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IS THE ATRIAL NEURAL PLEXIS A THERAPEUTIC TARGET IN ATRIAL FIBRILLATION?

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Abstract

Circumferential pulmonary vein isolation is the mainstay of atrial fibrillation (AF) ablation, but alternative approaches and techniques have been developed to improve the outcomes. One of these additional ablation targets are ganglionated plexi of the intrinsic cardiac autonomic system that contain a variety of sympathetic and parasympathetic neurons that communicate with the extrinsic cardiac autonomic nervous system. The ganglionated plexi of the heart do not serve as a simple relay station but could modulate the autonomic interaction between the extrinsic and intrinsic cardiac autonomic system. Intrinsic cardiac autonomic nerve activity is an invariable trigger of paroxysmal atrial tachyarrhythmia, including atrial fibrillation. Although multiple studies have shown that ganglionated plexi play an important role in initiating atrial fibrillation, there is no consensus on a standardized protocol for selecting target sites and determining how ganglionated plexi ablation can best be accomplished. Recent clinical trials have demonstrated the feasibility and efficacy of ganglionated plexi ablation in addition to pulmonary vein isolation, but novel technologies and strategies are necessary to improve the current ablation techniques in managing patients with atrial fibrillation. This review focuses on the relationship between atrial ganglionated plexi and atrial fibrillation and the potential benefits and limitations of ganglionated plexi ablation in the management of atrial fibrillation.

Introduction

Atrial fibrillation (AF) ablation has evolved from targeting the triggering source within the pulmonary vein, to segmental ostial ablation, to circumferential pulmonary vein isolation (PVI), and finally to minimally invasive surgical ablation. While circumferential PVI has been the mainstay of AF ablation, ganglionated plexi (GP) ablation has emerged as an alternative technique to improve outcomes in patients with AF. Ganglionated plexi contain a variety of sympathetic and parasympathetic neurons and communicate with the extrinsic cardiac autonomic nerve system (ANS).[1] In 1973, Lazzara et al.[2] reported the parasympathetic response while stimulating nerve bodies, which later were identified as GP located adjacent to the sinus node and AV junction. Since then, numerous reports and studies have been published regarding the anatomy, function, and interconnection within GP.[3,4] In this review, we focus on the relationship of atrial GP and AF and the potential benefits and limitation of GP ablation in the management of AF.

Intrinsic Cardiac Autonomic Nervous System – Ganglionated Plexi

The heart is highly innervated by a complex intrinsic cardiac nervous system that contains more than 14,000 neurons.[3] More than 200 of these form the cardiac ganglia, which in turn gather to form the GP located within the epicardial fat pad.[3] Although the intrinsic cardiac autonomic nerves are extensively distributed, most GP are located near the large vessels and posterior surface of the atria.[3] In human atria, four major GP near the antrum of the pulmonary veins (PV) are categorized as follows: (1) superior left GP (located on the roof of the left atrium, near the medial side of the left superior pulmonary vein), (2) anterior right GP (located anterior to the right superior PV), and (3, 4) inferior left and inferior right GP (located at the inferior aspect of the posterior left atrial wall, just below the left and right inferior PV).[5] The density of nerves around the PV junction is greatest in the left atrium, within 5 mm of the LA-PV junction, and higher in epicardium than endocardium.[6] Therefore, ablation lesions created by circumferential PVI have significant overlap with areas of dense GP and may unintentionally result in autonomic denervation.

Studies have shown that GP in the heart can modulate the autonomic interaction between the extrinsic and intrinsic cardiac ANS.[4] Parasympathetic preganglionic neurons originating from the nucleus ambiguus of medulla were shown to project to postganglionic neurons distributed in GP.[7] One study found cardiac sympathetic nerves originating from the cervical and thoracic spinal cord projecting to postganglionic neurons located in paravertebral ganglia—including the superior cervical ganglion, middle cervical ganglion, cervicothoracic (stellate) ganglion, and the thoracic ganglia—and finally connecting to adrenergic neurons within the GP.[8] Armour found that multiple inputs from the extrinsic cardiac ANS gave sufficient information to the "little brain on the heart" to modulate cardiac indices.[1] However, GP could self-activate without the influence of extrinsic cardiac ANS.

Our group[9] measured the extrinsic cardiac nerve activity (ECNA) and intrinsic cardiac autonomic nerve activity (ICNA) in an ambulatory canine model and found that most ICNA had a temporal relationship with ECNA, but a small portion was activated without a temporal relationship with ECNA. These findings suggest that ICNA may be independently arrhythmogenic. Furthermore, ICNA always preceded the onset of

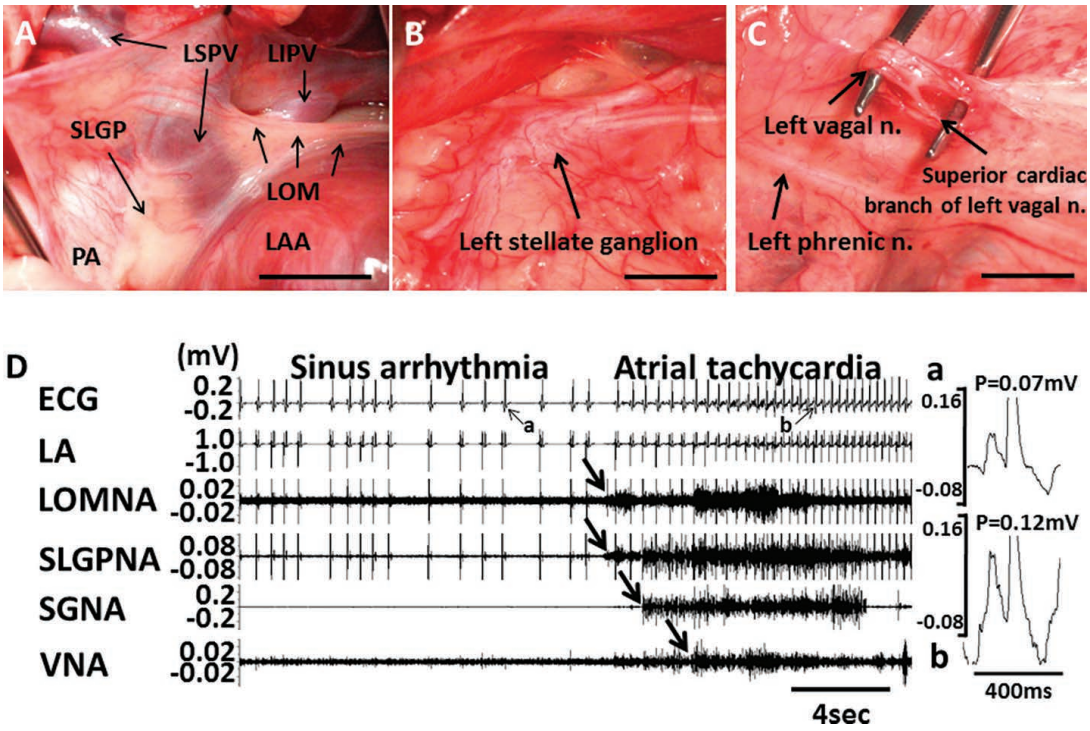

Figure 1. Intrinsic and extrinsic cardiac autonomic nerve recording sites. (A) Ligament of Marshall (LOM) and superior left ganglionated plexi (SLGP). The LOM originates from the coronary sinus and connects to the left superior pulmonary vein (LSPV). SLGP is located between the left atrial appendage (LAA) and the LSPV. (B) Left stellate ganglion. (C) Superior cardiac branch of the left vagal nerve. (D) An example in which intrinsic cardiac nerve activity (LOMNA and SLGPNA) occurred before extrinsic cardiac nerve activity (SGNA and VNA) and a PAT episode. The magnified pseudo-ECG shows the different P-wave morphologies during sinus rhythm (Da) and during PAT (Db). LA: left atrium; LOMNA: ligament of Marshall nerve activity; SLGPNA: superior left ganglionated plexi nerve activity; SGNA, stellate ganglion nerve activity; VNA, vagal nerve activity. Reprinted from Choi et al.[9] with permission.

paroxysmal atrial tachyarrhythmia (AT), suggesting that ICNA is an invariable trigger of paroxysmal atrial tachyarrhythmia in this model (Figure 1). When the intrinsic cardiac ANS disconnected from the extrinsic cardiac ANS, it could facilitate AF/AT burden. These findings suggest a proarrhythmic effect of the intrinsic cardiac ANS.[10]

High frequency stimulation at a GP area was shown to induce heart rate slowing or AV conduction delay but also could shorten action potential duration, induce early afterdepolarization, and trigger activity from isolated canine PV myocardium.[2,11] In humans, high frequency stimulation on presumed GP from an endocardial approach could also induce PV ectopy and AF.[12]

Ablation of Ganglionated Plexi

In an experimental animal model, GP stimulation at the base of the right superior PV could provide a substrate to convert PV firing to AF, and injection of lidocaine, a neuronal blocker, suppressed the AF inducibility.[13] Ablation of GP at the base of the PVs suppressed the vagal responses and rendered AF noninducible.[14] Although multiple studies have shown that GP play an important role in initiating AF, there is no consensus on a standardized protocol for ablation. Specifically, it is unclear how to select target sites and determine if successful GP ablation has been accomplished.

Recent clinical trials have demonstrated the feasibility and efficacy of GP ablation (Table 1). Two small studies (n = 54) have compared the efficacy of GP ablation alone versus PVI, and one meta-analysis using these two studies has been published.[15-17] Comparing GP ablation alone with PVI, GP ablation alone was not superior in maintaining sinus rhythm. The group receiving GP ablation alone had higher early recurrence and lower AF-free survival compared to the PVI group. GP ablation alone could not achieve complete isolation of the PV, whereas additional GP ablation resulted in a more durable PVI. However, GP ablation in addition to PVI was superior to PVI alone in maintaining AF-free survival, although there was no significant difference in early recurrence.[5,18,19] A recent study comparing PVI alone, GP ablation alone, and PVI with additional GP ablation showed that conventional PVI with additional GP ablation had the best clinical outcome after ablation in patients with paroxysmal AF.[20] In this study, GP ablation was performed using an anatomical approach, and the endpoint of GP ablation was confirmed by the elimination of atrial activity at the targeted GP areas and of any vagal response elicited by RF application. Additional GP ablation to PVI showed better AF- and AT-free survival compared to either PVI or GP ablation alone in patients with paroxysmal AF.

The GP ablation was performed either with selective high-frequency stimulation (HFS) to identify the location of the GP or by anatomical location without electrical stimulation.[15,16,21] With the first approach, HFS was used to elicit a parasympathetic response (hypotension or atrioventricular block), whereas the latter approach using anatomical location ablated four major atrial GP areas without first performing HFS. Selective GP ablation could be verified if there was vagal response by HFS. However, GP include both sympathetic and parasympathetic neurons, so vagal response could be attenuated and variable.[22] Also, the energy of HFS from the endocardial side might not be enough to evoke epicardial GP stimulation. The location of the four major GP may not have been significantly different among patients, but their borders could not be clearly defined. In a recent study comparing the efficacy of GP ablation techniques, selective GP ablation was inferior to anatomic GP ablation in managing patients with paroxysmal AF.[21] Most of the studies for GP ablation have enrolled only patients with paroxysmal AF. GP ablation alone in patients with longstanding persistent AF had 38% AF-free survival, and subsequent repeat PVI increased that rate to 60%.[23]

Minimally invasive surgical ablation show a potential advantages with a smaller incision and reduced complications related to cardiopulmonary bypass than Cox-Maze surgery, making it a reasonable option in patients with lone AF. Also, this technique could be more effective in ablating epicardially located GP than a percutaneous approach. However, there is no

Study	Year	Experiment vs. Control group	Ablation sites	Study design	AF type	Number of study patients	Outcomes
Scherlag BJ[31]	2005	GP+PVI vs. PVI	Endocardial	Unknown	Paroxysmal or persistent	60	AF free survival: 91% in GP+PVI group vs. 71% in PVI group (no statistic comparison)
Scanavacca M[32]	2006	High frequency stimulation->GP ablation or PVI	Epicardial and/or endocardial	Observational study	Paroxysmal	10	Recurrence in 5/7 patients who underwent denervation
Katritsis DG[15]	2008	GP vs. CPVI	Endocardial	Case-controlled study	Paroxysmal	38	AF recurrence: 74% (GP ablation group) vs. 37% (PV isolation group) (log-rank test P=0.017)
Po SS[5]	2009	GP+PVI	Endocardial	Observational study	Paroxysmal and persistent	80	Free of symptomatic AF or atrial tachycardia after a single ablation procedure : 80% at 12 months and 86% at a mean follow-up of 22 months
Pokushalov E[21]	2009	Selective GP vs. anatomic GP ablation	Endocardial	RCT	Paroxysmal	80	Free of symptomatic paroxysmal AF: 42.5% in selective GP ablation vs. 77.5% in anatomic GP ablation (P=0.02)
Pokushalov E[23]	2010	Anatomic GP ablation	Endocardial	Observational study	Persistent	89	AF free survival: 38.2%
Pokushalov E[33]	2010	Anatomic GP ablation	Endocardial	Observational study	Paroxysmal	56	AF free survival at 12 months: 71%
Mikhaylov E[16]	2011	GP vs. CPVI	Endocardial	Case-controlled study	Paroxysmal	70	Freedom from any atrial tachyarrhythmia without antiarrhythmics: 34.3% (GP ablation group) vs. 65.7% (PVI group) (log-rank test P=0.008)
Katritsis DG[18]	2011	GP+PVI vs. PVI	Endocardial	RCT	Paroxysmal	67	Arrhythmia (AF or AT) free survival: 85.3% in PVI+GP group vs. 60.6% in PVI group ((log rank test, P=0.019)
Katritsis DG[20]	2013	GP+PVI vs. GP vs. PVI	Endocardial	RCT	Paroxysmal	242	AF free survival: 74% (GP+PVI) vs. 48% (GP) vs. 56% (PVI) (log-rank test P=0.004)

Table 1. Summary of clinical studies regarding ganglionated plexi ablation.

randomized study defining the benefit of GP ablation in minimally invasive surgical ablation, whereas several studies using PV isolation with GP ablation reported 1-year AF-free survival rates of 65% to 81%.[24,25] The implication of GP ablation on outcomes needs further evaluation. In preclinical studies, novel drug delivery systems can be magnetically targeted to the GP to reduce the risk of catheter ablation and achieve selective denervation.[26]

Limitations and Questions for Ganglionated Plexi Ablation

Endocardial GP ablation has technical limits that can result in partial denervation. Partial GP ablation not only is less effective than complete GP ablation but may also increase the risk of AF by increasing the heterogeneity of refractoriness within the atria.[27] Also, GP ablation without PVI might be proarrhythmic, with a decreased atrial effective refractory period and increased atrial sympathetic and parasympathetic innervation.[28] Selective GP ablation could create a channel for macroreentrant atrial tachycardia. Autonomic reinnervation after GP ablation could be one of the reasons of treatment failure. This has been shown in an animal study in which reinnervation occurred 4 weeks after GP ablation.[29] In another study, the denervation effects of fat pad ablation disappeared after 4 weeks.[30]

Conclusion

Ganglionated plexi play an important role in triggering atrial fibrillation. Many studies have shown that ablating GP in addition to PVI is more effective than either one alone in AF ablation. While GP ablation might be useful in improving outcomes in patients undergoing PVI, many questions must be answered, such as how to achieve complete GP ablation and avoid partial denervation by localizing the true boundary of GP, and how to prevent reinnervation and end-organ hypersensitivity. It is clear that novel technologies and strategies are needed to improve current GP ablation techniques in managing patients with AF.

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Keywords: atrial fibrillation, ganglionated plexi, cardiac autonomic nervous system, catheter ablation

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