

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

Ismail Adeniran¹, David H MacIver², Henggui Zhang¹

¹University of Manchester, Manchester, UK

²Taunton & Somerset Hospital, Taunton, UK

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 energetics (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 Ca^{2+} handling proteins arising from altered Ca^{2+} /calmodulin kinase II (CAMKII) signaling pathways; and b) increased Ca^{2+} 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].

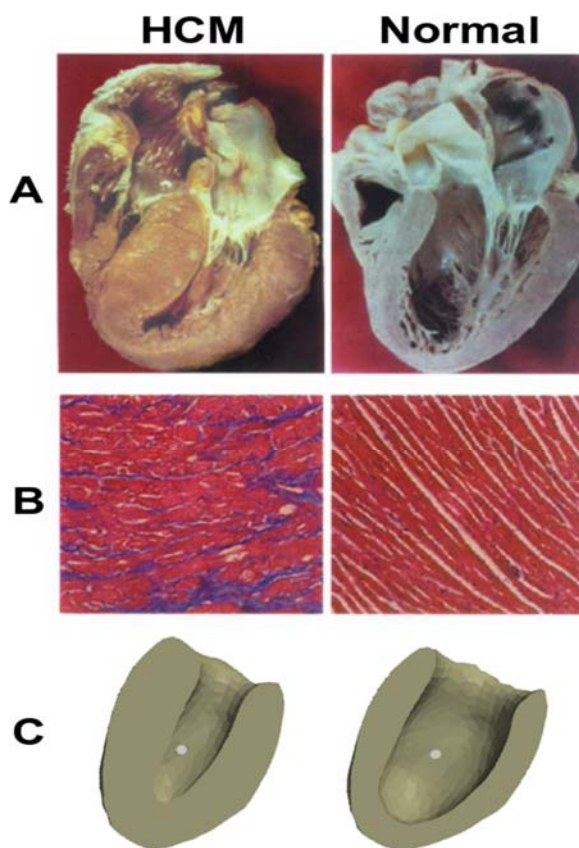


Figure 1. Pathology of hypertrophic cardiomyopathy. A. Heart from an HCM patient demonstrating massive asymmetric left ventricular hypertrophy, with associated reduction in left ventricular cavity size, compared to a normal heart. B. Histopathology showing significant fibre disarray and interstitial 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.

	HCM
Volume	+100%
Capacitance	+59%
G_{NaL}	+107%
G_{Kr}	-34%
G_{Ks}	-27%
G_{to}	-85%
G_{K1}	-15%
G_{CaL}	+19%
G_{NaCa}	+34%
SERCA	-43%
CAMKa	+350%
PLB	-40%
*Hill Coefficient	-50%

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

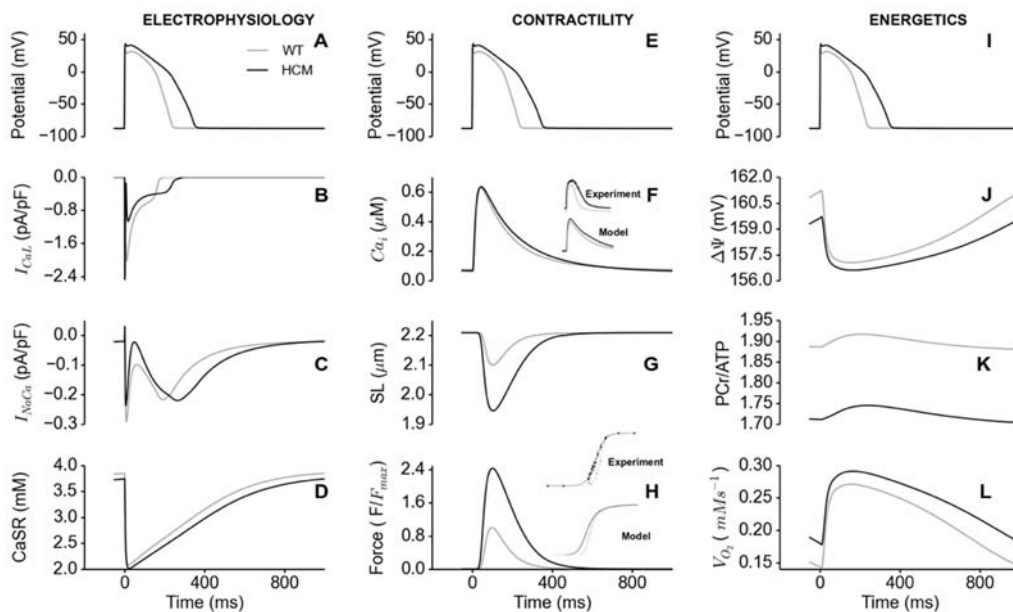


Figure 2. Electrophysiological (A-D), contractile (E-H) and bioenergetics (I-L) properties under control (grey) and HCM (black) at 1Hz cycle length. **(F) inset:** Comparison of $[Ca]_i^{2+}$ between experiment and model simulations at 0.2 Hz pacing rate. **(H) inset:** Comparison of F-Ca relation between experiment and model. PCr/ATP = phosphocreatine to ATP ratio, V_{O_2} = oxygen consumption rate.

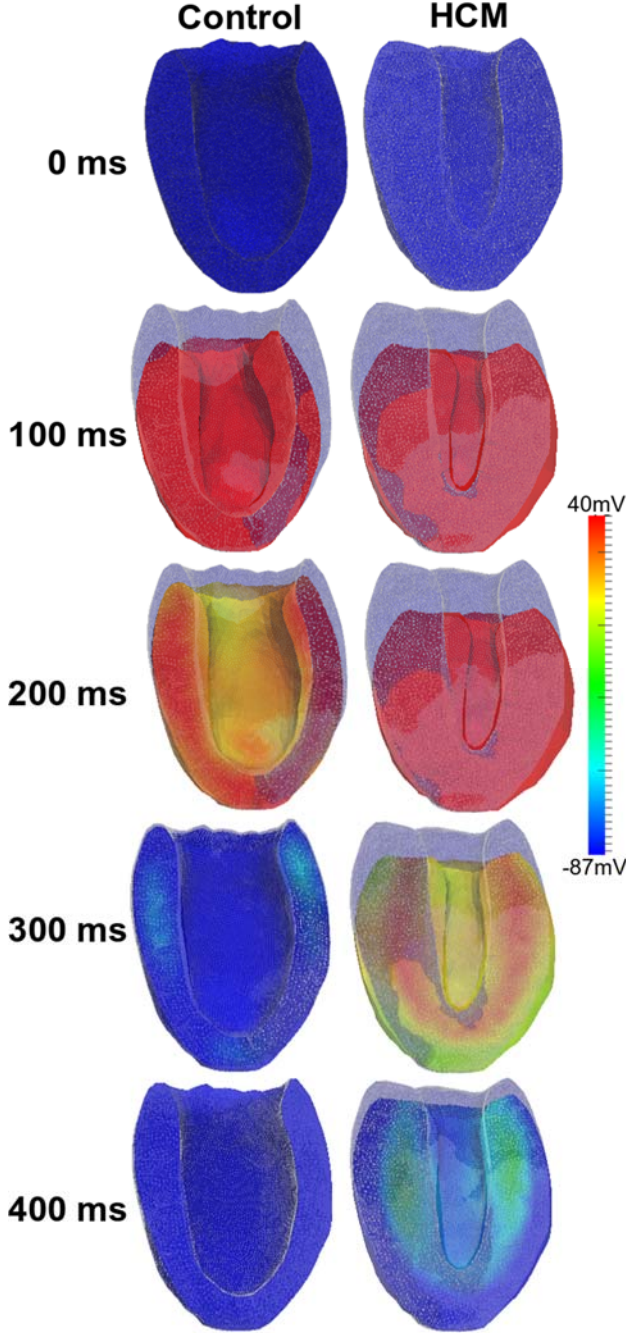


Figure 3. Electrical wave propagation and contraction of the left ventricle in control and HCM conditions. The contracting LV is superimposed on a static mesh (grey). Membrane potential is colour-coded from -87 mV (blue) to +40 mV (red) as indicated by the colour key.

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:

$$D = \sigma_f \xi_f (f) + \sigma_s (s \otimes s) + \sigma_n (n \otimes n) \quad (2)$$

with the eigenaxes f oriented along the fibres, s perpendicular to the fibres but within the laminar sheet and n perpendicular to the sheets. σ_f , σ_s and σ_n are the conductivities in the fibre, sheet and cross-sheet directions respectively. ξ_f 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:

$$\xi_f = \kappa_f I + (1 - 3\kappa_f)(f \otimes f) \quad (3)$$

where κ_f is the fibre dispersion parameter. To take into account the fibre diasarray in HCM (Figure 1B), κ_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 Π for the mechanics problem is formulated as:

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

where $\Pi_{int}(u, p)$ is the internal potential energy of the body and $\Pi_{ext}(u)$ 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). $[Ca]_i^{2+}$ 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 $[Ca]_i^{2+}$ (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 2J). The inefficient energy usage can be observed in the tension cost – impaired energy

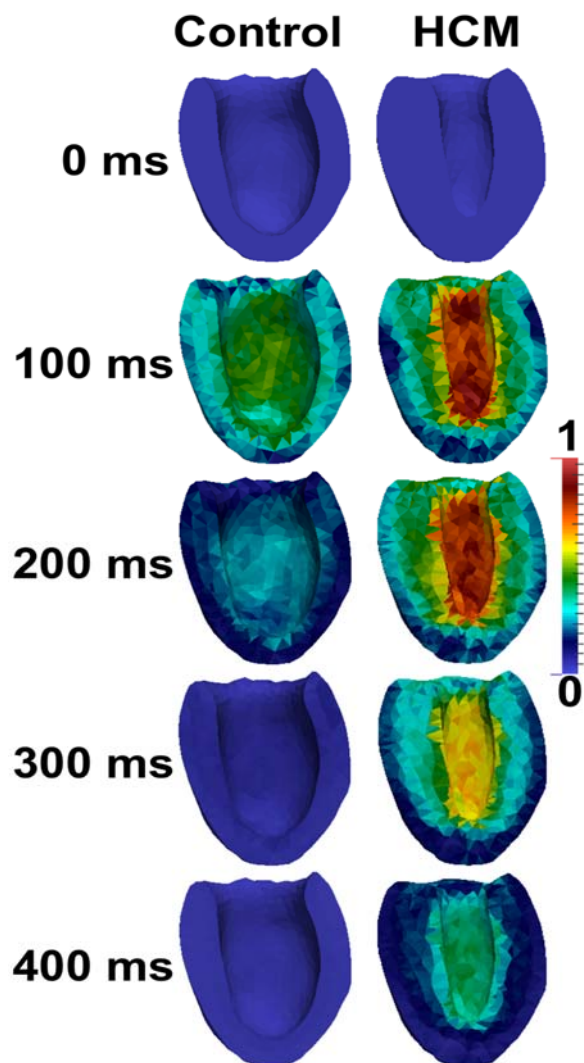


Figure 4. Strain distribution in the 3D model of the human ventricle in control and HCM conditions. Strain was colour-coded from 0 (blue) to 1 (red) as indicated by the colour key.

metabolism, as indicated by a decreased phosphocreatine to ATP ratio (-9%) (Figure 2K) and the increased oxygen consumption rate (Figure 2L).

Figure 3 shows the electrical wave propagation and contraction in control and HCM. Despite, the LV hypertrophy, EF was 43% in HCM compared to 49% in control. The greater strain distribution across the ventricular walls needed to maintain the relatively normal EF in HCM is shown in Figure 4.

4. Discussion and conclusion

HCM cardiomyocytes exhibited greater contractility (Figure 2) due to the combination of a) slowed $[Ca]_i^{2+}$ 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

This work was supported by the project grant from Engineering and Physical Science Research Council UK (EP/J00958X/1; EP/I029826/1).

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.
- [2] Chung MW, Tsoutsman T et al. Hypertrophic cardiomyopathy: from gene defect to clinical disease. *Cell Res* 2003;13:9-20.
- [3] Coppini R, Ferrantini C et al. Late sodium current inhibition reverses electromechanical dysfunction in human hypertrophic cardiomyopathy. *Circulation* 2013;127:575-584.
- [4] O'Hara T, Virag L et al. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Comput Biol* 2011;7: e1002061.
- [5] Tran K, Smith NP et al. A metabolite-sensitive, thermodynamically constrained model of cardiac cross-bridge cycling: implications for force development during ischemia. *Biophys J* 2010;98: 267-76.
- [6] Cortassa S, Aon MA et al. An integrated model of cardiac mitochondrial energy metabolism and calcium dynamics. *Biophys J* 2003;84: 2734-55.
- [7] Adeniran I, Hancox JC et al. In silico investigation of the short QT syndrome, using human ventricle models incorporating electromechanical coupling. *Front Physiol* 2013;4: 166.
- [8] Eriksson TS, Prass AJ et al. Modeling the dispersion in electromechanically coupled myocardium. *Int J Numer Method Biomed Eng* 2013;29:1267-84.

Address for correspondence.

Ismail Adeniran
Biological Physics Group, School of Physics and Astronomy
University of Manchester, Oxford Road, Manchester M13 9PL
ismail.adeniran@manchester.ac.uk