SUPPLEMENTARY METHODS

In Silico Simulations

The CPVT phenotype was modelled as described in our recent study using computationally reduced CASQ2 by modifying the Soltis-Saucerman model[1] and the Morotti-Grandi mouse cardiac cell model.[2]

We reduced the CASQ2 total protein (B_{max_CASQ2}) concentration by 25%, 50% and 75% in the following equation.

Calsequestrin buffer:

$$d\frac{[CASQ2]}{dt} = k_{on\_CASQ2}[Ca]_{SR}\left(B_{max\_CASQ2} - [CASQ2]\right) - k_{off\_CASQ2}[CASQ2]$$

Buffer	B_{max_CASQ2} [mM]	K_{off_CASQ2} (ms^{-1})	K_{on_CASQ2} ($mM^{-1}ms^{-1}$)
Calsequestrin	2.7	65	100

Cellular and tissue simulations

Mouse ventricular myocyte model: The I_{Na} channel was replaced in the Morotti-Grandi mouse cardiac cell model [2] with our published Markov model.[3] We then adjusted three transition rates for the mouse model to simulate the mouse I_{Na} kinetics:

Transition rates	
O→C1	β13 * 0.45
O→IF	α2 * 0.45
O→IS	αx * 0.45

Virtual myocytes were paced using a -9.5 pA/pF current stimulus for 5 ms in single cells for 2 mins at 2Hz pacing frequency in the presence of 1.0μM ISO.

Rabbit ventricular myocyte model: The I_{Na} channel was replaced in the Soltis-Saucerman rabbit cardiac cell model.[1] Virtual whole cells and tissues were allowed

to “rest” without external stimuli for 10 minutes to establish initial conditions. Cells were then virtually paced using a -80 pA/pF current stimulus for 0.5 ms in single cells and -500 pA/pF stimulus for 2.0 ms in tissues. Cells were paced for 2 minutes in the presence of 1μM ISO. Parameters including upstroke velocity, action potential duration (APD), and the number of early and delayed after-depolarizations (DADs) were tracked over the course of each simulation.

One-dimensional tissue was simulated as a fibre of 165 cells $(1.65cm)^4$ with reflective boundary conditions. Transmural heterogeneity was incorporated into the tissue by a linear decrease to 25% maximal I_{to} conductance,[5] corresponding to a linear transition from epicardial to endocardial tissue [6] and an APD gradient of 205-224ms. The diffusion coefficient D_x was set to 0.002 cm^2/ms to establish a conduction velocity of 61-73 cm/s (epicardium-endocardium in wild type conditions).[7]

REFERENCES

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