

Left atrial remodeling in atrial fibrillation – mechanisms, assessment and therapeutic implications

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ABSTRACT

Left atrial remodeling reflects a spectrum of pathophysiological changes that have occurred in atrial fibrillation progression. These changes include alterations at the levels of ionic channels, cellular energy balance, neurohormonal expression, inflammatory response, and physiologic adaptations. There is convincing evidence demonstrating an important pathophysiological association between left atrial remodeling and atrial fibrillation. Measures that will prevent, attenuate, or halt these processes of left atrial remodeling may have a major public health impact with respect to the epidemic of atrial fibrillation. We aim to describe the mechanisms involved in left atrial remodeling, the assessment methods and potential therapeutic options for its reversal, and implications for atrial fibrillation development.

Key words: atrial fibrillation, left atrial, atrial remodeling

INTRODUCTION

Sustained atrial fibrillation (AF), the most common arrhythmia met in medical practice, determines a high morbid-mortality rate and has an evolutionary epidemic tendency. For over a decade it is known that approximately 90% of the AF is initiated by unique or multiple ectopic foci (“triggers”) at the level of the pulmonary veins (1). The evolution of this arrhythmia is progressive. It is estimated that 14-24% of the paroxysmal AF evolves towards to the

persistent form (2,3), and 31% of the patients with paroxysmal or persistent AF progress to permanence, most of them during the first 15 years from their diagnosis (4). □

MECHANISMS OF THE LEFT ATRIAL REMODELING IN ATRIAL FIBRILLATION

Once appeared, AF determines during the first time the atrial electrophysiological and mechanic remodeling through the shortening, mal-adaptation and increase of the dispersion of the atrial effective refractory periods, the

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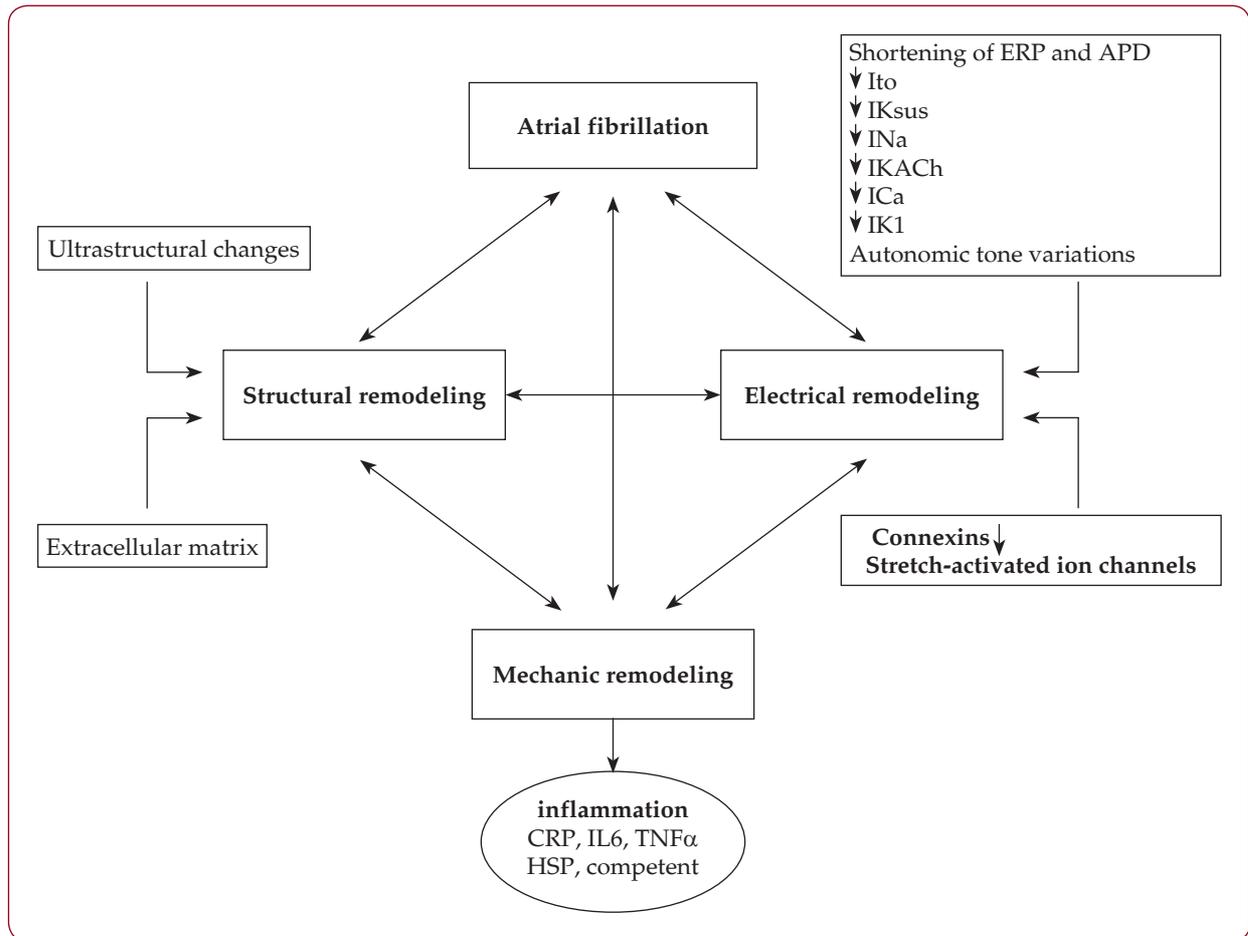


FIGURE 1. The interrelations between the different pathogenic mechanisms involved in atrial remodeling and the development and maintenance of AF (APD indicates action potential duration; ERP-effective refractory period; CRP-C-reactive protein; IL-interleukin; TNF-tumor necrosis factor; HSP-heat shock proteins; Ito-transient outward potassium current; IKsus- sustained outward potassium current; INa-sodium current; IKAch-G protein-coupled inward rectifying potassium current; ICa-L-type calcium current; IK1- inward rectifying potassium current).

depression of the intra-atrial conduction with the loss of the contractile function and then structural remodeling (FIGURE 1) (5). The latter is considered an adaptation process similar to the hibernation of the ventricular myocytes affected by ischemia, with the purpose of extending cellular viability (6). Electrical, mechanic and structural remodeling determines the perpetuation of AF and the progression of the paroxysmal form to the persistent and permanent ones.

Electrical remodeling

Atrial electrical remodeling appears most frequently after 24-48 hours or after months from the AF debut and results in increased and progressive susceptibility, upon new arrhythmia

episodes. The functional and structural atrial modifications that appear after the initiation of the AF facilitate its self perpetuation ("AF begets AF") (7). It means that regardless of the existence or not of initiators ("triggers"), AF will have a tendency to perpetuation, through the decisive contribution of the substrate represented by the atrial myocardium.

During the first 48 hours from the AF onset, electrophysiological processes with important consequences take place at the cellular level (7). The changes of the effective refractory periods, of the intra-atrial conduction as well as the functionality of the sinus node are stages of the atrial electrical remodeling. AF represents a cell stress factor. Physiologically, during the contraction, the calcium ion penetrates the

cells contributing to the cell repolarization. The extremely rapid atrial activation of 350-600/min induces an excess of this ion at the level of cardiomyocytes through the L-type calcium channels. The excessive loading with calcium ions of the myocytes with high fibrillatory activity leads to the decrease in its input current through the L-type calcium channels, which results in the shortening especially of the phase 2 of the action potential. Nevertheless, this shortening together with the excessive number of fibrillatory waves determines important increases in the calcium inflow. In order to avoid the overloading of the cell with this ion, the inactivation of the I_{CaL} currents occurs on a short term and the decreasing of the channels for I_{CaL} occurs on a long term, as compensatory mechanisms. The diminishing of the expression of the L-type calcium channels and myolysis determines the atrial contractile dysfunction. This can be seen first in the lack of the A wave in the atrial post-cardioversion pressure curve. The reduction in time of the L-type calcium currents will be reflected in the shortening of the effective refractory periods and their lack of homogeneity, resulting in the decrease of the length of the fibrillatory waves, the promotion of the micro-re-entries and the increase in the vulnerability of the substrate (8-10). This is the key link of a vicious circle, as the action potential is shortened even more by the shortening of the refractory periods, with their mal-adaptation to high rates. Another essential aspect is the modification of the activity of the specific phosphatases and kinases, with the modulation of the intracellular key proteins involved in the activity of the calcium (as well as the calcineurin). This is to protect the myocyte against the overloading with calcium but creates a substrate for the promotion of the AF and thus another vicious circle emerges.

After the initiation of the AF, other cellular changes occur, such as the decrease in the sodium current, with the possible diminishing of the conduction velocity, the increase in the potassium rectification current, the ultrastructural myocyte acquiring a predominant fetal-type phenotype. The quick sodium channels are submitted to a down-regulation process (the diminishing of their number secondary to the increase in the sodium ions), thus being involved in the slowing of the intra-atrial conduction and the shortening of the wave length (11). There are also alterations of the potassium cur-

rents: the decrease in the output currents (I_{to}, I_{ksus}, I_{kur}) and the ATP-dependant currents (I_{KATP}), the increase in the rectifying input current (I_{k1}) and the decrease/increase in the activated acetylcholine currents (I_{KACH}) (8, 12, 13). The change in these currents alters the membrane potential of repose and the cell repolarization. The persistence of the arrhythmia induces the activation of the calpain (a cysteine protease) in a late phase, the degradation of the L-type calcium channels and of the contractile proteins, with the presence of myolysis. The activation of the cysteine proteases initiates and performs the apoptosis (14). Particularly, the apoptosis of the cardiomyocytes is not complete. Depending on the intensity of the stress to which the atrial myocyte are liable, the activation of the cysteine proteases may induce atrial remodeling through L-type calcium channels and degradation or depletion of the contractile apparatus; this is followed by the shortening of the duration of the potentials of action, myolysis and contractile dysfunction, with the AF persistence (15,16). The heat shock proteins (HSP) – a protein family involved in defending the cell against stress – seem to have the role of preventing atrial remodeling and the progression of the paroxysmal form to the permanent one. HSPB1 may relate to the myofibrils and the ionic channels in order to preserve their function and may inhibit the calpain activity (17).

Structural remodeling

Structural remodeling through the left atrium dilatation increases the surface available to the multiple waves, which together with the interstitial fibrosis (that increases the anisotropy and generates conduction blocks) causes AF to become more and more persistent. The model of multiple waves was revealed in the study of the atrial activation pattern in patients undergoing heart surgical interventions (18). Using first mathematical models and then animal models, it was observed that it takes at least 6 microwaves for AF to become persistent (19). The larger the “caught” atrial mass, the higher the tendency to persistence, and the notion of necessary critical mass is a condition for the perpetuation of the AF. The fast atrial activity determines the intracellular matrix inflammation and the activation of the fibroblasts with fibrosis “in the islands”. Interstitial fibrosis is

generated by the apoptosis of atrial myocytes, the accumulation of glycogen granules, the loss of myofibrils and gap type cell coupling junctions. This may appear in any heart condition inducing atrial dilatation and is accompanied by the increase in the activity of the angiotensin-converting enzyme and angiotensin II, multiplied approximately by 3 (20). The interposition of the fibrosis areas with the normal atrial myocytes leads to the lack of homogeneity and conduction anomalies (unidirectional blocks), with arrhythmogenic potential. A histological study that compared the atrial myocardium placed around the pulmonary veins to the one at the level of the left appendage, in patients with AF associated to the mitral valvular disease, revealed that in the perivenous tissue the interstitial fibrosis is 3 times more intense, the density of the myocardial capillaries is significantly reduced and the oxygen diffusion distance is significantly higher (21). In patients with heart failure (condition that is frequently associated with AF) at atrial level there were areas with reduced or without (“scars”) electrical activity, as well as delays in impulse conduction, which are processes similar to the ones that appear with age.

Atrial structural remodeling is associated with sustained AF and occurs after weeks or

months from the AF initiation, structural alterations were detected both in the preclinical phase and especially in the clinical phase of the AF (TABLE 1). Parts of the structural changes that take place during the evolution of this arrhythmia are irreversible. The AF-induced structural changes in atrial myocytes include most frequently: increase in cell size, perinuclear accumulation of glycogen, central loss of sarcomeres (myolysis), changes in mitochondrial shape and alterations in connexin expression (22-25). In patients submitted to cardiac surgery for mitral valvular disease, fibrosis predominates around pulmonary veins, the location of the ectopic sources that initiates frequently AF (25). In AF the over expression of the matrix metalloproteinase’s and the type I and III collagen, the atrial “stretch” and the insufficient ventricular diastolic filling contribute to the apparition of structural alterations of the atrial myocardium (26-29).

Atrial fibrillation determines also the functional remodeling of the sinus node, which was revealed by the prolonged sinus pause after the electrical cardioversion. Since the term “atrial remodeling” was used for the first time by Wijffels in 1995, this concept has been evolving remarkably and brought an essential contribution to the understanding of the AF mecha-

	Structural changes
Preclinical phase	Reduction of the connexins 40 expression Homogeneous distribution of the nuclear chromatin Accumulation of glycogen around the nucleus Localization of cellular proteins Alteration of the size and form of mitochondria’s Fragmentation of the sarcoplasmatic reticulum Myolysis The increase in the cell size Atrium enlargement
Clinical phase	Severe cell degeneration Up-regulation of matrix metallo-proteinases Down-regulation of the tissue inhibitor of metallo-proteinase The increase in the expression of the active form of matrix metallo-proteinase 9 and of the proteinase-1 chemoattractives for monocytes Apoptosis and myolysis The increase in the I- and III-type collagen expression “Islands” fibrosis Interstitial fibrosis around the pulmonary veins Myocarditis Non-inflammatory cardiomyopathy The increase in the antero-posterior diameter of the atrium

TABLE 1. Structural changes detected in patients with AF

nisms through animal and experimental clinical models (30). Atrial remodeling as a therapeutic target may become effective in the prevention or delay of the AF apparition.

Mechanic remodeling

The mechanic (contractile) remodeling is initiated as fast as the electrical one, namely during the first 48 hours from the AF onset. Both the reduced release of the calcium ion secondary to the “down-regulation” of the responsible channels and the sarcomeres loss (myolysis) are contributors of contractile remodeling. The loss of the mechanic atrial activity will induce atrial dilatation and the formation of thrombus, as well as the AF progression through the creation of a larger space of perpetuation of the fibrillatory waves. The recovery of the contractile activity after the conversion to sinus rhythm is more difficult than the reverse electrical remodeling due to the loss of sarcomeres. Reverse mechanic remodeling, namely the recovery of the mechanic function of the atrium after the conversion to sinus rhythm occurs in a very variable period, of a few hours/days up to 3-4 weeks. It is unknown why this chronologic evolution is. In a study carried out at Louvain Catholic University of Belgium regarding the epicardial ablation of the ganglionated plexi concomitant with the isolation of the posterior wall of the left atrium in patients with persistent AF, the recovery of the mechanic function of the left atrium was revealed echocardiographically (due to the presence of the A wave in transmitral Doppler) in some patients immediately after the conversion to sinus rhythm (31). □

ASSESSMENT OF THE LEFT ATRIAL REMODELING IN ATRIAL FIBRILLATION

The assessment of the atrial structural remodeling is carried out – by practical judgments – most frequently echocardiographically, by measuring a linear dimension, namely the antero-posterior diameter (2D or M mode). The interest of the more complex assessment of the size of the left atrium grew after the correlation of its antero-posterior diameter with its angiographic dimension was ascertained (32). The advancement of the ultrasound technology allowed the measuring not only of the linear dimensions but also of the area and volume of

the left atrium bi-dimensionally and tri-dimensionally. The area may be measured both in the 4 and 2 apical chamber views, excluding the ostium of the pulmonary veins and the appendage. Its volume is a parameter that uses the area and/or linear dimensions in calculations.

The dilatation of the left atrium in the AF, secondary to the “stretch” phenomenon, is asymmetric due to its neighboring structures (the aorta, the spine etc.) and the “atrialization” of the antrum of the pulmonary veins. Thus the atrial dilatation will have different consequences over the anatomic segments of the left atrium, determining the change of its morphology (33). The mitral annular, the mitral-aortic and the inter-atrial septum are less susceptible to dilatation as they are relatively fixed. Due to the lack of the fibrous components, the rest of the atrial myocardium, namely the junction of the pulmonary veins and their antrum, will modify their morphology (34). The result will be the change in the atrial geometry, the form of the left atrium dilated becoming trapezoidal (35). The electrocardiographic evaluation through a single linear dimension (the antero-posterior diameter) is inappropriate in such situations; the modification of the geometry of the left atrium thus imposed a more complex evaluation. The measurement of the area or indexed volume as a ratio between the atrial volume and the body surface is a parameter closer to its real size, allowing comparisons regardless of gender or body weight.

The American Society of Echocardiography and the European Association of Echocardiography recommend the evaluation of the left atrium as its indexed volume, as a marker of cardiovascular risk, indicator of the existence of a heart condition and predictor of the cardiovascular complications (36). The 2 above mentioned echocardiography societies recommend for the measurement of the atrium volume the use of the ellipsoid method or the Simpson method (as the disks method used in calculating the volume of the left ventricle). Moreover, they consider that this determination should become routine in the echocardiography laboratories.

The imagistic methods such as the computer-tomography and the magnetic resonance imaging offered new ways of study of the morphology and structure of the atria and marked out the limits of the echocardiography in evaluating them. The echocardiographic

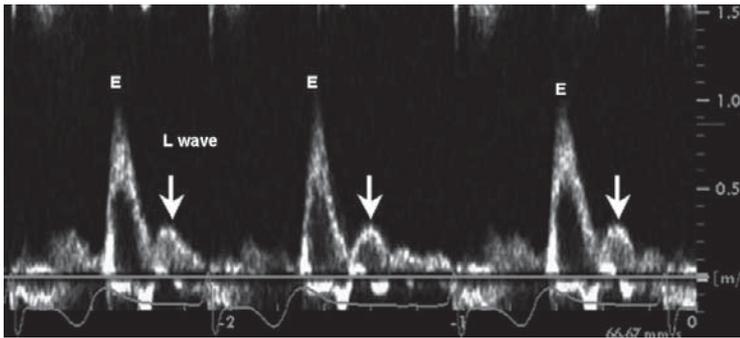


FIGURE 2. The presence of the mitral L wave in a patient with persistent AF and LA enlargement (with the absence of the A wave)

measurement of the left atrium volume is correlated to the computer-tomography one, the biplane contrast ventriculography and the magnetic resonance imaging (37-39). Besides of the good correlation, the tendency of the echocardiography to underestimate the left atrium volume also stood out, as it cannot appreciate correctly its maximum sizes (40). Echocardiographically the size of the left atrium is up to 40% underestimated in comparison to the three-dimensional reconstruction by computer tomography (41).

The echocardiographic functional evaluation of the left atrium may be obtained by assessing the atrial ejection fraction, the flow in the pulmonary veins and the mitral one. The atrial contractility is correlated to the maximum velocity of wave A and the velocity-time integral. The evaluation through the trans-esophageal of the velocity of the flow in the left appendage through pulsed Doppler offers additional information. The maximum velocity during the atrial contraction is correlated to the contraction force of the appendage when it is emptied. To this purpose, the determination of the atrial “strain” (deformation/tension of the wall) may also be used (42).

Other non-invasive parameters that can give information about the atrial remodeling are the following:

- on the surface electrocardiogram (ECG): the analysis of the rates of the fibrillatory activity, the P wave on the ECG mediated by the signal, markers of the autonomous tonus (heart rate variability – HRV), extrasystoles with P/T wave;
- on the intra-atrial electrograms: their morphology and amplitude, the analysis of the rates of the fibrillatory activity;

- in the blood: the collagen or its metabolites; mediators of the inflammation (TNF- α , interleukins, C-reactive protein, adhesion molecules), platelet markers (factor von Willebrandt, thrombocyte markers, fibrinolysis indices), neurohormonal factors (angiotensin II, aldosterone, the atrial natriuretic peptide, B-type natriuretic peptide);
- molecular and histological markers: the size of the atrial myocytes, interstitial fibrosis, ultrastructural modifications in atrial myocytes, components of the signaling ways.

The echocardiographic identification of mitral wave L (representing the mid-diastolic ventricular filling) in patients with persistent AF is relatively common and indicates an advanced diastolic dysfunction (FIGURE 2) (43). The mitral wave L prevalence is associated with higher E/E' ratio, higher level of B-type natriuretic peptide and with the left atrium enlargement.

There are some new echocardiographic techniques like tissue Doppler imaging and 3D or 4D echocardiography useful for the evaluation of regional myocardial function or the interstitial fibrosis level and also to assess the cardiac chambers volumes (44). □

LEFT ATRIUM REMODELING AS POTENTIAL THERAPEUTIC TARGET IN ATRIAL FIBRILLATION

Drugs that modify the renin angiotensin-aldosterone system appear to have particularly potent effects on LA remodeling (as shown in TABLE 2), beyond their beneficial effects on blood pressure regulation (45-58). The therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACE-Is/ARBs) in patients with left atrial dilatation may induce reverse structural remodeling (regression of the dilatation), the diminishing of the progression of the atrial fibrillation from paroxysmal to persistent and the decrease in the number of the relapses of this arrhythmia (59-61). Thus, the irbesartan and amiodarone treatment, after the electrical cardioversion, determines a relapse rate lower than the amiodarone treatment exclusively (62). The angiotensin II receptor blockers combined with diuretics decrease the AF incidence after the catheter ablation of the typical atrial flutter (63). The mechanisms through which the renin angiotensin

Therapeutic agents	Mechanisms
Aldosterone receptors antagonists (45-48)	<ul style="list-style-type: none"> – modify the extracellular matrix, especially the collagen deposition and fibrosis – reduce atrial hyperexcitability – inhibition of vascular Ang-I/ Ang-II conversion
Angiotensin-converting enzyme inhibitors (49-52, 59,60)	<ul style="list-style-type: none"> – effects on atrial stretch – decrease interstitial fibrosis – decrease inflammation
Ang-II receptor blockers (51, 53-64)	<ul style="list-style-type: none"> – reduce interstitial fibrosis – reduce myolysis – loss of contractile proteins
Statins (59,65-69)	<ul style="list-style-type: none"> – ameliorate the inflammatory process – inhibits profibrotic atrial fibroblast responses – antioxidant effects – plaque stabilization
Atrial selective blockers (72-95)	<ul style="list-style-type: none"> – act on ionic channels specific to the atrium: Ito, INa, I_{Kur}, I_{KACH}, I_{Ks} and increase the atrial refractoriness
Glucocorticoids (70,71)	<ul style="list-style-type: none"> – ameliorate the inflammatory process
Omega-3 poly-unsaturated fatty acids (97)	<ul style="list-style-type: none"> – attenuate atrial fibrosis
Pirfenidone (96)	<ul style="list-style-type: none"> – antifibrotic, anti-inflammatory

TABLE 2. Therapeutic agents studied in atrial remodeling

aldosteron system delays the appearance, prevents the permanent character or reduces the relapses in AF are the following: decrease in the left atrium pressure and the wall stress, prevention of the left atrial and ventricular structural remodeling (fibrosis, dilatation, hypertrophy), inhibition of the neuro-hormonal activation, decrease in the arterial pressure, prevention and improvement of the heart failure, prevention of the hypokaliemia (64).

Statins are well-known for their lipid lowering ability and consequently their cardioprotective effects. A few studies of statins therapy in patients with AF have been published (65). The overall results of these trials support the idea that statins therapy might affect the natural history of AF by ameliorating the inflammatory process (66-69).

Most of the studies involving glucocorticoids as anti-remodeling therapy of the atria in AF were done in patients undergoing cardiovascular surgery, and the results were equivocal (70,71).

The selective blockers of the atrial potassium channels, such as the dofetilide, increase atrial refractoriness, restore and maintain sinus rhythm without adverse effects (72). The block-

ing of potassium channels both, at atrial and ventricular level is carried out with the risk of the QT interval increasing and torsade de pointes induction. The selective action at the level of potassium channels existent only in the atrial myocardium avoids these proarrhythmic effects.

The voltage-dependent potassium channels are involved in the atrial repolarization through the following currents: I_{to}-transient outward potassium current, output-rectifiers with ultrarapid delayed potassium current (I_{Kur}), rapid delayed potassium current (I_{Kr}) and slow delayed potassium current (I_{Ks}), inward rectifying potassium current (I_{K1}) and G protein-coupled inward rectifying potassium current (I_{K,ACh}). Parts of these channels are submitted to electrical remodeling in AF. In chronic AF, the I_{to} currents amplitude reduction is associated to the decrease messenger RNA involved in the synthesis of α subunit of the channel (Kv4.3). The data related to I_{Kur} are still unclear and I_{Kr} and I_{Ks} appear not to be involved. The I_{K1}-type currents are amplified through the increase in the synthesis of the proteins of the subunit α of Kir2.1/Kir2.3 of the channel in question. The activated rectifying currents of acetyl-choline

(I_{K,ACh}) diminish in AF by the decrease of the synthesis of the subunit Kir3.1/Kir3.4 of the channel. The I_{Kur} and I_{K,ACh} channels are to be found at atrial level. Starting from this assertion, there are ongoing a series of preclinical studies with “atrial specific” antiarrhythmics with these channels as target. Nevertheless the properties of the atrial channels may change along upon the electrical remodeling and thus the effects of the antiarrhythmics may differ in sinus rhythm from chronic AF, but not necessarily from the recently installed one. A good example is AVE0118, a derivative of bipyridine, which induces the sinus rhythm on animal models with AF but not on humans. Electrical remodeling may limit the using of the I_{Kur} channel as a possible therapeutic target in AF. Vernakalant is part of the same group but also blocks the sodium channels, which is why it converts and maintains the sinus rhythm both on animal and human models.

The studies currently carried out focused on the agents with selective action on these ionic, exclusively atrial channels, blockers of multiple ionic channels and modifiers the gap junction. Agents such as vernakalant, AVE0118, AVE1231 and AZD7009 act on some ionic channels specific to the atrium (I_{to}, I_{Na}, I_{Kur}, I_{K,ACh}, I_{Ks} – essentially involved in the repolarization at fast heart rates and I_{Kr} – contribute decisively in the repolarization at physiological heart rates) (73-83). With minimal effects on the ventricular repolarization, the blocking of these currents increase the atrial effective refractory period, favors restoration of sinus rhythm. Azimilide, dronedarone and tedisamil, through the blocking of some ionic channels in different stages of the action potential, optimize the antiarrhythmic action with minimal proarrhythmic effects (84-90). Agents such as rotigaptides (ZP123) and AAP10 act on the connexins (subunits of the gap junctions, which facilitate the electrical communication between cells) and favor the normal intercellular conduction (91-95). The 40 and 43 connexins are the main components of the gap junctions at the level of the human atrium involved upon the appearance of AF.

The vagal activation determines the shortening of the action potential and the effective refractory period; it increases the dispersion of the atrial repolarization and it creates an arrhythmogenic underlayer through the I_{K,ACh} type channels. In the chronic atrial fibrillation

there was noticed a reduction of the muscarinic receptors for I_{K,ACh}. Tertiapin, a selective blocker of I_{K,ACh}, prolongs the duration of the action potentials and it converts the atrial fibrillation induced by rapid pacing into sinus rhythm. Ideally, such an agent should block selectively only the constitutive element of the I_{K,ACh} with no effect over the component activated by the agonists because the latter modulates the function of the pacemaker cells and the conduction of the impulses at the level of the sinoatrial node. But the blocking of the I_{K,ACh} currents leaves the sympathetic activity non-counterworked with the increase of the conduction at the level of the atrioventricular node. The long-term use of the quinidine confirms this mechanism. These ionic channels are not found at ventricular level; the constitutive component of the I_{K,ACh} appears in case of atrial remodeling from the atrial fibrillation and its selective suppression will not create proarrhythmic effects.

Pirfenidone is a potential antifibrotic agent that can prevent development of AF substrate by reducing TGF- β 1 (transforming growth factor) levels (96). Recently, omega-3 poly-unsaturated fatty acids have been found to prevent the cardiac heart failure-associated AF substrate (97).

Many things remain still uncertain regarding the remodeling of the ionic channels in the atrial fibrillation; one thing is certain: the amiodarone, a blocker of the potassium channels and not only, is the most efficient antiarrhythmic in this arrhythmia with epidemic tendency.

Although the statins and ACE-I/ARBs (so-called “up-stream” therapies) have shown the most promise by modulating the inflammatory effects and inhibiting cardiac remodeling, the current evidence does not support the administration of statins and ACE-I/ARBs for the sole purpose of preventing AF, because many of the current published reports available were retrospective and observational in nature, with limited sample size. \square

CONCLUSION

Left atrial remodeling reflects a spectrum of pathophysiological changes that have occurred in atrial fibrillation progression. These changes include alterations at the levels of ionic channels, cellular energy balance, neurohormonal

expression, inflammatory response, and physiologic adaptations. There is convincing evidence demonstrating an important pathophysiological association between left atrial remodeling and atrial fibrillation. Measures that

will prevent, attenuate, or halt these processes of left atrial remodeling may have a major public health impact with respect to the epidemic of atrial fibrillation. □

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