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REVIEW

Atrial fibrillation: Neurogenic or myogenic?

Fibrillation auriculaire : neurogénique ou myogénique ?

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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.

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

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MOTS CLÉS
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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.

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.

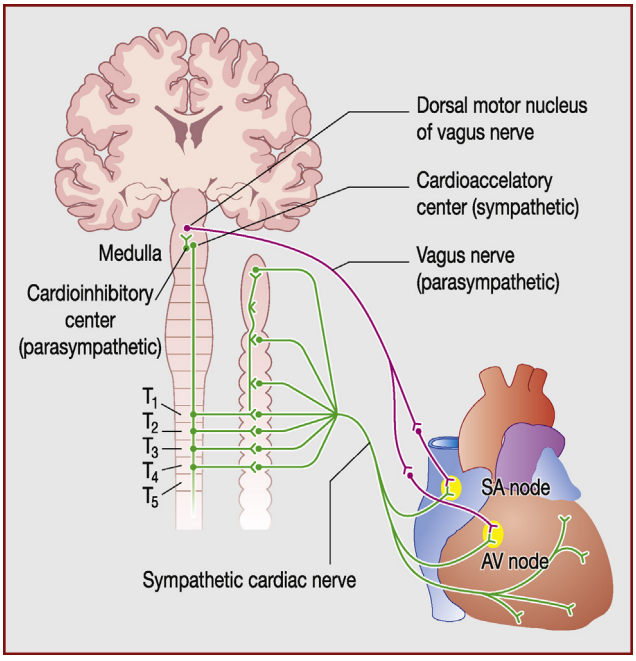

Figure 1. Anatomy of the sympathetic and parasympathetic innervation of the heart. AV: atrioventricular; SA: sinoatrial.

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, 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_1–T_4 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

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