

Pulmonary Vein Denervation Enhances Long-Term Benefit After Circumferential Ablation for Paroxysmal Atrial Fibrillation

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Background—There are no data to evaluate the relationship between autonomic nerve function modification and recurrent atrial fibrillation (AF) after circumferential pulmonary vein ablation (CPVA). This study assesses the incremental benefit of vagal denervation by radiofrequency in preventing recurrent AF in a large series of patients undergoing CPVA for paroxysmal AF.

Methods and Results—Data were collected on 297 patients undergoing CPVA for paroxysmal AF. Abolition of all evoked vagal reflexes around all pulmonary vein ostia was defined as complete vagal denervation (CVD) and was obtained in 34.3% of patients. Follow-up ended at 12 months. Heart rate variability attenuation, consistent with vagal withdrawal, was detectable for up to 3 months after CPVA, particularly in patients with reflexes and CVD, who were less likely to have recurrent AF than those without reflexes ($P=0.0002$, log-rank test). Only the percentage area of left atrial isolation and CVD were predictors of AF recurrence after CPVA ($P<0.001$ and $P=0.025$, respectively).

Conclusions—This study suggests that adjunctive CVD during CPVA significantly reduces recurrence of AF at 12 months. (*Circulation*. 2004;109:r7-r14.)

Key Words: ablation ■ arrhythmia ■ atrium ■ fibrillation ■ nervous system, autonomic

Pulmonary vein (PV) ablation is an effective preventive strategy for treating paroxysmal atrial fibrillation (AF), but its antiarrhythmic mechanisms remain unclear.¹⁻⁵ Increased vagal tone is frequently involved in the onset of AF in patients with structurally normal hearts.⁶ Vagal denervation in a canine model prevents inducible AF,⁷ and long-term vagal denervation of the atria renders AF less easily inducible.⁸ Radiofrequency (RF) applications around PV ostia often induce vagal reflexes,^{2-4,9,10} but there are no data from large-scale studies to evaluate the potential relationship between autonomic nerve function modification and AF recurrence. Therefore, in a large series of patients undergoing circumferential PV ablation (CPVA) for paroxysmal AF, we assessed the effects of RF on PV innervation, heart rate variability (HRV), and recurrence of AF.

Methods

Patient Population

Of 470 consecutive patients with paroxysmal AF who underwent CPVA between January 1999 and April 2002, 297 were included in the present study. Exclusion criteria included diabetes mellitus, sinus node disease, AV block, permanent pacing, recent myocardial

infarction (<6 months), β -blocker therapy, >5% premature complexes on Holter monitoring, renal failure, thyroid dysfunction, or left ventricular ejection fraction <45%. Digoxin or antiarrhythmic agents, including verapamil and diltiazem, were discontinued for at least 5 half-lives before the study or for 5 months in the case of amiodarone. Written informed consent was obtained from every patient in accordance with a protocol approved by the hospital's ethics committee.

RF Catheter Ablation

The details of the CPVA have been described previously.³⁻⁵ Two additional ablation lines were performed in the posterior left atrium (LA), and an ablation line was placed in the mitral isthmus to prevent postablation LA flutter.^{4,5} Briefly, 3D LA maps were reconstructed through a transseptal route with an electroanatomic mapping system (CARTO, Biosense-Webster). Energy was applied for 15 to 30 seconds at a target temperature of 60°C and a power output of 40 to 85 W. Patients with a history of atrial flutter also underwent ablation of the cavotricuspid isthmus.

Assessment of PV Innervation

Potential vagal target sites were identified during CPVA. Vagal reflexes were defined as sinus bradycardia (<40 bpm), asystole, AV block, or hypotension that occurred within a few seconds of the onset of RF application. If a reflex was elicited, RF energy was delivered until such reflexes were abolished, or for up to 30 seconds. The end

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TABLE 1. Comparison of Patients According to AF Recurrence or No Vagal Reflexes/PV Denervation

	All Patients (n=297)	AF Recurrence			No Vagal Reflexes (n=195)	PV Denervation (n=102)	P
		No (n=267)	Yes (n=30)	P			
Age, y	49.2±6.6	49.0±6.5	51.4±6.9	0.06	49.6±6.6	48.5±6.4	0.15
AF duration, y	7.0±2.1	6.9±2.0	7.1±2.8	0.82	7.0±2.3	6.9±1.6	0.74
EF, %	58.3±5.2	58.3±5.4	58.4±3.2	0.96	58.5±4.8	58.0±5.8	0.45
LAD, mm	39.4±3.5	39.3±3.6	40.5±2.5	0.02	39.6±3.5	39.0±3.6	0.23
% LA ablated	28.2±2.8	28.7±2.2	23.9±3.4	<0.001	27.9±2.9	28.9±2.3	0.001
Pre-RF SDNN, ms	130.4±30.5	130.5±31.7	130.1±16.5	0.91	130.5±34.3	130.4±21.6	0.98
Pre-RF rMSSD, ms	30.2±9.0	30.1±9.4	31.3±4.1	0.18	30.4±9.5	29.7±8.0	0.52
Pre-RF mean HR, bpm	72.4±8.4	72.1±8.4	75.1±7.8	0.06	72.1±7.7	73.1±9.5	0.33
Pre-RF minimum HR, bpm	41.4±8.4	41.1±8.4	44.1±7.8	0.07	41.1±7.7	42.1±9.5	0.33
Pre-RF maximum HR, bpm	134.0±8.5	133.7±8.6	135.8±8.0	0.22	133.6±7.9	134.7±9.7	0.27
Pre-RF ln LF	5.57±0.47	5.56±0.49	5.60±0.27	0.47	5.55±0.50	5.59±0.42	0.57
Pre-RF ln HF	5.11±0.45	5.10±0.46	5.15±0.31	0.48	5.11±0.48	5.09±0.37	0.73
Pre-RF LF/HF	1.09±0.05	1.09±0.05	1.10±0.05	0.92	1.09±0.04	1.10±0.05	0.10
Male/female gender, n (%)	165/132 (55.6/44.4)	149/118 (55.8/44.2)	16/14 (53.3/46.7)	0.80	107/88 (54.9/45.1)	58/44 (56.9/43.1)	0.74
PV denervation, no/yes, n (%)	195/102 (65.7/34.3)	166/101 (62.2/37.8)	29/1 (96.7/3.3)	<0.001
SHD, no/yes, n (%)	204/93 (68.7/31.3)	183/84 (68.5/31.5)	21/9 (70/30)	0.87	130/65 (66.7/33.3)	74/28 (72.5/27.5)	0.30
ERAF, no/yes, n (%)	277/20 (93.3/6.7)	247/20 (92.5/7.5)	30/0 (100/0)	0.24*	188/7 (96.4/3.6)	89/13 (87.3/12.7)	0.003
Time to ERAF, days†	1.9±1.6	3.4±1.9	1.1±0.3	0.02
AF recurrence at 12 months, no/yes, n (%)	267/30 (89.9/10.1)	166/29 (85.1/14.9)	101/1 (99/1)	<0.001
Inappropriate sinus tachycardia, no/yes, n (%)	272/25 (91.6/8.4)	242/25 (90.6/9.4)	30/0 (100/0)	0.09*	194/1 (99.5/0.5)	78/24 (76.5/23.5)	<0.001

EF indicates ejection fraction; LAD, left atrium diameter; and SHD, structural heart disease.

*Fisher's exact test.

†Data obtained in 20 patients.

point for ablation at these sites was defined as a termination of the reflex, followed by sinus tachycardia or AF. Failure to reproduce the reflexes with repeat RF was considered confirmation of denervation. Complete vagal denervation (CVD) was arbitrarily defined by the abolition of all vagal reflexes. The most common sites were tagged on electroanatomic maps.

Heart Rate and HRV

HRV was used as an indicator of autonomic activity in accordance with guidelines for standardization.¹¹ Heart rate (HR) and time- and frequency-domain HRV were analyzed from Holter 24-hour ECG data before and after ablation (1 week, then 1, 3, and 6 months) with commercially available software (Mortara Rangoni Europe).

Postablation Follow-Up

After ablation, patients received anticoagulation with warfarin. Patients were discharged without antiarrhythmic therapy. Patients had 4 transtelephonic ECG rhythm strips per day and 48-hour Holter recordings before and 1 week after CPVA and once monthly thereafter until follow-up ended at 12 months. Patients were instructed to report any symptoms. Recurrence of AF was defined as AF that lasted at least 30 seconds. AF was considered sustained if it lasted more than 30 minutes. Early recurrent AF (ERAF) was defined as recurrence of AF within 1 week after ablation, and late recurrence was defined as AF that occurred between 1 week and 12 months after ablation. Inappropriate sinus tachycardia was defined as a resting sinus rate of >100 bpm without physiological or hemodynamic causes. Patients experiencing their first recurrence of AF did not receive antiarrhythmic therapy. Study end points were freedom from recurrent AF in patients with or without CVD and predictors of

outcome. Because ERAF within 1 week after ablation may be a transient phenomenon, AF limited to the first week after the procedure was excluded from the analysis.

Statistical Analysis

Data are expressed as mean±SD. The power of each frequency band was logarithmically transformed to normalize the distribution. For categorical variables, the Pearson χ^2 test was performed unless the exact test was required. The general linear model was applied for analysis of repeated measures, with recurrent AF or complete PV denervation as between-subject factors. Bonferroni's test was used to compare main effects. The unpaired Student *t* test was used to compare patient groups. A Kaplan-Meier analysis with the log-rank test was used to determine the probability of freedom from recurrent AF in patients with or without vagal reflexes. Cox regression analysis was performed to determine the independent predictors of recurrence of AF. All tests of significance were 2-sided. A probability value of ≤ 0.05 was considered significant. SPSS software for Windows (SPSS Inc) was used for statistical analysis.

Results

Population Characteristics

Population characteristics are shown in Table 1. Only 12 patients had vagotonic AF. Before ablation, all patients had frequent episodes of symptomatic and asymptomatic AF that lasted for a mean of 7 years despite a mean of 2 ± 1 antiarrhythmic drugs being used. Associated cardiovascular disease, including ischemic heart disease (n=15), dilated

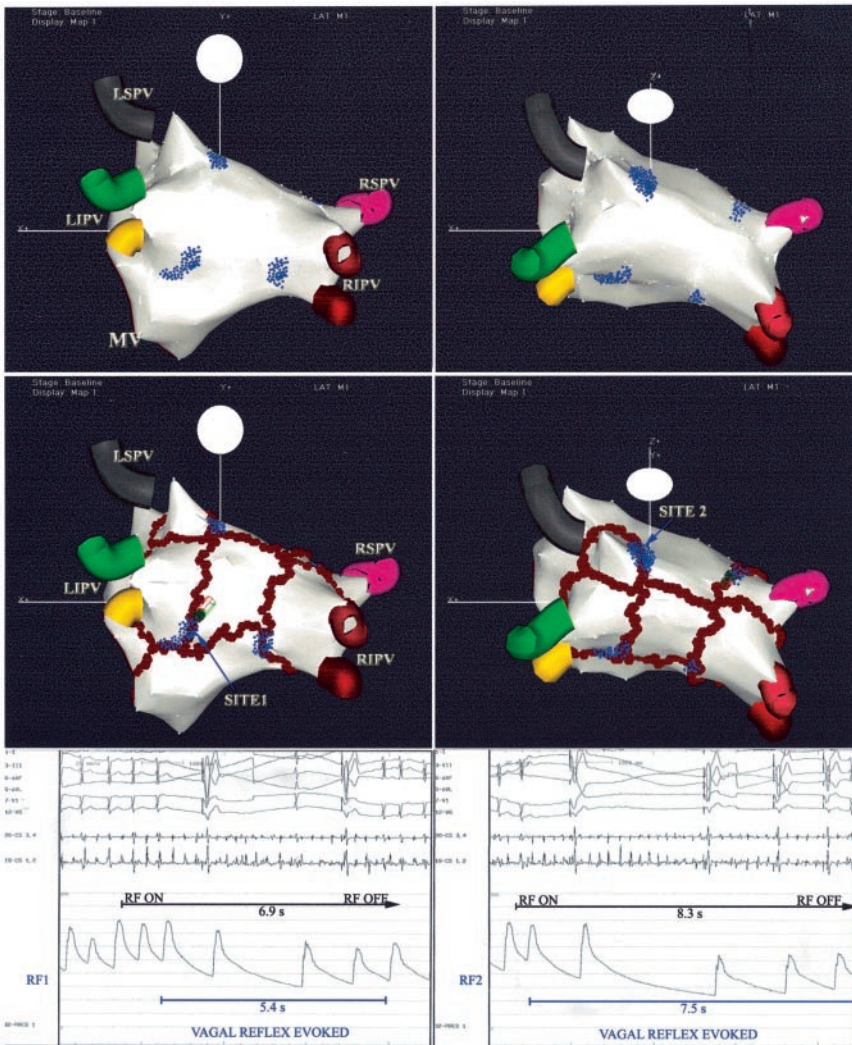


Figure 1. Top, 3D LA electroanatomic maps (posteroanterior view on left and coronal posteroanterior view on right), showing location and absolute number of sites at which vagal reflexes were evoked (blue dots). Middle, Correspondence of ablation lines of left- and right-sided PVs (red tags) and common locations for vagal reflexes can be seen. Bottom, Application of RF energy (RF ON) at 2 separate sites (sites 1 and 2) induced transient AF, hypotension, and high-grade AV block. MV indicates mitral valve; LSPV, left superior PV; LIPV, left inferior PV; RSPV, right superior PV; and RIPV, right inferior PV.

cardiomyopathy (n=38), hypertrophic cardiomyopathy (n=15), and valvular heart disease (n=25), was present in 31.3% of cases.

Ablation Results and PV Innervation

Procedures averaged 174 ± 25 minutes, with an ablation time of 61 ± 17 minutes for delivery of 98 ± 19 RF pulses. The percentage LA area ablated was $28.2 \pm 2.8\%$ of the total LA surface area. A vagal response was observed in 102 (34.3%) of the 297 patients, and CVD was obtained in 100 of 102 patients. Reflexes were elicited in more than 1 site in most patients. The most common locations of the sites were the cranial junction between the left superior PV and LA (97 patients, 95%) and the septal or anterior junction between the right superior PV and LA (26 patients, 25%). RF application at these sites generally caused immediate painless vagal reflexes. An additional site in the posteroinferior junction between the left inferior PV and LA (71 patients, 70%) or the posteroinferior junction between the right inferior PV and LA (51 patients, 50%) caused slightly delayed vagal reflexes (within 20 seconds of RF application) that were generally painful (Figures 1 and 2). Fewer reflexes were elicited in older patients (>65 years), and these reflexes were harder to abolish. Sinus bradycardia, asystole, and hypotension were

characteristic of reflexes elicited around the left PVs, whereas AV block and hypotension frequently occurred during ablation around the septal PVs. In 5 patients, reflexes were also elicited outside PV areas in the posterior region between inferior PVs or LA appendage. Up to 3 applications were required to eliminate reflexes around the left superior PV, whereas 1 or 2 applications were sufficient for the left inferior, right superior, or right inferior PVs. All patients were in sinus rhythm at the time of vagal reflexes, but in 5 patients, RF applications also induced transient AF, AV block, and hypotension (Figure 1). In 2 patients, reflexes were only attenuated despite repeated RF applications.

Clinical Outcome

At 12 months, 50 patients had had early (20 patients) or late (30 patients) recurrent AF. Overall, mean time to ERAF was 1.9 days, but no patients with ERAF experienced further AF; patients with late recurrences continued to experience recurrent AF during follow-up but did not receive antiarrhythmic drugs because the recurrent episodes became shorter and less frequent. Twenty-four patients with CVD developed an inappropriate sinus tachycardia, which lasted for up to 1 month after the procedure. Asymptomatic nonsustained AF was detected in 29 patients, principally in those with known

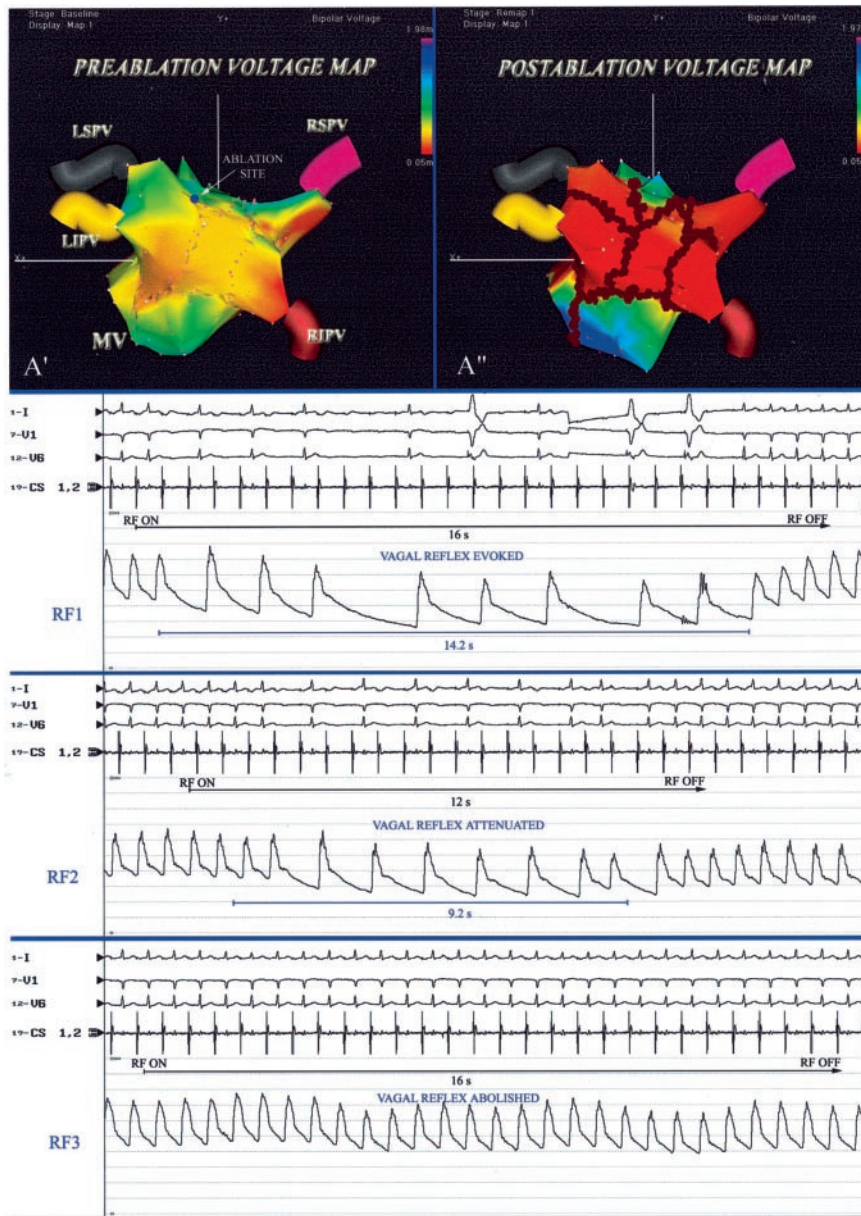


Figure 2. Top, Preablation and postablation 3D LA voltage maps in patient with vagal reflex evoked and abolished around left superior PV (arrow). Red represents low voltage and purple high. Reflex site is depicted as blue spot in left panel (A). In right panel (B), dark red circles represent ablation lines. Bottom, Surface, intracardiac, and arterial pressure tracings during RF application (RF ON) at reflex site. Recordings were obtained while pacing coronary sinus (CS) at cycle length of 620 ms. First application (RF1) at this site resulted in hypotension and high-grade AV block. Response was attenuated to 2:1 AV block during second application (RF2). No hypotension or AV block occurred on third application (RF3), which indicates abolition of reflex. MV indicates mitral valve; LSPV, left superior PV; LIPV, left inferior PV; RSPV, right superior PV; and RIPV, right inferior PV.

symptomatic late AF (15 patients, 50%). The incidence of detected AF in asymptomatic patients was low (14 patients, 5%), and all episodes were nonsustained. No episodes of asymptomatic AF were detected on any transtelephonic rhythm strips.

Recurrence of AF After CPVA and CVD

Characteristics of patients with and without long-term AF recurrences are shown in Table 1. Patients with AF recurrences had a slightly greater LA diameter ($P=0.02$) and a smaller percentage area of LA isolation ($P<0.001$). Late AF recurrences were less frequent in patients with CVD, although ERAF was more common. Inappropriate sinus tachycardia was more common in patients who had CVD (Table 1).

HR and HRV Changes

In the population as a whole, HR and HRV parameters showed significant changes over time for all variables

except maximal HR (Table 2). The mean and minimum HR increased from 1 week to 3 months and returned to preablation levels at 6 months. Time- and frequency-domain HRV parameters decreased, and the low-frequency (LF)/high-frequency (HF) ratio increased and remained elevated for 3 months, returning to preablation values by 6 months. In patients without recurrent AF, SDNN (SD of the normal RR interval), rMSSD (root mean square successive difference), and HF were lower from 1 week to 3 months, and mean and minimum HRs were higher in patients without recurrences from 1 week until 3 months after ablation (Figure 3). Patients with CVD had lower SDNN and HF at 1 week after ablation until 3 months, whereas rMSSD was lower only at 1 and 3 months after ablation. Patients who had CVD had higher mean and minimum HRs, as well as LF/HF ratio, at 1 week, 1 month, and 3 months after ablation than those who did not (Figure 4).

TABLE 2. Comparison of Changes of HR and HRV Before and After Ablation in the Study Population

	Preablation	1 Week	1 Month	3 Months	6 Months	P
SDNN, ms	130.4±30.5	81.4±18.8*	76.5±23.6*	94.8±24.1*	130.0±26.7	<0.001
rMSSD, ms	30.2±9.0	16.8±5.2*	15.2±6.8*	19.5±6.9*	30.3±9.4	<0.001
Mean HR, bpm	72.4±8.4	80.3±9.1*	81.4±9.3*	78.5±8.9*	72.5±7.9	<0.001
Minimum HR, bpm	41.4±8.4	46.3±9.4*	46.7±9.5*	45.2±9.1*	41.5±7.0	<0.001
Maximum HR, bpm	134.2±9.7	134.4±8.8	134.7±8.1	134.1±8.6	133.9±8.5	0.42
In LF	5.57±0.47	5.24±0.50*	5.23±0.49*	5.37±0.48*	5.56±0.51	<0.001
In HF	5.11±0.45	4.49±0.50*	4.38±0.54*	4.60±0.51*	5.11±0.46	<0.001
LF/HF	1.09±0.05	1.17±0.07*	1.20±0.07*	1.17±0.06*	1.09±0.05	<0.001

*P<0.001 vs preablation.

Predictors of Recurrent AF

At 12 months of follow-up, 85% of patients without vagal reflexes were free of symptomatic AF compared with 99% of patients with vagal reflexes and CVD (P=0.0002, log-rank test; Figure 5). By multivariate analysis, only a larger percentage of LA isolation and CVD were independent predictors of AF recurrence (Table 3).

Discussion

Main Findings

This study indicates that parasympathetic attenuation by PV denervation confers added benefit in patients undergoing CPVA for paroxysmal AF. Patients free of recurrent AF were characterized by marked and prolonged HRV changes consistent with vagal withdrawal that were more pronounced in

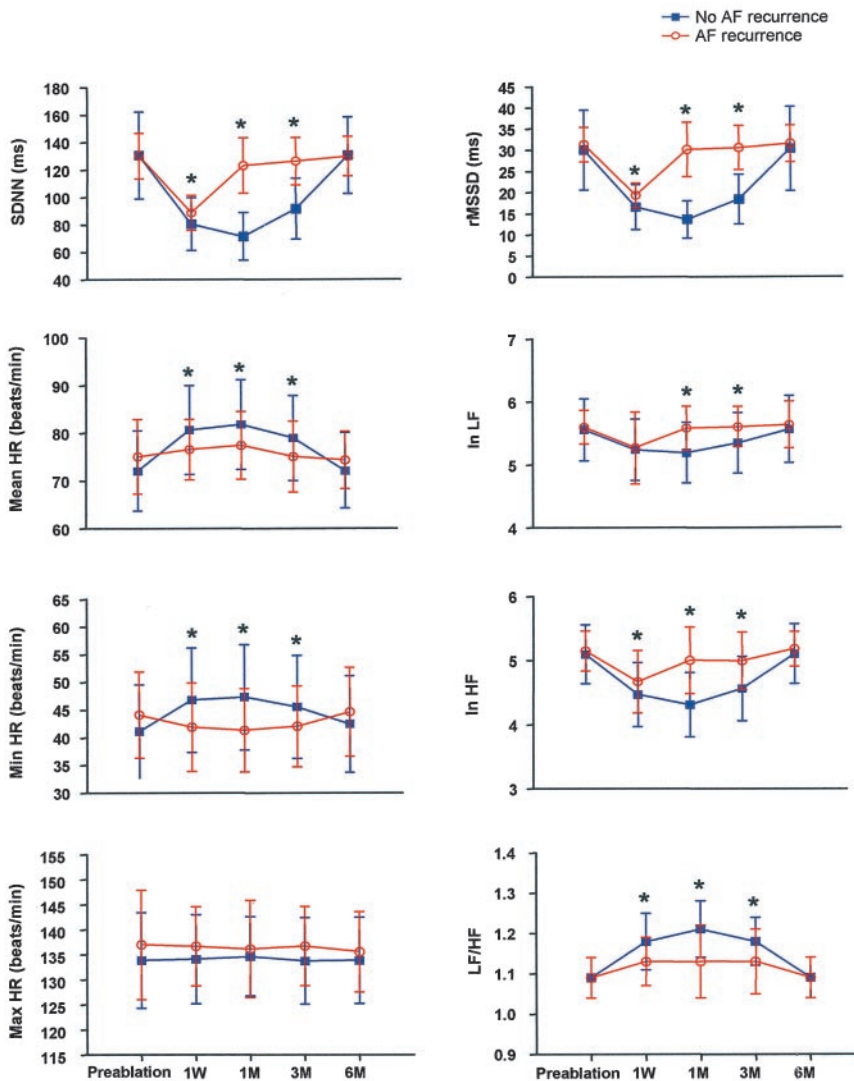


Figure 3. Changes in mean, minimum- (Min), and maximum (Max) HR and HRV before and 1 week (1 W), 1 month (1 M), 3 months (3 M), and 6 months (6 M) after ablation in patients with (red lines) and without (blue lines) AF recurrences. *P<0.05 among data obtained during different time sequences.

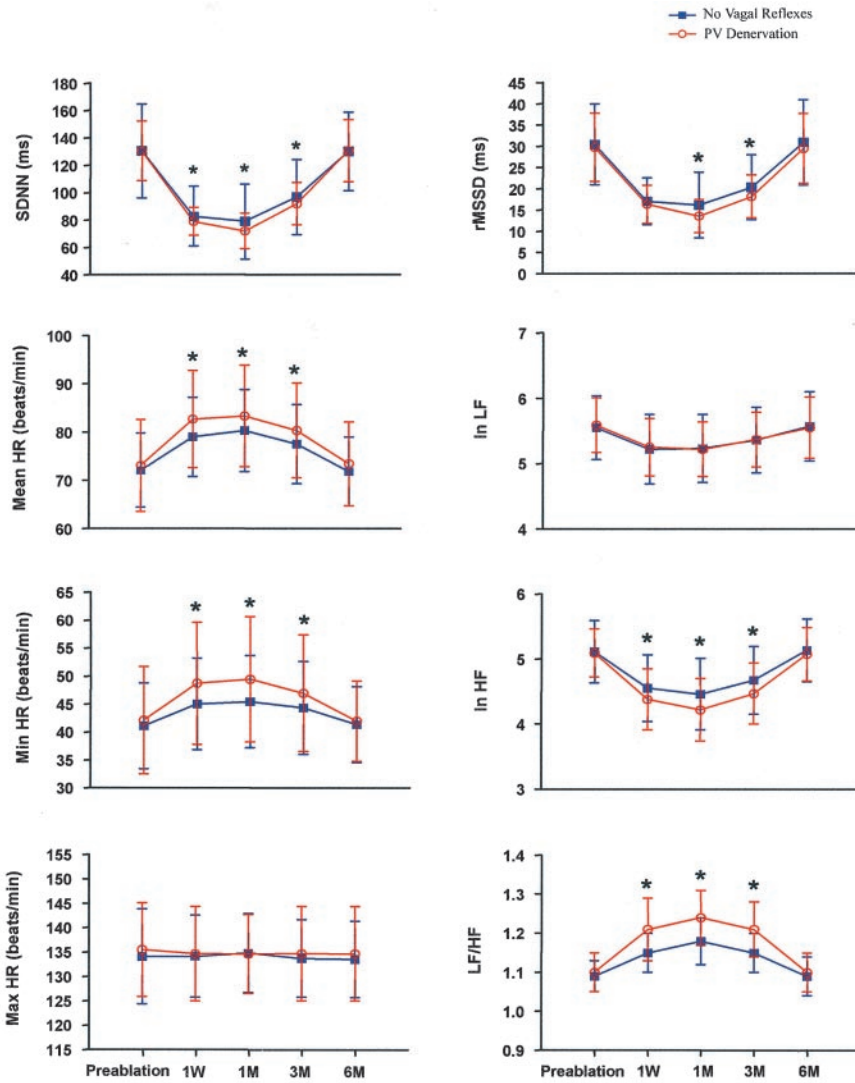


Figure 4. Sequential changes in HR and HRV in patients with PV denervation (red lines) and patients without vagal reflexes (blue lines). * $P < 0.05$ among data obtained during different time sequences.

those in whom vagal reflexes were elicited and abolished. This study also provides, for the first time, maps localizing parasympathetic innervation around and outside PV areas: the roof junction of the left superior PV and the posteroinferior

junction of the left and right inferior PVs are the optimal sites for eliciting and eliminating vagal reflexes.

Paroxysmal AF and the Parasympathetic Nervous System

Increased vagal tone is frequently involved in the onset of AF in patients with structurally normal hearts.⁶ Parasympathetic stimulation shortens the atrial effective refractory period, increases its dispersion, and decreases the wavelength of reentrant circuits that facilitate initiation and perpetuation of AF.¹²⁻¹⁴ The Maze procedure causes partial parasympathetic denervation, and high success rates have been reported.¹⁵ Long-term vagal denervation of the atria renders AF less easily inducible, presumably because of increased electrophysiological homogeneity.¹⁶

Location and Abolition of Vagal Reflexes

The present study indicates that vagal reflexes can be elicited and abolished in at least one third of patients during CPVA. However, patients with bradycardia and even low-grade heart block were excluded from the study, which possibly resulted in the removal of subjects with vagal predominance. In

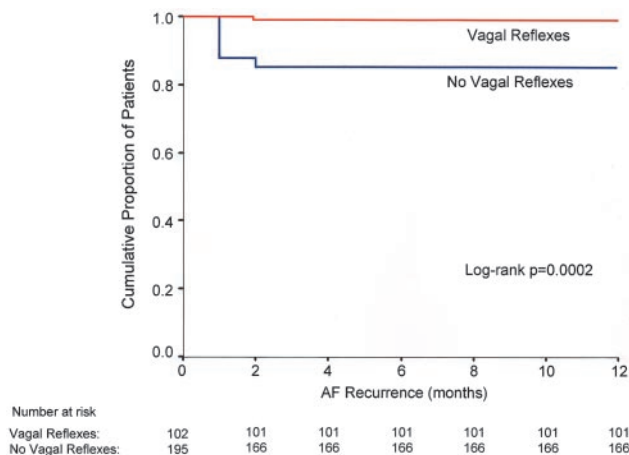


Figure 5. Kaplan-Meier curve of freedom from recurrent AF after CPVA in patients with or without vagal reflexes.

TABLE 3. Results of Cox Regression in the 297 Patients With Paroxysmal AF

Covariates	Regression Coefficient	P	Adjusted Hazard Ratio	95% CI
Age	0.037	0.214	1.038	0.979–1.100
Gender (0/1 = F/M)	−0.071	0.852	0.931	0.440–1.971
AF duration	−0.088	0.267	0.916	0.784–1.070
EF	0.034	0.488	1.035	0.940–1.139
LAD	0.108	0.100	1.114	0.980–1.266
% LA isolation	−0.324	<0.001	0.723	0.657–0.796
CVD (0/1 = no/yes)	−2.289	0.025	0.101	0.014–0.750
SHD (0/1 = no/yes)	−0.489	0.234	0.613	0.274–1.374

EF indicates ejection fraction; LAD, left atrium diameter; and SHD, structural heart disease.

addition, reflexes were elicited and abolished in the context of CPVA, and RF energy was not delivered to regions of the right atrium, which are known to be richly parasympathetically innervated. The stimulation of left-sided PV areas predominantly affected the sinus node, whereas stimulation of right-sided PV areas preferentially affected the AV node. Previous studies have demonstrated parasympathetic nerve terminals in the PV area, and the incidence of ablation-induced bradycardia-hypotension response was higher in PV areas than with ablation of other atrial tissues.^{17–20} Hsieh et al¹⁰ reported severe bradycardia and hypotension in 6 of 37 patients undergoing focal PV ablation. In their study, the ablation site was inside the left superior PV (4 patients) or inside the right superior PV (2 patients).¹⁰ We successfully abolished vagal reactions without complications despite longer and deeper application of energy, and after their abolition, AF recurrence was extremely low. Elimination of vagal reflexes followed by sinus tachycardia occurred in all but 2 patients, in whom the vagal reflex was only attenuated. RF was continued if bradycardia or hypotension occurred, whereas in previous studies, RF was stopped when vagal reflexes developed.¹⁰

Parasympathetic Modification and Recurrence of AF After CPVA

In the present study, CPVA induced a significant reduction in parasympathetic activity. However, patients in whom AF recurred had less marked HRV changes, which normalized by 1 month. In contrast, patients remaining free of AF had a more pronounced attenuation of HRV that persisted for at least 3 months after CPVA. Similarly, patients with CVD had the greatest reduction in HRV. These observations are similar to those reported in animal studies in which destruction of vagal nerves by RF caused changes in HR and HRV parameters.⁸ The present data collectively highlight the role of vagal denervation and parasympathetic attenuation in the success of CPVA, these changes being absent in patients with recurrent AF. Here, denervation was obtained through lesions in the LA only, but nonetheless, this would appear sufficient to alter the arrhythmogenic substrate enough to give clinical success in most subjects. In a previous study, of 40 patients with paroxysmal AF who underwent superior PV ablation, 15%

developed bradycardia-hypotension syndrome during RF, and all were free of AF during follow-up (mean 8 months).¹⁷ In another study,¹⁰ transient autonomic dysfunction was observed after focal PV ablation in 37 patients, and in 6 of them, vagal reflexes were elicited but not deliberately ablated; however, there were no differences in HRV or recurrences between those with and without reflexes. This may represent methodological differences in the ablation procedure or the smaller scale of these studies. The results of the present study suggest that CPVA per se modifies cardiac parasympathetic activity, but patients in whom vagal responses are not elicited do not have as much denervation as patients in whom vagal reflexes are abolished. Therefore, more extensive vagal denervation, as indicated by abolition of all vagal reflexes in the LA, is crucial for a better outcome. However, one cannot exclude that elicitation and ablation of reflexes in the right atrium might have additional benefit in the group of patients in whom reflexes cannot be elicited in the LA.

CVD as a Predictor of Freedom From AF Recurrence

Initially, attention was focused on the elimination of ectopic foci by the use of finely targeted RF applications within the PVs to cause isolation.¹ However, better results were obtained with CPVA, which creates more extensive lesions, which can affect several triggers, including ectopic foci, rotors, spiral waves, and the ligament of Marshall and also modify the autonomic nervous system.^{2–5} The present study demonstrates that CVD is an additional predictor of long-term benefit after CPVA and that abolition of vagal reflexes should be considered an important end point for PV ablation to achieve greater parasympathetic denervation and higher probability of success.

Destruction or damage of vagal nerve fibers after CPVA may result in a short-lived, excessive, or uncontrolled release of acetylcholine at the atrial level, promoting arrhythmias. This may explain the apparent vagal predominance early after CPVA³ and the possible mechanism of ERAF. One week after ablation, a prolonged and stable vagolytic effect may contribute to the prevention of further AF recurrence, presumably by reversing AF-induced atrial electroanatomic remodeling, which may persist even after HRV parameters return to baseline.

Study Limitations

Every effort was made to screen patients for asymptomatic AF, but asymptomatic episodes were very rare in patients free of symptomatic AF, whereas they were common in patients with symptomatic recurrences of AF. The study population was composed predominantly of relatively young patients with relatively normal LA size and good cardiac function, and therefore these results cannot necessarily be extrapolated to all AF patients. Finally, additional studies will clarify whether the group of patients with vagal reflexes may represent a subset of vagally mediated AF or whether these reflexes can be evoked in more patients with the use of more sophisticated technology.

Conclusions

Vagal attenuation is an additional mechanism of the antiarrhythmic action of CPVA. Vagal reflexes can be elicited in several specific sites around all PV ostia and should be specifically targeted to cure paroxysmal AF.

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