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Diagnostic and prognostic electrocardiographic features in patients with hypertrophic cardiomyopathy

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The standard 12-lead electrocardiogram (ECG) represents a cornerstone for the diagnosis and evaluation of hypertrophic cardiomyopathy (HCM), the most common genetically determined heart muscle disease, due to its cost-effectiveness and wide availability. The ECG may surprisingly look normal in 4–6% of adult patients, and in less than 3% of paediatric patients, but it is abnormal in the vast majority of the remaining patients. 'Specific' features comprise pathological Q-waves, deep S-waves in V1–V3, or high R-waves in V4–V6 due to left ventricular hypertrophy with T-wave (TW) depression or negative TWs. Negative giant TWs are often found in apical HCM. However, in many patients, the ECG may only show non-specific ST–T changes with diphasic or flat TWs. An isolated inverted TW in lateral leads (usually aVL) may be the only marker for HCM in some patients. Electrocardiogram helps to diagnose sarcomeric HCM and distinguish it from different phenocopies, such as cardiac amyloidosis, glycogen storage, or Fabry disease. Electrocardiogram may also have a prognostic role, identifying high-risk features that could impact the clinical outcome.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetically determined heart muscle disease with an estimated prevalence of 1:500 in adult population and 1:2500 in children. By consensus, a wall thickness greater than 15 mm assessed by echocardiography (ECHO) or cardiac magnetic resonance (CMR) in any segment of the left ventricular (LV) wall is required for HCM diagnosis, while a lower threshold of 13 mm is used for family members. In children, HCM diagnosis needs a LV wall thickness greater than 2 standard deviations from the predicted mean in patients with a positive family history or a positive genetic test and 2.5 in those without.[1,2]

In clinical practice, standard 12-lead electrocardiogram (ECG) and ECHO are the basic exams that are needed for diagnosing most patients. Cardiac magnetic resonance imaging with late gadolinium enhancement (LGE) may help to detect myocardial fibrosis as well as LV hypertrophy in areas not easily identified by echocardiography, such as the apex and the lateral and midventricular walls. However, ECG remains a cornerstone for HCM diagnosis due also to its cost-effectiveness and wide availability. In Italy, an impressive reduction in sudden cardiac death (SCD) was observed in athletes, as a result of the use of ECG in the screening program for eligibility for competitive sports.[3] An abnormal ECG may also represent an early marker of HCM in genotyped positive family members.[4]

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Finally, the ECG may aid in risk stratification for arrhythmic risk when certain features are present. We here review the distinct ECG features of HCM and its potential for prognostication in contemporary management.

Role of electrocardiogram in the diagnosis of hypertrophic cardiomyopathy

According to the most recent European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines, ECG has a class I recommendation for all patients with suspected HCM and patients' follow-up every 12–24 months or whenever there is a change in symptoms.[1,2]

Electrocardiogram interpretation in HCM patients must reconsider traditional concepts such as 'hypertrophy', 'Q-waves', and ischaemic abnormalities, usually derived from ischaemic or valvular heart disease, shifting to a cardiomyopathy-specific mindset capable of explaining the effect of structural alterations on the myocardium and the conduction system.[5,6] Some patterns are considered specific of HCM, such as pathological Q-waves (*Figure 1*), deep S-waves in V1–V3, or high R-waves in V4–V6 due to left ventricular hypertrophy (LVH) with abnormal T-waves (TWs) (*Figures 1*, *2*, *3*, *4*). Giant symmetric negative T-waves are suggestive of apical HCM (*Figure 3*). However, a standard ECG may look normal in 4–6% of HCM adult patients[7] and in less than 3% of paediatric ones.[8] Prominent ST segment elevation in anterior leads, with a 'pseudo-STEMI pattern' (*Figure 4*), is not rare and was identified in 17% of HCM patients.[7] Mild ST–T-wave modifications or lonely diphasic T-waves can sometimes be the only abnormality, as well as an isolated inverted T-wave in aVL (*Figure 5*).

In a cohort of 257 HCM patients, diagnosed by ECHO and CMR, 56% showed 'non-specific' ST–T changes, which prompted further investigations, while only 38% showed specific ECG patterns highly suggestive such as giant negative T-waves or inferolateral Q-waves (*Figure 6*).[9] By screening family members, ECG was found abnormal in 21% of genotype positive without imaging evidence of LVH.[4] These patients showed abnormal Q-waves, ST–T abnormalities, and LVH assessed by Sokolow–Lyon Index; the ECG changes were more evident in nine patients that later developed LVH, detected by ECHO in a mean follow-up of 4 ± 2 years.

P-wave

P-wave prolongation ≥140 ms is a frequent finding in advanced disease stages as a consequence of diastolic LV dysfunction, increased LV filling pressures, mitral regurgitation, and possibly atrial myopathy. It is a marker of disease progression[9] and is associated with an increased risk of atrial fibrillation (AF) when left atrial dilatation is also present.[10] Left atrial dilatation is a well-known prognostic marker in HCM, with an increased risk for HCM-related mortality, independent of co-existent AF or LV outflow tract obstruction.[11] Atrial fibrillation is the most common cardiac event in the follow-up of HCM patients and is associated with a higher risk for stroke and worse clinical course and outcome.[12]

Atrioventricular conduction

Ventricular pre-excitation, defined by the association of short PR interval and delta wave, is rare in patients with HCM. It should lead to further investigations which could eventually diagnose glycogen storage diseases due to *PRKAG2* or *LAMP2* mutations or mitochondrial disorders such as Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) or myoclonic epilepsy with ragged red fibres (MERFF).[6] The presence of a fasciculo-ventricular pathway in the context of asymptomatic pre-excitation in sarcomeric HCM was also described. Atrioventricular (AV) delay which could progress to second- or third-degree AV block may be detected

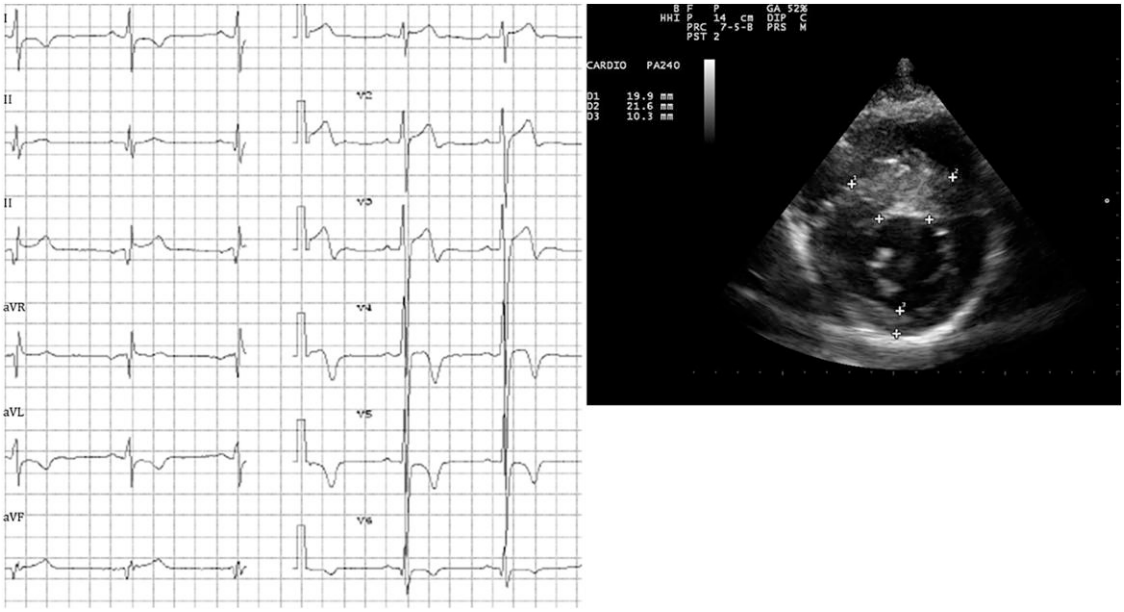

Figure 1 Male, 21 years old, with sarcomeric HCM (MYBPC3). Abnormal ECG with inferior Q-waves, anterolateral T-wave inversion, ST depression in aVL, deep S-waves in V3–V5. Echo: asymmetric hypertrophy with a septal wall thickness of 21 mm.

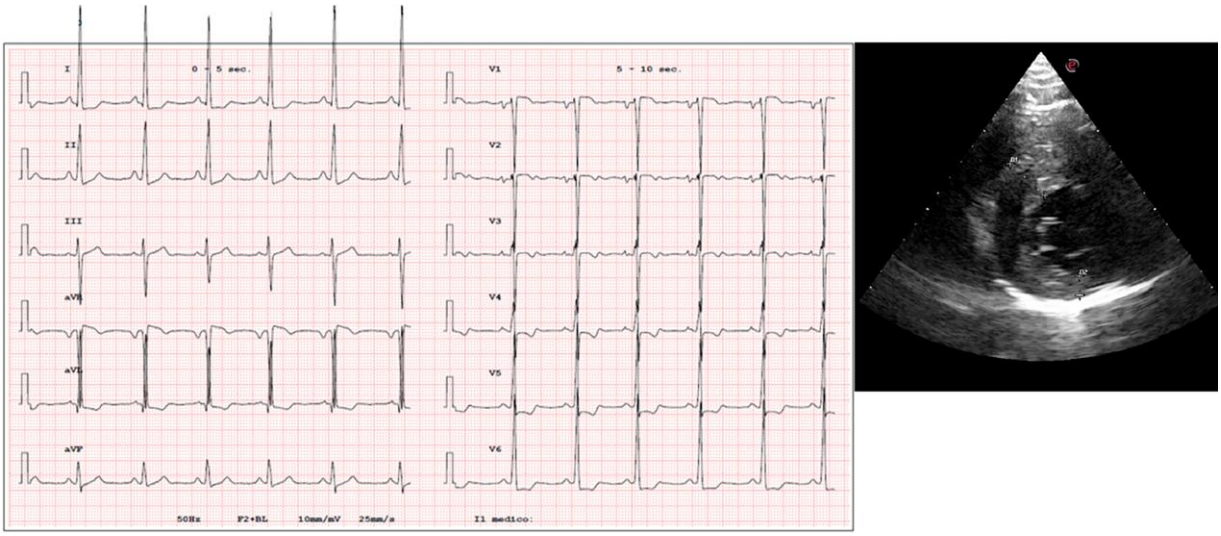

Figure 2 Female, 23 years old, with sarcomeric HCM (TNNT2); ECG: left ventricular hypertrophy with ST depression in anterolateral leads. Echo: asymmetric septal hypertrophy with a maximum wall thickness of 25 mm.

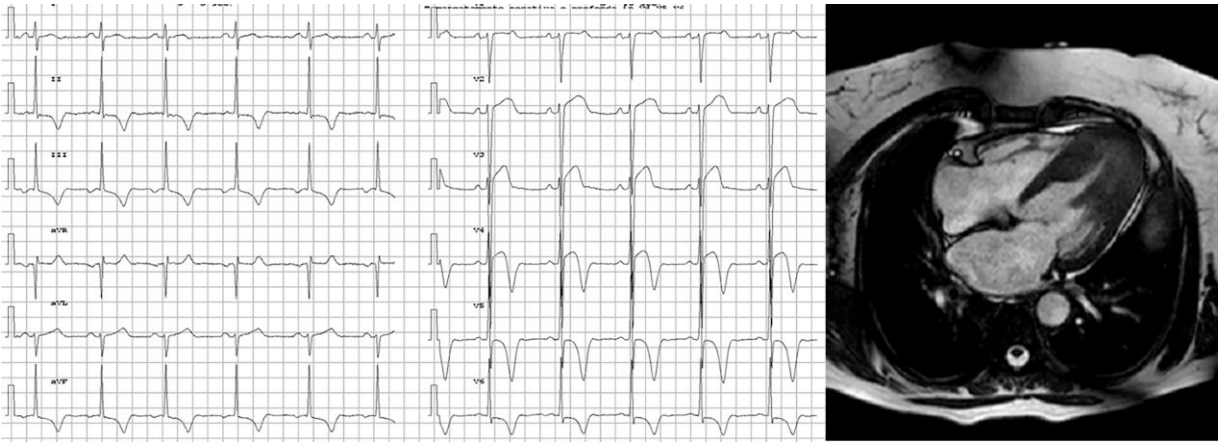

Figure 3 Male, 37 years old, with apical HCM. ECG: giant negative T-waves in V4–V6 and inferior leads, ST segment elevation (pseudo-STEMI pattern) in V2–V3. CMR: left ventricular hypertrophy limited to distal septal and lateral wall and apex.

in the subsequent clinical course of HCM patients, reflecting progressive fibrosis of the AV node. It is more often found in phenocopies such as Fabry cardiomyopathy.

Intraventricular delay and atrioventricular block

Progressive intraventricular delay may reflect disease progression and heart failure (HF), mediated by extensive myocardial fibrosis. Right bundle branch block (RBBB) is a common sequela of septal reduction therapy by alcohol ablation, while left bundle branch block (LBBB) frequently results after septal myectomy. QRS fragmentation is also a common finding in advanced stages of HCM and has been associated with areas of fibrosis detected by CMR.

Abnormal Q-waves

Pathological Q-waves (amplitude ≥25% of the ensuing R-wave and/or duration ≥0.04 s) may be detected in up to 53% of the patients, often in the earliest stage of the disease. They can disappear or change with age and disease progression.[9,13] Q-waves with an upright T-wave in the same leads are quite specific for HCM and should be distinguished by Q-waves following myocardial infarction. They may be explained by the presence of areas of transmural fibrosis leading to loss of electrical forces or abnormal electrical activation of the septum due to disproportionate hypertrophy of its upper anterior part.[13] However, the latter explanation appears more likely, as no relation between abnormal Q-waves and the presence of LGE has been consistently shown.[9,13] The absence of normal septal Q-waves in I-aVL and V5–V6 may also be present and associated with areas of LGE in the septal, anterior, or inferior LV segments.[13]

QRS voltage

QRS voltage is generally increased in HCM; the standard ECG criteria for LVH have a mild prediction power in

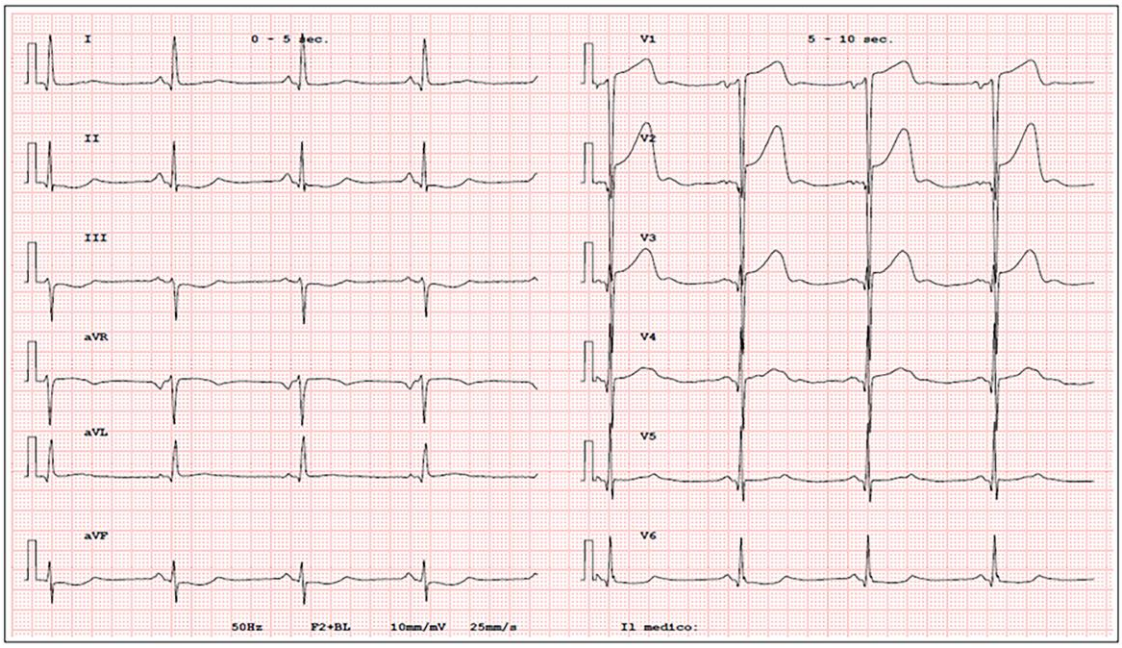

Figure 4 Male, 47 years old, with obstructive HCM. QS pattern in V1–V2, marked ST elevation (pseudo-STEMI pattern) (V2–V3), deep S-waves in V1–V4, ST depression in inferior leads, QTc prolongation (490 ms).

identifying increased LV mass by CMR, with an accuracy ranging from 66% of Romhilt-Estes score to 55% of Cornell Voltage Duration score.[9] The presence of isolated QRS voltage criteria for LVH in the absence of other ECG markers is present in less than 2% of HCM patients. An extremely high voltage must raise the suspicion of a storage disease, such as Anderson–Fabry or Danon storage disease due to *LAMP2* variants, particularly if ventricular pre-excitation is also detected. On the other hand, a discrepancy between LVH by ECHO and low-voltage QRS is typical of infiltrative diseases such as AL or ATT amyloidosis. End-stage HCM patients with massive myocardial fibrosis may also show low-voltage QRS.[6]

Repolarization abnormalities

Repolarization abnormalities are common, including isolated ST–T depression (usually not predictive of coronary disease), ST–T depression associated with T-wave (TW) inversion, or TW inversion alone.[9] Recently, a peculiar pattern defined as 'pseudo-STEMI' pattern was found in 17% of patients, with ST segment elevation and/or giant positive T-waves in at least two contiguous leads in the absence of LBBB.[7] Giant negative symmetric inverted T-waves are not common, and when present, raise the suspicion of apical HCM. The depth of the T-wave may be associated with maximal apical thickness, the presence of midventricular obstruction, and apical fibrosis.[13] Conversely, the presence of tall positive T-waves is associated with more basal forms of hypertrophy. When the ECG is used as a screening tool in athletes, isolated inverted T-waves in inferior leads may be rarely found in a minority of black or white athletes with normal LV wall thickness while when detected in lateral leads may be found in HCM. In athletes, they should be considered suspicious, leading to further investigation by imaging.[5]

QT interval

QT may be prolonged in a minority of HCM patients (*Figure 4*). In a large cohort, 13% of patients showed a QTc over 480 ms and 5% over 500 ms in the absence of LBBB or QT-prolonging drugs. In some patients, QT prolongation was associated with LVOT obstruction, severe LVH, and heart failure symptoms.[14] The mechanism causing QT prolongation is currently unknown. It might be due to the sheer mass of ventricular myocardium with hypertrophic myocyte disarray and LV outflow tract obstruction, but also to well-documented electrophysiological remodelling of the cardiomyocyte membrane.[15]

Electrocardiogram in prognosis

Electrocardiogram may have a prognostic role in patients with HCM. The small cohort of those with a normal ECG has been reported to have a more favourable clinical course than those with ECG abnormalities.[16] Moreover, a normal ECG has a very high negative predictive accuracy (96%) for massive LVH, with its clinical implications.[9] Patients with a simple abnormal parameter such as intraventricular conduction delay and QRS > 120 ms in the absence of LBBB block showed higher cardiovascular mortality (55%) vs. those with QRS <120 ms (7.1%) at 8 years follow-up.[17]

In a retrospective detailed analysis of a wide multicentre cohort of HCM patients with a mean follow-up of 7.4 years, a QRS >120 ms, a 'pseudo-STEMI' pattern, and low QRS voltages were all associated with an increased risk for SCD or appropriate implantable cardioverter defibrillator (ICD) discharge.[7] When these three ECG variables were added to the conventional SCD risk factors reported in HCM populations [such as family history of SCD, non-sustained ventricular tachycardia (NSVT) runs at ambulatory monitoring, unexplained syncope, maximum wall thickness ≥ 30 mm], they improved the risk stratification

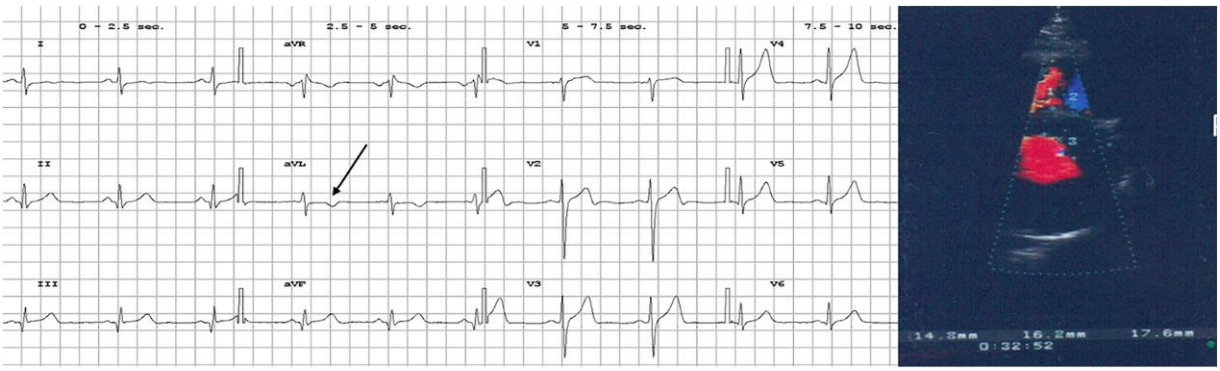

Figure 5 Elite male athlete, 28 years old, with sarcomeric HCM (MYBPC3 and TTN2). ECG: isolated T-wave inversion in aVL (arrow). Echo: septal and lateral maximal wall thickness 17 mm.

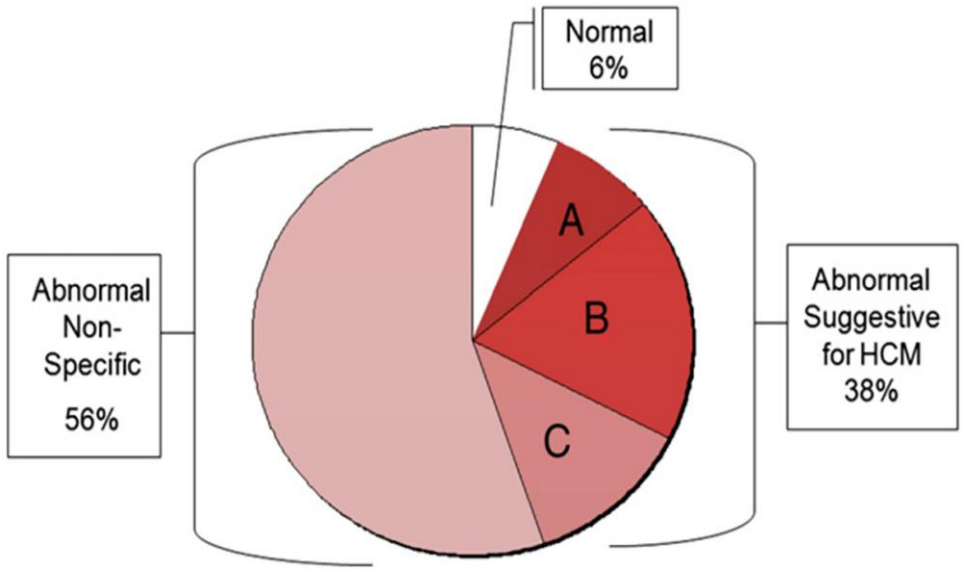

Figure 6 Prevalence of ECG patterns in a cohort of 257 patients with HCM. (*A*) Patients with giant T-waves (8%); (*B*) inferolateral Q-waves, positive Romhilt-Estes point score, repolarization abnormalities (18%); (*C*) inferolateral Q-wave and positive Romhilt-Estes point score (12%).[9]

model. Specifically, their absence allowed the identification of subjects at very low risk of SCD or ICD intervention. The authors concluded that detailed qualitative and quantitative ECG analyses proved to be an independent predictor of prognosis that could be integrated with the available tools in order to improve the power of prediction of the current models.

On the other hand, the prognostic impact of QT prolongation in HCM patients is still controversial and yet to be defined.[14] QRS fragmentation has also been suggested to be a marker of an increased arrhythmic risk in patients with obstructive HCM,[18] but a clear definition of its significance still needs to be confirmed.

Role of the electrocardiogram in differential diagnosis

Standard ECG can help differentiate sarcomeric HCM from phenocopies. Short PR interval, prolonged QRS duration, right bundle branch block, R in aVL ≥1.1 mV, and inferior ST depression independently predicted Anderson-Fabry Disease (AFD) in a recent multicentre retrospective study on individuals presenting with an HCM phenotype.[19] As mentioned earlier, extremely high voltages must rule out ventricular pre-excitation or storage disease, while, instead, a relative QRS voltage reduction compared to LVH on imaging must suggest an infiltrative disease such as amyloidosis, especially AL type. Atrioventricular delay and block, pseudo-infarction pattern, incidence of atrial fibrillation, and RBBB or LBBB could be present in amyloidosis as well as in HCM. In *PRKAG2*-related disease, characterized by HCM and ventricular pre-excitation, the incidence of atrial fibrillation and AV block are even higher than that in sarcomeric HCM, but the ECG criteria for LVH are not always fulfilled in this subset of patients.

The remodelling in cardiac structure, function, and electrical activity due to intense exercise in athletes could result in ECG changes overlapping with those in patients with HCM. The electrocardiogram criteria for LVH based on QRS voltage do not usually correlate with heart disease

in athletes if no other abnormal findings are detected. A J point and convex ST segment elevation followed by inverted TW in V2–V4 is considered a normal variant in black athletes, as well as isolated inverted TW in inferior leads in a minority of black or white athletes. Conversely, TW inversion in lateral leads should be considered pathological until proven otherwise and investigated with imaging.

Future trends

The use of ECG in screening and diagnosis for HCM may be limited by high false-positive rates due to non-specific features or more rarely by ECG that may be apparently normal. The use of artificial intelligence (AI) algorithms seems promising in refining the ECG detection of HCM. In the future, the use of machine learning technologies on large datasets may allow the detection of ECG features that are now not easily identified even by a trained physician. In a recent paper by *Ko et al.*, a fully automated, AI-based algorithm on a standard ECG showed high accuracy in detecting HCM with an AUC of 0.96.[20]

Conclusions

The standard ECG is an effective tool to help the clinician to diagnose HCM and identify high-risk features that could impact the clinical course. The cost-effectiveness and wide availability confirm ECG as a cornerstone for the diagnosis and evaluation of HCM patients.

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Data availability

No new data were generated or analysed in support of this research.

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