Physics of Heart and Circulation

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

Summary

The early stages in the development of sciences were characterized by universality. It was mainly the technical revolution of the 20th century that brought about strict specialization that was necessary to handle the rapidly growing knowledge in all scientific fields, among them physics, biology, medicine and engineering. The new millennium, however, will require universality again, or more precisely, interdisciplinarity. Physics and medicine provide complementary methods of analysis and solution. The combination of both will have more effect than only the sum of the individual efforts. To this goal physics starts to explore novel fields of research at the interface to life sciences. Classical concepts from mechanics and electrodynamics, together with new developments, like nonlinear dynamics and irreversible thermodynamics open new ways to approach clinical problems and contribute to their solution, e.g., in the form of intelligent implants for the electrotherapy of the heart.

Key Words

Physics, heart, circulation, mechanics, electrodynamics, thermodynamics

Introduction

The leading role of physics in natural sciences is based on quantifiability, which has its root in determinism and predictability. Systems from the living nature in contrast very often lack deterministic features and the concepts and methods developed for the description of classical physical processes cannot be applied to explain their temporal development, as chance seems to dominate. Nevertheless, some evolving fields of physics attempt to explore the behavior of complex open systems that constantly exchange mass and energy with their environment and exhibit self-organization in thermodynamic states far from equilibrium. The hope for success stems from the belief that the basic rules of life cannot be different from those of classical physics, although they might still be well hidden before our mind. We are only beginning to develop a more profound understanding of complexity by starting to define rules that describe complexity itself, without having to pay too much attention to all the details of a given system. Once having understood complexity, some simple assumptions will be sufficient to make statements about complex systems and even allow the prediction of their temporal evolution.

The concepts of physics that are applied to heart and circulation originate mainly from mechanics, electrodynamics, nonlinear dynamics and thermodynamics. In this article physical approaches to physiological and clinical problems will be introduced.

The heart is a sophisticated mechanical pump that builds up the necessary pressure to ensure blood, and, thus, nutrient and oxygen supply even to the most distant cells of the body. The laws of mechanics and hydrodynamics govern the pulsatory pumping function as well as the details of blood flow patterns in the elastic vessels. A variety of sensors continuously regulate pressure and flow in complex feedback loops with the heart as the main actuator, the most prominent among them being the baroreflex. The coordinated action of the pump is achieved by a control system that comprises the sinus node as a tunable clock generator and the highly specialized cardiac conduction system that functions as a series of delay lines. It is just the electri-

cal activity of the heart that attracted many physicists over the past two decades and the description of the myocardium with the physical concepts of excitable media considerably advanced the understanding of the clinical observations of atrial and ventricular fibrillation. Ilya Prigogine pointed out that most of the physics that determines our everyday environment deals with irreversibilities and that classical physics with its foundation on time-reversibility is nothing but a specialization to a few rare cases that exhibit (almost) complete reversibility [1]. As evidenced by our personal experience, life is in fact totally irreversible and moreover not represented by successive states of thermodynamic equilibrium.

Mechanics of the Heart and Circulatory System

As far as mechanics is concerned, the application of the fundamental laws of physics is straightforward, but quite complicated when aiming at numbers. Newton's law of mechanics states that a force F applied to an object of mass m leads to an acceleration a of the object. Physiological or clinical problems that are related to mechanics mainly focus on the question of how to define a model that best describes the pumping function of the heart under different boundary conditions. The objective is to obtain the macroscopic pressure-volume (p-V) relation that results from the collective contraction of a huge number of individual cells and to subsequently correlate microscopic parameters with macroscopic observables in healthy and diseased states. Figure 1 shows examples of p-V plots obtained from a heart in healthy condition (1a) and in case of congestive heart failure (1b).

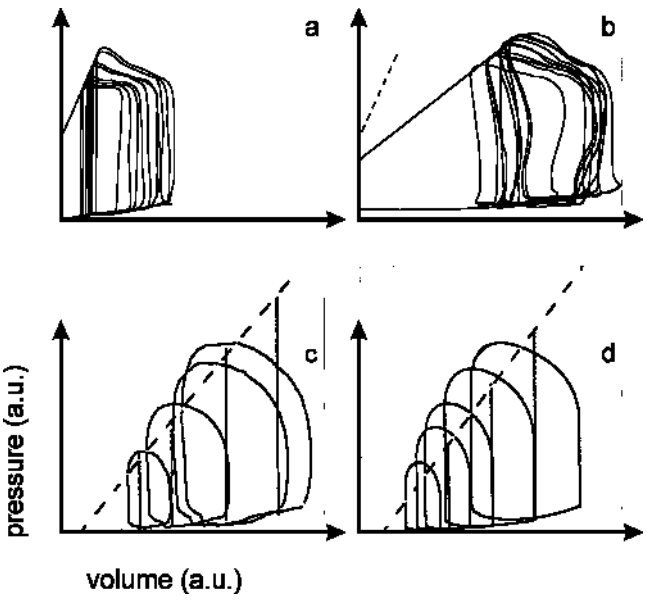

Figure 1. p-V diagrams of the left ventricle. Data obtained from a healthy human heart (a) and from a subject suffering from congestive heart failure (b). Comparison of experimental data obtained from a dog ventricle (c) with results of the simulation of the cardiac contraction with a simple spherical model heart (d); (a),(b): modified after [2]; (c),(d): modified after [3].

In case of the heart the force F is not applied externally, but is generated in the contractile elements of the myocardial cells by a Ca^{2+}-triggered chemical reaction between the macromolecules actin and myosin (see e.g. [4]). The accelerated mass m comprises the masses of the myocardium and the enclosed blood volume. The myocardium can thus be represented by a material that exhibits elastic properties that depend on time, i.e. with a dynamic stress-strain diagram. A simple mechanical model that relates the muscle stress σ and strain ε to the pressure p and volume V is a thick-walled sphere with uniform properties and with σ assumed to represent the average stress across the wall. Under these assumptions the model formulates as follows [5]:

$$r_i = (3V/4\pi)^{1/3}$$

$$r_o = [(3/4\pi)(V+V_{wall})]^{1/3}$$

$$p = \sigma(r_o^2 - r_i^2)/r_i^2,$$

where V_{wall} is the volume of the myocardial wall. By an appropriate choice of the muscle length it is then possible to adjust the strain ε to its correct values for the relaxed and contracted heart. Using this simple heart model and a mathematical formulation of the Ca^{2+}-triggered interaction between actin and myosin many fundamental aspects of ventricular performance are accounted for and even a realistic estimate for the time course of tension-dependent heat generation in the myocardium can be obtained [3]. The comparison between experimental data (Figure 1c) and simulation (Figure 1d) shows very good agreement, despite the simplicity of the model.

From the given example it becomes clear that even seemingly oversimplified models can be very useful in providing insight into the physical mechanisms behind physiological processes. However, they need refine-

ment and must be combined with models for other subsystems in order to correctly reflect the properties of a complex organ or even a system of organs, like heart and circulation.

In a second step the spherical heart model can be replaced by a so-called sphere-ellipsoid model. A thick-walled sphere models the left ventricle and one half of a thin-walled ellipsoid that is attached to it represents the right ventricle [6]. This setup is shown in Figure 2a. With this model, equations for the three ventricular walls are obtained, namely the free walls of the left and right ventricle (lfw and rfw in Figure 2a) and the septum (spt in Figure 2a). These equations again relate the pressures that are developed in the left and right ventricle (p_{LV} and p_{RV}) to the volumes and take elementary characteristics of the muscle dynamics into account [6]:

$$p_{LV} = 2\sigma_{lfw}/(r/d_{lfw}-1)$$

$$p_{RV} = 2\sigma_{rfw}/(r/d_{rfw}-1)$$

$$p_{LV} - p_{RV} = 2\sigma_{spt}/(r/d_{spt}-1).$$

For an explanation of the symbols see Figure 2a. This more complex model allows to simulate the simultaneous contractions of the left and right ventricles and includes their mutual interaction. The wall tensions of the left and right free walls as well as the septum are depicted in Figure 2b. It is thus possible to investigate the influence of microscopic properties of the myocardium on the ability of the heart to generate the necessary pressure, like e.g. details of the length-tension relationship or of the sympathetic and parasympathetic activity. From the model p-V diagrams are readily obtained for both ventricles and an example is shown in Figure 2c. The two models described above do not yet take into account the complex fiber structure of the myocardium that leads to a contraction along a ‚screw trajectory'. The inclusion of this more realistic heart geometry and of other inhomogeneous properties of the myocardium will give answers to more complex questions but requires finite-element models with considerably higher numerical effort.

Equipped with a mechanical model of the heart it is possible to extend the latter and include the circulatory system. For this purpose so called Windkessel models are employed. The combined properties of the vessels as flow resistors and blood reservoirs are separately treated in these models. Simulations of the circulatory

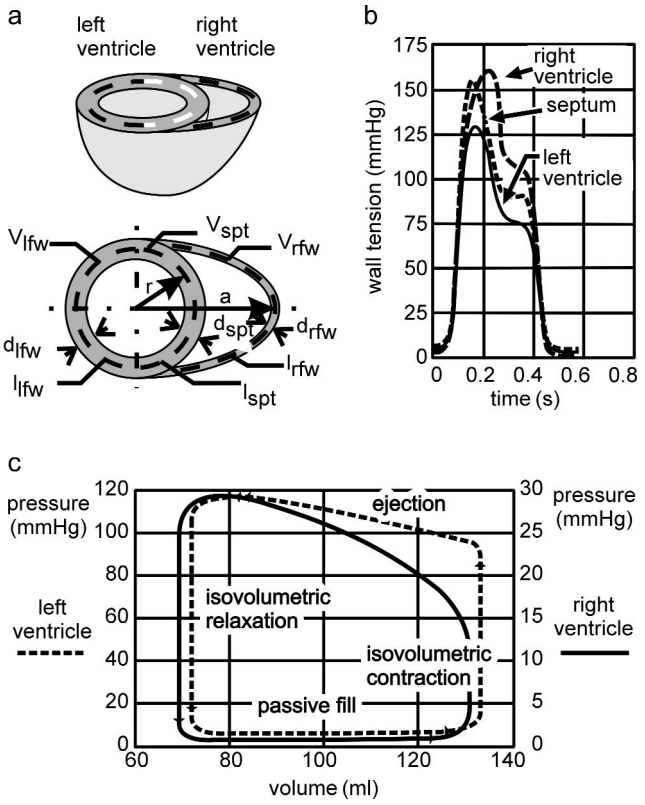

Figure 2. The sphere-ellipsoid model of the heart [6]: geometric setup (a), wall tension as a function of time for the three walls of the model (b) and p-V diagrams for the left and right ventricles obtained from the simulation (c). Explanation of symbols: lfw: left free ventricular wall, rfw: right free ventricular wall, spt: septum, V: volume, d: wall thickness, l: circumference of the wall section, r, a: diameters of the sphere and the ellipsoid.

system with up to 13 passive compartments have already been performed [7]. The relations that govern the blood flow in the different compartments, i.e. in the vessels can be defined as analogs to electrical circuits with resistors, capacitors and inductivities. In this way pressure can be related to electrical potential, volume flux to current, volume to charge, flow resistance to electrical resistance, compliance to capacity and inertance to inductance [6]. The short-term regulation of the mean arterial blood pressure is simulated by modeling the baroreceptor reflex as an electrical regulation circuit that mimics the function of the physiologic neural feedback loop [7].

In order to contract, each and every cell of the heart needs a Ca^{2+}-trigger, i.e. an influx of Ca^{2+}-ions into the intracellular space. This Ca^{2+}-supply is provided by the

sudden release of calcium from intracellular reservoirs which in turn is initiated indirectly by an electrical stimulation of the cell membrane. Details of this electromechanical coupling influence the shape of the p-V diagram and thus the efficiency of the pump. The partial loss of the electromechanical coupling has severe consequences and manifests directly and indirectly in various forms of clinically observed cardiac malfunctions.

Electrodynamics of the Heart

Besides the electromechanical coupling the correctly timed conduction of electrical excitation along the different branches of cardiac conduction paths and within the myocardium itself is the basis of a coordinated mechanical contraction and thus of the pumping action. The mechanisms of the various forms of cardiac arrhythmia are closely related to disturbances of the conduction that finally results in an impaired pumping power. The details of the conduction process and especially the speed of excitation spreading are influenced by processes acting at different structural levels of the myocardium. These levels are depicted in Figure 3. The macroscopic arrhythmic state is triggered by a microscopic source of irregular electrical activity, due to the malfunction of a group of ion channels. The reentry-based arrhythmias are often triggered by early afterdepolarizations (EADs). Hypotheses concerning the mechanisms of EADs can be tested and validated on the cellular level by using a computer model of cardiac action potentials [8]. The model is constructed according to findings from electrophysiological investigations. The essential mechanism consists in the generation of a so-called calcium window during the repolarization phase of the action potential, which is due to an alteration of the calcium L-type channel caused by excessive ß-adrenergic stimulation of the cardiac tissue. The most critical consequence of EADs is a pronounced prolongation of the action potential duration, which increases the dispersion of refractoriness. This in turn may locally induce a unidirectional transient block of excitation spreading, which favors reentrant circuits. The existence of an excitable gap finally is required for the reentry to be stable.

Model based investigations of cardiac arrhythmia are performed in two steps. Microscopic phenomena are investigated at the cellular level, whereas a model description at tissue level is performed to analyze the

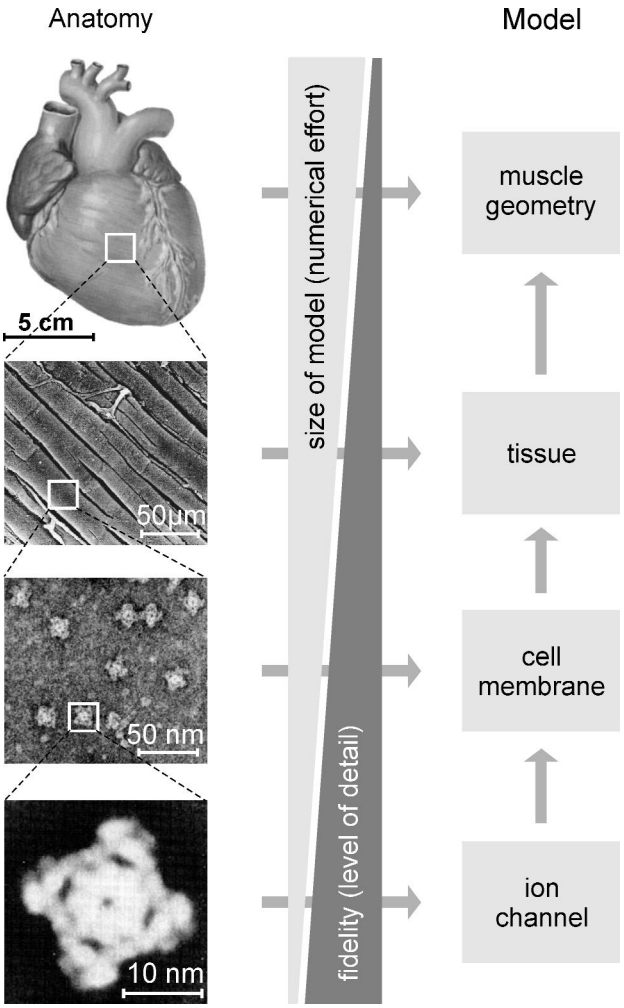

Figure 3. The different levels of model-based investigations of the electrodynamics of the heart [9]. Each level has its own balance between the possible level of detail and the necessary numerical effort.

macroscopic processes. The models are designed according to the basic principles of simulation theory. Considering the discrete structure of cardiac tissue, the system is divided into subsystems - the tissue into cells and the cells into subcellular structures like ionic channels, pumps, and exchangers. These subsystems are modeled separately and combined later according to their physiological interactions. The main limitations of simulations are at any time given by the available computational power. The ever advancing computer technology will continuously shift this balance to a higher level of detail (Figure 3).

A very successful alternative description of the process of excitation spread is provided by the physical con-

cept of excitable media. The currently available computing power makes it possible to integrate the underlying reaction-diffusion equations on large two- or three-dimensional grids and thus realistic models of the heart can readily be obtained. The basic equations that define the properties of the myocardium as an excitable medium are in their simplest form given as

$$\varepsilon\, \partial u/\partial t = \varepsilon^2\, \Delta u + f(u,v)$$

$$\partial v/\partial t = g(u,v),$$

where u describes the activation of the excitable elements, v is the inactivation, ε is a small parameter that describes the ratio of the time constants of activation and inactivation and f and g are the source terms for activation and inactivation. The activator u can be identified as the transmembrane voltage and v as the sum of the inactivating or repolarizing currents. The source terms f and g are defined in the underlying model for the cellular ionic exchange currents and ionic concentrations.

The objective of the electrodynamic model of the heart is to quantify the influence of microscopic cellular properties on macroscopic observables, like e.g. the susceptibility of the atrial or ventricular myocardium to fibrillation. This goal is achieved by analyzing the solutions of the equations for different sets of system parameters, like e.g. the maximum conductances of the various ion channels. Making use of the clinical knowledge about empirical correlations between channel properties and manifestations of various forms of diseases it is possible to gain insight into the hidden microscopic processes that determine the macroscopic observations, like it has already been the case for the mechanical subsystem in the last section.

It can be shown analytically and numerically that one class of solutions of the reaction-diffusion equations consists of so-called rotors that lead in the course of time to turbulence in the excitable medium. According to A.T. Winfree the generation of rotors originates from a fundamental property of cardiac cells and all other biological clocks [10-11]. The latter are vulnerable to a complete loss of information about the absolute time when subjected to an ill-timed stimulus of definite strength. The vast majority of stimuli will merely set the clock to another time, while the critical stimulus puts the clock into a mathematically undefined state, in a so called singularity. It can be shown that all excitable media are vulnerable to such stimuli

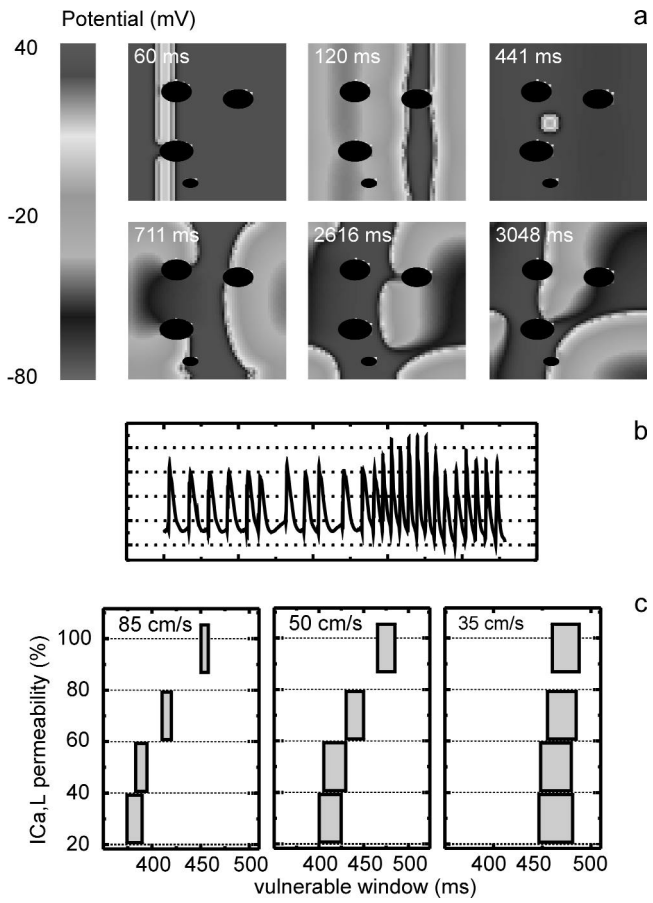

Figure 4. Simulation sequence showing the development of rotors (after 711 ms) and finally of electrical turbulence on the human atria (a). The turbulence manifests itself in an irregular intracardiac electrogram (b). The width of the vulnerable window can be obtained from simulations performed with different sets of system parameters (c). The temporal width of the vulnerable window increases with reduced excitation velocity (85 -> 35 cm/s) and reduced Ca^{2+}-channel permeability (100 - 30%). It is a measure for the susceptibility of the atria to support fibrillation. (The squares depicted in (a) represent the projection of the surface of both atria. The black ellipses denote the positions of blood vessels [12]).

and that the window in time and stimulus strength strongly depends on the system parameters that are contained in u and v. Figure 4a shows an example for the simulation of the generation of a rotor on the human atria [12]. These rotors are the precursors for the clinically observed phenomenon of fibrillation (Figure 4b).

The analysis of an electrodynamical model of the heart within the physical-mathematical framework of excitable media thus led to the novel interpretation of

(atrial) fibrillation as a consequence of a universal property of all biological clocks. In a second step, the major microscopic parameters have been identified that determine the susceptibility of the myocardium to fibrillation. Figure 4c shows how the size of the vulnerable window, i.e. the probability for the occurrence of fibrillation, depends on the velocity of the spread of excitation and the maximum calcium channel conductance [12]. Although both parameters had already before been suspected to favor fibrillation, there has only been empirical evidence. The excellent agreement of the simulated results and of clinical data allows to quantify the clinical observation and is the basis of a targeted development of novel therapeutic strategies.

Thermodynamics of the Heart

The myocardial contraction and the underlying cellular mechanisms are commonly described using the terminology of mechanics and electrodynamics, like it has been outlined above. Thermodynamics offers an alternative approach to the description of the myocardial function. The laws of thermodynamics, however, were originally derived for closed systems in which the actions of all physical processes drive the system to an equilibrium state that is characterized by some energetic minimum and a maximum of entropy. Living systems, in contrast, are always open systems that exchange matter and energy with their environment and thus do not exist in equilibrium states in the sense of thermodynamics. It is nevertheless possible to use the term efficiency in connection with the heart when considering it as a thermodynamic machine that transform the supplied energy into mechanical work that is performed on the blood volume that is ejected in each cardiac cycle.

Cesarman et al. [13-14] discuss the cardiac function from the point of view of irreversible thermodynamics. Without considering the detailed functioning of the system it is possible to introduce the concept of entropy and redefine diastole and systole as active and resting thermodynamic states. The constant struggle of the organism against the increase of entropy moves to the center of interest. New ways to interpret the healthy and diseased states of the heart and circulation are defined and therapy is associated with supporting the organism in this struggle. This notion is especially useful in connection with a discussion of various aspects of Closed Loop Stimulation.

Conclusion

All the above said leads to a new point of view about the interrelation between physics and medicine. The object under investigation is in fact the same, only the conceptions of observation and interpretation and the applied tools are different, although highly complementary to each other. An important first task is the definition of a common language that allows to exchange and potentiate the expert knowledge of physiologists, physicians and physicists. In this way novel solutions for clinical problems will be found and a large number of patients will benefit from these efforts.

References

[1] Nicolis G, Prigogine I. Self-Organization in Nonequilibrium Systems. John Wiley & Sons, New York, 1977.

[2] Braunwald E. Essential Atlas of Heart Diseases. Appleton & Lange, Current Medicine, 1997.

[3] Burkhoff D. Explaining Load Dependence of Ventricular Contractile Properties with a Model of Excitation-Contraction Coupling. J Mol Cell Cardiol. 1994; 26: 959.

[4] Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. Molecular Biology of the Cell, Garland Publishing. New York, London, 1994.

[5] Grossman W, Braunwald E, Mann T, et al. Contractile State of the Left Ventricle in Man Evaluated from End-Systolic Pressure-Volume Relations. Circulation. 1977; 56: 845.

[6] Urbaszek A. Konzeption und technische Lösungen zur Optimierung der frequenzadaptiven Elektrostimulation des Herzens. Fachverl. Schiele und Schön, Berlin, 1995.

[7] Polley R. Thesis: Modellbildung des kardiovaskulären Systems zur Untersuchung der hämodynamischen Kurzzeitanpassung. University of Erlangen-Nuremberg, 1998.

[8] Weiss I, Urbaszek A, Schaldach M. Biophysical mechanisms of cardiac arrhythmogenesis. Herzschrittm. 1999; 19: 63.

[9] Weiss I. Thesis: Analyse der elektrischen Funktionsmechanismen von Herzrhythmusstörungen als Grundlage neuer Ansätze zur elektrotherapeutischen Prävention. University of Erlangen-Nuremberg, 1999.

[10] Winfree AT. The Geometry of Biological Time. Springer, Berlin, Heidelberg, New York, 1980.

[11] Winfree AT. When Time Breaks Down. Princeton University Press, 1986.

[12] Lang V. Thesis: Entstehung und Stabilität von Rotoren in erregbaren Medien. University of Erlangen-Nuremberg, 1999.

[13] Cesarman E, Brachfeld N. Thermodynamics of the Myocardial Cell. A Redefinition of its Active and Resting States. Chest. 1977; 72: 296.

[14] Cesarman E, Brachfeld N. Bioenergetics and Thermodynamics of the Cardiac Cycle. In: New Horizons, Cardiovascular Disease. Part 1. Kones, RJ (ed). Futura, New York, Mount Kisko, 1980.