Atrial fibrillation – novel insights from pathophysiology

An article from the series «Atrial fibrillation – update 2014»

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Summary

Pathomechanisms underlying atrial fibrillation (AF) are very complex and include various electrical and structural remodelling processes involving focal ectopic activity of atrial cells and reentry mechanisms through atrial tissue. This article reviews basic mechanisms related to AF and gives an update on hypotheses, which are currently thought to provide the most comprehensive concepts.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice occurring at any age with a prevalence rising from 0.7% in the age group 55 to 59 years to 17.8% in those aged 85 years and above [1]. The development of AF is associated with substantial morbidity and mortality and it behaves as a progressive disease in which the arrhythmia itself may induce further structural changes and a worsening in the underlying diseases, thus creating a vicious circle [2, 3].

Currently, many ways are used to describe and classify AF but these classifications, although useful in a clinical setting, remain arbitrary and eventually do not relate to underlying arrhythmogenic mechanisms. Such heterogeneity has brought up difficulties in comparing different therapeutic strategies and one study or trial with another.

Further, present therapeutic approaches to AF still have major limitations with regards to efficacy and significant adverse effect liability. These limitations have inspired substantial efforts to develop our understanding of the mechanisms underlying AF, with the premise that better mechanistic insights will lead to innovative and improved therapeutic approaches [4]. In fact, our understanding of AF pathophysiology has progressed significantly over the past 10 to 15 years thanks to different advanced mapping modalities and animal models and not the least through an increased awareness of the role of "structural and electrical atrial remodelling", which promotes AF by acting on fundamental arrhythmia mechanisms: focal ectopic activity and reentry. In this context, two mechanistic principles have gained much attention: factors triggering the onset and factors perpetuating AF [5]. These observations finally led to the notion and clinically gross generalisation that patients exhibiting frequent paroxysmal AF episodes may predominantly have factors triggering AF, while those with persistent AF rather have factors maintaining AF. However, much evidence has been gathered in recent years, highlighting a considerable overlap of these mechanisms; e.g., a patient with selfterminating paroxysmal AF may also have clearly identifiable "electrically remodelled" atrial structures rendering AF more inducible and sustained, while patients with persistent AF may be treated with a substantial success by elimination of a single triggering focus/multiple foci or reentrant circuit/rotor [6, 7].

Electrophysiological properties / electrical remodelling

In general, AF is associated with a variety of conditions and established cardiovascular risk factors that may cause structural and/or electrical (ion-channel) remodelling (table 1) [8]. In addition, AF itself causes ionic current remodelling playing a significant role in AF pathophysiology. Atrial electrical properties are modified by affecting expression and function of ion-channels, pumps, and exchangers, thus creating a reentryprone substrate and promoting arrhythmia. This concept, known as atrial tachycardia remodelling (ATR) was first described in animal models showing that long-term rapid atrial pacing or maintenance of AF favours the occurrence and maintenance of AF ('AF Begets AF') [9, 10]. The molecular mechanism of ATR consists of a series of modifications that result in refractory period shortening due to action potential duration (APD) abbreviation: (1.) decreased L-type Ca^{2+} – current, (2.) increased inward-rectifier K⁺ current, and

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Table 1

Risk factors and possible associated structural and electrical remodelling processes (modified from [8]).

| Risk factor | Possible remodelling process |
|-------------------------------|---|
| Age | Structural remodelling |
| Male sex | lon currents involved in repolarisation |
| | Structural remodelling |
| Arterial hypertension | Structural remodelling |
| Valvulopathy | Structural remodelling |
| Heart failure | Structural remodelling |
| | Abnormal calcium handling |
| Coronary artery disease with: | |
| – Acute atrial ischaemia | Conduction slowing, block |
| - Prior atrial infarction | Structural remodeling |
| | Abnormal calcium handling |
| Obesity | Structural remodeling |
| Obstructive sleep apnea | Structural remodeling |
| Smoking | Structural remodeling |
| Endurance exercise | Structural remodeling |
| | Autonomic changes |
| Diabetes mellitus | Structural remodeling |
| | Autonomic changes |
| Thyroid disease | Structural remodeling |
| | Ion current remodeling |
| | |

(3.) abnormal expression/distribution of the gap junction connexin hemichannels [11].

Abnormal automatic activity occurs when an increase in time-dependent depolarising inward currents carried by Na⁺ or Ca²⁺ (making the cell interior more positive) or a decrease in repolarising outward currents carried by K⁺ (which keep the cell interior negative) causes progressive time-dependent cell depolarisation. When threshold potential is reached, the cell fires, producing automatic activity. If automatic firing occurs before the next normal (sinus) beat, ectopic atrial activation results [12].

Clinically typical short-cycled ectopic atrial foci (Pon-T) are thought to arise via triggered activity, most typically caused by delayed afterdepolarisations (DADs), but in some cases by early afterdepolarisations (EADs). DADs are membrane potential oscillations occurring after full repolarisation of the triggering action potential. They constitute the most important mechanism of focal atrial arrhythmias and are favoured by conditions producing Ca^{2+} overload, like ischaemia, beta-adrenergic stimulation, low extracellular K⁺ concentration, and tachycardia [13, 14]. They result from abnormal diastolic leak of Ca^{2+} from the sarcoplasmic reticulum (SR) via Ca^{2+} release channels known as ryanodine receptors [15]. Excess diastolic Ca^{2+} is handled by the cell membrane Na⁺, Ca^{2+} -exchanger (NCX), which transports three Na⁺ ions into the cell per single Ca²⁺ ion extruded, creating a net depolarising current (called transient inward current, or I_{ti}) that produces DADs - large enough to reach threshold for ectopic firing. Repetitive DADs cause focal atrial tachycardias. Conversely, EADs are membrane oscillations occurring during phase 2 or 3 of the action potential. They originate when action potential duration (APD) is excessively prolonged and cell membrane Ca²⁺ currents recover from inactivation and allow Ca²⁺ to move inward, thus generating a new action potential upstroke [16]. Myofibroblasts may increase reentry potential of adjacent myocardial cells, bringing them nearer to threshold to fire and to initiate focal activity. Ectopic activity can be transient, manifesting as isolated ectopic beats or sustained causing tachycardia (fig. 1).

Tissue properties / structural remodelling

Structural remodelling is characterised by atrial enlargement and tissue-fibrosis. Morillo and colleagues first described structural modifications in a dog model of atrial tachypacing [10]. Electron microscopy showed increase in the number and size of mitochondria and disruption of the sarcoplasmic reticulum. Enlarged nuclei and dilatation of the rough endoplasmic reticulum were also observed. Ausma and colleagues described structural changes during prolonged AF in a goat model [17]. They found dedifferentiation with depletion of contractile material (sarcomeres) and accumulation of glycogen but rather multiple small mitochondriae. The cells did not show atrophy, on the contrary, they were enlarged and no degenerative changes or alterations in the extracellular matrix were observed. Nevertheless, studies done in dog and human atria did show degenerative changes and evidence of myocyte apoptotic and necrotic cellular death [18–20]. The clinical implication of this difference would be reversibility in the case of dedifferentiation as compared to irreversibility for degeneration. Atrial fibrosis is a common feature of many atrial fibrillation precursors



Figure 1

Focal ectopy / triggered activity.

A EAD based on prolonged repolarisation.

B DAD based on altered Ca²⁺-handling.

such as congestive heart failure, ischaemic heart disease, valve disease, senescence and atrial fibrillation itself [21]. In fact, the persistence of AF is correlated to the amount of fibrosis and contributes to therapeutic resistance in long standing arrhythmia [22, 23]. Fibrosis basically consists of extracellular matrix (ECM) protein deposition by fibroblasts, which are non-excitable cells and the most frequently found cells in the heart [24]. This ECM creates a barrier to impulse propagation. Besides, interactions between cardiomyocytes and fibroblasts through gap junction creation may cause arrhythmogenic changes in cardiomyocyte bioelectricity and conduction properties [25-28]. On the other hand, it has been proven that rapid activation of atrial cardiomyocytes induces fibrosis, thus creating a cycle of arrhythmia and fibrosis [29]. Structural remodelling only seems to be reversible during the first phases of the arrhythmic disorder, but its extent is crucial because it may reach a threshold beyond which sinus rhythm can no longer be restored. Atrial enlargement is very often present in AF and a strong independent predictor for the development of AF [30]. It can in fact be a cause or a consequence of AF and can be partially reversed after restoration of sinus rhythm [31, 32].

Focal ectopic (triggered) activity – initiation of atrial fibrillation

Clinical studies have shown that up to 94% of atrial triggers that initiate frequent paroxysms of AF originate in one of the PVs, in fact, from myocardial sleeves extending beyond the venoatrial junction into the PVs [33]. These sleeves are more extensive around the superior than around the inferior pulmonary veins [34-36]. This arrangement concurs with the distribution of foci of atrial premature depolarisations for spontaneous initiation of AF in reported clinical series [37]. The highly arrhythmogenic properties of the thoracic veins has been linked to an anisotropy due to discontinuous myocardial fibers separated by fibrotic tissue, promoting reentrant excitation, automaticity and triggered activity. Moreover, the PVs and PV ostia of patients with AF frequently show abnormal conduction properties (fragmentation, high dominant frequency) further promoting arrhythmogenesis [38]. Interestingly, congruent histological patterns have also been found in the junctions between atrial myocardial cells and vascular smooth musculature in the coronary sinus (CS) and AV valves, where under physiologic conditions, synchronous electrical activity is observed, while afterdepolarisations and triggered activity occur during catecholamine stimulation, rapid atrial pacing and/or atrial stretch [38]. Thus, triggering sources of AF can also be localised in the posterior wall of the left atrium, superior vena cava, ligament of Marshall, ostium of the CS, interatrial septum, crista terminalis and the region

adjacent to the AV valve annuli. Even rare congenital anomalies such as a persistent left superior vena cava may trigger AF [39–41].

Reentry – maintenance of atrial fibrillation

Reentry requires a suitable vulnerable substrate, as well as a trigger that acts on the substrate to be initiated [42]. Such substrates can be caused by altered electrical properties (functional reentry) or by fixed structural changes (anatomical reentry). Numerous cardiac conditions may cause structural substrates for reentry basically mediated by atrial enlargement and fibrosis. As a matter of fact, atrial dimension affects the amount of tissue that can accommodate reentry circuits and is an important determinant of the occurrence of AF-related reentry by making long pathways available [43]. Induction and maintenance of reentry require a critical balance between refractory and conduction properties. As a consequence, a shortened refractory period and/or a slowed conduction are the main mechanisms contributing to the perpetuation of either one or multiple reentrant circuits. In other words, the combination of all electrical and structural remodelling processes promote shortening of atrial tissue refractoriness and thereby decreases the wavelength (WL) of reentry-circuits, since the latter is the product of the refractory period (RP) and the conduction velocity (CV) (WL = $RP \times CV$). It is crucial to keep in mind that any wavefront propagation is dependent on a critical interplay between the "source" and the "sink" of a depolarising current. If the sink, acting as a sort of downstream tissue to the activation wavefront, is too large, propagation fails since the source current is too weak for its excitation (scenario of a convex wavefront curvature). However, if the opposite is the case (scenario of a concave wavefront curvature), a large number of cells encounter a smaller dimension of downstream tissue resulting in increased conduction velocity [44] (fig. 2).

AF-related reentry is currently thought to occur through two main general concepts/forms: (1.) the leading-circle concept and (2.) spiral wave reentry. These mechanisms may underlie AF perpetuation once continuously firing sources or triggers such as the PVs are eliminated.

Leading-circle concept

In 1973, Allessie and co-workers were the first to demonstrate reentrant activity to be functional and thus to exist without the need of an anatomical obstacle. Based on their observations of a tachycardia, which was induced in left atrial rabbit atria by premature stimulation showing excitation by rotating waves, they introduced their leading-circle concept [45]. Their paradigm consists of a reentry circuit establishing itself in a smallest possible loop that permits the wave to propagate. Inside the leading circle, multiple impulses propagating centripetally render the core tissue refractory and extinguish. Conversely, centrifugal propagation of impulses at the leading edge of the leading circle depolarises adjacent tissue as fast as possible, earliest during the relative refractory period (fig. 3) [45, 46].

Spiral wave reentry

Many recent studies in animals and/or patients have demonstrated AF-related reentry to be rather the result of uninterrupted periodic activity of a stable, *meandering* self-sustained spiral wave reentry adapting the shape of a rotor, the spiral wave rotating around a microreentrant circuit (fig. 4) [47, 48].

Spiral waves are well known from observations with chemical reactions in excitable media and have been adapted to electrophysiologic phenomena after experiments gathered from mathematical models of inter-cellular electrical propagation (Fitzhugh-Nagumo model [46]) and having been reproduced in cardiac tissue models [49–52]. As a result of a premature ectopic activation within the atrium initiating a wavefront, which collides with the previous sinus beat (and



Figure 2

Conduction velocity is substantially affected by wave front curvature. As a consequence, a convex wavefront (A) is associated with a dispersed current, and thus, propagation slowing of the current ahead of the wavefront, whereas a concave wavefront (B) accelerates propagation.



Figure 3

The leading-circle concept. Activity in form of a reentry circuit establishes itself in a smallest possible loop that permits the wave to propagate. Inside the leading circle, multiple impulses propagating centripetally render the core tissue refractory and extinguish. thus encountering its refractory and recovery front), this may serve as a typical scenario: The propagation of the ectopic wavefront may collide and block sooner or later at the edge of not-recovered and thus refractory tissue. At the moment, when the latter regains excitability it is activated by the premature wavefront, generating a curve continuously following the recovery front until a complete revolution is achieved. The point, where excited and refractory tissues collide is called the "phase singularity" [46]. Of note, the radius of the wavefront curvature decreases towards the vortex of the rotor where conduction velocity is infinitesimal due to a source-sink mismatch. Currently, this hypothesis is considered the most popular of reentrant mechanisms in AF despite its main shortcoming, namely the fact it has never been reliably documented in humans. Such "putative" rotors have gained much attention after



Figure 4

Spiral wave model (adapted from [48]).

Top: A schematic illustration of the activation (with arrows) and repolarisation (inner curvature without arrows) front of a meandering self-sustained spiral wave rotating around a microreentrant circuit (dotted circle).

Bottom: Various trajectories of the spiral wave. Of note, these trajectories produce irregular local activation pattern and frequency.

- A Circular.
- B Hypocycloidal.
- C Epicycloidal.
- D Hypermeandering.
- E Cycloidal.
- F Linear.

having been shown to be associated with sustained freedom from AF when successfully ablated [7, 53]. Furthermore, these rotors are also thought to act as periodic background foci generating wavefronts, which may break up into multiple wavelets when encountering anatomical obstacles such as orifices or scar tissue. The recent progress in electroanatomical and novel body surface mapping systems may soon permit their reliable verification or identification.

Multiple-circuit reentry / multiple-wavelet hypothesis

Our current understanding of AF maintaining mechanisms are also partly based on observations gained through computer modelling and key experiments in the early 1960s. Moe and coworkers described probably the most frequent common final pathway in sustained AF, namely an irregular wavefront fractionating and dividing into independent and eventually unstable daughter wavelets after having collided with islets or strands of refractory tissue [54]. These daughter wavelets show a very rapid activity with a variable and very short cycle length, may divide again, collide with each other and/or extinguish when encountering refractory tissue (functional block) or sites of slow conduction. Finally, numerous wavelets guarantee the sustenance of AF, particularly when advanced structural and electrical remodelling processes are present, favouring their "survival". However, proving that multiple wavelets may be the main mechanism for AF-related reentry is challenging, since this would basically require a differentiation from other mechanisms such as the above-mentioned ones or fibrillatory conduction remote from the site of interest (see below). So far, we are not able to identify every single local source of AF-related reentry, which is also why this concept keeps its hypothetical nature.

Focus with fibrillatory conduction

Less frequently, a single, very rapidly firing focus (PV or non-PV) may be identified as the initiating and maintaining mechanism of AF. In these cases, an ectopic focal activity has been shown to propagate into the atria encountering partly recovered and refractory tissue. Of note, the cycle length of such a driver is by definition shorter than the refractory periods of the adjacent tissue, which is why not all the tissue of that cardiac chamber can be depolarised in a regular 1:1 fashion and irregular, fibrillatory conduction and fragmented activation may result [44].

Typical atrial flutter and atrial fibrillation

Typical atrial flutter (AFL) and AF frequently coexist, however, whether they are causally related remains unclear. This not least, since the substrate of AFL is right atrial while AF is considered to be mainly a LA- related arrhythmia. In the past years, many predominantly experimental studies have investigated this phenomenon and built the basis for different possible explanatory scenarios [55-58]. Hereby, AFL may either play an active role as an AF-trigger or "mother wave" sustaining AF or occur passively after cessation of AF and AF-triggering and maintaining factors (PV ectopy, left atrial substrate). Of note, it has been suggested that the latter scenario may possibly necessitate a right atrial substrate such as a critically sized posterior intercaval block zone. However, current evidence has emphasised that AF is not a precondition for AFL to be induced and vice versa and that both arrhythmias may have similar triggers, such as e.g., atrial ectopics, which may remain residually once typical AF-triggers are ablated. Accordingly, AFL has been shown to be inducible by such triggers without any documentation of AF [58, 59].

Clinical implications of the pathophysiological concepts

Linking the diversity of risk factors and pathomechanisms leading to AF and the understanding of involved pathophysiological concepts may yield an improved performance in AF prevention and treatment. Accordingly, we keep implementing more and more innovative diagnostic as well as therapeutical approaches directing towards specific targets. Emerging approaches are non-invasive three-dimensional electroanatomical and body surface mapping systems with increasing spatial and temporal resolution, catheter-based multielectrode diagnostic and combined ablation catheters and specific pharmacological blockade or current enhancement of atrial Na⁺ or K⁺-channels. Although these currently available novel invasive and non-invasive tools do not allow a comprehensive exhaustion of our knowledge of AF-related mechanisms, they may at least pave the way for further improvement and selective and tailored therapy.

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