The Virtual Heart: Physiology and Pathophysiology in Computers

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Summary

Today's pacemakers are able to almost entirely imitate the body's physiologic cardiac function for the treatment of various heart arrhythmias, and help improve the patient's quality of life. However, a much broader range of functions will be required of future implantable systems. Future implants must precisely quantify the risk of single events, such as sudden cardiac death, by constantly monitoring the organ status, thereby facilitating the early introduction of preventive measures. At the same time, the implants must feature a redundant design and offer both conventional defibrillation as well as various intervention options for the gentle termination of tachyarrhythmias. Currently, the scientific principles for such therapy types are being tested with the aid of computer simulations on a virtual heart model. This paper summarizes the physiologic and pathophysiologic cellular mechanisms that are used in computer simulations to depict atrial fibrillation. The virtual heart model describes all aspects of the physiologic expansion of electrical excitation within the atria, including circulating excitation caused by an anatomic obstruction.

Key Words

Virtual heart, computer model, cardiac physiology, cardiac pathophysiology

Introduction

The complexity of the human anatomy with its multifaceted illnesses poses one of the greatest challenges for research because a fine line is drawn between medicine and the natural and engineering sciences. The first task is to clarify the causal relationships between the molecular and cellular physiologic processes towards the level of the organ. The targets and mechanisms of pathologic changes can subsequently be identified using the developed quantitative models, and strategies for countermeasures can be established. The research and development phase yields novel medical products, therapy forms, or drugs, which must prove themselves during the course of daily clinical application.

Many conduction disturbances of the heart originate in specific ion channels of cellular membranes, whose quantity is decreased in the presence of disease as compared to normal physiologic values [1]. The resulting decreased conduction of Na^+, K^+, and Ca^{2+} ions in the membrane results in a diminished electrical excitation of individual cells or a weaker reciprocal electrical connection. This initially leads to a decreased conduction speed, and ultimately to an intermittent or permanent conduction disturbance on a macroscopic scale.

Pathologic changes to the ion channels can also result in a marked increase in the rate of excitation, i.e., tachycardia. This often manifests itself as a self-contained, circulating, electrical excitation of the heart during which the rate-determining function of the primary pulse generator of the heart, the sinus node, is overridden. Such tachycardias, i.e. fibrillation, can affect both the atria and the ventricles. The pumping function of the heart is constricted during atrial as well as ventricular fibrillation. Ventricular fibrillation is such a grave condition that death occurs within minutes. This is commonly known as sudden cardiac death. Today's implantable defibrillators are capable of effectively combating these kinds of single events by

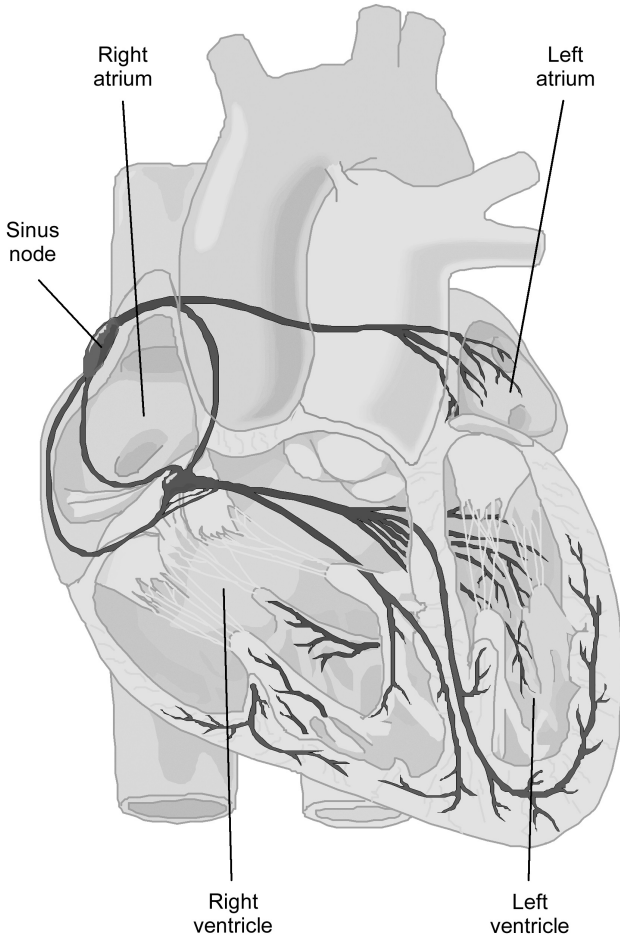


Figure 1. Schematic structure of the heart's conduction system.

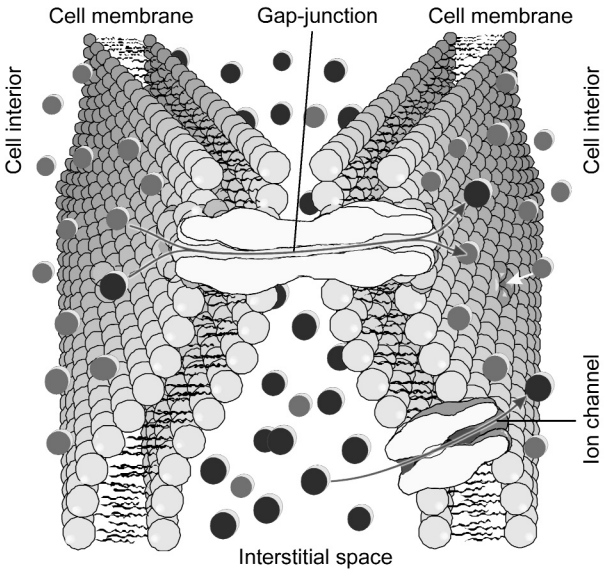


Figure 2. Schematic structure of the cell membrane (lipid bilayer) with ion channels (proteins), which facilitate the specific transport of ions from the cell interior to the interstitial space, and with gap junctions, which create a direct connection between two cells.

delivering a strong electrical shock to the heart after detecting ventricular fibrillation, thereby resynchronizing the cells of the heart muscle. Although defibrillation can often save lives, this exceedingly powerful shock produces a high degree of stress on the patient. Therefore, the future goal is to use defibrillation only in exceptional cases. Instead, fibrillation should be detected before it occurs and gentle countermeasures, such as targeted pacing methods, should be undertaken, which counteract or suppress the fibrillation during its formation phase. This vision for the future clearly outlines the tasks ahead for physicians, scientists, and engineers.

Physics plays an important role in elucidating the mechanisms and triggers that lead to atrial fibrillation or sudden cardiac death. In recent years, various concepts in physics that quantitatively describe biological clocks and turbulent waves in excitable media were successfully transferred to the heart [2,3]. The application of such universal concepts facilitated the first quantitative description of fibrillation and determined the required causal relationships between the ion channels and the heart, as a whole. However, these major strides were also made possible by complex numerical simulations, built upon the increasingly powerful calculating capability of modern computers, as well as improved software technology.

Physiology and Pathophysiology in Computers

Due to the close interconnection of physiologic and pathophysiologic processes in the human body, it is often impossible to establish definite "cause-and-effect" relationships through experimental observation. This is mainly because individual in vivo processes cannot be observed in an isolated manner largely out of principle or due to ethical reasons, thereby impeding the creation of clear-cut test conditions. Unfortunately, in vivo experiments do not offer an alternative in this respect, because the crucial feedbacks in terms of the control loop are often lacking. This is why numerical simulation on a virtual patient is continuously increas-

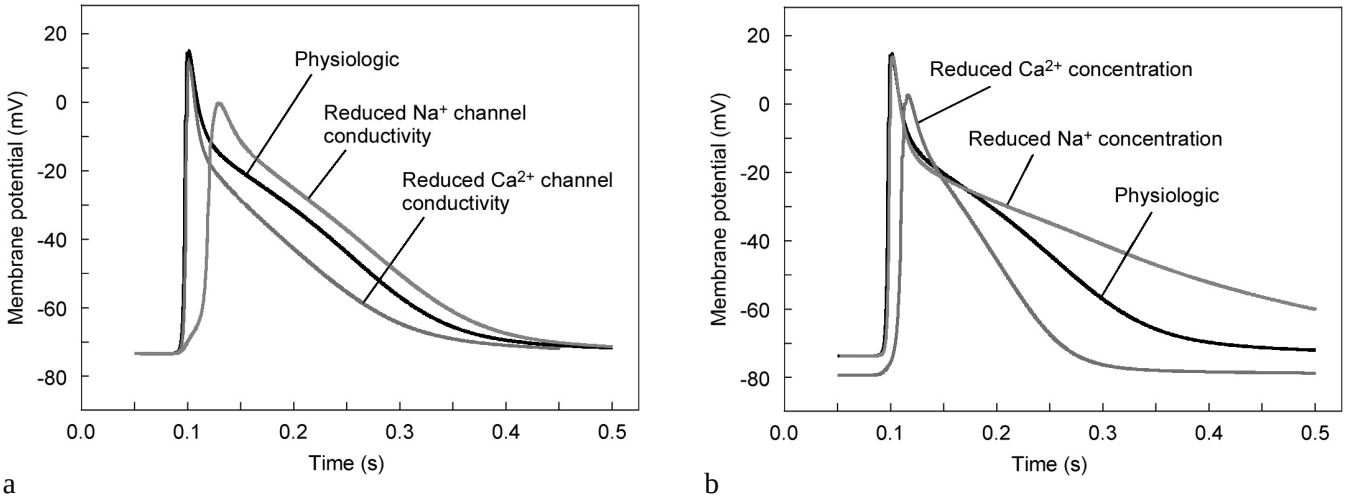


Figure 3. Panel a) Simulated electrical action potentials of cells from the human atrium. The effect of pathologically reduced conductivity of the Na^+ channel and the Ca^{2+} channel on the form of the action potential is exemplarily illustrated. Panel b) Same as Panel a. The effect of pathologically reduced extracellular concentrations of Na^+ and Ca^{2+} on the form of the action potential is exemplarily illustrated.

ing in importance. However, it must be emphatically stated that the development of this process is in its infancy, and very few questions can be reliably answered. Nevertheless, the vast potential of this method has already become apparent, especially for the development of complex medical products such as pacemakers and defibrillators.

The numerical simulation of the behavior of living systems rests upon the mathematical description of the cooperation among a countless number of individual elements. In the case of the heart, hundreds of thousands of cells contribute to the transmission of electrical excitation. Passing through the Ca^{2+} channels of the cells, this electrical signal ultimately triggers the microscopic mechanism of the force generation, which in turn generates vital blood flow by contracting the heart muscle as a whole.

In 1959, Hodgin and Huxley compiled differential equations that accurately described the dynamics of the various ion channels of the nerve and heart muscle cells [4]. Today, the experimental patch clamp technique can be used to determine the individual parameters of practically every cell type, and the electrical behavior of the cells can be precisely reproduced with the aid of an elaborate system of Hodgkin-Huxley equations. An example of this is the equation system for human atrial cells developed in 1998 by Nygren et al [5].

However, the quantitative description of individual cells' electrical behavior does not suffice to explain the collective phenomenon of fibrillation. In the case of the virtual heart, the required coupling of the cells takes place through so-called reaction-diffusion equations, which among other things, are also successfully used for describing other excitable media, such as Belousov-Zhabotinsky chemical reagents.

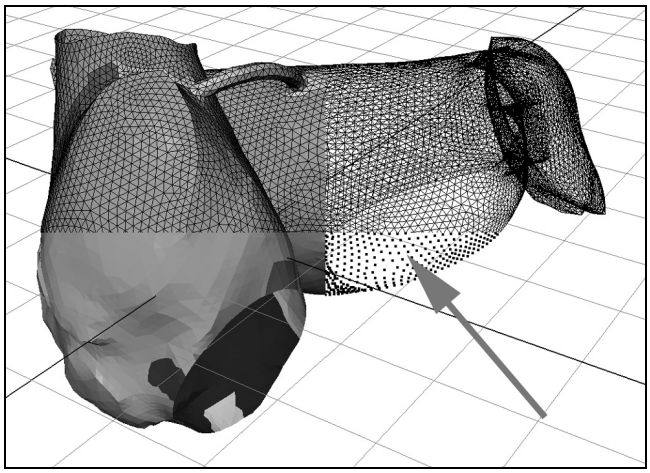


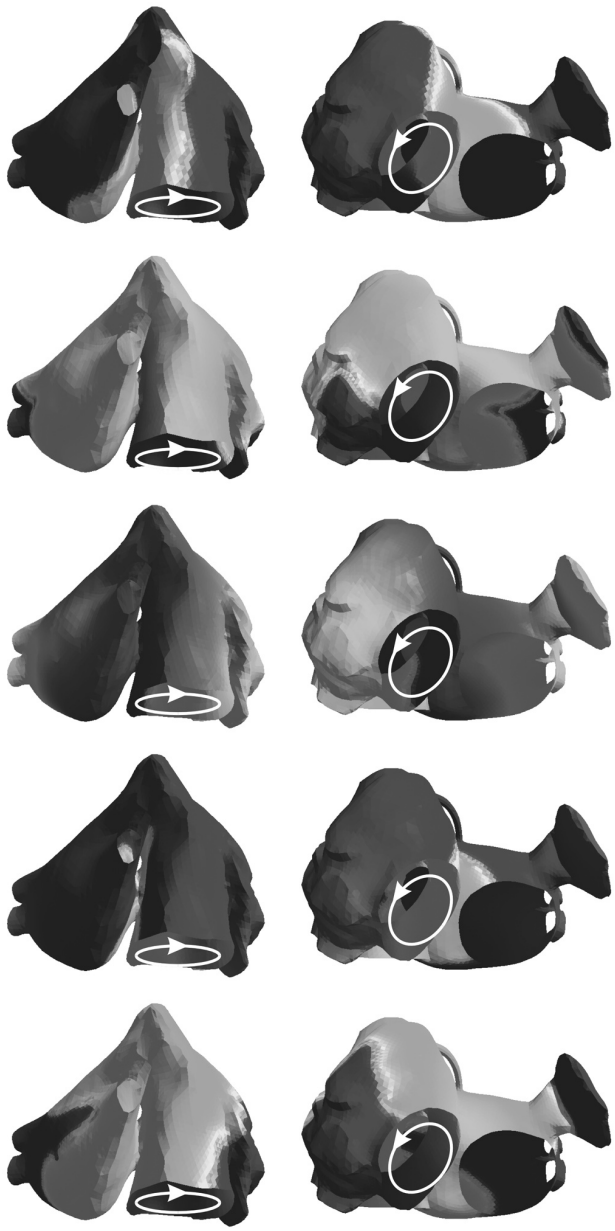
Figure 4. The virtual heart is comprised of both atria consisting of 37,000 supercells (see arrow). The coupling to the neighbor is shown as a grid in the upper right. Various tissue areas can be assigned individual microscopic parameters (shown here with different greyscales). In the lower right both ventricles are attached (see also Figure 1).

The Virtual Heart

The causes of atrial fibrillation and the possibility of gentle termination are research focal points at our institute. For this reason, the virtual heart is comprised of only the atria, to be viewed in this context as an independent system. Additionally, the atria can be described as a two-dimensional surface, because the tissue thickness measures only a few millimeters. In order to manage the sizeable calculation efforts, approximately 1,000 cells are combined to so-called supercells having an average diameter of 1 mm. It has been proven that this selection of parameters in no way decreases the significance of the simulation [6].

Figure 4 shows the geometric surface of the virtual heart, which is comprised of 37,000 nodes. Each node represents a supercell and is electrically coupled to its direct neighbors. Each supercell can be assigned individual parameters for the simulation, such as a specified conductivity for each ion channel. The same holds true for the strength of the coupling to its neighbor. In this manner, specific conduction pathways, such as Bachmann's bundle, or areas with varying conduction speeds can be simulated.

The model could be successfully validated for physiologic purposes and accurately describes all aspects of the expansion of electrical excitation in the atria [7]. Subsequently, the microscopic cell parameters were modified to resemble those values obtained from patch clamp measurements on atrial cells with chronic or paroxysmal fibrillation. It was proven that stable, self-preserving circulating excitation cannot exist in healthy human atria, i.e., the danger of fibrillation is extremely slight. Reduced cell coupling and a simultaneous partial block of certain ion channels increases this risk, and in rare cases causes an almost spontaneous tendency towards fibrillation. These results are consistent with the majority of clinical observations. A good example of this is shown in Figure 5, which illustrates an image sequence with circulating excitation that has developed around an anatomic obstruction, in this case the inferior vena cava.



a b

Figure 5. Simulation of circulating excitation around anatomical obstructions (Panel a – lower hollow veins, Panel b – tricuspid valve). The time interval between two consecutive images is 50 ms respectively.

Conclusion

The first experiments on the virtual heart have confirmed the possibility of using modern simulation technology for the quantitative reproduction of the most important aspects of physiologic and pathophysiologic processes. Future research will focus on developing techniques that can be used both to measure parameters as well as provide information about existing dangers of the occurrence of fibrillation. An additional objective will be to investigate whether gentle termination of atrial fibrillation is in fact possible, and if yes,

how this can be effectively implemented with an implantable pacemaker. The virtual heart offers sufficient potential to rise to this challenge.

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