Myocardial Electrophysiological, Contractile and Metabolic Properties of Hypertrophic Cardiomyopathy: Insights from Modelling

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Abstract

Hypertrophic cardiomyopathy (HCM) is characterised by cellular dysfunction, asymmetric left ventricular (LV) hypertrophy, ventricular arrhythmias and sudden death. HCM is associated with mutations in sarcomeric proteins and is usually transmitted as an autosomal-dominant trait. The aim of this in silico study was to investigate the mechanisms by which HCM alters electrophysiological activity, contractility and energy metabolism regulation at the single cell and organ levels.

We developed a human ventricular, electromechanical, mitochondrial energetic (EMME) myocyte model incorporating electrophysiology, metabolism and force generation. The model was validated by its ability to reproduce the experimentally observed kinetic properties of human HCM induced by a) remodelling of several ion channels and Ca2+ handling proteins arising from altered Ca2+/calmodulin kinase II (CAMKII) signaling pathways; and b) increased Ca2+ sensitivity of the myofilament proteins.

Our simulation results showed energy metabolism was impaired, as indicated by a decreased phosphocreatine to ATP ratio (-9%) and there was energy expenditure beyond supply. 3D EMME human LV model simulation incorporating septal hypertrophy showed ejection fraction was not significantly altered but contractile efficiency was reduced.

1. Introduction

Hypertrophic cardiomyopathy (HCM) usually results from mutations of sarcomeric proteins; the sarcomere being the fundamental contractile unit of the cardiomyocyte [1]. HCM is transmitted as an autosomal-dominant trait [1].

Clinically, HCM is characterised by asymmetric left ventricular hypertrophy and a decrease in the LV chamber size. Histopathology features include disorganized myocyte architecture, including disarray of myocyte fibres, intertwined hypertrophied myocytes, and focal or widespread interstitial fibrosis (Figure 1) [2]. Ejection Fraction (EF) of the heart is preserved but relaxation capacity is diminished [1-2]. It affects ~1 in 500 individuals [1-2] and is associated with heart failure, arrhythmias, and sudden cardiac death at any age [1-2].

Figure 1. Pathology of hypertrophic cardiomyopathy. A. Heart from an HCM patient demonstrating massive asymmetric left ventricular hypertrophy, with associated reduction in left ventricular cavity size, compared to a normal heart. B. Histopathology showing significant fibre disarray and interstitial fibrosis in HCM. C. Clipped view of the 3D LV geometry used for the in silico simulations in this study. Modified from [2].
Coppini et al. [3] recently elucidated functional changes in human HCM myocardium, which stem from a complex remodelling process involving alterations of CAMKII-dependent signalling rather than being a direct consequence of the causing sarcomeric mutations. In this study, we investigated how these functional changes altered electrophysiological activity, contractility and energy metabolism regulation at the single cell level and cardiac systolic and diastolic performance at the organ level in human HCM.

2. Methods

2.1. Single cell simulations

To investigate the functional consequences of HCM, we developed a human ventricular, electromechanical, mitochondrial energetics (EMME) myocyte model by integrating models of the electrophysiological, Ca$^{2+}$ handling, myofilament and mitochondrial oxidative phosphorylation sub-systems of the cardiac myocyte. For electrophysiology, we used the O’Hara-Rudy (ORd) single cell human ventricular model with Ca$^{2+}$ handling [4] and for mechanics, we used the Tran et al. myofilament model [5]. For mitochondrial bioenergetics, we used the thermokinetic model of Cortassa et al. [6].

To simulate HCM cardiomyocytes in agreement with Coppini et al.’s [3] experimental results, we made the following changes to the ORd ventricular model as listed in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HCM Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>+100%</td>
</tr>
<tr>
<td>Capacitance</td>
<td>+59%</td>
</tr>
<tr>
<td>$G_{NaL}$</td>
<td>+107%</td>
</tr>
<tr>
<td>$G_{Kr}$</td>
<td>-34%</td>
</tr>
<tr>
<td>$G_{Ks}$</td>
<td>-27%</td>
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<tr>
<td>$G_{to}$</td>
<td>-85%</td>
</tr>
<tr>
<td>$G_{Ki}$</td>
<td>-15%</td>
</tr>
<tr>
<td>$G_{CaL}$</td>
<td>+19%</td>
</tr>
<tr>
<td>$G_{NaCa}$</td>
<td>+34%</td>
</tr>
<tr>
<td>SERCA</td>
<td>-43%</td>
</tr>
<tr>
<td>CAMKa</td>
<td>+350%</td>
</tr>
<tr>
<td>PLB</td>
<td>-40%</td>
</tr>
<tr>
<td>*Hill Coefficient</td>
<td>-50%</td>
</tr>
</tbody>
</table>

Table 1. HCM functional changes [3] made to the ORd and myofilament models. * Myofilament model only [5].

2.2. 3D electromechanical simulations

Similar to previous studies [7], the mono-domain representation [7] of cardiac tissue was used for the electrophysiology model.

$$ C_m \frac{dV}{dt} = -(I_{ion} + I_{stim}) + \nabla \cdot (D \nabla V) \quad (1) $$

where $C_m$ is the cell capacitance per unit surface area, $V$ is...
Figure 3. Electrical wave propagation and contraction of the left ventricle in control and HCM conditions. The contracting LV is superimposed on a static mesh (grey). Membrane potential is colour-coded from -87 mV (blue) to +40 mV (red) as indicated by the colour key.

The membrane potential, $I_{ion}$, is the sum of all transmembrane ionic currents from the electromechanics single cell model, $I_{stim}$ is an externally applied stimulus and $D$ is the anisotropic diffusion tensor given by:

$$D = \sigma_f \xi(f) + \sigma_s (s \otimes s) + \sigma_n (n \otimes n)$$  \hspace{1cm} (2)$$

with the eigenaxes $f$ oriented along the fibres, $s$ perpendicular to the fibres but within the laminar sheet and $n$ perpendicular to the sheets. $\sigma_f$, $\sigma_s$ and $\sigma_n$ are the conductivities in the fibre, sheet and cross-sheet directions respectively. $\xi$ is a structure tensor modelling the dispersion of the fibre direction around its mean orientation following the work of Eriksson et al. [8] and is given by:

$$\xi = \kappa_f I + (1 - 3\kappa_f)(f \otimes f)$$  \hspace{1cm} (3)$$

where $\kappa_f$ is the fibre dispersion parameter. To take into account the fibre diastasis in HCM (Figure 1B), $\kappa_f$ is set to 0.0886 for HCM [8] and set to 0 for control.

We modelled cardiac tissue mechanics within the theoretical framework of non-linear elasticity as an inhomogeneous, anisotropic, nearly incompressible, non-linear material similar to previous studies [7]. The coupling between cardiac mechanics and electrical excitation propagation is addressed in a framework in which the electrical potential dictates the active strain of the muscle. We used a two-field variational principle with the deformation $u$ and the hydrostatic pressure $p$ as the two fields [7]. The total potential energy functional $\Pi$ for the mechanics problem is formulated as:

$$\Pi(u, p) = \Pi_{int}(u, p) + \Pi_{ext}(u)$$  \hspace{1cm} (4)$$

where $\Pi_{int}(u, p)$ is the internal potential energy of the body and $\Pi_{int}(u)$ is the potential energy of the external loading of the body.

3. Results

HCM increased the action potential duration (APD₉₀) from 231 ms to 342 ms (Figure A, E, I). In association with this, the L-type Ca²⁺ current density ($I_{CaL}$) was increased in HCM at the onset of AP depolarisation but reduced in amplitude during the plateau phase (Figure 2B). $[Ca]_{l}^{2+}$ amplitude was similar in HCM and control (Figure 2F) but its kinetics, as indicated by decay time was slower in HCM. The slowed kinetics of $[Ca]_{l}^{2+}$ (Figure 2F) coupled with the transient increase in $I_{CaL}$ increased the amplitude of the reverse-mode of the Na⁺/Ca²⁺ exchanger (NCX) with its forward mode unchanged (Figure 2C).

The mitochondrial membrane potential $\Delta \Psi$ was lowered, implying a lowered electron transport chain oxygen radical and hence, energy expenditure beyond supply (Figure 2I). The inefficient energy usage can be observed in the tension cost – impaired energy
4. Discussion and conclusion

HCM cardiomyocytes exhibited greater contractility (Figure 2) due to the combination of a) slowed $[Ca^{2+}]_c$ decay kinetics; b) reduced SERCA activity and PLB and c) greater myofilament $Ca^{2+}$ sensitivity all of which led to $Ca^{2+}$ accumulation in the cytoplasm. The greater myocyte contractility enabled the LV to maintain a relatively normal EF despite the wall hypertrophy and reduced chamber size (Figure 3). To achieve normal EF, the LV required greater strain from the myocytes on the myocardial walls (Figure 4) and consequently, a greater maximal oxygen consumption rate (Figure 2K-L).

Our results show that a relatively normal EF is maintained in HCM due to $Ca^{2+}$ handling abnormalities but at the cost of greater energy expenditure. Our results support the notion for inefficient energy utilisation as a unifying mechanism in HCM.

Acknowledgements

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References

[1] Spudich JA. Hypertrophic and dilated cardiomyopathy: four decades of basic research on muscle lead to potential therapeutic approaches to these devastating genetic diseases. Biophys J 2014;106:1236-49.

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