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Ganglionated plexi ablation in the right atrium for the treatment of cardioinhibitory syncope

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Neurocardiogenic syncope, also called vasovagal syncope, represents one of the clinical manifestations of neurally mediated syncopal syndrome. Generally, the prognosis of the cardioinhibitory form of neurocardiogenic syncope is good, but quality of life is seriously compromised in patients who experience severe forms. Drug therapy has not achieved good clinical results and very heterogeneous data come from studies regarding permanent cardiac pacing. In this scenario, the ganglionated plexi ablation has been proposed as an effective and safe method in patients with cardioinhibitory neurocardiogenic syncope, especially in young patients in order to avoid or prolong, as much as possible, the timing of definitive cardiac pacing. Certainly, making this procedure less extensive and limiting the ablation in the right atrium (avoiding the potential complications of a left atrial approach) and at level of anatomical regions of the most important ganglionated plexy, considered 'gateway' of the sino-atrial and atrio-ventricular node function (through the recognition of specific endocardial potentials), could be very advantageous in this clinical scenario. Finally, randomized, multicentre, clinical trials on a large population are needed to better understand which is the best ablation treatment (right-only or bi-atrial) and provide evidence for syncope guidelines.

Introduction

Neurocardiogenic syncope (NCS, also called vasovagal syncope) represents one of the clinical manifestations of neurally mediated syncopal syndrome.[1,2] The latter includes the carotid sinus syncope, situational forms (micturition, gastrointestinal stimulation, cough, sneeze, post-exercise, etc.) and non-classical forms (without prodromes, apparent triggers, and typical presentation). Neurocardiogenic syncope, the most common cause of syncope in both children and adults with an average incidence of 22% in the general population, is distinguished by three main pathophysiological mechanisms: (i) 'vasodepression', which refers to conditions in which insufficient sympathetic vasoconstriction causes hypotension; (ii) 'cardioinhibition', which is expressed by bradycardia, systole or atrioventricular (AV) block secondary to predominant parasympathetic hypertone, and (iii) mixed cardioinhibitory/vasodepressor mechanism. Generally, the prognosis of the cardioinhibitory NCS (also defined CNS) is good if syncope pictures are not associated with structural heart disease, but quality of life is seriously compromised in patients who experience severe forms of CNS.[3,4] Drug therapy has not achieved good clinical results and very heterogeneous data come from studies regarding permanent cardiac pacing, actually to be considered in aged more than 40 years, with spontaneous documented asystolic pauses (due to sinus arrest) more than 3 and 6 s in symptomatic and asymptomatic patients, AV block, or the combination of the two.[1] In this scenario, ganglionated plexi

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(GPs) ablation, although there are no data on large populations, is proposed as a very promising method precisely in young subjects, in order to avoid or prolong as much as possible the implantation of a cardiac pacemaker. Indeed, permanent cardiac pacing may be associated with an increased risk of infections due to the need for frequent device replacement if implanted at a young age.

Anatomical and pathophysiological rationale of ganglionated plexi ablation

The pathophysiological rationale of GPs ablation in CNS is based on anatomical studies that showed a heterogeneous distribution of the main GPs in the right and left atrium (RA and LA, respectively).[5-7] Armour *et al.*[6] showed (*Figure 1*) that human intrinsic atrial cardiac ganglia and their associated nerves, situated in epicardial fat, form five GPs: (i) *the superior right atrial GP* (placed on the posterior superior surface of the RA adjacent to the junction of the superior vena cava (SVC) and RA); (ii) *the superior left atrial GP* [SLGP, ganglia identified on the posterior surface of the LA between the pulmonary veins (PVs)]; (iii) *the posterior right atrial GP* (on the posterior surface of the RA adjacent to the interatrial groove); (iv) *the posteromedial left atrial GP* (on the posterior medial surface of the LA), (v) *postero-lateral left atrial GP* (on the posterior lateral surface of the left atrial (LAtl) base on the atrial side of the AV groove). Some years later, Hou *et al.*[7] evaluated the effect of vagal stimulation on sinoatrial (SA) and AV node function before and after sequential ablation of the *superior left GP* (near the junction of the left superior PV and left PV), *anterior right GP* (ARGP, near the SA node), and *inferior right GP* (IRGP, at the junction of the inferior vena cava and atria). This study confirmed that major epicardial GPs could be considered as 'integration centres' integrating the autonomic innervation between extrinsic and intrinsic cardiac autonomic nervous system. In fact, the IRGP seems to be the integration centre for the extrinsic autonomic nervous system to innervate the AV node, while the ARGP seems to serve as the integration centre for both the right and the left vago-sympathetic trunks to modulate SA node function (*Figure 2*).

Several investigations have shown very heterogeneous results concerning biatrial or LAtl GPs ablation in CNS patients.[8-13] Pachon *et al.*[8] was the first to introduce the concept of 'cardioneuroablation', i.e. a methodology of vagal denervation based on the identification (through Fast Fourier Transformation) of LA and RA endocardial fragmented signals, markers of the neuro-myocardial interface (fibrillar myocardium), where parasympathetic fibres, in the context of the atrial wall compact myocardium, are placed. This pattern was found mainly in the sinus and AV node areas and in the endocardial regions near the three main atrial GPs [Ganglion A, located between the SVC and the aortic root just above the right superior pulmonary vein; Ganglion B, located between the right superior pulmonary vein and the RA; and finally, Ganglion C, located between the inferior vena cava (IVC) and the RA and LA].

For several years, our group has been advocating a vagal denervation or 'cardioneuroablation' procedure focused in the RA and with a good success in the medium- and long-term follow-up.[14,15] Two fundamental assumptions guided us in supporting the hypothesis of a right atrial (RAtl) GPs ablation procedure: (i) the good success of this procedure that we had observed in patients with vagal atrial fibrillation,[16] and (ii) the limitation of a LAtl ablative approach due to potential complications (trans-septal puncture, anticoagulation, etc.), especially in the absence of post-procedural efficacy data regarding a large patient population.

Right atrial ganglionated plexi ablation: the rational and clinical results

Some anatomical and pathophysiological observations from experimental studies in animal and human models may justify a GPs ablation limited in the RA.

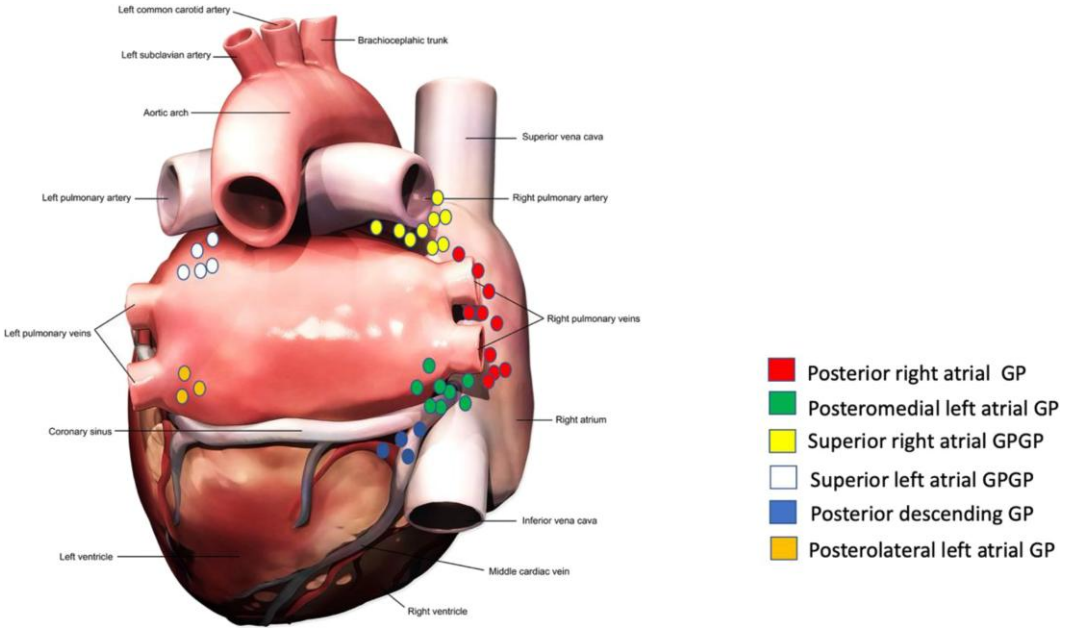

Figure 1 Topographic localization of the main ganglionated plexi based on anatomical studies performed by Armour *et al.*[6] GP, ganglionated plexi.

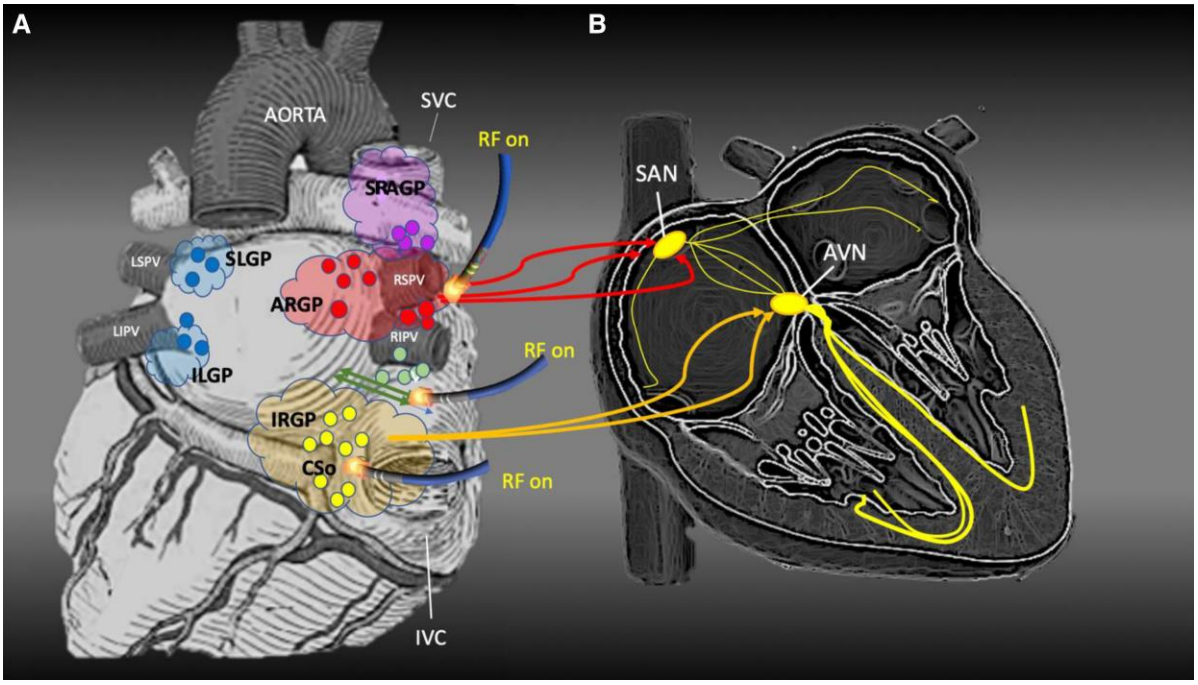

Figure 2 Anatomical location (*A*) of the major ganglionated plexi that are considered gateways for the atrioventricular node and sinoatrial node function (*B*). The inferior right ganglionated plexi and the anterior right ganglionated plexi have functional distribution territories extending from the left to the right atrium. Therefore, the right atrial ablation at level of the supero-posterior wall results in a 'cardioneuromodulation' of the third fat pad (violet territory, superior right atrial ganglionated plexi) and the anterior right ganglionated plexi (red territory) with consequent sinoatrial node modulation (*B*). Moreover, radiofrequency application a little lower than the superior site affects the neural interconnections between the right and left atrium (green arrows). Finally, right atrium radiofrequency application at level of the infero-posterior wall favours a 'cardioneuromodulation' of the posterior right atrium ganglionated plexi and of the inferior right ganglionated plexi (modulation of atrioventricular node, *B*) if ablation is performed down, in the inferior posteroseptal site, at level of area placed between the coronary sinus ostium and the atrioventricular groove (yellow territory). Dots, ganglionated plexi localization points; SVC, superior vena cava; SRAGP, superior right atrial ganglionated plexi; SLGP, superior left ganglionated plexi, ARGP, anterior right ganglionated plexi; IRGP, inferior right ganglionated plexi; CSo, coronary sinus ostium; IVC, inferior vena cava; AVN, atrioventricular node; SAN, sinoatrial node; RSPV and RIPV, right superior and right inferior pulmonary veins, respectively; LSPV and LIPV, left superior and left inferior pulmonary vein, respectively.

First, as previously stated, at least 50% of the atrial GPs are placed at level of RAtl posterior wall adjacent to the interatrial groove (the so-called RAtl GPs).[6] Among these, anatomical targets of this ablative procedure are considered the following: (i) 'third fat pad' (or the superior RAtl GP) positioned on the posterior surface of the RA, adjacent to the junction of the SVC and the aorta. The 'third fat pad' represents the nexus point for the vagal input to the GP prior to innervating the atria, (ii) the ARGP that seems to play an important role in a gateway for autonomic innervation of SA node, (iii) the IRGP considered the gateway for the autonomic innervation of AV node. This main GP is very well represented in the LA but also in the RA. In fact, radiofrequency (RF) application at level of the anatomical space among the coronary sinus ostium (CSo), the AV groove, and the infero-postero-septal RAtl wall results in vagal denervation that, significantly, affects the function of the AV node, and (iv) the multiple neural biatrial interconnections that may favour a modulation by the RAtl GPs towards the LAtl GPs.[7]

Moreover, an anatomical approach characterized by an extensive RF application at the anatomical sites of the most important RAtl GPs has been shown to be more advantageous than a selective ablative approach in areas where a vagal reflex was evoked during high-frequency stimulation.[16] The rationale for an 'extensive' anatomical ablation approach is precisely based on the non-perfect knowledge of the exact anatomic borders of GP clusters. In fact, in our study[14,15] patients with CNS recurrences after ablation, showed a less extensive RF lesions especially at the level of IRGP, ARGP, and 'third fat pad 'sites (*Figure 2*). However, if an extended anatomical approach can be considered effective in patients with vagal AF, the same approach could be excessive in patients with CNS. In fact, as mentioned earlier,[8,15] it has been scientifically observed that 'cardioneuroablation' based on the RF delivery on the sites of high-amplitude fragmented potentials, expression of the neuronal fibres presence in the context of the atrial compact myocardium, is both effective and safe. Therefore, it should not be underestimated that limiting the 'cardioneuroablation' or 'cardio-neuro-modulation' to two strategic areas placed at the level of the posterior superior and inferior wall of the RA could be considered clinically advantageous.

Finally, one of the ever-present questions is whether post-GPs ablation recurrences could be related to the re-innervation phenomenon. In our experience, ablation of the ganglionic plexuses in the RA resulted in a significant reduction in parasympathetic and sympathetic tone (assessed by heart rate variability), especially in the acute setting. In symptomatic patients at follow-up, we observed a complete recovery of sympathetic tone within one year, while parasympathetic tone remained reduced at least until 24 months post-ablation. In fact, endocardial

ablation is able to affect, by eliminating them, the parasympathetic postganglionic neural bodies that are located in the atrial wall, which instead contains only the terminations of sympathetic post-ganglionic fibres (*Figure 2*). The result is that vagal reinnervation is a much rarer event than sympathetic reinnervation, especially if the procedure is correctly performed.

Conclusions

Ganglionated plexi ablation in the RA has been shown to be proposed as an effective and safe method in severe forms of CNS, especially in young patients in order to avoid or prolong, as much as possible, the timing of definitive cardiac pacing. Certainly, making this procedure less extensive and limiting the ablation in the anatomical regions of the most important GP considered 'gateway' of the SA and AV node function (through the recognition of specific endocardial potentials) could be very advantageous in this clinical scenario (*Figure 2*). A biatrial approach should not be underestimated in patients with significant syncopal recurrences after initial RAtl approach. Indeed, a recent systematic review and meta-analysis regarding 465 patients with CNS undergone cardioneuroablation, has shown good procedural success showing an 81.5 and 92.7% of freedom from syncope after GP ablation in the RA and biatrial, respectively.[17]

Finally, randomized, multicentre, well-designed clinical trials on a large population are needed to better understand which is the best ablation treatment (right-only or bi-atrial) and provide evidence for syncope guidelines.

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Data availability

No new data were generated or analysed in support of this research.

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