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Development of new human models to determine age-related cardiotoxicity of drugs

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One of the main causes of drug withdrawal from the market is their unexpected toxic effect on the heart, such as arrhythmia generation. The Comprehensive In Vitro Proarrhythmia Assay (CiPA) from the Food and Drug Administration (FDA) promotes the use of in silico human models into the safety assessment workflow for early prediction of drug-induced cardiotoxicity. Despite being age a primary risk factor for cardiac arrhythmia and the elderly a primary object population of pharmacology, age-dependent effects are not considered in the CIPA initiative.

The goal of our study is to create in silico human ventricular models of cellular electrophysiology that enable risk stratification of drugs according to age to optimize drug safety assessment.

Two human adult ventricular electrophysiological models ORd 1 and Jae 2 were used to generate experimentally-calibrated populations of action potentials (AP) and calcium transients (CaT). Using the results of our previous age-related transcriptomic data analysis3, the effects of aging on ionic current properties were applied to such populations, with aging evaluated using two parameters of cardiac biological aging (BA): CDKN2A expression (CDKN2A-age), a single indicator of cell senescence, and apparent age (AppAge), a complex index computed from nearly 3000 age-related genes. For each of the three populations, namely adult, aged-CDKN2A and aged-AppAge, drug effect simulations were carried out for a list of CiPA high-risk compounds.

The two aged populations were significantly different (p-value < 0.001) to their adult homologue in all the evaluated AP- and CaT-related parameters studied, both for ORd and Jae basis models. In particular, prolongation of AP duration (APD), increased AP triangular morphology and decreased membrane voltage peak were observed with aging.

When analyzing drug effects, a higher number of individuals presenting arrhythmogenic events were found in the elderly populations than in the adult ones for all tested drugs, i.e. bepridil, dofetilide, quinidine and sotalol. Of those individuals with normal AP repolarization, drug effects on APD were significantly more accentuated on aged models compared to adult ones. As an example, treatment with dofetidile 50 nM lead to 16.67 % of arrhythmic events on adults, while it lead to 26.7% and 33.3% on aged individuals according to AppAge and CDKN2A-age, respectively. Dofetidile increased mean APD to 94.3% (CDKN2A-age) and 96.9% (AppAge) on elder over untreated individuals as compared to 78.59% in adults.

To conclude, we created and tested a battery of in silico cellular models of cardiac electrophysiology that integrate age as pro-arrhythmic risk factor. Results show important differences between elder and adult populations both at baseline and after the administration of four different drugs. Our human in silico models may lead to improved early detection of potential cardiotoxic events in preclinical drug studies.