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Supporting Material

Anthropomorphizing the mouse cardiac action potential via a novel dynamic clamp method

Rebecca C. Ahrens-Nicklas and David J. Christini

SUPPLEMENT

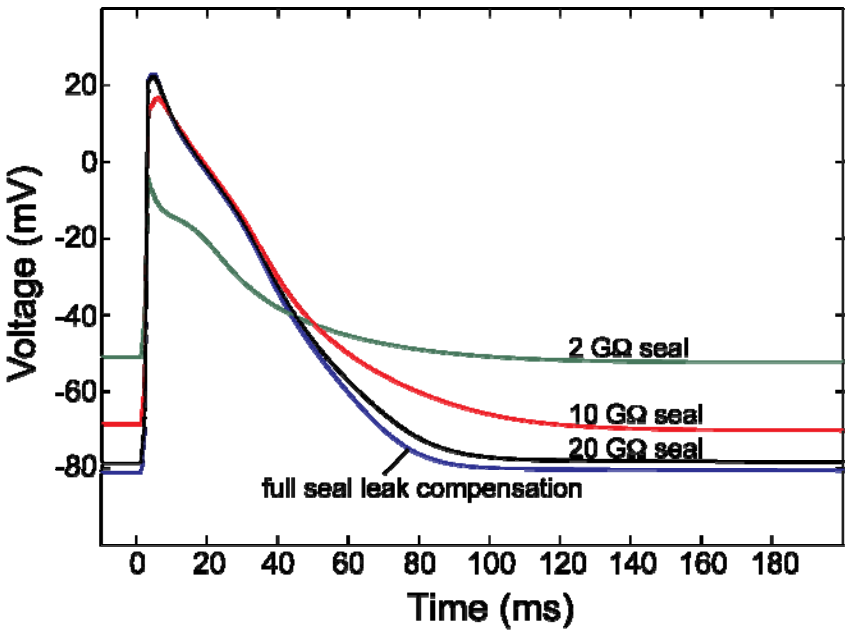


Figure S1: The effects of patch clamp seal leak current on the neonatal mouse action potential *in silico*

The Wang-Sobie neonatal cardiac ventricular myocyte model was simulated with different values of leak through a virtual patch clamp seal. Seal leak current was calculated as in Equation 4. Due to the very small size of murine neonatal cells (15.4 pF model cell capacitance), even a small leak, such as that through a 2 GΩ seal (green trace) can cause substantial resting membrane depolarization. At higher seal resistances (red and black traces), the resting membrane potential became more polarized. When the seal leak was fully compensated (blue trace), the action potential morphology was normal, i.e., the same as with no seal leak. Seal leak compensation was used throughout the experiments of this study. The model cells were stimulated at a rate of 1Hz with a 100 μA/μF stimulus of 0.5 ms duration.

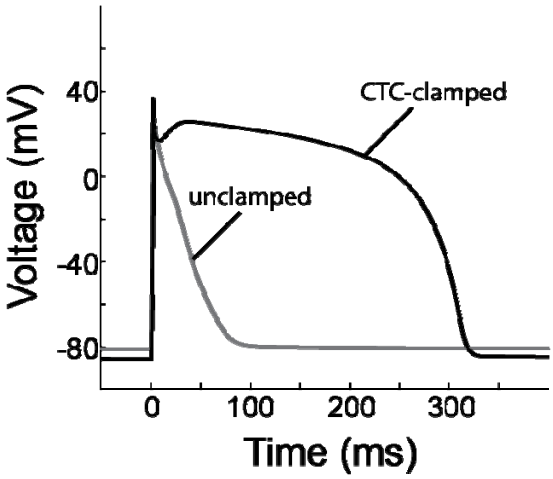
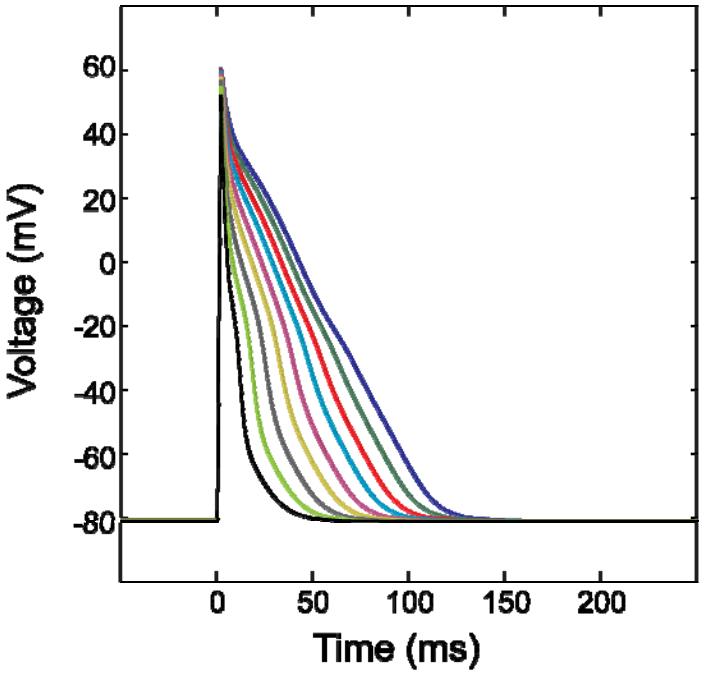


Figure S2: The reduced ten Tusscher model can successfully be used as the recipient model in untreated CTC studies *in silico*.
A Wang and Sobie neonatal model target cell was paced without (gray) and with (black) CTC-clamping. The recipient model cell in the circuit was a reduced ten Tusscher ventricular myocyte model. The cells were stimulated at 1 Hz, with 100 μA/μF stimuli of 0.5 ms duration.



APD	Gs and Gk,slow factor
100 ms	0.315
90 ms	0.355
80 ms	0.41
70 ms	0.475
60 ms	0.575
50 ms	0.7
40 ms	0.9
30 ms	1.2
20 ms	1.7

Figure S3: Adaptations made to the Pandit mouse model to produce the target-canceling model cells used in experiments

Nine different adapted "neonatal" Pandit mouse models were made for the experimental CTC circuit. The nine models had APDs that differed in 10 ms increments. The models were created by multiplying the conductances of two major repolarizing potassium currents of the model (G_s, and $G_{k,slow}$) by different factors as listed in the table. G_{to}, the conductance through the transient outward potassium channel, was reduced by a factor of 0.01 in each neonatal model because adult myocytes (and the corresponding adult Pandit model formulation) have much more transient outward current than neonatal cells. In each experiment, the mean APD of the specific isolated myocyte was found, and then the most appropriate mouse model (out of the nine possibilities) was chosen. The model cells were stimulated at a rate of 1Hz with a 100 μA/μF stimulus of 0.5 ms duration.

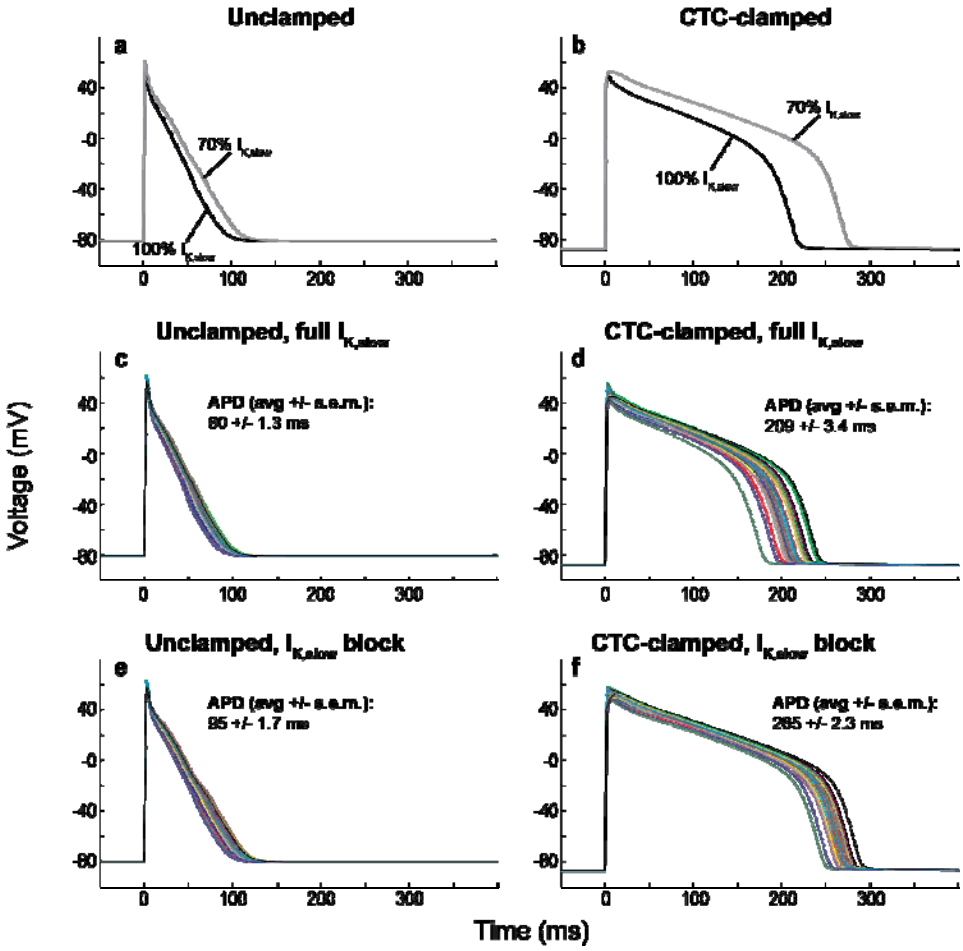


Figure S4: The CTC can prolong the action potential of a modified Pandit mouse target cell, and can detect potassium channel blockade-induced action potential prolongation even in the presence of target cell / target-canceling model mismatch *in silico.*

A modified Pandit model cell with an APD of 80 ms was used as both the target cell and target-canceling cell in the CTC circuit. Unlike the Wang and Sobie model, the Pandit model does not have an I_{Kr} formulation; therefore, to investigate the effects of repolarizing channel blockade, $I_{K,slow}$ was decreased by 30%. Potassium channel blockade slightly increased the unclamped target cell APD (*a*, 80.0 vs. 95.6 ms). During CTC-clamping, the target cell APD prolonged, a plateau was induced, and potassium channel blockade had a more substantial effect on APD (*b*, 212.0 vs. 268.5 ms). As in Fig. 6, experimental cell-to-cell variability was modeled using a Monte Carlo method to perturb the 9 target cell conductances by a percentage selected from a normal distribution (mean 0, standard deviation 10%). In unclamped cells in the presence of variability, block-induced prolongation was seen (*c* vs. *e*); however, during CTC-clamping prolongation was more evident (*d* vs. *f*). Unlike in the studies of I_{Kr}-blockade of Wang and Sobie target cells, no mismatch-induced EADs were seen in CTC-clamped cells (*f* vs. Fig.6 *d*). This could be due to differences between the effects of I_{Kr} blockade and $I_{K,slow}$ blockade or other differences between the Pandit and Wang and Sobie models. All models were solved using a time step of 0.1 ms. Cells were paced at a rate of 1 Hz, with stimuli of 100 μA/μF amplitude and duration of 0.5 ms.