Mechanosensitive Channel Piezo1 in R403Q Hypertrophic Cardiomyopathy: A Computational Study

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Abstract

Piezo1 is a tension-gated cation channel with a voltage-dependent inactivation and Ca^{2+}-permeability. In mice, cardiac Piezo1 shows maladaptive dynamics and evokes a hypertrophic response to pressure overload. Mutation-specific hypertrophic feedback to Piezo1 has not been addressed before. Here, we present a novel mechanistic model of Piezo1 current and add it to our in silico whole-cell model of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) to study the mechanotransduction in the presence of $MYH7^{R403Q/+}$ condition. Our biophysical model of Piezo1 has a tension-dependent activation and a novel voltage-dependent inactivation gate. We modeled $MYH7^{R403Q/+}$ hypertrophic cardiomyopathy (HCM) following our previous model by altering DRX/SRX myosin ratio and elevating myofilament MgADP and inorganic phosphate. Normalized current-tension relationships of Piezo1 showed a 27.9% increase in Boltzmann slope due to $MYH7^{R403Q/+}$ HCM. However, the half-maximal activation (P50) elevated 16.7%. This work contributes to investigations on the capacity of mechanotransduction, particularly cardiac Piezo1 channel, as a potential drug target for mutation-specific HCM.

1. Introduction

Mechanotransduction plays a pivotal role in many cascades of human physiology. The expeditious detection of mechanical forces, which transpires within milliseconds, is accomplished through force-gated ion channels that transform mechanical energy into electrochemical signals [1]. Cardiac Piezo1 is a cation channel that is activated by mechanical forces and has the ability to detect membrane tension with a remarkable level of sensitivity [2]. Aberrant Piezo1 channel activity, resulting from hereditary mutations, genetic manipulation, or physiological regulation, has been associated with a range of pathological disorders, including xerocytosis, lymphedema, arthrogryposis, and abnormal vascular development [3]. In addition, Piezo1's significant proarrhythmic role in cardiac remodeling has been reported for hiPSC-CMs [4]. However, Piezo1 dynamics in mutation-specific HCM has not been addressed before. Theoretical frameworks capable of providing mechanistic insights and predictions on the pathophysiology of Piezo1 would be of great importance [2].

In this study, we aim to provide a novel *in silico* biophysical model of cardiac Piezo1 and incorporate it in our electro-mechano-energetic model of hiPSC-CMs [5] (hiMCE; Figure 1). We parameterize the voltage-current and voltage-inactivation time constant relationships with *in vitro* data from different labs. Finally, we aim investigate the tension-sensitivity of cardiac piezo1 in the presence of $MYH7^{R403Q/+}$ HCM condition.

2. Methods

2.1. Piezo1 model

Extending previous mechano-sensitive channel formulations [7], we defined I_{Piezo1} with a tension-dependent activation gate, m_a, and a new voltage dependent inactivation [2] gate, Xn, as follows:

$$I_{Piezo1} = g_p m_a Xn(V - E_p) \quad (1)$$

$$J_{Piezo1} = c|I_{Piezo1}| \quad (2)$$

$$Xn_{inf} = \frac{2}{1+e^{\frac{-Vm}{16}}} \quad (3)$$

$$\alpha_{Xn} = \frac{1}{\sqrt{1+e^{\frac{-60+Vm}{50}}}} \quad (4)$$

$$\beta_{Xn} = \frac{270}{1+e^{\frac{171-Vm}{72}}} \quad (5)$$

$$\tau_{Xn} = \alpha_{Xn}\beta_{Xn} \quad (6)$$

$$\frac{dXn}{dt} = \frac{Xn_{inf}-Xn}{\tau_{Xn}} \quad (7)$$

$$m_{ainf} = \frac{1}{1+e^{\frac{-(d-2.5)}{0.25}}} \quad (8)$$

$$\frac{dm_a}{d_t} = \frac{m_{ainf}-m_a}{\tau_a} \quad (9)$$

The voltage-dependent inactivation (Eqs. 3-7) was reparametrized from slow delayed rectifier K^+ current, I_{Ks}, inactivation gate in [6]. The tension-dependent activation (Eqs. 8-9) was introduced following [7]. The constants and the corresponding references have been given in Table 1. Eq. 2 represents Piezo1 Ca^{2+} flux and c is a factor converting A/F to mM/s. Eq. 8 represents Piezo1 activation gate open probability where d denotes the normalized active tension developed by hiMCE model [5]. We set the default open channel probability equal to 50% consistent with human Piezo1 evoked current-tension *in vitro* findings [8]. *Vm* is voltage in mV, and τ_a and τ_{Xn} represent activation and inactivation gate time constants, respectively.

Table 1. Piezo1 model constants.

Parameter	Value	Ref.
E_p (mV)	0	[9]
c	0.116	[6]
τ_a	0.1	N/A
g_p (S/F)	0.304	[10]

We integrated Piezo1 into our hiMCE model as a sarcolemmal current:

$$C\frac{dV}{dt} = -(I_{Na} + I_{NaL} + I_{CaL} + I_f + I_{K1} + I_{Kr} + I_{Ks} + I_{to} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{bNa} + I_{bCa} + I_{Piezo1} - I_{stim}) \quad (10)$$

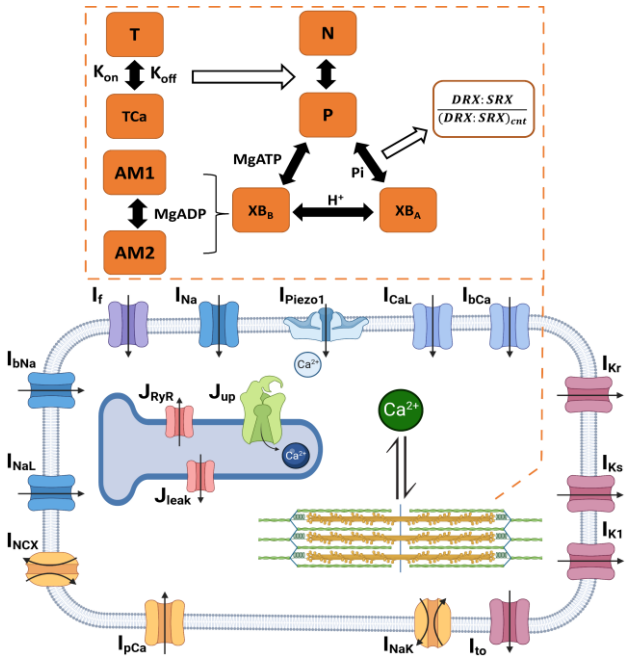

Figure 1. The schematic of hiMCE+Piezo1 model giving the electrophysiology, the metabolite-sensitive contractile component, and Piezo1 in hiPSC-CMs (Created with BioRender.com).

2.2. MYH7$^{R403Q/+}$ cardiomyopathy model

The pathophysiology of MYH7$^{R403Q/+}$ HCM was simulated following the method in [5]. We altered the metabolic and the crossbridge (XB) cycling parameters in hiMCE model as given in Table 2.

Table 2. The contractile element parameters used in modeling MYH7$^{R403Q/+}$ cardiomyopathy following [5].

Parameter	Control	MYH7$^{R403Q/+}$
Pi_{ref} (mM)	2	18.9
MgADP	0.036	0.072
ap2 coef.	1	0.315
R	1	1.3

Pi_{ref} represents the reference value of inorganic phosphate in the hiMCE model, ap2 influences the forward transition between XB_A and XB_B states and also impacts XB detachment, R denotes the myosin disordered relaxed state to super relaxed state (DRX:SRX) ratio (Figure 1).

3. Results

3.1. Validations of the model

The hiMCE+Piezo1 model simulates action potential (AP) morphology and fractional cell shortening (FCS) consistently with the previously validated model and *in vitro* data (Figure 2A&C). We parametrized the I_{Piezo1} formulation with respect to the *in vitro* data of current vs membrane potential (Figure 2B) and voltage-dependent inactivation time constant (τ_{Xn}) vs voltage (Figure 2D) relationships. As a semiquantitative validation, the simulated I_{piezo1} morphology (Figure 2E) aligns with *in vitro* data [11]. The new model also simulates key contractile and electrophysiological biomarkers within hiPSC-CMs *in vitro* ranges (Table 3).

Table 3. Select electrophysiological and biomechanical simulated biomarkers and the *in vitro* ranges. APA: AP amplitude, MDP: maximum diastolic potential, CL: AP cycle length, APD_{90}: AP duration at 90% of repolarization, DRT: Ca^{2+} transient (CaT) duration, RT_{1050}: rise time from 10 to 50% of maximum threshold in CaT, DT_{9010}: decay time from 90 to 10% of maximum threshold in CaT, ATM: active tension magnitude, CRT_{50}: time from peak contraction to 50% of relaxation.

Biomarker	hiMCE [5]	hiMCE+ Piezo1	*in vitro* [12]
APA (mV)	103	103	104±6
MDP (mV)	-75.0	-75.2	-75.6±6.6
CL (ms)	1644	1695	1700±548
APD_{90} (ms)	403	413	415±119
DRT (ms)	693	694	805±188
RT_{1050} (ms)	45.9	54.1	82.9±50.5
DT_{9010} (ms)	343	317	410±100
ATM (kPa)	0.055	0.0557	0.055±0.009
CRT_{50} (ms)	158	155	158±12.1
FCS (%)	3.23	3.46	3.27±0.37

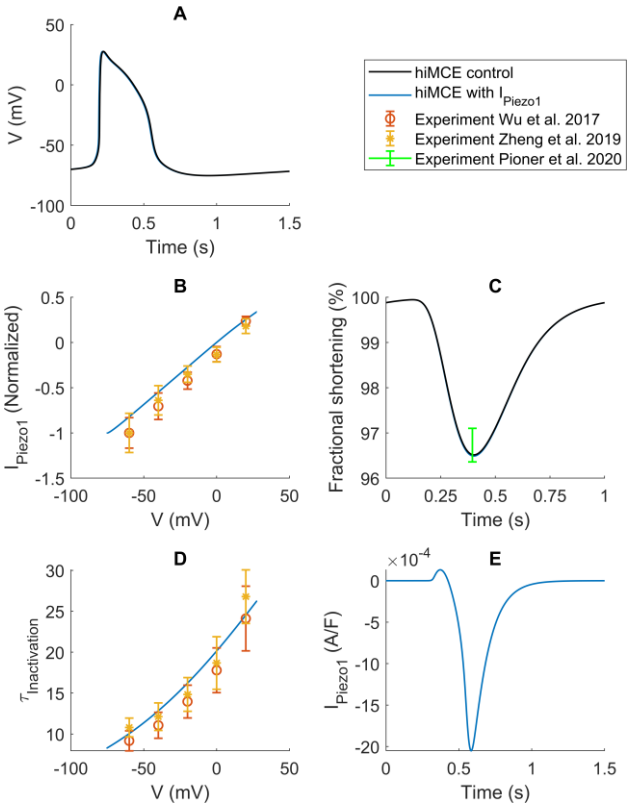

Figure 2. The hiMCE+Piezo1 model readouts against *in vitro* data [11]–[13]. Action potentials (A), Piezo1 current-voltage relationship (B), fractional cell shortening (C), Piezo1 voltage-dependent inactivation vs voltage (D), and Piezo1 current morphology (E).

3.2. Model response to $MYH7^{R403Q/+}$ cardiomyopathy

The response of hiMCE+Piezo1 model to $MYH7^{R403Q/+}$ condition was evaluated through simulating APs, I_{Piezo1} vs time, and Normalized I_{peizo1} vs tension relationships (Figure 3). The simulated P_{50} for control condition, 0.534, in current-tension relationships (Figure 3C) is quantitatively consistent with P_{50}=0.5 (normalized) reported *in vitro* for human Piezo1 [8]. The current-tension relationships revealed 27.9% increase in the Boltzmann slope as a result of $MYH7^{R403Q/+}$ HCM (0.0182 to 0.0233). On the other hand, the P_{50} also increased by 16.7% in response to $MYH7^{R403Q/+}$ HCM condition. The hiMCE+Piezo1 model did not predict a significant impact on Piezo1 voltage-dependent inactivation in response to $MYH7^{R403Q/+}$ HCM condition.

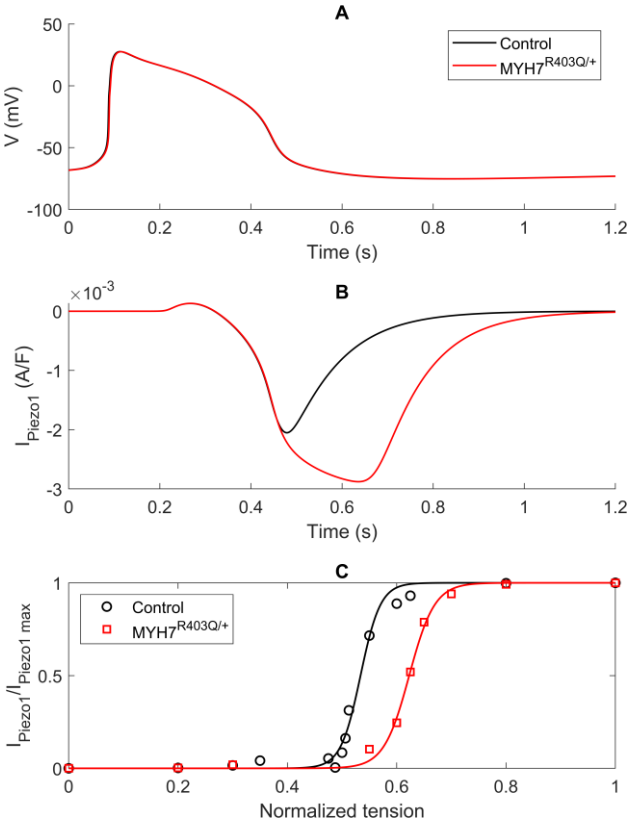

Figure 3. The hiMCE+Piezo1 model in response to $MYH7^{R403Q/+}$ cardiomyopathy condition detailing the action potentials (A), I_{piezo1} current profile (B), and tension-sensitivity of Piezo1 channel (C).

4. Discussion

Piezo ion channels are known to be responsive to mechanical stimuli, including localized membrane stretch, whole-cell poking, and fluid flow, specifically shear stress [14]. Furthermore, it has been observed that intracellular traction forces, which are produced through the phosphorylation of myosin II by myosin light chain kinase, are capable of generating localized Ca^{2+} fluctuations mediated by Piezo1, even in the absence of externally applied force [14]. Our new *in silico* model of hiPSC-CMs featuring a validated biophysical mechanistic model of Piezo1 current can be used as a tool to predict the impact of abnormal electrophysiological and contractile functions on the mechanosensitivity, especially, mutation-specific

HCM.

Cardiac Piezo1 has been reported to initiate a hypertrophic response in pressure overload in adult mice cardiomyocytes [15]. Furthermore, the removal of Piezo1 was reported to correlate with reduction in the hypertrophic response [15]. Our model takes a new step toward deep-phenotyping $MYH7^{R403Q/+}$ HCM by mapping Piezo1 domain of impact in presence of $MYH7^{R403Q/+}$ cardiomyopathy. The findings here indicating losing tension-sensitivity of Piezo1 due to $MYH7^{R403Q/+}$ HCM while gaining faster dynamic (increase in the slope) could be potentially insightful for developing HCM drugs targeting Peizo1 for inhibition of the channel activity in presence of $MYH7^{R403Q/+}$ HCM condition.

Although limited availability of hiPSC-CM Piezo1 *in vitro* data restricted the validation of the current formulation, the presented framework provides the first robust biophysical description for cardiac mechanosensitivity at cellular level. A promising future direction can be studying the Piezo1-SERCA crosstalk [16] regarding the HCM-induced metabolite changes affecting SERCA. Moreover, Piezo1 has been reported to function as the upstream and mediator of Na^{+}-Ca^{2+} exchanger (NCX) in pressure-overload induced hypertrophy pathway [15]. Thus, the crosstalk could also be refined by considering the effect of Piezo1 on NCX dynamics.

As a step toward deep-phenotyping mutation-specific HCM, probing the pathological feedback to Piezo1 and its role in the $MYH7^{R403Q/+}$ cardiomyopathy pathway can increase the current understanding for the design of therapeutics targeting cardiac mechanosensitive channels.

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