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Atrial fibrillation and sympatho-vagal imbalance: from the choice of the antiarrhythmic treatment to patients with syncope and ganglionated plexi ablation

Marco Rebecchi[1]*, Ermenegildo De Ruvo[1], Marianna Sgueglia, Carlo Lavalle[2], Stefano Canestrelli[1], Alessandro Politano[1], Ilaria Jacomelli[1], Paolo Golia[1], Cinzia Crescenzi[1], Lucia De Luca[1], Marco Panuccio[1], Alessandro Fagagnini[1], and Leonardo Calò

[1]Department of Cardiology, Policlinico Casilino, Via Casilina 1049, Rome 00100, Italy; and [2]Department of Cardiovascular, Respiratory, Nephrology, Anaesthesiology and Geriatric Sciences, Sapienza University of Rome, Viale del Policlinico, 155, Rome 00161, Italy

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For several years, the autonomic nervous system has played a central role in the pathophysiological mechanism of atrial fibrillation (AF), so much so that it has been considered one of the cornerstones of Coumel's triangle. The clinical and therapeutic management of AF secondary to sympatho-vagal imbalance represents one of the most important examples of how precision medicine should be applied. Increasing knowledge of this kind of arrhythmias has made it possible to select specific antiarrhythmic drugs and to diversify their use according to vagal or adrenergic AF forms. Ablative strategies, such as cardioneuroablation and non-direct cardiac neuromodulation methods (such as renal denervation and peripheral vagal stimulation), have gradually emerged. In the possibly near future, there will be a development of new acquisitions regarding new pharmacological therapeutic strategies and gene therapy. Finally, finding an AF in patients experiencing syncopal episodes opens a whole chapter regarding interesting, but also complex, diagnostic and therapeutic strategies, ranging from neurally mediated forms to convulsive seizure that could also increase the risk of sudden death.

Introduction

It has been several years since Coumel *et al.*[1,2] introduced the concept of Coumel's triangle, based on the observation that the genesis of a tachyarrhythmia requires three basic ingredients: triggering factors, arrhythmogenic substrate, and modulating factors, and among the latter, the most important is the autonomic nervous system (ANS). Indeed, the role of ANS in the complex pathophysiological mechanism of atrial fibrillation (AF) has already appeared indisputable in several investigations based on the use of 24 h Holter ECG and electrophysiological study.[2]

Interestingly, we have long been accustomed to classifying and differentiating vagal and adrenergic AF based on the greater or lesser involvement of the same sympathetic or vagal tone at the time of clinical presentation. However, such a rigid mode of classification clashes with a not infrequent clinical reality, characterized by vagally and adrenergically mediated AF forms that may coexist in the same patients.[2,3]

This premise highlights (i) how, in real life, there are clinical contexts that are not always so easy to classify and (ii) the need for increasingly individualized pharmacological and electrophysiological treatments aimed at correcting the various pathophysiological, biomolecular, and genetic mechanisms underlying ANS tone imbalance.

*Corresponding author. Tel: +390623188406, Fax: +390623188410, Email: marcorebecchi3@icloud.com, marcorebecchi3@virgilio.it

Clinical scenarios of atrial fibrillation secondary to autonomic nervous system imbalance

The standard clinical scenario

In many patients with a clinical history of paroxysmal AF secondary to ANS involvement, we usually identify two different clinical scenarios: adrenergic AF and vagal AF.[2] Adrenergic AF occurs most frequently throughout the day, with diurnal episodes, and is triggered by psychophysical stress and physical activity. The same occasionally may occur in subjects with hyperthyroidism and pheochromocytoma. Vagal AF, most frequently, affects male and young (age 30-50 years) patients without structural heart disease. It occurs more in bradycardic patients with onset during nocturnal or post-prandial rest, and, finally, large meals, especially in the evening, and alcohol abuse are considered triggering events. Furthermore, it is much more common to find structural heart disease in a patient with adrenergic AF than in vagal-mediated forms of AF. However, this clinical differentiation, although overly rigid and schematic, finds a rational explanation in the anatomical, pathophysiological (*Figure 1*), and biomolecular mechanisms underlying ANS role in the initiation and maintenance of AF.[4] In fact, the focal mechanism of AF is due to

(1) sympathetic contribution in promoting the initiation activity through automaticity (due to decreased inward rectifying K+ current and increased funny current during diastolic depolarization), early atrial depolarizations that generate (affecting phase 2 of the atrial action potential) and delayed atrial depolarizations that induce, as a result of calcium overload and abnormal calcium release by the sarcoplasmic reticulum,
(2) adrenergic and vagal contribution (red lines and arrows) through activation of G- protein regulated inward-rectifier K+ (GIRK) channels, and finally,
(3) parasympathetic contribution in the reentrant mechanisms.

In addition, several investigations showed the reason why an adrenergic AF usually terminates spontaneously while a vagal AF tends to be maintained. In one of these, Ashihara T. *et al.*,[5] using an ion channel model, observed whether a reentry spiral wave induced by vagal and adrenergic stimulation tended to be maintained or interrupted. In fact, after sympathetic stimulation, the waves tended to organize and terminate immediately, whereas after parasympathetic stimulation, in the presence of spatial dispersion of refractoriness, the spiral wave reentries showed a tendency to maintain. As previously mentioned,
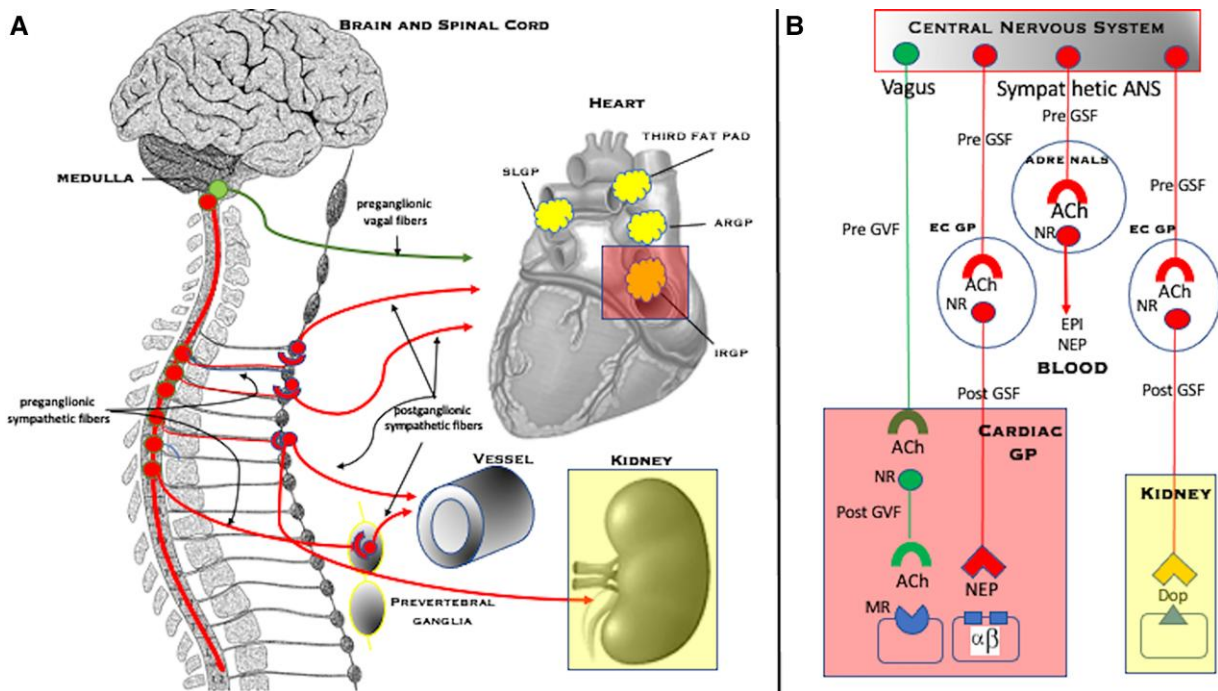
Figure 1 Autonomic nervous system: anatomy and main mechanisms of cardiovascular regulation. Vagal or parasympathetic nerves that originate from medulla vagal nuclei (*pre-ganglionic vagal or parasympathetic fibres*, *A* and *B*) establish synapses with *post-ganglionic vagal fibres* (*B*) placed within small ganglia located near the target tissue (e.g. cardiac ganglionated plexi). Release of acetylcholine (ACh) and subsequent binding to nicotinic receptors (NR) results in activation of post-ganglionic vagal fibres (*B*) that release ACh capable of interacting with tissue muscarinic receptors (MR). The pathway of sympathetic fibres is different from that of vagal fibres. In fact, sympathetic nerves, after originating within the medulla, establish synapses with *pre-ganglionic cells* located within the spinal cord (*A* and *B*). The *pre-ganglionic sympathetic fibres* enter into synaptic relationship with the cell body of the *post-ganglionic sympathetic fibres* located in the paravertebral ganglia (*A* and *B*) using ACh as a neurotransmitter that binds to NR. At this point, the *sympathetic post-ganglionic fibres* directly reach the target tissues releasing several neurotransmitters and among them are norepinephrine (NEP) at the cardiac and vascular levels and dopamine (Dop) at the renal level. In addition, the *sympathetic pre-ganglionic fibres* reach the adrenals and directly release norepinephrine (NEP) and epinephrine (EPI), which are released into the circulating blood. **SLGP**: superior left ganglionated plexi. **IRGP**: inferior right ganglionated plexi. **ARGP**: anterior right ganglionated plexi. **ACh**: acetylcholine. **NR**: nicotinic receptor. **MR**: muscarinic receptor. **Pre- and Post-GVF**: pre- and post-ganglionic vagal fibres. **Pre- and Post-GSF**: pre- and post-ganglionic sympathetic fibres. **EPI**: epinephrine. **NEP**: norepinephrine. **ECGP**: extracardiac ganglionated plexi.

it often happens that AF forms secondary to vagal and both sympathetic imbalances could coexist in the same patients. In fact, de Vos et al.,[3] analysing patients belonging to the Euro Heart Survey, noted that those with paroxysmal AF associated with autonomic triggers were distributed as follows: 6% vagal, 15% adrenergic, and 12% mixed form (vagal and adrenergic).

It should not be underestimated that several dynamic triggering factors[4] can be recognized in most clinical manifestations of AF associated with sympatho-vagal imbalance. In fact, very often, correction and treatment of such dynamic factors significantly reduces AF recurrences. Among them, obesity and obstructive sleep apnoea (OSA) are considered particularly important in the clinical scenario. It is known that visceral fat (abdominal, epicardial, etc.) represents a true inflammatory tissue capable of producing proinflammatory molecules (cytokines, growth factors) that can promote the initiation and maintenance of AF.[6] In addition, in patients with OSA, nocturnal hypoxic events may promote AF initiation, through a predominantly vagal biomolecular mechanism, but also activation of the left stellate ganglion that may interfere with the shortening of the effective refractory period. At the same time, increased hypoxic damage, inflammation, oxidative stress, and tendency to left atrial myopathy are observed in patients with OSA and obesity.[4] The intensity and type of sports and physical activity, because of its influence on autonomic tone, may also be associated with the risk of AF. Indeed, in sports subjects with predominant vagal activity at rest and during low-intensity physical work, episodes of vagal AF are observed. On the other hand, a different scenario, characterized by adrenergic-mediated AF, occurs in athletes subjected to high sympathetic activity during acute, strenuous endurance exercise.[7] Therefore, the vagus-mediated mechanical role in swallowing (gastroesophageal reflux) and rapid ingestion of cold food and drinks should not be forgotten. In addition, several studies have demonstrated the association between food and AF through a mechanism related to sympatho-vagal imbalance. Indeed, it appears that a predominant diet based on low-carbohydrate intake may be associated with an increased risk of AF recurrence due to increased oxidative stress, which could also promote central nervous system imbalance.[4] Finally, moderate-to-high alcohol intake is also known to be associated with AF. The most important underlying mechanism is due to a variable spectrum of clinical situations, including predominant vagal or hyperadrenergic activity and mixed forms, as sometimes occurs in patients with structural heart disease.

Syncope, autonomic nervous system, and atrial fibrillation: what we know and what we should know

Syncope is defined as transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery.[8] The pathophysiological classification of syncope recognizes three main groups: reflex, cardiovascular, and syncope secondary to orthostatic hypotension.

Syncope and AF are clinical scenarios that can, not infrequently, coexist in the same patients. The pathophysiological mechanism is highly variable and sometimes even uncertain, depending on the initial clinical presentation and patient characteristics. In fact, in the real world, it happens that patients (often of advanced age) with permanent AF may experience syncope with physical trauma. In this specific case, an atrioventricular (AV) node dysfunction, requiring a cardiac pacemaker implantation, would be very likely. Sometimes the syncopal episode in AF patients is related to sinus rhythm restoration preceded by a significant electrical pause indicative of sino-atrial (SA) node dysfunction, requiring therapeutic measures ranging from optimization of drug treatment to definitive cardiac electrostimulation.[9]

Moreover, if an AF is immediately diagnosed after syncope with the following characteristics: (i) syncope preceded by various prodromes such as sensation of flushing, diaphoresis, nausea, abdominal pain or discomfort, lightheadedness, and pallor and (ii) syncope occurred in certain situations, such as after night-time micturition and after a large meal, definitely we are dealing with a vagal AF associated with neurally mediated syncope.[8]

However, in this complex scenario of AF/syncope, there are structural heart disease situations (aortic stenosis, coronary artery disease, hypertrophic cardiomyopathy, cardiac tumours, pericardial disease/tamponade, congenital coronary artery abnormalities, prosthetic valvular dysfunction) and other clinical conditions (such as pulmonary embolism, acute aortic dissection, and pulmonary hypertension) that may predispose to the syncopal event due to haemodynamic changes typical of the underlying pathology and independently of the AF presence.[8]

Finally, the role of ANS imbalance in epileptic seizures has been previously described, including sinus tachycardia, which occurs in 80–100% of patients, and sinus bradycardia, which occurs in about 5% of patients. In addition, several investigations have demonstrated the infrequent, but possible, presence of an AF and atrial flutter. Indeed, increased vagal tone during the seizure, which results in sinus bradycardia, is generally considered the mechanism responsible for AF initiation. In addition, some arrhythmias observed in patients with ictal seizures have a different prognosis, depending on whether they appear during the ictal or post-ictal phase. Van der Lende et al,[10] evaluating the presence of an arrhythmic burden during and after seizure, observed that ictal asystole, ictal bradycardia, and ictal atrioventricular AV block occurred predominantly during focal seizures and were self-limiting. In contrast, post-ictal arrhythmias, including asystole, AV block, and less frequently AF and ventricular fibrillation, usually occurred after a seizure and were often associated with sudden unexpected death in epilepsy (SUDEP). Finally, *Figure 2* shows a schematic mechanism on which the association between arrhythmias and ictal/post-ictal seizure is based.

The cornerstones of drug therapy: the present and the future

Currently, among antiarrhythmic drugs (AD), flecainide (class IC) is the most widely used in AF in structurally healthy hearts and in patients with vagal AF.[11] Already several years ago, in experimental animal models, the efficacy of flecainide in vagal forms of AF was attributed to its most important pharmacological mechanisms: slowing atrial conduction and increasing the effective atrial refractory period with a tachycardia-dependent mechanism.[12]
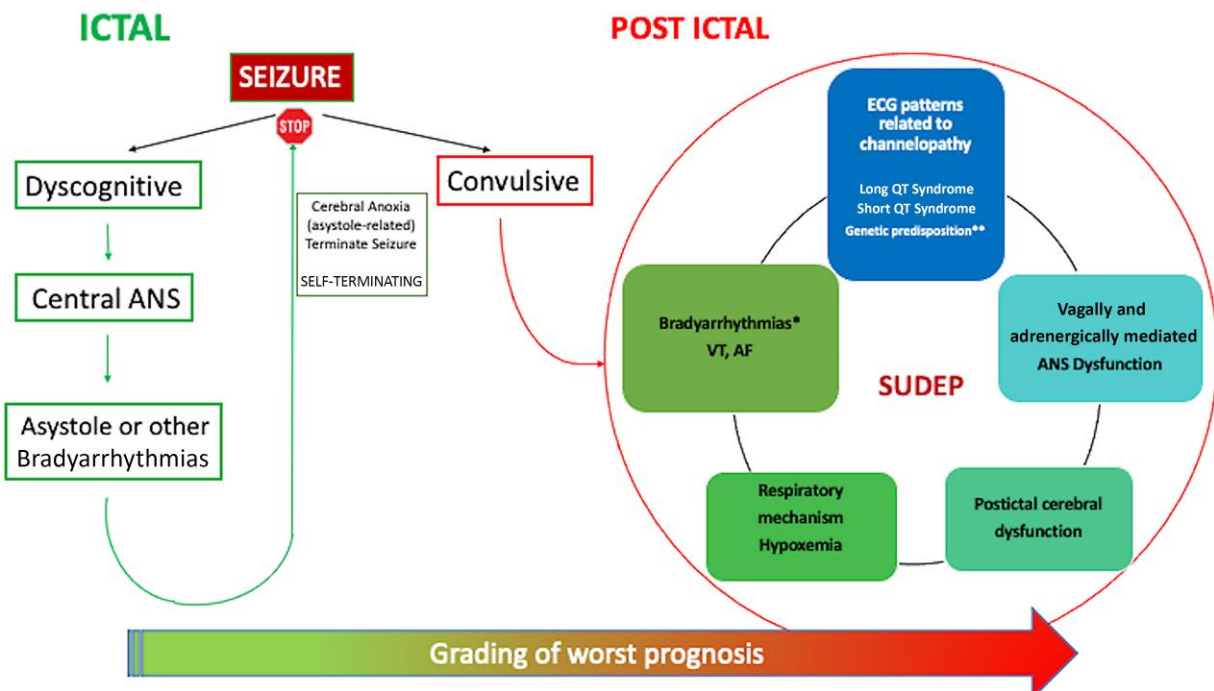
Figure 2 Pathophysiological mechanism of sudden unexpected death in epilepsy. Epileptic seizures can occur in either focal discognitive or convulsive form. Focal ictal discognitive seizures (temporal lobe seizures) promote activation of the central ANS, resulting in asystole (or less frequently other bradyarrhythmias). The good prognosis of these epilepsy forms is related to the fact that asystole is self-limiting and asystole-dependent temporary cerebral anoxia results in cessation of the same seizure. Conversely, in post-stroke forms, the bradyarrhythmic events and apnoea are prolonged over time causing convulsive scenarios, further apnoea, and asystole prolongation, until high risk of sudden unexpected death in epilepsy (SUDEP). The SUDEP also recognizes other concomitant situations, such as triggering of prolonged atrial fibrillation forms and of ventricular fibrillation, persistent sympatho-vagal imbalance, and, finally, several genetic predispositions to ion channel alterations affecting both the brain and heart. **ANS**: autonomic nervous system. *Asystole, sinus bradycardia, and atrio-ventricular block. **AF**: atrial fibrillation. **VF**: ventricular fibrillation, **AF**: atrial fibrillation.**Voltage-gated sodium channels (SCN5A), voltage-gated potassium channels (KCNH2), hyperpolarization-activated cation channels, and ryanodine receptors. **SUDEP**: sudden unexpected death in epilepsy.

Among class IC AD, optimal (100% effectiveness) results were obtained after using of pilsicainide in dog patients, showing a significant increase in intra-atrial conduction time and a decrease in wavelength index.[12] Propafenone, another class IC AD, is not considered for use in patients with vagal AF because it has intrinsic beta-blocking activity that could possibly potentiate the effects of vagal tone. In any case, such characteristics of all beta-blocker drugs (class II AD) and those with intrinsic beta-blocker activity could play a very important role in therapeutic strategies for patients with adrenergic AF. Finally, good results have been obtained with disopyramide (class IA AD) because of its significant sodium channel-blocking properties and vagolytic effects.[12]

What does the future hold for us? Certainly, we cannot underestimate scientific experimentation concerning new AD.[4] In the specific case of influence on autonomic function, the target of this innovative drug therapy is represented by small-conductance calcium-dependent potassium channels (SK channel), molecular targets involved in intracellular calcium kinetics such us Ca^{2+}/calmodulin-dependent protein kinase, and the acetylcholine-gated potassium currents (Ik, ACh).

Cardiac ganglionated plexi ablation and non-direct cardiac neuromodulation

An excellent anatomical knowledge (*Figure 3A*) is *a sine qua non* condition to better understand the pathophysiologic mechanisms and reasons for choosing, in addition to a classic pulmonary vein (PV) isolation, an ablative strategy targeting to perform a 'ganglionated plexus (GP) ablation' at the level of the anatomic regions sites of the most important GPs. Armour *et al.*[13] showed 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 right atrium (RA) adjacent to the junction of the superior vena cava (SVC) and RA], (ii) *the superior left atrial GP* [ganglia identified on the posterior surface of the left atrium (LA) between the 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), and (v) *the postero-lateral left atrial GP* (on the posterior lateral surface of the left atrial base on the atrial side of the AV groove). Individual neurons and small ganglia were also found scattered through atrial and ventricular tissues (*Figure 3A*). Subsequently, Aksu and Pauza *et al.*[14] described five atrial epicardial ganglionated subplexi (sGPs) under neural control of one intrinsic epicardial GP: (i) *the ventral (anterior) right atrial sGP* that occupies the ventral superior right atrial region, the ventral side of the root of the SVC, and the ventral inferior right atrial region; (ii) *the ventral (anterior) left atrial sGP* that occupies the ventral superior left atrial region; (iii) *the left dorsal (posterior) sGP* that occupies the region of the dorsal left coronary sulcus and the middle left atrial region
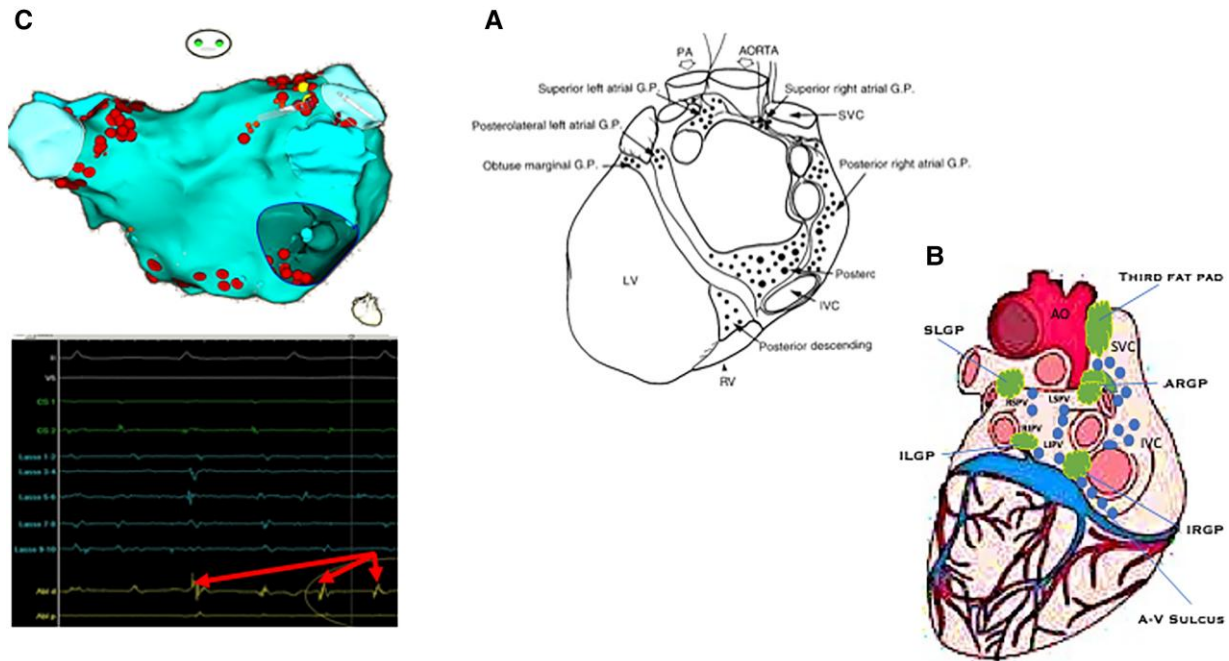
Figure 3 (*A*) Classic anatomical representation of the most important ganglionated plexi (GPs) in the right and the left atria (picture from Armour *et al*. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec.1997; 247:289-98). (*B*) Ablation sites in anatomical areas of the right and the left atria considered strategic locations of the most important GPs. **IRGP**: inferior right GP. **ARGP**: anterior right GP. **ILGP**: inferior left GP. **SLGP**: superior left GP. **IVC**: inferior vena cava. **SVC**: superior vena cava. **LSPV**: left superior pulmonary vein. **RSPV**: right superior pulmonary vein. **LIPV**: left inferior pulmonary vein. **RIPV**: right inferior pulmonary vein. (*C*) Anatomical 3D map of the left atrium in a patient who underwent pulmonary vein isolation and cardioneuroablation. In the areas where the vagal reflex was evoked during radiofrequency delivery, high-amplitude frequency electrograms (HAFE) were observed. These endocardial signals would appear to be an expression of the ANS fibres' presence in the context of a compact myocardium.

regions; (iv) *the middle dorsal (posterior) sGP* that occupies the dorsal superior left atrial region and around the crux cordis; and (v) *the dorsal (posterior) right atrial sGP* that occupies the dorsal superior right atrial region, the dorsal side of the root of the SVC, and the region over the interatrial septum. It is also interesting to note that the post-ganglionic nerves from the ventral right atrial sGP could innervate the sino-atrial node, while those originating from the left, middle, right atrial dorsal, and part (interatrial) of ventral right atrial sGP could extend to the AV node. In this regard, Hou *et al*.[15] evaluated the effect of vagal stimulation on SA and AV node function before and after sequential ablation of the *superior left ganglionated plexi* (*SLGP*, near the junction of the left superior PV and left PV), *anterior right ganglionated plexi* (*ARGP*, near the SA node), and *inferior right ganglionated plexi* (*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 ANS. In fact, the IRGP seems to be the integration centre for the extrinsic ANS to innervate the AV node. In fact, in this study, the ablation of IRGP, especially if preceded by inferior left ganglionated plexi (ILGP)-ARGP sequence ablation, showed a significant influence on AV node function, slowing the response induced by vagosympathetic stimulation. Moreover, the ARGP seems to serve as the integration centre for both the right and the left vagosympathetic trunks to modulate SA node function (*Figure 3A, B*).

The earliest examples of the left atrial autonomic denervation ablation came from epicardial ablation procedures in animal models. In humans, one of the first examples of GP ablation (although not directly intended) comes from Pappone *et al*.[16] who observed an improved outcome of VP isolation when associated with a significant vagal reaction, evoked during radiofrequency applications. For years, several strategies have been introduced basing on the different types of approach: selective or anatomic. Over the years, the selective GP ablation approach (based on RF application in the atrial site where a vagal reaction was elicited during high-frequency stimulation) has proven to be less effective than the anatomical approach, based, instead, on delivering RF to anatomical atrial areas, sites of more important cardiac GP.[17]

In addition to a left atrial or biatrial ablative approach, some considerations convinced our group to limit GP ablation in the RA as first approach, moreover achieving good post-procedural success, in terms of reducing vagal AF recurrences.[18] Indeed, anatomical studies, as previously mentioned, show a numerous distribution of ganglia in the RA. The 'third fat pad', placed at the level of the junction between the RA and the SVC and between the SVC and the aorta, is considered the point of entry of vagal input to the GP before innervating both the RA and LA. Another evidence of the effectiveness of the right atrial ablation is that the right atrial GPs could remotely modulate the left atrial GPs' function through anatomical interconnections.[4] In addition, Caló *et al*.[18] noted that the anatomical approach effectiveness could be due to the extent of ablation lesions, because the exact anatomic borders of GP clusters are not well known for certainty.

Furthermore, one of the most important anatomical and pathophysiological targets of the right atrial GP ablation is the IRGP site. This GP, considered an integrating centre for extrinsic ANS and a gateway for AV node function, appears to be crucial to achieve a significant autonomic denervation. Moreover, the identification (through particular electroanatomic mapping systems) and the ablation of particular high-amplitude electrograms (HAFEs, *Figure 3C*), expression of the presence of ANS fibres in the context of compact myocardium, has proven to be particularly effective. We should not forget that Pachon *et al.*,[19] from several years, first introduced the concept of 'cardioneuroablation' for the treatment of neurocardiogenic syncope, functional AV block, and SA node dysfunction. The real target of this procedure was represented by an endocardial ablation focused to eliminate post-ganglionic parasympathetic body neurons (*Figure 1*) over and inside the atrial wall, unable to regenerate.

Finally, a mention regarding the 'non-direct cardiac neuromodulation' methods should be made. The renal sympathetic denervation, usually proposed in patients with not controlled hypertension, could play an important role for the treatment of AF related to sympathetic imbalance, especially when associated with pulmonary vein isolation.[4] Other two examples of non-direct cardiac neuromodulation are represented by stellate ganglion ablation and vagal nerve stimulation (e.g. ear tragus stimulation) that showed good results in terms of AF suppression in animal models.

Final considerations

The ANS imbalance represents one of the most frequent causes of AF. The related complex pathophysiologic mechanism explains the great variability of clinical scenarios that, sometimes, can go beyond the classic and simplistic definition of vagal and adrenergic AF. Over the years, pharmacological treatments (e.g. flecainide and beta-blocker therapy), focused on the different vagally or adrenergically mediated AF forms, have emerged and not always with full success. Cardioneuroablation with heterogeneously effective strategies (left atrial only, biatrial, or right atrial) and other methods of 'non-direct cardiac neuromodulation' have also been included in this scenario.

Finally, the increased personalization of medicine has highlighted the need to simultaneously correct the previously mentioned dynamic factors (diet, OSA, obesity, gastroesophageal reflux, alcohol abuse, and so on) and, at the same time, to also focus on new treatments both pharmacological and gene therapy–based.[4-20,21]

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