Differential Response of Hypertrophic Cardiomyopathy to Ischemia Caused by Remodelling of Late Sodium and Rapidly Delayed Rectifier Channels

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Abstract

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy and a leading cause of sudden cardiac death (SCD) in the young. Myocardial ischemia plays a central role in HCM, as characterised by multiple microvascular disease and perfusion studies. However, the electrophysiological mechanisms linking SCD and ischemia in HCM remain poorly understood.

Using the ToR-ORd ventricular cardiomyocyte model, populations of experimentally calibrated action potential models for control and HCM cardiomyocytes were created. The populations were subjected to acidosis, hyperkalemia and hypoxia separately and in combined cases of ischemia.

HCM cardiomyocytes exhibited increased sensitivity to ischemia, with effective refractory periods significantly decreasing by (-153 ± 57) ms in HCM during hyperkalemia, yet increasing by $(+14 \pm 45)$ ms in control models. Selective removal of HCM ionic remodelling demonstrated that remodelling of the late sodium and rapidly delayed rectifier channels caused this abnormal response.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiomyopathy, with a population prevalence in excess of $1 : 500$ [1]. Although the risk of sudden cardiac death (SCD) in the general HCM population is low, HCM is a leading cause of SCD in the young, including young athletes [2]. Given that perfusion defects occur in the majority of HCM patients [3], myocardial ischemia is likely a key contributor to this increased SCD incidence. A refined understanding of ischemia-related mechanisms in HCM is then expected to improve risk stratification or yield novel therapies for SCD prevention in these patients.

The electrophysiological mechanisms relating to ischemia, although well understood in normal cardiomyocytes, have not yet been explored in HCM cardiomyocytes - in spite of extensive ionic remodelling. It is hypothesised that increased dispersion of action potential duration (APD) in HCM during ischemia may be the cause of increased SCD incidence. The present study aimed to test this hypothesis by identifying changes in action potential (AP) biomarkers in simulated HCM cardiomyocytes during phase 1A ischemia.

2. Methods

2.1. Control and HCM Populations

The population of models methodology developed by Britton et al. [4] was used to create a population of healthy cardiomyocyte models with variability in AP morphology, as observed experimentally.

1000 candidate models were generated by randomising the 11 main conductances (g_{CaL}, g_{Na}, g_{to}, g_{NaL}, g_{Kr}, g_{Ks}, g_{K1}, g_{NaCa}, g_{NaK}, g_{rel} and g_{up}) within $\pm 50\%$ of their original values using Latin hypercube sampling, with the ToR-ORd ventricular endocardial cardiomyocyte model used as a baseline [5]. Each candidate model was simulated for 100 beats at 1 Hz pacing and AP and Ca^{2+} transient biomarkers were measured. Models were removed from the population if any biomarker fell outside of the experimentally observed ranges.

After this process, the remaining models formed the control population. The analogue HCM population was then constructed by applying previously established ionic remodelling to each control model [6].

2.2. Simulating Phase 1A Ischemia

We focus on phase 1A ischemia (first 2-10 minutes post-occlusion) due to its association with SCD. This was modelled considering [7]: (i) hyperkalemia, an increased extracellular K^+ concentration - raised from 5 to 9 mM; (ii) acidosis, decreased pH which causes impairment of L-type Ca^{2+} and Na^+ channels - I_{Na} and I_{CaL} were each down-regulated by 25%; (iii) hypoxia, insufficient oxygen for normal cell function - ATP-sensitive K^+ channels were added to the ToR-ORd model and the fraction of activated channels was simulated for $f_{KATP} \in [0.03, 0.06, 0.09]$.

3. Results

3.1. HCM cardiomyocytes have greater refractory periods

The calibration of the control population to human physiological ranges of AP and Ca^{2+} transient biomarkers is shown in Fig. 1. The 228 accepted models formed the control population of healthy cardiomyocytes. By then applying previously established ionic remodelling [6] to these models, 228 paired HCM models were formed.
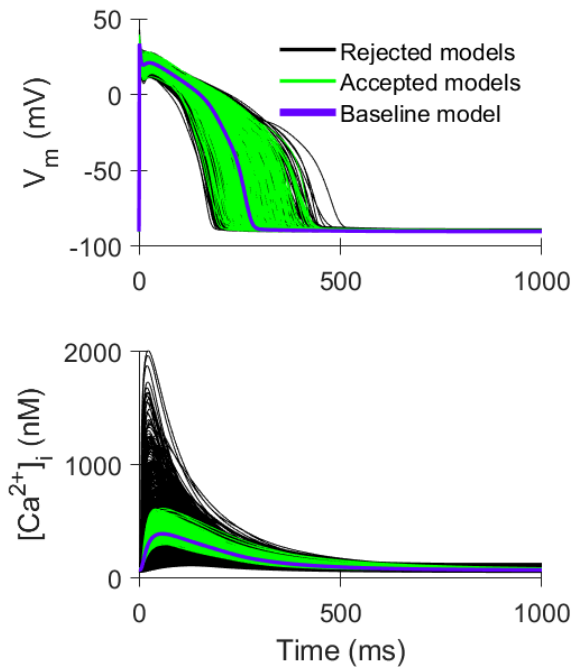

Figure 2. Action potentials of the control and HCM populations, each consisting of 228 models.

Figure 1. Action potentials (top) and Ca^{2+} transients (bottom) of the 1000 candidate models. 228 accepted models (green traces) had biomarker values within physiological ranges for healthy human electrophysiology.

Figure 3. Distribution of AP and Ca^{2+} transient biomarkers for the control and HCM populations. APD90: AP duration measured at 90% repolarisation; ERP: effective refractory period; PRR: post repolarisation refractoriness; CaT90: Ca^{2+} relaxation time to 90% decay.

The APs of all models in both populations are shown in Fig. 2. There is visible intra-population variability in AP shape in Fig. 2, alongside inter-population differences. Most noticeably, the HCM models have a far longer APD than control models, consistent with human experimental findings [6]. This is quantified in Fig. 3, showing distributions of AP and Ca^{2+} transient biomarkers for both populations. Importantly, the increased APD in the HCM population is matched by their effective refractory period (ERP).
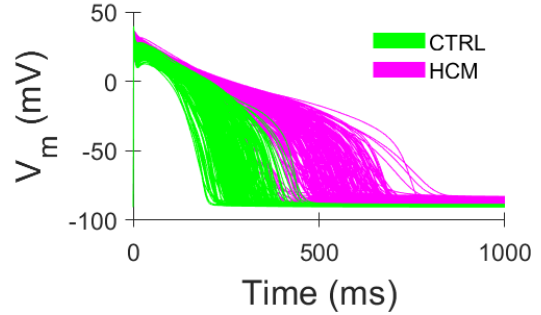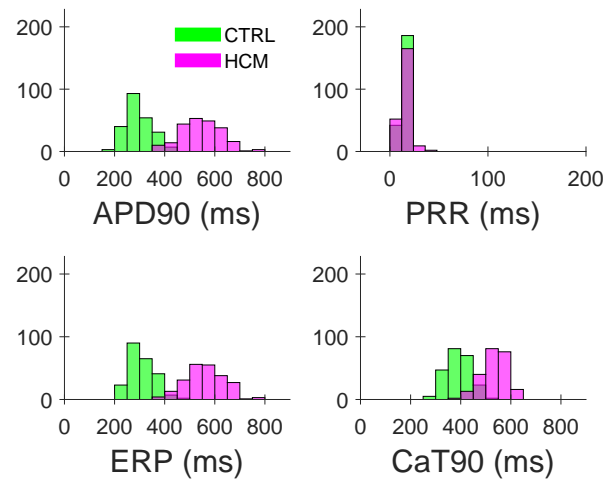
3.2. Differential response of refractory periods to hyperkalemia

Simulated hyperkalemia, by increasing extracellular K^+ concentration from 5 to 9 mM, raised the resting membrane potential (RMP) similarly by 12-15 mV in both the control and HCM populations. Between populations, however, differential effects on refractoriness were observed. The distributions of biomarkers concerning refractoriness under the effect of hyperkalemia are shown in Fig. 4. Subsequent to the increase in RMP, control and HCM models respond in vastly different ways. Whereas a significant decrease in ERPs is observed in HCM, there is only a slight increase in control. Moreover, HCM models showed a far greater sensitivity in their observed decrease in APD.
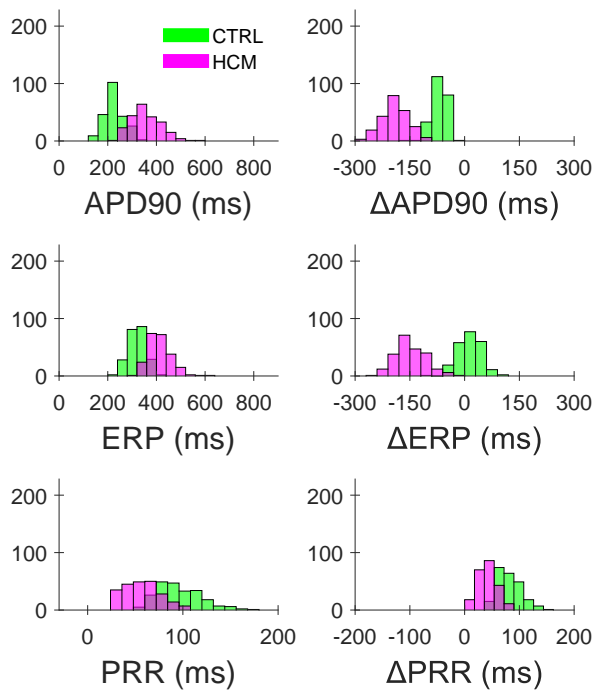
Figure 4. Distributions of refractoriness biomarkers (left) and their relative changes (right) under the effects of hyperkalemia for control and HCM populations. APD90: AP duration measured at 90% repolarisation; ERP: effective refractory period; PRR: post repolarisation refractoriness.

Further investigations were conducted by selectively removing each of the components associated with HCM remodelling. The significant differences in APD and ERP responses to hyperkalemia were almost entirely reversed when late I_{Na} upregulation and I_{Kr} downregulation were not considered as part of HCM remodelling, due to the voltage rectification of these channels by RMP.

3.3. Enhanced response of HCM refractoriness to hypoxia

Activation of ATP-sensitive K^+ channels reduced APD, ERP, Ca^{2+} transient amplitude and relaxation by an extent dependent on the fraction of activated channels f_{KATP}. As shown in Fig. 5, the extent of ERP shortening was greater in the HCM population than in control at all values of f_{KATP} tested. The same differences were observed in terms of APD response. These results suggest a likely contribution of K-ATP channels to increased dispersion of repolarisation and refractoriness in HCM in ischemia. However, given the results presented in Fig. 4, hyperkalemia is still the main contributor to changes in refractoriness in HCM during ischemia in this study.
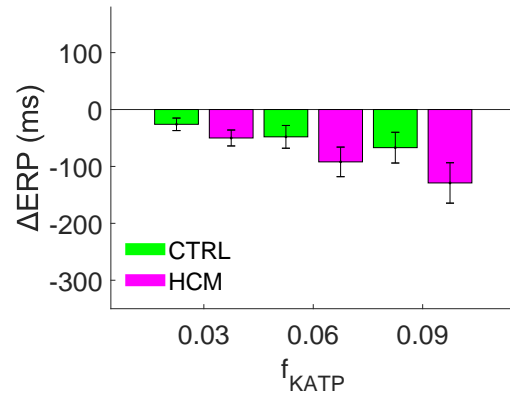

Figure 5. Extent of ERP shortening during hypoxia, for $f_{KATP} \in [0.03, 0.06, 0.09]$.

3.4. Combined response to acidosis, hyperkalemia and hypoxia

The biomarker changes presented in Fig. 6 result from full ischemia, simulated as the combined effects of hyperkalemia, hypoxia ($f_{KATP} = 0.06$) and acidosis. Changes in refractoriness in HCM due to simulated ischemia are vastly different to those in healthy cardiomyocytes. APD is decreased in HCM to an extent over double that in control. The distribution of ERPs is significantly decreased in the HCM population, while it is almost totally unchanged in the control population. A greater extent of post repolarisation refractoriness occurs in the control population.
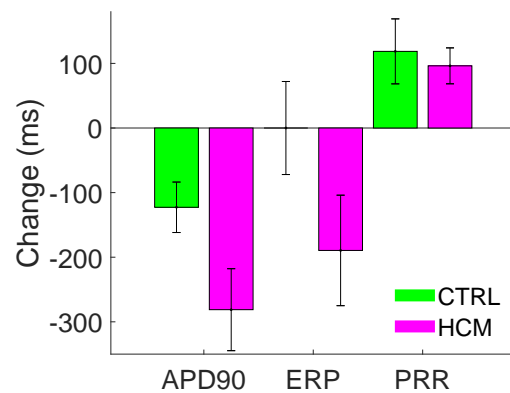

Figure 6. Median change to biomarkers concerning refractoriness during ischemia.

These differences between control and HCM responses to ischemia follow from the differential response to hyperkalemia shown in Fig. 4. However, the previous effect of increased ERPs in control models is now counteracted by K-ATP channel activation (Fig. 5), such that the net effect

on ERP is almost zero. Conversely, in HCM models, hypoxia synergistically combines with hyperkalemia to further reduce APD and ERP. Due to the mosaicism exhibited in HCM ventricles, where HCM and control regions coexist, such dispersion of refractoriness may have implications for re-entrant arrhythmias under ischemic conditions.

4. Discussion

The present study demonstrates that the HCM electrophysiological phenotype has an opposite response of refractoriness to hyperkalemia and an enhanced response to hypoxia, when compared to control models. Our results therefore suggest an increased arrhythmic risk in HCM patients under ischemia, due to increased dispersion of repolarisation between regions of hypertrophic and normal myocardium. Late sodium current inhibitors, such as ranolazine or disopyramide [8], could modulate arrhythmic risk in this context.

Historically, the increased incidence of SCD in hypertrophied hearts was hypothesised as arising due to greater ischemic vulnerability, caused by (i) coronary circulation abnormalities associated with hypertrophy; (ii) greater oxygen consumption by the hypertrophic myocardium and (iii) intrinsic electrophysiological abnormalities [9].

All of these considerations likely extend to HCM. Circulation abnormalities are common in HCM, both locally - through microvascular dysfunction due to excessive deformation in hypertrophic regions [3], and globally - through left ventricular outflow obstruction that worsens during exercise [10]. Larger energy demands in regions of hypertrophy may also contribute locally to ischemic vulnerability.

More fundamentally, energetic inefficiency of the sarcomere could be the root cause of HCM myocyte dysfunction and compensatory hypertrophy [11]. Energetic impairment of ATPases may further decrease resilience of the HCM cardiomyocyte to exercise, perhaps through reduced Na^+-K^+ pump function leading to greater extracellular K^+ accumulation at high pacing frequencies.

The present study adds evidence to support the role of intrinsic electrophysiological abnormalities associated with hypertrophy, particularly with regard to repolarisation and refractoriness dispersion in regional ischemia. When considered alongside a possible abnormal β-adrenergic response in HCM [12], intrinsic electrophysiological abnormalities may play a key role in SCD incidence in HCM during exercise due to demand ischemia.

Acknowledgements

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