Electrophysiologic Parameters for Triggering and Maintaining Atrial Electrical Turbulence

V. LANG, M. SCHALDACH
Department of Biomedical Engineering, Friedrich-Alexander University Erlangen, Erlangen, Germany

Summary

Atrial electrical turbulence (atrial fibrillation, AF) is assumed to be triggered by a premature atrial contraction (PAC) during the vulnerable phase of the atrial action potential (AP). The physiologic conditions for triggering and maintaining atrial electrical turbulence have not yet been quantitatively investigated. Using the atrial cell model by Nygren, this paper presents a realistic simulation of the atria in a two-dimensional reaction-diffusion model. The results of the model are correlated to clinical data of APs measured during intrinsic onset of AF. Six out of 26 patients (16 male, 69±12 years) developed AF in the first 36 h following aortic valve replacement. The monophasic action potential (MAP) from the right atrial wall was continuously recorded with an epicardial MAP lead (MAPOX, BIOTRONIK, Germany). The recordings provided information about the electrical state of the atrial cells during the transition from sinus rhythm to AF. The clinical results were used to adjust the parameter of the computer model of the atria. Before AF, specific and significant alterations of the MAP were observed. In 9 of 12 episodes, the MAP shortened by 24±4% 60 min before onset of AF. In the 3 remaining episodes, the beat-to-beat variability of the cycle length increased from 24±7 to 137±27 ms 30 min before AF, indicating extended PAC activity. Computer simulation showed that shortening the atrial AP, which is correlated to the MAP duration, by more than 22% enables a single PAC to trigger electrical turbulence. In addition, the atrial model confirmed that the number of PACs per time unit is linearly correlated to AF probability. But physiologic speed of the excitation across the atrium (50 to 70 cm/s) together with cyclic boundary conditions prevent the maintenance of the turbulence. If the excitation speed is slowed by >45%, electrical turbulence is stable under cyclic boundary conditions. During stable electrical turbulence, simulated intracardiac electrograms (IEGM) were similar to the IEGMs recorded in a clinical setup. In conclusion, the significant alteration of the MAP before AF was interpreted with a computer model of the atria. A shorter AP increased the vulnerable area in which a single PAC is able to trigger AF. Slowed excitation speed ensured stable electrical turbulence. Thus, the model provides a tool for quantitative investigation and interpretation of mechanisms underlying AF. This may allow new concepts for treatment of AF to be tested and optimized.

Key Words

Atrial fibrillation, MAP, simulation of physiological systems

Introduction

With an incidence of 1%, atrial fibrillation (AF) is the most common arrhythmia. The incidence and importance of AF increase with age [1]. Detailed knowledge about the mechanisms underlying AF is the prerequisite for successful preventive therapy. Currently, two basic mechanisms are in discussion [1]. One explains AF by one or more ectopic foci firing at a high rate [2]. The other is Moe's theory, in which AF is caused by multiple re-entrant waves travelling over the atria [3]. The latter theory was confirmed by animal experiments [4]. Nevertheless, neither Moe's theory nor Allessie's animal experiments explain the origin of the re-entrant waves. In reaction-diffusion systems, such as the heart muscle or Belousov-Zhabotinsky reactions [5], the origin of re-entrant waves is explained by the theory of phase resetting [6]. This theory states that re-

entrant waves are triggered by a premature beat in the vulnerable phase of the ongoing excitation front. Generated by the premature stimulus, rotors arise which, in time, break up into several re-entrant waves. This process causes electrical turbulence. Several computer simulations in 2 and 3 dimensions confirm that rotors are likely to be at the origin of atrial and ventricular fibrillation re-entrant waves [7-9]. Most of these computer simulations use a 2-parameter model of atrial or ventricular cells with Fitzhugh-Nagumo equations, simplifying the behavior of the cells [10-12]. Because simple models do not allow the shortening of the cellular action potential (AP) or the increase in intracellular Ca^{2+} with a higher rate to be modeled, the electrophysiologic parameters influencing the triggering of electrical turbulence cannot be investigated quantitatively.

Using a realistic atrial cell model, this paper studies the parameters for triggering and maintaining electrical turbulence in reaction-diffusion systems [13]. The simulation parameters were adjusted to recordings of the monophasic action potential (MAP) during intrinsic transition from sinus rhythm to AF [14]. Furthermore, the natural mechanisms suppressing electrical turbulence are presented when discussing new methods for preventive therapy of AF.

Materials and Methods

Setup for Clinical Recordings

In 26 patients (16 male, 69±12 years), epicardial leads (Mapox, BIOTRONIK, Germany) were implanted in the right atria (n=22) and in the right and left atria (n=4) after an aortic valve replacement, for MAP recording. The MAP was recorded continuously during the patients' in-hospital stay as described in Pichlmaier et al. [14]. Eight of the patients developed AF following open heart surgery. Therefore, the shape and duration of the APs were available during the intrinsic transition from sinus rhythm to AF. The MAP was evaluated in respect to duration at 25, 50, and 90% repolarization (MAPd25, MAPd50, MAPd90), beat-to-beat changes in cycle length, and amplitude. Additionally, in 4 of the patients with two atrial MAP leads, the velocity of the excitation spread was calculated from the time difference between the first excitation in the right and left atrial MAP recordings.

Model of the Atria

The atria were simulated as a rectangle with 64 x 64 atrial cells. Each cell represented a 2 x 2 mm piece of the atria according to the atrial cell model presented by Nygren [13]. The electrical coupling of the cells was simulated using a 2-dimensional diffusion equation.

$$\frac{\partial V}{\partial t} = D_x \frac{\partial^2 V}{\partial x^2} + D_y \frac{\partial^2 V}{\partial y^2} + V(t)$$

V: transmembrane potential
D_x, D_y: diffusion constants in x and y directions

The boundaries of the atria were simulated as cyclic boundary conditions. Therefore, the atrium was, geometrically, an infinite cylinder with closed-ended circles.

$$f(x_1,..,x_k)_{1,j} = f(x_1,..,x_k)_{64,j}$$
$$f(x_1,..,x_k)_{i,1} = f(x_1,..,x_k)_{i,64}$$

$f(x_1,.., x_k)$ represents the functions determining the transmembrane potential

The vessels and valves in the atria were simulated as holes with no-flux boundaries. Therefore, the excitation front passes the holes without reflections or extinction. The parameters of the cell model, as well as the diffusion constants D_x and D_y, were adjusted to simulate physiologic excitation velocity (50 to 70 cm/s) [15].

Results

Clinical Results

During the observation period, 8 of the 26 patients (31%) suffered from at least one AF episode. In total, 12 episodes of AF were documented. All AF episodes started during the first 36 h following open heart surgery. Before AF, specific and significant alterations of the MAP were observed. As demonstrated in Figure 1, the atrial MAP 3 h prior to AF onset showed a more triangular shape than the control recording during implantation.

This morphological change was observed in 9 out of 12 episodes. In these patients, MAP shortened by 24±4% at least 60 min before onset of AF. In the 3 remaining episodes, the beat-to-beat variability of the

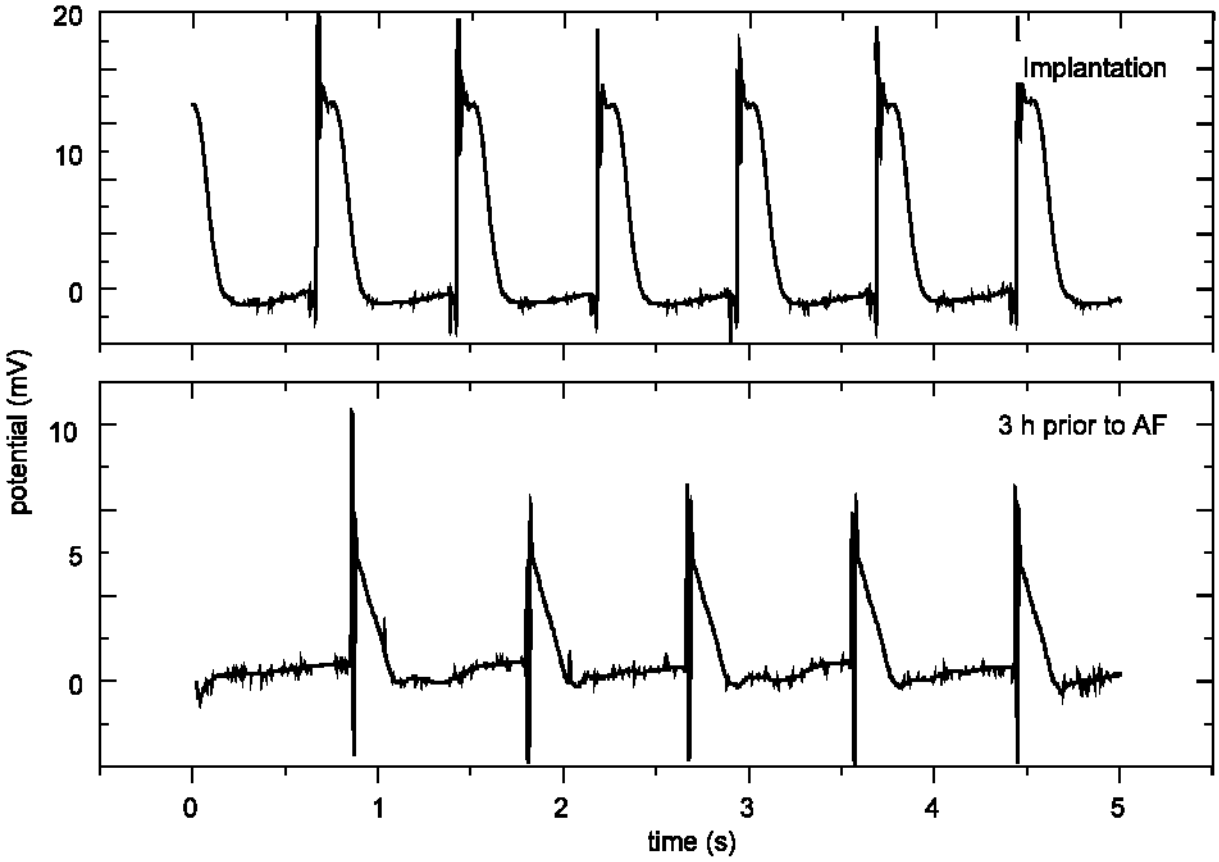

Figure 1. Epicardial MAP from the right atrial wall. The upper trace shows the MAP 2 h following implantation, referred to the control recording. The MAP in the lower trace was recorded 3 h prior to the intrinsic transition from sinus rhythm to AF. The amplitude decreased, the MAP duration shortened, and the shape changed to a triangular morphology.

cycle length increased from 24±7 to 137±27 ms 30 min before AF, indicating extended premature atrial contraction (PAC) activity (Figure 2).

Simulation Results

The triangular shape of the MAP before AF onset was simulated by reducing Ca^{2+} influx through the ICaL ion channel as depicted in Figure 3.

Computer simulation showed that shortening the simulated atrial MAP by more than 22%, which corresponds to a 70% blocking of the I_{CaL} ion channel, allows triggering a rotor and, thus, leads to primary electrical turbulence by a single PAC (Figure 4). If, in contrast, the simulated atrial AP duration was within the physiologic range and the calcium channel was not blocked, the vulnerable phase was too short. Therefore, the vulnerable area was too small for PACs to trigger electrical turbulence.

While a blocked calcium channel may trigger electrical turbulence, physiologic speed of the excitation across the atrium (50 to 70 cm/s), together with cyclic boundary conditions, leads to the self-destruction of the rotor and, therefore, the electrical turbulence, because the rotor arms hit refractory areas.

In addition, the atrial model confirmed that the number of PACs per time unit is linearly correlated to the probability of triggering electrical turbulence. Nevertheless, a high rate of PACs or short AP duration trigger only unstable rotors when combined with normal excitation speed. Stable rotors could only be simulated if either the excitation speed was slowed by >45% or the cyclic boundary conditions were replaced by no-flux boundaries. No-flux boundaries, e.g.

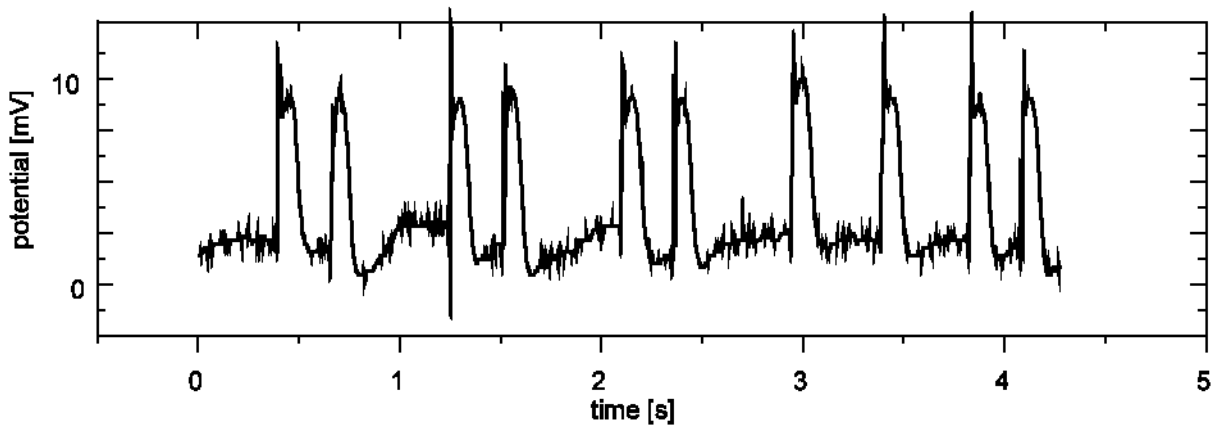

Figure 2. Epicardial MAP from the right atrial wall 20 min before onset of AF. The irregular rhythm indicates increased PAC activity.

ischemic scars, enable stable rotors because the excitation front originating from the rotor arms extinguishes at the no-flux boundary and cannot travel around the atrium to extinguish the rotor center. Slowed excitation speed allows 3 or more stable rotor arms. If two rotor arms extinguish themselves due to cyclic boundary conditions, stable electrical turbulence is still preserved by the remaining rotor arm(s).

During stable electrical turbulence with no-flux boundaries, simulated intracardiac electrograms (IEGM) show a uniform and periodic morphology at 180-220 bpm, which is not a typical IEGM for AF. Holes in the atrium modeling the vessels and valves lead to the breakup of the rotors splitting them into several re-entrant

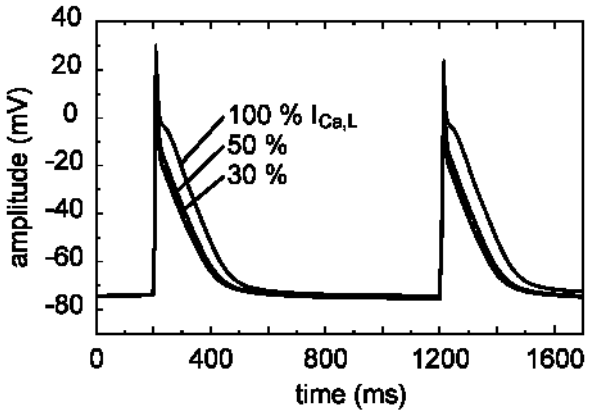

Figure 3. Simulated cellular AP with increasing blocking of the Ca,L ion channel. The AP shortens and the amplitude decreases. The morphological changes were similar to those observed in atrial MAPs prior to AF (compare Figure 1).

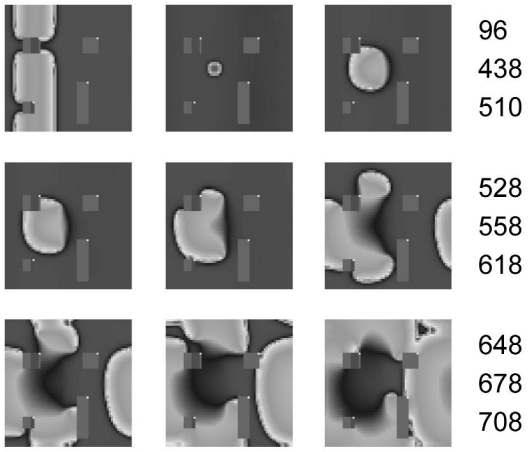

Figure 4. Simulated electrical turbulence using cyclic boundary conditions. The rectangular holes simulated the vessels in the right and left atrium. The Ca,L channel was blocked to reduce its conductance to 30% (compare Figure 3). Excitation velocity was slowed to 28 cm/s. On the right side, the time in ms is displayed. An initial excitation front runs across the atria and extinguishes by itself (96 ms). A PAC at 438 ms in the vulnerable phase of the preceding excitation initiates a rotor (510-618 ms). Due to the vessels, the rotor splits into several arms (648-678 ms). See also Figure 5 for the simulated IEGM of this electrical turbulence.

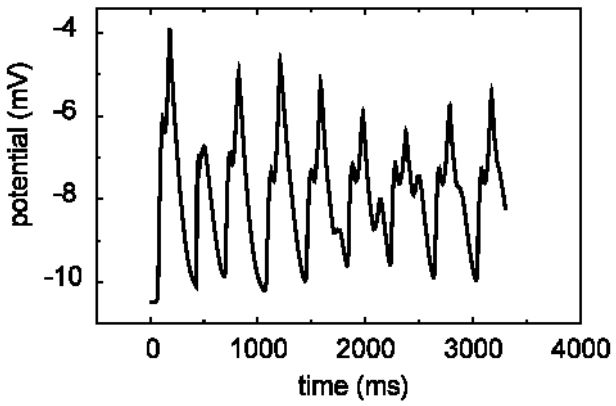

Figure 5. Simulated IEGM during electrical turbulence. The electrical turbulence starts with a regular but fast rhythm and is fractionated in time.

waves. An IEGM simulation with such split re-entrant waves produces the typical fractionated IEGM. Figure 5 depicts simulated IEGM during AF.

Discussion

The results of the simulation confirm and complement the clinical results. The atria are susceptible to AF, triggered by a PAC in the vulnerable phase, if the AP is shortened by more than 22%, e.g. by blocking the calcium channels. Nevertheless, the physiologic velocity of the excitation spread and the cyclic boundary conditions are natural safety mechanisms prompting the self-destruction of triggered rotors. Therefore, there must be at least one additional pathological change to maintain the rotors leading to electrical turbulence. Either ischemic scars form no-flux boundaries, or slowed excitation velocity leads to a minimum number of rotor arms. The slowed excitation velocity, which has been reported during AF by other investigators [15-17], seems more likely to be a fundamental reason for AF. Only this condition, in combination with the holes in the atria, enables stable electrical turbulence and leads to the typical fractionated atrial IEGM. Furthermore, the simulation confirms the hypothesis that stable electrical turbulence is based on 3 or more re-entrant waves, as reported also from a dog model [18,19].

The results show the limitations of studying the mechanism underlying AF using an extracted piece of the atria [20]. The important natural safety mechanism, offered by the cyclic boundary conditions, is not modeled. Therefore, neither the stability of electrical turbulence can be investigated, nor the influence of drugs or pacing patterns on its maintenance can be estimated.

The model suggests that there are two basic mechanisms to prevent triggering of AF by a single PAC. Either the vulnerable area has to be reduced or the refractory area has to be increased.

Conclusions

Computer simulation with a realistic cell model confirmed Moe's theory that AF is the result of several re-entrant waves travelling over the atria. The parameters for triggering and maintaining electrical turbulence were quantitatively calculated for the first time. In addition, the use of a realistic cell model connects these pro-arrhythmic parameter settings with pathophysiologic changes of the ion channel properties. This may allow new concepts for antiarrhythmic therapy of AF to be developed and tested.

Limitations

The main limitation of the computer model is that the geometrical form models the atrium as a rectangle. Though more anatomically realistic atrial or ventricular models are available to simulate excitable media, these models need 2 to 3 additional orders of magnitude of cell units [21]. Therefore, months of computer time would be required to simulate realistic cell models in a realistic anatomical structure. Another limitation, the more clinical data are insufficient to confirm that the triangular shape of the atrial MAP preceding AF is based on limited conductance of the calcium channel $I_{Ca,L}$. This requires further study at the cellular level.

References

[1] Levy S, Breithardt G, Campbell RW, et al. Atrial fibrillation: current knowledge and recommendations for management. Working Group on Arrhythmias of the European Society of Cardiology [In Process Citation]. Eur Heart J. 1998; 19 (9): 1294-1320.

[2] Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998; 339 (10): 659-666.

[3] Moe GK. A conceptual model of atrial fibrillation. J Electrocardiol. 1968; 1 (2): 145-146.

[4] Allessie MA, Kirchhof CJ, Konings KT. Unravelling the electrical mysteries of atrial fibrillation. Eur Heart J. 1996; 17 (Suppl C): 2-9.

[5] Cross AL, Armstrong RL, Gobrecht C, et al. Three dimensional imaging of the Belousov-Zhabotinsky reaction using magnetic resonance. Magn Reson Imaging. 1997; 15 (6): 719-725.

[6] Winfree A. When time breaks down. Princeton: Princeton University Press; 1987.

[7] Fenton F, Karma A. Vortex dynamics in three-dimensional continuous myocardium with fiber rotation: Filament instability and fibrillation. Chaos. 1998; 8 (1): 20-47.

[8] Gray RA, Jalife J. Ventricular fibrillation and atrial fibrillation are two different beasts. Chaos. 1998; 8(1): 65-77.

[9] Pertsov AM, Davidenko JM, Salomonsz R, et al. Spiral waves of excitation underlie reentrant activity in isolated cardiac muscle. Circ Res. 1993; 72 (3): 631-650.

[10] Berenfeld O, Abboud S. Simulation of cardiac activity and the ECG using a heart model with a reaction-diffusion action potential. Med Eng Phys. 1996; 18 (8): 615-625.

[11] FitzHugh R. Sinusoidal voltage clamp of the Hodgkin-Huxley model. Biophys J. 1983; 42 (1): 11-16.

[12] Nagumo J, Sato S. On a response characteristic of a mathematical neuron model. Kybernetik. 1972; 10 (3): 155-164.

[13] Nygren A, Fiset C, Firek L, et al. Mathematical model of an adult human atrial cell: the role of K+ currents in repolarization. Circ Res. 1998; 82 (1): 63-81.

[14] Pichlmaier AM, Lang V, Harringer W, et al. Prediction of the onset of atrial fibrillation after cardiac surgery using the monophasic action potential. Heart. 1998; 80 (5): 467-472.

[15] Rensma PL, Allessie MA, Lammers WJ, et al. Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res. 1988; 62 (2): 395-410.

[16] Gaspo R, Bosch RF, Talajic M, et al. Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. Circulation. 1997; 96 (11): 4027-4035.

[17] Kirchhoff S, Nelles E, Hagendorff A, et al. Reduced cardiac conduction velocity and predisposition to arrhythmias in connexin40-deficient mice. Curr Biol. 1998; 8 (5): 299-302.

[18] Kumagai K, Khrestian C, Waldo AL. Simultaneous multisite mapping studies during induced atrial fibrillation in the sterile pericarditis model. Insights into the mechanism of its maintenance. Circulation. 1997; 95 (2): 511-521.

[19] Jalife J, Berenfeld O, Skanes A, et al. Mechanisms of atrial fibrillation: mother rotors or multiple daughter wavelets, or both? J Cardiovasc Electrophysiol. 1998; 9 (8 Suppl): S2-12.

[20] Wood MA, Caponi D, Sykes AM, et al. Atrial electrical remodeling by rapid pacing in the isolated rabbit heart: effects of Ca++ and K+ channel blockade. J Interv Card Electrophysiol. 1998; 2 (1): 15-23.

[21] Berenfeld O, Jalife J. Purkinje-muscle reentry as a mechanism of polymorphic ventricular arrhythmias in a 3-dimensional model of the ventricles. Circ Res. 1998; 82 (10): 1063-1077.