REVIEW

Atrial remodeling in atrial fibrillation - independent rhythm evaluation

Andreea Cuculici[1], Eduard Apetrei[1]

Abstract: Atrial fibrillation is the most prevalent rhythm disorder ,associated with electrical, structural and contractile remodeling of the atria.The progression of atrial fibrosis is the symbol of structural remodeling and considered the substrate of atrial fibrillation recurrence. Left atrial (LA) size is a marker of atrial structural remodeling and is associated with increased risk for atrial fibrillation and cardiovascular disease and has a prognostic importance. Left atrial function may be related to atrial fibrillation, irrespective of left atrium structure.Left atrium function index, an echocardiographic index of LA structure and function, rhythm independent measure, may predict and better characterize atrium remodeling and can be used for detecting arrhythmia recurrence.

Keywords: atrial fibrillation, atrial remodeling, echocardiography, left atrium, atrial function.

Rezumat: Fibrilația atrială este cea mai răspândită aritmie cardiacă și se asociază cu remodelarea electrică, structurală și contractilă a atriilor. Progresia fibrozei atriale este simbolul remodelării structurale și este considerată substratul recidivei fibrilației atriale. Dimensiunea atriului stâng reprezintă un marker al remodelării structurale atriale și este asociată unui risc crescut de fibrilație atrială și de boli cardiovasculare, având o importanță prognostică. Funcția atriului stâng poate fi asociată cu fibrilația atrială, independent de structura atriului stâng. Indicele funcției atriului stâng, un indice ecocardiografic al structurii și funcției atriului, evaluare independentă de ritm, poate prezice și poate caracteriza mai bine remodelarea atriului și poate fi utilizat pentru detectarea recurenței aritmiei.

Cuvinte cheie: fibrilația atrială, remodelare atrială, ecocardiografie, atriul stâng, funcția atrială.

INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. While significant progress has been made in the last years to reduce the burden of AF on morbidity and mortality, this arrhythmia remains one of the leading causes of stroke, heart failure, sudden death worldwide[1]. With the ever-ageing population, the prevalence of AF is also increasing in the coming years and for effective care of patients with AF new information is continually generated and published[2].

Similar to the increasing prevalence of AF, the incidence of AF is estimated to double with each passing decade of adult life[3]. Estimates suggest an AF prevalence of approximately 3% in adults aged 20 years or older, with greater prevalence in older persons and in patients with conditions such as hypertension, heart failure, coronary artery disease (CAD), valvular heart disease, obesity, diabetes mellitus, or chronic kidney disease (CKD). While males have greater risk of developing AF than females, the independent risk factor for death that the arrhythmia causes is lower in males (1.5 vs. 1.9 relative risk)[4].

PATHOPHYSIOLOGY

Changes in atrial structure and function that can act as a substrate for atrial arrhythmias are defined as arrhythmogenicatrial remodeling. Various diseases like underlying cardiac conditions, systemic processes, aging, or even AF itself can trigger atrial remodelling[5]. There are four main pathophysiological mechanisms

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contributing to AF 1-4: electrical remodeling, structural remodeling, autonomic nervous system changes, and $Ca2^{+}$ handling abnormalities.

Many forms of atrial remodeling promote the occurrence or maintenance of AF by acting on the fundamental arrhythmia mechanisms illustrated in Figure 1.

Both rapid ectopic firing and reentry can maintain AF. Reentry requires a vulnerable substrate, as well as a trigger that acts on the substrate to initiate reentry. Ectopic firing contributes to reentry by providing triggers for reentry induction. Atrial remodeling has the potential to increase the likelihood of ectopic or reentrant activity through a multitude of potential mechanisms[6].

Electrical remodeling. Electrophysiological remodelling is represented by the shortening of the duration of the action potential and refractory period. Evan a few minutes of rapid atrial rates can result in intracellular calcium overload, which decreases the L-type calcium current (ICaL) because of a decreased trans-sarcolemmal calcium gradient and calcium induced inactivation of the L-type calcium channel, with consequent reduction in the IcaL[7]. This phenomenon was named „pseudo-remodelling". The behaviour of L-type calcium channels can be influenced by sustained high atrial rates – leading to downregulation and a subsequent decrease in ICaL favoring short atrial refractory periods. In long standing AF, atrial tissue (obtained during cardiac surgery) demostrated a similar reduction in ICaL and inactivation of calcium channels[7]. Several studies have shown that this fall in the IcaL current is the cornerstone for electrical remodelling due to AF – while other currents play only a secondary role[8].

Altered gene expression resulting in changes in ion channel density and function has lasting effects (from hours to days) over the ionic currents and is the real substrate for electrical remodelling[8].

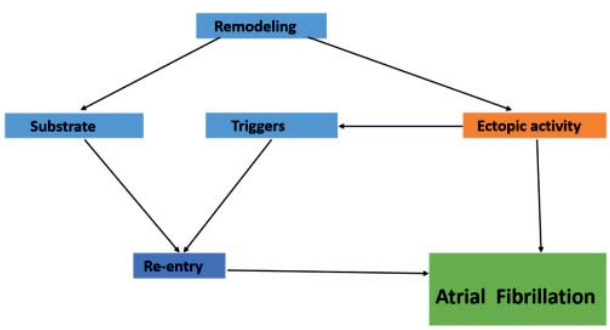

Figure 1. Fundamental arrhythmia mechanisms.

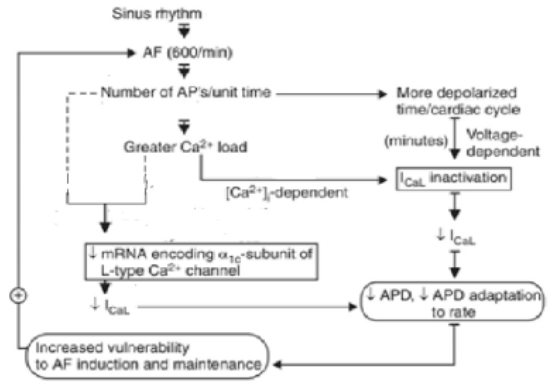

Figure 2. The modification of the calcium current by rapid atrial activation (AF atrial fibrillation, AP action potential, APD action potential duration) – modify by G.L. Botto[26].

Autonomic Nervous SystemChanges. Disturbances in the autonomic nervous system can lead both to the initiation and to persistence of AF since it controls directly the atrial electrical activity. Increased adrenergic drive may play a critical role in AF due to promotion of ectopic activity favored by a suscepitble substrate secondary to atrial remodelling. Moreover, AF induced hyperinnervation is another consequence of remodeling and adds to the vulnerable AF substrate[10].

Structural remodeling. Atrial structural remodeling is due to increased interstitial fibrosis adding to cardiac structural alterations[11], in the end leading to atrial enlargement and fibrosis. At the basis of atrial structural remodeling may be any process that favors the development of atrial fibrosis. Fibrosis promotes AF by interrupting fiber bundle continuity and causing local conduction disturbances[12].

At cellular level, the process is initiated by various profibrotic factors including Ang II, transforming growth factor beta, and platelet-derived growth factor - that may act individually or synergistically[13] to promote fibrosis.

Atrial fibrosis appears to be a common endpoint of a wide range of AF-promoting conditions and may predict recurrences[14]. Furthermore, the relation between AF and fibrosis is bidirectional, since AF appears to promote atrial fibrosis[15], which contributes importantly to therapeutic resistance in patients with long-standing arrhythmia[16].

Functional remodeling. Atrial functional remodeling results in decreased function independent of alteration in LA size. Atrial tachyarrhythmias, alterations in LA pressure may result in functional changes. LA functional remodeling may also be associated with

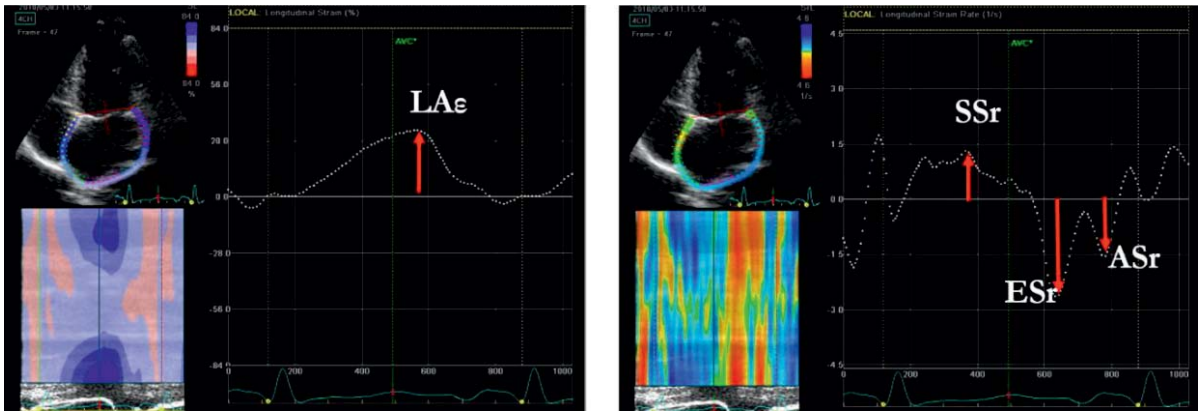

Figure 3. Speckle tracking 2D strain echocardiography- used to assess Left atrial reservoir function by [LAε (left atrial systolic strain) and SSr (systolic strain rate)], LA conduit function by (ESr = Eary diastolic strain rate), LA booster pump by (ASr=Late diastole strain rate).

the development of LA fibrosis and consequent structural changes.

The process in wich LA remodeling demonstrates the concept of improving or restoring atrial function is named Reverse remodeling. LA reverse remodeling has been more definitely described in the early stages of LA structural and functional remodeling[17]. Noninvasive imaging would be the most practical option to monitor LA reverse remodeling, but the extent of structural change, i.e., percentage reduction in LA volume, and the specific functional parameter(s) to be utilized are poorly defined.

The left atrium is considered a biomarker for adverse cardiovascular outcomes, particularly in patients with left ventricular diastolic dysfunction and atrial fibrillation in whom left atrial enlargement is of prognostic importance[18].

LA remodeling is monitored in clinical practice using various noninvasive imaging modalities However, specific monitoring of LA remodeling has not been incorporated into clinical decision-making. From the Framingham Heart study, LA remodeling, was defined as an encrease of LA diameter wich was 1 of 3 independent echocardiographic predictors for future development of AF[19]. Another reports have used a change in LA volume >15% compared with baseline, by echocardiographic assessment or cardiac magnetic resonance (CMR), as a result of LA remodeling. Alterations in LA function (LA strain) may precede changes in LA volume, both in normal subjects[20] as well as in diseased states[21]. More, a combination of structural and functional remodeling may be more sensitive in monitoring diseased states. Yoon et al.[22] evaluated LA volume and function by strain analysis demonstrating that LA indexed volume >34 ml/m^2 and LA strain <31% had increase for patients with paroxysmal AF to develop persistent AF.

Another echocardiographic parameters have been used to evaluate atrial function including the peak A wave velocity of transmitral flow in late diastole (obtained by pulsed wave Doppler and its velocity time integral (VTI). The fraction of atrial contribution (from transmitral flow)[23] was estimated as the A wave VTI as a fraction of total mitral inflow VTI, has also been an established marker of atrial function. More recently the A0 velocity using Doppler tissue imaging has been used as a global measure of atrial function. The peak A0 velocity represents intrinsic atrial contractility and has been reduced in atrial dysfunction similar to the peak A wave velocity. The problem with these parameters is that they only can be be easily measured in sinus rhythm and are often not evaluated in AF and this makes the comparison of atrial function sinus rhythm vs atrial fibrillation, often difficult.

An echocardiographic evaluation of atrial function wich is rhythm independent was described to be LA

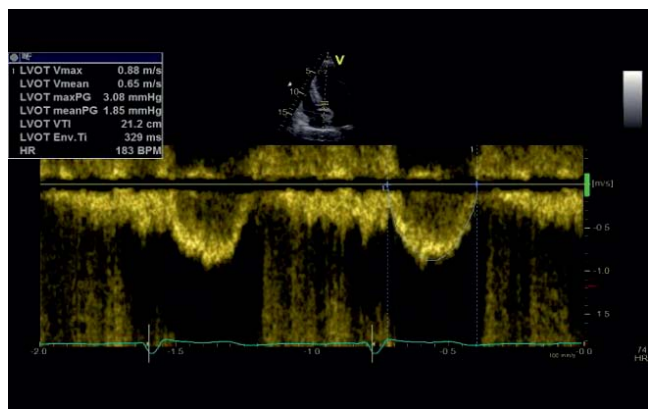

Figure 4. Pulsed wave doppler. Interrogation in LVOT used to measureVTI (Left ventricular outflow tract velocity time integral measure).

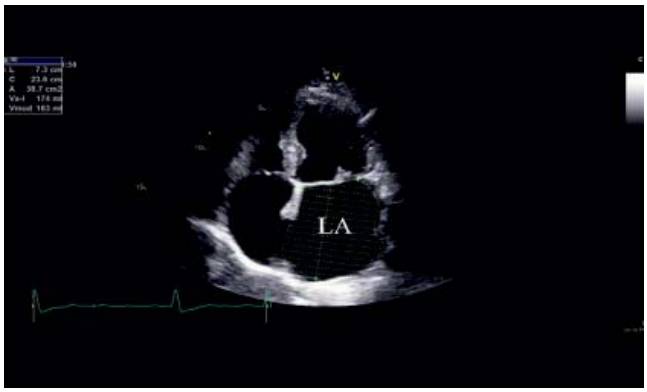

Figure 5. 2D echocardiography - LA maximum volume in the apical 4 chamber view.

function index (LAFI), a marker who incorporates analogues of cardiac output, LA size and atrial reservoir function.LAFI is inversely proportional to LA size and directly proportional to LA reservoir function and stroke volume. This marker is calculated as a ratio, LAFI=LAEF (LA emptying fraction) x LVOT-VTI (cm)/ LAESVI (and LAESVI is the largest LA volume measure in ventricular systole (LAESV) in ml indexed to body surface area or ml/m)[24].

LAFI was associated with AF and CVD and remained associated with them even among those with normal LA size, which persisted after adjustment for clinical prediction scores and echocardiographic measures. So, we have the hypothesis that LAFI, beyond LA structure can be a predictor of AF and CVD events[25].

Left atrial function index was associated with an increased risk of developing incident atrial fibrillation independent of validated clinical risk prediction scores and echocardiographic measures of adverse cardiac remodeling. Left atrial function index can be measured using widely available 2-dimensional echocardiography and the studies demonstrated independent association of left atrial function index with adverse outcomes even in the presence of normal left atrial size[25].

CONCLUSIONS

The evaluation of LA size and function provides a marker of cardiovascular disease status that can be used to quantify the structural and functional remodeling. LA remodeling represents a state of maladaptive deterioration whereas reverse remodeling reflects improvement in response to medical or nonmedical intervention, but clear definitions are required. There are some measure to evaluate atrial function and traditional parameters are rhythm dependent. The LAFI is a rhythm independent measure of atrial function and may be a more sensitive marker of changes in atrial function such as in AF.

Conflict of interest: none declared.

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