EDITORIAL

Vagal Stimulation and Atrial Electrical Remodeling

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Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice and that which is associated with most visits to the hospital and admissions.[1] The treatment of AF is a therapeutic challenge since the effectiveness of anti-arrhythmia drugs used to regain and hopefully maintain sinus rhythm is poor (at least 50% of patients suffer a relapse by one year). Furthermore, these drugs are often associated with adverse events, the most serious of which are pro-arrhythmic effects that can endanger the life of the patient.[1] Safer and more effective anti-arrhythmia drugs are therefore needed. The search for such agents requires we understand the electrophysiological mechanisms involved in the genesis and maintenance of AF, and identify possible therapeutic targets. Three mechanisms have been implicated in the genesis and maintenance of AF: *a)* during the second half of the 20th century the predominant hypothesis for explaining AF was the simultaneous activation of the atrium by multiple waves that were propagated in a random, disorganized manner, and which divided, joined or disappeared (the multiple wavelet hypothesis)[2]; *b)* the presence of one or more automatic atrial foci in the pulmonary veins or their proximity generating high frequency activation fronts that become fractionated and disorganized in the surrounding tissue, giving rise to "fibrillatory conduction"[3]; and *c)* the presence of one or more high frequency rotors anchored at the mouths of the pulmonary veins and the posterior wall of the left atrium (produced as a consequence of a functional micro-reentry that locally activates the surrounding tissue to give rise to fibrillatory conduction affecting the rest of the atrial myocardium).[4,5]

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Atrial fibrillation is an arrhythmia that tends to perpetuate itself, passing through the paroxysmal stage to become persistent and, finally, permanent. This is the consequence of important changes (remodeling) that take place in the electrical, mechanical and structural properties of the atrium.[1,6] Atrial stimulation at high frequencies produces a rapid and heterogeneous shortening of the duration of the action potential (DAP) and of the atrial effective refractory period (AERP). This reduces the wavelength of the reentry circuits and facilitates the coexistence of multiple activation wave fronts and the maintenance of AF. This shortening is due to a number of changes in the ion currents that determine the repolarization of the atrium: a reduction in the transitory currents of K^+ exit (I_{to}) and Ca^{2+} entry via the L channels (I_{Ca}), and an increase in the K^+ exit current showing internal rectification (I_{K1}).[7] Internal rectification involves the channels moving K^+ from the extracellular to the intracellular medium more efficiently than in the other direction.[7,8] Thus, the channels with this property determine the membrane potential of the cardiac cells during diastole (stage 4) and participate in the final stage of repolarization (stage 3) of the cardiac action potential. In the atrial myocardium there is also a K^+ exit current activated by acetyl choline (Ach), known as the I_{KACh}, that also shows internal rectification. The channels that generate the I_{KACh} are formed from heterotetramers of two I_{KACh} subunits known as Kir3.1 and Kir3.4.[8,9]

Under physiological conditions, the ACh released from the parasympathetic nerve endings interacts with the M2 receptors coupled to G proteins on the surface of the membranes of the atrial myocytes and those of the sinoatrial and atrioventricular nodes.[8,10] The interaction of ACh with these M2 receptors leads to the dissociation of the heterotrimeric Gi protein into its α and $\beta\gamma$ subunits, the latter activating the I_{KACh}[11] through interaction with Kir3.1 and Kir3.4. The increase in the exit of K^+ hyperpolarizes the membrane potential leading to a marked shortening of the DAP and AERP and

a reduction in the firing frequency of the sinoatrial node.

In animal models, vagal stimulation markedly and heterogeneously shortens the DAP and AERP and hyperpolarizes the membrane potential. These effects reduce the wavelength of the reentry circuit and facilitate the coexistence of a larger number of wave fronts, thus facilitating the induction and/or maintenance of AF.[12-16] The heterogeneous distribution of vagal innervation and the density of M2 receptors in the atria also contribute to the heterogeneous shortening of the AERP, facilitating the persistence of AF. In addition, the hyperpolarization of the resting potential increases the availability of the NA^+ current and increases excitability; thus the increase in the I_{KACh} allows the stabilization and acceleration of the rotors maintaining AF. The finding in Kir3.4 KO mice that the stimulation of the M2 receptors does not produce AF[17] confirms the functional role of the I_{KACh} in the genesis of AF.

It has been shown in isolated sheep hearts that AF is maintained by one or more rotors anchored at the mouths of the pulmonary veins and the posterior wall of the left atrium.[4,5] In this model, ACh accelerates the frequency of activation of the atrial rotors, but its effect is more marked in the left atrium than the right. This has been correlated with an increase in the quantity of Kir 3.1/3.4 mRNA and the density of I_{KACh} in the left atrium; ie, ACh increases the frequency gradient between the atria during AF.[16] In dogs, the density of M2 receptors and I_{KACh} is greater in the left and right atrial appendages, and in the left atrium, than in the right atrium, the pulmonary veins or the superior vena cava.[18] The posterior area of the left atrium and the pulmonary veins has an important role in the genesis and maintenance of AF. In animal models, the pulmonary veins-left atrium is where focal discharges and reentries occur during AF; indeed, the anatomical substrate of the region (discontinuity and brusque changes in the orientation of the muscle fibers) facilitates reentries.[19] Autonomic innervation (cholinergic and sympathetic) is at its highest in the left atrium, in the anterosuperior segments of the superior pulmonary veins, in the inferior segments of the lowermost two, and at about 5 mm from the union of the pulmonary veins and left atrium. In addition, it is greater in the epicaridal region than the endocardial region.[19] However, no areas are predominantly sympathetic or parasympathetic. Furthermore, the high frequency stimulation of the pulmonary veins and superior vena cava produces a shortening of the DAP in both tissues. In the isolated pulmonary veins, however, the response is more heterogeneous since the DAP is shortened in some cells while in others it is prolonged, accompanied by early afterdepolarizations that can induce AF.[14] In patients with paroxysmal AF, the activation of the I_{KACh} with adenosine increases the maximum dominant frequency at the union of the pulmonary veins-left atrium, amplifying the frequency gradient between the left and right atria. In patients with persistent AF, however, the increase in maximum dominant frequency is seen outside the region of the pulmonary veins.[20] This indicates that paroxysmal AF is maintained by the activity generated at the union of the pulmonary veins and left atrium.

Vagal tone can also modify the recovery of electrical remodeling via the shortening of the AERP following the suppression of atrial overstimulation. In goats subjected to rapid atrial stimulation (RAS) (300 beats/min for 24 h), a marked shortening of the AERP is seen that recovers when stimulation is suspended. It has been observed that vagal stimulation shortens AERP even more during stimulation, and delays the recovery of electrical remodeling.[21] However, in anaesthetized dogs, vagal stimulation prior to RAS prevents the shortening of the AERP.[22] In patients with no history of AF subjected to RAS (300 beats/min for 5 min), atropine does not modify the shortening of the AERP, but accelerates its normalization after suspending RAS.[23] These results indicate that vagal stimulation might modify the atrial electrical remodeling that occurs in the first few minutes after RAS. To study whether this might be the case, Zhao et al,[24] publishing in this issue of the *Revista Española de Cardiología,* analyzed the changes in the AERP and the amplitude of the I_{KACh} under controlled conditions following the stimulation of the right vagus nerve (RVN) and/or the left superior pulmonary veins (LSPV) at 500 beats/min for 4 h in anesthetized dogs. The stimulation of the LSPV produced a shortening of the AERP associated with an increase in the dispersion of the AERP, and induced AF in all animals thus treated. In the LSPV+RVN group, no changes in AERP were seen, although the dispersal of the AERP was similar to that observed in the LSPV group; AF appeared in only 25% of the animals and always for a short period only (around 5 s). The amplitude of the I_{KACh} was lower in the left superior pulmonary veins than in the atrial myocytes, and lower in the myocytes of the right atrium than in those of the left. The density of the I_{KACh} increased in the animals subjected to LSPV stimulation, while in those of the LSPV+RVN group the I_{KACh} density tended to diminish (ie, not significantly so). The authors of the work conclude that the shortening of the AERP produced after LSPV stimulation is related to an increase in I_{KACh}, and that stimulation of the RVN before the LSPV might inhibit atrial

vulnerability to AF by inhibiting this increase. Furthermore, they propose that the shortening of the AERP, and not the dispersion of the AERP, is the basis of the initiation of AF.

This study, however, suffers a number of limitations inherent to the methodology used: *a)* the small sampling density limits the precise determination of the AERP; *b)* the inducibility of AF was not analyzed in the areas of greatest dispersion of the AERP but only in fixed areas of the right atrium and the posterolateral zone of the left atrium; *c)* no complete study of the effects of RVN stimulation was performed, something that would have provided much interesting information; and *d)* LSPV stimulation was performed over the relatively short period of 4 h; it is unknown whether this period is long enough for stable electrical remodeling to be achieved in this experimental model. In fact, in the atrial myocytes of animals subjected to RAS for several days,[25] and those of patients with chronic AF, there is a reduction in the quantity of Kir3.1 and Kir3.4 mRNA and of the $I_{KACh,}$[6,8,26] with the aim of countering the shortening of the atrial DAP. However, in the atrial myocytes of patients who have suffered AF for more than 7 days the activity of a current generated by channels of the Kir3.x family, known as the constitutive I_{KACh} (I_{KAChc}), increases. This current is activated in the absence of ACh as well as in the presence of atropine.[27-29] An increase in the I_{KAChc} in patients with chronic AF would increase atrial vulnerability to tachyarrhythmias and facilitate the perpetuation of AF.[28,29] In contrast, the selective blockage of the I_{KAChc} with tertiapine has been reported to prolong the DAP and AERP and stop AF in remodeled atria without modifying the electrophysiological properties of the ventricles, confirming the role of I_{KAChc} in the genesis of AF.[30]

Despite these limitations, it is clear that gaining knowledge of the mechanism involved in the genesis and maintenance of AF is the first step in understanding arrhythmia in all its magnitude, and in identifying therapeutic targets that would allow safer and more effective therapies based on the pathophysiology of arrhythmia to be developed. From this point of view, the work of Zhao et al.[24] represents an advance in the analysis of the mechanisms that might participate in atrial electrical remodeling during the first hours of AF. The search for knowledge in this area must now continue.

REFERENCES

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines. Eur Heart J. 2006;27:1979-2030.
2. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharges. Am Heart J. 1959;58:59-70.
3. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659-66.
4. Mandapati R, Skanes AC, Chen J, Berenfeld O, Jalife J. Stable microreentrant sources as a mechanism of atrial fibrillation in the isolated sheep heart. Circulation. 2000;101:194-9.
5. Jalife J. Rotors and spiral waves in atrial fibrillation. J Cardiovasc Electrophysiol. 2003;14:776-80.
6. Nattel S, Maguy A, Le Bouter S, Yeh YH. Arrhythmogenic ion-channel remodeling in the heart: heart failure, myocardial infarction, and atrial fibrillation. Physiol Rev. 2007;87:425-56.
7. Nichols CG, Lopatin AN. Inward rectifier potassium channels. Annu Rev Physiol. 1997;59:171-91.
8. Tamargo J, Caballero R, Gómez R, Valenzuela C, Delpón E. Pharmacology of cardiac potassium channels. Cardiovasc Res. 2004;62:9-33.
9. Krapivinsky G, Gordon EA, Wickman K, Velimirovic B, Krapivinsky L, Clapham DE. The G-proteingated atrial K+ channel IKACh is a heteromultimer of two inwardly rectifying K+ channel proteins. Nature. 1995;374:135-41.
10. Wickman K, Clapham DE. Ion channel regulation by G proteins. Physiol Rev. 1995;75:865-85.
11. Logothetis DE, Kurachi, Y, Galper J, Neer EJ, Clapham DE. The beta gamma subunits of GTP-binding proteins activate the muscarinic K+ channel in heart. Nature. 1987;325:321-6.
12. Zipes DP, Mihalick MJ, Robbins GT. Effects of selective vagal and stellate ganglion stimulation of atrial refractoriness Cardiovasc Res. 1974;8:647-55.
13. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol. 1997;273:H805-16.
14. Schauerte P, Scherlag BJ, Pitha J, Scherlag MA, Reynolds D, Lazzara R, et al. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation. 2000;102:2774-80.
15. Kneller J, Zou R, Vigmond EJ, Wang Z, Leon LJ, Nattel S. Cholinergic atrial fibrillation in a computer model of a two-dimensional sheet of canine atrial cells with realistic ionic properties. Circ Res. 2002;90:E73-87.
16. Sarmast F, Kolli A, Zaitsev A, Parisian K, Dhamoon AS, Guha PK, et al. Cholinergic atrial fibrillation: IK, Ach gradients determine unequal left/right atrial frequencies and rotor dynamics. Cardiovasc Res. 2003;59:863-73.
17. Kovoor P, Wickman K, Maguire CT, Pu W, Gehrmann J, Berul CI, et al. Evaluation of the role of IKACh in atrial fibrillation using a mouse knockout model. J Am Coll Cardiol. 2001;37:2136-43.
18. Huang CX, Zhao QY, Liang JJ, Chen H, Yang B, Jiang H, et al. Differential densities of muscarinic acetylcholine receptor and IK,ACh in canine supraventricular tissues and the effect of amiodarone on cholinergic atrial fibrillation and IK,ACh. Cardiology. 2006;106:36-43.
19. Tan AY, Li H, Wachsmann-Hogiu S, Chen LS, Chen PS, Fishbein MC. Autonomic innervation and segmental muscular disconnections at the human pulmonary vein-atrial junction: implications for catheter ablation of atrial-pulmonary vein junction. J Am Coll Cardiol. 2006;48:132-43.
20. Atienza F, Almendral J, Moreno J, Vaidyanathan R, Talkachou A, Kalifa J, et al. Activation of inward rectifier potassium channels accelerates atrial fibrillation in humans: evidence for a reentrant mechanism. Circulation. 2006;114:2434-42.

21. Blaauw Y, Tieleman RG, Brouwer J, van den Berg, de Kam PJ, de Langen CD, et al. Tachycardia induced electrical remodeling of the atria and the autonomic nervous system in goats. Pace. 1999;22:1656-67.
22. Takei M, Tsuboi M, Usui T, Hanaoka T, Kurogouchi F, Aruga M, et al. Vagal stimulation prior to atrial rapid pacing protects the atrium from electrical remodeling in anesthetized dogs. Jpn Circ J. 2001;65:1077-81.
23. Miyauchi M, Kobayashi Y, Miyauchi Y, Abe J, Morita N, Iwasaki YK, et al. Parasympathetic blockade promotes recovery from atrial electrical remodeling induced by short-term rapid atrial pacing. Pacing Clin Electrophysiol. 2004;27:33-7.
24. Zhao Q, Tang Y, Okello E, Wang X, Huang C. Cambios diferentes del periodo refractario efectivo auricular y de la tras estimulación vagal más estimulación rápida en venas pulmonares. Rev Esp Cardiol. 2009;62:742-9.
25. Dobrev D, Graf E, Wettwer E, Himmel HM, Hála O, Doerfel C, et al. Molecular basis of downregulation of G-proteincoupled inward rectifying K+ current IK,ACh in chronic human atrial fibrillation: decrease in GIRK4 mRNA correlates with reduced IK,ACh and muscarinic receptor-mediated shortening of action potentials. Circulation. 2001;104:2551-7.
26. Brundel BJ, van Gelder IC, Henning RH, Tieleman RG, Tuinenburg AE, Wietses M, et al. Ion channel remodeling is related to intraoperative atrial effective refractory periods in patients with paroxysmal and persistent atrial fibrillation. Circulation. 2001;103:684-90.
27. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, et al. The G-protein gated potassium current IK, ACh is constitutively active in patients with chronic atrial fibrillation. Circulation. 2005;112:3697-706.
28. Ehrlich JR, Cha TJ, Zhang L, Chartier D, Villeneuve L, Hébert TE, et al. Characterization of a hyperpolarization-activated time-dependent potassium current in canine cardiomyocytes from pulmonary vein myocardial sleeves and left atrium. J Physiol. 2004;557:583-97.
29. Voigt N, Maguay A, Yeh YH, Qi X, Ravens U, Dobrev D, et al. Changes in IK,ACh single channel activity with atrial tachycardia remodeling in canine atrial cardiomyocytes. Cardiovasc Res. 2008;77:35-43.
30. Cha TJ, Ehrlich JR, Chartier D, Xiao L, Nattel S. Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias. Circulation. 2006;113:1730-7.