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Autonomic Denervation Added to Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation

A Randomized Clinical Trial

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Objectives The aim of this study was to investigate whether the combination of conventional pulmonary vein isolation (PVI) by circumferential antral ablation with ganglionated plexi (GP) modification in a single ablation procedure, yields higher success rates than PVI or GP ablation alone, in patients with paroxysmal atrial fibrillation (PAF).

Background Conventional PVI transects the major left atrial GP, and it is possible that autonomic denervation by inadvertent GP ablation plays a central role in the efficacy of PVI.

Methods A total of 242 patients with symptomatic PAF were recruited and randomized as follows: 1) circumferential PVI (n = 78); 2) anatomic ablation of the main left atrial GP (n = 82); or 3) circumferential PVI followed by anatomic ablation of the main left atrial GP (n = 82). The primary endpoint was freedom from atrial fibrillation (AF) or other sustained atrial tachycardia (AT), verified by monthly visits, ambulatory electrocardiographic monitoring, and implantable loop recorders, during a 2-year follow-up period.

Results Freedom from AF or AT was achieved in 44 (56%), 39 (48%), and 61 (74%) patients in the PVI, GP, and PVI+GP groups, respectively (p = 0.004 by log-rank test). PVI+GP ablation strategy compared with PVI alone yielded a hazard ratio of 0.53 (95% confidence interval: 0.31 to 0.91; p = 0.022) for recurrence of AF or AT. Fluoroscopy duration was 16 ± 3 min, 20 ± 5 min, and 23 ± 5 min for PVI, GP, and PVI+GP groups, respectively (p < 0.001). Post-ablation atrial flutter did not differ between groups: 5.1% in PVI, 4.9% in GP, and 6.1% in PVI+GP. No serious adverse procedure-related events were encountered.

Conclusions Addition of GP ablation to PVI confers a significantly higher success rate compared with either PVI or GP alone in patients with PAF. (Circumferential Versus Ganglionated Plexi Ablation for Atrial Fibrillation [AF]; NCT00671905) (J Am Coll Cardiol 2013;62:2318–25) © 2013 by the American College of Cardiology Foundation

Circumferential pulmonary vein isolation (PVI) transects the sites where the major atrial ganglionated plexi (GP) are located, and inadvertent autonomic denervation has been proposed as a critical element in the therapeutic effect of PVI in patients with atrial fibrillation (AF) (1–3). Although GP ablation alone has produced inconsistent clinical results in paroxysmal AF (PAF) (4–9), addition of GP ablation to PVI has increased AF-free survival in both catheter (endocardial approach) (7,10–12) and minimally invasive surgical ablation (epicardial approach) (13–16). Currently, PVI is the most widely used ablation approach to treat PAF. With a 5-year success rate of <30% after a single procedure (17), and <40% off antiarrhythmic drugs (18), PVI alone is clearly not sufficient to maintain sinus rhythm.

See page 2326

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In the context of our autonomic denervation project, we previously conducted the only randomized trial that has compared the efficacy of PVI with that of PVI with additional GP ablation in patients with PAF (11). The addition of GP ablation resulted in improved outcome (83.5% vs. 60.6% AF freedom at 1 year with approximately 20% of patients having undergone a repeat procedure). However, this pilot study was relatively small (67 patients were included), and followed patients only as long as 12 months. In addition, the safety profile of the ablation catheter used for that study (Ablation Frontiers, Medtronic, St. Paul, Minnesota) was later questioned (19). Moreover, our previous trial did not evaluate the comparative efficacy of GP ablation alone, that is, therefore, not known.

Because conventional PVI transects 3 of the 4 major atrial GP as well as the ligament of Marshall, it is possible that autonomic denervation by GP ablation plays a central role in the efficacy of PVI. The present study was designed to answer the following questions: 1) Is GP ablation alone as effective as PVI? 2) Does the addition of GP ablation to PVI increase the success rate of AF ablation in patients with PAF without an increase in the procedural risks and complication rates?

Abbreviations and Acronyms

AF = atrial fibrillation
AT = atrial tachycardia
CI = confidence interval
GP = ganglionated plexi
HFS = high-frequency stimulation
ILR = implantable loop recorder
PAF = paroxysmal atrial fibrillation
PV = pulmonary vein
PVI = pulmonary vein isolation
RF = radiofrequency

Methods

This study was a 2-center randomized trial that took place at the Department of Cardiology, Athens Euroclinic, Athens, Greece, and the Arrhythmia Department, State Research Institute of Circulation Pathology, Novosibirsk, Russia. The study protocol was approved by the Institutional Ethics Committee at both centers, and was conducted in compliance with the protocol and in accordance with standard institutional operating procedures. Patients who met all the inclusion criteria and were willing to participate were enrolled, and randomized after providing written informed consent. The trial was registered at ClinicalTrials.gov (NCT00671905).

Study patients. Patients were recruited and ablation procedures were performed from June 2009 to December 2010. Patients were included in the study if they were 18 to 75 years of age with symptomatic PAF, and left atrial size <50 mm (as obtained from transthoracic echocardiography). Exclusion criteria were left ventricular ejection fraction <35%, malignancies, serious comorbidity, and history of ablation procedures to treat atrial tachyarrhythmias.

Procedures. Participants were randomized to 1 of the following 3 groups.

Group 1. CIRCUMFERENTIAL PVI. Patients underwent conventional PVI by circumferential antral ablation according to standard procedures. Circumferential ablation around the antra of the PV was accomplished with the aid of electroanatomic mapping (Carto, Biosense Webster Inc., Diamond Bar, California) at a distance ~2 cm from the ostia of the left and right PVs (Fig. 1), aimed at a reduction of the voltage of the local electrogram by >80% or a peak-to-peak bipolar electrogram <0.1 mV.

Group 2. ANATOMIC ABLATION OF THE 4 MAJOR LEFT ATRIAL GP. Patients underwent specific anatomic ablation of the 4 major left atrial GP (Fig. 1), using the method initially described by Katritsis et al. (4), and modified by Pokushalov et al. (20). We previously showed that anatomic GP ablation (i.e., targeting the areas where the 4 major atrial GP are usually located) produces a better outcome than GP ablation guided by a positive parasympathetic response (hypotension or atrioventricular block) induced by high-frequency stimulation (HFS) (20). HFS-guided identification of the GP, therefore, was not deemed necessary for successful GP ablation. In brief, spiral computed tomography was performed for all patients. After computer processing (CartoMerge, Biosense Webster), the resulting image of the left atrium was integrated with the electroanatomic map of the left atrium. Presumed GP clusters were ablated 1 to 2 cm outside the PV–left atrium junctions at

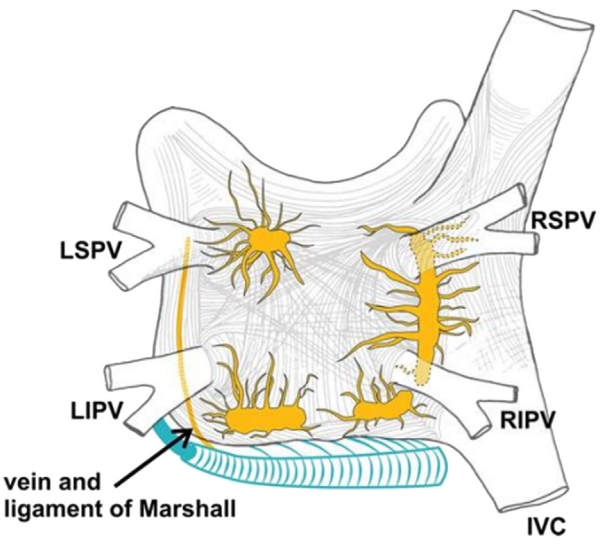

Figure 1 Anatomic Location of the 4 GPs

Schematic posterior view of the left and right atria. The 5 major left atrial autonomic GP and axons (superior left GP, inferior left GP, anterior right GP, inferior right GP, and ligament of Marshall) are shown in yellow, whereas the coronary sinus and the vein and ligament of Marshall are shown in blue, which travels from the coronary sinus to the region between the left superior PV and the left atrial appendage. GP = ganglionated plexi; IVC = inferior vena cava; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein. Reprinted with permission from Calkins et al. (21).

the following sites: left superolateral area (superior left GP-SLGP), right superoanterior area (anterior right GP-ARGP), left inferoposterior area (inferior left GP-ILGP), and right inferoposterior area (inferior right GP-IRGP). The crux GP in the inferoposterior area of the left atrium was not ablated to minimize the potential of ablation-related proarrhythmia. According to our protocol, only GP adjacent to the circumferential ablation line that was necessary for PVI were targeted. A 7.5-F, 3.5-mm irrigated tip catheter (NaviStar ThermoCool, Biosense Webster) delivering radiofrequency (RF) energy at 46°C, 30 to 35 W, 17 ml/min for 40 s (Stockert, Biosense Webster) was used. The endpoint of GP ablation procedure was elimination of atrial electrical activity (peak-to-peak bipolar electrogram <0.1 mV) at the sites where RF applications were delivered, as well as abolition of any parasympathetic effects elicited by RF energy delivery.

Group 3. CIRCUMFERENTIAL PVI FOLLOWED BY ANATOMIC ABLATION OF THE 4 MAJOR LEFT ATRIAL GP. Patients underwent PVI followed by anatomic ablation of the 4 major left atrial GP. Care was taken that the PVI circumferential line as indicated in Figures 2 and 3 were in continuation with the GP ablation sites to avoid introducing arrhythmogenic channels. Thus, during completion of the PVI, extra lesions were delivered at the anatomic sites of GP as previously described (4,20). The endpoint of PVI for both groups 1 and 3 was the verification of PVI by demonstration of both entrance and exit block with the use of a circular mapping catheter.

Study endpoints and procedural complications. The primary study endpoint with respect to ablation efficacy was freedom from AF or other sustained (duration >30 s) atrial tachyarrhythmia after a single procedure. Follow-up was conducted according to the Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) 2012 Consensus Statement (21). Patients were prospectively assessed for recurrence of AF or other atrial arrhythmia. It has been shown in animals that autonomic reinnervation occurred 4 weeks after GP ablation (22), and the effects of autonomic reinnervation on AF progression and recurrence are not known. Thus, patients underwent monthly clinical assessment and ambulatory electrocardiographic monitoring for 2 years, instead of the minimum 1-year period required by the HRS/EHRA/ECAS statement. All patients were instructed to maintain personal records with descriptions of every episode of symptomatic palpitations and, in case of persistent arrhythmia episodes, to obtain transtelephonic or direct electrocardiographic documentation of the underlying rhythm. Patients were encouraged to use transtelephonic monitoring even when their symptoms were not typical of recurrent AF. Moreover, 121 patients also received an implantable loop recorder (ILR), at the operator's discretion. A successful outcome during the follow-up period was defined as the lack of electrocardiographically recorded AF and no AF or other sustained atrial arrhythmia on an ambulatory electrocardiography device and subjective symptomatic improvement after a 3-month blanking period. We adopted a blanking period, the immediate period post-ablation during which recurrence of transient atrial arrhythmias were not considered as RF catheter ablation failure (21). As part of our routine AF ablation protocol, all patients received beta-blockers (unless contraindicated), whereas all patients were kept on anticoagulation for at least

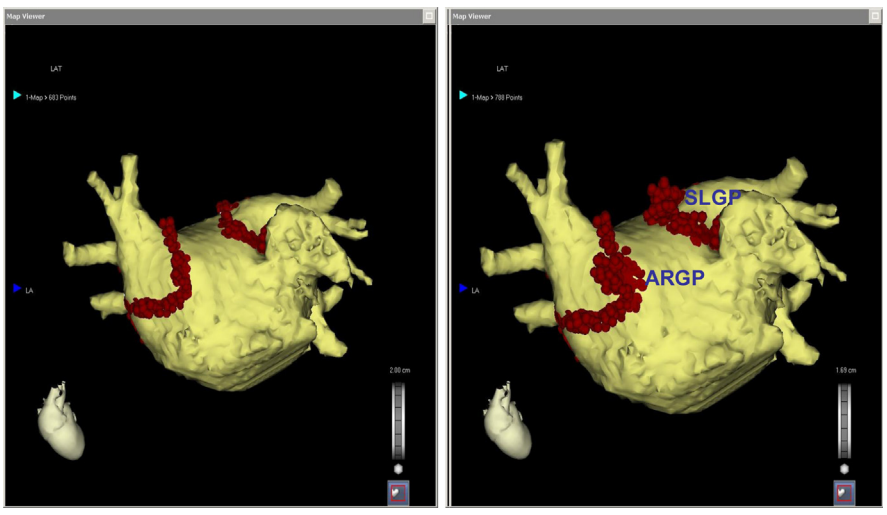

Figure 2 **Anatomic Ablation of the Superior Left and Anterior Right GP**

After pulmonary vein isolation, the ablation lesions are expanded to cover the anatomic site of presumed ganglionated plexi (GP) clusters. LSGP = left superior ganglionated plexi; RAGP = right anterior ganglionated plexi.

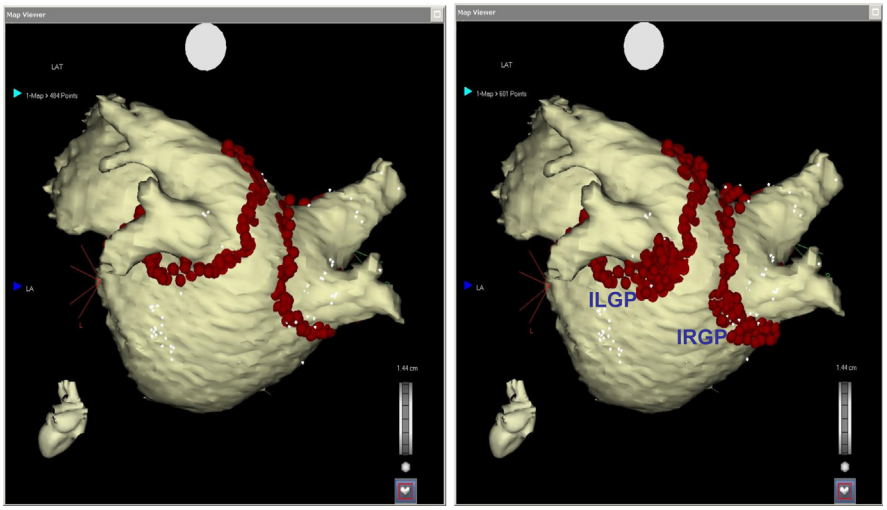

Figure 3 Anatomic Ablation of the Inferior Left and Right GP

After pulmonary vein isolation, the ablation lesions are expanded to cover the anatomic site of presumed GP clusters. ILGP = inferior left ganglionated plexi; IRGP = inferior right ganglionated plexi.

3 months post-ablation. Secondary endpoints included RF delivery time and fluoroscopy time. Procedure-related adverse events (including death, myocardial infarction, cardiac tamponade, and stroke) were also recorded.

Outcome determination was performed by the local site investigators in each of the 2 contributing centers, whereas all statistical analyses were performed independently by 2 investigators who were not involved in data collection or outcome documentation.

Sample size calculation. A study sample of 80 patients in each group was calculated to detect a 30% difference in primary endpoint between any groups of comparison at a statistical power of 80% at a 5% significance level.

Randomization protocol. For allocation of the participants, a computer-generated list of random numbers was used. Participants were randomly assigned after simple randomization procedures (computerized random numbers) to 1 of 3 ablation groups mentioned earlier. Allocation concealment was safeguarded by ensuring that allocation was obtained by computer output after the patients had consented. Due to the invasive nature of the procedures, performing physicians were not blinded to the randomization allocation, whereas outcome assessors during follow-up were blinded to the intervention group. Random assignment was performed in a 1:1:1 ratio to 1 of the 3 strategies, stratified by study site.

Statistical analysis. Patients and procedural characteristics were summarized and presented as mean ± SD or as absolute values and percentages, as appropriate. Comparisons of discrete and continuous variables between the 3 groups were performed by using the Kruskal-Wallis test. The primary analysis was based on an intention-to-treat analysis of all randomized patients who underwent each one of the above ablation strategies. For the primary study endpoint (freedom from AF or other sustained atrial arrhythmia), event rates were calculated from the time since the end of the blanking period (a 3-month blanking period was adopted since ablation procedure as mentioned earlier). Kaplan-Meier analysis was used for each group to assess the percentage of freedom of AF or other atrial arrhythmia at follow-up, and data were censored at 2 years or when the endpoint occurred. Event-free curves were compared by the log-rank test. All analyses were stratified by study site. For the primary endpoint, hazard ratios and 95% confidence intervals (CIs) were estimated with the use of Cox proportional hazards models.

All reported p values were based on 2-sided tests, and a p value <0.05 was considered significant. All statistical analyses were performed using STATA software, version 12.0 (StataCorp., College Station, Texas).

Results

Patient characteristics and treatment assignment. During the 3-year enrollment period, a total of 242 patients were eligible and randomly assigned to 1 of the 3 ablation strategies (PVI group = 78, GP ablation group = 82, PVI+GP ablation group = 82) (Table 1). Participants attended clinic visits at the time of randomization (baseline) and at 1-month intervals for 2 years. Two-year follow-up was completed for all enrolled patients, and ablation strategy crossover was not required for any of the patients.

Table 1 shows baseline and clinical characteristics, medical history, and therapy across different groups. In summary, there were 159 men and 83 women, with an age of 56 ± 8.1 and a range of 28 to 77 years. Values of left ventricular

Table 1 Baseline Characteristics of Patient Population

	Ablation Group			
	PVI (n = 78)	GP (n = 82)	PVI+GP (n = 82)	p Value
Age, yrs	56 ± 7.6	56 ± 8.2	56 ± 8.5	0.99
Male	53 (68)	49 (60)	57 (70)	0.51
Medical history				
Arterial hypertension	63 (81)	63 (77)	58 (71)	0.54
Diabetes	1 (1)	4 (5)	3 (4)	0.92
Thyroid disease	14 (18)	9 (11)	18 (22)	0.47
Antihypertensive drugs				
ACE	20 (26)	10 (10)	11 (13)	0.27
ARB	5 (6)	6 (7)	6 (7)	0.99
Beta-blocker	54 (69)	46 (56)	53 (65)	0.34
Calcium-channel blocker	7 (9)	3 (4)	5 (6)	0.84
Diuretics	4 (5)	7 (9)	9 (11)	0.81
Antiarrhythmic drugs*				
Class I antiarrhythmic drugs	23 (30)	26 (32)	29 (35)	0.81
Amiodarone	31 (40)	38 (46)	27 (33)	0.33
Sotalol	3 (4)	3 (4)	6 (7)	0.90
LVEF, %	63 ± 6.8	63 ± 6.6	62 ± 8.1	0.61
LA size, cm	4.8 ± 0.7	4.9 ± 0.6	4.8 ± 0.6	0.40

Values mean ± SD or n (%). *Before ablation procedure.
ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; GP = ganglionated plexi; LA = left atrium; LVEF = left ventricular ejection fraction; PVI = pulmonary vein isolation.

ejection fraction and left atrial size were 63 ± 7.2% and 4.8 ± 0.63 cm, respectively, for the whole study population. Finally, ILRs were available for 121 patients (39, 41, and 41 patients in PVI, GP, and PVI+GP ablation group, respectively).

Primary and secondary endpoints. During a 2-year follow-up period after the ablation procedure, a total of 44 (56%), 39 (48%), and 61 (74%) patients in the PVI, GP, and PVI+GP ablation groups, respectively, remained in sinus rhythm (Table 2). The proportion of patients free from AF or any sustained atrial arrhythmia was significantly higher in the PVI+GP group compared with PVI or GP strategies alone (p = 0.0036 by log-rank test) (Fig. 4). In the PVI+GP ablation group, the hazard ratio for the recurrence of AF or other sustained atrial arrhythmia was 0.53 (95% CI: 0.31 to 0.91; p = 0.022) and 0.42 (95% CI: 0.25 to 0.71; p = 0.001) compared with the PVI and GP ablation strategy alone, respectively. The comparison of GP and PVI ablation did not yield any statistically significant difference (hazard ratio: 1.26; 95% CI: 0.80 to 1.98; p = 0.314). However, as shown in Figure 4, after the first year of follow-up, the GP ablation strategy was less effective than the PVI strategy alone. Post-ablation atrial flutter was seen in 13 patients without any trend for increased risk in a specific ablation group: 4 patients in the PVI group (5.1%), 5 patients in the GP ablation group (4.9%), and 5 patients in the PVI+GP ablation group (6.1%).

When considering only patients with ILRs (n = 121), at least an episode of AF or other sustained atrial arrhythmia was detected in 20 of 39 (51%, PVI group), 22 of 41 (53%, GP ablation group), and 5 of 41 (12%, PVI+GP ablation group) patients.

For the primary outcome of freedom from AF or other sustained atrial arrhythmia, there was no significant treatment-by-site interaction (p = 0.197 to 0.572 for the interaction terms in the 3 pairwise comparisons), and PVI+GP ablation was the best strategy at both sites.

The duration of RF delivery time was 41 ± 10 min for PVI and 46 ± 12 min for GP, whereas for the PVI+GP ablation group, it was 67 ± 18 min (p < 0.001 between-group comparison). A significant difference in fluoroscopy duration was also recorded across the 3 ablation strategies: duration of 16 ± 3 min, 20 ± 5 min, and 23 ± 5 min for the PVI, GP, and PVI+GP ablation groups, respectively (p < 0.001 between-group comparison) (Table 2).

Procedural complications. No death, myocardial infarction, or stroke was recorded as an ablation-related complication. There was only 1 case of cardiac tamponade in a patient

Table 2 Study Endpoints

	Ablation Group			
Endpoints	PVI (n = 78)	GP (n = 82)	PVI+GP (n = 82)	p Value
Primary, 2-yr follow-up				
Freedom from AF or other sustained atrial arrhythmia	44 (56)	39 (48)	61 (74)	0.001
Secondary				
Radiofrequency time, min	41 ± 10	46 ± 12	67 ± 18	<0.001
Fluoroscopy time, min	16 ± 3	20 ± 5	23 ± 5	<0.001

Values n (%) or mean ± SD. Analyses were stratified by study site.
AF = atrial fibrillation; other abbreviations as in Table 1.

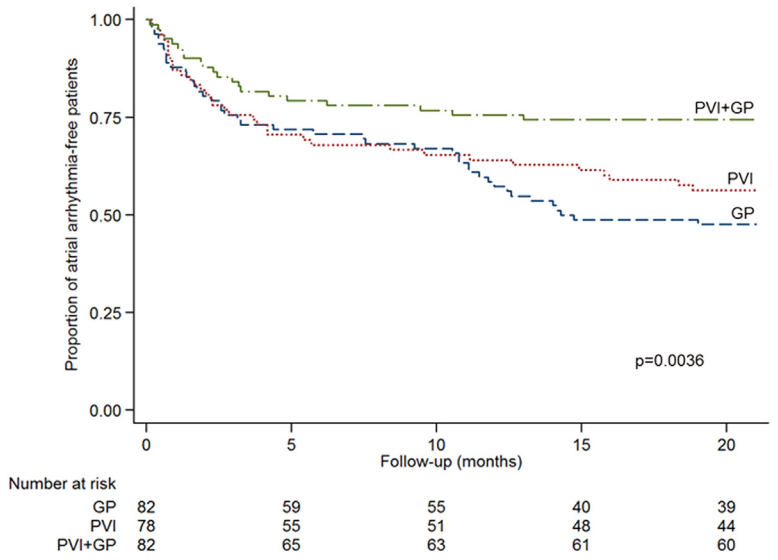

Figure 4 **Atrial Fibrillation or Other Sustained Atrial Arrhythmia Recurrence Across the 3 Different Ablation Strategies**

Kaplan-Meier estimates were used to calculate the 2-year event rates and comparison was performed using the log-rank test stratified by study site. A 3-month blanking period after the ablation procedure was adopted. GP = ganglionated plexi; PVI = pulmonary vein isolation.

in the PVI group who was treated with percutaneous pericardial drainage. The patient had an uneventful recovery.

Discussion

Our results indicate that addition of anatomic GP ablation to conventional PVI improves clinical outcome in patients with PAF. Notably, the success rate of GP ablation alone was not significantly different from that of conventional PVI; the lesion sets of both approaches have significant overlap, but the latter covers a substantially larger area in the left atrium.

Anatomic GP ablation used with our approach is not technically challenging because the locations of the 4 major atrial GP vary minimally among patients. In the present study, we elected to ablate the GP according to their anatomic locations instead of relying on the parasympathetic response (hypotension or atrioventricular block) elicited by HFS. Endocardial HFS at lower voltage often may not elicit a parasympathetic response, and HFS at higher voltages is painful and difficult to perform in patients not under general anesthesia. It is known that both sympathetic and parasympathetic elements reside in all 4 major atrial GP (23–25), as well as the ligament of Marshall (24,25). HFS at sites that are richly innervated by both the sympathetic and parasympathetic neural elements may not elicit a parasympathetic response at all, and subsequently underestimates the extent of the GP. Although earlier studies on GP ablation were guided by the vagal responses elicited by HFS, later studies demonstrated that the outcome of GP ablation guided by HFS was inferior to that guided by the anatomic locations of the GP (20). We postulate that GP ablation guided by HFS underestimates the extent of the major atrial GP and thus translates into significantly less autonomic denervation and subsequently a lower success rate.

Although inferior to the other 2 approaches, GP ablation alone still maintained sinus rhythm in 50% patients at 2 years. In these patients, the PV antra were not isolated, indicating that autonomic denervation is a major contributor to the efficacy of PVI. It cannot be overemphasized that the conventional PVI transects the SLGP, ligament of Marshall, ARGP, and part of the IRGP as well as many small clusters of autonomic ganglia and nerves. Complete isolation of the PV antra also eliminates the triggers and substrate in the PV antrum and ensures that PV firing cannot conduct into the atrium to initiate AF, rendering a slightly better but not statistically significant outcome compared with GP ablation alone.

We hypothesize that the additional benefit of PVI+GP ablation may result from a combination of destroying and/or isolating the triggers of PV firing by PVI, and more complete autonomic denervation by GP ablation combined with PVI. Another possibility is that ablation at the GP area resulted in elimination of the complex electrical activity located at these parts of the left atrium. Katritsis et al. (26,27) previously showed that fractionated electrograms are usually found in the areas of GP. Choi et al. (28) also identified intrinsic cardiac nerve activity as a source of electrogram fractionation and trigger of paroxysmal atrial tachyarrhythmias including AF, consistent with the possibility that GP ablation may target both autonomic neural elements and fractionated electrograms.

The PVI+GP approach did not confer a higher risk of ablation-induced proarrhythmia despite more RF applications delivered and longer ablation time. Selective GP modification added to PVI has been reported to carry a higher risk of iatrogenic left atrial tachycardias than PVI (10). Selective anatomic or HFS-mediated GP ablation was complicated by atrial macroreentry in 2% to 10% of patients after ablation, but did not always require a repeat procedure because these tachycardias may spontaneously resolve with time (4,11,20,29). In the present study, GP ablation sites were either on the circumferential PVI lines or were extended to connect with the circumferential lines to avoid creating arrhythmogenic channels. This precaution may account for the lower incidence of left atrial tachycardias that potentially can be introduced by adding GP ablation to PVI.

Study limitations. The present study included only patients with PAF. Although a recent meta-analysis suggested that autonomic denervation plus PVI significantly increase the freedom from recurrence of AF both in paroxysmal and nonparoxysmal patients (12), the value of additional ablation (e.g., lines or fractionated electrograms) to PVI in persistent AF continued to be questioned (30). As a stand-alone therapy, GP ablation is not enough to confer a favorable outcome in patients with long-standing persistent AF (29). However, GP ablation alone was still effective in maintaining sinus rhythm in 38.2% (at 24 ± 3 months) patients with long-standing persistent AF (29), indicating that the autonomic nervous system still contributes to the maintenance of AF in more advanced stages of AF. Although the efficacy of PVI+GP on patients with persistent/permanent AF is not known, a clinical study to answer this question is currently under way at our institutions. Our study entailed selective ablation of the major left atrial GP; ablation of the crux GP in the left atrium or of the right atrial GP that might have improved success rates (8) was not undertaken. The strategy of documentation of any atrial arrhythmia recurrence certainly has room for improvement. However, this is a standard approach for post-ablation assessment according to the 2012 HRS/EHRA/ECAS Expert Consensus Statement. It is important to point out that a considerable proportion of patients received ILRs, and recordings from the ILRs further verified the documented the superior efficacy of the PVI+GP approach. In the last 10 months of follow-up, the success of PVI and GP ablation continues to decline, but the Kaplan-Meier curve of the PVI+GP appears to remain flat. Whether PVI+GP will continue to outperform the other 2 approaches will require a longer follow-up period, which is ongoing at both centers.

Conclusions

Our data indicate that the outcome of adding anatomic GP ablation to PVI is better than PVI or GP ablation alone. The PVI+GP approach is not technically challenging, does not entail a considerable increase in fluoroscopy time, and can be easily adopted as a modification of conventional PVI by circumferential ablation.

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Key Words: atrial tachycardia ■ catheter ablation ■ ganglionated plexi ■ implantable loop recorder ■ paroxysmal atrial fibrillation ■ pulmonary vein isolation.