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Challenging cardiac electrophysiology

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At the launch of this new Journal in the field of cardiac electrophysiology, Frontiers in Cardiac Electrophysiology, one may wonder which challenges lie ahead in cardiac electrophysiology. Are the textbooks on cardiac electrophysiology complete?

In the past century enormous progress has been made in the understanding of cardiac electrophysiology and this has contributed to the prolongation of life expectancy of patients with cardiovascular diseases. The increments in knowledge of the electrophysiological effects of acute myocardial ischemia and infarction illustrate this point, although other examples are abundantly available.

Sir James Mackenzie wrote in his 'Diseases of the Heart' in 1913 (Mackenzie, 1913), that angina pectoris was caused by a nervous irritation, and that patients may die 'during the faint'. The ability to record and interpret the electrocardiogram (Einthoven, 1895) has since then led to better diagnosis and monitoring of cardiovascular disease. As a result we now recognize that acute myocardial ischemia is highly arrhythmogenic and may lead to ventricular fibrillation within several minutes after the start of coronary occlusion (Julian, 1996). Reentry has been hypothesized as a mechanism of cardiac arrhythmias by Mines as early as 1914 (Mines, 1914), but it took until 1980 before it was directly demonstrated that a reentrant mechanism underlies ventricular fibrillation in the setting of acute myocardial ischemia (Janse et al., 1980). The occurrence of the arrhythmia is facilitated by heterogeneities in excitability and refractoriness (Janse and Wit, 1989; Coronel et al., 1991) and is initiated by a premature beat resulting from a 'current of injury' (Janse et al., 1980). The development of the defibrillator has contributed to the institution of specialized emergency coronary care units (Alexander et al., 1961). Also, better understanding of cardiac ion channel physiology and recording of the cardiac transmembrane potential (Weidmann, 1951) has played a role in the development of specific anti-arrhythmic drugs. Antiarrhythmic cardiac surgery and cardiac catheter ablation has played an important role in the treatment of patients with drug-refractory arrhythmias (Wallace et al., 1974; Guiraudon et al., 1981). The implantable automatic defibrillator offers protection to an increasing number of patients since its application to humans by Mirowski et al. (1980). We also have gained information about the role of familial predisposition to develop ventricular fibrillation following myocardial ischemia (Dekker et al., 2006).

Although these developments have contributed to improved prevention, diagnosis, and treatment of cardiac arrhythmias in the setting of ischemia and infarction and similar advances have occurred in other fields in cardiac electrophysiology, sudden arrhythmic death is still one of the major modes of death in Western Society (Myerburg and Spooner, 2001). Thus, treatment and prevention are suboptimal. Also, large multicenter randomized placebo controlled trials on the efficacy of antiarrhythmic drugs have failed to show a beneficial effect (Cairns et al., 1997; Julian et al., 1997), or even have demonstrated an adverse effect (Echt et al., 1991). This in itself is a sufficient rationale for research in cardiac electrophysiology.

Another reason for facing the challenges of cardiac electrophysiology is the altered cardiac patient population. Since patient management in the setting of acute coronary syndromes has improved the cohort of patients that has survived the acute event has increased (Myerburg and Spooner, 2001). These patients tend to present later in life with chronic cardiac diseases such as hypertrophy, heart failure and cardiomyopathies. At present, approximately 14 million people in Europe alone suffer from heart failure and this number is forecast to increase to 30 million by the year 2020[1]. About half of these patients will die from brady- or tachyarrhythmias (Kjekshus, 1990).

Thus, the patient population in the electrophysiological cardiology wards will be older, have multiple, and more complex diseases, and more often suffer from chronic heart diseases than before. At the same time, a young population of apparently healthy individuals that is at risk for sudden death is now increasingly recognized by genetic screening. Association studies have identified numerous genes that are coupled to cardiac diseases, but the functional role of mutations in these genes is often not clear. The relations between the electrophysiological changes in patients with hereditary or chronic cardiac diseases is often far from clear. This calls for an integrated type of research, combining relevant models of these diseases with electrophysiological studies.

Additionally, a remarkable discrepancy exists between the level of detail obtained in the molecular biological and functional levels of study in some areas in cardiac electrophysiology. Our understanding of cardiac repolarization may serve as an example in case. In recent years the understanding of the repolarization process has soared with a multitude of the molecular biological (genetic and proteomic) studies on mutated ion channels responsible for repolarization, linking (altered) structure of the channel with altered function (Nerbonne and Kass, 2005). The literature on the hereditary Long QT syndromes is a good example of this scientific approach (Schwartz et al., 2001). The functional experiments supporting the molecular biological studies often use expression systems of human ion channels in cultured, non-cardiac, cells (Bebarova et al., 2008). The extrapolation of these results to the organ or to the organism is difficult, because not enough detailed mechanistic information is available from the more integrative levels of research about the genesis of the (normal and abnormal) T-wave or its relation with the arrhythmias (Opthof et al., 2009). The morphology of the T-wave, already described by Einthoven (1895) has been attributed to the reverse transmural repolarization sequence in comparison with the endo- to epi-cardial activation sequence. This mechanism is generally accepted and has been presented in many textbooks (Bayes de Luna et al., 2006). However, the exclusive causal relation between the transmural gradient of repolarization and the T-wave is a matter of controversy, because mapping experiments in intact hearts have demonstrated that repolarization is almost

[1]Study group on Heart failure Awareness and Perception in Europe (SHAPE): http://www.heartfailure-europe.com/index1.php?item=153

synchronous between the various transmural layers (Coronel et al., 2005, 2007; Janse et al., 2005; Opthof et al., 2009).

Apart from the apparent gaps in knowledge identified above, many other questions remain to be answered. Some of these questions relate to modulation of electrophysiology by diseases and modulation of disease by electrophysiology (as in the mutual relation between atrial structural remodeling and arrhythmogenesis), to the interaction between mechanical work and electrophysiology (how can biventricular pacing be most effective, how does pacing affect electrophysiology?), and to the many modulating influences on the heart as a whole or its electrophysiology (influences of the brain, diet, environmental factors, cholesterol levels, gender, concurrent disease, drugs, genetic variations). Many other unresolved problems remain, such as the influence of the phosphorylation status of proteins and of intracellular ion concentrations on ion channel function, and on fundamental issues as the inverse problem (how to quantitatively reconstruct an activation- or repolarization-sequence from the body surface electro-cardiogram). The textbooks on cardiac electrophysiology are therefore not yet complete, and significant information is still lacking.

Closing the gap between molecular and whole-heart electrophysiology, and gaining equally detailed knowledge on all levels of research and in relation with chronic diseases is the main challenge in current and future research in the field of cardiac electrophysiology. With the launch of Frontiers in Cardiac Electrophysiology, a novel platform is created for high quality research on clinical and experimental level, aimed at facing these challenges in the exciting field of cardiac electrophysiology. Frontiers in Cardiac Electrophysiology provides new tools for these challenges. Open access, tiered publication in four levels, open peer review, and direct interaction with the reviewers set the stage for optimal exchange of scientific information.

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