Atrial electrical remodeling from barn to bedside
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1999

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 18-07-2019
Pathophysiological Mechanisms of Atrial Fibrillation
Multiple-wavelet reentry  Today, the general accepted theory of the electrophysiologic mechanism behind AF is the “Multiple Wavelet” hypothesis, which was originally described by Moe and colleagues around 1960.\textsuperscript{1-3} It was the result of an evolution of ideas which started with the observation of circus movement in the jelly-fish ring preparation by Mayer in 1906.\textsuperscript{4} Inspired by this, Mines\textsuperscript{5} and Garrey\textsuperscript{6} performed animal experiments demonstrating circular contractions in cardiac tissue. Mines identified that slow conduction and a short refractory period favored the induction of reentry around an anatomical obstacle, which could be initiated and terminated using a single extrastimulus,\textsuperscript{5} while Garrey recognized the importance of tissue mass, shifting areas of local conduction block and multiple circulating wavelets during atrial fibrillation.\textsuperscript{6} In 1921, Lewis\textsuperscript{7} described electrocardiographic observations in humans with AF and concluded from the shifting atrial electrical axis that AF, like flutter, was the result of a single circulating wavelet, but without the constant course which it pursued in atrial flutter.

Almost 4 decades later, Moe and colleagues\textsuperscript{1-3} designed experiments to study the initiation and self-perpetuating nature of AF. The results of these studies, together with the previous observations, led to the “Multiple Wavelet” hypothesis, in which multiple independent wavelets circle randomly through the atria, around constantly changing areas of local conduction block. After initiation, typically by a premature atrial activation, the original wave front becomes fractionated and breaks up due to strands of refractory tissue around which the new wavelets can re-initiate themselves or each other, making AF a self-sustaining arrhythmia. Only when all independent wavelets run into inexicitable tissue at the same time, the arrhythmia terminates and sinus rhythm can resume. The chance for this to occur decreases when an increasing number of wavelets are present in the atria at the same time. The number of wavelets that fit into the atria depends on the atrial mass, the conduction velocity and the atrial refractory period.\textsuperscript{1-3}

Allessie and co-workers\textsuperscript{8} confirmed this hypothesis in 1985 by mapping the atria of isolated Langendorff perfused canine hearts in which AF was induced by acetylcholine application. They demonstrated that during AF, multiple independent wavelets activated the atria in a random reentrant way. Individual wavelets could brake-up, fuse or collide with each other, and wavelets would extinct if they reached the border of the atria or met refractory tissue. From time to time a varying number of wavelets was present in the atria and the duration of each individual wavelet lasted only several hundreds of milliseconds. They showed that indeed the number of wavelets that fit into the atria determined the perpetuation of AF. Below a critical number of wavelets (between 3 and 6), there was a considerable chance for the wavelets to die out all at the same time. In case more than 6 independent wavelets were present, the arrhythmia would not convert spontaneously anymore.\textsuperscript{8} During the last decade, mapping studies in humans with AF have further confirmed the multiple wavelet theory.\textsuperscript{8,10}
Alternative mechanisms of AF  

Opposed to the circus movement theory of Lewis and the multiple wavelet theory of Garrey and Moe was the ectopic focus theory by Engelmann, later confirmed by Scherf. This theory postulated a single rapid firing focus with a rate so high, that uniform excitation to the surrounding atrial tissue was no longer possible. The circular wavefront would break up and a fibrillatory conduction would ensue. In the experiments by Scherf et al aconitine injection in the wall of the atrial appendage resulted in AF due to a rapid firing focus at the site of aconitine application. Cooling of this site immediately terminated AF in the atrium, illustrating that both the initiation and perpetuation of AF were due to the rapid firing focus. Moe and colleagues repeated the experiments by Scherf, but they showed that in case of vagal stimulation AF continued in the atria, despite clamping off the appendage at which aconitine was administered, demonstrating the self-perpetuating character of AF. This demonstrated that in the right circumstances (vagal stimulation shortens the refractory period, which shortens the wavelength, see below) AF did not depend on the rapid firing focus any more, which convinced people that AF was a reentry arrhythmia. However, recently, Jais and colleagues demonstrated a focal mechanism in patients with AF similar to the experiments by Scherf. In these patients a fast firing focus, typically originating from one of the orifices of the pulmonary veins, causes fibrillatory conduction to the surrounding atrial tissue with identical electrocardiographic characteristics as the more classical forms of multiple wavelet AF. However, patients with this so-called focal AF can be cured by ablating the single fast firing focus, whereas patients with AF based upon multiple wavelet reentry do not benefit from ablation of a single site. Therefore, in focal AF, the induction and perpetuation of AF is different from the mechanisms explaining the initiation and perpetuation of multiple wavelet AF, which are described below. The percentage of patients with AF that could be cured by this focal approach is not known.

Finally, AF could also be the result of a single small reentrant circuit or multiple unstable reentrant circuits with a very short cycle length with fibrillatory conduction to the rest of the atria. Single reentrant circuits have indeed been demonstrated during intraoperative mapping of the atria in patients with AF. However, in the opinion of these investigators, the small reentrant circuits were just one end of the continuous spectrum of complexity of atrial activation during AF. To bring order into chaos, Konings et al categorized AF into 3 subclasses. In type I AF, there is quite organized atrial activation with 1 broad wavefront propagating at a normal speed with small areas of slow conduction or block. Type II AF is characterized by 2 waves, or single waves but longer or multiple lines of conduction block or slow conduction. More complex activation occurs in type III AF, with 3 or more independent wavelets and multiple areas of local conduction slowing or block.

Determinants of AF vulnerability  

As mentioned above, the number of wavelets that fit into the atria depends on the atrial refractory period and the con-
duction velocity. This relation which is of general importance for all reentry arrhythmias is described by the wavelength of excitation. This wavelength is the distance traveled by the activation front of the wavelet during its refractory period (wavelength=conduction velocity x refractory period). Reentry arrhythmias around fixed obstacles perpetuate when the circuit length of the arrhythmia exceeds the wavelength, so that the activation front does not run into its “tail” of refractory tissue. During AF, reentry does not occur exclusively around fixed obstacles, but small differences in refractory period or conduction velocity already can cause small areas of local conduction block, around which the activation front can circle. In this functional reentry of the leading circle type, the activation front will reenter its own relative refractory tail, and the circuit size will be approximately the same size as the wavelength, leaving no or only a small excitable gap. When the refractory period is short or the conduction velocity is low, the wavelength will be short. As a result, more independent wavelets will fit into atria of a certain size, increasing the perpetuation of AF. As was demonstrated by Rensma et al., the wavelength was also of importance for the induction of atrial arrhythmias including AF. In chronically instrumented conscious dogs, the inducibility of AF was tested by delivering single premature stimuli. The wavelength was changed using a variety of drugs (acetylcholine, propafenone, lidocaine, ouabain, quinidine, d-sotalol). It was demonstrated that the refractory period or the conduction velocity were bad predictors for the induction of AF, whereas the wavelength was a strong predictor. Likewise, the action of various anti-arrhythmic drugs in converting AF can be explained by their ability to increase the atrial wavelength.

Random reentry (and also fibrillation-like conduction) only occurs in the setting of heterogeneous electrophysiologic properties of the atria, such as dispersion of the refractory periods, anisotropic tissue properties, or a decrease of the negative membrane potential as in diseased or dilated atria. These regional differences in repolarization or conduction cause areas of local conduction delay or block, around which the initiating activation front can reenter its circuit. In animal experiments, an increased dispersion of refractoriness is associated with an increased inducibility and maintenance of AF. Furthermore, patients with paroxysmal AF seemed to express shorter refractory periods and an increased dispersion of refractoriness when compared with controls.

The autonomic nervous system and AF vulnerability One of the oldest models to induce sustained AF is applying vagal stimulation. The resulting increased parasympathetic tone will shorten the atrial refractory period through opening of the acetylcholine-dependent potassium channels ($I_{K_{ACh}}$). Furthermore, due to inhomogeneous distribution of the vagal nerve endings, the spatial dispersion in refractoriness will increase. In this way, AF will persist after induction with premature stimuli or atrial burst pacing as long as the parasympathetic system is stimulated, either by vagal nerve stimulation or by acetylcholine application.

Interestingly, also sympathetic activation shortens the atrial refractory period, due to
cAMP-dependent shortening of the plateau phase. However, this effect is less pronounced and sympathetic activation by epinephrine administration in isolated strips of atrial tissue from rabbit hearts resulted in either an increase in wavelength at slow heart rates or no change at high heart rates. On the other hand, in the clinical situation sympathetic stimulation may increase the number of spontaneous premature atrial activations due to increased automaticity or triggered activity, which may increase the incidence of AF. This may especially be true in patients after cardiac surgery, and explains the significant efficacy of beta-adrenergic blocking drugs in preventing post-operative AF. Finally, experimentally induced regional sympathetic denervation facilitates sustained AF, possibly by increasing dispersion of refractoriness.

The Atrial Action Potential  The atrial action potential has a high negative resting membrane potential, a steep upstroke, and a repolarization phase which is generally shorter than repolarization in ventricular myocardium (figure 1). The phase 0 depolarization is caused by a rapid inflow of sodium ions through the voltage-gated and time-dependent Na-channels. Furthermore, a more slowly depolarizing current is provided by the influx of calcium through the L-type calcium channels. This last current is thought to be at least partly responsible for the plateau phase during repolarization and initiates calcium release from the sarcoplasmic reticulum which binds to the contractile filaments of the myocardial cell, causing contraction. Phase 1 of repolarization is caused by the Ito-current. This current ends depolarization and lasts only very short, but has important consequences for the action potential duration by its influence on other repolarizing currents. It consists of 2 components; a calcium-independent current which can be blocked with 4 amino-pyridine (I_{to}), and a calcium-dependent chloride current which is activated by calcium and blocked by verapamil (I_{to} or I_{Cl(Ca)}). During phase 2 of repolarization, outward potassium currents such as I_{ks}, I_{kr}, and I_{kch} compete with the inward calcium current, which results in formation of the plateau phase. During phase 3 the action potential returns to its transmembrane resting potential, which remains at that level during phase 4 of the action potential until the cell becomes re-activated. Furthermore, the sodium-potassium ATPase-pump and the reversed mode of the sodium-calcium exchanger also contribute to repolarization (the current flows to where the sodium goes).

The main difference between atrial and ventricular myocardial action potentials is the distribution and magnitude of the ionic currents responsible for the resting
membrane potential and action potential repolarization. The inward rectifier current $I_{k1}$, responsible for maintenance of the resting membrane potential, is smaller in atrial cells compared with ventricular cells. On the other hand, the acetylcholine-dependent potassium current $I_{kAch}$ is very important in maintaining and hyperpolarizing the resting membrane potential in atrial cells, while not present in ventricular cells. It is this current which is responsible for hyperpolarization and shortening of the atrial action potential during parasympathetic stimulation.

### Types of Atrial Action Potentials

Apart from the calcium-dependent, slowly depolarizing cells of the SA- and AV-node, with their characteristic spontaneous diastolic depolarization (pacemaker activity), there are 2 different kinds of atrial action potentials. Some cells have action potentials with a distinct plateau phase, while other cells have more triangular-shaped action potentials with a shorter action potential duration. Histological examination revealed that both action...
potentials originate from ordinary atrial myocardial cells.\textsuperscript{57} Escande et al\textsuperscript{58} showed in human atrial tissue that with an increase in age the morphology of the atrial action potentials changes from a triangular shape to a plateau phase action potential (figure 2). It is therefore suggested that the triangular-shaped action potential resembles the early developmental stage of the atrial cell. Furthermore, examination of strips of atrial tissue obtained from patients with AF identified atrial cells with short refractory periods, and with a significant increase in the percentage of triangular shaped action potentials.\textsuperscript{59-61} This was in agreement with other studies which demonstrated short refractory periods in AF patients after electrical cardioversion.\textsuperscript{62,63} Furthermore, an absence of rate adaptation of the atrial refractory period was demonstrated in patients vulnerable for atrial arrhythmias\textsuperscript{64,65} and in strips of atrial tissue from AF patients.\textsuperscript{59} At that time, these electrophysiologic abnormalities were all considered to be an important cause of AF.

**Electrical remodeling of the atria** In 1995, 2 studies performed at the same time by separate groups reported on the induction of chronic AF by rapid atrial pacing or repeated induction of AF. Morillo et al\textsuperscript{66} demonstrated that 6 weeks of rapid atrial pacing induced chronic AF in a significant number of previously healthy dogs. After this period a shortened atrial refractory period and a marked atrial dilatation explained the increased vulnerability for AF.

The other study by Wijffels and colleagues from the group of Allessie described how AF itself can cause the atria to become more vulnerable for reinduction and perpetuation of AF.\textsuperscript{67} Using healthy chronically instrumented goats, they repetitively induced AF by burst pacing. Generally, the induced episodes of AF lasted only a few seconds before converting spontaneously to sinus rhythm. An automatic “fibrillation pacemaker” which was able to recognize the absence of AF after spontaneous conversion then re-induced AF by another burst-pace. Using this experimental

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**Figure 2**

Pen recordings of atrial transmembrane action potentials. The left action potential is recorded in a 22 month-old boy with a ventricular septum defect. The right recording is from a 30 year-old woman with syphlic aortitis. Driving rate 1 Hz. (From Escande et al\textsuperscript{58})
Protocol, they were able to sustain AF 24 hours a day, 7 days a week. This artificial maintenance of AF prolonged the duration of the induced episodes, the longer the arrhythmia was sustained, until it eventually became chronic, ie did not convert spontaneously any more (Figure 3). The time till the development of chronic AF varied widely among different goats between 2 days and 2 weeks. When they investigated the electrophysiologic changes which occurred during their experiments, it appeared that with a prolonged duration of the experimental protocol, the atrial refractory period shortened significantly, with loss of the physiologic rate adaptation. Since the conduction velocity did not change significantly, the calculated wavelength decreased, which explained the increased vulnerability for AF. Of interest, after cardioversion of AF that had been present for 2 to 4 weeks, this so-called atrial electrical remodeling appeared to be completely reversible within one week after restoration of sinus rhythm.67

Modulation of Electrical Remodeling In an attempt to unravel the initiating mechanisms behind this newly discovered electrophysiological phenomenon, we administered various drugs during rapid atrial pacing and evaluated the time course of atrial electrical remodeling and recovery from remodeling.

Figure 3 Prolongation of the duration of electrically induced episodes of AF after maintaining AF for respectively 24 hours and 2 weeks. The 3 tracings show a single atrial electrogram recorded from the same goat during induction of AF by a 1 second burst stimulus (50 Hz). In the upper tracing the goat had been in sinus rhythm all the time and AF self-terminated within 5 seconds. The second tracing was recorded after the goat had been connected to the fibrillation pacemaker for 24 hours, showing a clear prolongation of the duration of AF to 20 seconds. The third tracing was recorded after 2 weeks of electrically maintained AF. After induction of AF this episode became sustained and did not terminate any more. (From Wijffels et al67)
Furthermore, modulation of atrial electrical remodeling may have several clinical effects. Drugs which can reduce electrical remodeling during AF may have a beneficial influence on the arrhythmia prognosis by reducing the fibrillation-induced decrease in wavelength. On the other hand, drugs which help to normalize the atrial electrophysiology during recovery from electrical remodeling may increase maintenance of sinus rhythm after successful cardioversion of AF. Therefore the studies presented in the following chapters do not only give insight into the mechanisms of atrial electrical remodeling, they also may initiate new therapeutic approaches to patients with AF.

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