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Ganglionated Plexi Ablation for Atrial Fibrillation

Yong Zhang, Mei Gao, Jiangrong Wang and Yinglong Hou
Department of Cardiology, Qianfoshan Hospital of Shandong University, Jinan City, China

1. Introduction

With an estimated prevalence of 0.4%~1% in the general population, atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice [1]. As an emerging technology, catheter ablation is becoming more and more important in the treatment of AF at present. In a sense, catheter ablation is more superior to the antiarrhythmic drug and surgery treatment, but this technology remains a challenge, because long-term success rate is low, most patients require repeat procedure and there is no established ablation method.

The importance of the autonomic nervous system (ANS) in the initiation of AF has been proved in the early 1990s [2-4], and the ganglionated plexi (GP), found in epicardial fat pads, was subsequently shown to play a role in initiation and maintenance of AF [5, 6]. Studies have shown that chemical or electric stimulation of GP can initiate rapid firing from the pulmonary vein (PV) or PV-atrial junction, which is similar to the focal firing observed in patients with AF [7-9]. Moreover, several studies indicate that ablation of the major atrial GP can suppress the inducibility and maintenance of AF [9].

Therefore the GP ablation has received more and more attentions nowadays, and it promises to be a more superior ablation technology of AF. However, the long-term success rate of GP ablation is quite variable (40%~90%, approximately), and the reasons remain under investigate.

2. Cardiac ANS and its effects on the initiation and maintenance of AF

The cardiac ANS can be divided into the extrinsic and intrinsic components. The extrinsic cardiac ANS consists of the soma in brain nuclei and chains of ganglia along the spinal cord and the axons that course en route to the heart. The intrinsic cardiac ANS is composed of a neural network formed by axons and autonomic ganglia concentrated at the GP embedded within epicardial fat pads on the heart itself and the ligament of Marshall (LOM) [10]. There are four main GPs on the atrium of mammalian hearts [11]: the anterior right GP (ARGP) at the right superior PV (RSPV)–atrial junction; the inferior right GP (IRGP) at the junction of inferior vein cava and both atria; the superior left GP (SLGP) near the left superior PV (LSPV)–atrial junction and left pulmonary artery, and inferior left GP (ILGP) at the left inferior PV (LIPV)–atrial junction (see Figure 1 and 2).

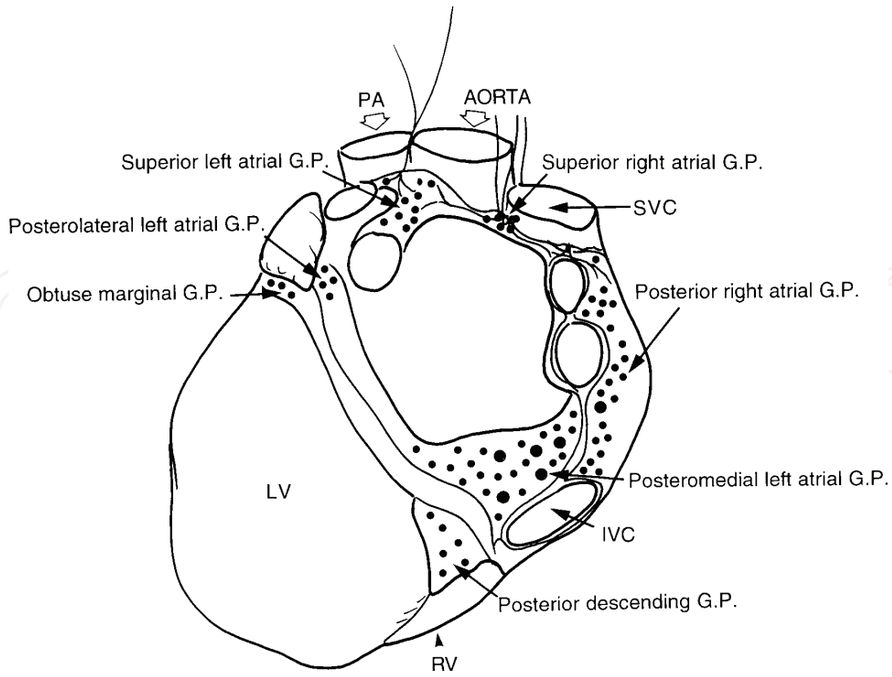

Fig. 1. Drawing of a posterior view of the human heart and major vessels illustrating the locations of posterior atrial and ventricular GP. Note the mediastinal nerves coursing adjacent to the aortic root and joining the two superior atrial GP. SVC = superior vena cava, IVC = inferior vena cava, RV = right ventricle, LV = left ventricle. (Armour JA, et al. Anat Rec 1997; 247(2): 289-98)

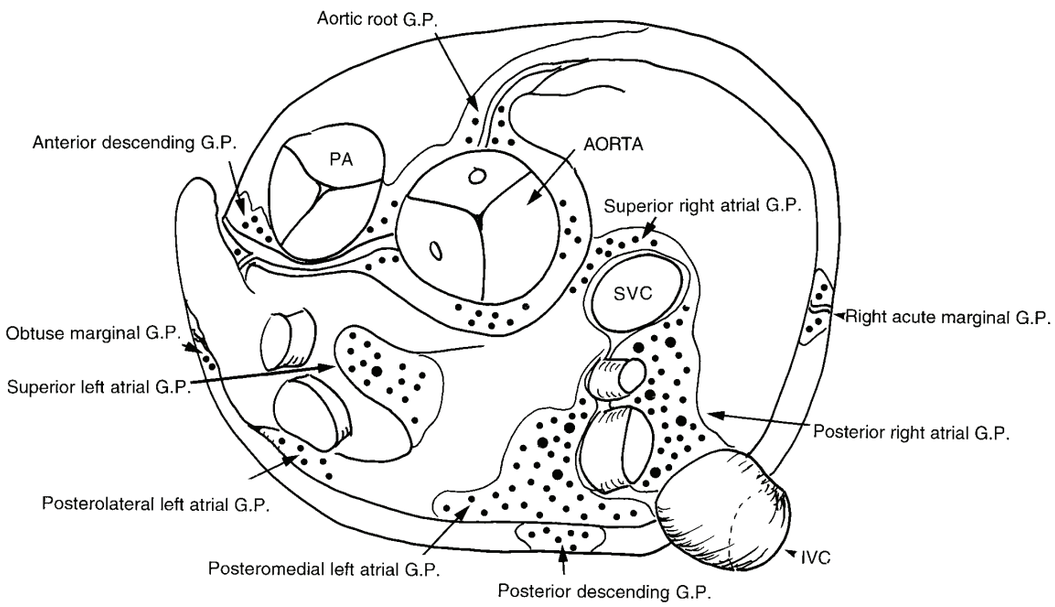

Fig. 2. Drawing of a superior view of the human heart illustrating the distribution of ganglionated plexuses on the surface of the atria and ventricles. For abbreviations, see Figure 1. (Armour JA, et al. Anat Rec 1997; 247(2): 289-98)

In 1947, Scherf [12] found that AF could be induced by application of aconitine to the atrium in the experimental condition. He proposed that a focal firing source could initiate AF. Moe et al. [13] in 1964, using a computer model, hypothesized that AF could exist as a stable mechanism independent of the triggering event. They assumed that this self-sustaining mechanism could be described as multiple wavelets in randomly rotating circuits within the atrial confines. In 1985, Allessie et al. [14] on the basis of an elegant mapping technique, found that at any given time at least three to six self-perpetuating wavelets could be found wandering over the surface of the atrium during AF. The focal mechanism resurfaced, based on Haissaguerre's discovery [15] that rapidly firing foci within the PV could induced AF in 1998, and since then, research on the genetic, trigger, electrophysiology, structure and adjustment of the initiation and maintenance of AF has witnessed considerable breakthrough.

In recent years, with the continuous development of our knowledge, more and more profound researches on the relationship between ANS and AF have been conducted. Moreover, some researchers even studied the difference between the effects of vagus and sympathetic nerves on the initiation of AF. In 2000, Schauerte et al. [16] found that radiofrequency ablation of parasympathetic nerve fibers along right pulmonary artery, inferior or superior vena cava blunted the atrial effective refractory period (AERP) shortening caused by vagal stimulation (VS), and abolished the increase covariance of AERP caused by VS, and led to an increase of the baseline AERP. Before the ablation, VS could induce and maintain AF; while after the ablation, it could not induce AF any more. Further study [5] carried out by this team in 2001 found that high-frequency stimulation (HFS) on pulmonary and superior vena cava could lead to the initiation of atrial premature depolarization, atrial tachycardia (AT) and AF. More importantly, in this study, blockers of autonomic nerves receptor were used to intervene, which were found to blunt or abolish the response of atrial to HFS. Later, more attention was turned to myocardial sleeves of PV. A study [17] in 2005 found that HFS on PV myocardial sleeves could shorten the action potential duration (APD) of myocardial sleeve cells and trigger AF, and this phenomenon could be blocked by atropine and atenolol, which indicated that the rapid discharge of myocardial sleeves of PV was the result of combined action of sympathetic and parasympathetic neurotransmitters. In 2007, the effects of the VS or isoproterenol on the PV tachycardias, which were created by burst pacing from a PV or the application of aconitine onto the PV, were evaluated [18]. The result indicated that VS effects affecting the PVT and atrium facilitate the onset and maintenance of PV-triggered AF, but not isoproterenol. In another study [19], complete atrioventricular block (AVB) was produced by radiofrequency current in 17 dogs. After 8 weeks, the atrial dimensions and the percentage of fibrosis in the atrium were observed significantly greater. However, atrial and PV effective refractory periods were shorter, and atrial conduction velocity increased during sympathetic stimulation, but not during VS, which indicated that contrary to the normal atrium, sympathetic stimulation was crucial for the genesis of AF in the remodeled atrium.

As previously mentioned, the intrinsic cardiac ANS is composed of a neural network formed by axons and autonomic ganglia concentrated at GP. Therefore, GP is certainly quite important during the research of ANS, and there are several studies involving the relationship between GP and AF. According to the study performed by Scherlag et al [7], the HFS at the base of RSPV provide a substrate for the conversion of PV firing into AF, and the more intense the HFS, the easier the conversion became. Study [8] in 2006 pointed out that the injection of acetylcholine and carbachol, two parasympathomimetic agents, into the GP of RSPV could result in autonomic or easily-triggered AF and rapid discharge could be

detected in the PV and atrium near the injected position. Thus, it suggested that the high excitation of GP might be the important link in the transformation from the trigger of PV into AF. In 2009, Lu et al. [9] exerted HFS on atrium and PV in the refractory period of the cardiac muscles of dogs to trigger AF, and GP ablation was conducted to observe its effect. The results showed that HFS could initiate rapid discharge by activating cardiac autonomic nerve network. The GP on both sides could facilitate the initiation of rapid discharge or the trigger of AF by HFS on the same side or the opposite side. What's more, it could increase the trigger threshold of AF through GP ablation, or even prevent AF. A large number of studies have confirmed that GP played an important role in the initiation and maintenance of AF. The advancement of these studies promotes GP ablation to become a therapy, thus providing the theoretical basis for the clinical application of GP ablation.

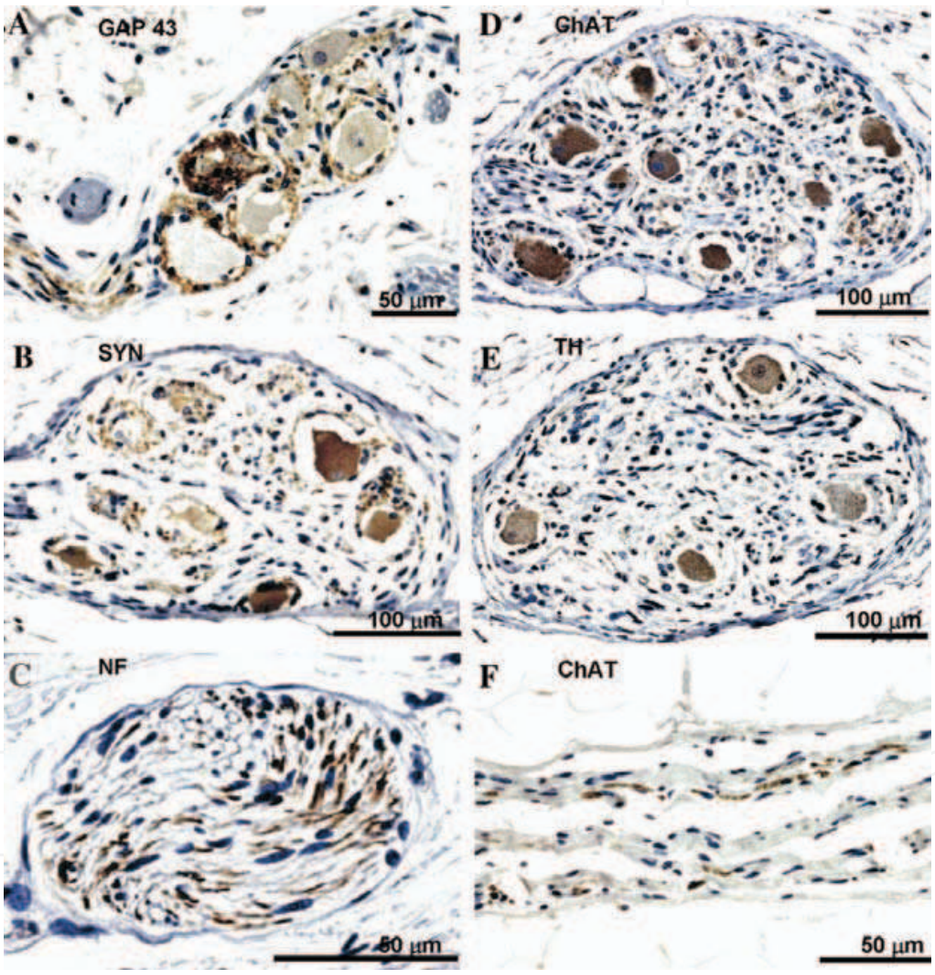

Fig. 3. Examples of immunohistochemical staining results in cardiac ganglia and nerves. (A) Growth-associated protein 43 (GAP 43) demonstrating axonal growth within the ganglion; (B) synaptophysin (SYN) staining demonstrating synaptic endings; (C) neurofilament (NF) staining confirming the presence of nerve fibers; (D) choline acetyltransferase (ChAT) staining showing cholinergic nature of most ganglion cells; (E) tyrosine hydroxylase (TH) staining showing co-localization of adrenergic cells within the same ganglion; and (F) ChAT positivity of nerve adjacent to ganglion. (Tan AY, et al. J Am Coll Cardiol. 2006; 48(1): 132-43)

With the deepening of the functional research, further anatomic studies of ANS have been performed, which have revealed the anatomic basis of the important role of cardiac ANS in the initiation and maintenance of AF. In 2005, Chevalier et al. [20] conducted 43 autopsies and found that there was a high intensity of innervation at the junction of PV and left atrium, and they found the nerve density was significantly higher at the ostia of the PVs than in their distal part, and there were gradients of innervation from right to left and from the front to the rear of the atrium. This study attempted to provide some clinical implications for radiofrequency ablation of AF. In 2006, Tan et al. [21] conducted further research on the heart obtained from the autopsy, which revealed that at the junction of PV and the left atrium, there were a great deal of discontinuous muscles and abrupt fiber orientation changes. And starting from this junction, within a range of 5mm in the left atrium, the density of autonomic nerves reaches its highest, with the coexistence of adrenergic and cholinergic nerves (see Figure 3). The anterior superior walls of two superior PV had a relatively higher density of nerves; the inferior walls of two inferior PV had a higher density of nerves (see Figure 4); the density of nerves of epicardium was higher than that of endocardium.

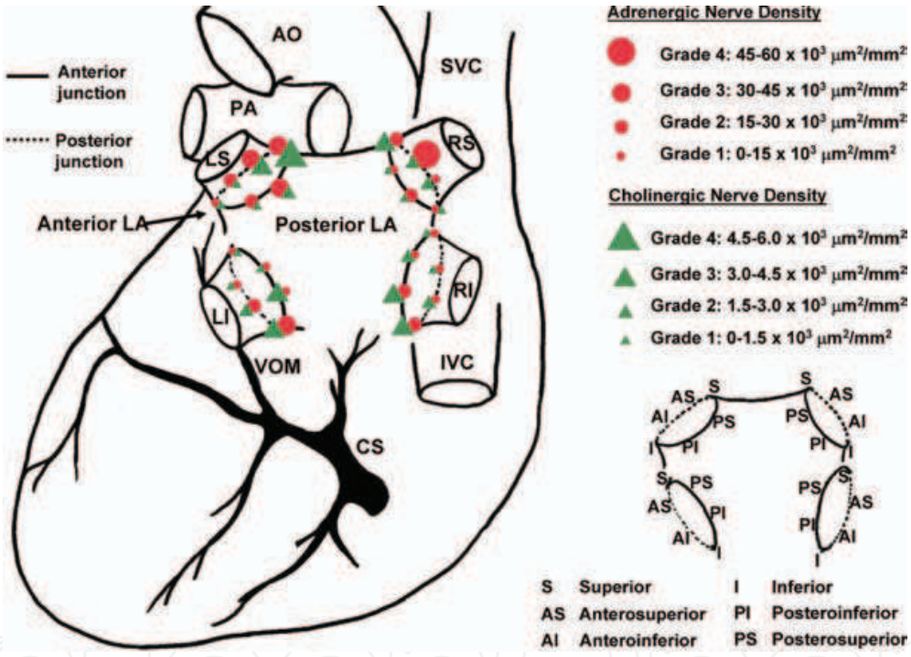

Fig. 4. Circumferential distribution of autonomic nerves at the PV-left atrium junction. AO = aorta; CS = coronary sinus; LA = left atrium; LI = left inferior PV; LS = left superior PV; PA = pulmonary artery; RI = right inferior PV; RS = right superior PV; VOM = vein of marshall, other abbreviations, see Figure 1. (Tan AY, et al. J Am Coll Cardiol. 2006; 48(1): 132-43)

3. GP ablation for AF

Either the adrenergic or vagal arm of the ANS may be involved in atrial electrical instability. Vagal activation shortens AERP and increases their dispersion, and adrenergic stimulation enhances atrial myocardial automaticity. Coumel [3] who studied patients with paroxysmal AF and the relationship between this arrhythmia and ANS, was the first to identify two different clinical patterns: vagal and adrenergic AF. In 2008, a research [22] was conducted in Europe including 1517 patients with paroxysmal AF. In this study, AF was divided into sympathetic,

vagal and mixed type in terms of the trigger mode. Observations revealed that the three types of AF constituted 15%, 6% and 12% of the total respectively, suggesting that the cause of AF in at least one third of the patients might have associated with ANS (see Figure 5).

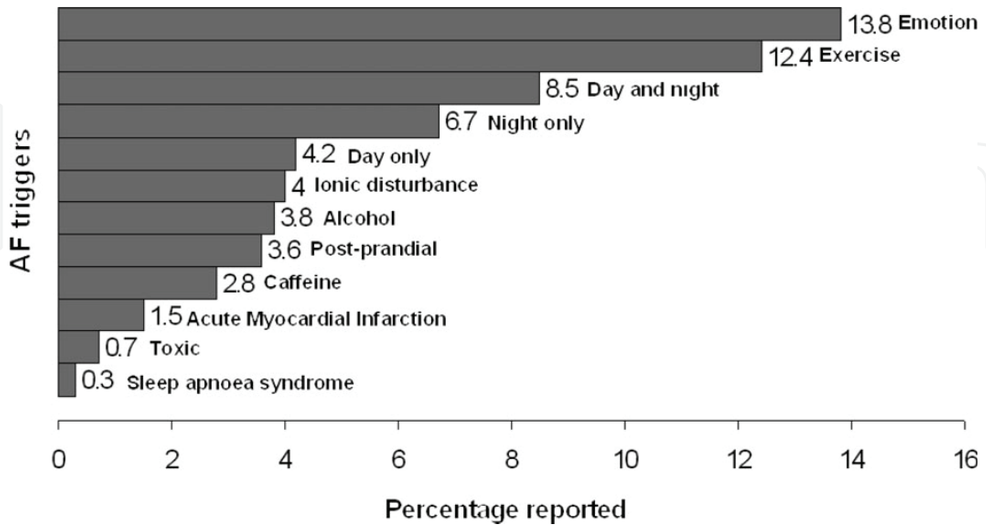

Fig. 5. Percentages of triggers reported in patients with paroxysmal atrial fibrillation in the Euro Heart Survey. (de Vos CB, et al. Eur Heart J. 2008; 29(5): 632-9)

As described above, profound researches have been conducted on the role of cardiac ANS in the initiation and maintenance of AF. In recent years, clinical studies based on these theories have been carried out. Besides traditional radiofrequency ablation therapy of AF (such as circumferential PV ablation and PV isolation), an additional, even independent GP ablation therapy has been attempted with certain curative effect. In this chapter, a brief introduction would be presented on the clinical studies concerning GP ablation recently.

According to the method of localization of GP, there are two different ablation manners: selective ablation of GP identified by HFS and extensive regional ablation targeting the anatomic areas of GP. Each GP contains both parasympathetic and sympathetic neural elements; stimulation of the former typically elicits an immediate response (within 2~4 seconds), while stimulation of the latter induces a delayed response (8~10 seconds). It is the rationale of localization of GP by HFS [23]. Therefore, HFS is usually delivered at each site for only 2~5 seconds, and the sites of positive parasympathetic responses are considered the GP sites. The predominant efferent parasympathetic responses include bradycardia, hypotension and high grade AVB (or obvious increase in mean R-R interval during AF).

In 2004, Pappone et al. [24] conducted radiofrequency ablation for patients with AF. Thirty four percent of 297 patients reported an apparent vagal response such as bradycardia at the high energy radiofrequency current at some sites in the left atrium when receiving circumferential PV ablation. Continuous ablation on these sites could make vagal response disappear. At a mean follow-up of 12 months 99% of the patients who had reported a vagal response suffered from no reoccurrence of AF; while the percentage for those who had not reported vagal response was only 74%. These sites might be the corresponding area of endocardium to GP of epicardium, and in fact, radiofrequency ablation was conducted on GP of epicardium via endocardium, suggesting that GP ablation based on circumferential PV ablation might help to increase the success rate.

In 2004, Platt et al. [25] reported a research involving 26 AF patients receiving only GP ablation without PV isolation. The clinical results were that immediate success rate of the operation was 88% (23/26). For patients who had positive vagal response, GP ablation was performed, and the immediate success rate was 96% (22/23); in the 22 cases of immediate success, 14 needed to take antiarrhythmic drugs which had no effect before the operation and 8 didn't need any drug to maintain sinus rhythm. Follow-up averaging 6 months showed that 85% (22/26) of the patients still maintained sinus rhythm, which indicated GP ablation alone could also obtain a satisfactory effect.

In 2005, Scherlag et al. [26] reported the results of ablation for 60 AF patients. Twenty seven received standard PV isolation and 33 received standard PV isolation + GP ablation. For the standard group, follow-up averaging 12 months showed the non-reoccurrence rate was 71% (19/27); while follow-up averaging 5 months of the group with additional GP ablation indicated a rate of 91% (30/33). Therefore, it was suggested that GP ablation could help to increase the success rate of PV isolation for AF.

In 2006, Lemery et al. [27] localized GP by endocardial HFS. GP ablation was conducted on 14 patients with paroxysmal and persistent AF. The result showed the success rate was only 50%.

In 2006, Scanavacca et al. [28] conducted GP mapping and ablation applying endocardial and epicardial HFS. The results revealed that 7 out of 10 cases showed vagal response; 3 cases failed to show the vagal response but accepted circumferential PV ablation. During the mean follow-up of 8.3 months, 2 out of 7 cases after GP ablation were free from symptoms without taking antiarrhythmic agents; 4 cases underwent circumferential PV ablation for frequent recurrence of AF; and 1 case suffered from slight AF without using antiarrhythmic agents.

In 2008, Pokushalov et al. [29] reported the results of the conduction of GP ablation alone in 58 patients with AF. This concurrently eliminated AF in 94% of cases in the process of the ablation and vagal response was shown in 93% of cases. There were not any arrhythmia episodes in 86% of patients over the mean follow-up of 7.2 months, with no need to take any antiarrhythmic agents.

In 2008, Danik et al. [30] reported the results of GP ablation in 18 cases suspected of vagal AF. After elimination of all vagal response sites from endocardium, 17 cases still suffered from HFS-induced AF. The researchers believed in that GP ablation could not prevent the immediate induction of AF.

In 2008, Katritsis et al. [31] also conducted GP ablation in 19 cases of paroxysmal AF by means of anatomically based GP ablation, and compared the results with 19 cases of age, gender-matched patients with conventional circumferential PV ablation. The results showed that in the process of ablation, vagal response occurred only in 4 cases, and during the mean follow-up of 1 year, the recurrent rate of arrhythmia was 74% and 37% in GP ablation group and circumferential PV ablation group, respectively. Among them, 2 patients suffered from atrial flutter besides the recurrence of AF, suggesting that anatomically-based GP ablation might be inferior to circumferential PV ablation.

In 2009, Pokushalov et al. [32] compared the results of the selective GP ablation identified by applying HFS with those of the anatomically based regional GP ablation in 80 cases (40 cases in each group) of paroxysmal AF. Ablation targets of selective GP were the vagal response sites evoked by HFS. The end point of the procedure was marked by the failure to evoke vagal responses by HFS. Regional GP ablation was defined as the more extensive ablation conducted at the anatomic sites of GP for anatomical damage. During the mean follow-up of 13.1 months, no symptomatic paroxysmal AF occurred in 42.5% and 77.5% of the cases in

the two groups, respectively, indicating that the anatomic ablation might improve the success rate of AF ablation.

In 2009, Han et al. [33] reported the results of applying thoroscopic pulmanory vein isolation + GP ablation + Marshal liganents ablation + left auriculectomy therapy in 45 cases (33 cases of paroxysmal AF and 12 cases of persistent AF). The results showed that, during the mean follow-up of 1 year, 65% of the patients did not suffer from atrial tachyarrhythmias that lasted for more than 30 seconds; in most of the cases where atrial tachyarrhythmias reoccurred, another ablation procedure or application of antiarrhythmic agents were effective.

In 2009, Po et al. [23] also reported the therapeutic results of 83 cases of AF after GP ablation and PV isolation. Patients who did not suffer from AF or AT after the single procedure of ablation accounted for 80% during the mean follow-up of 1 year and 86% during the mean follow-up of 22 months. The researchers held that the benefits of GP ablation based on PV isolation increased with time, especially 12 months after ablation, and suggested that this later benefits might be due to the irreversible damage of the autonomic neuron in GP.

In 2010, Pokushalov research group [34] also reported the results of anatomic GP ablation therapy in 89 cases of chronic AF, of which 29 needed additional circumferential PV isolation and 5 cases needed circumferential PV isolation once more. The follow-up averaged 2 years. The maintenance rate of sinus rhythm without medications following the single procedure of anatomic GP ablation was 38.2%.

And in the same year, Pokushalov research group [35] reported the results of the ablation of left atrial GPs in 56 patients with paroxysmal AF. Seventy one percent of the patients (40/56) did not suffer from the recurrence of arrhythmia over the mean follow-up of 12 months, suggesting that local ablation applying to the left atrial GPs might become an alternative therapy for paroxysmal AF.

In 2010, Mikhaylov et al. [36] reported the long-term follow-up results of a group undergoing GP ablation. The case control study included 70 cases of paroxysmal AF, of which 35 cases underwent GP ablation and 35 circumferential PV ablation. The incidence of arrhythmia over the mean follow-up of 36.3 months was 34.3% in GP ablation group and 65.7% in circumferential PV ablation group, respectively, suggesting that the long-term therapeutic effect of GP ablation was not as good as that of circumferential PV ablation.

In 2011, Krul et al. [37] reported the curative effect of thoracoscopic PV isolation + GP ablation in 21 cases of AF. Eighty six percent (19/21) of the patients were free of the reoccurrence of AF, atrial flutter, and AT over the mean follow-up of 1 year, without the use of antiarrhythmic agents.

In 2011, Katritsis et al. [38] reported a randomized controlled trial between a group with PV isolation alone and the group with PV isolation + GP ablation. It was found during the mean follow-up of 1 month that 60.6% (20/33) of the patients in the PV isolation group and 85.3% (29/34) of patients in the PV isolation +GP ablation group were free of arrhthymia, respectively, suggesting that adding GP ablation to PV isolation might help improve the efficacy of ablation.

Thus, studies on GP ablation in the treatment of AF are increasing year by year. In addition, the types of researches are shifting from retrospective ones to randomized controlled trials, initiating an in-depth exploration of the safety of GP ablation, such as the canine model by Cui et al [39], which observed whether GP ablation produced acute effect on the functions of sinoatrial node and atrioventricular node.

It has been found that, in the process of AF ablation, GP ablation, whether single or additional, direct or indirect, is effective to certain extent. It has also been found that there

exist significant curative differences among GP ablation therapies, the reason of which will be discussed in the next section. GP ablation in the treatment of AF is now in its initial stage, lacking large-scale clinical researches and the number of randomized controlled trials is very small. However, related works are now being carried out. Several issues are yet to be addressed, such as whether GP ablation is beneficial at all, which type of patients with AF is more suitable for GP ablation, which method is more acceptable in terms of GP localization, etc. We believe that, in near future, GP ablation will be better understood through large number of randomized controlled trials as well as meta-analysis.

4. Possible reasons for the variable long-term success rate of GP ablation

As stated above, the efficacies of GP ablation differs significantly, for which there are many possible reasons, including the clinical features of the cases selected, methods to apply ablation, localization for GP sites, the extent of denervation, criteria to judge success, time and index for follow-up, and the performer's experiences, etc. Among them, localization of GP sites has attracted more attention. Most of the existing studies target GP by HFS-induced vagal responses, however, either GP mapping through endocardium or epicardium cannot result in ideal success rate. It is assumed that the sites where vagal responses occur are not necessarily the anatomic GP sites.

Chen et al. [40] believed that HFS mapping primarily revealed the sites of ANS afferent nerves, because only stimulation of the afferent nerves could explain the vagal responses such as reflex bradycardia and vasodilatation. Therefore, the sites presented by vagal responses were not necessarily consistent with those of GP and efferent nerves (see Figure 6). Moreover, according to the "octopus theory" hypothesized by Po et al. [41] explaining from another point of view, there existed within the atrium a highly integrated neural network and neurotransmitters would be secreted after GP activation, further causing AF. And the activation of axons would excite GP reversely and also cause neurotransmitter release, inducing AF. Similar in shape to octopus, activation of GP (octopus's head) might trigger neurotransmitter release, inducing AF, while axons (octopus's cirrus), when stimulated, might activate GP (octopus's head) reversely and cause neurotransmitter release, thus also triggering AF (see Figure 7).

Therefore, many studies have come up with reasonable explanations regarding the differences between positive vagal response sites and actual anatomic GP sites. Just as mentioned above, some studies [32, 34] have applied radiofrequency ablation on anatomic GP sites and obtained satisfactory effect. However, even with the same anatomically based GP mapping, the above mentioned research results by Katritsis et al. [31] are disappointing.

For this, we also did a series of research. In our first study [42], with vagosympathetic trunk stimulation, sinus rate, and ventricular rate during AF were compared before and after sequential ablation of SLGP, ARGP, and IRGP in dogs, and in our second study [43], sinus rate, AH interval during atrial pacing, and ventricular rate during AF were compared before and after GP stimulation and after their ablation. We found that GP is the "integration center" not only between extrinsic and intrinsic cardiac ANS (see Figure 8), but also within the intrinsic cardiac ANS (see Figure 9), and the integration is substantially more complicated than previously thought, which may lead the variable long-term success rate of GP ablation. Moreover, in the second study, we also optimized the GP ablation strategy. As described above, one or more of the GP may serve as the "integration center" in the complex neural network, so a carefully designed ablation strategy targeting the "integration center"

would have substantial impact on the outcome of AF ablation. If the "integration center" was ablated before HFS is applied to other GP, stimulation may fail to induce ventricular rate slowing during AF and subsequently decreases the ability to localize the GP. Therefore the "integration center" needs to be ablated after other clinically relevant GP have been localized in order to achieve sufficient attenuation of the intrinsic cardiac ANS. For instance, the IRGP should not be ablated until the SLGP has been localized. Based on this postulation, Po et al. [23] stimulated and ablated the GP in 83 cases of AF in the following order: (1) SLGP, (2) ILGP, (3) ARGP, and (4) IRGP, and obtained satisfactory success rate.

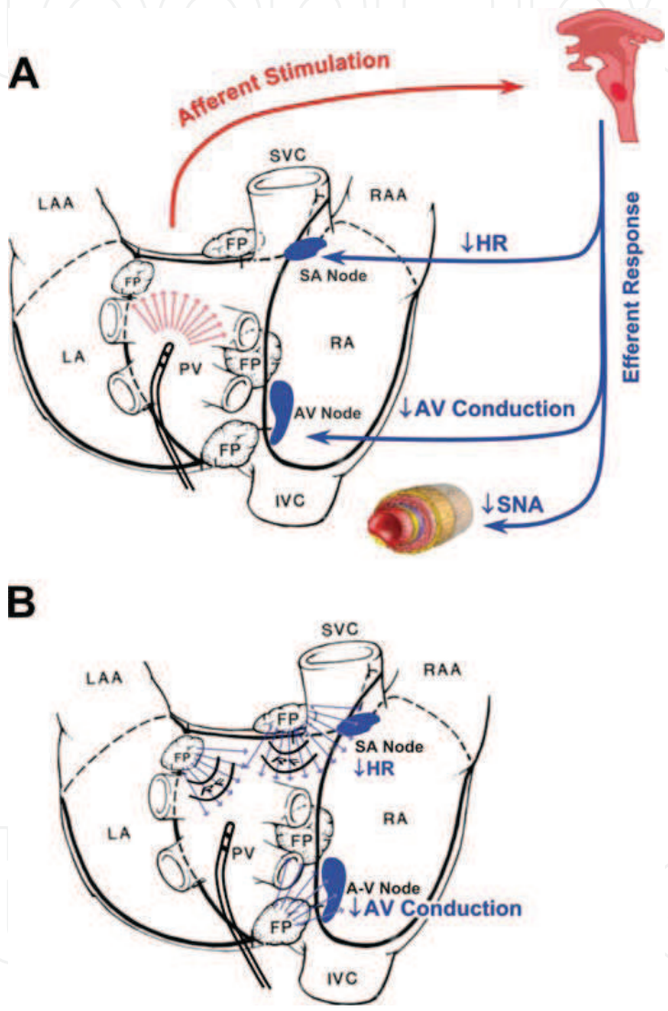

Fig. 6. Illustration of the possible mechanisms of denervation associated with RF ablation. Posterior view of the heart. (A) RF ablation applied at the pulmonary vein ostia stimulating vagal afferent nerve fibers, inducing reflex bradycardia, atrioventricular block, and decreased efferent sympathetic nerve activity leading to hypotension. Repeated RF ablation at these sites could result in damage to the afferent limb of the reflex. (B) RF ablation applied at the pulmonary vein ostia stimulating postganglionic efferent parasympathetic fibers. Repeated RF ablation at these sites could potentially damage efferent postganglionic parasympathetic fibers. RA = right atrium; LAA = left atrial appendage; RAA = right atrial appendage; FP = fat pad, other abbreviations, see Figure 1 and 4. (Chen J, et al. PACE. 2006; 29(4): 413-21)

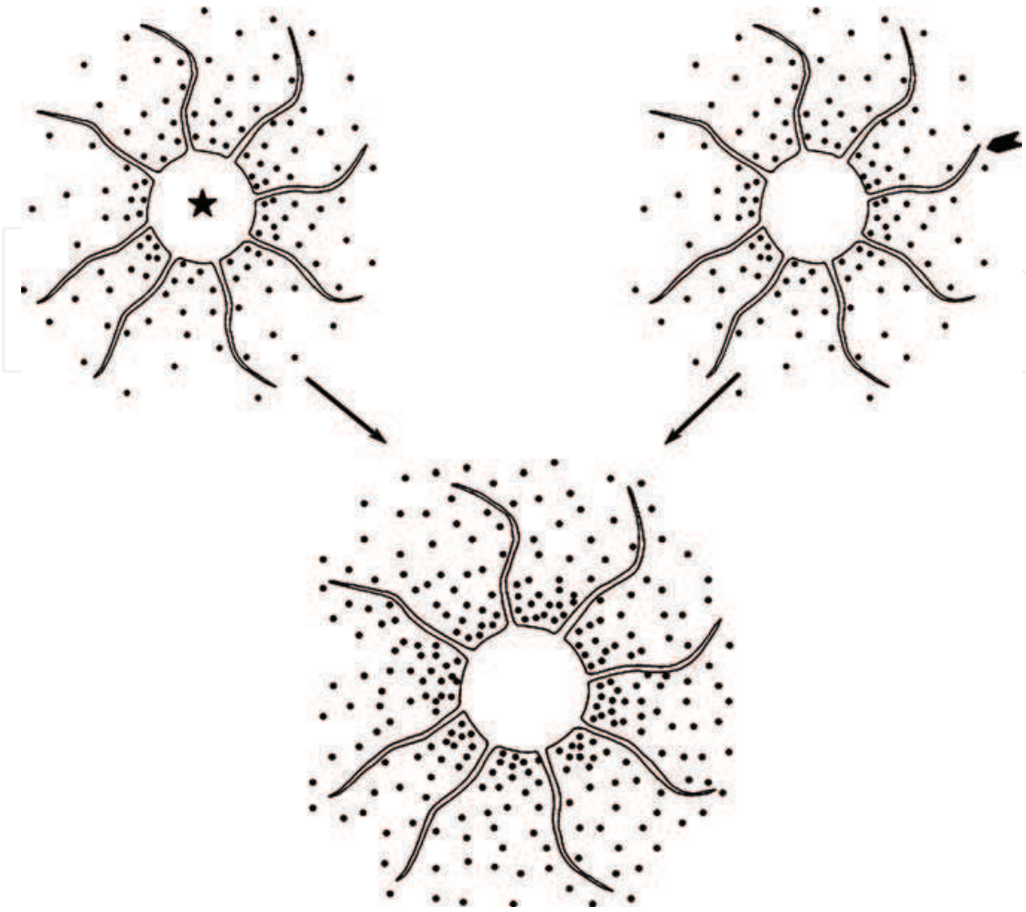

Fig. 7. The "Octopus" hypothesis. A hyperactive state of the GP (head of octopus, left upper panel) may trigger local release of a gradient of excessive amounts of neurotransmitters and subsequently initiate AF (lower panel). When the axons (tentacles) are excited (right upper panel), the GP can be retrogradely activated and elicit a similar response. Star: a hyperactive of the GP. Arrowhead: axons are excited. Black dots: local release of neurotransmitters. (Zhou J, et al. J Cardiovasc Electrophysiol. 2007; 18(1): 83-90)

Recently, Po's research group [44] has continued their study, trying to make a breakthrough in traditional GP mapping methods. They blocked GP by means of superparamagnetic nanoparticles (MNPs) carrying neurotoxicity drug N-isopropylacrylamide monomer (NIPA-M), and achieved satisfactory results. The agent was found to be potentially targeting to IRGP. It does open a new train of thought, though research in this field has just begun.

Apart from the localization of GP, many researches with respect to mechanism in the curative differences in GP ablation therapy have been conducted. Studies by Zhao et al. [45] revealed that local increases occurred to the concentration levels of TNF-α and iterleukin-6 after GP ablation might be considered as a factor that increases the vulnerability to AF. This also provides us with a new train of thought. There are many issued, such as whether there is any other high expression of inflammatory factors besides TNF-α and iterleukin-6 in local GP ablation and whether these inflammatory factors can be blocked by certain means and therefore improving the effectiveness of GP ablation, remain to be addressed.

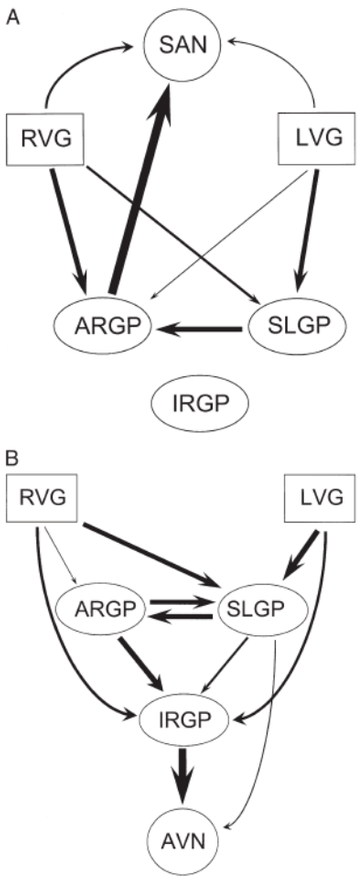

Fig. 8. Interactions among vagosympathetic trunks, ARGP, IRGP, and SLGP on SAN and AVN function (A) Modulation of sinus rate by vagosympathetic stimulation. (B) Modulation of ventricular rate during atrial fibrillation by vagosympathetic stimulation. Thick lines and thin lines indicate strong and weak regulatory effects, respectively. ARGP = anterior right GP, IRGP = inferior right GP, SLGP = superior left GP, AVN = atrioventricular node; LVG = left vagosympathetic trunk; RVG = right vagosympathetic trunk; SAN = sinoatrial node. (Yinglong Hou, et al. J Am Coll Cardiol, 2007; 50(1): 61–8).

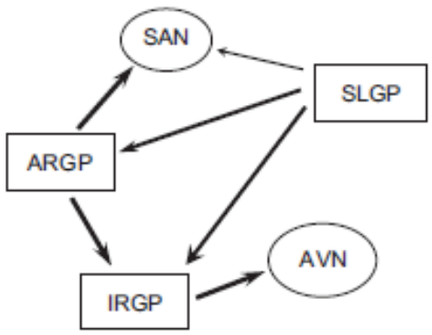

Fig. 9. Summary of the interactions among ARGP, IRGP, and SLGP on SAN and AVN function. Thick lines and thin lines indicate strong and weak regulatory effects, respectively. The abbreviations, see Figure 8 (Yinglong Hou, et al. Heart Rhythm, 2007; 4(1): 56–63).

5. Regeneration of nerve tissues after GP ablation

Regeneration of nerve tissues after ablation may be associated with long-term curative effect of GP ablation. However, scientists' opinions diverge on the existence of regeneration.

In 2006, studies by Oh et al. [46] revealed that responsiveness to VS by both sinoatrial and atrioventricular nodes as well as the inductivity of AF had declined significantly immediately after radiofrequency ablation of dog fat pads, yet inductivity returned to pre-ablation levels 4 weeks after ablation, suggesting that fat pad ablation did not have the long-term preventive effect on AF.

In 2007, Verma et al. [47] studied 20 cases of patients who accepted PV isolation once more for recurrent AF. The mean interval between two ablations was 4 months. No vagal response was observed after this ablation, suggesting that there was no more regeneration of GP tissues.

In 2009, Po et al. [23] reported 83 cases of patients who received GP ablation and single PV ablation. The incidence of post-procedure non-AF or non-AT were 80% during 1-year follow-up and 86% during 22-month follow-up, suggesting that the benefits of GP ablation based on PV ablation increased with time, especially 12 months after ablation, with no regeneration of ablated GP.

In 2010, Sakamoto et al. [48] divided 18 dogs into three groups, to perform GP ablation, GP ablation + PV isolation, and GP ablation + left atrial posterior wall isolation, respectively. The results showed that GP ablation could significantly reduce vagal innervation, while vagal response restored 4 weeks after the procedure, suggesting that there might be early regeneration of atrial nerve tissues.

In 2010, Zhao et al. [49] put forward the concept of post-GP ablation autonomic nerve reconstruction. They randomized, in their studies, 13 dogs into GP ablation group and sham-operated group, performing ARGP ablation and IRGP ablation, respectively. The results showed that it was extremely easy to induce AF 8 weeks after GP ablation and that growth-associated protein 43-positive, tyrosine hydroxylase-positive, and choline acetyltransferase-positive nerve densities in the right atrium in GP ablation group were significantly lower than those of the sham-operated group. The researchers held that the reconstruction of the atrial autonomic nerves might be the mechanism of the AF reoccurrence after GP ablation. The study also revealed that unilateral GP ablation might lead to imbalanced nerve reconstruction and therefore the reoccurrence of AF.

The information above revealed that it is still an unsolved issue whether nerves regenerate after GP ablation. There have been no sufficient evidence so far to demonstrate that ANS regeneration is directly associated with the recurrence of AF. However, if the nerves regeneration really exists, are there some certain substances, such as the inflammatory factors mentioned above, contributing to nerve regeneration after GP ablation? And can these substances be suppressed in some ways to further improve the efficacy of GP ablation? These issues leave much space for research.

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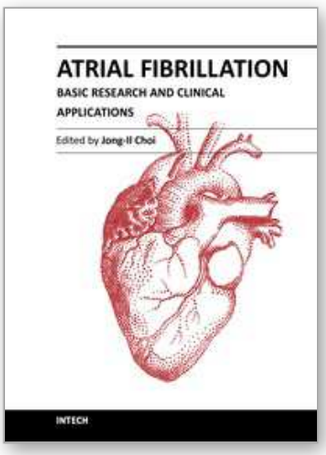

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Atrial Fibrillation-Basic Research and Clinical Applications is designed to provide a comprehensive review and to introduce outstanding and novel researches. This book contains 22 polished chapters and consists of five sections: 1. Basic mechanisms of initiation and maintenance of atrial fibrillation and its pathophysiology, 2. Mapping of atrial fibrillation and novel methods of signal detection. 3. Clinical prognostic predictors of atrial fibrillation and remodeling, 4. Systemic reviews of catheter-based/surgical treatment and novel targets for treatment of atrial fibrillation and 5. Atrial fibrillation in specific conditions and its complications. Each chapter updates the knowledge of atrial fibrillation, providing state-of-the art for not only scientists and clinicians who are interested in electrophysiology, but also general cardiologists.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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