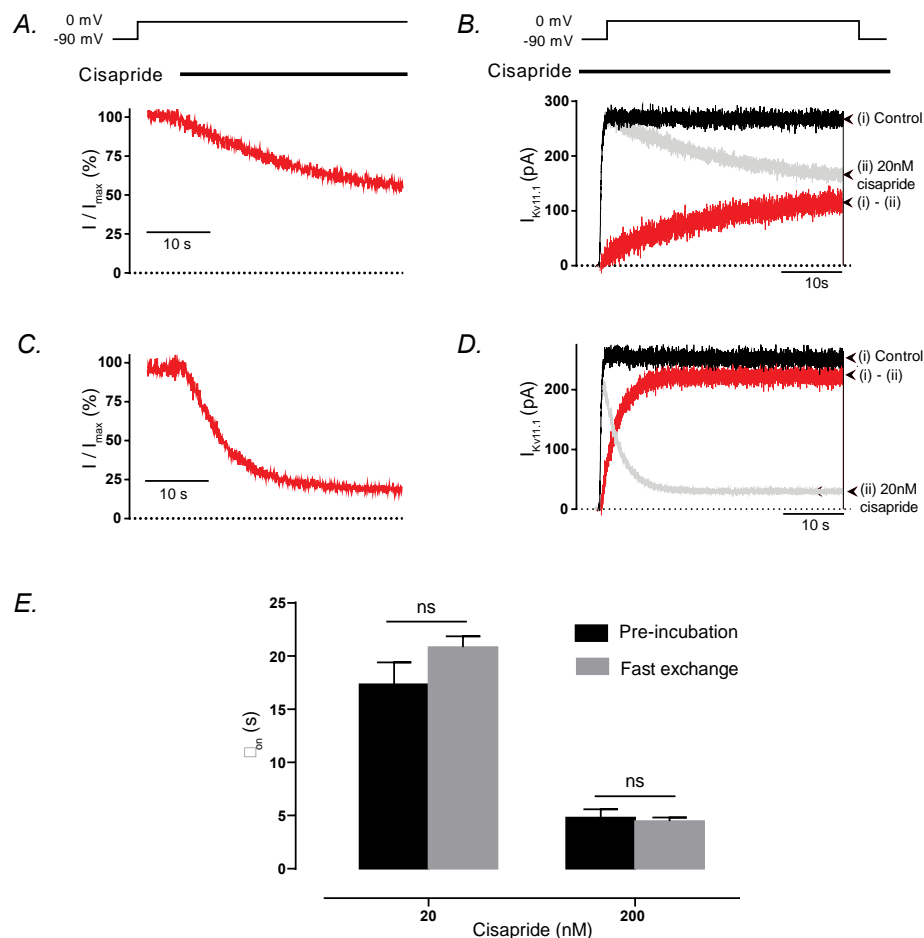


Temperature effects on kinetics of Kv11.1 drug block have important consequences for *in silico* proarrhythmic risk prediction.

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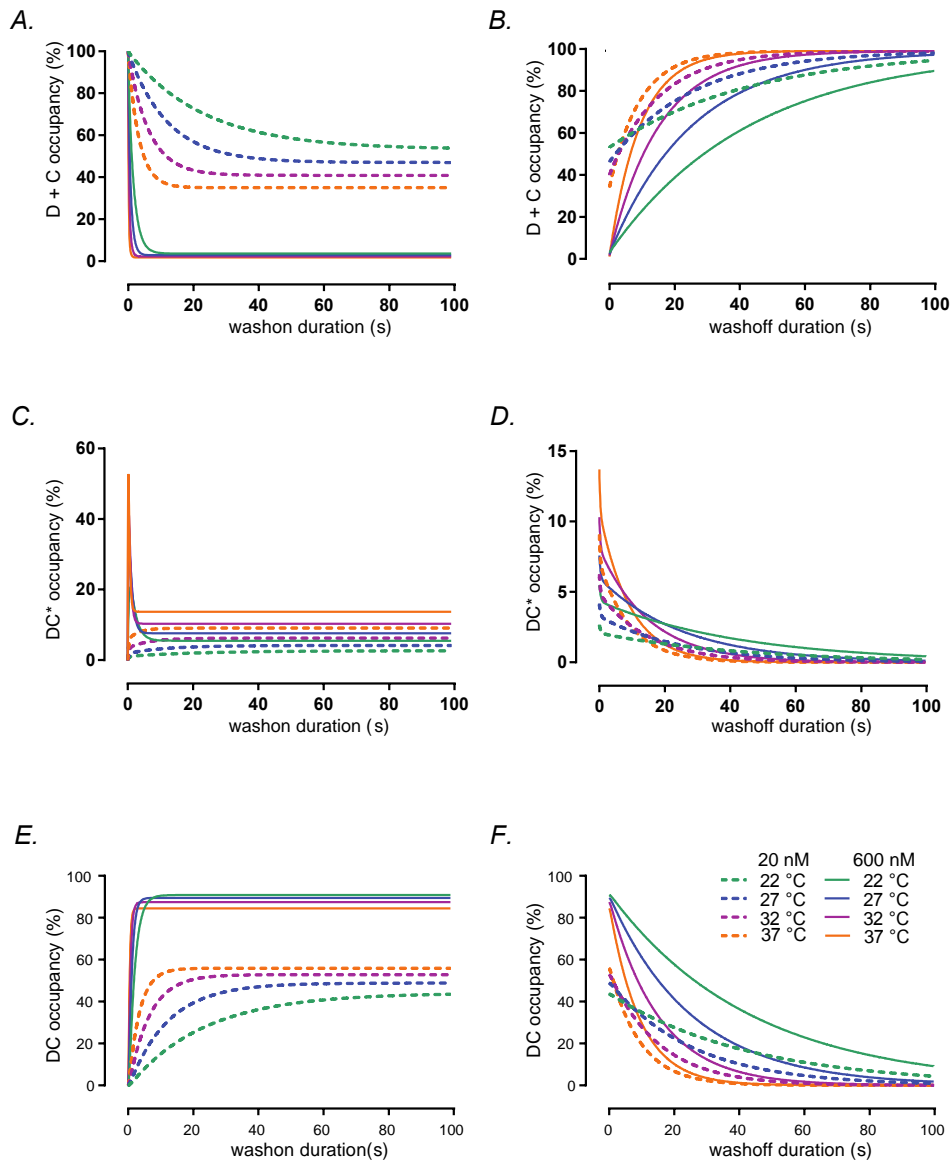


Supplementary Figure 1

Figure 1

Comparison of pre-incubation and fast exchange application of cisapride. **(A)** Typical traces recorded in response to fast exchange (left) or pre-incubation (right) application of 20 (top) and 200 nM (bottom) cisapride. Fast exchange responses were recorded from cisapride applications delivered following

channel activation evoked by a voltage step to 0 mV (left inset). Pre-incubation responses were also recorded at 0 mV from a holding potential of -90 mV (right inset), initially in the absence of cisapride (dark grey) and following a 10s pre-incubation with cisapride (light grey) while channels are held closed at a membrane potential of -90 mV followed by channel activation at 0 mV and continued application of cisapride. The red trace represents the offline subtraction of the current in response to cisapride from the response in the absence of drug. **(B)** Comparison of exponential fits directly to fast exchange responses and to the subtracted response for pre-incubated responses. No significant difference was found between the time constant values from pre-incubation and fast exchange application for 20 and 200 nM cisapride applications ($n = 4-5$, $p > 0.05$, Mann Whitney test).



Supplementary Figure 2

Figure 2

Summary of state occupancy calculated from the modeled data. The percentage values indicate the portion of channels occupying a given state at a period of time following the initiation of cisapride application **(A-C)** or cisapride washout **(D-F)**. The top **(A, D)**, middle **(B, E)** and bottom **(C, F)** panels represent the drug-free channel (D + C), the encounter complex (DC*) and the drug-blocked channel (DC), respectively, as described by scheme 2. Each of the state

occupancies are depicted in response to 20 nM (broken lines) or 600 nM cisapride (solid lines) at 22, 27, 32 and 37 °C (green, blue, purple and orange, respectively).