Electrocardiographic Findings in Genotype-Positive and Non-Sarcomeric Children with Definite Hypertrophic Cardiomyopathy and Subclinical Variant Carriers.

Priyanka Anvekar (priyankaanvekar.pa@gmail.com)
Children's Hospital of Philadelphia

Paul Stephens JR
The Children's Hospital of Philadelphia, University of Pennsylvania

Renzo JC. Caldero-Anyosa
McGill University

Hunter Kauffman
Children's Hospital of Philadelphia

Danielle S. Burstein
Children's Hospital of Philadelphia

Alyssa L. Ritter
Children's Hospital of Philadelphia

Rebecca C. Ahrens-Nicklas
Children's Hospital of Philadelphia

Victoria L. Vetter
The Children's Hospital of Philadelphia, University of Pennsylvania

Anirban Banerjee
The Children's Hospital of Philadelphia, University of Pennsylvania

Research Article

Keywords:

Posted Date: May 9th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2886949/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Version of Record: A version of this preprint was published at Pediatric Cardiology on September 19th, 2023. See the published version at https://doi.org/10.1007/s00246-023-03281-z.
Abstract

Background

In children with hypertrophic cardiomyopathy (HCM), the genotype-phenotype association of abnormal electrocardiographic (ECG) features in the backdrop of gene positivity have not been well described. This study aimed to describe abnormal ECG findings in children with HCM harboring genetic variants and determine the association with Major Adverse Cardiac Events (MACE).

Methods

We retrospectively analyzed 81 variants positive, phenotype positive (V+P+), 66 variant positive, phenotype negative (V+P-), and 85 non-sarcomeric subjects. We analyzed ECG findings and clinical outcomes in these three groups.

Results

Combined ST and T wave changes and pathologic Q waves were the most common abnormalities in variant and non-sarcomeric subjects. The V+P+ group showed higher occurrence of ST segment changes and T wave abnormalities compared to V+P- group. Independent predictors of MACE included ST segment changes, (OR=3.54, CI= 1.20-10.47, p=0.022). T wave changes alone did not predict outcome (OR=2.13, CI= 0.75-6.07, p=0.157), but combined repolarization abnormalities (ST+T changes) were strong predictors of MACE (OR= 5.84, CI=1.43-23.7, p=0.014) than ST segment changes alone. Maximal wall z-score by echocardiography was a predictor of MACE (OR=1.21, CI=1.07-1.37, p=0.002). Despite significant myocardial hypertrophy (z score>4.7), voltage criteria for LVH were much less predictive. In the non-sarcomeric group, RVH was significantly associated with MACE (OR=3.85, CI= 1.08-13.73, p= 0.038).

Conclusion

Abnormal ECG findings described in subjects with known genetic status and myocardial hypertrophy, may add incremental value to the diagnosis and surveillance of disease progression in children with HCM. Select ECG findings, particularly repolarization abnormalities, may serve as predictors of MACE.

Introduction

Hypertrophic Cardiomyopathy (HCM) is a common inherited genetic heart disease in young adults, where it has been studied intensely [1–4]. In most adult HCM studies, subjects with non-sarcomeric gene variants have been excluded. In children, both sarcomeric and non-sarcomeric HCM subjects may have similar outcomes. [5, 6]. In both groups, there is a tendency to develop left ventricular outflow tract obstruction (LVOT), need for myomectomy, and risk for life-threatening arrhythmias. [3, 7]. A recent international, multicenter study has shown that the 10-year cumulative incidence of sudden cardiac death was similar in RASopathy-induced HCM (RAS-HCM) and primary sarcomeric HCM [8]. Additionally, the 10-
year cumulative incidence of non-arrhythmic deaths and heart transplants was higher in RAS-HCM. In this context, in children it is important to evaluate ECG findings in both sarcomeric and non-sarcomeric HCM to determine similarities and differences in clinical outcomes between these two groups. Previous studies have described abnormal ECG findings in pediatric HCM. [9] Most of these papers were limited to a primarily echocardiographic or clinical diagnosis of HCM. In contrast, our study is unique in that ECG abnormalities were assessed in the presence of two strong diagnostic layers, characterized by echocardiographic diagnosis of HCM and confirmed by genetic testing. (Fig. 1).

In the presence of both clinical (phenotypic) and genotypic diagnosis, the role of ECG in HCM may be additive. With the advent of genetic testing, the genotype-phenotype associations of HCM with imaging modalities and clinical outcomes have been assessed in many adult studies [4, 10]. More recently, the association between gene variant burden and major adverse cardiac events (MACE) in children with HCM has been investigated as well. [11, 12]. These studies have proposed models of risk stratification for MACE in children with HCM. It is notable that, although they included a combination of clinical and echocardiographic data, these models did not include ECG data in their parameters for risk assessment. The additive role of ECG abnormalities in the risk stratification of subjects with confirmed sarcomeric gene mutations has been studied quite infrequently in children [13]. Our study analyzing ECG abnormalities in children with pathogenic variants may provide incremental value to the established models for risk stratification in pediatric HCM.

This study aims to 1) describe the specific ECG findings in genotype positive and phenotype positive children with HCM, 2) assess the differences in the ECG findings between sarcomeric variant and non-sarcomeric groups, and 3) determine if abnormal ECG findings are associated with the MACE in a genotyped population of HCM. We hypothesize that sarcomeric variant and non-sarcomeric HCM children will both show a high percentage of ECG abnormalities, with differences in ECG findings between the two groups. We further hypothesize that select ECG findings may predict MACE in gene positive HCM subjects.

**Methods**

**Study Population**

This is a retrospective, longitudinal study from the database of HCM subjects evaluated at Children's Hospital of Philadelphia between 2003 to 2021. All subjects were aged between 0-21 years with primary diagnosis of HCM or referred for HCM screening. HCM was defined as per the American College of Cardiology /American Heart Association (ACC/AHA) guidelines for unexplained left ventricular hypertrophy in the absence of another cardiac or systemic disease [14]. The inclusion criteria for the subjects were the availability of ECG and echocardiograms from our institutional database. Subjects with HCM secondary to metabolic disorders, systemic hypertension or endocrine disorders were excluded.
The variants identified by genetic testing were classified as pathogenic or variant of uncertain significance (VUS) in genes associated with sarcomeric or non-sarcomeric cardiomyopathy. For our study, in the sarcomeric group subjects with pathogenic variants and subjects with VUS were grouped together to create a combined, variant-positive (V+P+) group, as described in previous studies [12]. They were grouped together because both groups had clear-cut clinically diagnosed HCM (including the VUS group). For statistical analysis, the V+P+ group was subdivided into subjects with actual pathogenic mutations in genes encoding sarcomere proteins (G+P+) and subjects with VUS (VUS+P+) (Figure 2).

The subclinical variant carriers (V+P-) were comprised of subjects positive for the gene variant (G+/VUS+) but without the presence of LV hypertrophy (P-)

All subjects in the non-sarcomeric group were previously diagnosed with Friedreich's ataxia (FA) or RASopathies. The non-sarcomeric group includes only subjects with FA and RASopathies because they constituted the dominant causes of HCM in our institutional database. RASopathies consist of a group of phenotypically related disorders arising from variants in genes within the Ras/mitogen-activated protein kinase (Ras/MAPK) pathway and in our study consisted of subjects with Noonan syndrome and Noonan syndrome with multiple lentigines (NSML).

**Classification of variants and genotyping**

Per institutional practice, each patient had undergone either HCM panel testing or cardiomyopathy next generation sequencing panel testing. The updated American College of Medical Genetics and Genomics guidelines [15] were used to classify variants in HCM-associated genes. Variant analysis was completed as previously published [13]. The composition of representatives panel is shown in the Supplementary Table 1. Abstracted data from clinical notes were evaluated by a clinical geneticist, and any benign or likely benign variants were excluded. The impact of multiple VUS was not assessed, as this was not the focus of our study.

Variants in MYH7, MYBPC3, and TNNI3, TTN and TNNT2 (Troponin complex) were the most commonly identified. In addition, there were multiple variants identified in: FXN, RYR1, PTPN11, RAF1, SOS1, PKP2, PRKAG2, CASQ2, ACTC, LAMA, and ABCD. For subjects with FA, we took into consideration the number of repeats to further explain their genetic status. Genomic location of the variant and population frequency were obtained from a large genomic dataset (gnomAD version 3.0) [16].

**Study outcomes**

In our study, adverse outcomes were defined as occurrence of any one of the following events: appropriate insertion of Implantable Cardioverter Defibrillator (ICD), myomectomy, heart transplant and death. Based on a convention established in previous studies these individual outcomes were grouped together in a single group labeled as Major Adverse Cardiac Events (MACE). [11]

**Echocardiography**
LVH was defined as the maximal septal or LV posterior wall thickness exceeding the pediatric Boston z score of 2, corrected for age, gender, and body surface area (BSA), [17]. Other conventional measurements were abstracted from official clinical reports. In this study the primary role of echocardiography was to confirm the diagnosis of HCM and detect any LVOT obstruction.

**Electrocardiogram**

Conventional 15-lead resting ECGs were obtained in the supine position. All the electrocardiograms were re-analyzed by three senior cardiologists (AB, VLV, and PS) blinded to the clinical and echocardiographic data. In V+P+ and non-sarcomeric groups, the first ECG at the time of disease manifestation was included. The second ECG in this group was recorded when the patient showed maximal LV hypertrophy during follow-up. The ECGs at the first encounter and the last follow-up were included in the V+P- group. The criteria for defining ECG abnormalities are summarized in Table 1.

Leads V1-V4 were considered as anterior leads, leads I, V5, V6 and aVL were considered as lateral leads and II, III, aVF were considered as inferior leads. For our study, pathologic Q wave was defined as ≥ 4mm in two or more leads. This is an institutional preference and contrasts with the more restrictive definition of ≥ 3mm proposed by the Seattle criteria [18].

T wave abnormalities included T wave inversion, flat T, biphasic T, and notched T waves. Inverted T waves in lateral, or inferior leads were considered abnormal, but not in leads aVL, V1-V2. T wave inversion can vary with age, gender, race/ethnicity. LVH was defined by two pediatric-based criteria (Table1).

In this study, ECG features corresponding to repolarization abnormalities were extracted and grouped into two categories. For statistical analysis, subjects were classified having ST segment abnormalities, T-wave abnormalities, or grouped together as ST and T wave abnormalities, termed as “combined” repolarization abnormalities (defined in Table 1).

The study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

**Statistical Analysis**

Normally distributed data are presented as mean ± standard deviation (SD), whereas nonparametric data are presented as median with interquartile ranges (IQRs). Unpaired samples were analyzed by the unpaired 2-tailed Student’s t-test, whereas the Mann-Whitney U test was utilized for nonparametric data. Logistic regression was used to evaluate the association between ECG features and MACE. The analysis was adjusted for age, sex, and race. Categorical variables were compared between groups using Fisher’s exact test. Timed outcome endpoints were assessed with Kaplan-Meier survival curves using univariate Cox regression to compare cumulative outcome rates between groups. The primary endpoint for Kaplan-Meier analysis was the occurrence of MACE. For all significance testing, a difference was considered significant if p value < 0.05. The statistical analysis was performed using StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.
Results

Demographics

The study cohort was comprised of 232 subjects who were screened for HCM. Of the 232 subjects, 166 had definite HCM by echocardiography (Table 2). Based on the results of genetic testing, 81 subjects with sarcomeric HCM were diagnosed as variant-positive (V+P+), 66 as genotype-positive, phenotype negative (V+P-), and 85 as non-sarcomeric. The variant-positive group consisted of G+P+ (n= 50) and variant of unknown significance (VUS+/P+) (n=31). The proportion of male subjects (78%) was higher than females.

Genetics

Only subjects with a positive genotype were included in our study. The genes identified to have variants are depicted in Figures 3A and B. MYH7 (n= 24, 29%), MYBPC3 (n=23, 28%) and Troponin complex (n=18, 23%) were the most prevalent genes in the variant positive group. The breakdown of variants in individual subjects is shown in supplemental table 1.

Echocardiographic features

In our cohort of 232-subjects 71% met the criteria for HCM (z score >2) and were classified as having sarcomeric or non-sarcomeric HCM. The remaining 28% were classified as the subclinical V+P- group. In the sarcomeric group, the median septal z score was 4.73 (2.82; 9.94). In the non-sarcomeric group, the mean septal z score was 4.4 (2.94; 6.71). Conventional echocardiographic parameters are depicted in Table 3.

Electrocardiographic features

A total of 464 ECGs were evaluated in a de-novo manner for this study. The ECG findings in all three groups are depicted in Table 4. Abnormal ECG findings were present in 85% of the V+P+ sarcomeric group, 83% of the non-sarcomeric group and 35% of the V+P- group. When comparing the three groups in our cohort, combined ST+T changes were found to be more prevalent in the non-sarcomeric group (n=50, 59%) as compared to the sarcomeric group (n=33, 41%). Pathologic Q waves were mainly seen in lateral and inferior leads in both groups. The pathologic Q waves were seen in 20% of sarcomeric and in 12% of the non-sarcomeric group. Figure 4 illustrates the proportion of abnormal ECG findings between the sarcomeric and non-sarcomeric group.

Moreover, within the non-sarcomeric group of subjects, ECG abnormalities varied significantly between Friedreich's ataxia and the RASopathies (Figure 5).

The characteristic ECG findings of sarcomeric and Friedreich's subjects are shown in figure 6 A and B.

In contrast, the V+P- group showed fewer T wave abnormalities than the V+P+ sarcomeric group (19% vs 59%). Similarly, ST abnormalities and pathologic Q waves were detected at a much lower frequency.
Comparison of the G+P+ subgroup to the V+P- group revealed significant differences in the frequency of abnormal ECG findings. The G+P+ group showed higher occurrence of ST segment changes (54.0% vs. 19.4%, p<0.05), and T wave abnormalities (54.0% vs. 16.4%, p<0.05) compared to V+P- group (Table 4B). Subsequent comparison of the VUS+P+ subgroup to the V+P- subgroup revealed similar changes in the ECG findings however the frequency of the changes was much less in the V+P- group (90.0 % vs. 35.0 %) (Table 4C). There was no significant difference in the frequency of RVH, LVH, and Pathological Q waves between these groups.

**Clinical Outcomes**

MACE occurred in 45.6 % of V+P+ and 30.58 % of non-sarcomeric subjects. (Table 5) The median age for MACE was 13.0 years in sarcomeric subjects and 8.5 years in non-sarcomeric subjects. MACE occurred an average of 4 years after initial evaluation in the sarcomeric group and 6 years following initial evaluation in the non-sarcomeric group.

In the V+P+ subjects, independent predictors of MACE included ST segment abnormalities (OR= 3.54, CI=1.20-10.47, p= 0.022), The T wave changes did not predict outcome (OR=2.13, CI= 0.75-6.07, p=0.157) (Table 6). When ST and T waves were combined into a single group, it was a significant predictor of MACE (OR= 5.84, CI=1.43-23.74, p=0.01).

In our cohort ICD placements were performed for primary prevention in 31 subjects, whereas 9 had ICD placements secondary to a life-threatening event. On Kaplan-Meier analysis, subjects in the V+P+ group who showed ST segment abnormalities showed a higher incidence of MACE when compared to subjects without ST segment abnormalities (OR:1.83, CI=0.91-3.71, p=0.092) when corrected for age, sex, and race (Figure 7).

No other parameters showed significant or near significant differences in the occurrence of MACE upon univariate survival analysis.

Pathologic Q waves, LVH and right ventricular hypertrophy (RVH) did not have any significant association with total MACE (Table 6). In the non-sarcomeric group, RVH was significantly associated with MACE (OR=3.85, CI= 1.08-13.73, p= 0.038).

**Discussion**

There is a knowledge gap in children regarding the relationship between ECG and MACE in genotyped HCM subjects. Our study, consisting of 81 subjects, is fairly large by pediatric standards and was performed in the backdrop of gene-positivity, demonstrating characteristic ECG findings in subjects with both sarcomeric and non-sarcomeric HCM. Describing specific ECG changes in this background may increase the value of ECG in childhood HCM and improve the comfort level of physicians regarding ECG in clinical practice. In most adult HCM studies, subjects with non-sarcomeric gene variants have been
excluded. In children, both sarcomeric and non-sarcomeric HCM subjects may have similar outcomes. In fact, the 10-year cumulative incidence of non-arrhythmic deaths and heart transplants was higher in RAS-HCM [8]. Therefore, we have described ECG findings and outcomes in both sarcomeric and non-sarcomeric HCM in children in this study.

Sarcomeric HCM group

Repolarization changes are the most distinguishing abnormalities in children with HCM. Unlike adults, pathologic Q waves were detected less frequently in our cohort (20% in children vs 42% in adults) [17]. Despite the presence of significant myocardial hypertrophy (z score>4.7), voltage criteria for LVH were much less prevalent and detected in one-third of this group. These findings corroborate similar findings reported in a smaller study by Guerrier [19]. The evaluation of HCM in the presence of confirmed gene variants sets our study apart from previous studies in children. A similar genotype-ECG association has been evaluated in a study consisting of 55 adults and only 2 pediatric subjects (>14 years) with overt HCM, indicating a paucity of such studies in the pediatric age group, particularly in the recent era of advanced genetic testing. [20] There have been limited studies to evaluate the association of variant burden on phenotypic expression in the past. A recent study by Mathew et al. elicited that even though most secondary variants were those of unknown significance, they had a considerable impact on outcome. To understand this relationship in the pediatric population, in our study we organized the Gene-positive and the VUS studies in one single group [11]. In this study, we suggest that reappraisal of specific ECG changes in HCM in the setting of known gene positivity may strengthen the role of ECG in this disease.

Non-sarcomeric HCM group

Friedreich's ataxia and RASopathies were the most common patient population in the non-sarcomeric cohort. The ECGs of subjects with FA showed characteristic T wave inversion in the inferior and lateral leads along with the dome-shaped ST segment elevation in the anterior precordial leads. Previous ECG studies in FA, have described T wave abnormalities, but have not reported the characteristic dome shaped ST elevation described by us [22]. This combination was a hallmark of Friedreich's ataxia in our cohort (Figure 6B). ECG findings differed greatly between FA and RASopathy subjects (Figure 5). This suggests that ECG may highlight differences between non-sarcomeric variant etiologies of HCM. Future studies of many more syndromic and neuromuscular forms of HCM are needed to fully elucidate the role of ECG in diagnosis and management of these entities.

Subclinical Variant Carriers

Repolarization abnormalities and pathologic Q waves may discriminate at-risk carriers of variants from non-carriers in adults [19]. Similar studies in children are quite limited [23]. In our study 35% of V+P-subjects showed abnormal ECG changes. The ECG findings were similar to those noted in the sarcomeric group, including ST segment and T wave abnormalities, as well as presence of pathologic Q waves.
**Prediction of Outcome in HCM**

MACE has been defined by a variety of events and most of the events are based on institutional preferences. A recent study in a pediatric cohort demonstrated the association between genetic variant burden and MACE [12]. Similar studies utilizing ECG findings as predictors of MACE are almost non-existent in the pediatric population. Past studies in pediatric HCM have considered defining MACE as ICD placement, surgical myomectomy, transplantation, and death [11]. We have accepted a similar definition of MACE in our study. One recent study tested the incremental value of a novel ECG risk score for predicting sudden cardiac death (SCD) in a large cohort of pediatric HCM subjects. Interestingly, this study found no significant association of ECG factors with their endpoint of SCD. Therefore, the authors conclude that, while ECG abnormalities are highly prevalent in pediatric HCM, they offer little additional predictive value toward risk stratification for SCD in this population. [5] In contrast, our data show that although T wave changes did not predict any outcome, ST segment changes and combined ST+T wave changes may predict MACE in gene positive HCM subjects.

**Clinical Utility:**

Prediction of MACE is a challenge in HCM subjects. Several models for predicting SCD, specifically, have been proposed. These methods lack the incorporation of ECG data, which may provide incremental predictive value [24-26]. Follow up studies have shown that the addition of ECG findings adds predictive value to the existing models for SCD prediction. [9, 27, 28] Although existing models use SCD as a primary endpoint for risk stratification, we used MACE as our endpoint, due to the low number of deaths in our study cohort. Furthermore, these models primarily aim toward the use of multivariate analysis to detect risk factors for SCD in subjects with a clinical diagnosis of HCM. Our goals were more modest. We demonstrated that repolarization changes in gene-positive sarcomeric HCM subjects were strong predictors of MACE.

Since ECGs are often used world-wide for primary evaluation in families with HCM, we speculate that the ECG findings described in this study may help physicians with limited access to imaging and genetic tools.

Current guidelines advise subjects with familial HCM to undergo genetic testing by 12 years of age [14]. Despite the recommendation from physicians, some parents refuse or defer genetic testing due to concerns about the future insurability or employment opportunities of the child. We speculate that in these subjects, a genotype-ECG association would be of incremental value in providing clinical counseling.

**Study Limitations:**

The sample size of the HCM subjects is an important limitation of this study. HCM is a rare disorder in children and our study incorporated the maximal achievable number for a single tertiary-care institution. A multicenter study would have been preferable but was beyond the scope of our study due to time...
constraints and lack of funding. In our study, the number of SCD were fortunately low. This precluded us from performing analysis using SCD as an endpoint. We wish to point out that describing ECG changes was the primary goal of this study. Therefore, more echocardiographic details like tissue Doppler and strain patterns were not described here. It should be noted that genetic testing was performed at various laboratories and the genetic testing panel changed during the study timeline, which might have influenced the genetic yield.

**Conclusion**

In conclusion, children with sarcomeric and non-sarcomeric HCM show a high frequency of ECG changes, with differences in ECG findings between the two groups. The study has shown that select ECG findings, particularly repolarization abnormalities in the setting of gene positivity should be further explored, as they may offer incremental value to existing risk stratification models in pediatric HCM.

**Supplemental Data:**

The breakdown of the genetic makeup is described in supplemental table (A, B, C).

**Abbreviations**

ECG=Electrocardiogram

G+P+=Genotype positive, Hypertrophy present

HCM=Hypertrophic cardiomyopathy

ICD=Implantable Cardioverter Defibrillator

MACE=Major adverse cardiac events

VUS+P+=Variant of uncertain significance positive, Hypertrophy present

V+P-= Variant positive, Hypertrophy absent

**Declarations**

**Funding:** No funds, grants, or other support was received.

**Statements and Declarations:** The authors have no relevant financial or non-financial interest to disclose.

**Ethical approval:** This is an observational study. The Children’s Hospital of Philadelphia Research Ethics Committee has confirmed that no ethical approval is required.

**References**


Tables

Table 1: Definitions for ECG abnormalities
<table>
<thead>
<tr>
<th>Abnormal ECG Findings</th>
<th>Definitions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-wave inversion (TWI)</td>
<td>&gt;1mm depth in two or more leads (except V2, V3 and aVL); abnormal T wave morphology like notched, biphasic, or flat</td>
</tr>
<tr>
<td>ST-Segment depression</td>
<td>≥1.5 mm depth in two or more leads.</td>
</tr>
<tr>
<td>ST-Segment elevation</td>
<td>&gt;1 mm elevation in two or more leads.</td>
</tr>
<tr>
<td>Combined Repolarization</td>
<td>Both ST + T wave changes</td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
</tr>
<tr>
<td>Pathologic Q waves</td>
<td>≥4 mm in depth and/or &gt;1/3 of the ensuing R wave in depth and present in at least two leads.</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>• <strong>Davignon criteria</strong>: Amplitude R in lead V6 + S in lead V1 [29].</td>
</tr>
<tr>
<td>pattern</td>
<td>• <strong>Pediatric Heart Network (PHN) criteria</strong>: R amplitude in V6 + S amplitude in V1 by sex, race, and age group [30].</td>
</tr>
<tr>
<td>Right Ventricular Hypertrophy</td>
<td>R amplitude in V1 + S amplitude in V6 &gt; 10.5mm; right axis deviation &gt;120°</td>
</tr>
<tr>
<td>pattern</td>
<td></td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>Depth and duration of the negative portion of the P wave in V1 exceeds 1 mm x 1mm.</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>-30° to -90°</td>
</tr>
<tr>
<td>Intraventricular conduction</td>
<td>Any QRS duration ≥120ms</td>
</tr>
<tr>
<td>block</td>
<td></td>
</tr>
<tr>
<td>Left Bundle Branch Block (LBBB)</td>
<td>Predominantly negative QRS complex in lead V1(QS or rS) and upright monophasic R wave in leads I and V6</td>
</tr>
<tr>
<td>Ventricular Arrhythmias</td>
<td>Couplets, triplets, and non-sustained ventricular tachycardia.</td>
</tr>
</tbody>
</table>

*Adapted and modified from Drezner et al. [11]

Table 2: Demographic and Genetic Characteristics
<table>
<thead>
<tr>
<th></th>
<th>V+P+ N=81</th>
<th>V+P- N=66</th>
<th>Non-sarcomeric N=85</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, Female (%)</strong></td>
<td>22.3</td>
<td>53.7</td>
<td>37.4</td>
</tr>
<tr>
<td><strong>Age (Years)</strong></td>
<td>12 (7,15)</td>
<td>5 (1.9, 11)</td>
<td>9 (0.6, 13)</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>114 (104, 124)</td>
<td>106 (99, 118)</td>
<td>99 (91, 114)</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>61 (59, 66)</td>
<td>64 (58, 66)</td>
<td>58 (51, 65)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>57.2 (25.25, 68.8)</td>
<td>24.65 (13.95, 49.75)</td>
<td>25.1 (7.75, 43)</td>
</tr>
<tr>
<td><strong>BSA (m²)</strong></td>
<td>1.6 (0.84, 1.7)</td>
<td>0.15 (0.8, 0.55)</td>
<td>1.0 (0.50, 1.51)</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>Caucasian</td>
<td>74</td>
<td>4</td>
<td>66</td>
</tr>
<tr>
<td>Black American/African</td>
<td>17</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td><strong>Sarcomere Genes (n):</strong></td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>MYH7</td>
<td>21 (31%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>24 (29%)</td>
<td>31 (46%)</td>
<td>-</td>
</tr>
<tr>
<td>Troponin Complex</td>
<td>23 (28%)</td>
<td>4 (6%)</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>18 (23%)</td>
<td>11 (17%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (20%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range)

BSA: Body Surface Area

Table 3: Echocardiographic Features
<table>
<thead>
<tr>
<th></th>
<th>V+P+</th>
<th>Non-sarcomeric</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=81</td>
<td>N=85</td>
<td></td>
</tr>
<tr>
<td>Septal z Score</td>
<td>4.73</td>
<td>4.4</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>(2.8, 9.94)</td>
<td>(2.9, 6.7)</td>
<td></td>
</tr>
<tr>
<td>PW z score</td>
<td>1.5</td>
<td>3.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>(0.19, 3.4)</td>
<td>(2.07, 5.06)</td>
<td></td>
</tr>
<tr>
<td>SF (%)</td>
<td>41</td>
<td>41</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>(36, 47)</td>
<td>(36, 48)</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>67</td>
<td>66.5</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>(63, 72)</td>
<td>(62, 71.2)</td>
<td></td>
</tr>
<tr>
<td>LVIDd (cm)</td>
<td>4.03</td>
<td>3.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>(3.4, 4.5)</td>
<td>(2.5, 4)</td>
<td></td>
</tr>
<tr>
<td>LVIDs (cm)</td>
<td>2.4</td>
<td>2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>(1.5, 2.8)</td>
<td>(1.3, 2.5)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (interquartile range)

PW: Posterior Wall; EF: Ejection Fraction; SF: Shortening Fraction; LVIDd: Diastolic Left Ventricular Internal Dimension; LVIDs: Systolic Left Ventricular Internal Dimension.

Table 4A: Electrocardiographic Features from Second ECG
<table>
<thead>
<tr>
<th></th>
<th>V+P+</th>
<th>V+P-</th>
<th>Non-sarcomeric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=81</td>
<td>N=66</td>
<td>N=85</td>
</tr>
<tr>
<td>Abnormal ECG findings n (%)</td>
<td>69 (85)</td>
<td>23 (35)</td>
<td>70 (83)</td>
</tr>
<tr>
<td>ST Changes</td>
<td>42 (51.8)</td>
<td>10 (15.0)</td>
<td>58 (68.2)</td>
</tr>
<tr>
<td>T Wave Abnormalities</td>
<td>48 (59.2)</td>
<td>13 (19.0)</td>
<td>64 (75.2)</td>
</tr>
<tr>
<td>Pathological Q Waves n (%)</td>
<td>16 (19.7)</td>
<td>9 (13.4)</td>
<td>12 (14.1)</td>
</tr>
<tr>
<td>LV Hypertrophy n (%)</td>
<td>27 (33.3)</td>
<td>9 (13.4)</td>
<td>19 (22.3)</td>
</tr>
<tr>
<td>RV Hypertrophy n (%)</td>
<td>13 (16.0)</td>
<td>4 (6.0)</td>
<td>29 (34.1)</td>
</tr>
<tr>
<td>Left axis deviation n (%)</td>
<td>12 (14.8)</td>
<td>1 (1.5)</td>
<td>19 (22.35)</td>
</tr>
<tr>
<td>LA enlargement n (%)</td>
<td>14 (17.2)</td>
<td>1 (1.5)</td>
<td>7 (8.2)</td>
</tr>
</tbody>
</table>

LV: Left Ventricular; RV: Right Ventricular

Table 5 – Outcome data from V+P+ and non-sarcomeric HCM groups
<table>
<thead>
<tr>
<th></th>
<th>V+P+</th>
<th>Non-sarcomeric</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=81</td>
<td>N=85</td>
<td></td>
</tr>
<tr>
<td>Myomectomy</td>
<td>6 (8.6)</td>
<td>3 (3.5)</td>
<td>0.224</td>
</tr>
<tr>
<td>Heart Transplant</td>
<td>4 (6.1)</td>
<td>0</td>
<td>0.054</td>
</tr>
<tr>
<td>Death</td>
<td>4 (6.1)</td>
<td>12 (14.11)</td>
<td>0.039</td>
</tr>
<tr>
<td>ICD Placement</td>
<td>26 (34)</td>
<td>5 (5.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICD=Implantable Cardioverter Defibrillator

Table 6: Odds Ratio for Outcomes

<table>
<thead>
<tr>
<th>Abnormal findings</th>
<th>V+P+</th>
<th>Non-sarcomeric</th>
<th>OR</th>
<th>95%CI</th>
<th>P-value</th>
<th>OR</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ECG 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST Changes</td>
<td>3.54</td>
<td>0.27-10.47</td>
<td>0.02</td>
<td>0.8</td>
<td>0.27-2.4</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T wave changes</td>
<td>2.13</td>
<td>0.75-6.07</td>
<td>0.16</td>
<td>1.8</td>
<td>0.46-7.4</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined (ST+T changes)</td>
<td>5.8</td>
<td>1.43-23.74</td>
<td>0.01</td>
<td>1.3</td>
<td>0.3-6.2</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiographic z-score</td>
<td>1.2</td>
<td>1.07-1.37</td>
<td>0.002</td>
<td>1.0</td>
<td>0.91-1.19</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV Hypertrophy</td>
<td>2.6</td>
<td>0.5-12.36</td>
<td>0.21</td>
<td>3.8</td>
<td>1.08-13.7</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LV: Left Ventricular; RV: Right Ventricular; OR= Odds ratio; CI= Confidence interval; *=p-value <0.05
Figures

Figure 1. Schematic representation of diagnostic platforms that form the basis of ECG abnormalities.

Figure 1

See image above for figure legend.
G=Genotype
VUS=Variant of uncertain significance
P=Phenotype

Figure 2. Schematic representation of grouping of subjects for this study.

Figure 2

See image above for figure legend.
Figure 3

See image above for figure legend.

Figure 4

T wave and ST segment changes were the most frequently found ECG abnormalities in both groups.

Figure 4

See image above for figure legend.
Figure 5. T wave inversion in inferior and lateral leads and ST segment elevation were the hallmark of FA while RVH was more common in RASopathies. This diagram shows a stark difference between the two groups.

Figure 5

See image above for figure legend.
Figure 6

See image above for figure legend.
Figure 7: The Kaplan-Meier survival curve shows that V+P+ subjects with ST elevation had lower freedom from MACE.

Figure 7

See image above for figure legend.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Centralillustration.png
- Supplementarymaterial.docx