Service Insight

Non-invasive method to calculate changes in conductances of human cardiac repolarisation ion channels

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The conventional use of ECG safety biomarkers to identify drugs which can produce potentially fatal cardiac rhythm disturbances are generally considered unreliable. At the cardiac cellular level, the common electrophysiological drug induced abnormality underpinning the observed arrhythmogenesis is the inhibition of the cardiac repolarisation ionic channels. There are insuperable difficulties, due to species differences, in using animal cardiac ionic channel data to reliably predict the proarrhythmic potential of new compounds.. A Governmental Science and Technology grant funded development of a novel technique enabling the non-invasive measurement of drug induced changes in conductance of human cardiac repolarisation ion channels with the ambition to develop human surrogate biomarkers of the TRIaD proarrhythmic index, which comprise action potential transmural dispersion of repolarisation, action potential triangulation, action potential reverse use dependence and action potential instability. The scope of this discussion is restricted to determining changes in the conductance values of the repolarisation ion channels.

The apical epicardial ECG measured transversely across a human wedge of myocardium can be modelled by simulating the propagation of action potentials through a matrix of human cardiac cellular tissue using the diffusion equations applied to the lumped model of endocardial, M cell and epicardial myocardial layers. A similar simulation on animal myocardial wedge section was achieved and validated by Rudy and co-workers.

Consider the simulated human epicardial ECG, based on normal human physiological values, as the normal template epicardial ECG. The Fourier transform of the pre-drug baseline normal human surface apical (lead V5) ECG can then be considered as a product of the Fourier transforms of the simulated epicardial ECG and the Fourier of the biophysical electrical transmission characteristics of the individual (BETC). The BETC calculated at baseline can be used with the Fourier transform of post drug human apical (lead V5) ECG to calculate the change in morphology of the simulated template epicardial ECG. The pre and post drug epicardial ECGs T wave tail ends are found to be morphologically identical to the tail ends of the lumped M cell action potentials. Therefore calculation of changes in the pre and post drug voltage and currents in the tail end of the epicardial T waves enables calculation of changes in the tail end M cell action potential allowing calculation of the changes in magnitude of repolarisation ion channel conductances.

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Method: The invention uses a computer simulation of a human ventricular wedge preparation to generate a normal baseline apical epicardial ECG T wave. Fourier Transform of the simulated normal epicardial T wave combined with Fourier Transform of the human baseline chest lead V5 ECG apical T wave are used to derive the BETC filter transfer function (embodying the biophysical transfer factors and distant potential contributions) which in effect map the localised simulated 'normal' apical epicardial ECG T wave recording onto the corresponding apical surface (V5) ECG T wave recordings made at baseline. Following administration of a compound, this same transfer function or system function will then be used to inversely map the human recorded apical surface ECG T wave back to the apical epicardial ECG T wave derived from the simulated wedge of myocardium. As the tail end action potential voltage of the lumped M cell layer is the predominant contributor to the tail end of the apical ECG T wave , it is then possible to make relative comparisons between pre and post drug induced changes in the tail end of the M cell lumped action potentials, by comparing the tail ends of the pre and post drug epicardial T waves. By reverse engineering the total ionic currents from the epicardial apical ECG T wave tail voltages, using Hodgkin-Huxley formalism, simple linear algebra allows calculation of the changes from baseline in the magnitude of conductances for the IKr, IKs and IK1 repolarisation ionic channels.

Validation: Baseline ECG data, from a previous pharmacological study, was used to first calculate the biophysical transfer function for 22 healthy subjects. The 3 hour post placebo and post sotalol (an IKr channel inhibitor) ECGs, were used to determine changes from baseline in the IKr conductance. Significant changes in the IKr conductance calculated by the method described above differentiated the subjects taking sotalol from those taking placebo with a sensitivity of 0.7 and a specificity of 0.8. There were no significant changes detected in the conductances of IKs and IK1 channels. These results are unpublished because it is anticipated that future research using larger amounts of less noisy, pre-processed data, at a higher sample rate, will further optimise results. We will seek collaborative partners in order to further validate this inventive method.

The full details of method can be found in patent EP2170163 and WIPO document W02008149159. Contact tonyhunt@cardio-qt.com for further information or discuss collaboration.

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