Outcome of anatomic ganglonated plexi ablation to treat paroxysmal atrial fibrillation: a 3-year follow-up study

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Aims
A new strategy for anatomically based ganglonated plexi (GP) ablation for the treatment of paroxysmal atrial fibrillation (AF) has been proposed recently. We aimed to assess the long-term outcome of patients undergoing anatomic GP ablation for paroxysmal AF, in comparison with circumferential pulmonary vein (PV) isolation.

Methods and results
The study population consisted of 70 patients (mean age 56.6 ± 10.9 years; 41 males) with paroxysmal AF and no history of structural heart disease: 35 subjects underwent anatomic GP ablation, while 35 consecutive patients had circumferential PV isolation (CPVI) (control group). The groups were not different in demographic and clinical parameters. Anatomic GP ablation required more ablation points (85.6 ± 5.5 vs. 74.4 ± 6.2, P < 0.05) and equal duration of total procedure and fluoroscopy times. During a mean follow-up period of 36.3 ± 2.3 months, freedom from any atrial tachyarrhythmia without antiarrhythmics was achieved in 34.3% patients after anatomic GP ablation and 65.7% patients after CPVI (log-rank test P = 0.008). Early arrhythmia recurrences and anatomic GP ablation were independent predictors of late recurrence [HR 6.44 (CI 95%; 3.14–13.18; P < 0.001) and HR 2.08 (CI 95%; 1.03–4.22; P = 0.04), respectively]. Six patients in the group of GP ablation underwent subsequent CPVI, plus peri-mitral flutter ablation in two of them, with no further arrhythmia episodes in five patients.

Conclusion
Anatomic GP ablation yields a significantly lower success rate over the long-term follow-up period, when compared with CPVI. Recurrences include AF and macro re-entrant atrial tachycardias.

Keywords
Atrial fibrillation • Anatomic • Ablation • Autonomic • Ganglionated plexi • Follow-up • Pulmonary vein isolation

Introduction
Pulmonary vein (PV) isolation has become a therapeutic option for patients with atrial fibrillation (AF). Reports showing more than 80% freedom of paroxysmal AF during long-term follow-up have been published.1,2 However, PV isolation using point-by-point technique is still a challenging procedure and it requires significant experience in catheter manipulation. A large number of different approaches and techniques are currently available to achieve PV isolation. It has been shown that endocardial or epicardial ablation of left atrial (LA) ganglionated plexi (GP) can improve outcome of patients undergoing AF ablation.3,4 Recently, a new strategy for anatomically based GP ablation has been proposed for the treatment of paroxysmal and even long-standing persistent AF.5–7 The midterm success rate of this approach for alleviating symptoms of paroxysmal AF was found to be promising.5 However, long-term results have not been published. The aim of this study is to assess the 3-year outcomes of patients undergoing anatomic GP ablation for paroxysmal AF, in comparison with circumferential PV isolation (CPVI).
Anatomic GP ablation: long-term follow-up

Methods

Study population
A total number of 70 patients (mean age 56.6 ± 10.9 years; 41 males) were included in this case-controlled study. Group of anatomic LA GP ablation consisted of 35 consecutive patients with paroxysmal AF. Inclusion criteria were the following: refractoriness to antarrhythmic treatment with at least two drugs class IC or III and age <65 years. Exclusion criteria consisted of valve disease, previous ablation in the LA, significant LA enlargement (LA diameter > 45 mm), and left ventricle (LV) systolic dysfunction. From patients consecutively undergoing CPVI, we selected 35 controls in 1:1 manner according to a number of clinical parameters: age, LA volume (calculated during 3D map reconstruction), history of arterial hypertension, coronary artery disease (CAD), and the presence of chronic obstructive pulmonary disease. Both groups were followed up using the same protocol (see below). Clinical characteristics of the study population are shown in Table 1. During the first 3 months of the follow-up period, recurrences were not included into the analysis; this period was considered a blanking period. The study was approved by the local ethics committee. All patients signed informed consent forms.

Catheter ablation
The patients were on adequate oral anticoagulation (INR 2.0–3.0) for at least 1 month before ablation, and anticoagulation was not interrupted. Transesophageal echocardiography was performed in all patients 1–3 days before the ablation to exclude LA thrombus. Electrophysiology procedure was carried out under general anaesthesia with propofol and fentanyl. Surface electrocardiograms and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (Biotok Space-Vision, Biotok, Tomsk, Russia). From the right subclavian vein, a 6-F decapolar diagnostic catheter (Webster, Biosense Webster, Diamond Bar, CA, USA) was inserted into the coronary sinus (CS); from the right femoral vein, a 10-F haemostatic sheath (Cordis, Johnson and Johnson, Miami, FL, USA) was inserted to facilitate transseptal sheath manipulation. A single transseptal puncture was performed under fluoroscopic guidance. Selective PV angiography was performed by hand injection of 5–10 mL contrast media via an angiographic catheter (Cordis, Johnson and Johnson, Miami). The 3.5 mm tip open-irrigated ablation catheter (Navistar ThermoCool, Biosense Webster) was placed into the LA through an 8-F transseptal sheath (Preface, Johnson and Johnson). A bolus of non-fractionated heparin 50–70 IU/kg (considering the actual INR level) was administered immediately after the transseptal sheath was placed. ACT was maintained between 250 and 350 s. Electroanatomic navigation was performed with the CARTO XP system (Biosense Webster). Pulmonary vein ostia were defined by PV angiogram, impedance change on the map catheter, and by map catheter jump during drawing from distal part of a PV.

Concomitant cavotricuspid ishmust (CTI) ablation was performed in patients with previously registered or induced during the electrophysiological intervention typical atrial flutter.

Anatomic ganglionated plexi ablation
Anatomic distribution of areas with maximum GP concentrations has been described. The major clusters of LA GPs are located near the PV ostia and frequently found in the posterior interatrial septum. Accumulations of the LA GPs are the following: left superolateral area (left superior GP), right superoanterior area (right anterior GP of the LA), left inferior GP, and right infero-posterior area (right inferior GP of the LA). In contrast to selective GP ablation, where radiofrequency (RF) ablation is delivered to sites with vagal response to high-frequency stimulation, the anatomical approach is based on empiric high-density ablation at sites with frequent location of GP clusters. The endpoint of this strategy is elimination of the local atrial potentials at the described areas. Pulmonary veins are not targeted for ablation, thus PV isolation is not aimed for curing of AF. Anatomic GP ablation was described recently in detail.

After creation of an LA anatomic map, RF ablation was performed at the described areas (40° in left anterior oblique projection on the 3D electroanatomical map) with minimal distance from the PV ostia 5–10 mm: left superolateral area around the LSPV ostium from 11 to 1 o’clock, right superoanterior area from 5 to 9 o’clock, right superoanterior area around the RSPV from 7 to 12 o’clock, and right infero-posterior area 5 to 8 o’clock (Figure 1). The size of each ablated area was from 1.4×0.8 to 2.2×1.5 cm. Each ablation point was of 40–60 s in duration with maximum power set at 40–45 W, 43°C (Stockert EP Shuttle, Biosense Webster), with irrigation at 17–20 mL/min via the CoolFlow pump (Biosense Webster). The endpoint of the ablation procedure was abatement of local electrograms (<0.1 mV) in the described areas.

Circumferential pulmonary vein isolation
After creation of a LA anatomic map, circumferential ablations of left and right ipsilateral veins were performed. Maximum RF energy delivery was set at 43°C, 40–45 W and irrigation at 12–20 mL/min. After circumferential ablation, mapping and additional ablation of conduction gaps were performed. The endpoint was complete PV isolation and non-inducible AF. If AF was inducible after CPVI or was not spontaneously terminated, additional linear ablations at the LA roof and the mitral isthmus were performed with the verification of conduction block.

<table>
<thead>
<tr>
<th>Table 1 Clinical characteristics of the patient population</th>
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<tbody>
<tr>
<td>Anatomic GP ablation (n = 35)</td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Age (yr)</td>
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<td>Male gender</td>
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<td>LA volume, mL</td>
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<td>Hypertension</td>
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<td>CAD</td>
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<td>LVEF</td>
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<td>Duration of AF history, months</td>
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<td>Diabetes mellitus</td>
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<td>Thyroid disease</td>
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<td>Chronic obstructive pulmonary disease</td>
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<td>Previous stroke</td>
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</table>

AF, atrial fibrillation; CAD, coronary artery disease; CPVI, circumferential pulmonary vein isolation; GP, ganglionated plexi; LA, left atrium; LVEF, left ventricle ejection fraction.
Electrophysiological testing after left atrial ablation

Pulmonary vein isolation was verified either by using a decapolar circular mapping catheter (Lasso, Biosense Webster) or using extensive mapping by the ablation catheter in 15–20 points within the isolated area. At the end of the procedure programmed (basic cycle length 600 ms; 1, 2, and 3 extrastimuli) and burst pacing (decremental cycle length form 500 to 170 ms, duration of salvos 5–10 s) from the CS electrode was used for tachyarrhythmia induction.

After catheter ablation, the patients were extubated and further observed in the intensive care unit until the next morning.

Follow-up

Follow-up visits were scheduled at 3, 6, 9, and 12 months during the first year and then every 6 months. At every scheduled visit, 24 h 12-lead Holter ECG monitoring was performed for detection of the arrhythmia recurrence. If any symptoms suggestive for recurrence, additional ECGs and Holter monitoring were performed. If a patient missed a scheduled visit, he/she was contacted by phone, asked for symptoms, and requested to present at the outpatient clinic. Patients from very distant regions (four patients) were regularly contacted by phone and asked to send ECGs and Holter monitoring results by fax or via e-mail. Referring physicians were asked to send medical records too. Anticoagulation was continued up to 3 months after ablation. It was stopped in patients with CHADS2 score 0. In patients with no recurrence and CHADS score 1, warfarin was replaced by aspirin at 6 months after ablation.

Antiarrhythmic drugs

Antiarrhythmic medication was continued in all patients during the first 3 months of follow-up. If no recurrence was detected, antiarrhythmic treatment was ceased. In a case of symptomatic recurrences, antiarrhythmic therapy was reinitiated or changed to another drug. Since the population of the study consisted of patients with no structural heart disease, class IC antiarrhythmics were preferred as first line therapy.

Heart rate and heart rate variability analysis

Autonomic nervous system activity evaluation was performed by heart rate variability (HRV) analysis. Taking into account that any change in antiarrhythmic treatment (including beta-blockers) may affect HRV parameters and, therefore, alter interpretation of autonomic nervous system activity dynamics analysis, we assessed HRV and mean heart rate parameters only in patients with fixed medical treatment schemes and without change in beta-blockers and antiarrhythmics dosage before ablation, at 3 days (before discharge) and at 3 months postablation. Heart rate variability analysis was performed on 24 h Holter monitoring ECGs with 256 Hz sample rate (Cardiotechnika-04, Incart, Saint-Petersburg, Russia). According to the standards of measurement, frequency domain methods [low frequency (LF), high frequency (HF), percent of high-frequency power (nHF)] were evaluated on short intervals of 5 min, selected from Holter recordings at the time before a tagged moment of falling asleep (a period of relatively physiologically stable conditions). Time-domain methods [the standard deviation of RR intervals (SDNN), the root-mean-square of differences between successive RR intervals (rMSSD)] were evaluated on 24 h recordings with at least 18 h of analysable ECG data that included the whole night. Since antiarrhythmic medication was stopped or changed at 3 months after ablation in almost all patients, no HRV analysis was performed beyond this period.

Redo ablation and subsequent follow-up

Redo ablation was proposed to patients with symptomatic drug-refractory recurrence. Redo procedure was not performed during the blanking period. All patients underwent CPVI as a subsequent procedure. In patients after anatomic GP ablation, a LA voltage map was created before PV isolation. Pulmonary vein isolation was carried out according to above-described details.
Follow-up scheme and recurrence detection methods were the same as after the index procedure.

**Statistical analysis**

Continuous variables were expressed as mean ± SD, and categorical variables were reported as absolute and relative (%) frequencies. Associations between categorical variables were tested with Fisher’s exact test or the Chi-square test, as appropriate. Differences between continuous variables (dependent and independent samples) were tested with Student’s t-test. Kaplan–Meier curves represented the probability of freedom from recurrence. Survival analysis was performed using the log-rank test. One patient was lost for follow-up in 1 month after anatomic CPVI ablation; therefore, an intention-to-treat analysis was performed. Univariate and multivariate Cox proportional hazard analysis of selected variables was performed to identify factors independently related to arrhythmia recurrence. Results are expressed as hazard ratios with 95% CIs. Survival and regression analysis did not require data from any additional procedures patients may have required. Differences were considered statistically significant when \( P < 0.05 \). Statistical analysis was performed using Statistica 6.0 software (StatSoft Inc., Tulsa, OK, USA), and Cox proportional hazard analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA).

**Results**

**Anatomic ganglionated plexi ablation**

Pulmonary vein potentials were recorded in all patients inside all PVs at baseline. Two patients were present in the electrophysiological laboratory with AF and in one more patient sustained AF was induced by catheter manipulation. A mean number of RF applications were 85.6 ± 5.5 with the following distribution among GP ablation areas: left superolateral area 30.6 ± 4.3; inferoposterior area 12.8 ± 3.5; right inferoposterior 14.6 ± 4.1; and right superoanterior 28.6 ± 4.3. A mean power of actually delivered RF energy was 35.4 ± 6.2 W. During RF ablation vagal reaction, as sinus rhythm pauses and/or ventricular rate slowing by 30%, was noted in eight (22.9%) patients. Episodes of ectopic rhythm acceleration and/or short bursts of atrial tachycardia were noted in five (14.3%) patients. Multiple episodes of AF induction and termination during RF energy delivery were noted in two (5.7%) patients. In three (8.6%) patients who were present with AF at the beginning of the procedure, sinus rhythm was not spontaneously restored and electrical cardioversion was required. At the end of the ablation procedure, PV potentials were not registered inside right PVs in two (5.7%) patients, suggesting inadvertent PV isolation. After anatomical GP ablation, sustained AF was non-inducible in 31 (88.6%) patients. Induction of AF was not attempted in two patients with required cardioversion. Non-sustained AF was induced in two (5.7%) patients. Concomitant CTI ablation was carried out in seven (20%) patients. A total procedure time was 162 ± 28 min, and fluoroscopy time was 35.4 ± 17.3 min.

**Circumferential pulmonary vein isolation**

At the beginning of the procedure, PV potentials were noted in all PVs. Circumferential PV isolation required less number of RF ablation points when compared with anatomic GP ablation (74.4 ± 6.2 vs. 85.6 ± 5.5, respectively, \( P < 0.05 \)). A mean power of RF energy delivered was 36.4 ± 5.4 W. Episodes of rhythm slowing or pauses were registered in four (11.4%) vs. eight (22.9%) patients, \( P > 0.05 \). Atrial fibrillation was initially present in six patients. After PV isolation, AF was not terminated or was induced in five patients, therefore additional roof and/or mitral isthmus lines were created in five (14.7%) patients. In one patient, a perimital flutter was induced and successful mitral isthmus ablation was performed. Atrial fibrillation continued despite complex ablation in one patient, and electrical cardioversion was required. Cavotricuspid isthmus ablation was carried out in five (14.3%) patients (\( P > 0.05 \)). A total duration of the procedure was 167 ± 24 min (\( P < 0.5 \)), fluoroscopy time was 34.5 ± 13.5 (\( P > 0.05 \)) min.

**Follow-up**

One patient in the group of anatomic GP ablation was lost for follow-up in 1 month after the ablation procedure.

Within the first 3 months, early episodes of arrhythmia recurrence were noted in 13 (38.2%) patients after anatomic GP ablation (AF in 11 patients and regular atrial tachycardia in 2 patients). Twelve patients with early arrhythmia episodes (92% out of the 13 patients) developed late recurrence in a mean period of 3.8 ± 1.9 months. One more patient was present with regular atrial tachycardia in 7 months after the index procedure. Transesophageal pacing within 2 weeks after ablation was necessary for termination of atrial tachycardias in two patients. In one of them, the atrial tachycardia relapsed in 4 days and in other patient only in 10 months. After CPVI, early recurrences were noted in eight (23.5%) patients, there was no documented atrial tachycardia in any patient.

At 12 months after ablation, freedom from any recurrences without antiarrhythmic medication was 54.3% (19 patients) in the group of anatomic GP ablation and 74.3% (26 patients) in the group of CPVI (statistically non-significant, \( P = 0.08 \)).

Further follow-up showed increased recurrence rates in both groups. With a mean follow-up period of 36.3 ± 2.3 months, free from arrhythmia episodes without antiarrhythmics were 12 (34.3%) patients after anatomic GP ablation and 23 (65.7%) patients after CPVI (\( P = 0.009 \)). Antiarrhythmic treatment increased freedom from recurrences up to 15 (42.9%) patients after anatomic GP ablation and up to 25 (71.4%) patients after CPVI (\( P = 0.016 \)) (Figure 2).

Univariate analysis identified two factors related to late arrhythmia recurrence: the presence of early arrhythmia episodes, within the first 3 months after ablation, and anatomic GP ablation (Table 2). Neither duration of AF history nor the LA volume had significant effect on arrhythmia-free survival in the studied groups. According to a stepwise multivariate analysis, the best model predicting unsuccessful outcome consisted of early arrhythmia episodes and anatomic GP ablation (Table 2).

**Heart rate and heart rate variability analysis**

Heart rate variability analysis was performed in 21 patients with GP ablation and 17 patients with CPVI, in whom dosages of antiarrhythmics (including beta-blockers) were similar before ablation and within the first 3 months after ablation. Initially, the relative activity of the HF spectrum was higher among the group of...
CPVI, all other HRV parameters were comparable (Table 3). After ablation, time domain and frequency domain parameters significantly and equally changed in both groups of patients. Thus, SDNN decreased by about 50% in both groups, rMSSD decreased by 40% after GP ablation and by 30% after CPVI ($P = \text{ns}$ between groups). According to spectral analysis of short ECG intervals, the activity of the LF and HF spectra very significantly decreased by more than 90% each, with no statistical significance between groups. However, the nHF showed relative prevalence of parasympathetic activity, suggesting more significantly depressed sympathetic activity after anatomic GP ablation. After CPVI the nHF decreased, suggesting relative prevalence of sympathetic activity. Minimal heart rate increased in both groups, whereas mean heart rate did not change after CPVI. We found a trend towards decrease of maximal heart rate in both groups, and this could be explained by lower physical activity of patients during first days after ablation procedures. At 3d month after ablation, autonomic nervous system changes were still present, except rMSSD, which turned to its initial values. The nHF parameter, showing autonomic balance, was even more elevated after GP ablation.

### Redo ablation and subsequent follow-up

After anatomic GP ablation, redo procedure was carried out in six (17%) patients (four patients due to AF and in two patients due to regular atrial tachycardia plus AF).

In all six patients, undergoing redo procedure after GP ablation, a LA bipolar voltage map was created prior to ablation. A mean amplitude of atrial bipolar potentials at the previously ablated area was $0.27 \pm 0.21 \text{ mV}$, compared with the rest areas of the LA (excluding LA appendage) $1.09 \pm 0.77 \text{ mV}$. It should be
noted that during voltage mapping, two patients were on AF and one patient on atrial tachycardia. Percent of the amplitude decrease in the previously ablated area was 69.5 ± 11.3% (P < 0.01).

Pulmonary vein potentials were registered in all six patients in all veins. A peri-mitral flutter was diagnosed and successfully ablated at the mitral isthmus in two patients. Pulmonary vein isolation was completed in all patients.

In the group of CPVI, redo ablation was carried out in two patients, both had recurrent AF (P > 0.05). In all these patients, a LA–PV reconnection of at least one vein was revealed and re-isolation was performed.

After the most recent ablation, free from any recurrences without antiarrhythmics medication were 15 (42.9%) patients in the group of GP ablation, with a mean follow-up period of 33.4 ± 7.9 months. In the group of CPVI, 25 (71.4%, P = 0.016) patients were free from arrhythmias (a mean follow-up period after the most recent ablation was 30.9 ± 5.7 months, P > 0.05). Of note, the number of redo ablations was not enough to have the arrhythmia-free rate significantly changed.

Complications
In the group of anatomic GP ablation, there were two (5.7%) patients with major complications. In one patient, a cardiac tamponade occurred immediately after anatomic GP ablation and it was refractory to pericardial drainage; surgical revision was carried out, however a distinct site of perforation was not revealed. In one patient, haemoptysis and dyspnoea occurred in 5 h after the ablation procedure. Computed tomography scan revealed significant stenosis of three PVs, however due to acute pneumonia, interventional procedure was postponed. After 5 days, repeated computed tomography scan and then direct PV contrasting showed a non-significant (<40%) stenosis in all affected PVs. During the further follow-up, the patient had no respiratory complaints. CT scan at 8 months showed only a non-significant narrowing of both superior PVs.

After CPVI, significant left superior PV stenosis occurred in one patient, and was diagnosed at 4 months after the ablation. Subsequent PV stenting was successfully performed. In one patient from this group, warfarin therapy was discontinued 25 months after the procedure due to significant repeated upper respiratory tract bleeding. Symptomatic AF relapse occurred and led to ischaemic stroke without significant disability.

Discussion
The major finding of this study is that the long-term success rate of anatomic GP ablation is significantly lower than CPVI. Although anatomic GP ablation has a 1-year outcome statistically not different from CPVI, the recurrence rate is progressively increased at 3-year period. Our results indicate that two factors, anatomic GP ablation without PV isolation and early arrhythmia recurrence, independently predict treatment failure.

Selective ganglionated plexi ablation
Although cardiac nerves in the atria have been studied by numerous investigators,10,17,18 the precise anatomic localization of autonomic nerves can vary among patients. Taking into consideration the latter fact, a high-frequency pacing technique has been developed for localization and ablation of the autonomic ganglia in the human heart.19 The technique allows precise determination of the location, threshold, and predominance of parasympathetic or sympathetic response of the GP.

Table 3 Analysis of heart rate variability and heart rate dynamics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial</th>
<th>3 days after ablation</th>
<th>3 months after ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN, ms</td>
<td>151.6 ± 47.3</td>
<td>68.2 ± 27.7†</td>
<td>93.4 ± 16.5†</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>28.4 ± 7.7</td>
<td>17.3 ± 12.5†</td>
<td>28.4 ± 8.2</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>542.3 ± 180.5</td>
<td>19.3 ± 8.8†</td>
<td>39.5 ± 16.1†</td>
</tr>
<tr>
<td>HtR, %</td>
<td>199.6 ± 84.1</td>
<td>15.9 ± 9.6†</td>
<td>682.9 ± 9.4†</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>29.3 ± 7.7</td>
<td>55.6 ± 17.2†</td>
<td>634.4 ± 7.1†</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>63.2 ± 6.9</td>
<td>72.2 ± 9.5†</td>
<td>783.8 ± 8.0†</td>
</tr>
<tr>
<td>nHF, %</td>
<td>46.1 ± 5.8</td>
<td>58.3 ± 5.7†</td>
<td>627.2 ± 11.2†</td>
</tr>
<tr>
<td>HtR mean</td>
<td>122.2 ± 12.1</td>
<td>103.3 ± 8.9†</td>
<td>110.3 ± 7.3</td>
</tr>
<tr>
<td>HtR max</td>
<td>138.8 ± 21.2</td>
<td>65.0 ± 14.1†</td>
<td>79.0 ± 15.2†</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>26.5 ± 6.3</td>
<td>19.2 ± 4.1†</td>
<td>29.1 ± 7.1</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>291.2 ± 89.1</td>
<td>6.6 ± 6.1†</td>
<td>872.4 ± 12.2†</td>
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<tr>
<td>LF, ms²</td>
<td>44.4 ± 9.1*</td>
<td>33.1 ± 4.1*</td>
<td>53.4 ± 11.1†</td>
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<td>HF, ms²</td>
<td>65.4 ± 7.1</td>
<td>68.2 ± 10.1</td>
<td>687.8 ± 5.3</td>
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<tr>
<td>nHF, %</td>
<td>49.3 ± 6.6</td>
<td>63.1 ± 6.2†</td>
<td>624.5 ± 5.1†</td>
</tr>
<tr>
<td>HtR mean</td>
<td>113.3 ± 4.1</td>
<td>106.9 ± 8.1</td>
<td>119.6 ± 6.4</td>
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</table>

CPVI, circumferential pulmonary vein isolation; GP, ganglionated plexi; HtR, heart rate; nHF, percent of high frequency power; LF, low frequency; rMSSD, root mean square of all successive differences of normal RR intervals; SDNN, standard deviation of normal RR intervals.

*P < 0.05 comparing with initial value.
†P < 0.05 between groups.
Study by Schauer et al.\textsuperscript{20} showed that in seven dogs, parasympathetic nerve system modification by intravascular RF ablation (in right pulmonary artery and superior or inferior caval vein) abolished vagally mediated AF. It has been noted in studies in humans that during RF application near the PV orifice, reflex bradycardia or even significant pauses may occur.\textsuperscript{21} Other results suggested that ablation of ganglia and autonomic nerves around PVs improves the success rate of AF ablation.\textsuperscript{1} A bradycardic response to RF ablation is an indirect evidence of vagal nerve activation, and its subsequent disappearance with continued RF application a sign of vagal denervation. Pappone et al.\textsuperscript{1} showed that among 297 patients undergoing CPVI complete vagal denervation was obtained in 34.3%. During 12 months follow-up period, 85% patients without vagal denervation and 99% with vagal denervation were free from symptomatic arrhythmia.

Several groups have demonstrated a positive role of stand-alone selective GP ablation in the treatment of AF\textsuperscript{5,8} However, overall freedom from recurrences was still relatively low (50 and 29% of patients, respectively). Thus, high-frequency pacing-guided GP ablation, without additional ablation targets, has been shown as a low-effective treatment for AF.

**Anatomic ganglionated plexi ablation**

It has been proposed that shortcomings of selective GP ablation are related to underdetection of many GPs while using high-frequency pacing method.\textsuperscript{8} Thus, pacing-guided RF ablation might not eliminate all important parts of autonomic ganglia in the LA. Wider regional ablation at the anatomic GP sites is proposed in order to produce more prominent parasympathetic denervation and, therefore, higher success rate than selective GP ablation. Moreover, extensive regional ablation may affect not only parasympathetic, but sympathetic nerve endings, responsible for AF initiation.\textsuperscript{21} Another possible mechanism is a concomitant ablation of sites with fractionated electrograms, which are frequently located in the areas around PVs.\textsuperscript{8,24} However, until now we lack the evidence showing ablation of sites with complex fractionated atrial electrograms to add any benefit in the treatment of paroxysmal AF.\textsuperscript{5,25}

The first study describing the anatomic approach for LA GP ablation showed high success rate in a mixed patient population during a relatively short follow-up period of 7.2 months.\textsuperscript{5}

Another study compared outcomes of 19 patients, who underwent anatomic GP ablation, with patients after circumferential PV ablation.\textsuperscript{6} Parasympathetic reaction (heart rate slowing) was observed in 21% of patients during anatomic GP ablation. It was found that anatomic GP ablation was feasible and safe in the electrophysiology laboratory, required less fluoroscopy and RF energy delivery time. But this approach yielded inferior clinical results when compared with circumferential ablation during 1-year follow-up.\textsuperscript{6}

In another study, the efficacy of selective high-frequency stimulation-guided GP ablation and anatomic GP ablation was compared in patients with paroxysmal AF.\textsuperscript{8} Interestingly enough that in this study an additional ablation of the interatrial septum (from the right atrial side) was performed. High success rate was reported at an average follow-up period of 13 months. The majority of patients (almost 78%) were free from arrhythmia recurrence.\textsuperscript{8} The authors described the decrease of high-frequency components and increase of low-frequency components of heart rate variability with normalization of the parameters at 6 months after ablation, but these reverse changes did not influence long-term outcome. Autonomic changes were more prominent in patients with anatomic GP ablation in comparison with selective GP ablation.

A recent study by the same authors demonstrated promising results of anatomic GP ablation even in patients with long-standing persistent AF, however the authors proposed a combination of ablation methods (GP and CPVI) for better improvement of persistent AF ablation.\textsuperscript{7}

We achieved inferior success rate using anatomic GP ablation when compared with previous studies.\textsuperscript{5,8} A low freedom from arrhythmias after anatomic GP ablation in our study could be explained by a poor reproducibility of the technique.\textsuperscript{27} In the study by Katritsis et al.\textsuperscript{6} anatomic approach had even lower success rate. The authors subsequently explained lower efficacy by limited ablation lesions and their distribution in a linear rather than diffuse nature.\textsuperscript{8,24} Furthermore, in the present study, we performed RF ablation only in the LA, without targeting the interatrial septum from the right side. Another possible explanation for the low success rate of GP ablation is much longer follow-up in our study. Although at 12 months after ablation, more than half of the patients remained in sinus rhythm without symptoms, only one-third of the patients were free from AF at the end of the 3-year follow-up period. Although, a total number of ablation points for anatomic GP ablation was even more than in the study of Pokushalov et al.,\textsuperscript{8} we cannot exclude a slight difference in location of ablation areas between studies. Vagal reactions were seen in one-fifth of patients during anatomic GP ablation (compared with one-third in the study by Pokushalov et al.).\textsuperscript{8} This is more consistent with the results of Katritsis et al.\textsuperscript{6}

A higher appearance of sinus rhythm and atrioventricular nodal conduction slowing could be expected in a non-sedated status. All patients in our study were ablated under general endotracheal anaesthesia.

In three patients, atrial tachycardia developed after anatomic GP ablation. In two of them, highly symptomatic atrial tachycardia was present shortly after the index procedure and was terminated by transoesophageal pacing. During subsequent redo procedure, perimital flutter was diagnosed and ablated in two of these patients. No patient developed regular atrial tachycardia after CPVI during the follow-up period. It seems that a large area of RF ablation under the left inferior PV can predispose to slowing of electrical conduction and development of re-entry. These findings are in accordance with previous studies.\textsuperscript{6,8}

We found significant decrease in all studied HRV parameters after ablation, however there was no statistical difference in the HRV variables after anatomic GP ablation and CPVI. Interestingly, both components of the autonomic nervous system were affected by ablations. Moreover, the HF component had relative prevalence over the LF component in patients after GP ablation. This may suggest significant deterioration of sympathetic nerve endings by ablation at anatomic location of autonomic ganglia. This finding is not in accordance with previous reports, where authors showed increase in the LF power after anatomic GP ablation.\textsuperscript{8} Such a difference in our results could be explained by the low reproducibility of
LA sites selected for anatomic GP ablation; therefore, change of the ablation site may predispose to alteration of different nerve structures and further autonomic variance. Furthermore, no information regarding change of medical treatment in patients with HRV analysis was published in previous reports.\textsuperscript{5,8} After CPVI, the nHF parameter decreased, showing relative prevalence of sympathetic activity; and the latter finding is in agreement with previous reports upon circumferential ablation for paroxysmal AF.\textsuperscript{1}

In contrast to the recently published series,\textsuperscript{5} our data suggest that a stand-alone anatomic GP ablation is an independent predictor of arrhythmia recurrence. Early episodes of AF and/or atrial tachycardia after both GP ablation and CPVI are also strong predictors of late recurrence. Left atrial volume was not a predictor of AF recurrence. This finding can be explained by the fact that all patients included in the study had a non-significant LA enlargement.

In the present study, fluoroscopy time and total duration of both procedures did not differ significantly, in contrast to previous studies.\textsuperscript{5,8} We had two patients with PV stenosis (in one partially transient, which did not require PV stenting). One tamponade in the group of anatomic GP ablation was not related to transseptal puncture or rough manipulations. We suppose that excessive regional RF ablation was probably related to this event. These unfavourable findings might be related to the fact that two of the three operators performing AF ablation procedures at that time were obtaining their ‘learning curve’.

During redo procedure after anatomic GP ablation, in all six patients the low-voltage areas at the previously ablated regions of the LA were revealed. No more vagal reactions were seen during circumferential ablation at these areas.

**Clinical implications**

According to our results, anatomic GP ablation cannot be recommended as a stand-alone procedure for the treatment of paroxysmal AF due to low success rate over the long-term follow-up period. Pulmonary vein isolation is required for sinus rhythm maintenance. We presume that the combined approach can be carried out in order to increase freedom from AF; however, this might significantly affect overall procedure time. Future studies are necessary to test this hypothesis.

**Study limitations**

The most important limitation of this study is a non-randomized design. Another important limitation is the small sample size, although it is statistically large enough to support the two main findings: anatomical GP ablation is inferior to CPVI and that the strongest predictors of AF ablation outcome are early arrhythmia recurrence and anatomic GP ablation without PV isolation. Further, 24 h Holter monitoring is less effective for the detection of asymptomatic recurrence, compared with transtelephonic daily monitoring or implantable loop recorders.\textsuperscript{28} We did not perform HRV analysis beyond the third month after ablation, because almost all patients underwent medical treatment change at that moment, and this could affect HRV. In previous reports, the HRV variables completely recovered at 6 months after both approaches for LA ablation.\textsuperscript{1,6}

**Conclusion**

Anatomic GP ablation yields a relatively low success rate over the midterm and a very low success rate during the long-term follow-up period, when compared with CPVI. Recurrences include AF and macro re-entrant atrial tachycardias. Redo ablation targeting PV isolation is often required for maintaining sinus rhythm.

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**References**


