The majority of participants with suspected hypertrophic cardiomyopathy documented during screening Echocardiography have a normal electrocardiogram (EKG)

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease *(1,2)* and is the most frequent cause of sudden cardiac death (SCD) in young individuals, particularly athletes with a high level of training *(3–5)*.HCM is a prevalent hereditary cardiovascular condition that affects one in 500 people in the general population *(6,7)*. The cumulative proportion of sudden cardiac death (SCD) events in childhood hypertrophic cardiomyopathy (HCM) within five years of diagnosis ranged from 8% to 10% *(8,9)*. It is characterized by inadequate relaxation, hypercontractility, reduced compliance, and left ventricle hypertrophy *(10–12)*. HCM manifests as a chronic, progressive illness that can have a severe, transformative effect on a person's life and significantly lower quality of life. Data on the cost to society associated with HCM has shown significant increases in all-cause hospitalizations, hospital days, outpatient visits, and total healthcare costs. The majority of cost increases can be attributed to increased hospitalizations and hospital days among symptomatic patients *(13)*. The most often reported symptoms include syncope, palpitations, exertional dyspnea, shortness of breath, ankle swelling, exhaustion, sense of disorientation, and lightheadedness *(14,15)*.

Among the estimated 700,000 patients with HCM, only 100,000 have been diagnosed in the United States *(16)*. Underdiagnosis may be due in part to challenges in the diagnosis of asymptomatic HCM patients, who typically receive a diagnosis by chance or via systematic screening efforts *(12)*. However, developments in the understanding of genetic and phenotypic characteristics of HCM have promise for improving the identification of the condition. Over the last twenty years, the condition has been linked to abnormalities in genes that encode proteins of the cardiomyocyte's contractile machinery *(6,17,18)*. It appears that significant progress has been made in understanding the illness from both a genetic and clinical standpoint *(19)*.

Despite new developments, HCM remains underdiagnosed. Although the population prevalence of HCM is between 1:200 and 1:500, only 10–20% of cases are found by clinical means *(20)*. Patients with HCM can have a normal life expectancy but a notable percentage can develop HCM-related complications including heart failure, atrial fibrillation (AF), and cardioembolic stroke, while a smaller percentage have SCD or life-threatening ventricular arrhythmias *(21)*. SCD is the most common cause of mortality among these patients and frequently occurs during exercise. However, it often goes undetected until death, as many individuals experience minimal or no significant symptoms *(6,11)*. Consequently, a high index of diagnostic suspicion, accurate identification, and a thorough clinical examination of patients and family members are crucial for early identification and treatment *(20)*. Identifying high-risk patients is crucial to lowering the risk of SCD in young individuals with HCM, as effective treatment has the potential to significantly reduce HCM mortality and morbidity *(22,23)* This can be achieved through exercise limitation, medication therapies, and the use

of implantable cardioverter defibrillators (ICDs) *(24)* . Therefore, there has been considerable interest in improving diagnostic accuracy among HCM patients, especially young patients, to inform intervention *(21)*.

The HCM diagnosis is based on imaging techniques, such as echocardiography or cardiovascular magnetic resonance (CMR), that reveal increasing LV wall thickness *(21)*. Thorough investigation has led to a better comprehension of risk categorization for patients with HCM. The latest European Society of Cardiology (ESC) guidelines propose evaluating clinical examination, family history, 48-hour electrocardiography (ECG), echocardiography, and exercise testing for this purpose *(6,11)*. The European Society of Cardiology (ESC) has proposed specific cardiac screening guidelines for young competitive athletes *(25)*, which include assessing symptoms and family medical history (e.g., premature death, HCM), conducting a physical examination, and performing a resting 12-lead ECG. A recent Danish study revealed that a large proportion of individuals who experienced SCD due to HCM had previous symptoms, and most of them had sought medical attention before their death, in contrast to the control group *(26)*. These findings suggest there is an opportunity to improve the identification of HCM among at-risk patients, as many patients seek treatment.

The ECG continues to be a fundamental aspect of evaluating patients with HCM. Moreover, it is experiencing a "renaissance" in the realm of cardiomyopathies, not only due to its cost-effectiveness and widespread accessibility, but also because it offers information pertinent to morphology, function, and genetic foundation simultaneously *(21)* HCM has diagnosis so far relied on identification of left ventricular hypertrophy (LVH) with a wall thickness greater than 15 mm using echocardiography or CMR. However, this degree of LVH is not exclusive to HCM and may stem from various other pathological conditions, widening the differential. In such instances, the ECG is highly valuable in assisting with the differentiation between sarcomeric HCM and its phenocopies *(21)*. There is a growing body of literature evaluating the accuracy of ECG markers in predicting HCM, however, there remains a need for research on the extent to which ECG findings are predictive of HCM identified on echocardiography. Therefore, the aim of this study was to evaluate the prevalence of abnormal ECG findings, including LVH, T wave inversion, left bundle branch block (LBBB), and left atrial enlargement in participants with suspected HCM detected during screening echocardiography.

Methods

The Anthony Bates Foundation was established in memory of Anthony Bates who suffered sudden cardiac death. The foundation has been performing screening echocardiography and ECG in high schools across the United States in order to prevent sudden death since 2001 by detecting asymptomatic cardiac abnormalities. The evaluation includes a questionnaire, physical examination, electrocardiogram, and echocardiogram performed on-site. Informed consent is obtained from the participant and participants younger than 18 needed consent from their parents. The populations studied were volunteers screened for prevention of sudden death. Although the screening was aimed at young subjects, everybody willing to participate would be screened. Any suspected abnormal echocardiographic or significant EKG findings will be recommended for follow-up with the participant's physician. Data analysis was performed using SPSS program. A p-value of less than 0.05 is accepted as statistically significant. Board-certified cardiologists would interpret the results of EKG and echocardiograms. For our study, we evaluated the prevalence of abnormal ECG in participants with suspected HCM defined as any left ventricular wall thickness [?] 15 mm in comparison to controls among subjects presenting for screening.

Results

The final analytic sample consisted of 682 subjects. Approximately 10% of the sample was Age distribution seen in Figure 1. African American, with the remainder being of other race/ethnicity (Figure 2). Chi-square tests were conducted to compare individuals with suspected HCM to controls in rates of LVH, T wave inversion, LBBB, and left atrial enlargement. Rates of ECG abnormalities across HCM patients and controls are presented in Figure 3. Consistent with our hypotheses, our findings indicated that rates of LVH were higher in patients with suspected HCM (23.5%) than in patients without suspected HCM (5.6%) (p = .002). Similarly, we found elevated rates of T wave inversion among patients with suspected HCM (17.6%) in comparison to controls (4.1%) (p = .007). Comparisons of rates of LBBB and left atrial abnormalities

were unable to be conducted, as there were no patients with suspected HCM who showed evidence of these abnormalities on ECG in our sample. Examinations of the presence of any identified ECG abnormality showed that less than 25% of suspected HCM patients had an ECG abnormality observed on screening, though rates of any abnormality among HCM patients (23.5%) remained significantly elevated relative to controls (8.7%) ($p = .036$).

Discussion

This study aimed to examine the rates of ECG abnormalities among patients with suspected HCM in comparison to controls in a sample of individuals presenting for echocardiographic screening as part of the Anthony Bates Foundation's screening programs. Our primary hypotheses were supported, indicating that individuals with suspected HCM have significantly higher rates of LVH and T wave inversion. Aggregated analysis showed that HCM identified on echocardiography was also associated with a significantly higher rate of any ECG abnormality compared to controls. However, despite significant differences from control subjects, rates of any ECG abnormality among HCM patients were still low, at less than 25%. Taken together, our findings suggest that though HCM is associated with greater rates of ECG abnormalities compared to controls, due to low rates of ECG abnormality among this population, ECG alone is likely considerably lacking in sensitivity for the identification of HCM. In sum, though ECG abnormalities may suggest potential HCM, they are insufficient for successful prediction and identification of the condition in the absence of additional confirmatory markers.

Our findings are consistent with research demonstrating that ECG alone has inadequate sensitivity for the diagnosis of HCM. However, some studies have used automation to improve upon sensitivity in identifying HCM. For example, one study discovered that an automated algorithm exhibited 88.6% sensitivity and 98% specificity in identifying patients with HCM based on ECG data. Another study concentrated on classifying HCM patients through ECG analysis. These insights indicate that while ECG can provide valuable information, it may not be comprehensive enough for accurate HCM identification when used in isolation *(27–29)*. Despite advancements, at present the diagnosis of HCM still must involve a combination of tests including echocardiography, genetic testing, and clinical evaluation.

However, some emerging research has shown that novel ECG techniques may have the potential to improve predictive validity. For example, some studies suggest that integrating ECG monitoring techniques with machine learning and novel analytical strategies has the potential to improve the predictive validity of ECG in identifying HCM. This advancement may enhance the effectiveness of current therapies for individuals with this condition. Furthermore, artificial intelligence-enhanced electrocardiography (AI-ECG) has shown potential utility for the diagnosis of HCM. These developments offer promise for improving the management and diagnosis of individuals with HCM *(30,31)*.

At present, the gold standard for the identification of HCM is echocardiography, specifically 2D echocardiography or CMR imaging for adult patients *(12)*. These imaging techniques are crucial for establishing a clinical diagnosis of HCM *(12)*. In cases where HCM is suspected due to cardiac symptoms, an abnormal 12-lead ECG, or a family history of inherited heart disease, and where the echocardiographic examination is inconclusive, CMR imaging is a crucial supplementary test for establishing a clear diagnosis *(32–38)*. In such clinical scenarios, CMR imaging can pinpoint specific areas of LVH, especially when hypertrophy is localized to particular regions of the LV wall, such as the anterolateral wall, posterior septum, and apex. The enhanced sensitivity of CMR imaging in detecting LVH is due to its high spatial resolution and the absence of limitations caused by poor acoustic windows resulting from pulmonary or thoracic parenchyma *(35–37)*. Some studies state that the most predictive modality for diagnosing HCM is CMR imaging. This imaging technique offers detailed insights into the heart's structure and function, enabling accurate evaluation of myocardial hypertrophy, fibrosis, and other pathological changes linked to HCM. Its exceptional visualization and characterization of the myocardium make it an invaluable tool for diagnosing HCM and gauging its severity. Furthermore, CMR imaging aids in risk assessment and assists in determining the most suitable treatment approach for individuals with HCM *(33,39)*. Despite advancements in ECG technology and novel approaches for the use of ECG data via automation and artificial intelligence-based models, echocardiography

is still warranted for confirmation and CMR remains a useful tool in cases of inconclusive echocardiography.

Conclusion

Our findings suggest that standard ECG is limited in its ability to identify the condition. In our sample, the prevalence of abnormal ECG among participants with HCM detected during screening echocardiography was less than 25%. This suggests that even in the presence of normal ECG findings, there is value in additional workup for HCM via echocardiography and CMR imaging to comprehensively rule out the condition. It is especially important to conduct comprehensive screening among high-level athletes, as these individuals are at increased risk for SCD.

Limitation:

We evaluate volunteers in high schools with a relatively young population. Therefore, our results may not be accurate for the older population. Echocardiographic measurements are body habit dependent and a hand-held echocardiography has limited accuracy in a participant with poor window. Furthermore, other causes of increased left ventricular thickness such as hypertension or infiltrative diseases could be excluded limiting our results.

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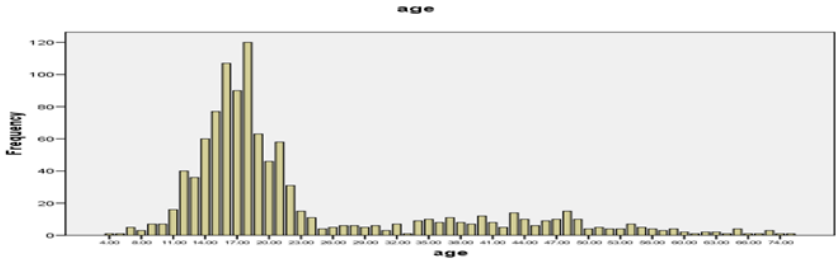

Figure 1 Age distribution

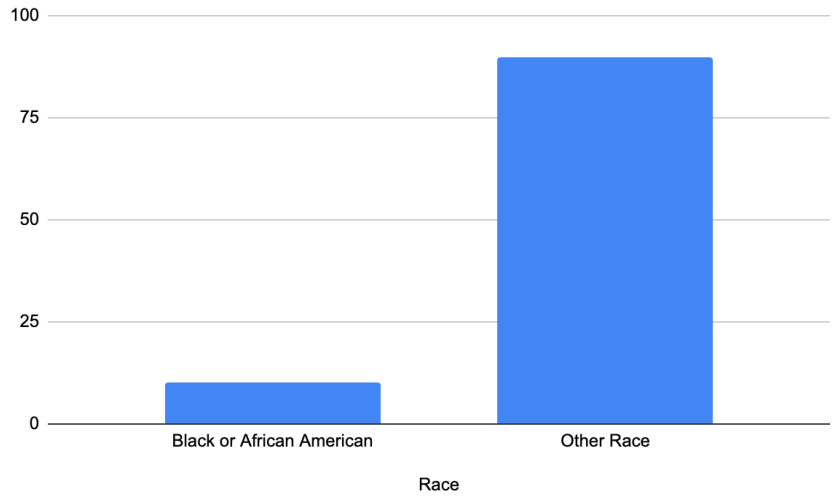

Figure 2: Race distribution.

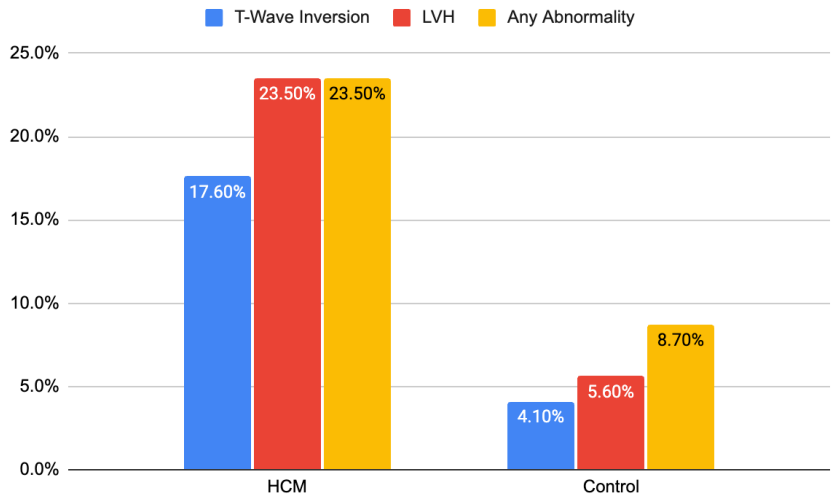

Figure 3: Presence of abnormal EKG in participant with suspected hypertrophic cardiomyopathy