Computational cardiac electrophysiology is ready for prime time

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In 1952, Hodgkin and Huxley published their paradigm mathematical model of the squid nerve action potential,1 for which they received the Nobel Prize in Physiology and Medicine in 1963. Since then, mathematical models in physiology have developed through the integration of knowledge acquired by experimental and clinical means and improvements in computational methodologies, and importantly they have gained a key role in the investigation of most physiological systems. Their application to the heart was soon realized through Noble’s work,2 and right from the beginning, cardiac modelling allowed to gain physiological insights through predictions of phenomena and mechanisms later confirmed or disproved experimentally.

For over half a century now, computational models have been used in synergy with experimental techniques to improve our understanding of the heart in health and disease.3 The contributions of computational modelling in cardiac physiology are numerous and the methodology is now well established within the cardiac basic science community (see, e.g. the Cardiac Physiome special issue of Journal of Physiology4). Currently, one of the challenges ahead is its translation to research closer to the bedside, through investigating the pathological states of the human heart and improving diagnosis and therapy. A sophisticated computational cardiac technology is now available, with whole-organ human heart models spanning from ionic to body level towards clinically observable parameters.

Its importance as a tool in different branches of clinical arrhythmology and therapy. A sophisticated computational cardiac technology is ready for prime time. The number, and quality, of submissions was even larger than expected, so that we decided to arrange two issues, in which the accepted papers are grouped according to the main focus of their computational analysis: ‘Arrhythmias mechanisms’ and ‘Diagnosis and interventions’. While the former is included in the present issue of EP-Europace, the latter will appear in the May 2014 issue.

We also expect that EP-Europace will continue to feature papers on Computational Cardiac Electrophysiology. Whereas some papers specifically illustrate the potential of computer simulation of cardiac processes, future studies will feature computational approaches as an established tool used, together with in vitro, animal and/or clinical studies, to investigate and find answers to specific research questions in cardiac electrophysiology.

This issue includes review and original research articles, which provide a broad overview on how outstanding questions on the mechanisms of arrhythmogenesis can be effectively addressed by in-silico experiments. They concern both atrial and ventricular arrhythmias, resulting from either genetic defects or acquired factors of clinical relevance (ischaemia, adrenergic activation, haemodialysis, hypothermia).

The work by Colman et al.5 identifies in a three-dimensional model the properties of pulmonary vein tissue which may make it naturally prone to the generation of wave breaks, but it also points out that electrical remodelling may be required for such wave breaks to induce atrial fibrillation (AF). It also predicts that K+ channel blockade may be adequate to counter the remodelling-induced substrate.

Filippi et al.6 evaluate the mechanisms underlying hypothermia-induced AF in two-dimensional epicardial and endocardial models. In addition to its relevance to hypothermia during surgery, this study provides an interesting evaluation of how channel-gating kinetics (highly sensitive to temperature) may affect dynamic electrical behaviour and, thus, electrical stability. The results obtained also show how the outcome of hypothermia-induced changes in refractoriness and propagation velocity may critically depend on the starting conditions and on atrial dimensions.

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By combining a case report with simulations at the cell level, Vincenti et al. address the mechanisms underlying the genesis of AF during haemodialysis sessions. Modelling is applied to understand key arrhythmogenic factors in the specific conditions presented by the case report. The results obtained assign a primary role to large and sudden changes in plasma K⁺ levels and to vagal activation. In addition to conclusions of potentially general relevance, the study provides an interesting example of how modelling can be applied to real-world clinical problems.

The predictive relevance of specific gating abnormalities in mutations with qualitatively similar effects (gain or loss of channel function) is an open question. Loewe et al. applied one- and two-dimensional modelling to assess the proarrhythmic potential of two gain-of-function (GOF) HERG mutations associated with AF. The GOF mechanism differed between the two mutants, being faster activation in one case and defective inactivation (rectification) in the other one. The simulations led to assign to faster activation a higher proarrhythmic potential, thus highlighting the importance of the specific gating abnormality in predicting the risk of mutations with a qualitatively similar effect.

The study by Verkerk and Wilders evaluated the extent of Iᵦ deficiency expected from the gating abnormalities resulting from various HCN4 and KCNE1 mutations occurring in sick sinus syndrome patients. The Iᵦ models were tested under action-potential clamp conditions, with the aim of assessing the primary effect of gating abnormalities on current expression during the human action potential. Interestingly, a remarkable discrepancy was found in several cases between the predicted change in Iᵦ expression and responsiveness to adrenergic stimuli and the actual mutation phenotype in terms of resting heart rate and chronotropic competence. The results suggest that other factors beside the Iᵦ abnormality may contribute to the clinical manifestation of HCN4 mutations.

Ferrero et al. revised the application of multiscale modelling to the understanding of arrhythmogenic mechanisms in the setting of acute ischaemia and established myocardial lesions. The problem was addressed at the level of single cell and tissue level, with a focus on gradients occurring at the border of ischaemic tissue. In addition to information relevant to prediction of electrical vulnerability, the article provides an extensive and organic revision of ischaemia-induced abnormalities and of their impact on arrhythmogenesis. Further information on the effects of acute ischaemia is provided in the contribution by Ramirez et al., who analysed the respective roles of extracellular K⁺ accumulation and junctional uncoupling in the generation of unidirectional block at the Purkinje–myocardial junction. The results presented lead to the conclusion that, when associated with K⁺ elevation, only moderate junctional uncoupling is suitable to support unidirectional conduction and favour reentry at this specific anatomical location.

Xie et al. addressed the mechanisms by which adrenergic activation may foster the transition between VT and VF. The analysis extends to reentry their recent work on the relevance for EADs generation of the different velocities by which I_CaL and I_Ks respond to β-receptor activation. The results highlight the importance of the rate at which the adrenergic input increases during sympathetic activation, coming to conclusions of potential practical relevance.

The relevance of transmural gradients in repolarization course to arrhythmogenesis is a matter of long-standing debate. Indeed, in the intact wall, electrotonic coupling between layers is claimed to minimize such gradients. By two-dimensional simulation of transmural tissue ‘slices’, the work by Mao et al. addresses the role of transmural coupling inmodulating the extreme epicardial repolarization gradients generated by the ionic abnormalities peculiar to the Brugada syndrome. The simulations come to interesting and partially unexpected conclusions.

Taken together the contributions in this issue demonstrate the significant achievements of Computational Cardiac Electrophysiology to increase our understanding of arrhythmias mechanisms. As already mentioned this is only the first part of the story, since there will be a second part made of computational analyses specifically devoted to the diagnosis and interventions, both pharmacological and non-pharmacological, in arrhythmias. Keep in touch with EP-Europace!

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References