Preface

Biomedical science has been driven in the eighteenth through the twentieth centuries by the promise to deliver lifesaving therapies against disease and to extend human life. Development of all branches of biomedical sciences, including cardiac electrophysiology, went through a periodic adherence to either reductionist or integration approaches. Cardiac electrophysiology strived to deliver therapy against arrhythmias, which are still responsible for one of four deaths in the industrialized world.

Reductionist Approach to Arrhythmia

A dramatic increase in understanding of the molecular mechanisms of normal and abnormal cellular electrophysiology led to development of new theories of arrhythmia. A number of these theories have been supported by a convincing empirical evidence “from cell to bedside.” And, as a result, the field has been propelled by promises to society of elegant, “silver bullet” pharmacological solutions against lethal cardiac arrhythmias. Nearly every generation of electrophysiologists has come up with a target of their own “silver bullet”: sodium channel, calcium channel, potassium channel, gap junction, and so forth. Visions of several generations have crystallized into the recent development of theory of chanelopathies.

According to one saying, every new thought is a long forgotten old one. The state of the arrhythmia research is reminiscent in some sense of an earlier history of the elementary particle physics. It appeared to many physicists at the time that the foundation of laws of matter can be eloquently explained by the interaction of very few elementary particles and very few fundamental laws governing these interactions. Yet, as more and more unexpected particles or peculiar properties of the existing particles were uncovered, the increasingly more sophisticated theories were produced, making irrelevant the elegance and eloquence of the earlier theories. And this process goes on.

Cardiac electrophysiology went along a very similar path in search of antiarrhythmia therapy. A giant of the field, Carl J. Wiggers, drafted a road map more than a half a century ago:

As to the fundamental mechanisms of fibrillation we have plenty of theories, but none is universally accepted ... they all center around two ideas, viz., (a) that the impulses arise from centers, or pacemakers, or (b) that the condition is caused by the re-entry of impulses and the formation of circles of excitation.

The old ion channel–based theory seemed to have done a pretty good job explaining both focal and reentrant theories of arrhythmia. These early theories of arrhythmia, with their four classes of antiarrhythmic drugs, were almost Aristotelian. But they fell under the
pressure of empirical evidence: ever multiplying channel isoforms and subunits; alternative splicing variants of these proteins; mutations in genes encoding ion channels; numerous increasingly complex signaling pathways; unexpected proteins expressed and functioning in concert with channels. These important players had been unknown, overlooked, or neglected in the past and present new opportunities in the future.

Can a cardiac arrhythmia with broad clinical impact be explained within a framework based on a single channel biophysics or even a single cell physiology? And, most importantly, can a treatment be developed for it based on such a mechanism? Despite the explosion in the number of filed patents offering exactly such answers, it is becoming more and more apparent that these questions will not be so easy to answer. Integrative approaches are needed to synthesize the wealth of knowledge obtained by the reductionists.

**Integrative Approach**

Integrative physiologists looked at the arrhythmia from an opposite direction: How one can restore normal rhythm in hearts with failed sinoatrial or atrioventricular nodes using technological means available to us at the present time? How one can terminate lethal ventricular fibrillation using biomedical engineering approaches? Electrotherapy, including implantable devices and ablation, has emerged as the only effective therapeutic approach to treat arrhythmia, often without precise knowledge of the mechanisms of arrhythmia it treats. History of cardiac bioelectric therapy is long and fascinating, spanning several centuries, many countries, and several continents. Ideas to use electricity for treating cardiac disorders apparently have been born in the minds of the Italian, French, and British physicians and physiologists as evident from the numerous eighteenth-century publications in these languages, culminating in arguably the first report of a patient’s treatment for cardiopulmonary arrest by electricity from Charles Kite. The nineteenth-century cardiac physiology has brought about both recognition of importance of arrhythmia as a direct cause of death and provided compelling evidence for the ability of electric stimulation to restore normal sinus rhythm in cases of both bradycardia and tachyarrhythmia. The twentieth century finally brought to fruition three centuries of research and developed an array of therapies that now save millions of patients worldwide with more than a million new implantations annually.

In this book major aspects of the development of this truly outstanding achievement are presented: bioelectric therapy of cardiac arrhythmia that allowed a significant extension of human life. Leading experts in the field contributed rigorous accounts of historical, theoretical, experimental, engineering, and clinical tracks of the development of implantable device therapy. A history of cardiac bioelectric therapy has not yet been written. However, let me conclude with a vision that was formulated by Hubert Humphrey in the U.S. Senate in October 13, 1962, after his meeting with Professors Vladimir Negovsky and Naum Gurvich that led to his recognition of importance of defibrillation and to subsequent increased federal and private financial support for this important field of physiology and medicine.
I do, however, want to state that it is one of the most important of all phases of medical research. Why? Because it concerns the most universal interest of man; namely: the prolongation of human life, the postponement of death, and, yes, perhaps the greatest scientific frontier—the reversibility of death...

What do I urge, therefore? I urge establishing under NIH support of specialized centers or institutes on the physiology of death, on resuscitation and on related topics. I urge that the United States compete with the U.S.S.R. in bold research toward at least partial conquest of death. Already our scientists and Russian scientists are cooperating in categorical studies of heart ailments, cancer and other diseases. Now, let us recognize that a new category has emerged—the oldest category in the world—but one which commands our newest efforts—the category of death, itself...
References

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