Mutiscale computational analysis of the effect on heart rate of a HCN4 gene double mutation: from the single channel to the clinical phenotype

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The sinoatrial node (SAN) is the primary pacemaker of the heart. Several anatomical and physiological aspects of this important tissue are still unknown: computational models can be a valuable tool to provide insights about the underlying mechanisms of pacemaking and can bridge the gap between functional changes and clinical phenotype. This work aims to assess: I) the effects of the I479V/A485E HCN4 channel double mutation (DM), II) the role of cellular coupling (ρ) and III) the role of cellular heterogeneity (σ) on systems of increasing complexity: ionic channel, single cell, 1D fibre and 2D tissue. The Fabbri et al. model was used to describe the human SAN cell and to build the 1D and 2D models, which are constituted of 100 and 2500 (50x50) cells, respectively. $\sigma = 0.05$, 0.1, 0.1873, 0.3, 0.4 and $\rho = 10$, 100, 1000, 10000 and ∞ $\mathrm{M\Omega \cdot m}$ were simulated, in order to test their effect on the heart rate (HR). The reduction of I_f current due to the heterozygous condition ($g_f(WT0.5 + DM) = 45\%$ of $g_f(WT)$) leads to an increase of the cycle length of the simulated action potential of a single cell (924 vs 814 ms; +14%). This WT0.5+DM bradycardic effect is confirmed also by the 1D model (802 vs 690 ms; +14%) as well as by the 2D one (908 vs 794 ms; +14%). These results were obtained for σ = 0.1873 and $\rho = 100$ $\mathrm{M\Omega \cdot m}$ (50 $\mathrm{M\Omega \cdot m}$ in 1D). We assumed these values of ρ and σ to be physiological since they provided values of conduction velocity similar to those reported in literature ($\sim$ 11 cm/s). Other combinations of σ and ρ can provide changes in HR greater than 50%, highlighting the importance of these two parameters in the establishment of a physiologic pacing in the human SAN.