ATRIAL FIBRILLATION IN DAILY PRACTICE
ATRIAL FIBRILLATION: AN OLD DISEASE STILL BEING UPDATED

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Atrial fibrillation (AF) represents the arrhythmic epidemics of the 21st century. It is not only the most common cardiac arrhythmia encountered in daily clinical practice, but it is associated as well with high cardiac morbidity and mortality [1]. The rate of death among patients with non-valvular AF reaches about 5% per year [1]. To complicate the situation further, it is undoubtful that management of patients with AF is complex. It depends on the clinical presentation and on the underlying diseases and requires decisions about rhythm or rate control strategies as well as antithrombotic therapy. Furthermore, it is resource-consuming, since this arrhythmia is frequently refractory to both pharmacological and non-pharmacological therapies, it lowers significantly the quality of life and often requires the hospitalization of the patients affected [2]. Indeed, the aging of the population associated with the increase in the prevalence of chronic heart diseases has led and will lead to a significant increase in hospital admissions for AF. Hospitalization represents the major share of cost of care related to AF [3-5]. Algorithms and flow-charts for management and treatment of AF have been proposed in the recent years in order to lighten its huge economic and societal burden [1], but there’s still an urgent need of improvement in the field, above all in the understanding of its pathophysiology.

Despite improvements in technology, the development of several animal models of AF and a large number of clinical studies, the uncertainty in the understanding of mechanisms underlying AF is related to the difficulty of creating a suitable and universal animal model of this arrhythmia. As stated by Lewis, producing a sustained episode of AF in normal canine atria and mapping it is challenging [6]. To increase the chances to obtain AF in these animal models, it is necessary to intervene with • application of substances • vagal stimulation • prolonged rapid atrial or ventricular pacing • heart failure or inflammation. In any case, not one of these models reproduces exactly the arrhythmia we face daily in our clinical practice.

The initial hypotheses on AF date back to the early 1900s when the two main theories of focal activity and multiple reentry circuits were proposed.

The first theory came from the work of Scherf et al. who induced both a rapid, regular atrial rhythm consistent with atrial flutter and a rapid, irregular atrial rhythm consistent with AF, by placing aconitine on the atria [7-8]. In addition, these authors demonstrated that isolating the area where aconitine was applied by cooling, clamping or removal broke each of the two tachycardias. The rate of firing at the aconitine site was critical in determining the consequent arrhythmia: atrial flutter and AF were inducible according to the ability of the remainder of the atria to follow the abnormal focus with a 1:1 conduction. AF was the result of this pharmacological challenge when the rest of the atria could not follow the firing with a 1:1 conduction (the so-called fibrillatory conduction). Induction of AF by administration of aconitine gave body of evidence to the theory that a single focus firing at high rate can provoke AF as a result of fibrillatory conduction. Even though this theory was not universally accepted when the study of Scherf and coworkers was published, it is now well known that, irrespective of the underlying electrophysiological mechanism (i.e. reentry, abnormal automaticity, triggered activity), an atrial focus firing at high rate is potentially capable of initiating and sustaining AF.

The second main theory on the mechanisms underlying AF was generated in 1959 by Moe and Abildskov [9]. Based on a vagally-mediated model of AF in the canine heart, they introduced the multiple reentrant wavelet hypothesis, in which random reentry was considered the main cause of AF. They stated that a critical number of randomly distributed reentrant wavelets is necessary to provoke and maintain AF: the most interesting and novel part of this theory was that the pathways used by these reentrant wavelets are not real but functional, relying on local atrial refractoriness and excitability. Due to the fluctuation in size and speed of these wavelets, activation of the atria is therefore completely unpredictable and random. Even if Moe and his coworkers recognized that AF is a complex arrhythmia and that other mechanisms could be advocated in the explanation of its occurrence (e.g. a single firing focus firing rapidly, multiple ectopic foci firing at high rate, or a single reentrant impulse proceeding along a fixed circuit), they privileged the multiple reentrant wavelet hypothesis because it explains better the stability of AF episodes, which can potentially last for years in a subset of patients [10]. Anyway, the most important contribution to this theory was given by Allessie, who was the first scientist able to create an electrophysiological map of AF [11]. Using a Langerdoff-perfused canine atrial model, Allessie was...
able to induce AF associating rapid atrial pacing and administration of acetylcholine. Thanks to a specially designed electrode egg inserted in cardiac chambers through tricuspid and mitral valve orifices, Allessie and coworkers obtained several activation maps during AF and demonstrated mostly the presence of multiple randomly circulating reentrant wavelets, with closed-loop reentrant activation only in few cases.

As mapping technology developed and new animal models of AF employed, a new concept in the pathophysiology of AF has been discovered: AF needs to be generated and sustained by one or more “drivers,” i.e. sites in the atria able to fire rapidly and to generate a rhythm with a very short cycle length that other parts of the atria cannot follow in a 1:1 fashion. The underlying mechanism of these drivers could be, as reported above, abnormal automaticity, triggered activity, reentry or an external pacemaker. The concept that one or more drivers are needed to sustain AF has been confirmed in the catheter ablation era: the ablation of complex fractionated atrial electrograms (CFAEs) demonstrated that it could reduce the recurrence of AF in a group of patients with persistent AF undergoing AF ablation in association with pulmonary vein isolation [12]. The first experimental demonstration of driver-generated AF has been given by Schuessler et al., who demonstrated in an in vitro canine right atrial model the presence of a figure-of-eight closed-loop reentrant circuit of very short cycle length (45 msec) during acetylcholine infusion [13]. Even if these reentrant closed-loop circuits were demonstrated only during acetylcholine administration and it is still unknown if they have a real equivalent in the clinical AF, they provided body of evidence to the driver-producing-AF concept.

A mitral regurgitation model of AF developed by Cox et al. [14], associated with a simultaneous multisite electro-anatomical mapping of both atria has confirmed how AF may be related to a wide range of abnormal patterns of activation, from a simple single reentrant circuit able to activate the remainder of the atria with a fibrillatory conduction to a pattern where no consistent pattern of activation can be identified. In the canine sterile pericarditis model of AF, in which a surgical-induced pericarditis is associated with rapid atrial pacing to induce AF, two main mechanisms have been identified during electro-anatomical mapping of the arrhythmia [15]. One is due to multiple unstable reentrant circuits with closed-loop reentry of very short cycle length (≈ 100 ms) driving the atria to high rates through a fibrillatory conduction. The second mechanism is on the other hand a single, stable closed-loop reentrant circuit of very short cycle length (110 ms) generally located at the ostia of one or more pulmonary veins with irregular conduction to the remainder of the atria. As already shown in some of the previous experiments, elimination of reentrant circuits favors the interruption of the arrhythmia [16-17].

Other models of AF have been developed such as the rapid atrial pacing model or the heart failure model obtained with a ventricular prolonged high rate pacing followed by a period of atrial pacing. None of these models unfortunately have provided a final word in the understanding of the mechanisms underlying AF. The most accepted theory is that of a stable or unstable single circuit or multiple reentrant circuits causing fibrillatory conduction to the remainder of the atria and impairment of atrial contraction.

The contribution of these mechanisms in human AF is far from being completely understood. Since rapid atrial pacing is one of the simplest ways to induce AF in human hearts, it is reasonable to think that also in human atria drivers can initiate AF and sustain it through a fibrillatory conduction. The technique to induce persistent AF following termination of pacing was first described by Moreira et al. [18]. In a patient with an atrial tachycardia, refractory to all rate control drugs and causing a tachycardiomypathy, burst atrial pacing via a custom-made rapid atrial pacemaker produced AF ensuring an easier rate control and resumption of left ventricular systolic function. Interestingly, when the pacing was stopped after months of stimulation, AF continued. The mechanism of AF continuation after pacing withdrawal is unknown. Several attempts to map AF in patients with Wolff-Parkinson-White syndrome undergoing surgical ablation [19], or in patients during open-heart surgery, have been made showing single closed-loop reentrant circuit of variable but short cycle length in some instances and short, regular and irregular rhythms with short cycle length in other instances. Both findings confirmed that human AF could also be dependent on a driver producing fibrillatory conduction.

The most striking discovery in the research of the causes of human AF has been made by Haissaguerre et al. in a group of patients with paroxysmal AF in the absence of structural heart disease [20]: they found that driver-rhythms of very short cycle length were localized mainly in the pulmonary veins (PVs) but also in other structures such as superior vena cava, the ligament of Marshall and coronary sinuses. A lot of studies have confirmed this finding, even if there is no animal model counterpart of these observations on pulmonary vein potentials. PVs are widely recognized as an important source of ectopic beats.

There is now a general agreement that myocardial muscle fibers extend from the left atrium (LA) into all the PVs for 1 to 3 cm; the thickness of the muscular sleeve is highest at the proximal ends (1-1.5 mm) and then gradually decreases distally [21-23]. Unfortunately, the mechanism of this focal firing originating from PVs is not completely clarified. PV-sleeve cardiomyocytes have discrete ion channel and action potential properties that together with shorter action potential duration compared with atrium muscle sleeves which predispose them to arrhythmogenesis [24-25]. PVs demonstrate to have shorter action potential duration compared with atrium muscle sleeves, a feature that may favor triggered activity and focal firing. In addition, as demonstrated during
electrophysiological evaluation of the PVs using a multi-electrode basket catheter, they demonstrate effective refractory period heterogeneity and conduction abnormalities that promote reentry. Moreover, their electrical activation seems to be correlated to the increase of left atrial pressure, helping to explain the clinical link between AF and increased atrial pressure [26]. PV isolation (PVI) is therefore the preferred approach to cure AF in patients refractory to antiarrhythmic drugs. PVI consists in obtaining electrical isolation of the PVs by creating circumferential lesions around the right and the left PV ostia. Initially, ablation was performed inside or very close to the output into the atrium (the so-called segmental PVI).

It is now well-known that ablation in the PVs needs to be avoided as much as possible, primarily to avoid PVs stenosis, and more importantly to include in the ablation also the atrial-PV junction that may provide a substrate for reentrant circuits that generate or perpetuate AF.

Very recently, Allessie et al. added new important insights about the physiopathology of persistent AF in humans [27]. They performed an epicardial mapping of the right atrium, of the lateral wall and of the posterior wall of the left atrium in a group of patients undergoing cardiac surgery and known for a long-standing persistent AF. No evidence for the presence of stable foci or rotors was found, whereas a number of lines of block in the wavelet propagation was reported. Interestingly, these lines of block predominantly oriented parallel to the atrial musculature, were not fixed but continuously changed on a beat-to-beat basis and were concentrated around the ostia of the PVs. Since the incidence of these lines of block was significantly higher than the incidence found in previous studies in patients with paroxysmal AF, the authors concluded that electric dissociation of neighboring atrial muscle bundles is fundamental in the development of the substrate of human AF. In addition, the electric features of the reentry wavelets mapped on the atrial epicardium (above all the presence of R-waves in the unipolar electrograms at their site of origin) favor the hypothesis that they are not focal as origin but represent the epicardial breakthrough of micro reentries going on in the deeper layers of the atrial myocardium. Hence, keeping in mind that epicardial breakthroughs must be considered reentry points, their incidence then directly represents the number of reentrant circuits in the atria. Furthermore, since very few reentrant circuits have been found both on the epicardium and on the endocardium, the authors concluded that most reentrant circuits must be exclusively transmural and that the consequent endocardial-epicardial dissociation is the anatomical representation of the so-called fibrillatory conduction and is another key element in the development of a substrate of persistent AF in humans [28].

As shown above, lots of efforts should still be devoted to understand the mechanisms underlying AF and this is the reason why we can consider AF an old disease but still in need to be updated.

REFERENCES


