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Catheter Ablation of Right Atrial Ganglionated Plexi in Patients With Vagal Paroxysmal Atrial Fibrillation

Leonardo Calò, MD, FESC; Marco Rebecchi, MD; Luigi Sciarra, MD; Lucia De Luca, MD; Alessandro Fagagnini, MD; Lorenzo Maria Zuccaro, MD; Pietro Pitrone, BS; Serena Dottori, BS; Maurizio Porfirio, MD; Ermenegildo de Ruvo, MD; Ernesto Lioy, MD

Background—Catheter ablation of ganglionated plexi (GP) in the left atrium has been proposed in different subgroup of patients with atrial fibrillation (AF). Anatomic studies found a high prevalence of GP in the posterior surface of the right atrium (RA). Experimental data suggested the potential role of right atrial GP in the AF initiation and maintenance. The aim of our study was to assess the efficacy of GP ablation in RA in patients with vagal AF.

Methods and Results—Thirty-four patients without structural heart diseases were randomly assigned for a selective ablation procedure targeted on the elimination of vagal reflex evoked by high frequency stimulation or an extensive approach at anatomic sites of GP. All patients underwent Holter ECG and heart rate variability evaluation at baseline and at 3, 6, 12, and 18 months of follow-up. At a mean follow-up of 19.7 ± 5.2 months, AF recurred in 5 of 17 patients with anatomic ablation and in 13 of 17 patients with a selective approach ($P=0.01$). No patient had major complications. After ablation, heart rate variability parameters showed a significant parasympathetic (and sympathetic) denervation in the first 6 months, which was more prominent in patients with anatomic GP ablation and in those without AF recurrence.

Conclusions—This study demonstrates that in a selected population of vagal paroxysmal AF, the anatomic ablation of GPs in the RA is effective in about 70% of patients. These results confirm that atrial vagal denervation can abolish AF, as suggested by experimental and clinical data. (*Circ Arrhythm Electrophysiol.* 2012;5:22-31.)

Key Words: atrial fibrillation ■ ablation ■ ganglionated plexi ■ autonomic denervation

Catheter ablation of atrial fibrillation (AF) has evolved rapidly over the past years, since the recognition of the pivotal role of the pulmonary veins (PV).¹ Several approaches have been suggested to increase the success of AF ablation.^{2,3} However, the potential procedural risks (4–6% of major complications),^{4,5} the complexity of these approaches, and the frequent requirement of multiple ablative sessions limit patient selection and restricts procedure performance to selected centers.

Clinical Perspective on p 31

More recently, based on experimental and clinical data that suggest the important role of the autonomic nervous system in the pathogenesis of AF,^{6–19} catheter ablation of ganglionated plexi (GP) in the left atrium has been proposed in different clinical condition but with conflicting results.^{20–26} Anatomic studies showed^{27–29} the high prevalence of cardiac ganglia in the posterior surface of the right atrium (RA). Experimental data suggested the potential relevant role of RA GP in the AF initiation and maintenance.^{15–18}

AF results from the interplay between trigger, substrate, and autonomic nervous system in each patient.⁶ In patients

with vagal paroxysmal AF and no structural disease, we can postulate the prevalent role of vagal stimuli in the induction of AF by rapid PV firing^{9–13,19} and in the maintenance of AF by shortening the atrial effective refractory period.⁷

Accordingly, the aim of this prospective study was to evaluate the efficacy and safety of catheter ablation of GP in the RA in a selected population of patients with vagal paroxysmal AF. Patients were randomly assigned for a selective ablation procedure targeted to eliminate parasympathetic response evoked by transcatheter high-frequency stimulation (HFS) or an extensive approach at anatomic sites of GP.

Methods

Study Population

Thirty-four patients (mean age, 48.6 ± 4.6 years; 22 men) with a history of symptomatic vagal paroxysmal AF were enrolled between September 2008 and August 2009. Paroxysmal AF was defined as recurrent AF that terminates spontaneously within 7 days.

Inclusion criteria were symptomatic AF episodes despite prophylaxis with at least 2 different antiarrhythmic drugs, no sign of structural heart disease evaluated through echocardiographic assessment, age between 18 and 65 years, and documented episodes of

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Table 1. Demographic Characteristics of the Study Population

	Overall (n=34)	Anatomic GP Abl (n=17)	Selective GP Abl (n=17)
Age, y*	48.6±4.6	49.5±4.8	47.7±4.4
Sex, males, n (%)	22 (64.7)	10 (58.8)	12 (70.6)
AF vagal triggers, n (%)			
During sleep	23 (67.6)	11 (64.7)	12 (70.6)
After meals	8 (23.6)	5 (29.4)	3 (17.6)
Coughing	3 (8.8)	1 (5.9)	2 (11.8)
AF history, y*	4.9±1.3	4.9±1.4	4.9±1.2
AF episodes/y*	83.6±22.3	85.4±25.6	81.8±23.3
Risk factors for cardiopathy, n (%)			
Hypertension	3 (8.8)	2 (11.8)	1 (5.9)
Dyslipidemia	3 (8.8)	1 (5.9)	2 (11.8)
Echocardiogram*			
Left atrium AP diameter, mm	37.2±0.8	37.1±0.6	37.3±0.9
LVEDD, mm	48.3±3.7	46.4±3.6	47.5±3.8
LVESD, mm	28.4±3.6	27.7±3.4	28.2±3.4
EF, %	63.4±5.3	63.3±5.1	63.5±5.2
Septal thickness, mm	9.7±0.4	9.4±0.6	9.6±0.5
Posterior wall thickness, mm	8.9±0.5	8.7±0.4	8.8±0.6

GP indicates ganglionated plexi; Abl, ablation; AF, atrial fibrillation; AP, anteroposterior; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction.

*Data presented as mean±SD.

vagal tone predominance such as during sleep, after meals, at rest, and in relationship to other vagal triggers (coughing, burping, and swallowing). Exclusion criteria were considered persistent AF, previous AF ablation procedures, sinus node and atrioventricular disturbances, a permanent pacemaker, diabetes mellitus, thyroid dysfunction, renal and hepatic failure, and lung diseases. The clinical characteristics of the patients are shown in Table 1.

Study Protocol

Our institutional review board approved the study protocol. All patients provided written informed consent before being included in the study and randomly assigned. Eligible patients were assigned to 1 of the 2 study arms immediately before the ablation procedure according to a computer-generated randomization list.

According to random assignment, 17 patients underwent selective ablation procedure targeted for the elimination of vagal reflex evoked by transcatheter high-frequency stimulation (HFS), whereas 17 underwent extensive approach at anatomic sites of GP. The clinical characteristics of the patients in the 2 groups were similar (Table 1).

Flecainide or propafenone was discontinued for at least 5 half-lives and amiodarone for at least 1 month before ablation procedure. Patients in both groups were treated with flecainide or propafenone for 2 months after ablation.

Every patient underwent 24-hour Holter ECG and heart rate variability (HRV) 2 days before ablation procedure (baseline) and at 3, 6, 12, and 18 months of follow-up. The personnel who performed postablation Holter ECG and HRV analysis were blinded to ablation grouping. Moreover, a clinical evaluation and resting ECG was performed at 1, 3, and every 3 months after the ablation procedure or in the case of occurrence of any clinical symptom.

The primary end point of this study was considered freedom from AF and atrial flutter/tachycardia recurrences. AF recurrence was defined as any electrocardiographically confirmed episode of AF lasting >30 seconds. Time to AF recurrence was computed as the number of days between the ablation procedure and the ECG confirmation of the arrhythmia. The first 2 months after the ablation procedure (blanking period) were excluded from the analysis of patient outcome and of autonomic function during the follow-up.

RA Electroanatomic Mapping and Electrophysiological Study

Mapping and ablation procedure were performed in a fasting state using a mild sedation and under local anesthesia. A decapolar diagnostic catheter was placed into coronary sinus. A special deflectable 8-mm tip catheter (Navistar DS, Biosense Webster) was used for mapping and ablation. Electroanatomic mapping of the RA was performed through CARTO XP (Biosense Webster, Diamond Bar, CA) for patients enrolled until July 2009 and with CARTO 3 for those enrolled after this period. CARTO XP electroanatomic mapping system was described in detail previously.^{2,3} In patients who underwent CARTO 3 system, a 3-dimensional fast anatomic mapping of the RA was performed (Figure 1B and Figure 2B).

Before GP mapping and ablation, all patients underwent electrophysiological study. Bipolar electrograms were filtered from 80–500 Hz and displayed and acquired on a Bard, Laboratory System Duo. Surface ECG leads I, II, V₁, and V₅ were recorded continually during the study. A programmed digital stimulation (Micropace EPS320, Bard Electrophysiology) was performed at twice diastolic threshold. Programmed atrial stimulation, with up to 2 extrastimuli during a pacing cycle length of 600 ms and 400 ms, continuously and decrementally reducing the pacing cycle length up to 200 ms to perform AF and atrial flutter induction. In cases of induction of isthmus-dependent RA flutter, cavotricuspid isthmus ablation was also performed. The inducibility of AF was not tested in patients that presented restored sinus rhythm during radiofrequency application.

During AF and after ablation, the prevalence of complex fractionated atrial electrograms (CFAEs) was determined by using CFAEs software of CARTO System, as previously described.³⁰ Interval confidence level displays the total amount of intervals counted for each point (all intervals, between 2 consecutive peaks, included between a minimum and maximum duration of 15 ms and 30 ms, respectively). The minimum threshold voltage was 0.05 mV; in the case of relevant noise, the minimum voltage was increased to 0.07 mV. The maximum voltage was set to 1 mV to consider all signals. The prevalence of CFAEs was determined by using the interval confidence level map, distinguishing points with high, medium, and low fragmentation.³⁰ Both the points with high fragmentation and those with medium fragmentation were considered for our CFAE analysis.

Autonomic Denervation Through the Anatomic Approach

This ablation procedure is based on radiofrequency delivery at the anatomic sites of GP previously described in several studies regarding human hearts.^{27–29} We have considered as ablation sites (radiofrequency energy at 60°, 30–70 W for 30–60 seconds, Stockert Biosense Webster) the following areas where all the presumed RA GP clusters are located (Figure 1A and 1B): the superoposterior area (superior RA GP, adjacent to the junction of the superior vena cava [SVC] and the posterior surface of the RA), the middle posterior area (posterior RA GP, posterior surface of the RA adjacent the interatrial groove), the inferoposterior area (GP placed between inferior vena cava, coronary sinus ostium and near the atrioventricular groove). Considering that the exact anatomic borders of GP clusters are unknown, we decided to perform this ablation procedure delivering an expanded number of radiofrequency applications and forming a cloudlike shape ablation model, previously described in detail.²⁴ All patients underwent AF induction before anatomic GP ablation. Ablation was performed until atrial electric activity was significantly reduced (peak to peak bipolar electrogram <0.05 mV) and vagal

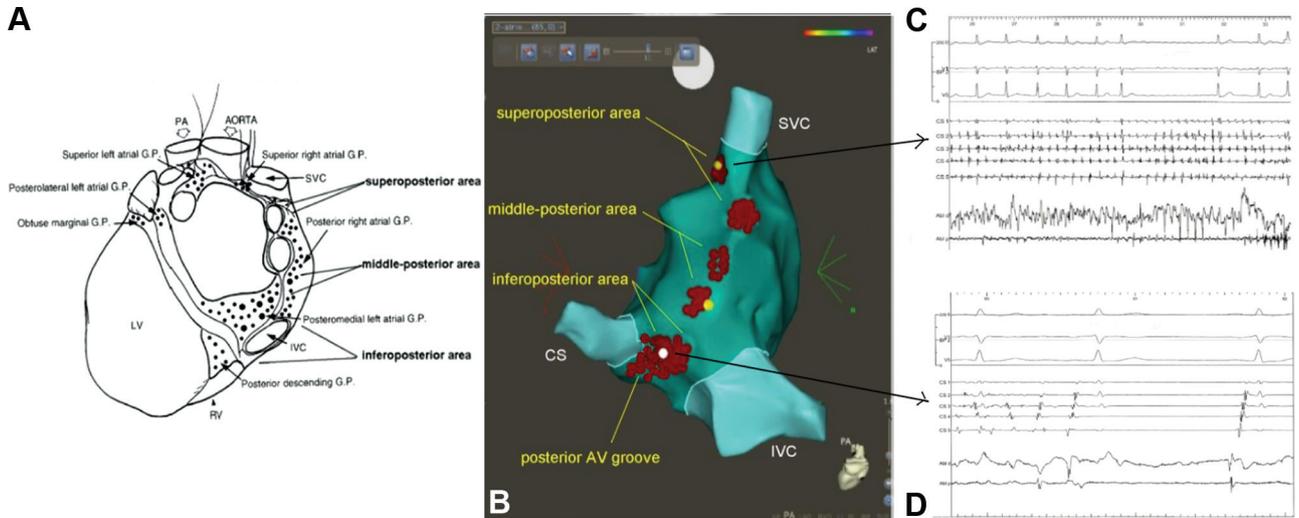


Figure 1. **A**, Posterior view of the human heart illustrating the locations of major atrial ganglionated plexi (GP). **B**, CARTO 3 Fast Anatomic Map of the right atrium (RA) (posteroanterior projection) in a case of anatomic GP ablation. **Red dots** represent sites of radiofrequency pulse; **yellow dots**, sites of parasympathetic response elicited during radiofrequency application; and **white dots**, sites where atrial fibrillation (AF) terminated during ablation. CS indicates coronary sinus; IVC, inferior vena cava; SVC, superior vena cava; and AV, atrioventricular. **C**, Parasympathetic response evoked during anatomic ablation. **D**, Restoration of sinus rhythm during anatomic ablation (I, V₁, and V₆, surface ECG; CS1–CS5, distal and proximal coronary sinus; Abl d/p, bipolar distal and proximal mapping and ablation catheter; and BP, blood pressure).

reflex during radiofrequency application disappeared. High output pacing was performed near the SVC to avoid phrenic nerve ablation.

Autonomic Denervation Guided by HFS

Ablation sites were identified as the places where HFS evoked a vagal response. HFS was performed at the posterior and septal surface of RA adjacent to the junction of the SVC and RA (superior RA GP), adjacent to the interatrial groove (posterior RA GP), between the inferior vena cava and septum near the coronary sinus

ostium (inferior RA GP), and adjacent to the atrial ventricular groove.

Rectangular electric stimuli were delivered at a frequency of 20 Hz, amplitude of 12 V increasing to 15 V in the case of no vagal reflex evoked, and pulse duration of 10 ms (Stimulator TECS II, Medico, Italy). A significant parasympathetic response (Figure 2A) was defined as prolongation of R-R interval by >50% during AF associated to a sudden >20 mm Hg decrease in blood pressure (recorded from continuous invasive arterial monitoring), as previ-

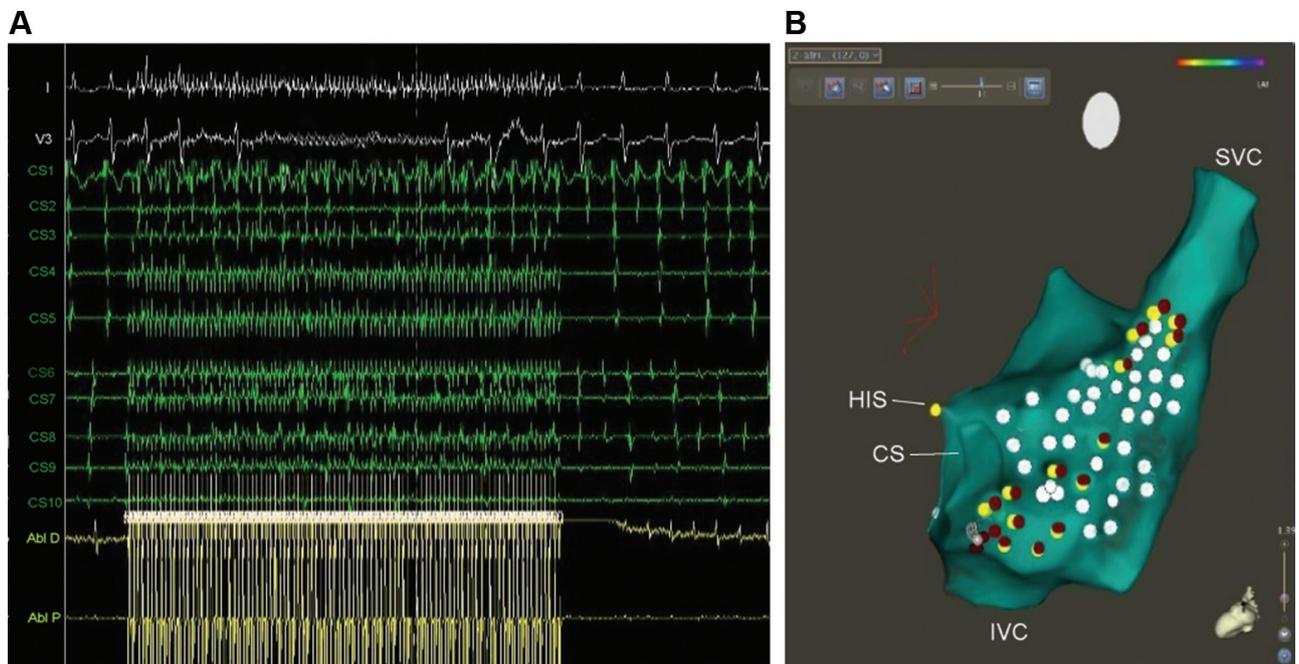


Figure 2. **A**, Parasympathetic response evoked during high-frequency stimulation (HFS) near coronary sinus ostium (I and V₃, surface ECG; CS1–CS10, distal and proximal coronary sinus; Abl d/p, bipolar distal and proximal mapping and ablation catheter). **B**, CARTO 3 Fast Anatomic Map of right atrium (RA) (lateral projection) in a case of selective ganglionated plexi (GP) ablation. **Red dots** represent sites of radiofrequency pulse near HFS-positive sites (**yellow dots**). **White dots** represent HFS-negative sites. HIS indicates proximal His bundle; CS, coronary sinus; IVC, inferior vena cava; SVC, superior vena cava; and AV, atrioventricular.

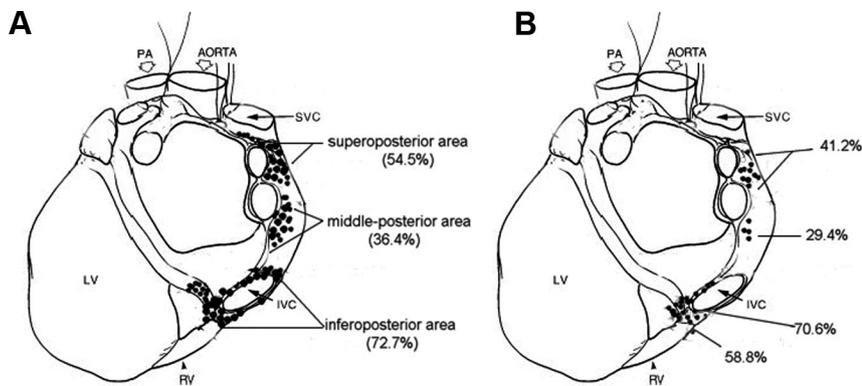


Figure 3. **A**, Distribution of sites where radiofrequency applications evoked a parasympathetic response during anatomic ablation. **B**, Distribution of sites where high-frequency stimulation evoked a parasympathetic response during selective approach. PA indicates pulmonary artery; IVC, inferior vena cava; SVC, superior vena cava; RV, right ventricle; and LV, left ventricle. See text for further details.

ously described.^{21,24,25} All sites where a significant parasympathetic response was elicited through HFS were recorded on the anatomic map of the atrium (Figure 2B). Radiofrequency energy was delivered until the abolition of all vagal reflexes evoked with repeated HFS. The order of HFS and ablation was superior RA GP, posterior RA GP, and the inferoposterior GP. Before HF stimulation applying to the atrial ventricular groove, the catheter tip was moved away from the annulus to avoid the risk of ventricular fibrillation induction.

Evaluation of Autonomic Function

Minimum, mean, and maximum heart rate (HR) and time-domain and frequency-domain HRV were analyzed from 24-hour Holter ECG monitoring (Medical, Synescope Multi Channel-Multi Day, Version 3.10, Italy). Ventricular ectopic beats, electric noise, or other aberrant ECG signals were excluded from HRV analysis.

Time-domain parameters were the standard deviation of all normal R-R intervals in the 24-hour ECG recording (SDNN), the root-mean-square of differences between successive R-R intervals (rMSSD), and the percentage of sinus cycles differing from the preceding cycle by >50 ms over the entire 24-hour ECG recording (pNN50). Power spectral analysis (through fast Fourier transformation) of all normal R-R intervals was performed.

Frequency-domain measures were the absolute value of the low (LF) and high frequencies (HF) and their logarithmic transformation (ln LF and ln HF). The sympathetic vagal balance was assessed through the LF/HF ratio.

Statistical Analysis

On the basis of previously published data, the study was designed to detect a 50% absolute difference in 18-month AF recurrence rate, between the anatomic and selective approach groups with a statistical power of 80% and a bilateral type I error of 0.05. Assuming that 78% (n=24) of patients in the anatomic group would have been free of AF recurrences in an 18-month follow-up, it was estimated that 17 patients per treatment group were necessary to reach the primary study end point.

Statistical analysis was performed using STATA SE 10 software package (StataCorp, TX). Continuous variables were presented as mean±standard deviation and categorical values as frequency (%). Comparisons between study groups of baseline and 3-, 6-, 12-, and 18-month follow-up repeated measures of continuous variables were performed by means of the Generalized Estimating Equation method with first-order autoregressive correlation structure. Scheffé test was used for post hoc analysis. Freedom from AF recurrences was determined by using Kaplan-Meier analysis and differences in AF-free survival were evaluated through the log-rank test. Statistical significance was defined as a 2-sided probability value <0.05.

Results

Procedural Data and Selective and Anatomic GP Ablation

All patients completed the planned interventional procedure. The mean procedure time was 61±12 minutes in the ana-

tomic ablation group and 94±17 minutes in the selective GP ablation group (P<0.01). The overall ablation time was 39±8 minutes for the anatomic approach and 21±6 minutes for the selective approach (P=0.001). Moreover, the mean x-ray time was 17±5 minutes for the anatomic approach and 18±6 minutes for the selective GP ablation (P=0.61).

RA burst pacing induced sustained AF in all patients of both groups.

A parasympathetic response (Figure 1B and 1C) was observed, at least in 1 site, in 11 patients (65%) during anatomic ablation: in 8 patients (73%) during radiofrequency application in the inferoposterior area, in 6 (54%) in the superoposterior area, and in 4 (36%) during ablation in the middle posterior area (Figure 3A). A total of 82±16 radiofrequency applications were delivered with a mean of 19±6 radiofrequency pulses at each anatomic site of GP and with the following distribution: 28±7 radiofrequency applications in the inferoposterior area, 16±6 in the superoposterior area, and 13±5 in the middle posterior area. The average diameter of cloudlike shape ablation model, indicating the extension of radiofrequency applications, ranged from 16.4±2.1 mm (inferoposterior area) to 11.7±5.2 mm (middle posterior and superoposterior area). radiofrequency ablation of GP placed near the inferior vena cava was less extended for risk of phrenic nerve injury (6.4±1.3 mm).

In 6 (35%) patients, AF terminated during ablation (Figure 1B and 1D). In only 1 patient, the ablation procedure in the superoposterior area was less extensive than in other patients for having captured phrenic nerve during high output pacing near SVC at the level of anteroseptal area.

In the selective ablation group, a mean of 25±6 atrial HF stimulations were performed for each patient. A parasympathetic response was observed in all patients with an average of 6±3.2 GP sites per patient. The sites where a vagal reflex was elicited were localized between inferior vena cava and coronary sinus ostium in 12 patients (71%), adjacent to the atrioventricular groove in 10 patients (59%), adjacent to the junction of the superior vena cava and the posterior surface of the RA in 7 patients (41%), and adjacent to the interatrial groove in 5 (29%) (Figure 3B). An average of 4.5±2.2 radiofrequency applications was necessary to eliminate the vagal reflex at the same targeted site (Figure 2B). In 4 patients (23%) a vagal reflex was observed during radiofrequency applications and in 8 patients (47%, P=0.7 versus anatomic approach) AF terminated during ablation.

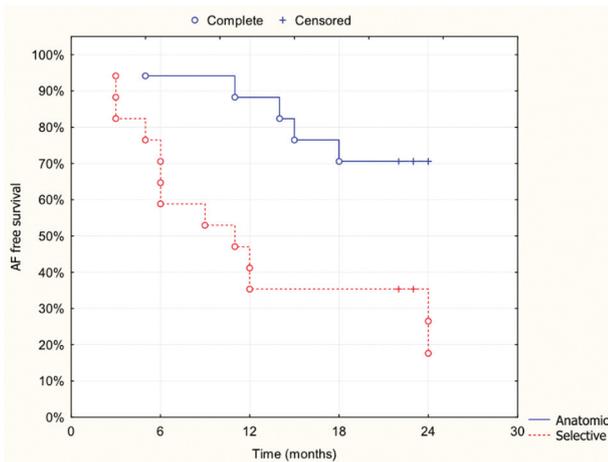


Figure 4. Kaplan-Meier curve and survival analysis indicates freedom from atrial fibrillation (AF) recurrences after anatomic (continuous line) and selective (dashed line) anglionated plexi ablation.

Overall, the CFAEs were present in 23% of the points acquired in the RA. The higher prevalence of CFAEs was found in the posteroseptal area close to coronary sinus ostium (33 of 34 patients), in the superior and midseptal areas (31 patients), and in the posterior wall, particularly in proximity of the SVC-RA junction (23 patients). Of the 34 patients, GP ablation caused CFAE disappearance and significant reduction in 12 and 21 patients, respectively. Finally, 1 patient of the selective GP ablation group and 1 patient of anatomic GP ablation group also underwent cavotricuspid isthmus ablation for inducibility of typical atrial flutter before GP ablation.

Clinical Outcome

Patients were followed for 19.7 ± 5.2 months. AF recurrences were observed in 18 of 34 patients. AF burden was reduced in 15 of 18 patients with recurrences, whereas in 3 patients it remained unchanged. The arrhythmia recurred in 5 of 17 patients with anatomic ablation and in 13 of 17 patients with selective ablation ($P=0.01$). The survival analysis (Figure 4) showed a worse clinical outcome of patients who underwent selective GP ablation when compared with those treated with anatomic approach (log-rank test, $P=0.005$). The Kaplan-Meier estimates of AF-free rates at 1 year were $88 \pm 9\%$ in the anatomic approach group and $35 \pm 12\%$ in the selective group.

After ablation, both in the selective and in anatomic GP ablation, many AF episodes were not related to vagal tone predominance, as observed before ablation. Only in 4 of 13 patients with AF recurrence after selective GP ablation and in 1 of 5 patients with AF recurrence after anatomic approach maintained the same vagal triggers.

Organized atrial tachyarrhythmias were not observed in any patient during the follow-up period. No patient had major complications related to ablation procedure. One case of symptomatic inappropriate sinus tachycardia was observed after anatomic approach and was completely resolved after 1 month of therapy with low-dose of β -blockers.

Autonomic Evaluation

At 3 months after ablation, Holter ECG and time-domain HRV parameters showed a significant modification in ana-

tomous and selective ablation groups when compared with baseline (Table 2). At 6-month follow-up, Holter ECG and time-domain HRV parameters remained different from baseline in the anatomic ablation group, whereas they returned to baseline in the selective ablation group (Table 2).

After anatomic GP ablation, a greater increase of minimal HR ($P<0.01$ at 6 months) and of mean HR ($P<0.01$ at 3 and 6 months) and a greater decrease of SDNN ($P<0.01$ at 3 and 6 months), rMSSD ($P<0.01$ at 3 and 6 months), and of pNN50 ($P<0.02$ and $P<0.01$ at 3 and 6 months, respectively) occurred when compared with selective approach (Table 2). LF and HF, at 3- and 6-month follow-up, showed a trend in a greater decrease in anatomic ablation group but did not reach statistical significance.

Finally, at 3 and 6 months, patients without AF recurrences during the follow-up showed a significant increase in mean and minimal HR and a significant decrease of SDNN, pNN50, LF, and HF when compared with baseline (Table 3). In patients with AF recurrences, modifications of minimal and mean HR, SDNN, and frequency-domain HRV parameters disappeared at 6-month follow-up.

Discussion

Main Findings

In this study, conducted in 34 symptomatic patients with vagal paroxysmal AF, the following were observed. (1) radiofrequency catheter ablation of GP in the RA determined significant autonomic changes and a relevant reduction of AF recurrence. (2) The anatomic ablation of GP in the RA was superior to selective GP ablation guided by HFS in maintaining patients free of AF recurrence during 19.7 ± 5.2 months. In fact, AF recurred in 5 of 17 who had undergone anatomic ablation and in 13 of 17 patients who had undergone selective GP ablation. (3) After ablation, HRV parameters showed a significant parasympathetic and sympathetic denervation in the first 6 months, which was more prominent in patients with anatomic GP ablation and in those without AF recurrence. (4) The procedure was safe and required a relatively short time. (5) CFAEs were mainly found in the posterior and septal wall in proximity of vagal sites evoked at HFS or during ablation. GP ablation induced the disappearance and a significant reduction of CFAE in 12 and 21 patients, respectively.

Previous Studies

Experimental studies^{7,15} have demonstrated that stimulation of GP, associated with a parasympathetic response caused by release of acetylcholine, increases vulnerability for AF by shortening the refractory period of atrial and PV sleeves and by increasing the dispersion of refractoriness. Furthermore, it has also been shown that GP stimulation determines rapid PV firing due to triggered activity.¹² In fact, GP activation produces contemporary increase of cholinergic activity that shortens PV refractory period and adrenergic activity that favors high intracellular calcium concentrations leading to early after-depolarization.

Animal studies have shown that catheter ablation of GP may prevent AF.^{8,16,18,19} In clinical practice, Platt et al³¹ first proposed GP ablation as a stand-alone treatment for AF, without isolation of PV. Of the 23 patients with a complete

Table 2. Heart Rate, Time-Domain HRV, and Frequency-Domain HRV Evaluation Before and After Anatomic and Selective GP Ablation

	Group	Before Ablation	3 Months	6 Months	12 Months	18 Months	P
HR, bpm							
Minimum	A	41.1±4.3	58.8±3.4*	55.6±3.3*	43.2±4.8	42.3±3.9	0.003
	S	42.3±4.6	53.6±3.8*	43.3±3.3†	44.2±3.6	43.4±4.1	
Mean	A	64.5±3.3	78.4±3.1*	72.1±3.4*	65.3±3.8	64.1±3.0	<0.001
	S	63.3±4.2	66.4±3.1†	62.1±4.5†	64.8±3.9	63.9±4.4	
Maximum	A	104.3±11.1	106.8±12.2	105.3±11.2	104.5±10.8	104.1±10.9	0.63
	S	105.4±10.6	107.1±10.1	106.3±11.6	105.5±11.1	105.1±10.9	
Td HRV, ms							
SDNN	A	152.2±9.9	98.7±4.5*	127.5±8.3*	149.8±9.1	151.6±9.4	<0.001
	S	42.3±4.6	53.6±3.8*†	43.3±3.3†	44.2±3.6	43.4±4.1	
rMSSD	A	55.5±4.4	38.7±4.9*	47.2±4.5*	53.4±4.6	54.3±4.2	0.001
	S	56.3±3.8	43.2±4.5*†	54.8±3.7†	54.4±3.8	55.9±4.1	
pNN50	A	29.1±1.7	18.3±4.3*	22.2±1.8*	28.4±1.9	28.9±1.7	<0.001
	S	29.7±1.9	22.3±4.6*‡	28.7±1.9†	28.9±1.5	29.2±1.8	
Fd HRV, ms ²							
Ln LF	A	6.81±0.92	5.12±0.92	5.83±0.92	6.57±0.89	6.75±0.87	0.12
	S	6.61±0.89	5.81±0.87	6.56±0.89	6.52±0.92	6.59±0.91	
Ln HF	A	6.12±0.85	4.03±0.61	4.55±0.81	5.92±0.95	6.04±0.91	0.14
	S	5.92±0.86	4.85±0.64	5.68±0.83	5.65±0.99	5.97±0.92	
LF/HF	A	1.61±0.55	1.83±0.51	1.94±0.63	1.72±0.58	1.65±0.53	0.63
	S	1.71±0.65	1.85±0.49	1.92±0.54	1.86±0.58	1.68±0.62	

HRV indicates heart rate variability; GP, ganglionated plexi; A, anatomic group; S, selective group; HR, heart rate; Td, time domain; Fd, frequency domain; SDNN, standard deviation of all normal R-R intervals; rMSSD, the root-mean-square of differences between successive R-R intervals; pNN50, the percentage of sinus cycles differing from the preceding cycle by >50 ms over the entire 24-hour ECG recording; LnLF, natural logarithm of low-frequency power; LnHF, natural logarithm of high-frequency power.

* $P<0.001$ vs preablation; † $P<0.01$ vs anatomic ablation group; ‡ $P<0.02$ vs anatomic ablation group. Results of the analysis are from time of procedure, excluding the blanking period.

study, 22 were AF-free during 6 months of follow-up. In the same year, Pappone et al² observed that the detection of vagal reflexes during encircling of PV significantly decreased AF recurrence leading to a 99% of success over 12-months. HFS with registration of vagal reaction was used to define the GP location by Lemery et al.²¹ radiofrequency ablation was delivered over each targeted positive vagal site extended to adjacent areas showing CFAEs. The authors specifically focused on GP in the PV antral regions. Only in 3 patients was ablation in the RA performed. After ablation of GP, HFS over previously sites, showed a negative response in 88% of cases. The procedure was effective in 7 of 14 patients with paroxysmal and persistent AF during a mean follow-up of 1 month. Scanavacca et al²⁰ located GP by applying HFS to both the endocardial and epicardial atrial regions, and, as observed by Lemery et al,²¹ only in few sites of radiofrequency delivery vagal reflexes was noted. Of the 7 patients in whom vagal denervation was obtained, 2 (29%) had no AF recurrence over a mean follow-up of 8 months. It should be noted that, as commented by the same authors,³² they found some limitations during GP mapping and epicardial ablation because in some patients GP sites could not be identified during HFS and some times were too close to the phrenic nerves or the esophagus, precluding epicardial delivery. Furthermore, Scanavacca et al²⁰ did not perform the ablation

in the superoposterior GP, the “head stage” for the vagal input to other GP.³³ Po et al²⁵ showed that combination of GP ablation with PV isolation in 83 patients with both paroxysmal and persistent AF was effective in 80% of patients at 12 months and 86% at 22 months. This late benefit of a single ablation procedure is remarkable. The authors postulate that the long-term efficacy of this approach may result from destruction of the neurons in the GP that cannot regenerate.

More recently, an alternative approach has been proposed, characterized by extended radiofrequency ablation of GP based on anatomic data of cardiac ganglia topography.^{22,24,26} Pokushalov et al²⁴ demonstrated that the anatomic approach confers better results than selective GP ablation guided by HFS in patients with paroxysmal AF (77.5% versus 42.5% AF-free at a mean follow-up of 13 months). In this study, GP ablation was mainly performed in the left atrium (LA). The same group did not observe a good result with this approach in longstanding persistent AF.²⁶

Potential Mechanisms of the Efficacy of the Ablation of RA GP

Our results can be, at least in part, related to the population involved. In fact, this study has been planned in a specific subgroup of patients with AF episodes suggestive of vagally induced paroxysmal AF. The effect of GP ablation in this

Table 3. Heart Rate, Time-Domain HRV, and Frequency-Domain HRV Evaluation in Patients With and Without AF Recurrences

	Group	Before Ablation	3 Months	6 Months	12 Months	18 Months	P
HR, bpm							
Minimum	W/O AF	49.3±5.3	59.3±1.3*	57.3±5.3*	50.2±3.4	49.8±5.1	0.001
	With AF	48.1±4.2	56.6±2.6*	48.4±4.3	49.1±3.6	48.9±3.9	
Mean	W/O AF	57.2±2.9	77.3±2.5*	65.1±3.1*	58.3±2.9	56.9±3.1	0.05
	With AF	59.5±3.3	69.3±3.6*	58.1±5.7	59.3±3.9	59.4±3.5	
Maximum	W/O AF	112.4±11.6	113.8±11.6	111.2±11.7	110.6±10.4	111.8±10.9	0.46
	With AF	110.3±11.1	107.8±12.2	107.3±11.7	109.5±10.3	111.2±11.1	
Td HRV, ms							
SDNN	W/O AF	145.2±8.2	96.7±3.5*	130.4±8.2*	145.8±9.1	145.3±8.9	<0.001
	With AF	148.2±8.7	135.2±7.4*†	144.6±8.8	146.8±7.2	148.6±8.1	
rMSSD	W/O AF	52.4±3.1	35.7±4.6	41.2±4.3	53.4±4.2	52.3±3.9	0.07
	With AF	50.3±2.8	42.2±4.4	49.8±3.3	52.1±3.6	51.1±3.1	
pNN50	W/O AF	33.4±1.5	19.3±4.3*	24.2±1.9*	31.3±1.8	32.5±1.7	0.001
	With AF	31.8±1.8	25.4±3.7*†	30.7±1.7†	32.4±1.7	31.6±1.9	
Fd HRV, ms ²							
Ln LF	W/O AF	6.43±0.73	4.72±0.92*	5.23±0.82*	6.01±0.72	6.35±0.75	0.001
	With AF	6.75±0.96	5.74±0.87*	6.42±0.97	6.66±0.92	6.71±0.86	
Ln HF	W/O AF	5.27±0.72	3.51±0.61*	4.02±0.81*	4.62±0.95	4.75±0.73	0.005
	With AF	5.32±0.72	4.31±0.61*	4.73±0.72	5.01±0.99	5.26±0.75	
LF/HF	W/O AF	1.75±0.35	1.74±0.62	1.82±0.53	2.35±0.58	2.18±0.56	0.37
	With AF	1.71±0.58	1.92±0.51	2.32±0.57	1.82±0.58	1.74±0.52	

HRV indicates heart rate variability; AF, atrial fibrillation; HR, heart rate; Td, time domain; SDNN, standard deviation of all normal R-R intervals; rMSSD, the root-mean-square of differences between successive R-R intervals; pNN50, the percentage of sinus cycles differing from the preceding cycle by >50 ms over the entire 24-hour ECG recording; Fd, frequency domain; LnLF, natural logarithm of low-frequency power; LnHF, natural logarithm of high-frequency power.

* $P<0.001$ vs preablation; † $P<0.001$ vs without AF recurrences. Results of the analysis are from time of procedure, excluding the blanking period.

subgroup of patients can be higher than other AF subsets. Coumel et al⁶ first reported that patients with vagal AF were typically young with nocturnal episodes of AF or after the intake of abundant food or alcohol, generally without heart disease. Thus, we can hypothesize that substrate for AF maintenance was poor in these cases. Moreover, the effect of GP ablation appears to be related also to a different AF substrate.

In previous reports, the GP were generally targeted for ablation only in the LA, although it has been observed that about 50% of such structures are present on the surface of the RA.^{27–29} We designed our study on the basis of anatomic distribution of atrial GP as described by studies in humans.^{27–29} Armour et al²⁷ observed that the largest number of ganglia (an average of 194 of the 458 per heart) is located on the posterior surface of the RA adjacent to the interatrial groove: the so-called posterior RA GP. Moreover, this GP presented ganglia containing much more neurons than ganglia in other GPs.²⁷ In the RA, the superior RA GP has also been described positioned on the posterior surface of the RA adjacent to the junction of the superior vena cava and between the SVC and the aorta. This superoposterior area also known as superior vena cava-aortic GP or “third fat pad” is the nexus point for the vagal input to the GP before innervating the atria.³³ Recently, Lu et al³⁴ demonstrated that direct injection

of acetylcholine into this GP initiated rapid superior vena firing. Moreover, they found that the ablation of this GP increased the effective refractory period, decreased the window of vulnerability, and eliminated the AF induction at the superior vena cava by HFS. Furthermore, the posteromedial LA GP that is the largest GP in the LA can be, at least in part, destroyed by delivering radiofrequency ablation in the RA (posteroseptal space and inside coronary sinus). The effectiveness of our anatomic approach could be due to the extension of our lesion in the area of GP. In fact, we have preferred to deliver multiple radiofrequency applications, forming a cloudlike shape and not a line, because, as Pokushalov et al²⁴ observed, “the exact anatomic borders of GP clusters are unknown and their location can vary slightly in different patients.” It should be noted that in patients with AF, the GP are hyperactive, thereby releasing excessive amounts of neurotransmitters, particularly in the vicinity of the GP.³⁵ Thus, an extensive anatomic GP ablation could be more effective than selective GP ablation for this reason, too. The physiopathological role of RA GP has been underlined by several experimental studies.^{14–18} In fact, the GPs in both atrial presented multiple interconnections, and thus the GPs in the RA can modulate distant GP in the LA. Hou et al¹⁵ observed that right vagosympathetic stimulation was more arrhythmogenic than left stimulation. In fact, GP ablation

eliminated AF inducibility only when performed in the anterior RA GP situated between the caudal end of the sinoatrial node and right superior pulmonary vein-atrial junction. The authors postulated that this GP can play a more active role in the AF initiation because of the larger axonal field extending into both atria. More recently, Lu et al¹⁸ observed that GP stimulation in the right side determines focal rapid firings and AF originating also from distant PV, suggesting that the focal firing was initiated by an autonomic mechanism that involves the activation of “integration centers” in the intrinsic cardiac autonomic nervous system. These data were confirmed by the observation that in this study the right-sided GP ablation on the atria significantly increased the AF threshold induced by HFS at a distant site.

The effect of our lesions in the RA can be also related to CFAE ablation. CFAEs point to areas with abnormal propagation of the electric impulse, and it is conceivable that they are involved in arrhythmogenic processes and can be an attractive target for AF treatment.⁴ Some studies^{11,14,21,24} observed that CFAE are consistently present in atrial areas adjacent to GP. This can be explained by the shortening of action potentials determined by the release of acetylcholine and the highest effect of this neurotransmitter is in the proximity of the autonomic neurons concentrated at the GP. Most important, it has been observed that application of acetylcholine in the RA produced activation of left atrial GP suggesting the presence of an interactive atrial neuronal network that connects each GP to multiple other GPs.^{14–18} The progressive organization of atrial electrograms with serial GP ablation confirms that the connection of GP is crucial in the AF maintenance.^{14–18} In our study, CFAEs have been observed around each positive vagal site the postero-septal region, particularly the postero-septal space, showed the greatest prevalence of such electrograms. GP ablation determined in 33 of the 34 patients studied the disappearance or the significant reduction of CFAE. We can hypothesize that an anatomic GP ablation is superior to a selective approach also because of a greater elimination of CFAE surrounding the GP is obtained. The importance of ablating GP and adjacent CFAE is clearly suggested by the finding that PV isolation has a lower efficacy in vagotonic AF than in adrenergic or random AF, suggesting that the PVs less often play an important role in this subgroup of patients.³⁶

Finally, some studies showed the relevance of RA ablation both in paroxysmal and in chronic AF.^{37–39} Gaita et al³⁷ demonstrated that a septal line can be effective in patients with vagal paroxysmal AF, particularly when the septum presented “disorganized” electric activity. The effectiveness of atrial lesions in the RA can be caused by several factors such as conduction deterioration, increased nonuniform anisotropy, and disorganized electric activity. Several mapping and ablation studies found the septum and posterior wall of the RA (regions with the largest prevalence of cardiac ganglia) as the areas with higher prevalence of CFAE.^{3,30,39} The higher efficacy of posterior and septal lesion in the RA^{38,39} can be probably explained by the vagal denervation due to the ablation of GPs that are largely represented in these atrial areas.^{27–29} On the other hand, we cannot exclude that our results could be, at least in part, due to radiofrequency

pulses that affect critical areas for AF independently from autonomic denervation.

Effect of GP Ablation in the RA on Autonomic Parameters

Our data showed that GP ablation in the RA determine a significant autonomic denervation that was more prominent and longer lasting in the group of patients with the anatomic approach and in patients without AF recurrence during the follow-up. In fact, the sympathetic and parasympathetic tone recovered at 12 months in patients who had undergone anatomic GP ablation and in those without AF recurrences and recovered at 6 months in patients treated with the selective approach and in those with AF recurrences. However, it is difficult to understand if results of this ablation procedure can be related to the persistence of a middle-term effect on autonomic function. On the other hand, despite that several investigations^{20,24,40} showed a recovery of autonomic nervous system within 3–6 months, there is still no evidence to suggest that the reinnervation can be directly related to an increase of AF recurrence rate.⁴¹ Pokushalov et al²⁴ reported a relevant effect of anatomic GP ablation on parasympathetic tone, whereas the sympathetic tone increased. Similar to our data, Scanavacca et al²⁰ found that in the first months after ablation, there is a reduction of LF and HF. Furthermore, patients without AF recurrence had more significant changes in HRV parameters when compared with patients with AF recurrences.

In conclusion, this study demonstrates that the anatomic ablation of GPs in the RA showed to be effective in about 70% of patients without performing the PV disconnection. These results confirm that atrial vagal denervation can abolish AF, as suggested by experimental and clinical data. It must be underlined that this study has been planned in a specific subgroup of patients with no sign of structural heart disease and with documented episodes of AF during vagal tone predominance such as during sleep, after meals, coughing, and so forth. These characteristics features identify the patients in whom RA GP ablation should be performed.

It can be hypothesized that a better understanding of GP localization in the single patient and the role of each GP in initiation and maintenance of AF will guide the future development of “neuroablation” strategies in an effective cure of AF. Further studies in larger population should clarify if biatrial ablation of GPs alone or in association with PV disconnection could significantly increase the success in AF ablation.

Study Limitations

Our study presents some limitations. First, in this study we have enrolled selected patients affected by vagal paroxysmal AF. The efficacy of our ablation approach could be inferior or absent in other forms of AF not related to vagal trigger.

Second, we cannot exclude that the effect of the extensive approach at anatomic sites of GP was also related to a reduction of atrial tissue (the so-called “debulking”).

Third, the prevalence of positive HFS sites was low, indicating a possible limit of stimulation output to identify and localize the GP sites. We used stimulation parameters

similar to other authors that showed heterogeneous results of the selective approach.^{20,24,25} A possible explanation of the reduced efficacy of GP ablation guided by HFS could be that as previous investigations showed,^{20,24} endocardial areas where HFS evoked a parasympathetic response can be smaller than those where GP clusters are really concentrated. Moreover, as Pokushalov et al²⁴ hypothesized, we cannot exclude that the areas with parasympathetic response to HFS may not necessarily correspond to the anatomic regions of GP concentration.

Fourth, the inclusion criteria of our study considered patients with vagal paroxysmal AF and documented episodes of vagal tone predominance such as during sleep, after meals, at rest, and in relationship to other vagal triggers (coughing, burping, and swallowing). Therefore, we have not included patients affected by AF episodes not related to vagal triggers. Nevertheless, we cannot exclude that in some patients there are AF episodes not related to vagal triggers.

Finally, a potential limitation is the absence of a comparison with a group of patients undergoing PV isolation.

Disclosures

Drs Pitrone and Dottori are employees of Biosense-Webster Inc.

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CLINICAL PERSPECTIVE

Transcatheter ablation is an established therapy to cure atrial fibrillation. Many ablative approaches were focused on the pathophysiological mechanism of the underlying arrhythmia. The autonomic nervous system is known to play an important role in the pathogenesis of atrial fibrillation. Catheter ablation of ganglionated plexi in the left atrium has been proposed in different subgroup of patients with atrial fibrillation. However, anatomic studies found a prevalence of ganglionated plexi also along the right atrial posterior wall. In the present study, we analyze the efficacy of ganglionated plexi ablation in the right atrium, in patients with vagal atrial fibrillation. We found that right atrial ganglionated plexi ablation may be successful to cure patient with vagal atrial fibrillation in approximately 70% of patients. An anatomic ablative approach was much more effective than a selective approach, with ganglionated plexi identified by means of high-voltage and high-frequency pacing. After ablation, heart rate variability parameters showed a significant parasympathetic denervation in the first 6 months that was more evident in patients with anatomic ganglionated plexi ablation and in those without atrial fibrillation recurrence. These results confirm that vagal denervation may abolish atrial fibrillation in selected patients. Subjects with vagal atrial fibrillation could be selected for safer and simpler ablative procedures.