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## REVIEW

# Atrial fibrillation: Neurogenic or myogenic?

*Fibrillation auriculaire : neurogénique ou myogénique ?*

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## KEYWORDS

Atrial fibrillation;  
Atrial neuropathy;  
Early diagnosis;  
Prediction;  
Therapy

**Summary** A 55-year-old hypertensive patient presents atrial fibrillation after vasovagal syncope. Non-invasive cardiac workup is normal. Without antiarrhythmic therapy, the patient has no recurrence for the next 3 years, then presents with a stroke. Echocardiography eventually reveals left atrial dilation. This sequence of events illustrates the well-known links between age, arterial hypertension, atrial fibrillation, atrial neuromyopathy and stroke. A frequently neglected common denominator in this equation is impaired sympathovagal balance. Contrary to what is often stated, autonomic imbalance is not a simple modulation factor of atrial fibrillation; both the trigger and the substrate of atrial fibrillation can be influenced by abnormal cardiac innervation. Here, we review the neurogenic theory of atrial fibrillation, based on literature and original data. We also provide evidence that this concept may help to improve atrial fibrillation prediction, early diagnosis and therapy.

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**Abbreviations:** AF, atrial fibrillation; ANS, autonomic nervous system; GP, ganglionated plexus;  $I_f$ , hyperpolarization-activated inward current;  $I_{K1}$ , inwardly rectifying Kir current;  $I_{K-ACh}$ , acetylcholine-activated potassium current;  $I_{Ks}$ , slowly activating delayed rectifier potassium current.

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## MOTS CLÉS

Fibrillation atriale ;  
Neuropathie atriale ;  
Diagnostic précoce ;  
Prédiction ;  
Thérapie

**Résumé** Un patient hypertendu de 55 ans présente une fibrillation atriale après une syncope vasovagale. Le bilan cardiologique non-invasif est normal. Après un intervalle libre de 3 ans, il est hospitalisé pour un accident vasculaire cérébral. L'échocardiographie révèle cette fois-ci une dilatation atriale gauche. Cette séquence d'événements illustre les liens bien connus entre l'âge, l'hypertension artérielle, la fibrillation atriale, la neuromyopathie atriale et l'accident vasculaire cérébral. Un dénominateur commun souvent négligé dans cette équation est le déséquilibre sympathovagal. Contrairement à ce qui est souvent dit, le déséquilibre nerveux n'est pas seulement un facteur modulateur de la fibrillation atriale; le déclenchement et le substrat de cette arythmie peuvent tous deux être influencés par une innervation cardiaque anormale. Nous proposons une revue de la théorie neurogénique de l'arythmie fibrillatoire basée sur la littérature et les données de notre équipe lyonnaise. Nous énumérons aussi les éléments qui, grâce à ce concept, peuvent aider à améliorer la prédiction, le diagnostic précoce et la thérapie de la fibrillation atriale.

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## Background

Estimates of atrial fibrillation (AF) relying on census projections predict an annual growth in AF prevalence of 4.3% between 2010 and 2030, considerably higher than the projected 2.9% annual increase in the elderly population [1]. We are regularly reminded of the need to deepen our understanding of how this arrhythmia arises and perpetuates. Looking more closely at the heart muscle and/or the cardiac nerves, outside of the pure electrophysiology box, may offer new pathophysiological insights.

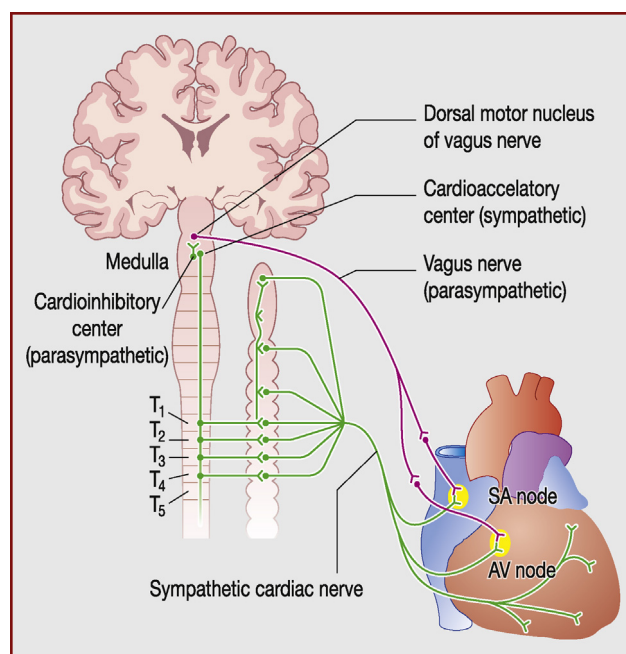
The heart is one of the most richly innervated organs, and the autonomic nervous system (ANS) finely regulates the electrophysiology of myocardial cells. Contrary to common belief, autonomic imbalance is not just a modulation factor of AF; both the trigger and the substrate of the arrhythmia can be influenced by autonomic imbalance. Studying the extent to which atrial neuropathy is a main cause of AF may help to identify AF predictors, early AF diagnosis markers and new antiarrhythmic therapies.

This review gathers evidence that highlights the neural perspective of AF pathophysiology; it provides anatomical, pathophysiological and therapeutic evidence supporting a major role for abnormal ANS in the complex AF disease process.

## Atrial neuroanatomy: a sophisticated spiderweb

The activity of the heart is influenced by both extrinsic and intrinsic cardiac nervous systems. Both regulators integrate information collected by cardiac afferent neurons located in intrathoracic (intrinsic and extrinsic), nodose and dorsal root ganglia from mechano- and chemosensory probes that constantly track variations in the heart and intrathoracic vessels.

The extrinsic cardiac nervous system mediates connections between the heart and the cervical, stellate and thoracic ganglia (sympathetic connections) on the one hand,



**Figure 1.** Anatomy of the sympathetic and parasympathetic innervation of the heart. AV: atrioventricular; SA: sinoatrial.

and the medulla oblongata (parasympathetic connections) on the other hand (Fig. 1). Preganglionic parasympathetic neurons are located primarily in the ventral lateral region of the nucleus ambiguus and, to a lesser extent, in the dorsal motor nucleus and the intermediate zone between these two medullary nuclei. These neurons project axons to postganglionic neurons located in the cardiac ganglionated plexi (GPs). Preganglionic sympathetic neurons located in the spinal cord project axons via the T<sub>1</sub>–T<sub>4</sub> thoracic nerves to neurons located mainly in the cervical and stellate ganglia. Although sympathetic and parasympathetic activation essentially have opposite effects on cardiac indices, neurons in the intrathoracic ganglia are in constant communication

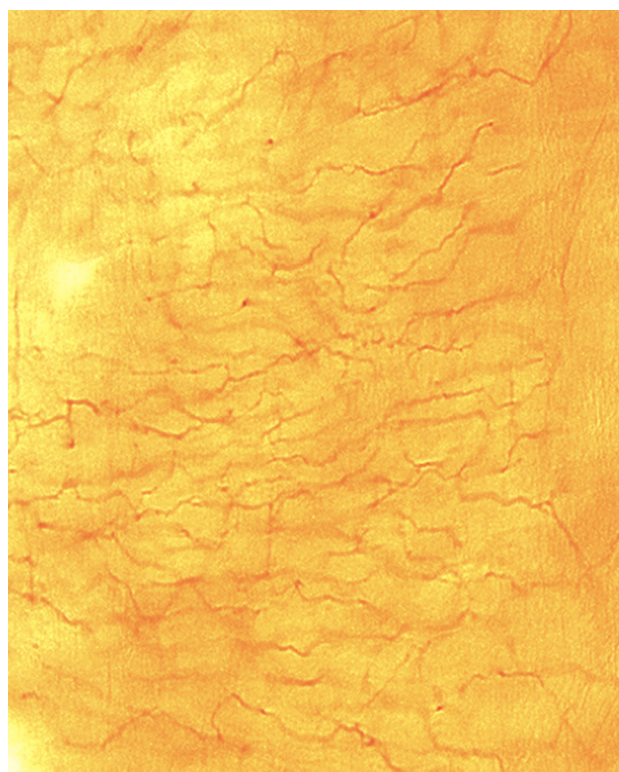
with one another and with central neurons, forming reflexes that control anatomically overlapping cardiac regions [2].

The intrinsic cardiac nervous system does not act as a simple relay station that processes centrifugal inputs to the heart. This system, consisting of a complex network of neurons and GPs nested within epicardial fat pads, is involved in the transduction of local signals (i.e. the system can regulate cardiac function directly, independent of higher autonomic centres). Signals arriving from the central nervous system via the extrinsic cardiac nervous system are also integrated by the intrinsic cardiac nervous system, which processes both centripetal and centrifugal information [3]. In a dog model of AF, Choi et al. demonstrated that although the majority of AF episodes were associated with activation of the extrinsic cardiac nervous system, some episodes were associated with isolated activation of the intrinsic cardiac nervous system [4].

GPs containing the somas of cholinergic, adrenergic, afferent and interconnecting neurons [5] have been identified in cardiac regions, such as the right atrium, the atrial posterior wall and the junctions between the inferior pulmonary veins and the left atrium or between the superior vena cava and the right atrium [6]. Electrical stimulation of these two latter sites changes the electrical activity of sinus node and atrioventricular node cells, respectively [7], suggesting that different GPs modulate specific anatomical regions. The projections of the parasympathetic nerves to the sinus node have also been shown to penetrate the epicardium at the pulmonary vein antrum, explaining the increased sinus rate often observed after pulmonary vein ablation [8]. Recently, Yu et al. found that a high sinus rate after catheter ablation for AF was associated with lower recurrence of the arrhythmia [9].

Although appealing, such findings still underestimate the complexity of the cardiac nervous system, the main feature of which is the constant interplay between different GPs [10]. Activation of neurons located in any of the major GPs has been shown to influence not only adjacent tissues, but all four chambers of the heart [11]. The flexibility of this neural network ensures fine cardiac regional coordination, allowing three critical feedbacks: with short latency (interconnections between intrinsic cardiac neurons that modulate cardiac indices during each cardiac cycle); medium latency (connections between intrinsic and extrinsic intrathoracic neurons that influence cardiac indices over several cardiac cycles); and long latency (connections between intrinsic and extrinsic intrathoracic neurons, and the higher autonomic centres that exhibit prolonged effects on cardiac indices) [2].

Armour demonstrated that there are fewer postganglionic cholinergic neurons than adrenergic neurons [12]. Colocalization of sympathetic and parasympathetic nerve fibres has been reported in nerve trunks of the left atrium [13,14], and a predominance of parasympathetic fibres has been noted, particularly in the posterior left atrium [13]. A gradient has been demonstrated in nerve density, with the ostia of the pulmonary veins (Fig. 2) being more richly innervated than their distal parts, the left superior pulmonary vein more densely innervated than the right inferior pulmonary vein, and the left side more innervated than the right side of the left atrium [15]. The innervation of the rear of the left atrium is also superior to that of its front



**Figure 2.** Autonomic nerve fibres in the pulmonary vein wall stained for acetylcholinesterase using the “direct colouring” thiocholine method of Karnovsky and Roots (unpublished data).

[15]. The presence in the left atrium of this intricate heterogeneously distributed neural network, together with an increased sympathetic nerve density [16], is likely to be a key contributor to AF initiation and perpetuation [10].

## Pathophysiology of AF: The role of the autonomic nervous system

Coumel’s triangle of arrhythmogenesis, which includes a trigger, an arrhythmogenic substrate and modulation factors, remains the mainstay of our understanding of AF pathophysiology. Each of these three components can be influenced by the ANS.

### Altered autonomic balance and electrical triggers (Table 1)

Three mechanisms underlie ectopic automatic activity in patients with AF—abnormal automaticity and early and delayed afterdepolarizations. The hyperpolarization-activated inward current ( $I_f$ ), one of the most important ion currents responsible for cardiac automaticity, is expressed in almost all cardiac cells. In non-pacemaker cells,  $I_f$  is counterbalanced by the inwardly rectifying  $K_{ir}$  current ( $I_{K1}$ ), and both  $I_f$  and  $I_{K1}$  are strongly modulated by the ANS. Stimulation of beta-adrenergic receptors enhances  $I_f$  activity in both nodal and extranodal cells, whereas stimulation of atrial alpha-adrenergic receptors reduces  $I_{K1}$  activity [17]. Simultaneous activation of alpha1- and beta1-adrenoceptors has



**Table 1** Sympathetic and parasympathetic effects on ion channels and atrial electrophysiology, promoting electrical triggers and reentry.

Sympathetic stimulation			Parasympathetic stimulation	
↑ $I_f$ ↓ $I_{K1}$	↑ $I_{Ca-L}$ ↓ $I_{K1}$ (AP prolongation)	↑ SERCA (SR $Ca^{2+}$ overload)	↓ $I_f$ (bradycardia—AP prolongation; ↓ overdrive suppression) EADs	↑ $I_{K-Ach}$ (AP shortening)
↑ Ectopic activity Electrical triggers	EADs ↑ $I_{Ks}$  AP shortening	DADs	↓ Gap junction conductance ↓ $I_{Na}$ (via VIP release)  ↓ Intra-atrial conduction velocity	Late-phase 3 EADs  ↑ $I_{Ks}$ ↑ $I_{K-Ach}$ ↓ $I_{Ca-L}$ Heterogeneous AP shortening
Reentry				
<p>AP: action potential; DADs: delayed afterdepolarizations; EADs: early afterdepolarizations; <math>I_{Ca-L}</math>: sarcolemmal L-type <math>Ca^{2+}</math> channel; <math>I_f</math>: hyperpolarization-activated inward current; <math>I_{K1}</math>: inwardly rectifying Kir current; <math>I_{K-Ach}</math>: acetylcholine-activated potassium current; <math>I_{Ks}</math>: slowly activating delayed rectifier potassium current; <math>I_{Na}</math>: sodium current; SERCA: SR <math>Ca^{2+}</math>-dependent adenosine triphosphatase; SR: sarcoplasmic reticulum; VIP: vasoactive intestinal peptide.</p>				

been shown to promote ectopic activity in the rat pulmonary vein [18]. Part of the antiarrhythmic effect of beta-blockade in patients undergoing cardiac surgery can be attributed to its potential to decrease  $I_f$  current activity [19]. On the other hand, vagal stimulation inhibits the  $I_f$  current, and is strongly proarrhythmic. Reduced  $I_f$  activity in nodal cells may alter the normal pacemaking hierarchy of the heart; it prevents the sinus node from overdrive pacing, allowing ectopic activity to arise. In addition, bradycardia-related action potential prolongation favours early depolarizations. In line with this concept, a meta-analysis of seven double-blinded randomized controlled trials associated ivabradine (an  $I_f$  current blocker) with a 1.15-fold increase in the relative risk of AF [20]. In patients with stable coronary artery disease, administration of ivabradine was also found to be associated with a 1.35-fold increase in the risk of new-onset AF [21].

Afterdepolarizations interrupt phases 2, 3 or 4 of the action potential in atrial myocytes. Excessive action potential prolongation, resulting from decreased activity of outward  $K^+$  currents or increased activity of inward cation currents, allows  $Ca^{2+}$  currents to recover from inactivation and to create inward cation movement, generating early afterdepolarizations. Spontaneous release of  $Ca^{2+}$  from the sarcoplasmic reticulum — as a result of  $Ca^{2+}$  overload, reduced  $Ca^{2+}$  binding to calsequestrin or increased sensitivity of ryanodine receptor (RyR2) channels — activates the electrogenic  $Na^+$ - $Ca^{2+}$  exchanger, creating an arrhythmogenic net inward cation movement and triggering delayed afterdepolarizations [22].

The critical role of the sympathetic nervous system in all processes related to  $Ca^{2+}$  inflow, storage and release underscores its proarrhythmic potential. Protein kinase A- and  $Ca^{2+}$ /calmodulin-dependent protein kinase II-induced phosphorylation of the sarcolemmal L-type  $Ca^{2+}$  channels ( $I_{Ca-L}$ ), mediated by the sympathetic nervous system, enhances transmembrane  $Ca^{2+}$  inflow during the plateau phase of

the action potential. Alpha-adrenergic-induced  $I_{K1}$  inhibition also prolongs action potential duration, favouring phase 3 afterdepolarizations [22]. Late-phase 3 afterdepolarizations have been linked to shortened, rather than prolonged, action potentials [23]. By activating the acetylcholine-activated  $K^+$  current ( $I_{K-Ach}$ ), increased parasympathetic tone promotes action potential shortening, particularly when paralleled by sympathetic-induced increase in  $Ca^{2+}$  transient [24]. This is particularly true for pulmonary vein cells, which intrinsically have shorter action potentials [25]. By promoting phosphorylation of phospholamban, and thereby removing phospholamban inhibition of the sarcoplasmic reticulum  $Ca^{2+}$ -dependent ATPase, beta-adrenergic stimulation also favours sarcoplasmic reticulum  $Ca^{2+}$  overload and delayed afterdepolarizations.

## Evidence for atrial neuromyopathy

When associated with a myocardial substrate, ectopic stimuli arising from any of the mechanisms mentioned previously could initiate AF. Muscarinic receptor activation has been shown to decrease gap junction conductance and intra-atrial conduction velocity via cyclic guanosine monophosphate (cGMP)-dependent pathways [26]. Vagally mediated release of non-cholinergic neurotransmitters, such as the vasoactive intestinal peptide, has been shown to decrease sodium current activity, further contributing to vagal-induced intra-atrial conduction slowing and reentry [27], as well as increasing the activity of the slowly activating delayed rectifier potassium current ( $I_{Ks}$ ), leading to atrial refractoriness shortening [27,28]. Vagal stimulation also abbreviates the atrial action potentials by augmenting  $I_{K-Ach}$ , while increasing the spatial dispersion of refractoriness and atrial activation frequencies, effects that appear to be larger in left compared with right atrial myocytes, because of greater abundance of Kir3.x channels and higher

$I_{K-Ach}$  densities [29,30]. In addition, parasympathetic activation suppresses  $I_{Ca-L}$ , further contributing to shortening of refractoriness [31]. Although sympathetic stimulation has also been incriminated in shortening of refractoriness, via  $I_{Ks}$  activation [32], the effect appears to be much less proarrhythmic, emphasizing the major proarrhythmic role of vagal-induced refractoriness heterogeneity.

The synergistic effect of sympathetic-induced intracellular calcium increase and parasympathetic-induced heterogeneous action potential shortening supports the idea of sympathovagal coactivation as a major contributor to AF initiation and maintenance. Using single-cell electrophysiology studies, Patterson et al. demonstrated that electrical stimulation of pulmonary vein ganglia causes both early afterdepolarizations and shortening of refractoriness [33]. In that model, atropine was able to prevent action potential shortening, whereas beta1-adrenergic blockade suppressed early afterdepolarization-induced firing within the pulmonary vein cells [33].

Brignole et al. suggested that in patients with AF presenting with syncope, an upright electrophysiological study combined with vasovagal manoeuvres might be useful to guide diagnosis and therapy [34]. In a small cohort of patients with paroxysmal AF, the authors demonstrated that patients with AF presenting with syncope may be predisposed to an abnormal neurally mediated response during both sinus rhythm and tachycardia. This was not the case in patients with AF without syncope, suggesting that the propensity toward a disturbance of the ANS was not directly related to the presence of the arrhythmia [34]. On the other hand, in a study by Oliveira et al., patients with AF presented a delayed increase in sympathetic tone and higher blood pressure with no difference in heart rate during the head-up tilt test compared with non-arrhythmic controls, indicating autonomic dysfunction and changes in baroreflex sensitivity in patients with AF [35]. Indeed, once installed, AF itself induces proarrhythmic functional and structural autonomic changes, favouring the persistence of the arrhythmia. During fast rates, the combination of increased cardiac filling pressure, activating cardiopulmonary mechanoreceptors, and decreased arterial blood pressure, unloading the arterial mechanoreceptors, generates conflicting messages, disturbing ANS functioning and altering baroreflex responses [36]. In the presence of AF, nerve sprouting (reinnervation) and heterogeneous sympathetic hyperinnervation of the atria promote dispersion of refractoriness [37,38]. In dogs, sympathetic hyperinnervation of the atria following myocardial infarction was also associated with increased AF inducibility [37]. In patients with AF, the density of sympathetic nerve twigs was significantly higher than that of other nerves [38].

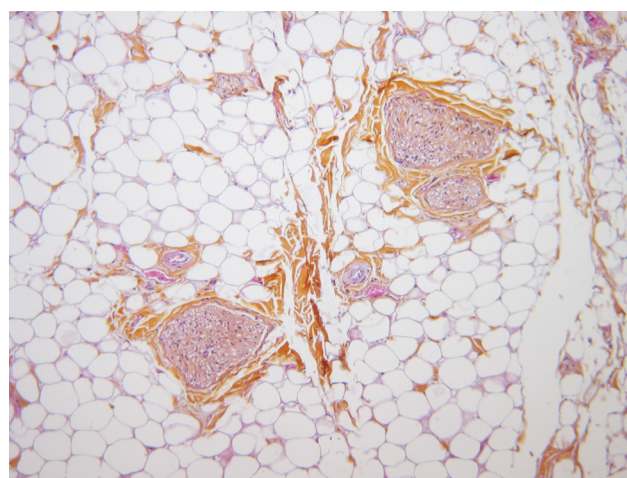
### Neural regulation of AF modulation factors

Although clinical and experimental studies clearly demonstrate that variations in the autonomic tone often precede AF onset, the direction and magnitude of this proarrhythmic autonomic imbalance are highly variable. In accordance with the results of experimental studies that suggest an arrhythmogenic adrenergic synergy, most clinical studies found a combined contribution of both autonomic branches to AF occurrence and maintenance, rather than an anomaly of one branch alone [33,39–41]. In a study by Bettoni and

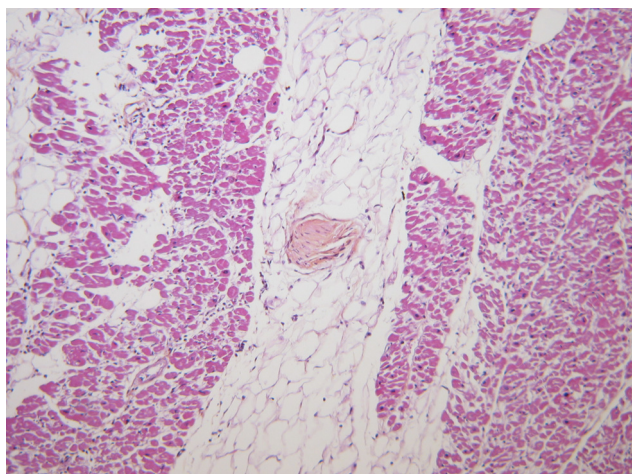
Zimmermann, an increase in sympathetic activity followed by vagal dominance was observed just before arrhythmia onset [39], whereas in a dog model of AF, sympathetic activity appeared to modulate both the initiation and persistence of vagally induced AF [42]. These data underline the concept that pre- and postsynaptic interactions between the sympathetic and vagal systems complicate the neurophysiology of the heart; vagal effects are greater in the presence of sympathetic stimulation, whereas sympathetic effects are lower in the presence of vagal stimulation (“accentuated antagonism”) [43]. In dogs, acetylcholine promoted the arrhythmias, whereas adrenergic blockade increased the threshold for acetylcholine-induced AF. By comparison, catecholamines decreased the threshold for acetylcholine-induced AF [42], demonstrating that vulnerability to vagally induced AF is largely attributable to parasympathetic-sympathetic interactions. Whereas complete vagal denervation during pulmonary vein ablation significantly reduces AF recurrence [44], reflex phenylephrine-induced vagal stimulation has been shown to paradoxically interrupt AF [45].

### Myocardial inflammation as a dysautonomia

There are clinical and experimental data that suggest that inflammation is an AF facilitator. Part of this effect can be attributed to inflammation-induced autonomic imbalance. Inflammation may modulate the intrinsic cardiac nervous system of the heart, promoting nerve growth and autonomic variations [46], whereas cytokines in the interleukin-6 family negatively modulate sympathetic activity and promote cholinergic transdifferentiation of cardiac sympathetic nerves [47]. Inflammation may also be a link between pericardial fat and AF. As the GPs of the heart are enclosed in the epicardial fat pads (Fig. 3), these latter may act as modulators for the ANS. Inflammatory molecules originating in the pericardial fat stimulate the GPs, promoting parasympathetic-mediated heterogeneous shortening of atrial refractoriness, coupled with sympathetic-mediated increase in  $Ca^{2+}$  transients [46]. Inhomogeneous fatty infiltration of the atria (Fig. 4) further increases the dispersion of



**Figure 3.** Autonomic nerves embedded in the epicardial fat (unpublished data).



**Figure 4.** Pericardial fat infiltrating the atrial myocardium (unpublished data).

atrial refractoriness, explaining why the volume of periatrial adiposity appears to correlate better with the AF burden than the volume of the adipose tissue of the entire heart [48].

## Neuromodulation as a therapeutic tool against AF

Although quantification of autonomic imbalance is not usually done in patients with AF, clinical identification of sympathetic or vagal AF may have a therapeutic impact. Vagal AF is most commonly seen in young patients with structurally normal hearts, during states of increased vagal tone, such as sleep, after heavy meals, after alcohol intake or soon after physical exercise (Fig. 5). Parasympathetic activation has also been linked to the high incidence of AF in trained athletes, although additional factors, including sports supplements, atrial remodelling, fibrosis and inflammation or electrolyte abnormalities, may also contribute to the increased propensity of this population to AF [49]. In long-term endurance cross-country skiers, low resting heart rates predicted the occurrence of future AF [50]. In rats submitted to intensive physical training for 16 weeks, Guasch et al. reported increased susceptibility to AF, coupled with increased vagal tone and increased  $I_{K-Ach}$  activity, probably as a result of decreased expression of regulators of G-protein signalling [51]. However, whereas sustained vigorous exertion appears to promote AF [52], regular mild-to-moderate exercise may offer protection against AF [53].

Adrenergic AF is usually related to exercise or emotional stress, and often occurs in men in their 50s [54]. Excessive adrenergic stimulation is also believed to be one of the dominant mechanisms in postoperative AF [55].

However, the complexity of sympathovagal interactions questions this simple clinical classification. In aging hypertensive rats with left ventricular hypertrophy and spontaneous AF, the arrhythmia occurred in the setting of autonomic imbalance with relative vagal hyperactivity [56]. Moreover, in those rats, sympathetic stimulation suppressed all arrhythmic episodes, whereas cholinergic stimulation

was highly proarrhythmic [56]. In the same model, chronic administration of pyridostigmine, an acetylcholinesterase inhibitor, increased the arrhythmia burden, suggesting that it might be timely to reconsider the classical assumption that vagal AF is confined to patients with structurally normal hearts [57].

In isolated canine pulmonary veins, beta1-adrenergic receptor blockade completely suppressed firing in eight of eight preparations [33]. On the other hand, with the exception of metoprolol CR/XL, which demonstrated a significant, but modest, reduction in AF recurrence following cardioversion [58], neither pure beta-blockers nor combined beta- and alpha-adrenergic blockers have demonstrated efficient antiarrhythmic effects. Part of the protective effects of amiodarone, flecainide and disopyramide may be derived from their potential to decrease  $I_{K-Ach}$  dispersion and spatial refractoriness heterogeneity [29,59]. More recently, other antiarrhythmic strategies targeting the ANS have been tested, including atrium-selective agents that target the acetylcholine-dependent Kir channels [60]. In a dog model, tertipapin-Q, a specific  $I_{K-Ach}$  antagonist, prolonged atrial refractoriness and terminated vagal-induced AF without affecting ventricular repolarization [61].

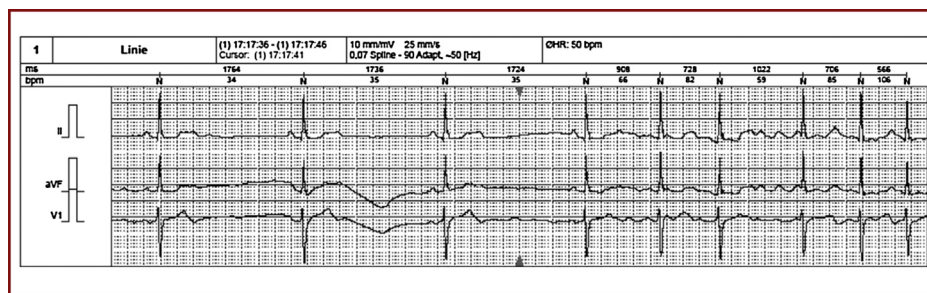
Many other interventions that decrease atrial electrical instability, including weight loss, exercise, control of sleep apnoea or dyslipidaemia, may also owe part of their effects to their impact on the autonomic control of the heart [62].

## GP ablation with pulmonary vein isolation

During pulmonary vein ablation, lesions are performed in areas with high densities of GPs, so the impact of ablation on atrial autonomic neuropathy could also contribute to the efficiency of these procedures. In fact, the higher efficacy of intrinsic cardiac nervous system ablation compared with pulmonary vein isolation observed in a model of vagal AF suggests that, in that setting, the ANS may be mechanistically more important than pulmonary vein triggers [63]. In experimental studies, ablation around the pulmonary vein-left atrium junction, an area with rich autonomic innervation, attenuated shortening of atrial refractoriness and decreased vagal-induced AF [64]. In a randomized multicentre clinical trial, ablation of GPs in addition to pulmonary vein ablation increased freedom from AF after 2 years of follow-up from 56% to 74% [65]. In dogs with AF, video-assisted thoracoscopic epicardial ablation of the left atrium [66] and transvascular radiofrequency ablation of atrial parasympathetic nerves [67] were both efficient in preventing the inducibility of vagal AF. High-frequency stimulation of the vein of Marshall triggered AF, whereas ethanol infusion in this area suppressed the arrhythmia [68]. On the other hand, in a recent study by Driessen et al., GP ablation during thoracoscopic surgery for advanced AF did not affect AF recurrence, and was associated with more adverse effects [69].

At present, ablation strategies targeting the parasympathetic nervous system are largely empirical, guided by non-specific responses to electrical stimulation, such as bradycardia. Increased susceptibility to atrial arrhythmias has been reported following GP ablation [70]. In addition, dissection of the anterior fat pad at the time of coronary artery bypass surgery was associated with a higher incidence of AF [71]. As GPs control anatomically overlapping cardiac





regions, and cardiac neurons are in constant communication with one another, as well as with more central neurons, it is not surprising that ablation of one or a few GPs does not provide long-lasting effects. It is likely that the complex neural architecture is designed to ensure recovery of function when one of its components becomes damaged [72]. Alternatively, the use of botulinum toxin to interfere with cholinergic neurotransmission may arise as a new strategy for atrial antiarrhythmic neuromodulation [73,74].

### Renal artery denervation with pulmonary vein isolation

## Low-level vagus nerve or tragus stimulation

activity at both pre- and postjunctional levels [87], but also with a significant increase in concentrations of inflammatory markers [88]. In addition to its antiadrenergic effects, low-level vagus nerve stimulation may also exert antiarrhythmic effects as a result of vasostatin-1 release [87]. Of note, non-invasive transcutaneous stimulation of the auricular branch of the vagus nerve (tragus stimulation) has antiarrhythmic effects similar to those of low-level cervical vagus nerve stimulation [86]. The procedure was associated with prolongation of atrial refractoriness, decreased AF duration and suppression of inflammatory markers [89]. In an animal model of heart failure, Ogawa et al. demonstrated that cryoablation of bilateral stellate and T<sub>2</sub>–T<sub>4</sub> thoracic ganglia was associated with reduced AF burden [90]. Transcutaneous blockade of the stellate ganglia using lidocaine was also associated with prolonged atrial refractoriness, reduced AF inducibility and decreased AF duration in almost half (11 out of 24) of the patients with pacing-induced AF [91].

## Spinal cord stimulation

## Gene therapy

Advances in gene therapy have opened the way for gene-guided approaches to AF-related atrial neuropathy. In a porcine model, atrioventricular nodal gene transfer with adenoviral vectors overexpressing an inhibitory G-protein subunit ( $G_{\alpha i}$ ) efficiently decreased atrioventricular conduction and led to a 15–25% reduction in heart rate during persistent AF [95,96], suggesting that rate control by gene therapy might provide an alternative to current rate control pharmacological therapy in AF. A compensatory increase in the expression of adenylyl cyclase was observed in those animals, causing important heart rate acceleration upon catecholamine application [96]. This was not the case in a porcine model of AF, in which rate control was obtained using genetic attenuation of a stimulatory



G-protein subunit ( $G_{\alpha s}$ ) in the atrioventricular node [97]. Delivery to the posterior left atrium of plasmids containing the complementary deoxyribonucleic acid (DNA) for the  $G_{\alpha i2}$  C-terminal peptide, which acts by selectively disrupting  $M_2$  muscarinic receptor- $G_{\alpha i2}\beta\gamma$  coupling and impeding  $G_{\alpha i2}\beta\gamma$  signal transduction, led to atrial-selective attenuation of vagal signalling [98]. When both  $G_{\alpha i2}$  C-terminal peptide and  $G_{\alpha o1}$  C-terminal peptide were delivered to the canine posterior left atrium, vagal responsiveness was almost entirely eliminated [95]. A significant prolongation in atrial action potential and a dramatic decrease in vagal-induced AF and in AF dominant frequencies were also found [99].

Overall, experimental studies appear to provide rather strong evidence for the therapeutic potential of neuromodulation strategies. However, data from clinical studies are less convincing. At least some of these discrepancies are probably related to the fact that, in experimental studies, neuromodulation strategies have been almost exclusively tested in animals free of concomitant diseases. Confounding factors often present in patients with AF (i.e. co-morbidities, concomitant medication) may impact on the success of such strategies in clinical settings. In addition, pacing- and vagally induced AF, used in most experimental studies, are not necessarily a faithful reproduction of the human clinical condition. The use of surrogate endpoints for antiarrhythmic efficacy in experimental studies, such as AF inducibility by electrical or vagal stimulation, may also contribute to the different results obtained in experimental compared with clinical studies. Assessing neuromodulation techniques in clinically relevant experimental models (e.g. aging hypertensive animals, which present spontaneous AF, possibly treated with drugs commonly used in patients with AF) would be of interest.

## Autonomic nervous system imbalance as an early marker of AF

A number of AF predictors have been identified, but clinical risk scores show a very limited ability to identify individuals at risk of AF. Although AF itself promotes atrial proarrhythmogenic remodelling ("AF begets AF"), autonomic changes probably develop far before the actual onset of the arrhythmia.

Long-term autonomic imbalance preceding AF has been studied rarely. In aging hypertensive rats that develop spontaneous AF [56,100], vagal hyperactivity was found to be an arrhythmia facilitator [56]. A similar pattern of autonomic imbalance, although less severe, was also observed in young hypertensive animals that did not yet present AF, suggesting that this sympathovagal imbalance precedes AF onset, and may be used to identify AF predisposition [56]. In a recent study involving more than 11,000 subjects with rather low heart rates (approximately 65 beats/min), cardiac autonomic dysfunction with low resting heart rate variability was associated with higher incidence of new-onset AF [101]. Similarly, in patients with coronary artery disease, a decreased short-term scaling exponent of the detrended fluctuation analysis and a decreased LF/HF ratio were strong predictors of AF, and outperformed echocardiographic left atrial

diameter in their ability to predict new-onset AF [102]. Impaired low-frequency components of the heart rate have also been shown to predict new-onset AF in a middle-aged population [103]. In patients undergoing cardiac surgery, a trigger of sympathetic surge, prophylactic beta-blockers efficiently prevented postoperative AF [104]. In dogs with AF induced by rapid atrial pacing, ablation of the stellate ganglion [70], as well as vagal ablation [19], efficiently prevented AF inducibility.

## Conclusions

Diagnostic and therapeutic strategies are dictated by AF occurrence, and are often suboptimal. The lack of safe and effective antiarrhythmic strategies reflects the highly heterogeneous combinations of different AF substrates, and the variable dominance of one mechanism over the other in different patients with AF. Personalized management of AF needs new therapeutic paradigms. The ANS is unique to each individual. Identifying and targeting the atrial neuropathy that underlies AF in its preclinical early stages could provide an upstream solution. Future studies will have to clarify the role of autonomic remodelling, to elucidate whether targeting autonomic imbalance could improve AF management, and to identify the most adequate time and means to intervene to correct this proarrhythmic autonomic imbalance.

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## Disclosure of interest

The authors declare that they have no competing interest.

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