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

Running title: Calò et al.; autonomic denervation for atrial fibrillation

Leonardo Calò, MD, FESC1; Marco Rebecchi, MD1; Luigi Sciarrà, MD1; Lucia De Luca, MD1; Alessandro Fagagnini, MD1; Lorenzo Maria Zuccaro, MD1; Pietro Pitrone, BS2; Serena Dottori, BS2; Maurizio Porfirio, MD1; Ermenegildo de Ruvo, MD1; Ernesto Lioy, MD1

1Division of Cardiology, Policlinico Casilino, ASL Roma B, Rome; 2Biosense Webster Italy, Johnson & Johnson Medical, Milan, Italy

Address for correspondence:
Dr Leonardo Calò
Division of Cardiology
Policlinico Casilino
Via Buonarroti, 16
00047 Marino (Rome) - Italy
Phone: +39-06-93668162
Fax: +39-06-93668162
E-mail: leonardo.calo@tin.it

Abstract:

**Background** - Catheter ablation of ganglionated plexi (GP) in the left atrium has been proposed in different subgroup of patients with atrial fibrillation (AF). Anatomical 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 randomized for a selective ablation procedure targeted on the elimination of vagal reflex evoked by high frequency stimulation (HFS) or an extensive approach at anatomical sites of GP. All patients underwent Holter ECG and heart rate variability (HRV) evaluation at baseline and at 3, 6, 12 and 18 months 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, HRV parameters showed a significant parasympathetic (and sympathetic) denervation in the first 6 months, that 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.

**Key words:** atrial fibrillation; ablation, ganglionated plexi, autonomic denervation

**Abbreviations:** AF = Atrial Fibrillation; CFAEs = Complex Fractionated Atrial Electrograms; GP = Ganglionated Plexi; HF = High Frequency; HFS = High Frequency Stimulation; HRV = Heart Rate Variability; LF = Low Frequency; PV = Pulmonary Vein; RA = Right Atrium; RF = Radiofrequency
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).\textsuperscript{1} Several approaches have been suggested to increase the success of AF ablation.\textsuperscript{2,3} However, the potential procedural risks (4-6\% of major complications),\textsuperscript{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.

More recently, based on experimental and clinical data that suggest the important role of the autonomic nervous system in the pathogenesis of AF,\textsuperscript{6-19} catheter ablation of ganglionated plexi (GP) in the left atrium has been proposed in different clinical condition but with conflicting results.\textsuperscript{20-26} Anatomical studies showed\textsuperscript{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 right atrial GP in the AF initiation and maintenance.\textsuperscript{15-18}

AF results from the interplay between trigger, substrate and autonomic nervous system in each patient.\textsuperscript{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 PVs firing\textsuperscript{9-13,19} and in the maintenance of AF by shortening the atrial effective refractory period.\textsuperscript{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 randomized for a selective ablation procedure targeted to eliminate parasympathetic response evoked by transcatheter high frequency stimulation (HFS) or an extensive approach at anatomical 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 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 atrio-ventricular 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 randomized. 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 randomization, 17 patients underwent selective ablation procedure targeted for the elimination of vagal reflex evoked by transcatheter high frequency stimulation (HFS), while 17 underwent extensive approach at anatomical sites of GP. The clinical characteristics of the patients in the 2 groups were similar (Table 1).
Flecainide or propafenone were 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 follow up. The personnel who performed post-ablation 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 following ablation procedure, or in case of occurrence of any clinical symptom.

The primary endpoint 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 \( \geq 30 \) seconds. Time to AF recurrence was computed as the number of days between the ablation procedure and the electrocardiographic confirmation of the arrhythmia. The first 2 months following ablation procedure (blanking period) were excluded from the analysis of patients outcome and of autonomic function during the follow up.

**Right atrial electroanatomical mapping and electrophysiological study**

Mapping and ablation procedure were performed in a fasting state using a mild sedation and under local anaesthesia. 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. Electro-anatomical mapping of the RA was performed through CARTO XP (Biosense Webster, Diamond Bar, CA, USA) for patients enrolled until July 2009 and with CARTO 3™ for those enrolled after this period. CARTO XP electro-anatomical mapping system was described in detail previously.\(^2\)\(^,\)\(^3\) In patients who underwent CARTO 3™ system, a three-
dimensional fast anatomical mapping of the RA was performed (figure 1, panel B and figure 2, panel B).

Before GP mapping and ablation all patients underwent electrophysiological study. Bipolar electrograms were filtered from 80 to 500 Hz, and displayed and acquired on a Bard, Lab 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 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 right atrial flutter, cavotricuspid isthmus ablation was also performed. The inducibility of AF was not tested in patients that presented restored sinus rhythm during RF 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. Interval confidence level displays the total amount of intervals counted for each point (all intervals, between two 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 case of relevant noise the minimum voltage was increased to 0.07 mV. The maximum voltage was set to 1 mV in order 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. Both the points with high fragmentation and those with medium fragmentation were considered for our CFAEs analysis.

**Autonomic denervation through the anatomic approach**
This ablation procedure is based on RF delivery at the anatomic sites of GP previously described in several studies regarding human hearts.\textsuperscript{27-29} We have considered as ablation sites (RF energy at 60°, 30-70 W for 30-60 seconds, Stockert, Biosense Webster) the following areas where all the presumed right atrial GP clusters are located (figure 1, panel A and panel B): the supero-posterior area (superior right atrial GP, adjacent to the junction of the superior vena cava and the posterior surface of RA), the middle-posterior area (posterior right atrial GP, posterior surface of the RA adjacent the interatrial groove), the infero-posterior area (GP placed between inferior vena cava, coronary sinus ostium and near the atrio-ventricular groove). Considering that the exact anatomic borders of GP clusters are unknown, we decided to perform this ablation procedure delivering an expanded number of RF applications and forming a cloudlike shape ablation model, previously described in detail.\textsuperscript{24} All patients underwent AF induction before anatomic GP ablation. Ablation was performed until atrial electrical activity was significantly reduced (peak to peak bipolar electrogram <0.05 mV) and vagal reflex during RF application disappeared. High output pacing was performed near SVC to avoid phrenic nerve ablation.

**Autonomic denervation guided by high frequency stimulation**

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 superior vena cava and right atrium (superior right atrial GP), adjacent to the interatrial groove (posterior right atrial GP), between inferior vena cava and septum near the coronary sinus ostium (inferior right atrial GP) and adjacent to the atrial-ventricular groove.

Rectangular electrical stimuli were delivered at a frequency of 20 Hz, amplitude of 12 V increasing to 15 V in case of no vagal reflex evoked, and pulse duration of 10 ms (Stimulator TECS II, Medico, Italy). A significant parasympathetic response (figure 2, panel A) was defined
as prolongation of R-R interval by >50% during AF associated to a sudden >20 mmHg decrease in blood pressure (recorded from continuous invasive arterial monitoring), as previously described.²¹,²⁴,²⁵ All sites where a significant parasympathetic response was elicited through HFS were recorded on the anatomical map of the atrium (Figure 2B). Radiofrequency (RF) energy was delivered until the abolition of all vagal reflexes evoked with repeated HFS. The order of HFS and ablation was: superior right atrial GP, posterior right atrial GP and the infero-posterior GP. Before HF stimulation applying to the atrial-ventricular groove, the tip catheter 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), 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, electrical 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**
Basing on 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% [24] 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 endpoint.

Statistical analysis was performed using STATA SE 10 software package (StataCorp, Texas, USA). Continuous variables were presented as mean ± standard deviation and categorical values as frequency (%). Comparisons between study groups of baseline, 3-, 6-, 12-, 18-month follow-up repeated measures of continuous variable was performed by means of the Generalized Estimating Equation (GEE) method with first order auto-regressive 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 Log-rank test. Statistical significance was defined as a two-sided probability value <0.05.

**Results**

**Procedural data, selective and anatomic GP ablation.**

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

The right atrial burst pacing induced sustained AF in all patients of both groups.
A parasympathetic response (Figure 1, panel B and panel C) was observed, at least in one site, in 11 patients (65%) during anatomic ablation: in 8 patients (73%) during RF application in the infero-posterior area, in 6 (54%) in the supero-posterior area and in 4 (36%) during ablation in the middle-posterior area (figure 3, panel A). A total of 82±16 RF applications were delivered with a mean of 19±6 RF pulses at each anatomical site of GP and with the following distribution: 28±7 RF applications in the infero-posterior area, 16±6 in the supero-posterior area and 13±5 in the middle-posterior area. The average diameter of cloudlike shape ablation model, indicating the extension of RF applications, ranged from 16.4±2.1 mm (infero-posterior area) to 11.7±5.2 mm (middle-posterior and supero-posterior area). RF ablation of GP placed near IVC was less extended for risk of phrenic nerve injury (6.4±1.3 mm).

In 6 (35%) patients, AF terminated during ablation (Figure 1, panel B and panel D). In only 1 patient the ablation procedure in the supero-posterior area was less extensive than in other patients for having captured phrenic nerve during high output pacing near SVC at the level of antero-septal 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 atrio-ventricular 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 3, panel B). An average of 4.5±2.2 RF applications was necessary to eliminate the vagal reflex at the same targeted site (Figure 2, panel B). In 4 patients (23%) a vagal reflex was observed during
RF applications and in 8 patients (47%, $P=0.7$ vs anatomic approach) AF terminated during 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 midspetal areas (31 patients) and in the posterior wall particularly in proximity of superior vena cava-RA junction (23 patients). Of the 34 patients, GP ablation caused CFAEs disappearance and significant reduction in 12 and 21 patients respectively. Finally, one patient of the selective GP ablation group and one patient of anatomic GP ablation group also underwent cavo-tricuspid 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 while in 3 patients 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±9% in the anatomic approach group and 35±12% in the selective group.

After ablation, both in the selective and in anatomical GP ablation many AF episodes were not related to vagal tone predominance, as observed before ablation. Only in 4/13 patients with AF recurrence after selective GP ablation and in 1/5 patients with AF recurrence after anatomic approach persisted 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 following anatomic approach and was completely resolved after 1 month of therapy with low dose of beta-blockers.

**Autonomic evaluation**

At 3 months post-ablation, Holter ECG and time-domain HRV parameters showed a significant modification in anatomical and selective ablation groups when compared with baseline (Table 2). At 6 months 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 months follow up, showed a trend in a greater decrease in anatomic ablation group but did not reach a 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 months follow up.

**Discussion**
Main Findings

In this study, conducted in 34 symptomatic patients with vagal paroxysmal AF, the following were observed. (1) RF 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. Infact, AF recurred in 5/17 undergone anatomic ablation and in 13/17 patients undergone selective GP ablation. (3) After ablation, HRV parameters showed a significant parasympathetic and sympathetic denervation in the first 6 months, that was more prominent in patients with anatomic GP ablation and in those without AF recurrence. (4) 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\textsuperscript{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.\textsuperscript{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.\textsuperscript{8,16,18,19} In clinical practice, Platt et al.\textsuperscript{31} first proposed GP ablation as a stand-alone treatment for AF, without
isolation of PV. Of the 23 patients with a complete study, 22 were AF free during 6 months of follow-up. In the same year, Pappone et al.\textsuperscript{2} 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.\textsuperscript{21} RF 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. Following 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 one month. Scanavacca et al.\textsuperscript{20} located GP by applying HFS to both the endocardial and epicardial atrial regions, and as observed by Lemery\textsuperscript{21}, only in few sites of RF 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,\textsuperscript{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 al.\textsuperscript{20} did not perform the ablation in the supero-posterior GP, the “head stage” for the vagal input to other GP.\textsuperscript{33} Po et al.\textsuperscript{25} 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 RF ablation of GP based on anatomical data of cardiac ganglia topography.\textsuperscript{22,24,26} Pokushalov et al.\textsuperscript{24} demonstrated that anatomic approach confers better results than selective GP ablation guided by HFS in patients with paroxysmal AF (77.5\% vs 42.5\% AF free at a mean follow-up of 13 months). In this study GP ablation was mainly performed in the LA. The same group did not observe a good result with this approach in longstanding persistent AF.\textsuperscript{26}

**Potential Mechanisms of the Efficacy of the Ablation of Right Atrial Ganglionated Plexi**

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 vagal-induced paroxysmal AF. The effect of GP ablation in this subgroup of patients can be higher than other AF subsets. Coumel et al.\textsuperscript{6} first reported that patients with vagal AF were typically young with nocturnal episodes of AF or following 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 seems 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.\textsuperscript{27-29} We designed our study on the basis of anatomic distribution of atrial GP as described by studies in humans.\textsuperscript{27-29} Armour et al.\textsuperscript{27} 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 right atrial GP. Moreover, this GP presented ganglia containing much more neurons than ganglia in other GPs.\textsuperscript{27} In the RA, the superior right atrial 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 superior vena cava and the aorta. This supero-posterior area also
known as superior vena cava-aortic GP or “third fat pad” is the nexus point for the vagal input to the GP prior to innervating the atria. Recently, Lu et al. 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 left atrial GP that is the largest GP in the LA can be, at least in part, destroyed by delivering RF 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 RF applications forming a cloudlike shape, and not a line, because, as Pokushalov et al. observed, “the exact anatomic borders of GP clusters are unknown and their location can vary slightly in different patients”. It should be underlined as in patients with AF the GP are hyperactive thereby releasing excessive amounts of neurotransmitters particularly in the vicinity of the GP. Thus, an extensive anatomic GP ablation could be more effective than selective GP ablation for this reason too. The physio-pathologic role of right atrial GP has been underlined by several experimental studies. 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 al. observed that right vagosympathetic stimulation was more arrhythmogenic than left stimulation. In fact, GP ablation eliminated AF inducibility only when performed in the anterior right atrial GP situated between the caudal end of the sino-atrial 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 al. 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. This 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. CFAE 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. Some studies 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. The progressive organization of atrial electrograms with serial GP ablation confirms that the connection of GP is crucial in the AF maintenance. In our study CFAEs have been observed around each positive vagal site the postero-septal region, particularly the posteroseptal 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.
Finally, some studies showed the relevance of RA ablation both in paroxysmal and in chronic AF.\(^\text{37-39}\) Gaita et al.\(^\text{37}\) demonstrated that a septal line can be effective in patients with vagal paroxysmal AF, particularly when the septum presented “disorganized” electrical activity. The effectiveness of atrial lesions in the RA can be caused by several factors such as conduction deterioration, increased not uniform anisotropy and disorganized electrical 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.\(^\text{3,30,39}\) The higher efficacy of posterior and septal lesion in the RA\(^\text{38,39}\) can be probably explained by the vagal denervation due to the ablation of GPs that are largely represented in these atrial areas.\(^\text{27-29}\)

On the other hand, we cannot exclude that our results could be, at least in part, due to RF 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 anatomical approach and in patients without AF recurrence during the follow up. In fact, the sympathetic and parasympathetic tone recovered at 12 months in patients undergone anatomical GP ablation and in those without AF recurrences while recovered at 6 months in patients treated with 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 several investigations\(^\text{20,24,40}\) 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 recurrences rate\(^\text{41}\). Pokushalov et al.\(^\text{24}\) reported a relevant effect of anatomic GP ablation on parasympathetic tone, whereas the
sympathetic tone increased. Similar to our data, Scanavacca et al.\textsuperscript{20} 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, etc. 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 can not exclude that the effect of the extensive approach at anatomical 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 have used stimulation parameters similar to other authors that showed heterogeneous results of the selective approach. A possible explanation of the reduced efficacy of GP ablation guided by HFS could be that, as previous investigations showed, endocardial areas where HFS evoked a parasympathetic response can be smaller than those where GP clusters are really concentrated. Moreover, as Pokushalov et al. hypothesized, we can not 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 can not 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.

**Conflict of Interest Disclosures:** Drs. Pitrone and Dottori are employees of Biosense-Webster Inc.

**References:**


### Table 1. Demographic characteristics of the study population

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

GP: ganglionated plexi; Abl: ablation; y: years; n: number; AF: atrial fibrillation; AP: antero-posterior; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; EF: ejection fraction; mm: millimeters. * data presented as mean ± standard deviation.
Table 2. Heart rate, time-domain HRV and frequency-domain HRV evaluation before and after anatomic and selective GP ablation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Before ablation</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>A 41.1±4.3</td>
<td>58.8±3.4*</td>
<td>55.6±3.3*</td>
<td>43.2±4.8</td>
<td>42.3±3.9</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>S 42.3±4.6</td>
<td>53.6±3.8*</td>
<td>43.3±3.3†</td>
<td>44.2±3.6</td>
<td>43.4±4.1</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>A 64.5±3.3</td>
<td>78.4±3.1*</td>
<td>72.1±3.4*</td>
<td>65.3±3.8</td>
<td>64.1±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>S 63.3±4.2</td>
<td>66.4±3.1†</td>
<td>62.1±4.5†</td>
<td>64.8±3.9</td>
<td>63.9±4.4</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>A 104.3±11.1</td>
<td>106.8±12.2</td>
<td>105.3±11.2</td>
<td>104.5±10.8</td>
<td>104.1±10.9</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>S 105.4±10.6</td>
<td>107.1±10.1</td>
<td>106.3±11.6</td>
<td>105.5±11.1</td>
<td>105.1±10.9</td>
<td></td>
</tr>
<tr>
<td>Td HRV, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>A 152.2±9.9</td>
<td>98.7±4.5*</td>
<td>127.5±8.3*</td>
<td>149.8±9.1</td>
<td>151.6±9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>S 42.3±4.6</td>
<td>53.6±3.8*</td>
<td>43.3±3.3†</td>
<td>44.2±3.6</td>
<td>43.4±4.1</td>
<td></td>
</tr>
<tr>
<td>rMSSD</td>
<td>A 55.5±4.4</td>
<td>38.7±4.9*</td>
<td>47.2±4.5*</td>
<td>53.4±4.6</td>
<td>54.3±4.2</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>S 56.3±3.8</td>
<td>43.2±4.5*</td>
<td>54.8±3.7</td>
<td>54.4±3.8</td>
<td>55.9±4.1</td>
<td></td>
</tr>
<tr>
<td>pNN50</td>
<td>A 29.1±1.7</td>
<td>18.4±4.8*</td>
<td>22.2±1.8*</td>
<td>28.4±1.9</td>
<td>28.9±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>S 29.7±1.9</td>
<td>22.3±4.6* ‡</td>
<td>28.7±1.9 †</td>
<td>28.9±1.8</td>
<td>29.2±1.8</td>
<td></td>
</tr>
<tr>
<td>Fd HRV, ms²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln LF</td>
<td>A 6.81±0.92</td>
<td>5.12±0.92</td>
<td>5.83±0.92</td>
<td>6.57±0.89</td>
<td>6.75±0.87</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>S 6.61±0.89</td>
<td>5.81±0.87</td>
<td>6.56±0.89</td>
<td>6.52±0.92</td>
<td>6.59±0.91</td>
<td></td>
</tr>
<tr>
<td>Ln HF</td>
<td>A 6.12±0.85</td>
<td>4.03±0.61</td>
<td>4.55±0.81</td>
<td>5.92±0.95</td>
<td>6.04±0.91</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>S 5.92±0.86</td>
<td>4.85±0.64</td>
<td>5.68±0.83</td>
<td>5.65±0.99</td>
<td>5.97±0.92</td>
<td></td>
</tr>
<tr>
<td>LF/HF</td>
<td>A 1.61±0.55</td>
<td>1.83±0.51</td>
<td>1.94±0.63</td>
<td>1.72±0.58</td>
<td>1.65±0.53</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>S 1.71±0.65</td>
<td>1.85±0.49</td>
<td>1.92±0.54</td>
<td>1.86±0.58</td>
<td>1.68±0.62</td>
<td></td>
</tr>
</tbody>
</table>

Group: A: Anatomic; S: Selective. HR: heart rate; Td: Time domain; Fd: Frequency domain; HRV: heart rate variability; 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. pre-ablation; † 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.
Table 3. Heart rate, time domain HRV and frequency-domain HRV evaluation in patients with (w) and without (w/o) AF recurrences.

<table>
<thead>
<tr>
<th>Group</th>
<th>Before ablation</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>w/o AF</td>
<td>49.3 ± 5.3</td>
<td>59.3 ± 1.3*</td>
<td>57.3 ± 5.3*</td>
<td>50.2 ± 3.4</td>
<td>49.8 ± 5.1</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>48.1 ± 4.2</td>
<td>56.6 ± 2.6*</td>
<td>48.4 ± 4.3</td>
<td>49.1 ± 3.6</td>
<td>48.9 ± 3.9</td>
</tr>
<tr>
<td>Mean</td>
<td>w/o AF</td>
<td>57.2 ± 2.9</td>
<td>77.3 ± 2.5*</td>
<td>65.1 ± 3.1*</td>
<td>58.3 ± 2.9</td>
<td>56.9 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>59.5 ± 3.3</td>
<td>69.3 ± 3.6*</td>
<td>58.1 ± 5.7</td>
<td>59.3 ± 3.9</td>
<td>59.4 ± 3.5</td>
</tr>
<tr>
<td>Maximum</td>
<td>w/o AF</td>
<td>112.4 ± 11.6</td>
<td>113.8 ± 11.6</td>
<td>111.2 ± 11.7</td>
<td>110.6 ±10.4</td>
<td>111.8 ± 10.9</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>110.3 ± 11.1</td>
<td>107.8 ± 12.2</td>
<td>107.3 ± 11.7</td>
<td>109.5 ±10.3</td>
<td>111.2 ± 11.1</td>
</tr>
<tr>
<td>Td HRV, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>w/o AF</td>
<td>145.2±8.2</td>
<td>96.7±3.5*</td>
<td>130.4±8.2*</td>
<td>145.8±9.1</td>
<td>145.3±8.9</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>148.2±8.7</td>
<td>135.2±7.4*</td>
<td>144.6±8.8</td>
<td>146.8±7.2</td>
<td>148.6±8.1</td>
</tr>
<tr>
<td>rMSSD</td>
<td>w/o AF</td>
<td>52.4±3.1</td>
<td>35.7±4.6</td>
<td>41.2±4.3</td>
<td>53.4±4.2</td>
<td>52.3±3.9</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>50.3±2.8</td>
<td>42.2±4.4</td>
<td>49.8±3.3</td>
<td>52.1±3.6</td>
<td>51.1±3.1</td>
</tr>
<tr>
<td>pNN50</td>
<td>w/o AF</td>
<td>33.4±1.5</td>
<td>19.3±4.3*</td>
<td>24.2±1.9*</td>
<td>31.3±1.8</td>
<td>32.5±1.7</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>31.8±1.8</td>
<td>25.4±3.7*</td>
<td>30.7±1.7</td>
<td>32.4±1.7</td>
<td>31.6±1.9</td>
</tr>
<tr>
<td>Fd HRV, ms²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln LF</td>
<td>w/o AF</td>
<td>6.43 ± 0.73</td>
<td>4.72 ± 0.92*</td>
<td>5.23 ± 0.82*</td>
<td>6.01 ± 0.72</td>
<td>6.35 ± 0.75</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>6.75 ± 0.96</td>
<td>5.74±0.87*</td>
<td>6.42 ± 0.97</td>
<td>6.66±0.92</td>
<td>6.71 ± 0.86</td>
</tr>
<tr>
<td>Ln HF</td>
<td>w/o AF</td>
<td>5.27 ± 0.72</td>
<td>3.51 ± 0.61*</td>
<td>4.02 ± 0.81*</td>
<td>4.62 ± 0.95</td>
<td>4.75 ± 0.73</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>5.32 ± 0.72</td>
<td>4.31 ± 0.61*</td>
<td>4.73 ± 0.72</td>
<td>5.01±0.99</td>
<td>5.26 ± 0.75</td>
</tr>
<tr>
<td>LF/HF</td>
<td>w/o AF</td>
<td>1.75 ± 0.35</td>
<td>1.74 ± 0.62</td>
<td>1.82 ± 0.53</td>
<td>2.35 ± 0.58</td>
<td>2.18 ± 0.56</td>
</tr>
<tr>
<td></td>
<td>w AF</td>
<td>1.71 ± 0.58</td>
<td>1.92 ± 0.51</td>
<td>2.32 ± 0.57</td>
<td>1.82 ± 0.58</td>
<td>1.74 ± 0.52</td>
</tr>
</tbody>
</table>

HR: heart rate; Td: Time domain; Fd: Frequency domain; HRV: heart rate variability; 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<0.001 vs. without AF recurrences. Results of the analysis are from time of procedure, excluding the blanking period.
Figure Legends:


Figure 2. Panel A: Parasympathetic response evoked during 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). Panel B: CARTO 3 Fast Anatomical Map of RA (lateral projection) in a case of selective GP ablation. Red dots represent sites of RF pulse near HFS positive sites (yellow dots). White dots represent high frequency stimulation negative sites. (HIS: proximal His bundle. For other abbreviations see Figure 1).

Figure 3. Panel A. Distribution of sites where RF applications evoked a parasympathetic response during anatomic ablation. Panel B: Distribution of sites where HFS evoked a parasympathetic response during selective approach. See text for further details.

Figure 4. Kaplan-Meier curve and survival analysis indicates freedom from AF recurrences after anatomic (continuous line) and selective (dashed line) GP ablation.
Catheter Ablation of Right Atrial Ganglionated Plexi in Patients with Vagal Paroxysmal Atrial Fibrillation
Leonardo Calò, Marco Rebecchi, Luigi Sciarrà, Lucia De Luca, Alessandro Fagagnini, Lorenzo Maria Zuccaro, Pietro Pitrone, Serena Dottori, Maurizio Porfirio, Ermenegildo de Ruvo and Ernesto Lioy

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