International Journal of Cardiology 203 (2016) 22–29

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

An update on atrial fibrillation in 2014: From pathophysiology to treatment

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ARTICLE INFO

Article history:
Received 9 July 2015
Received in revised form 6 October 2015
Accepted 12 October 2015
Available online 18 October 2015

Keywords:
Atrial fibrillation
Pathophysiology
Treatments
Ablation
Drug development

ABSTRACT

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia. The trigger for initiation of AF is generally an enhanced vulnerability of pulmonary vein cardiomyocyte sleeves to either focal or re-entrant activity. The maintenance of AF is based on a "driver" mechanism in a vulnerable substrate. Cardiac mapping technology is providing further insight into these extremely dynamic processes. AF can lead to electrophysiological and structural remodelling, thereby promoting the condition. The management includes prevention of stroke by oral anticoagulation or left atrial appendage (LAA) occlusion, upstream therapy of concomitant conditions, and symptomatic improvement using rate control and/or rhythm control. Nonpharmacological strategies include electrical cardioversion and catheter ablation. There are substantial geographical variations in the management of AF, though European data indicate that 80% of patients receive adequate anticoagulation and 79% adequate rate control. High rates of morbidity and mortality weigh against perceived difficulties in management. Clinical research and growing experience are helping refine clinical indications and provide better technical approaches. Active research in cardiac electrophysiology is producing new antiarrhythmic agents that are reaching the experimental clinical arena, inhibiting novel ion channels. Future research should give better understanding of the underlying aetiology of AF and identification of drug targets, to help the move toward patient-specific therapy.

1. Introduction

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia with a global incidence of 77.5 per 100,000 person-years in men and 59.5 per 100,000 person-years in women [1]. In addition, a large number of patients suffer from "silent," undiagnosed AF that often only manifests with a complication such as a stroke [2–4]. It is characterized by disorganized atrial depolarizations that result in the absence of effective atrial contraction and a rapid chaotic rhythm, which may or may not be symptomatic. The impact of AF on public health is tremendous, because it is associated with significant mortality and morbidity and significantly impaired quality of life [1]. Indeed, AF leads to frequent hospitalizations and increases mortality due to potentially fatal cardiovascular complications, i.e., thromboembolic events, heart failure, and sudden death [1,5–8]. AF increases the risk of thromboembolic stroke by about fivefold, independently of age [9], and is responsible for at least 15% of all strokes in Europe and the USA [2–4,10–12]. AF-related strokes are associated with high mortality and serious consequences for survivors [13]. One study suggested that nearly 80% of patients with AF and stroke will be dead or dependent within 6 months [14].

The frequency of AF and the high rate of AF-related morbidity and mortality mean that AF translates into a sizable public health problem with a number of associated unmet medical needs. In view of this, an Expert Meeting was organized at the University of Ferrara to review current questions surrounding AF, ranging from pathophysiology to treatment. This paper is a summary of these discussions, with the intention of providing a broad overview of the field.

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http://dx.doi.org/10.1016/j.ijcard.2015.10.089
0167-5273/

1.1. Mechanisms and pathophysiology of AF

One of the major problems in understanding the mechanism leading to AF is the lack of reliable experimental models resembling this complex arrhythmia. In general, AF requires both a trigger and a susceptible substrate (Fig. 1) [15–17]. The trigger for initiation and maintenance of AF is generally, but not exclusively, related to an enhanced electrical activity of the pulmonary vein cardiomyocyte sleeves, while non-pulmonary vein sources are more important as AF becomes more persistent. Thereafter, AF is often maintained by a primary "driver" mechanism, which may be either focal ectopic sources or rapid local re-entry in a vulnerable substrate (Fig. 1) [15–17]. Re-entry also requires both a substrate (a modified atrium or a portion of it) and a trigger (often an ectopic beat) [18]. The excitation appears to advance through the susceptible substrate with a circular or spiral wavefront, referred to as a rotor, thereby maintaining the AF and the modification of the structure of the atrium (substrate).

Sustained AF with atrial rhythms as high as 350 to 600 bpm, in turn, leads to electrophysiological remodelling, which can include the outward K^+ current (I_{to}), the ultrarapid delayed rectifier K^+ current (I_{Kur}), and L-type Ca^{2+} current ($I_{Ca,L}$), and, in parallel, increases in the inward rectifier K^+ current (I_{K1}), the agonist-independent form of the acetylcholine-dependent K^+ current ($I_{K,ACh}$), and the slow component of the delayed rectifier K^+ current (I_{Ks}) (Fig. 1). The result of these various changes in currents is a shortening of the action potential and effective refractory period (ERP), and therefore maintenance of AF [18]. Importantly, this electrophysiological remodelling may also be associated with abnormal Ca^{2+} handling and increased incidence of potentially proarrhythmic Ca^{2+} release events from sarcoplasmic reticulum during diastole, which can compromise atrial contractility and play an aggravating role in the initiation and maintenance of ectopic (triggered) activity [19–25].

Electrophysiological remodelling is absent when the heart is in sinus rhythm, and is less frequent in paroxysmal AF, possibly due to reversibility during AF-free intervals [15,24,26]. Remodelling can occur within hours, days, or weeks of the onset of arrhythmia, depending on the ion channel. It is associated with a higher incidence of delayed afterdepolarizations (DADs) and triggered activity [24].

AF is also accompanied by atrial structural remodelling, mainly hypertrophy and fibrosis [15,27]. By contrast to electrophysiological remodelling, this occurs on a longer timescale over months or even years, and appears to be associated with age, hypertension, and various comorbid cardiac diseases. This is the basis for early and aggressive treatment of associated conditions, such as hypertension, heart failure, and coronary artery disease, which may precede AF [28,29].

The intimate molecular mechanisms are not fully understood, though interstitial fibrosis, notably via the cardiomyocyte–myofibroblast interaction, is often evoked. Indeed, AF promotes the differentiation of fibroblasts into myofibroblasts, which secrete more collagen than fibroblasts, express some cardiac channels, including I_{Kur}, and exert a paracrine activity on cardiomyocytes. This interaction is critical to both electrophysiological and structural remodelling, including maintenance of the re-entrant substrate [30]. The real problem is the difficulty in reliably identifying and quantifying atrial fibrosis in vivo [31]; indeed, there is even some evidence for a lack of relationship between fibrosis (measured as collagen content), age, and AF.

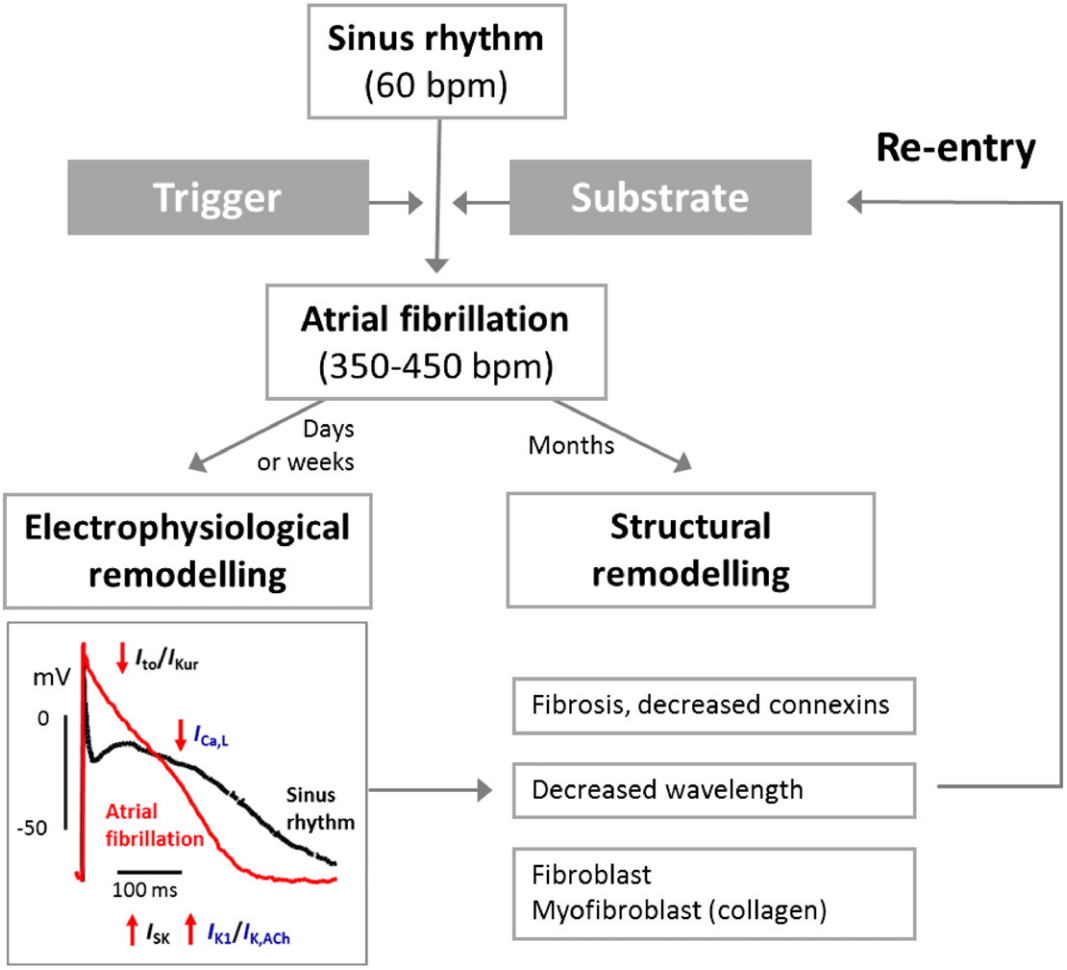

Fig. 1. Mechanisms of atrial fibrillation.