Mathematical Modeling and Simulations to Study Cardiac Arrhythmias

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INTRODUCTION

The availability of precise information on the formation and transmission of cardiac impulses, under both normal and pathological conditions, has helped elucidate the underlying mechanisms of cardiac arrhythmia.[1-3] Our understanding is still incomplete in many aspects, however, and there are limitations to some of the procedures used to treat various cardiac arrhythmias, for instance, fibrillation processes.

Several relevant topics have been considered in a number of experimental and clinical studies in the field of cardiac electrophysiology. These include analyses of the structure and function of the ionic channels that determine the action potential of cardiac cells, as well as the factors that regulate transmembrane ionic currents, such as voltage, time elapsed since activation, frequency, and ion concentrations,[2,4] and more recently, genetic determinants of the molecular characteristics of the channels and of hereditary diseases involving malignant arrhythmias.[5]

Another interesting subject for study is the factors that determine the propagation of the cellular activation process in cardiac tissues.[6,7] These factors included the intercellular connections and the spatial positioning of the cardiac fibers, since propagation occurs in a multicellular medium with anisotropic properties, i.e., a medium influenced by the orientation of the cardiac fibers. Moreover, there are numerous factors that can modify, destabilize or interrupt propagation, such as activation front curvature, myocardial fiber stretching, actions of the autonomic nervous system, medications, ischemia, necrosis, degeneration and fibrosis of the cardiac tissues.

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The mechanisms leading to the onset of cardiac arrhythmia include an abnormal formation of impulses due to increased normal sinoatrial node pacemaker activity, abnormal sinoatrial node pacemaker activity or activity triggered by post-potentials, both early and late. Arrhythmia can also result from abnormal impulse conduction, as occurs in the various forms of reentry, and its analysis should consider the bases for the therapeutic procedures used to correct it: drugs, ablation with radio frequency, electrical cardioversion, etc.[4,8-10]

Another topic of practical interest involves the analysis of electrical signals related to the characteristics of activation propagation in the cardiac tissues, whether recorded by stimulation within the cardiac chambers or from the body surface.

The creation of models, i.e., theoretical simulations of the electrophysiological phenomena based on mathematical formulas, forms a part of the efforts aimed at enhancing our understanding of these phenomena and predicting behavior in various normal and pathological situations.[1,2,6] The development of such models has been driven by several factors, including:

1. Precise experimental and clinical data collection. This has been essential to constructing models based on real data and verifying how well such models work.

2. Advances in information processing and compilation capabilities through the use of faster, increasingly more complex computers.

3. The use of the models and simulations themselves to improve our understanding of the underlying mechanisms of cardiac arrhythmia and to predict responses under conditions that are sometimes hard to reproduce in experimental preparations.

BACKGROUND

A look at the historical evolution of the models and simulations used to study cardiac arrhythmias shows

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how the available information has been growing in complexity and how advances have been made in our capacity to process it rapidly and efficiently.[1] Pioneer studies include those conducted in the early 20th century by van der Pol and van der Mark, who developed mathematical systems to describe the rhythmic activity of the heart and its relationship to the signals of the electrocardiogram. Around the mid-20th century, Neumann and Ulam developed cellular automata to create multicellular models for various purposes. An almost simultaneous historic milestone was work done by Hodgkin and Huxley that developed a description of the action potential of nerve fibers. These investigators used differential equation systems to quantify current flow through the membrane, based on previous studies done by Nernst and Planck. They also described the behavior of sodium and potassium ion channels based on membrane potential. Later studies conducted by various research groups developed cell models for Purkinje fibers and muscle cells.[2] These models have gradually incorporated the ionic currents discovered and described in experimental work, such as calcium and potassium currents of various kinds.[11]

Parallel to the development of mathematical models to study the formation of the action potential of cardiac cells, investigation has been undertaken to describe the process of cardiac activation propagation in multicellular models that provide a more precise representation of real phenomena.[1] These models, which usually assume that cardiac tissue is a continuous excitable medium, have been used to describe the propagation of the action potential by a diffusion-reaction equation in which the first term refers to voltage diffusion through the tissue, and the second to the current flow through the cell membrane. In order for propagation of the activation process to occur, the depolarized cell must provide the neighboring cell with sufficient electric charge for the latter to reach the excitation threshold. The ratio between the available charge and the charge needed to achieve this threshold determines the propagation of activation, a fact expressed by the term "safety factor." When the quotient between the load generated and the load consumed during the excitation process of neighboring cells is <1, transmission does not occur. By applying these concepts, one- and two-dimensional models have been developed to analyze the propagation of the action potential into heterogeneous tissues and have been used to estimate, among other aspects, the biophysics of the propagation of flat, round and spiral activation waves, as well as reentry mechanisms.

In the mid-20th century, simulation of activation in two-dimensional structures was used in Moe applications done to study fibrillatory processes. In the last quarter of the 20th century, two-dimensional simulations such as those developed by Panfilov and Pertsov provided useful information on the characteristics of reentrant activation in excitable media and in biophysical models of the cardiac tissue under normal and pathological situations. These models have been used to study the movement of spiral waves, the destabilization and rupture of wavefronts and their relationship with various factors, such as the slope of the restitution curve of the action potential, anisotropy, and the anatomical limits encountered by activation waves during propagation through the cardiac tissues.[1,3,6,12]

The complexity involved in describing these processes has increased by adding other relevant aspects, such as the fact that cardiac cells are not uniformly connected and electric propagation in cardiac tissues is discontinuous. The presence of intercellular bonds, which are responsible for the electrical connection between the cells by allowing intercellular flow of ions, allows the transmembrane action potential to be propagated from one cell to another and converts the cardiac muscle into a syncytium. The intercellular connections are not evenly distributed, and this fact also causes the propagation to vary according to whether the direction is perpendicular or parallel to the longitudinal axis of the cardiac fibers. For these reasons, and in order to provide a more realistic view, the models have incorporated the presence of different kinds of cells connected by different intercellular bonds that can simulate conditions such as ischemia, stretching of the fibers or variations in intercellular coupling.

FUTURE APPROACHES

Current simulations focus on creating three-dimensional models that attempt to place the propagation of cardiac activation in structures more closely resembling real structures, although high-powered computing systems are necessary to develop these models.[1,3,13] The models include cardiac function and morphological data in the three-dimensional structure of the heart. The aspects considered include the positioning and orientation of muscle fibers and connective tissue in the ventricular walls, the geometry of the heart chambers, and the differences in the electrophysiological characteristics of the subendocardial, mid-myocardial and subepicardial cells. This approach is taken in order to simulate the propagation of cardiac activation in anatomical models of the heart that take into consideration the heterogeneity and anisotropy of the cardiac tissues. The inclusion of data related to cardiac mechanics, the contraction process and hemodynamic and metabolic variables as well as the use of new mathematical tools based on the chaos theory are some of the aspects where development will

provide greater precision to the simulation of the real phenomena that govern the functioning of the heart.[1]

APPLICATIONS

The development and use of models allows cell processes to be simulated by means of membrane equations, also making it easier to describe the behavior of groups of cardiac cells in two-and three-dimensional models, under both normal and pathological conditions, for example, during ischemia or in the presence of necrotic tissue or genetic alterations that cause ion channel disorders.

The use of models to study these phenomena sometimes makes it possible to avoid the limitations of clinical research and improve our knowledge of arrhythmias by effective simulation. These aspects provide a better understanding of abnormal cardiac electrical activity at various levels, i.e., in the ion channels, cells, tissues and organ. In addition to elucidating the mechanisms behind arrhythmias, they can facilitate the development and evaluation of antiarrhythmic agents. Nevertheless, the bases for the models and simulations are mathematical equations derived from our knowledge -increasingly complex but always incomplete and simplified- of the real phenomena.

There are two main approaches toward the tools used to create the models and simulations of cardiac electrical activity:[1,3,14] *a)* the creation of cellular automata which do not apply the equations that quantify the cellular action potential and the currents conducted by the membrane channels, and *b)* the models that include equations to describe ionic currents. The latter represent a heavy burden for computation processes, whereas the former do not. However, cellular automata models present limitations for the incorporation of certain processes in functioning, for example, the phenomena related to post-potentials.

This issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA[15] reports on the development of an electric activation model that describes cardiac tissue as a cellular automata system and combines the description of activation as a probabilistic process and repolarization as a deterministic process. Furthermore, the electrograms are simulated by calculating the cell currents with the use of a prototype action potential. This probabilistic cellular automata model simulates complex phenomena such as fibrillatory conduction or reentrant activation under stable and unstable conditions. The article reports a rigorous, attractive approach to describing the electrical behavior of the cardiac tissue by using a cellular automata model that does not require excessively complex calculations and that reproduces the behavior of curved and reentrant activation fronts. The introduction of a calculation for the activation probability, which considers the relationship with the time elapsed since the previous repolarization and the number of active cells, provides a broader capacity to simulate complex phenomena such as the dependence of conduction velocity on frequency or the degree of curvature of the activation front.

CONCLUSION

Cardiac arrhythmias are a relevant problem because of their incidence and clinical importance. Major efforts must be taken to achieve effective control by perfecting diagnostic techniques and therapeutic procedures and, even more importantly, by effective prevention to impede or hinder its onset. Mathematical models and simulations, along with adequate experimental and clinical studies, are complementary tools needed to achieve these goals.

REFERENCES

1. Smye SW, Clayton RH. Mathematical modelling for the new millennium: medicine by numbers. Med Eng Phys. 2002;24: 565-74.
2. Rudy Y. From genetics to cellular function using computational biology. Ann NY Acad Sci. 2004;1015:261-70.
3. Pollard AE. From myocardial cell models to action potential propagation. J Electrocardiol. 2003;36 Suppl:43-9.
4. Moreno J, Warren M, Jalife J. Corrientes iónicas y dinámica de la fibrilación ventricular. Rev Esp Cardiol. 2004;57:69-79.
5. Brugada R, Brugada J, Brugada P. Genética y arritmias. Rev Esp Cardiol. 2002;55:432-7.
6. Nash MP, Panfilov AV. Electromechanical model of excitable tissue to study reentrant cardiac arrhythmias. Prog Biophys Mol Biol. 2004;85:501-22.
7. Clayton RH, Holden AV. Propagation of normal beats and reentry in a computational model of ventricular cardiac tissue with regional differences in action potential shape and duration. Prog Biphys Mol Biol. 2004;85:473-99.
8. Álvarez López M, Rodríguez Font E. Registro español de ablación con catéter. II informe oficial de la Seción de Electrofisiología y Arritmias de la Sociedad Española de Cardiología (2002). Rev Esp Cardiol. 2003:56:1093-104.
9. Gersh BJ. El pronóstico cambiante del infarto de miocardio en la era de la reperfusión: implicaciones para la evaluación y el tratamiento de las arritmias ventriculares. Rev Esp Cardiol. 2003; 56:535-42.
10. Vázquez Ruiz de Castroviejo E, Márquez García A, Fajardo Pineda A, Lozano Cabezas C, Guzmán Herrera M, Ramírez Moreno A, et al. Patrones clínicos de presentación de la fibrilación auricular en los pacientes hospitalizados. Rev Esp Cardiol. 2003; 6:1187-94.
11. Ferrero J Jr, Sáiz J, Ferrero J, Roa L, Thakor N. Simulation of action potential from metabolically impaired cardiac myocytes: role of ATP-sensitive K+ current. Circ Res. 1996; 79:208-21.

12. Garny A, Kohl P. Mechanical induction of arrhythmias during ventricular repolarization. Modeling cellular mechanisms and their interaction in two dimensions. Ann NY Acad Sci. 2004; 1015:133-43.
13. Xie F, Qu Z, Yang J, Baher A, Weiss JN, Garfinkel A. A simulation study of the effects of cardiac anatomy in ventricular fibrillation. J Clin Invest. 2004;113:686-93.
14. Zhu H, Sun Y, Rajagopal G, Mondry A, Dhar P. Facilitating arrhythmia simulation: the method of quantitative cellular automata modeling and parallel running. BioMed Eng Online. 2004;3:29-43.
15. Alonso Atienza F, Requena Carrión J, García Alberola A, Rojo Álvarez JL, Sánchez Muñoz JJ, Martínez Sánchez J, et al. Desarrollo de un modelo probabilístico de la actividad eléctrica cardíaca basado en un autómata celular. Rev Esp Cardiol. 2005; 58:41-7.