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 Ca2+-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 MYH7R403Q/+ condition. Our biophysical model of Piezo1 has a tension-dependent activation and a novel voltage-dependent inactivation gate. We modeled MYH7R403Q/+ 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 MYH7R403Q/+ 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 to investigate the tension-sensitivity of cardiac piezo1 in the presence of MYH7R403Q/+ HCM condition.

2. Methods

2.1. Piezo1 model

Extending previous mechano-sensitive channel formulations [7], we defined Ipiez01 with a tension-dependent activation gate, \( m_a \), and a new voltage-dependent inactivation [2] gate, \( X_n \), as follows:

\[
I_{\text{Piezo1}} = g_p m_a X_n (V - E_p) \tag{1}
\]

\[
J_{\text{Piezo1}} = c |I_{\text{Piezo1}}| \tag{2}
\]

\[
X_{n_{\text{inf}}} = \frac{2}{1 + e^{\frac{V - E_{50}}{\sqrt{1 + e^{\frac{V - E_{50}}{270}}}}}} \tag{3}
\]

\[
\alpha_{X_n} = \frac{1}{\sqrt{1 + e^{\frac{V - E_{50}}{270}}}} \tag{4}
\]

\[
\beta_{X_n} = \frac{1}{\sqrt{1 + e^{\frac{V - E_{50}}{270}}}} \tag{5}
\]

\[
\frac{dX_n}{dt} = \frac{X_n_{\text{inf}} - X_n}{\tau_{X_n}} \tag{6}
\]

\[
\tau_{X_n} = \frac{1}{\alpha_{X_n} + \beta_{X_n}} \tag{7}
\]
\[
m_{\text{ainf}} = \frac{1}{1 + e^{(d - 1.5)/0.25}} \\
dm = \frac{m_{\text{ainf}} - m_a}{\tau_a}
\]

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 Ca²⁺ 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 \(\tau_{XH}\) 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>
</tr>
</thead>
<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:

\[
\frac{\text{d}V}{\text{d}t} = -(I_{Na} + I_{NaL} + I_{CaL} + I_f + I_{K1} + I_{Kr} + I_{Ks} + I_{to} + I_{NaCa} + I_{Nak} + I_{pCa} + I_{bNa} + I_{bCa} + I_{\text{Piezo1}} - I_{\text{stim}})
\]

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. MYH7<sup>R403Q/+</sup> cardiomyopathy model

The pathophysiology of MYH7<sup>R403Q/+</sup> 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<sup>R403Q/+</sup> cardiomyopathy following [5].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>MYH7&lt;sup&gt;R403Q/+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pi&lt;sub&gt;ref&lt;/sub&gt; (mM)</td>
<td>2</td>
<td>18.9</td>
</tr>
<tr>
<td>MgADP</td>
<td>0.036</td>
<td>0.072</td>
</tr>
<tr>
<td>ap2 coef.</td>
<td>1</td>
<td>0.315</td>
</tr>
<tr>
<td>R</td>
<td>1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Pi<sub>ref</sub> represents the reference value of inorganic phosphate in the hiMCE model, ap2 influences the forward transition between XB<sub>A</sub> and XB<sub>B</sub> 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 \(I_{\text{Piezo1}}\) formulation with respect to the in vitro data of current vs membrane potential (Figure 2B) and voltage-dependent inactivation time constant (\(\tau_{XH}\)) vs voltage (Figure 2D) relationships. As a semiquantitative validation, the simulated \(I_{\text{Piezo1}}\) 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.

<table>
<thead>
<tr>
<th>APA: AP amplitude, MDP: maximum diastolic potential, CL: AP cycle length, APD&lt;sub&gt;90&lt;/sub&gt;: AP duration at 90% of repolarization, DRT: Ca²⁺ transient (CaT) duration, RT&lt;sub&gt;1090&lt;/sub&gt;: rise time from 10 to 50% of maximum threshold in CaT, DT&lt;sub&gt;300&lt;/sub&gt;: decay time from 90 to 10% of maximum threshold in CaT, ATM: active tension magnitude, CRT&lt;sub&gt;50&lt;/sub&gt;: time from peak contraction to 50% of relaxation.</th>
<th>APA</th>
<th>MDP</th>
<th>CL</th>
<th>APD&lt;sub&gt;90&lt;/sub&gt;</th>
<th>DRT</th>
<th>RT&lt;sub&gt;1090&lt;/sub&gt;</th>
<th>DT&lt;sub&gt;300&lt;/sub&gt;</th>
<th>ATM</th>
<th>CRT&lt;sub&gt;50&lt;/sub&gt;</th>
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<tr>
<td>APA: AP amplitude, MDP: maximum diastolic potential, CL: AP cycle length, APD&lt;sub&gt;90&lt;/sub&gt;: AP duration at 90% of repolarization, DRT: Ca²⁺ transient (CaT) duration, RT&lt;sub&gt;1090&lt;/sub&gt;: rise time from 10 to 50% of maximum threshold in CaT, DT&lt;sub&gt;300&lt;/sub&gt;: decay time from 90 to 10% of maximum threshold in CaT, ATM: active tension magnitude, CRT&lt;sub&gt;50&lt;/sub&gt;: time from peak contraction to 50% of relaxation.</td>
<td>APA</td>
<td>MDP</td>
<td>CL</td>
<td>APD&lt;sub&gt;90&lt;/sub&gt;</td>
<td>DRT</td>
<td>RT&lt;sub&gt;1090&lt;/sub&gt;</td>
<td>DT&lt;sub&gt;300&lt;/sub&gt;</td>
<td>ATM</td>
<td>CRT&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>Biomarker</td>
<td>hiMCE [5]</td>
<td>hiMCE+ Piezo1</td>
<td>( \textit{in vitro} ) [12]</td>
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<tr>
<td>APA (mV)</td>
<td>103</td>
<td>103</td>
<td>104±6</td>
<td></td>
<td></td>
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<tr>
<td>MDP (mV)</td>
<td>-75.0</td>
<td>-75.2</td>
<td>-75.6±6.6</td>
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<tr>
<td>CL (ms)</td>
<td>1644</td>
<td>1695</td>
<td>1700±548</td>
<td></td>
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<tr>
<td>APD(_{90}) (ms)</td>
<td>403</td>
<td>413</td>
<td>415±119</td>
<td></td>
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<tr>
<td>DRT (ms)</td>
<td>693</td>
<td>694</td>
<td>805±188</td>
<td></td>
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<tr>
<td>RT(_{100}) (ms)</td>
<td>45.9</td>
<td>54.1</td>
<td>82.9±50.5</td>
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<tr>
<td>DT(_{90\text{to}10}) (ms)</td>
<td>343</td>
<td>317</td>
<td>410±100</td>
<td></td>
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<tr>
<td>ATM (kPa)</td>
<td>0.055</td>
<td>0.0557</td>
<td>0.055±0.009</td>
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<tr>
<td>CRT(_{50}) (ms)</td>
<td>158</td>
<td>155</td>
<td>158±12.1</td>
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<td></td>
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<tr>
<td>FCS (%)</td>
<td>3.23</td>
<td>3.46</td>
<td>3.27±0.37</td>
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</table>

Figure 2. The hiMCE+Piezo1 model readouts against \textit{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, \( I_{\text{Piezo1}} \) vs time, and Normalized \( I_{\text{Piezo1}} \) 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 \textit{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), \( I_{\text{Piezo1}} \) 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 \( \text{Ca}^{2+} \) fluctuations mediated by Piezo1, even in the absence of externally applied force [14]. Our new \textit{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\textsuperscript{R403Q/+} HCM by mapping Piezo1 domain of impact in presence of MYH7\textsuperscript{R403Q/+} cardiomyopathy. The findings here indicating losing tension-sensitivity of Piezo1 due to MYH7\textsuperscript{R403Q/+} 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 MYH7\textsuperscript{R403Q/+} HCM condition.

Although limited availability of hiPSC-CM Piezo1 \textit{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\textsuperscript{+}-Ca\textsuperscript{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\textsuperscript{R403Q/+} cardiomyopathy pathway can increase the current understanding for the design of therapeutics targeting cardiac mechanosensitive channels.

Acknowledgments

MF was supported by the graduate school of Faculty of Medicine and Health Technology, Tampere University and the Pirkanmaa fund of Finnish Cultural Foundation.

References


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