Systems analysis of clinical variability in cardiac electrical phenotypes

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The electrocardiogram (ECG) represents the summed electrical activity of all ion channels in all the cells of the heart. It is an extraordinarily versatile non-invasive diagnostic tool, however, the precise origins and molecular basis of the main deflections on the ECG, denoted P, Q, R, S and T-waves remain an enigma. We have used a multiscale analysis based on a novel computational approach to interrogate how the timing, duration and morphology of the T-wave on the ECG, representing ventricular repolarization, emerge from interactions at the molecular, cellular and tissue level. Each T-wave parameter is a complex function of multiple conductances and in turn each conductance has pleiotropic effects on the T-wave. At resting heart rates the major influence on the T-wave is the rapid component of the delayed rectifier, IKr, with reduced IKr causing an increased QT duration, but decreased amplitude and width of the T-wave. Simulation of long QT syndrome type 2 (LQTS2), an inherited arrhythmia caused by loss of IKr channel activity, reproduced the notched T-waves characteristic of this syndrome. T-wave notching occurs as a result of a temporal deconvolution of the molecular components of repolarization. The extent of notching, while correlated with disease severity, is influenced by small changes in the level of multiple other ionic conductances as well as interactions at cellular and tissue levels, thereby providing a plausible explanation for the variable expressivity of ECG features in patients with the Long QT syndrome even within individual families. These data provide the first quantitative insight into the complex interactions across molecular, cell and tissue levels that contribute to repolarization. More broadly, our approach demonstrates the potential for systems analysis of whole organ function and opens up the possibility of unraveling the relationships between low-level inputs and emergent properties of any system for which causally cohesive genotype-phenotype models can be developed.