Abstract: P503

Inter-subject variability explains juxtaposed effects in pharmacological treatments: an in-silico approach for the personalization of atrial fibrillation drug treatments

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Introduction: Atrial Fibrillation (AF) is the most common arrhythmia, with huge social and economic costs specially in countries with a large expectancy of life. However, the efficacy of antiarrhythmic treatments is limited (40-60%) at the time of terminating AF and maintaining sinus rhythm, particularly in the case of chronic AF. Inter-subject differences in ionic properties explain different responses to antiarrhythmic drug treatments depending on the patient. This fact, together with the development of high performance simulation platforms, has motivated the introduction of populations of models accounting for inter-subject variability as a tool for the prediction of the response of an entire population to a determined drug treatment. In this work, in-silico simulations in a population of models are used to find the ionic profile characteristics that explain different responses to antiarrhythmic drug treatments.

Specifically, the aim of this work is to investigate the factors promoting variability in the response of AF dynamics to commonly used drug therapies (flecainidine and verapamil), together with pure sodium (INa) and calcium (ICaL) current partial block (50%).

Methods: A population of 173 electrophysiological atrial tissue models capturing variability in experimental measurements from 149 AF patients was used to perform reentry simulations in basal conditions and for each of the drug strategies listed above. The relation between the electrophysiological properties with AF termination efficacy and AF biomarkers (rotor meandering and dominant frequency) of the antiarrhythmic therapies was evaluated.

Results: The figure shows as an example, how during basal conditions 126 of the 173 (72.8%) models sustained stable reentries. Partial block of sodium terminated AF by collision between rotors in 64 fibrillation models (50.8%) whereas partial calcium block produced the reentrant termination in 38 (30.2%). Termination was associated with an increase in meandering and collision between rotors.

The effectiveness of sodium and calcium block was exclusive in 52 AF models: 39 models which terminated by sodium block did not terminate by calcium block, whereas 13 of the AFs which terminated by calcium block did not terminate with sodium block. Effectiveness of treatments was dependent on the ionic characteristics of each model. The same reason explained the juxtaposed effects in reentry biomarkers presented by Calcium block.
Conclusions: Simulations based on a population of models predict that a considerable number of AF patients may require completely different pharmacological strategies depending on their specific electrophysiological properties.