Figure 1). AF recurrence patients had no significant changes in any individual parameters. Up to 12 months after box isolation, the natural logarithm (Ln) LF, LnHF and LF/HF ratio differed significantly in patients without AF recurrence at each time point (Figures 2B, C), while in those with AF recurrence there were no significant changes from baseline. LnLF differed significantly in patients with AF recurrence at 2 days after box isolation, but no significant change was seen during long-term follow up

Table 3. Changes in Echocardiography Parameters Before vs After Box Isolation

	Baseline	3 months	6 months	12 months
Group without AF recurrence				
LVEF (%)	63.9±7.1	66.1±5.5*	67.4±6.5*	68.2±6.1*
LAD (mm)	40.2±5.7	38.5±5.8*	37.9±6.0*	37.4±6.2*
Group with AF recurrence				
LVEF (%)	66.2±8.4	66.3±7.6	67.9±8.6	67.9±7.6
LAD (mm)	42.0±7.7	40.1±6.2	39.6±6.8†	40.3±6.6

*P<0.05 vs before ablation in the group without AF recurrence. †P<0.05 vs before ablation in the group with AF recurrence.

Abbreviations see in Table 1.

(Figure 2A). The LF/HF ratio up to 12 months in those without AF recurrence was significantly increased as compared to that in patients with recurrent AF ($P=0.05$; Figure 2C).

In patients without AF recurrence, SDNN differed significantly 2 days vs 3, 6 and 12 months, and LnLF differed significantly 2 days vs 6 and 12 months after, box isolation. These increases were suggested to be due to restored sympathovagal activity immediately after box isolation. The LF/HF ratio at 2 days vs 12 months after box isolation in patients without AF recurrence was significantly increased from 2.04 ± 1.96 to 3.13 ± 2.23 ($P=0.03$). It was suggested that sympathovagal balance changed during this 12-month period in those without AF recurrence, despite sympathovagal nerve activity showing marked recovery immediately vs ≥ 3 months after the procedure. In contrast, in patients with AF recurrence, there were no significant changes in any individual parameters 2 days vs ≥ 3 months after the procedure.

Transthoracic Echocardiography After Box Isolation

LVEF and LAD differed significantly before vs after box isolation during the 12-month study period in patients without AF recurrence (Table 3). In those with AF recurrence, there were no significant changes in any individual parameters (excluding LAD at 6 months after box isolation).

Discussion

Major Findings

Sympathovagal modification varied among patients followed in the long term after box isolation. Sympathetic and parasympathetic nerve activity after box isolation was significantly lower and sympathovagal balance significantly higher in patients without than in those with AF recurrence. These findings persisted during the 12-month follow up in patients free of AF recurrence. We demonstrated that further sympathovagal modification and HRV alteration during the 12 month follow up after box isolation resulted in greater suppression of AF recurrence after this procedure. Moreover, box isolation contributed to increased cardiac function in patients without AF recurrence 12 months after the procedure, and there was no significant decrease in cardiac function in patients with AF recurrence.

Unique Profile of Box Isolation

Box isolation has a more unique profile than routine circumferential PVI. The first novel feature of this procedure was the complete isolation of four PVs including the posterior LA. There is a line of functional conduction delays, which is consistent with anatomical locations in the posterior LA in patients with structural heart disease.¹¹ This is most marked in conduction deficits associated with significant chronic atrial

enlargement and leads to circuitous wave front propagation, suggesting a role in arrhythmogenesis. Markides et al used NCM to describe the electrophysiological properties of the LA region in patients with paroxysmal AF.¹⁶ They demonstrated a functional conduction blockage line, descending in the posterior LA wall, between the superior and inferior PVs, which correlated with a region of change in subendocardial fiber orientation, observed pathologically. During AF initiation this blockage line formed the substrate for functional re-entry, causing wavefronts of PV origin to divide into daughter wavelets. Moreover, Lo et al reported that patients with symptomatic AF who underwent circumferential ablation with PV-LA block during the first procedure had a lower incidence of LA posterior wall ectopy near the PV ostium during AF recurrence,¹⁷ confirming the previous concept that the LA posterior wall may be the trigger and driver of AF progression^{9–11} and that circumferential ablation with PV-LA blockade may eliminate posterior wall ectopy more reliably than can segmental ostial PV ablation.¹⁷ The role of the posterior LA in maintaining AF was also highlighted by Todd et al, who successfully treated AF by surgically isolating the posterior LA en bloc.¹⁸ Furthermore, postoperative electrophysiology showed spontaneous or inducible AF in the isolated posterior LA, whereas the rest of the LA was unable to sustain AF.

The second special feature was the complete isolation of a larger LA area than with routine circumferential PVI. As recently reported, isolation of a large percentage of the LA predicted that AF would not recur after PVI.^{6,12,13} and long-lasting vagal denervation reportedly persisted.⁸ It was recently found that vagal denervation may prevent late paroxysmal AF recurrence independently of the PVI technique (segmental or circumferential PVI).¹⁹ Cha et al showed that PVs were not essential for atrial tachyarrhythmia promotion in an animal model in which all PVs were resected,²⁰ and Takahashi et al reported less change in AF cycle length during vagal excitation in chronic AF.²¹ This suggests a lower contribution of autonomic tone to arrhythmogenesis in chronic AF, which may be associated with the limited efficacy of PV isolation for chronic AF.^{21,22} The PVs are clearly important in clinical AF, and the elimination of PV input to the LA by PV isolation effectively suppresses AF.²³ PV isolation is less effective for persistent than for paroxysmal AF,^{22,24} however, and ablation involving the destruction of extensive LA tissues surrounding the PVs is more effective than segmental PV isolation in preventing AF.^{8,24,25} Elimination of LA rotors may be needed to optimally suppress AF, and eliminating only PV sources may at times be insufficient.²⁴

The third special feature was that autonomic denervation by NCM-guided box isolation might contribute to high efficacy of AF ablation. In the group without AF recurrence, we

found significant decrease of HF as well as increased LF/HF ratio after the procedure. Moreover, these findings persisted during the 12-month follow up in the patients without AF recurrence. Generally, there is no evidence of re-innervation for at least 1 year after circumferential PVI.⁸ We showed that our high success rate was attributable to the combined effects of both a wide ablation area and long-lasting sympathovagal denervation after box isolation in the present study.

Sympathovagal Alterations and AF Recurrence After Box Isolation

Parasympathetic fibers and muscarinic receptors are preferentially located in the posterior LA,^{9,10} suggesting that this region plays an important role in creating a vagal AF substrate.¹¹ A human anatomical study showed that adrenergic and cholinergic nerve densities were highest in the LA within 5 mm of the PV–LA junction.²⁶ Furthermore, at the tissue level there were no discrete regions of adrenergic or cholinergic nerve predominance. Instead, both nerve types clustered together to form a single neural plexus, and abrupt increases in stellate ganglion nerve and vagal nerve activities immediately preceded (by <5 s) the onset of paroxysmal AF.¹ We completely isolated the posterior LA including PVs close to these nerves, to achieve long-term attenuation of sympathetic and parasympathetic nerve activities and increase sympathovagal balance in patients without AF recurrence. We also had a high success rate on long-term follow up after box isolation. The anterior right GP is situated between the caudal end of the sinoatrial node and the right superior PV–LA junction, while the superior left GP is adjacent to the left PV–LA junction between the LA appendage and left pulmonary artery.³ The roof and floor ablation lines in box isolation located elsewhere might have provided additional effectiveness for these GPs in the present study.

Many investigators have suggested that parasympathetic attenuation after PV isolation might play a role in preventing AF recurrence.^{4–8} Long-lasting changes in sympathovagal balance and vagal denervation might be associated with the high rate of success in eliminating arrhythmias after box isolation. Changes in parasympathetic nerve activity immediately after segmental PVI were recently reported to be an independent predictor of paroxysmal AF recurrence, and vagal modification after segmental PVI may also help prevent late recurrence of paroxysmal AF.²⁷ Tan et al reported that simultaneous sympathovagal discharges preceded the onset of these paroxysmal atrial arrhythmias and that specific patterns of autonomic nerve discharge differed among paroxysmal atrial ectopy, AF and sinus tachycardia.¹ Cryoablation of the stellate ganglia and superior cardiac branches of the vagal nerve eliminated all paroxysmal AF episodes in an animal AF model. These anti-arrhythmic effects were associated with cardiac nerve sprouting and sympathetic hyper-innervation in the atria of cryoablated dogs. The data suggested that decentralization rather than denervation of sympathovagal nerves is the anti-arrhythmic mechanism of stellate ganglion and vagal nerve ablation, and HF/LF ratio was increased after box isolation. The intriguing possibility of autonomic balance being influenced by genetic factors²⁸ deserves consideration in future studies.

Vagal Denervation Is Necessary to Prevent AF After Box Isolation

Stimulation of autonomic nerves innervating the heart can reportedly induce AF.^{1–3} The existence of GPs around the heart has generated interest in the relationship of these sites

to AF pathophysiology.^{1,3,26} In experimental animal models, stimulation of GPs initiates and maintains AF.³ Furthermore, catheter ablation of GPs prevented vagal AF in a canine model.^{1–3} The standard PVI lesion set encompasses GP sites in all patients, also suggesting the mechanism by which PVI works to involve autonomic denervation.^{6–8} Based on these observations, we can speculate that selective ablation of all GP sites alone might successfully control AF. Scanavacca et al reported that vagal reflexes can be induced by trans-catheter HF stimulation of select epicardial and endocardial areas of the LA in most patients with paroxysmal AF.⁴ Radio-frequency catheter ablation of these areas eliminates such responses and promotes autonomic changes, suggesting vagal tonus withdrawal. Such parasympathetic changes obtained without PV disconnection, however, were enough to prevent clinical AF episodes in a few selected patients. These results suggested that box isolation itself promotes LA autonomic denervation even in patients in whom vagal reflexes could not be elicited by atrial stimulation.

Study Limitations

Box isolation effectively eliminated AF and changed sympathovagal balance via vagal denervation, but 12% of paroxysmal and 25% of persistent AF patients had AF recurrence after box isolation. Although no asymptomatic, short episodes of paroxysmal AF were documented on 24-h Holter recording or weekly telemetry ECG recording for 6 months after box isolation, we cannot completely rule out the possibility of asymptomatic AF in these patients.⁵ Moreover, we did not elicit vagal responses^{4–7} because we lacked specialized HF stimulation equipment, and GP sites varied in location among patients. We also did not perform ablation in the RA, including the SVC GP and coronary sinus GP.^{3–5} In fact, partial vagal denervation promoted rather than prevented initiation of vagal-mediated AF.²⁹ It is possible that there were no significant LnLF, HF and LF/HF ratio changes in the AF recurrence patients because they had taken anti-arrhythmic drugs since their AF recurred. This was a retrospective study on a relatively small patient population. Because sympathovagal balance differed significantly between the study groups, we believe that the patient numbers were adequate to demonstrate the mechanisms of recurrent AF after box isolation.

Conclusions

Box isolation has long-term curative effects on AF. Changes in sympathovagal balance and vagal denervation with box isolation may contribute to long-term AF prevention. Our box isolation strategy involves an enclosed wide ablation area that includes the source of focal atrial tachyarrhythmias and the peculiar autonomic characteristics of the PVs and posterior LA, which may create the setting necessary for AF to occur. Long-lasting sympathovagal changes are essential for long-term arrhythmia elimination in AF patients after box isolation.

Disclosures

None.

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