

SUPPLEMENTAL MATERIAL

Data S1: Supplemental Methods

Mathematical model of murine sinoatrial action potential: Equations and parameters that differ from original publication are provided below. All other equations and parameters are for central sinoatrial node cell in original publication.¹

TREK-1 current – TREK-1 is modeled as a time-independent K⁺ current with slight outward rectification (a_{rect}) fit to experimental data.² Maximal channel conductance, \bar{g}_{TREK1} , was chosen to produce a current of 1.2 $\mu A/\mu F$ at +30 mV in agreement with experimentally measured difference in background K⁺ current between wildtype and cardiac-specific TREK-1 knockout at room temperature (Figures 4A and 7A). E_K is the reversal potential for K⁺.

$$\begin{aligned}
 I_{TREK1} &= \bar{g}_{TREK1} a_{rect} (V_m - E_K) & [1] \\
 a_{rect} &= 1 / (1 + \exp((-V_m + 65)/52)) \\
 \bar{g}_{TREK1} &= 0.0311 \text{ nS/pF}
 \end{aligned}$$

Ca_v1.3 L-type Ca²⁺ current ($I_{CaL,D}$) – A formulation for Ca_v1.3 L-type Ca²⁺ current was included, consistent with presence of this distinct class of Ca²⁺ channels in sinoatrial node.³ Voltage-dependent activation (d_D) and voltage-dependent inactivation (f_D) were assumed to have same kinetics as Ca_v1.2 L-type Ca²⁺ current in original formulation but with respective steady state curves shifted 10 mV to the left.^{3, 4} Ca²⁺-dependent inactivation was assumed to have same kinetics and steady-state dependence as Ca_v1.2.^{5, 6} A smaller conductance than that estimated previously³ was used to produce a value for cycle length of spontaneous activation similar to that in original model.

$$\begin{aligned}
 I_{CaL,D} &= \bar{g}_{CaL,D} d_D f_D f_{Ca} (V_m - E_{Ca}) & [2] \\
 d_{D,\infty} &= 1 / (1 + \exp(-(V_m + 24.1)/6.0)) \\
 \alpha_{d,D} &= -0.02839 * (V_m + 35.0) / (\exp(-(V_m + 35.0)/2.5) - 1.0) - 0.0849 * V_m / (\exp(-V_m / 4.808) - 1.0) \text{ ms}^{-1} \\
 \beta_{d,D} &= 0.01143 * (V_m - 5.0) / (\exp((V_m - 5.0)/2.5) - 1.0) \text{ ms}^{-1} \\
 \tau_{d,D} &= 1 / (\alpha_{d,D} + \beta_{d,D}) \text{ ms} \\
 f_{D,\infty} &= 1 / (1 + \exp((V_m + 40)/5.0)) \\
 \tau_{f,D} &= 257.1 * \exp(-((V_m + 32.5)/13.9)) * ((V_m + 32.5)/13.9) + 44.3 \text{ ms} \\
 f_{Ca,\infty} &= 0.00035 / (0.00035 + [Ca^{2+}]_{ss}) \\
 \tau_{fCa} &= f_{Ca,\infty} / 0.021 \text{ ms} \\
 \bar{g}_{CaL,D} &= 0.0375 \text{ nS/pF}
 \end{aligned}$$

Table S1. Regression coefficients indicating how changes in model parameters affect AP and Ca^{2+} transient properties.

	APA	CL	DDR	APD	dV/dt_{\max}	MDP	CaT_{amp}	$\text{CaT}_{\text{width}}$	$[\text{Ca}^{2+}]_{\text{i,dia}}$
$g_{\text{CaL,d}}$	0.0737	-0.1958	0.2829	-0.1100	0.0319	4.373e-3	0.0934	0.0379	0.0677
g_{CaI}	0.3632	-0.1550	0.1224	0.0807	0.7833	-0.0265	0.7925	0.7648	0.2506
g_{CaT}	-0.1054	-0.2745	0.4415	-4.205e-3	-0.1298	0.0848	4.643e-3	-0.1257	0.2047
g_{H}	0.0188	-0.1723	0.2694	-0.1241	-0.0501	7.905e-3	0.0400	-0.0476	0.0643
g_{Kr}	0.2152	0.3956	0.0319	0.1607	0.0273	-0.8533	0.2115	-0.5523	-0.0913
g_{NaCa}	0.0914	-0.0235	0.0543	0.0879	0.3140	-0.0461	0.0467	-0.0480	-0.4972
g_{NaK}	0.4452	0.0264	0.2836	0.1178	0.5065	-0.5092	-0.3767	0.0308	-0.7573
g_{To}	-0.1359	0.1463	-0.2293	0.0687	-0.0866	0.0271	-0.0252	-0.0248	7.048e-3
g_{Trek}	-0.1235	0.2267	-0.4466	-0.0364	-0.0836	2.549e-3	0.0161	-0.2983	9.593e-3

AP indicates action potential; APA indicates AP amplitude; CL, cycle length; DDR, diastolic depolarization rate; APD, action potential duration at 50% repolarization; MDP, maximum diastolic potential; CaT_{amp} , Ca^{2+} transient amplitude; $\text{CaT}_{\text{width}}$, width of Ca^{2+} transient at half maximum; $[\text{Ca}^{2+}]_{\text{i,dia}}$, diastolic intracellular Ca^{2+} concentration

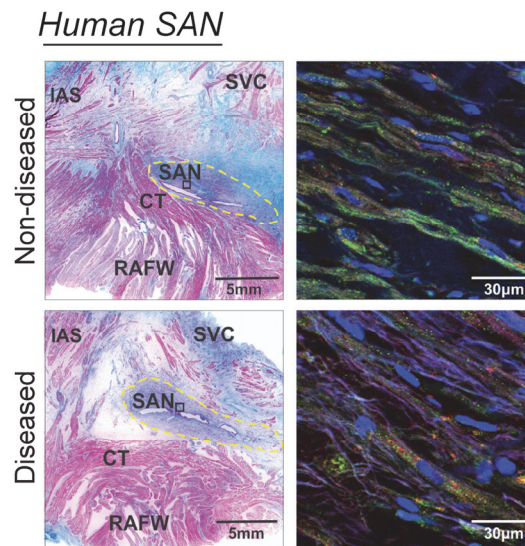


Figure S1. Masson's trichrome staining (*left*) or immunostaining for β_{IV} -spectrin (*green*) and alpha-actinin (*red*) (*right*) of paraffin embedded SAN sections from non-diseased human heart (identification number 921821) or from subject with coronary artery disease (identification number 168021). IAS - Intraatrial septum; SVC - Superior vena cava; SAN- sinoatrial node; CT – crista terminalis; RAFW – right atrial free wall.

REFERENCES

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