OPINION ARTICLE

Autonomic Nervous System and Atrial Fibrillation

Fibrilación auricular y sistema nervioso autónomo

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As it is well known from Framingham et al. records, atrial fibrillation (AF) is the most common arrhythmia, and it is estimated that one out of four people will suffer from an AF episode of different duration and clinical involvement over their lifetime. (1, 2)

An extremely simple and practical way is to classify AF -particularly self-limited, sporadic or paroxysmal, though in some cases also persistent AF- into two large groups: AF that occurs in a healthy heart, and AF that occurs in a diseased heart. The first group includes, with the exception of primary AF originating from genetic mutations, AF originating from functional disorders, in which the autonomic nervous systems (ANS) plays a key role. In this case, AF is considered to be an alteration that was once discussed as whether or not it was a disease. (3) Nevertheless, non-pathologic AF can lead to moderate or long-term changes in life quality, alterations in the atrial and even ventricular function, and even cause significant psychological and social impact, all of which justify its treatment.

Why are these –often asymptomatic– episodes generated in an apparently healthy heart or with minimal abnormalities? Undoubtedly, the ANS plays a key role both in its triggering and maintenance, as well as in its resolution.

Before analyzing the mechanisms that generate non-pathologic AF, this arrhythmia must be redefined as functional and autonomic. Non-pathologic, paroxysmal, self-limited AF is much more common than the AF that is usually registered as lone atrial fibrillation (LAF), and reaches in some cases 30% (4) of this arrhythmia carriers. It is usually urban, associated with stress situations and, in many cases, to gastroesophageal reflux, gastritis and esophagitis, (5) and in other cases, to sleep apnea, alcohol intake, (6) etc., all of which are predominantly vagal triggers in a predisposing physical and psychic situation. Frequent precipitation of non-pathologic AF episodes in the morning or late in the evening is also vagal. (7) In all cases, a trigger is needed, which necessarily begins with isolated atrial extrasystoles or salvos. Understanding in which situations these salvos are generated reduces their incidence and, therefore, non-pathologic AF -and in many cases pathologic AF- is preventable with lifestyle changes, including physical activity and diet. The change of doctor and patient mind regarding AF, as observed in recent years, is good news. Answers to basic questions related with AF are being known, bringing us closer to its prevention.

The role of the ANS has been established for many years, (8) and it is known that runs of extrasystoles remodel the atria, which end up forming rotors that eventually trigger AF. This has been published since 1962. (9) The brain, the lungs and the immune system are connected and interact to cause and even make persistent a self-limited or paroxysmal AF.

Treating and preventing AF is not easy and, for that reason, knowing what the brain-heart connection –i.e. the ANS- does is essential. The relationship between cardiac ANS innervation and AF was well established during the last century, when it was observed that stimulation of the vagal/sympathetic trunks heterogeneously shortened the refractory period of atrial cells, causing dispersion of refractoriness.

Pulmonary veins can cause arrhythmias by vagal stimulation. Acetylcholine induces reentrant tachycardia in those veins, one of the triggering bases of AF due to intracellular Ca++ overload and subsequent shortening of the refractory period.

In this case, the development of extrasystoles allows to induce the chaos (automaticity and excitability disorder) that AF represents. At the beginning of the 20th century, another aspect of the autonomic innervation of the heart from ganglionated plexi in the heart itself and the great arteries was investigated. (10) This was called “cardiac intrinsic autonomic nervous system”, which is a local system, different from the brain-spinal connection that innervates the heart, called “extrinsic system”. The intrinsic ganglionated plexi system is located at the margin of the pulmonary veins, acts as a repeater of stimuli of the extrinsic vagal/sympathetic system, but can act independently, modulating cardiac functions such as automaticity, excitability and conduction. Stimulation, either electric or chemical through neurotransmitters, induces focal pulmonary vein triggers. Ablation of ganglionat-

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ed plexi related with pulmonary veins reduces inducibility of AF. (11) Clinical and laboratory experience shows that this form of AF, secondary to variations in autonomic tone, does not respond to treatment with class III or IC antiarrhythmic drugs. (12)

The ganglionated plexi adjacent to the pulmonary veins are identified with high-frequency stimuli to these groups of nerves (13) (Figure 1).

Another proof of the role of vagal/sympathetic balance in AF persistence is the spectral analysis identification of high-frequency activity sites representing increased vagal tone. (14) In patients with persistent AF, the response was a marked reduction of the ventricular response (≥ 50%) during AF. Ganglionated plexi ablation results are variable regarding AF recurrence; in some cases, they are very high (96%), but low in other studies as a result of partial ablations. (15) It is known that partial ablation of the ganglionated plexi may even increase the incidence of AF by exacerbating the heterogeneity of refractoriness across the atria, which promotes macro-reentrant AF. (16) Several studies were conducted combining both techniques of pulmonary vein and ganglionated plexi isolation, (17) even with modern cryoablation techniques. (18) A recent randomized study (19) reveals that these combined techniques offer significantly better outcomes than pulmonary vein isolation alone during a follow-up period of 12 months. Functionally, the ganglions mentioned show higher sensitivity to cholinergic and adrenergic neurotransmitters than the adjacent atrial tissue.

It is necessary to understand both from the clinical and electrophysiological viewpoints that autonomic and myocardial mechanisms should be taken into account to explain AF triggering and persistence.

Experience shows that the incidence of AF episodes in an apparently healthy heart is greater between 50 and 70 years of age. The effect of age on autonomically mediated cardiovascular responses was studied in healthy 25-45 and 60-80 year-old men and women. There seems to be only a moderate attenuation of autonomic cardiovascular responses until approximately 60 years of age, after which there is a more rapid decline. (20) Another research showed that vagal/sympathetic stimulation of the trunk could abolish neural activation within the anterior right ganglionated plexi, adjacent to the right superior pulmonary vein. (21) The passage from paroxysmal to persistent AF is explained by the fact that as the burden of AF increases, the activity of the ganglionated plexi increases, resulting in an excessive release of muscarinic and adrenergic neurotransmitters locally and through their axonal fields to smaller groups of ganglions comprising the interactive atrial neural network. Excessive local release of neurotransmitters provides another factor that explains the "AF begets AF" effect. (22)

It should be pointed out that ablation of the ganglionated plexi as a complementary procedure for pulmonary vein isolation has not yet achieved the same level of success as that achieved by catheter ablation procedures for patients with abnormal pathways, intranodal reentry, or atrial flutter. Atrial fibrillation is certainly a more complex arrhythmia in which more than one mechanism or coexistence of mechanisms is involved.

A global vision for the treatment and prevention

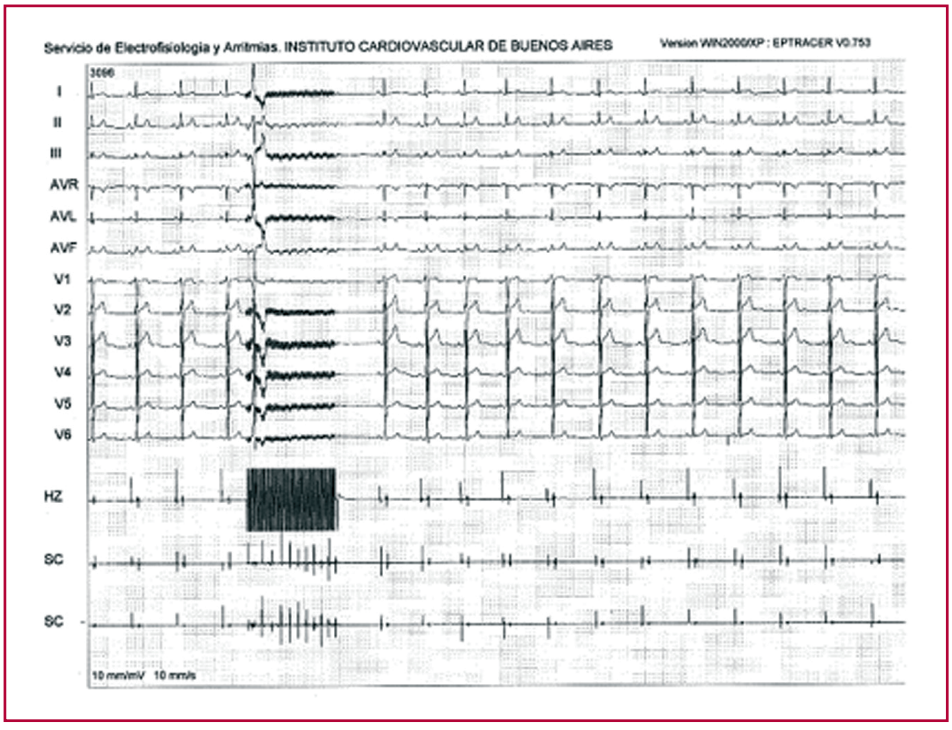

Fig. 1. High-frequency stimulation to ganglionated plexi during an ablation procedure is manifested with sinus bradycardia as a result of vagal influence

of AF in patients with an apparently normal heart implies, in the first place, that the doctor understands that these cases are related to a functional disorder in which personality, stress and even socio-economic factors have a key role (23), together with an important autonomic content. This allows the patient to feel supported, to understand that it is not a fatal condition, and that it will not cause a collapse except in specific comorbidities and circumstances. The doctor must talk to his patient, understand him, explain him the situation, and help him understand that the condition is not life-threating. (24) The condition may even be left untreated, since in more than 90% of cases it reverts spontaneously. It should be explained that the risk of stroke is minimal if there is no heart disease or certain morbidities known as the CHA2DS2-VASc Score. The approach to be followed does not start with drugs or interventions, but with what has always been called a "nutritional-hygienic regimen". (25) Strictly following the international guidelines for the treatment of AF shows us the way. (26, 27)

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