In-silico Evaluation of β-adrenergic Effects on the Long-QT Syndrome

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Patients suffering from the congenital Long-QT syndrome react highly sensitive to the presence of β-adrenergic agents that are produced by the sympathetic nervous system. In this work we use an anisotropic and electrophysiologically heterogeneous in-silico model to reproduce wedge experiments in which the Long-QT syndrome was induced pharmacologically. Although different research groups have tried this in the past, they were only partially successful as the effects of the β-adrenergic agents could not be considered. Recently we integrated a description of the β-adrenergic signaling cascade into a model of human ventricular cells. Using the bidomain reaction-diffusion equations we calculated transmural pseudo ECGs which could be compared to the wedge experiments. For LQT1, the in-silico model predicted a QT prolongation in the transmural ECG without an increase in transmural dispersion of repolarization (TDR). For LQT2 and LQT3 the QT prolongation was accompanied by an increased TDR (+20%, +13% respectivley). β-adrenergic stimulation always shortened the APD of epicardial cells (4%-21%). In case of LQT1 and LQT2, β-adrenergic stimulation increased the APD of the M cells (+21%, +7% respectivley), whereas no significant change was observable for LQT3. This leads to an increase in TDR under adrenergic influence. Except for the increase in TDR under adrenergic influence for LQT3, the results of the in-silico model are consistent with the experimental reports. However, there are crucial differences between the features of LQT1 and LQT2 in the wedge experiments and clinical ECG recordings. In case of LQT1, patients show broad-based T Waves which are not easily reproducible if a reduction of the heterogeneous current I_{Ks} is assumed. In contrast to that, wedge experiments of LQT2 show an increased TDR leading to broad T Waves of high amplitude which are unlike the low-amplitude T Waves seen clinically.