A Computational Model for the Human Foetal Ventricular Myocyte to investigate Foetal Arrhythmia

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Aims: Pregnancies complicated by intrahepatic cholestasis of pregnancy (ICP) exhibit an increased rate of unexplained stillbirth. Bile acid-induced cardiac arrhythmia has been identified as a potential mechanism. To investigate the arrhythmogenic effects of bile acids on the foetal heart during ICP, we developed a biophysical model of the human foetal ventricular myocyte electrophysiology.

Methods: The model incorporates the following ionic currents: I_{Na}, I_{K1}, I_{Kr}, I_{CaL}, I_{CaT}, I_{NCX} and $I_{Na/K}$ and is based on human foetal data. Voltage-clamp current recordings were available to constrain the T-type calcium channel. We compared T-type calcium current formulations of Dokos and Demir cell models. Fluorescence measurements of *Ca* transient were used to constrain intracellular dynamics at pacing rate of 1 Hz. Foetal ECG measures of QT interval were used to constrain the APD at a heart rate of 150 bpm. Ion channels gene expression data of human foetal ventricles were used as reference values for the fit and validation and to shift the model forward in time to simulate foetal electrophysiology in late pregnancy. Ion channel kinetics were based on the Ten Tusscher cell model while channel densities and calcium buffering were inferred using high density grid searches.

Results: The APD was fit to the QT interval of 176 ms. The Ca transient was fit to the recovery time of 290 ms, amplitude of 455 nM and time to peak of 220 ms. We performed 80 000 simulations to identify the optimal parameters set. The resulting model can replicate electrical signal and calcium dynamics of the healthy human foetal heart between 12 to 17 weeks of gestation and predict foetal cardiac action potential in later gestational ages.

Conclusions: We built the first electrophysiological model of the human foetal ventricular myocyte to simulate the impact of drugs and predict arrhythmias in the foetal heart throughout pregnancy.