ECG Deep Learning Dissects Physiology of Hypertrophic Cardiomyopathy

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Abstract

Hypertrophic cardiomyopathy (HCM) is mechanistically complex, and unravelling this would guide treatment and prognosis. One serious complication is left ventricular outflow tract (LVOT) obstruction, which increases afterload. Since afterload also increases with high blood pressure (BP), we hypothesised that obstructive HCM may share ECG features with hypertension. This study aimed to identify hypertensive-like ECG changes to discriminate physiological factors within HCM. A deep convolutional neural network was trained to quantify ECG changes in hypertension in n=37,378 UK Biobank participants and n=2,258 HCM Registry patients, generating a novel ECG strain score (ECG-SS). ECG-SS was raised in HCM independently of BP, indicating they have an alternative reason for strain. Sarcomere-negative HCM patients (no disease-causing gene) had bimodally distributed scores, suggesting two phenotypes distinguished by afterload. In this group, high ECG-SS was associated with obstruction and wall stress, but not with hypertrophy or fibrosis. To give clinical interpretability, a variational autoencoder allowed visualisation of ECG features, and demonstrated marked abnormalities in the high ECG-SS subgroup. In conclusion, ECG deep learning demonstrated, for the first time, LVOT obstruction to be the major cause of ECG abnormalities in HCM.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the commonest genetic heart disease. However, up to two-thirds of HCM patients do not carry disease-causing sarcomere gene variants (sarcomere-negative; SN-HCM). In comparison to sarcomere-positive patients (SP-HCM), SN-HCM is characterised by greater prevalence of hypertension, left ventricular outflow tract (LVOT) obstruction, obesity, and older age [1]. LVOT obstruction in HCM increases afterload: the pressure against which the heart pumps. Alongside LVOT obstruction, hypertension (high blood pressure; BP) also increases afterload. This hints that the ECG in the subset of HCM with obstructive pathology might share specific features with hypertension.

Given that hypertension induces ECG strain patterns (ST-segment depression, T-wave inversion), we hypothesised that building a tool to identify hypertensive-like ECG changes could then be applied to discriminate physiological factors in a different disease, i.e., HCM. We therefore trained a deep learning model to quantify ECG changes in hypertension, generating a novel ECG strain score (ECG-SS). To see if this captured physiological differences in HCM related to obstruction, we applied the ECG-SS to one of the largest prospective multicentre HCM studies.

Mechanisms that may generate ECG changes include cardiac structure and function. Structural changes, such as hypertrophy and fibrosis in hypertension, manifest as ECG strain, and this pattern regresses with antihypertensive treatment. Functional changes, such as decreasing LVOT gradient with myosin inhibitor therapy in HCM, improve ECG abnormalities within weeks [2]. Understanding these drivers of electrical remodelling thus elucidates underlying disease mechanisms and may help target therapeutics and guide prognosis. We investigated which reversible factors could be driving these ECG changes, including

hypertrophy, fibrosis, wall stress, and afterload, by testing whether ECG-SS is associated with structural and functional LV measures. Finally, we used a variational autoencoder (VAE) to visualise the salient ECG features detected by the model, lending clinical interpretability to the model's output.

2. Methods

2.1 Study population

12-lead resting ECGs from 37,520 UK Biobank (UKBB) [3] participants and 2,726 patients from the HCM Registry (HCMR) [1] were included. UKBB is a prospective cohort of 40–69-year-olds, recruited nationally between 2006-2010. HCMR is a multicentre, international prospective natural history study of HCM patients aged 18-65, recruited between 2014-2017, with comprehensive phenotyping (genetics, cardiac magnetic resonance imaging; CMR, biomarkers and clinical outcomes). Ethical approvals were obtained, and all participants provided informed consent.

UKBB ECGs (GE CardioSoft, 500Hz, 5µV resolution) were 10-second digital recordings. HCMR ECGs were digitised (AMPS www.amps-llc.com, 500Hz, 5µV resolution) from high-resolution scans of paper ECGs with 2.5-second recordings in each lead and a 10-second rhythm strip. Diastolic, systolic BP (DBP, SBP) and body mass index (BMI) were obtained at the time of ECG acquisition. Hypertension diagnosis was identified from ICD-10 coding or self-reported in UKBB, and from medical history in HCMR. Those with HCM in UKBB, invalid ECGs (missing lead, excess noise), and missing data (sarcomere status, hypertension diagnosis, BP), were excluded. Single ECGs from the remaining n=37,378 in UKBB and n=2,258 in HCMR were analysed in 4 diagnostic groups (Table 1): UKBB with no hypertension diagnosis (UKBB-N), UKBB with hypertension diagnosis (UKBB-H), HCMR sarcomere-negative (SN-HCM), and HCMR sarcomere-positive (SP-HCM).

Table 1. Baseline characteristics of diagnostic groups, showing mean values (standard deviation in parentheses).

	UKBB-N	UKBB-H	SP-HCM	SN-HCM
n	25,311	12,067	816	1,442
Age, yrs	54 (7)	57 (7)	47 (12)	52 (10)
% Male	44	58	66	75
BMI, kg/m^2	26 (4)	28 (5)	28 (5)	30 (6)
% Hypertension	0	100	21	45
DBP, mmHg	78 (8)	85 (9)	75 (13)	79 (14)
SBP, mmHg	132 (15)	147 (15)	125 (16)	132 (18)

2.1. Data processing

A single heartbeat was captured from each ECG lead by identifying R waves with a triangle convolution and extracting a 1-second trace centred 124ms after the R wave. Leads III, aVR, aVL, aVF, which are linearly dependent on I and II, were discarded. Notch filters at 50Hz and 60Hz removed electrical noise. Amplitude was expected to be abnormal in HCM and hypertension, so was not normalised. Signals were down-sampled to 100Hz using a sliding window mean (width 5, stride 5). Thus, each ECG became an 8x100 matrix.

2.2. CNN model design

A deep convolutional neural network (CNN) was constructed (Keras & Tensorflow) with 8 1D convolutional layers, and 2 dense layers (Fig. 1), each followed by batch normalisation. The output of a final 2-node softmax layer was compared to categorical hypertension diagnosis using binary cross-entropy loss. The adadelta optimiser was used for training. Training hyperparameters were tuned by grid

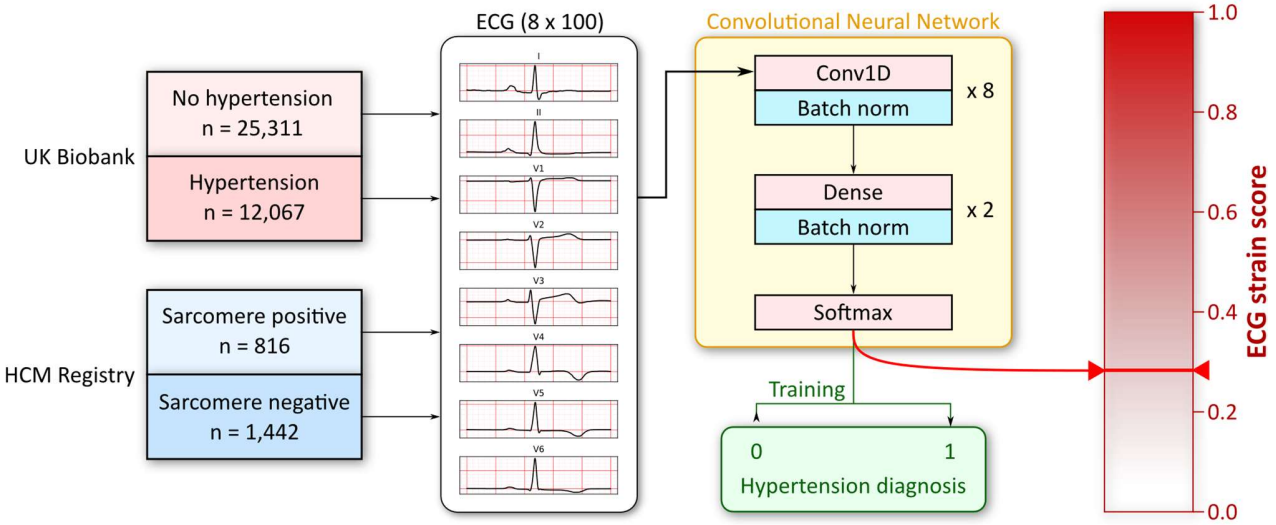

Figure 1. ECG sources and pre-processing, CNN model architecture, and construction of the ECG strain score.

search, giving a batch size of 50 and epoch count of 150.

Recognising that hypertension, and hypertensive ECG change, are a spectrum of pathology rather than a binary label, we took the continuous-valued softmax output (0 to 1) to represent the severity of hypertension-like change detected: the ECG-SS. Using 10-fold cross-validation, we ensured that for each fold, the model was trained on 80% of ECGs from each of the four diagnostic groups, then predicted hypertension scores for the remaining 20%. In each fold training and cross-validation sets did not overlap.

A test set was not required as the model was used to find the distribution of ECG features in the HCM disease group, rather than seeking to diagnose hypertension.

2.3. Statistical analyses

Mean and variance of ECG-SS were calculated for each diagnostic group. Mann-Whitney U tests were used to compare mean scores. Within HCMR, ECG-SS was modelled as a linear function of LV hypertrophy (maximum wall thickness on CMR), maximum LVOT gradient from echo (at rest or provocation by Valsalva), replacement fibrosis (late gadolinium enhancement with 6 SD threshold on CMR; LGE), and a wall stress biomarker (NT-proBNP), as well as age and body mass index (BMI) as potential confounding demographics. LVOT gradient, LGE and NT-proBNP were log-transformed to make them more normally distributed. Significance level was 0.05.

2.3. Variational autoencoder (VAE)

To visualise ECG phenotypes, we used a VAE. This model uses an encoder neural network (identical to the convolutional block in the CNN described above), followed by a single dense layer, to non-linearly transform high-dimensional ECG data into a point in a 32-dimensional "latent" space. A decoder network then reconstructs the ECG from a sampled point nearby in the latent space. The training loss function ensures a balance between perfectly reconstructing individual ECGs and ensuring a multivariate normal distribution in the latent space. This ensures a smooth distribution of ECG features in the latent space, so that ECGs reconstructed from neighbouring points in latent space have similar features.

The VAE was trained to reconstruct all ECGs in UKBB and HCMR. We generated the "average" ECG for data subgroups by applying the decoder to the subgroups' latent space centroids. These ECGs were visually scrutinised for clinically familiar and meaningful signals.

3. Results

Mean ECG-SS, DBP, and SBP were all higher in the UKBB-Hypertension group compared to UKBB-No hypertension group (ECG-SS 0.49 vs 0.39, DBP 85 vs 78 mmHg, SBP 147 vs 132 mmHg, all $p < .0001$) (Fig. 2a). In UKBB, DBP and SBP were positively linearly correlated to ECG-SS (DBP: $\beta = 0.034$, SBP: $\beta = 0.036$, both $p < .0001$). In striking contrast, in both SP-HCM and SN-HCM, neither SBP nor DBP associated with ECG-SS (all $p > 0.7$), and regression coefficients were significantly smaller than in the UKBB population (DBP × group interaction $p < 0.0001$). Thus HCM had increased hypertension-like change on the ECG, compared to UKBB even after matching for BP.

In fact, ECG-SS was bimodally distributed in SN-HCM, with a high-scoring subgroup driving the higher mean score (Fig. 2b). We define Group 1 by ECG-SS ≥ 0.5, and Group 2 by ECG-SS < 0.5. SP-HCM exhibited a positively skewed distribution of ECG-SS (Fig. 2c) with mean greater than UKBB-N (0.45 vs 0.39, $p < .0001$).

Given that ECG strain was not driven by BP in SN-HCM, other potential physiological factors were investigated using multivariable linear regression. ECG-SS was predicted by afterload (log LVOT gradient $\beta = 0.033$, $p = 0.002$), wall stress biomarker (log NT-proBNP

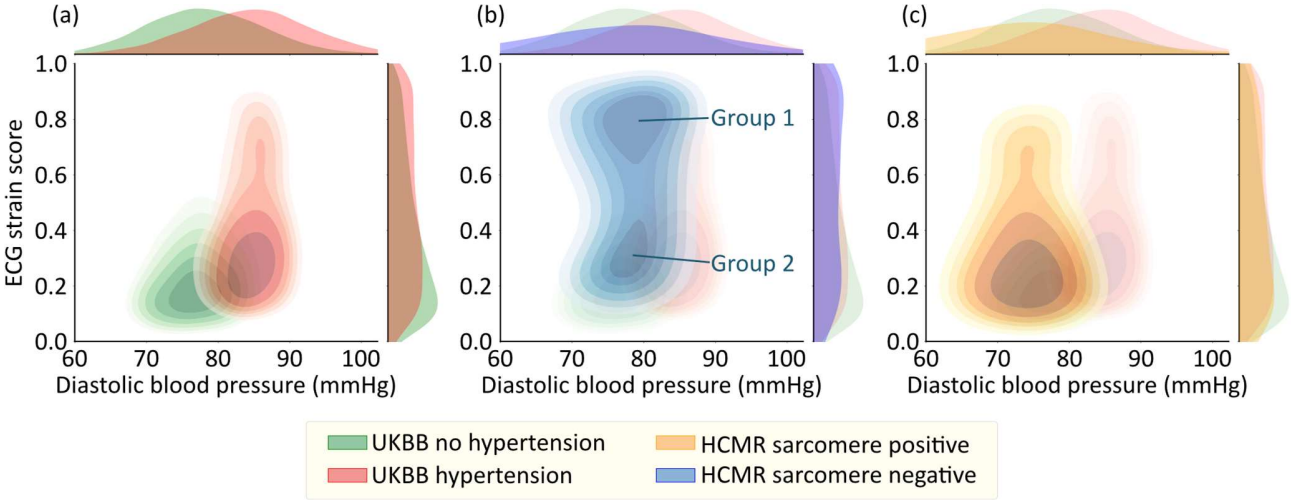

Figure 2. Joint density distribution of ECG strain score and diastolic BP, showing highest densities in (a) UKBB, (b) SN-HCM with UKBB in background, (c) SP-HCM with UKBB in background.

β = 0.028, p = 0.018) and baseline characteristics (age 0.042, p = 0.0001; BMI 0.035, p = 0.001), but not hypertrophy (max wall thickness β = 0.002, p = 0.85) or fibrosis (LGE β = -0.006, p = 0.62). Thus ECG-SS tracked LVOT obstruction and LV wall stress in SN-HCM, indicating that Group 1 is characterised by LVOT obstruction due to high afterload. However, in SP-HCM, ECG-SS was similarly related to NT-proBNP but notably not to LVOT gradient.

ECGs representing SN-HCM Group 1, Group 2, and an intermediate state, were generated by applying the VAE decoder to the centroids of the two groups and the midpoint of these two centroids (Fig. 3) in the latent space. Group 1 exhibits markedly increased QRS amplitude, increased QRS width, inferolateral ST-segment depression and T-wave inversion, and PR prolongation.

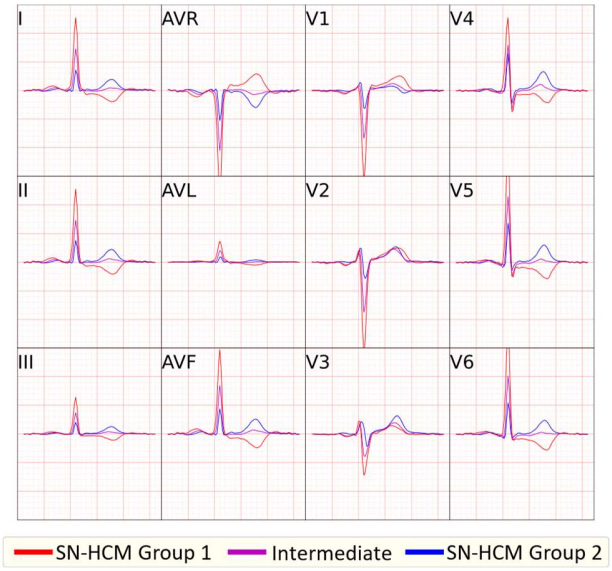

Figure 3. ECGs reconstructed from VAE latent space: Group 1 (red), intermediate (purple), and Group 2 (blue).

4. Discussion and Conclusions

The ECG-based dissociation between Groups 1 and 2 in SN-HCM suggests a pathophysiological difference. The model is trained only on hypertension diagnosis, yet in SN-HCM the ECG-SS is not correlated with measured BP. This implies the existence in SN-HCM of a pathological process other than hypertension that causes similar ECG changes. LVOT obstruction and hypertension increase LV afterload, and we show that LVOT gradient is correlated with ECG-SS in SN-HCM.

We deduce that LVOT obstruction drives increased ECG-SS through a causative mechanism similar to hypertension. This is supported by correlation with NT-proBNP, indicating increased wall stress due to afterload. Thus SN-HCM Group 1, compared to Group 2, represents patients with more severe LVOT obstruction and consequent increase in LV wall stress.

We acknowledge some limitations to this study. We have not included the effect of antihypertensive medications, which may affect ECG-SS. ECG acquisition methods were different in UKBB and HCMR. UKBB comprises mostly healthy participants, so abnormal ECGs may be under-represented in the training data.

Our work gives the first detailing of the causes of ECG abnormalities in HCM and quantifies the severity of change in individual patients. The identification of a bimodal distribution of ECG-SS delineates two physiological subtypes of SN-HCM. In practice our model could non-invasively identify patients with higher ECG-SS and therefore greater LVOT obstruction. ECG quantification of myocardial stress may help guide when to initiate HCM treatments such as myosin inhibitors and septal reduction therapy, and to track disease progression and treatment response. Further prospective study is required to confirm.

A crucial feature of our analysis is to apply a score trained on one pathology (hypertension) to understand changes in a different but physiologically related disease process (HCM). Using the sensitivity of a machine learning index facilitated understanding of a continuous spectrum of pathology. This allowed us to disentangle underlying mechanisms of the heterogenous SN-HCM disease group for the first time.

Our study gives interpretability to the deep CNN output using a VAE to reconstruct typical ECGs from different subgroups. Inspection of reconstructed ECGs suggests the ECG-SS reflects clinically relevant features. We show that a VAE can be used to visualise ECGs typical of specific disease groups. This could aid our recognition of important visually distinctive ECG signatures and deepens the relevance of machine learning to clinical practice.

Acknowledgments

SM is supported by Oxford British Heart Foundation Centre of Research Excellence, MRC IAA and Wellcome IP Revenue Retention. We acknowledge The National Heart Lung Blood Institute (grant U01HL117006-01A1).

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