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\textsuperscript{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\textsuperscript{R403Q/+} condition. Our biophysical model of Piezo1 has a tension-dependent activation and a novel voltage-dependent inactivation gate. We modeled MYH7\textsuperscript{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\textsuperscript{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 constant relationships with in vitro data from different labs. Finally, we aim investigate the tension-sensitivity of cardiac piezo1 in the presence of MYH7\textsuperscript{R403Q/+} HCM condition.

2. Methods

2.1. Piezo1 model

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

\begin{equation}
I_{\text{Piezo1}} = g_p m_a X_n (V - E_p)
\end{equation}

\begin{equation}
J_{\text{Piezo1}} = c |I_{\text{Piezo1}}|
\end{equation}

\begin{equation}
X_n_{\text{inf}} = \frac{2}{1 + e^{\frac{-V - E_p}{\alpha}}}
\end{equation}

\begin{equation}
\alpha_{X_n} = \frac{1}{\sqrt{1 + e^{-\frac{V - E_p}{\beta}}}}
\end{equation}

\begin{equation}
\beta_{X_n} = \frac{1}{\sqrt{1 + e^{-\frac{V - E_p}{\beta}}}}
\end{equation}

\begin{equation}
\tau_{X_n} = \frac{\alpha_{X_n} \beta_{X_n}}{\tau_{X_n}}
\end{equation}

\begin{equation}
dX_n = \left[ X_n_{\text{inf}} - X_n \right] \frac{\tau_{X_n}}{\tau_{X_n}}
\end{equation}
\[
\begin{align*}
\frac{dm_{a}}{dt} &= \frac{m_{a} \tau_{a}}{1 + e^{(d-m_{a})/0.25}} \\
\tau_{a} &= \frac{m_{a_{inf}} - m_{a}}{d_{a}}
\end{align*}
\]

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]. \( V_m \) is voltage in mV, and \( \tau_a \) and \( \tau_{XN} \) represent activation and inactivation gate time constants, respectively.

Table 1. Piezo1 model constants.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>( E_p ) (mV)</td>
<td>0</td>
<td>[9]</td>
</tr>
<tr>
<td>( c )</td>
<td>0.116</td>
<td>[6]</td>
</tr>
<tr>
<td>( \tau_{a} )</td>
<td>0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>( g_p ) (S/F)</td>
<td>0.304</td>
<td>[10]</td>
</tr>
</tbody>
</table>

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

\[
\frac{dV}{dt} = -(I_{Na} + I_{NaL} + I_{Cat} + I_f + I_{K1} + I_{Kt} + I_{Ks} + I_{to} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{bNa} + I_{bCa} + I_{piezo1} - I_{stim})
\]

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. MYH7R403Q+/cardiomyopathy model

The pathophysiology of MYH7R403Q/+ 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 MYH7R403Q+/cardiomyopathy following [5].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Control</th>
<th>MYH7R403Q/+</th>
</tr>
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<tbody>
<tr>
<td>( P_{ref} ) (mM)</td>
<td>2</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>MgADP</td>
<td>0.036</td>
<td>0.072</td>
<td></td>
</tr>
<tr>
<td>ap2 coef.</td>
<td>1</td>
<td>0.315</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
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\( P_{ref} \) 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 (\( \tau_{XN} \)) 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, \( RT_{100C} \): 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.
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<tr>
<td>APA (mV)</td>
<td>103</td>
<td>103</td>
<td>104±6</td>
</tr>
<tr>
<td>MDP (mV)</td>
<td>-75.0</td>
<td>-75.2</td>
<td>-75.6±6.6</td>
</tr>
<tr>
<td>CL (ms)</td>
<td>1644</td>
<td>1695</td>
<td>1700±548</td>
</tr>
<tr>
<td>APD90 (ms)</td>
<td>403</td>
<td>413</td>
<td>415±119</td>
</tr>
<tr>
<td>DRT (ms)</td>
<td>693</td>
<td>694</td>
<td>805±188</td>
</tr>
<tr>
<td>RT100 (ms)</td>
<td>45.9</td>
<td>54.1</td>
<td>82.9±50.5</td>
</tr>
<tr>
<td>DT100 (ms)</td>
<td>343</td>
<td>317</td>
<td>410±100</td>
</tr>
<tr>
<td>ATM (kPa)</td>
<td>0.055</td>
<td>0.0557</td>
<td>0.055±0.009</td>
</tr>
<tr>
<td>CRT50 (ms)</td>
<td>158</td>
<td>155</td>
<td>158±12.1</td>
</tr>
<tr>
<td>FCS (%)</td>
<td>3.23</td>
<td>3.46</td>
<td>3.27±0.37</td>
</tr>
</tbody>
</table>

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\textsuperscript{R403Q/+/+} cardiomyopathy

The response of hiMCE+Piezo1 model to MYH7\textsuperscript{R403Q/+/+} condition was evaluated through simulating APs, I\textsubscript{Piezo1} vs time, and Normalized I\textsubscript{Piezo1} vs tension relationships (Figure 3). The simulated P\textsubscript{50} for control condition, 0.534, in current-tension relationships (Figure 3C) is quantitatively consistent with P\textsubscript{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\textsuperscript{R403Q/+/+} HCM (0.0182 to 0.0233). On the other hand, the P\textsubscript{50} also increased by 16.7% in response to MYH7\textsuperscript{R403Q/+/+} HCM condition. The hiMCE+Piezo1 model did not predict a significant impact on Piezo1 voltage-dependent inactivation in response to MYH7\textsuperscript{R403Q/+/+} HCM condition.

Figure 3. The hiMCE+Piezo1 model in response to MYH7\textsuperscript{R403Q/+/+} cardiomyopathy condition detailing the action potentials (A), I\textsubscript{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\textsuperscript{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 MYH7R403Q+ HCM by mapping Piezo1 domain of impact in presence of MYH7R403Q+ cardiomyopathy. The findings here indicating losing tension-sensitivity of Piezo1 due to MYH7R403Q+ HCM while gaining faster dynamic (increase in the slope) could be potentially insightful for developing HCM drugs targeting Piezo1 for inhibition of the channel activity in presence of MYH7R403Q+ 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+-Ca2+ 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 MYH7R403Q+ cardiomyopathy pathway can increase the current understanding for the design of therapeutics targeting cardiac mechanosensitive channels.

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References


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