Cardiac Autonomic Denervation for Ablation of Atrial Fibrillation

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The influence of the autonomic nervous system (ANS) on triggering and perpetuation of atrial fibrillation (AF) is well established. Ganglionated plexi (GP) ablation achieves autonomic denervation by affecting both the parasympathetic and sympathetic components of the ANS. GP ablation can be accomplished endocardially or epicardially, i.e. during the maze procedure or thoracoscopic approaches. Recent evidence indicates that anatomic GP ablation at relevant atrial sites appears to be safe and improves the results of pulmonary vein isolation in patients with paroxysmal and persistent AF.

Keywords

Atrial fibrillation, ablation, ganglionated plexi, autonomic nervous system

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Currently, pulmonary vein isolation (PVI) is the most widely used ablation approach to treat atrial fibrillation (AF). However, even in patients with paroxysmal AF (PAF), there is a five-year success rate <30 % after a single procedure¹ and <40 % remain off anti-arrhythmic drugs,² so PVI alone is clearly not sufficient to maintain sinus rhythm. The influence of the autonomic nervous system (ANS) on triggering and perpetuation of AF is well established. Variations of the autonomic tone have been associated with paroxysms of AF and both sympathetic and parasympathetic activation may be proarrhythmic by shortening of atrial refractoriness.^{3–5} Vagal reflexes from clusters of autonomic ganglia, so-called ganglionated plexi (GP), at sites around the circumference of the left atrial–pulmonary vein (LA–PV) junction may induce and perpetuate AF through increased spatial heterogeneity of refractoriness.^{3,6} The anatomic sites of GP are located 1–2 cm outside the pulmonary vein (PV) ostia at the left superolateral area (superior left GP; SLGP), the right superoanterior area (anterior right GP; ARGP), the left inferoposterior area (inferior left GP; ILGP), and the right inferoposterior area (inferior right GP; IRGP) (see *Figure 1*).^{7–9} In clinical practice, inadvertent parasympathetic denervation has been proposed as a potential mechanism of circumferential or antral PV ablation for the treatment of AF.^{10–12} Thus, GP are a reasonable target of both surgical and catheter ablation techniques for the eradication of AF.

Early Experience with Autonomic Denervation

Initial studies on partial vagal denervation via epicardial fat pad ablation indicated that such a dedicated approach may prevent AF,^{13,14} although results have not been consistent.^{15–17} Most probably the selective nature and partial denervation of this kind of procedure, a recognised potentially proarrhythmic approach,¹⁸ is responsible for the inconsistency of results. Ablation of areas with prominent sympathetic innervation has also prevented sympathetic AF. The ligament of Marshall is a left atrial epicardial neuromuscular bundle, rich in sympathetic innervation, which has been associated with the

genesis of atrial tachyarrhythmias (AT) and AF.^{19–21} Epicardial ablation of the ligament of Marshall in the canine can terminate spontaneous atrial activity and prevent AF,¹⁹ whereas in the human epicardial (through the coronary sinus)²⁰ or endocardial^{21,22} ablation at the insertion site of the Marshall bundle may terminate AF. We now know that selective parasympathetic or sympathetic denervation may not be feasible. Both sympathetic and parasympathetic elements reside in all four major left atrial GP,^{7–9} and ablation lesions may unavoidably affect both components of the ANS. The area around the ligament of Marshall that had been previously thought to represent an area of predominantly sympathetic innervation has been shown to contain parasympathetic fibres as well.²³ Thus, pure parasympathetic or sympathetic denervation is difficult to achieve. Ablation of atrial areas containing autonomic innervation, such as GP, unavoidably results in autonomic denervation.

Techniques of GP Ablation

In the electrophysiology laboratory and the operating theatre, identification of major GP has been mainly accomplished through high-frequency stimulation (HFS) and induction of vagal responses in the atria.^{24,25} HFS is delivered at 1,200 bpm (20 Hz) with a pulse width of 10 ms at 12–24 V.²⁶ A predominant efferent vagal response is defined as induction of AV block (>2 sec) and hypotension or prolongation of the R–R interval by >50 % during AF, following a five-second application of high-frequency stimulation. During these studies the anatomic locations of these plexi in the human have been well characterised. However, although the HFS setting is variable from institution to institution, the method usually entails the discomfort of general anaesthesia, since conscious patients may not tolerate more than 15 V. Furthermore, it has been recently shown that that anatomic ablation, i.e. targeting the areas known to host GP in the left atrium (see *Figure 1*) without previous identification of GP (see *Figure 1*), yields superior clinical results to HFS identification and ablation of GP in patients with paroxysmal AF.²⁷

Figure 1: Anatomic Position of the Major Ganglionated Plexi Targeted for Catheter Ablation

Presumed ganglionated plexi (GP) clusters are ablated 1–2 cm outside the pulmonary vein–left atrial junctions at 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). Another GP (crux GP) the inferoposterior area between the ILGP and IRGP is not indicated. Reproduced with kind permission from Katritsis et al.³⁴

Clinical Experience

Endocardial Catheter Ablation

Isolated GP ablation has been employed for both paroxysmal and persistent AF with variable success. In paroxysmal AF, arrhythmia-free survival within the first year after the procedure ranged between 26 and 77 %.^{27–31} GP ablation in combination with PVI has yielded better results than PVI alone, with reported success rates up to 80 %.^{31–36} Katritsis et al. have investigated the potential efficacy of GP ablation in consecutive randomised trials in both paroxysmal and persistent AF. In the first study, which compared the efficacy of PVI with PVI plus GP ablation in 67 patients with PAF, at the end of follow-up 20 (60.6 %) patients in the PVI group and 29 (85.3 %) patients in the GP+PVI group remained arrhythmia free (log rank test, $P = 0.019$).³⁴ In the second trial on 242 patients with PAF, 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 ($p=0.0036$ by log-rank test). PVI+GP ablation strategy as compared with PVI alone yielded a hazard ratio (HR) of 0.53 (95 % confidence interval [CI] 0.31–0.91; $p=0.022$) for the recurrence of AF or AT. Post-ablation atrial flutter was not different between groups: 5.1 % in PVI, 4.9 % in GP, and 6.1 % in PVI plus GP.³⁶ Success rates of <40 % have been reported for persistent AF after a single procedure.³⁷ We have also compared linear lesion (LL) and GP ablation, in addition to PVI, in 264 patients with persistent AF. At 12 months after a single procedure, 47 % of the patients treated with PVI plus LL were in sinus rhythm compared

with 54 % of the patients treated with PVI plus GP ($P = 0.29$). At three years, 34 % of the patients with PVI plus LL and 49 % of the patients with PVI plus GP maintained sinus rhythm ($P = 0.035$). Atrial flutter was more frequent in the PVI plus LL group than in PVI+GP group (18 % vs 6 %; $P = 0.002$). After a second procedure in 78 patients of the PVI plus LL group and 55 patients of the PVI plus GP group, the long-term overall success rate was 52 % and 68 %, respectively ($P = 0.006$). Thus, PVI plus GP ablation confers superior clinical results with less ablation-related left atrial flutter and reduced AF recurrence compared with PVI plus LL in persistent AF.³⁸ Due to the epicardial location of GP, relatively higher energy settings than those used for endocardial ablation may be required.

Intraoperative Ablation

The epicardial location of GP argues in favour of a surgical approach, and addition of GP ablation to the conventional maze procedure has produced improved outcomes with success rates 83–93 % over the following year.^{25,39–42} Although this approach is interesting, it is associated with the risks of open heart surgery, and the maze nowadays is only considered in patients undergoing valve surgery.

Thoracoscopic Approaches

Thoracoscopic approaches combine PVI with selective GP ablation, with or without ligament of Marshall ablation or left atrial appendage amputation.^{43–50} The reported success rates over one year follow-up

range from 65–86 % , usually in mixed populations of paroxysmal and persistent AF, and the procedure does not appear to have any associated mortality, with pleural effusion, pneumothorax, haemothorax, and phrenic nerve injury the reported complications so far. McClelland et al.⁴³ reported freedom from AF during one year of follow-up in 75 % of patients overall, and 87.5 % of patients with paroxysmal or persistent AF. Han et al.⁴⁴ reported 65 % freedom from AT at 12 months in a patient cohort of paroxysmal (73 %) and persistent (27 %) AF, while recurrences after surgery were usually responsive to catheter ablation and/or antiarrhythmic drugs. Edgerton et al.⁴⁶ reported long-term freedom from AT of 86.3 % at six months and 80.8 % at 12 months in patients with paroxysmal AF. Yilmaz et al.⁴⁵ reported a 77 % freedom from AF during a mean follow-up of 11.6 months in a patient cohort with paroxysmal (63 %), persistent (27 %), and permanent (10 %) AF. Edgerton et al.⁴⁶ reported long-term freedom from AT of 86.3 % at six months and 80.8 % at 12 months in patients with paroxysmal AF. Beyer et al.⁵⁰ reported freedom from AF in 87 % of patients (paroxysmal 93 %, persistent 96 %, and permanent 71 %) at 13.6 ± 8.2 months.

There has also been evidence for beneficial effects of adding GP ablation to LA ablation lines and PVI, specifically in patients with persistent AF.⁴⁷ GP ablation has shown promise in catheter trials and is

becoming popular among groups adopting surgical ablation. However, no randomised data exist to clearly define its potential benefit.

Complications of GP ablation

Ablation-induced atrial or ventricular proarrhythmia has been reported with both endocardial and epicardial (thoracoscopic) approaches,^{33,49,51} and GP modification was initially considered to carry a higher risk of iatrogenic left ATs than PVI. In our experience, anatomic or HFS-mediated GP ablation is complicated by atrial macroreentry in <10 % of patients treated, and this incidence is lower than that of circumferential or, especially, linear ablation.^{34,36}

The Future

GP ablation appears to be a safe and efficacious method to improve PVI in patients with AF, and has been used in the electrophysiology laboratory, and during the maze procedure and thoracoscopic approaches. However experience is limited and long-term follow-up (i.e. more than five years) is still not available. This is particularly important since restoration of autonomic activity may occur as early as four weeks following ablation.⁵² Additional clinical experience is necessary to accurately assess the clinical usefulness of this promising technique, and the potential of autonomic modification for the treatment of arrhythmias. ■

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