The Electrocardiogram in the Diagnosis and Management of Patients with Hypertrophic Cardiomyopathy

Gherardo Finocchiaro[a] MD, Nabeel Sheikh[a] MRCP, PhD, Elena Biagini[b] MD, Michael Papadakis[c] MBBS, MRCP, MD, Nicolo' Maurizi [d] MD, Gianfranco Sinagra[e] MD, Antonio Pelliccia[f] MD, Claudio Rapezzi[b] MD, Sanjay Sharma[c] BSc, MBChB, MD, Iacopo Olivotto[d] MD

Institutions:

[a] Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, United Kingdom

[b] Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum, University of Bologna, Italy

[c] Cardiology clinical and academic group. St George's, University of London, London and St George's University Hospital NHS Foundation Trust. United Kingdom

[d] Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy

[e] Cardiovascular Department, A.O.U. Ospedali Riuniti, Trieste, Italy

[f] Sports Medicine and Science Institute, CONI, Rome, Italy

Word count: 4020

Running title: The electrocardiogram in hypertrophic cardiomyopathy

Conflict of interest: none

Author for correspondence:

Gherardo FInocchiaro MD, PhD Consultant Cardiologist,

Guy's and St. Thomas's Hospital, London, United Kingdom

Westminster Bridge Rd, Lambeth, London SE1 7EH

E-mail: gherardo.finocchiaro@nhs.net

Abstract

In an era of rapid technological development and evolving diagnostic possibilities, the electrocardiogram (ECG) is living an authentic "renaissance" in myocardial diseases. To date, the ECG remains an irreplaceable first step when evaluating patients with hypertrophic cardiomyopathy (HCM) and an abnormal ECG may be the only manifestation of disease at an early stage. In some instances specific electrical anomalies may differentiate HCM from phenocopies such as cardiac amyloidosis and glycogen storage diseases. The exponential growth in knowledge of the complexity of HCM has led to new challenges in terms of early identification of the disease, differential diagnosis, risk stratification and development of targeted therapies. In this scenario the apparently "old fashioned" ECG and the array of ECG-based techniques, ranging from Holter monitoring and loop recorders to exercise testing, are as contemporary as ever. In the present review, we discuss the current role of the ECG in the diagnosis and management of HCM, focusing on various clinical settings where its appropriate use and interpretation can make a difference.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetically determined heart muscle disease characterized by left ventricular (LV) hypertrophy in the absence of a cardiac or systemic cause and has an estimated prevalence of 1:500(1) in the general population. Disease-causing mutations in the genes encoding structural components of the cardiac sarcomere are identified in 40 to 60% of cases. The pathological hallmarks of the disease include myocyte hypertrophy and disarray, interstitial and replacement fibrosis, small-vessel abnormalities and electrical remodelling of the cardiomyocyte. Although patients may have a normal life expectancy, a significant proportion develop HCM-related complications including heart failure, atrial fibrillation and cardioembolic stroke, while a minority exhibit life-threatening ventricular arrhythmias or die suddenly(2).

The diagnosis of HCM relies on the detection of increased LV wall thickness by imaging modalities, such as echocardiography or cardiovascular magnetic resonance (CMR). The recent technological advances in cardiovascular imaging have permeated every aspect of clinical practice, and allow a comprehensive phenotypic and functional cardiac characterization including tomographic assessment of myocardial mechanics, wall motion, chamber size and function. Emerging possibilities include tissue characterization to identify oedema, fibrosis or infiltration. In such scenarios, it is easy to consider the old-fashioned electrocardiogram (ECG) as obsolete. Far from that, the ECG remains a cornerstone in the assessment of patients with HCM. Even more, it is undergoing a "renaissance" in the field of cardiomyopathies, not only because of its inexpensive nature and wide availability, but because it provides details that are related to morphology, function and genetic substrate at

the same time. In this review, we will discuss the current role of the ECG in the diagnosis, risk stratification and management of HCM, focusing on various settings where its correct interpretation can be decisive, in an increasingly high-tech and expensive clinical arena.

Systematic ECG interpretation: a cardiomyopathy-oriented framework

Electrocardiographic interpretation requires a systematic approach that examines every aspect of the electrical activity of the heart in its clinical context, taking into consideration demographic and clinical variables such as age, gender, ethnicity, family history and genotype. Another fundamental premise is that there is a need to reconsider traditional concepts such as "hypertrophy", "Q waves" and "ischaemic abnormalities" derived from patients with hypertensive, valvular and ischaemic heart disease (Figure 1 A) and to integrate them with other, specific electrocardiographic categories belonging to a cardiomyopathy-specific mindset (Figure 1 A and B). As a normal ECG is observed only in 5 to 10% of patients with echocardiographic evidence of HCM (usually at the milder end of the clinical spectrum)(3), the 12-lead ECG is the quintessential screening tool for this disease (Table 1). While certain patterns may be highly suggestive, there is no such thing as pathognomonic ECG for HCM.

Atrial abnormalities

The atria are often dilated in HCM. Left atrial enlargement reflects diastolic dysfunction, high filling pressures, outflow obstruction and functional mitral regurgitation, and may herald progression towards the end-stage phase. Left atrial dilatation and dysfunction is *per se* a marker of adverse prognosis(4). ECG signs of left and right

enlargement and P-wave prolongation (a known predictor of atrial fibrillation - AF) may be observed in HCM patients, rarely occurring in isolation: other ECG abnormalities as repolarization changes or signs of left ventricular hypertrophy (LVH) generally concur.

Ventricular pre-excitation

Ventricular pre-excitation manifests on the 12-lead ECG with a short PR interval and a delta wave at the origin of the QRS complex(5). When this feature is associated with cardiac symptoms as palpitations, syncope or arrhythmias, it is referred to as the Wolff-Parkinson-White (WPW) syndrome. Although ventricular pre-excitation is a primary electrical disorder, it may be associated with structural heart disease, as HCM. The association of LVH, often severe, with ventricular pre-excitation should raise suspicion of a glycogen-storage disease produced by *LAMP2* or *PRKAG2* mutations, or Anderson-Fabry disease, with important therapeutic and prognostic implications both for the patient and the family members(6).

Q waves

The lack of consensus regarding the definition of a pathological Q wave, with multiple proposed diagnostic criteria, constitutes a source of confusion. Q wave duration ≥40 ms or an absolute depth of >3 mm are considered pathological criteria by some, whereas others recommend an amplitude ≥25% of the ensuing R wave(7). Early studies showed that Q waves occur most frequently in patients with an unusual pattern of ventricular hypertrophy, lacking typical asymmetric septal hypertrophy(8). In histopathologic studies, abnormal Q waves were associated with transmural myocardial fibrosis, similar to that seen in myocardial infarction(9). Koga et al.(10) performed intracoronary electrocardiograms and showed two potential mechanisms for Q waves in

patients with HCM. One reflected loss of local electrical forces due to transmural fibrosis and the other was the result of initial QRS vector abnormalities due to disproportionate hypertrophy of the basal interventricular septum and/or basal left ventricular free wall. Recent studies investigating the correlation between Q waves on the ECG and myocardial LGE at CMR have reached discordant results(11). While some suggest that late gadolinium enhancement (LGE) may indeed correlate with pathological Q waves in HCM(12), others have failed to demonstrate a significant relationship(13).

The QRS complex and ventricular hypertrophy

While increased QRS voltages are often identified in isolation in young healthy individuals, this feature is generally associated with other abnormalities in HCM. In a study by Rowin et al.(14), the ECG was abnormal in 90% of patients with HCM according to the 2010 ESC recommendations for interpretation in athletes(15) and only 2% exhibited isolated QRS voltage criteria for LV hypertrophy (Sokolow-Lyon and Cornell voltage score). These findings were confirmed in a recent study by Calore et al.(16) where the ECG was abnormal in 96% of patients with HCM and increased QRS voltages occurred in isolation in only 2%. Low limb lead voltages are defined as a QRS amplitude ≤5 mm in each of the limb leads. The combination of low voltages with significant increase in wall thickness on the echocardiogram or CMR should raise the possibility of cardiac amyloidosis(17).

Complete bundle branch block is relatively uncommon in HCM and is often secondary to invasive interventions for alleviating left ventricular outflow obstruction. Septal myectomy often results in a left and alcohol septal ablation may cause right bundle branch block(18). Left bundle branch block may also be seen in advanced stages of disease progression with extensive, often transmural anteroseptal scar(19). Lesser degrees of

7

intraventricular conduction delay are non-specific and may be observed in healthy individuals and athletes. Similarly, isolated axis deviation is rare in patients with HCM and should not prompt further investigations in asymptomatic individuals without a family history of cardiac disease or sudden cardiac death (SCD)(20). Fragmentation of the QRS complexes (f-QRS), defined as presence of an additional R wave (R') or notching in the nadir of the S wave, reflects intraventricular conduction delay and may be a marker of myocardial fibrosis(21). Although F-QRS have been used to predict arrhythmic events in HCM patients with implantable cardioverter defibrillators (ICDs) for primary or secondary prophylaxis(1), its prognostic role remains unclear.

Finally, although some degree of right ventricular (RV) primary or secondary involvement may be present in HCM(22), isolated voltage criteria for right ventricular hypertrophy is extremely uncommon. ECG findings suggestive of RV strain suggest rare HCM phenocopies, such as storage diseases, where RV hypertrophy may be identified by cardiac imaging.

Repolarization abnormalities

ST-T segment abnormalities are common in HCM. Deep T wave inversion (TWI) in the lateral leads is a recognized feature of apical HCM (Figure 2) and should prompt an accurate evaluation of this morphologic variant with available imaging techniques(23). In patients with HCM, TWI commonly involves the inferior and lateral leads, T waves are deep ($\geq$-0.2 mV) and often preceded by ST segment depression (24). Both TWI and ST depression appear to be even more common in black individuals with HCM (25). Abnormalities of the ST segment are notoriously poorly predictive of epicardial coronary artery disease in HCM patients.

Isolated inferior TWI in the absence of LVH has been reported in up to 6% of healthy black athletes and 2% of white athletes[25]. However, TWI in the lateral leads may pre-date the development of a full phenotypic expression of HCM in highly trained athletes[23]. Therefore, clinical surveillance with annual follow-up is prudent in this context.

QTc prolongation

Significant QT prolongation (QTc > 480 ms) has been described in 1 out of 8 HCM, a prevalence that is significantly higher compared to healthy individuals[26]. QTc prolongation likely reflects the interplay of cardiac hypertrophy, fibrosis and outflow tract obstruction, although electrophysiological remodelling of cardiomyocytes, characterized by marked enhancement in the late sodium current and delayed repolarization, is also considered a major determinant[26,27]. Recently, QTc prolongation on baseline ECG was reported as a key clinical predictor of appropriate ICD therapies in patients with HCM[28].

The standard ECG in the diagnosis of HCM

HCM is generally diagnosed by demonstrating LVH with a wall thickness >15 mm at echocardiogram or CMR. However, this magnitude of LVH is not specific for HCM and may be secondary to various other pathological conditions. In this setting, the ECG is extremely useful in guiding the differential diagnosis between sarcomeric HCM and its phenocopies. A "red flag approach" should be part of routine assessment of patients with cardiomyopathies[29].

While Q waves with positive T waves in the same leads (Q/T discordance) and giant (>10 mm) T wave inversion in the anterolateral leads support the diagnosis of sarcomeric

HCM, short P-R and/or ventricular pre-excitation are common findings in storage diseases like glycogenosis, Danon disease (Figure 3), *PRKAG2*, and Anderson-Fabry disease, and can also be found in mitochondrial disease(29). These ECG abnormalities should be evaluated in the clinical context including inheritance pattern and specific signs and symptoms such as renal impairment, hearing impairment, diabetes, muscle weakness or mental retardation. In the long-term, storage and mitochondrial diseases may all progress to atrioventricular (AV) conduction delay and ultimately to high degree AV block; the latter is also a common complication of infiltrative disorders as cardiac amyloidosis. Storage diseases are invariably accompanied by strikingly high amplitude QRS complexes with voltage criteria for LVH with ST segment depression and T wave inversion in the lateral leads(29). Conversely, the expansion of myocardial interstitium secondary to extracellular infiltration (in conjunction with direct toxic of the myocyte by circulating precursor proteins) typically causes low QRS voltages in amyloidosis (Figure 4A). However, absolute reduction in voltage amplitude is seen in only 20% of patients with *ATTR*-amyloidosis (as compared to 60% with AL-amyloidosis) and therefore its absence does not rule out the disease. Rather, suspicion should arise in the presence of *relative* QRS voltage reduction compared to the degree of hypertrophy on echo or MRI (i.e. when electro-morphological discordance is present)(30). Low QRS voltages may be rarely seen in patients with end-stage sarcomeric HCM and represent an ominous sign of diffuse fibrosis(2) (Figure 4B).

Differential diagnosis with athlete's heart and normal variants

Long-term athletic training is associated with a series of alterations in cardiac structure, function and electrical activity that are collectively termed athlete's heart(31).

ECG changes observed in athletes often overlap with those of patients with cardiac conditions as channelopathies and cardiomyopathies including HCM. Recent international recommendations for ECG interpretation in athletes underscore which abnormalities should be considered as reflective of physiological adaptation to exercise and which instead should be regarded as highly suggestive of pathology(20). Isolated voltage criteria for LVH or left axis deviation are highly suggestive of a normal process, while repolarization abnormalities such as TWI (especially in the lateral leads) and ST depression or pathological Q waves are more likely expression of HCM. Occasionally, athletes may exhibit TWI in the absence of underlying structural disease, often creating a conundrum in differential diagnosis. Lateral TWI should always be considered pathological until proven otherwise. Notably, they may precede the full expression of HCM in otherwise healthy athletes and therefore mandate annual monitoring with echocardiogram and potentially CMR(23). TWI in leads V1-V4 is relatively common especially in black athletes commonly preceded by convex ST segment elevation (Figure 5) (32). TWI in V1-V2 may be present in up to 3-5% of white athletes and does not warrant investigation in the absence of symptoms or a relevant family history(33).

ECG changes along the natural history of HCM

HCM is associated with favourable mid-term prognosis in most patients, although various trajectories of disease progression may be observed and long-term studies are uncovering considerable late morbidity. The ECG may change significantly during this time, reflecting long-term morpho-functional evolution. In the phase of phenotypic development, commonly during adolescence, increase in QRS voltages and development of ST-segment and T-wave abnormalities may occur over a short time frame. Over following decades, the

most common changes are represented by the progressive evidence of left atrial enlargement and various degrees of QRS prolongation reflecting septal fibrosis and conduction tissue involvement. In the later stages, when myocardial fibrosis burden becomes significant, left bundle block may develop. Rarely, there is a decrease in the amplitude of the QRS voltages leading to a true "low-voltage pattern" in conjunction with end-stage disease, when transmural replacement fibrosis is predominant(2) (Figure 6). In a limited subset, the appearance of ST-segment elevation with negative T waves may mark the development of apical aneurysms, usually in the setting of mid-ventricular obstruction.

The standard ECG in gene carriers without LVH

Increased availability of genetic testing for HCM has led to emergence of a novel patient subset including genetically affected family members without LVH. Genotype-positive(+)-LVH-negative(-)(G+LVH-) individuals raise unresolved issues such as the optimal follow-up strategy to monitor conversion to overt HCM(1). Although no specific ECG pattern is characteristic of this status, certain ECG abnormalities may precede the development of LVH in children(34), most commonly increased precordial voltages and deep Q waves. These probably reflect microstructural rearrangement (myocardial disarray, interstitial fibrosis and microvascular remodeling) that can also precede LVH development. Hence, the ECG is more sensitive than echocardiography as a screening tool in HCM families.

The standard ECG for risk stratification and management

Despite its unquestionable use in the diagnosis of HCM and family screening, the role of the 12-lead ECG in risk stratification and management is less well established (Table 1). McLeod et al.(3) retrospectively examined the clinical phenotype and prognosis of HCM patients with a normal ECG in a cohort of 2,486 individuals. A normal tracing was identified in 6% of patients (n=135), who experienced a lower rate of cardiac-related mortality (including sudden cardiac death), compared to patients with an abnormal ECG. Montgomery et al.(35) failed to demonstrate the prognostic role of the ECG in a cohort of 448 patients with HCM. In a cohort of 245 Italian patients in which 7% exhibited a normal ECG(36) none of these patients experienced arrhythmic events or SCD, compared with 8% of patients with an abnormal tracing during a follow-up period of 8±6 years. Conversely, Sherrid et al(37) demonstrated no value for ECG abnormalities in predicting appropriate ICD intervention or SCD in a cohort of 330 patients with HCM.

Other studies have suggested correlations between various ECG parameters, phenotype and outcome in HCM. Konno et al(38) found low ECG voltages to be predictive of myocardial fibrosis on CMR. Delcrè et al(11) observed the number and severity of ECG changes to be directly related to phenotypic expression on CMR. Biagini et al(39) found an independent predictive value between certain ECG changes, including low QRS voltage, increased QRS duration and a "pseudo-ST-segment elevation myocardial infarction" pattern and SCD in HCM. Östman-Smith et al(40) assessed ECG patterns as predictors of SCD in 116 adult HCM patients, finding a correlation between cardiac arrest and TWI, ST-segment depression and a dominant S-wave in V4. They proposed an ECG risk score based on these parameters, combined with QRS amplitude and QTc measurements. Conflicting results from all these studies suggest that larger, multicenter studies with substantial follow up analysis

are required to assess the prognostic role of ECG patterns in HCM. Currently , no pattern alone or in combination can be used for clinical decision-making regarding prognosis or therapy with the exception of potential reassurance for patients with normal tracings.

Last but not least, the role of serial ECG testing in clinical practice is instrumental in considering cardiac resynchronization therapy in highly symptomatic individuals with wide QRS complexes who are in the end-stage phase of the disease(2) and in monitoring of the QTc in HCM patients taking QT-prolonging drugs such as disopyramide or amiodarone.

ECG-based techniques

ECG-based investigations such as 24-48 hour Holter monitoring and exercise tolerance test are widely used in the assessment of patients with HCM and for risk stratification and clinical management. Holter monitoring is indicated to assess supraventricular and ventricular arrhythmic burden, but may also prove useful for identifying bradyarrhythmias (e.g. in patients with history of syncope) and signs of microvascular ischemia.

AF is the most common arrhythmia in patients with HCM and a main predictor of heart failure-related mortality. AF is four- to six fold more common in HCM than in similarly aged individuals in the general population, with an incidence from 2 to 5% per year and a prevalence that ranges from 18% to 28%(41). However, its true prevalence is difficult to evaluate because of frequent silent occurrences. Detection of clinically silent AF, identified only by extended periods of monitoring, raises important implications for treatment strategy and stroke prophylaxis, as HCM patients with AF have 8 time greater risk of ischemic stroke compared with those in sinus rhythm[3,8]. Cardiac rhythm monitoring devices

like implantable cardioverter defibrillator (ICD), 24-hour Holter monitoring or loop recorder are useful in this context(42).

Non-sustained ventricular tachycardia (NSVT), defined as three or more consecutive ventricular beats at a rate of greater than 100 beats/min with a duration of less than 30 seconds, is detected in up to 54% of patients with HCM(1). A number of studies have reported an association between NSVT and risk of SCD in patients with HCM(43,44). NSVT is included both in the ESC and AHA/ACC guidelines among the risk factors that should be considered in primary prevention of SCD.

 ST-T segment depression may be detected frequently at Holter monitoring in patients with HCM, but has not been consistently linked with chest pain or perfusion abnormalities on SPECT imaging(45). The exercise tolerance test provides important information regarding functional capacity, investigation of symptoms and risk stratification. Exercise-induced arrhythmias and blunted blood pressure response predict risk for SCD especially in adults aged ≤ 40 years-old. Exercise may be helpful in unmasking microvascular ischemia by showing ST-segment depression (18).

Finally, exercise testing and Holter monitoring may be instrumental to diagnosing chronotropic incompetence which is present in up to 25% of patients with HCM(4). Chronotropic incompetence is likely multifactorial, including excessive doses of AV node blocking drugs. Autonomic dysfunction is frequent amongst patients with HCM and linked to the high prevalence of abnormal sinus-node function and His–Purkinje conduction in up to 2/3 of HCM patients undergoing electrophysiological study(46). Deranged autoregulation of the microvascular myocardial network may also play a role in abnormal chronotropic response(46).

Novel personal ECG devices

A wide range of novel personal portable devices have been developed recently with the aim of providing continuous patient monitoring. Smartphone technologies generally involve a single-lead ECG obtained on a small device that communicates with a smartphone. Various companies currently offer different versions of the smartphone ECG that generally operate using a similar principle of a collection device, consisting of two to six electrodes, and an application on a smartphone that processes data(47). The use of these affordable and easy-to-use technologies has not been established in HCM, but there is a potential for employing them for widespread screening in otherwise healthy individuals or for tele-monitoring of patients with an established diagnosis.

The ECG in the choice of the implantable cardioverter defibrillator

HCM patients at risk of SCD may require primary prophylaxis with an implantable cardioverter defibrillator (ICD)(1). However, in young individuals , the benefit of ICD protection must be weighed against the considerable likelihood of long-term device-related complications(48). The subcutaneous ICD (S-ICD) represents an advantageous alternative in this setting, avoiding intravascular leads related complications(49), as reflected in the IDE study and EFFORTLESS registry(50,51). The S-ICD continuously senses the surface ECG with a morphology-based rhythm discrimination algorithm and QRS complexes and T wave abnormalities – frequently observed in HCM - can cause sensing issues resulting in inappropriate shocks. In order to avoid these complications, ECG vector screening protocols using unconventional leads have been implemented to exclude patients with unsuitable ECG morphologies. Based on this strategy, from 11 to 16% of patients with HCM are not eligible

for S-ICD implantation- a greater proportion compared to other cardiac diseases, largely due to marked T wave inversion with ST-T segment depression, an R/T wave amplitude <3 and large amplitude of QRS complexes (52–54). These screening failure rates could be reduced by the development of novel interpretation algorithms.

Conclusions

The ECG remains a cornerstone in the diagnosis and management of patients with HCM (Figure 7). Despite the recent exponential development of imaging techniques, a learned interpretation of the ECG provides invaluable clues in the early identification of the disease, the differential diagnosis with other cause of LVH or with physiological adaptation in highly trained athletes and detection of features that may suggest a high risk of adverse outcomes. A combined assessment of the ECG with the most advanced imaging techniques is particularly useful in clinical practice, contributing to the enduring youth of this ancient instrument as cardiovascular medicine evolves.

REFERENCES:

1.   Authors/Task Force members., Elliott PM., Anastasakis A., et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35(39):2733–79. Doi: 10.1093/eurheartj/ehu284.

2.   Olivotto I., Cecchi F., Poggesi C., Yacoub MH. Patterns of Disease Progression in Hypertrophic Cardiomyopathy: An Individualized Approach to Clinical Staging. Circ Hear Fail 2012;5(4):535–46. Doi: 10.1161/CIRCHEARTFAILURE.112.967026.

3.   McLeod CJ., Ackerman MJ., Nishimura R, Tajik a. J., Gersh BJ., Ommen SR. Outcome of Patients With Hypertrophic Cardiomyopathy and a Normal Electrocardiogram. J Am Coll Cardiol 2009;54(3):229–33. Doi: 10.1016/j.jacc.2009.02.071.

4.   Finocchiaro G., Haddad F., Knowles JW., et al. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. JACC Heart Fail 2015;3(5):408–18. Doi: 10.1016/j.jchf.2014.11.011.

5.   Levitin DJ., Created B., Nature H. ScienceDirect Wolff – Parkinson – White syndrome (WPW) and athletes : Darwin at play ? 2015;48:356–61.

6.   Maron BJ., Maron MS., Semsarian C. Genetics of Hypertrophic Cardiomyopathy After 20 Years. J Am Coll Cardiol 2012;60(8):705–15. Doi: 10.1016/j.jacc.2012.02.068.

7.   Sharma S., Drezner JA., Baggish A., et al. International recommendations for

electrocardiographic interpretation in athletes. Eur Heart J 2017. Doi: 10.1093/eurheartj/ehw631.

8.   Maron BJ., Wolfson JK., Ciró E., Spirito P. Relation of electrocardiographic abnormalities and patterns of left ventricular hypertrophy identified by 2-dimensional echocardiography in patients with hypertrophic cardiomyopathy. Am J Cardiol 1983;51(1):189–94.

9.   Maron BJ., Epstein SE., Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. Am J Cardiol 1979;43(6):1086–102.

10. Koga Y., Yamaga A., Hiyamuta K., Ikeda H., Toshima H. Mechanisms of abnormal Q waves in hypertrophic cardiomyopathy assessed by intracoronary electrocardiography. J Cardiovasc Electrophysiol 2004;15(12):1402–8. Doi: 10.1046/j.1540-8167.2004.04314.x.

11. Delcrè SDL., Di Donna P., Leuzzi S., et al. Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: a cardiac magnetic resonance study. Int J Cardiol 2013;167(3):1038–45. Doi: 10.1016/j.ijcard.2012.03.074.

12. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012;14:13. Doi: 10.1186/1532-429X-14-13.

13. Papavassiliu T., Flüchter S., Haghi D., et al. Extent of myocardial hyperenhancement on late gadolinium-enhanced cardiovascular magnetic resonance correlates with q

waves in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2007;9(3):595–603. Doi: 10.1080/10976640600945465.

14. Rowin EJ., Maron BJ., Appelbaum E., et al. Significance of false negative electrocardiograms in preparticipation screening of athletes for hypertrophic cardiomyopathy. Am J Cardiol 2012;110(7):1027–32. Doi: 10.1016/j.amjcard.2012.05.035.

15. Corrado D., Pelliccia A., Heidbuchel H., et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. Eur Heart J 2010;31(2):243–59. Doi: 10.1093/eurheartj/ehp473.

16. Calore C., Melacini P., Pelliccia A., et al. Prevalence and clinical meaning of isolated increase of QRS voltages in hypertrophic cardiomyopathy versus athlete's heart: relevance to athletic screening. Int J Cardiol 2013;168(4):4494–7. Doi: 10.1016/j.ijcard.2013.06.123.

17. Finocchiaro G., Pinamonti B., Merlo M., et al. Focus on cardiac amyloidosis : a single-center experience with a long-term follow-up 2009. Doi: 10.2459/JCM.0b013e3283536534.

18. Maron BJ., Maron MS., Wigle ED., Braunwald E. The 50-Year History, Controversy, and Clinical Implications of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy. From Idiopathic Hypertrophic Subaortic Stenosis to Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2009;54(3):191–200. Doi: 10.1016/j.jacc.2008.11.069.

19. Cappelli F., Morini S., Pieragnoli P., et al. Cardiac Resynchronization Therapy for End-

Stage Hypertrophic Cardiomyopathy: The Need for Disease-Specific Criteria. J Am Coll Cardiol 2018;71(4):464–6. Doi: 10.1016/j.jacc.2017.11.040.

20.   Sharma S., Drezner JA., Baggish A., et al. International Recommendations for Electrocardiographic Interpretation in Athletes. J Am Coll Cardiol 2017;69(8):1057–75. Doi: 10.1016/j.jacc.2017.01.015.

21.   Pietrasik G., Zaręba W. QRS fragmentation: diagnostic and prognostic significance. Cardiol J 2012;19(2):114–21.

22.   Finocchiaro G., Knowles JW., Pavlovic A., et al. Prevalence and Clinical Correlates of Right Ventricular Dysfunction in Patients With Hypertrophic Cardiomyopathy. Am J Cardiol 2013. Doi: 10.1016/j.amjcard.2013.09.045.

23.   Pelliccia A., Di Paolo FM., Quattrini FM., et al. Outcomes in athletes with marked ECG repolarization abnormalities. N Engl J Med 2008;358(2):152–61. Doi: 10.1056/NEJMoa060781.

24.   Sheikh N., Papadakis M., Panoulas VF., et al. Comparison of hypertrophic cardiomyopathy in Afro-Caribbean versus white patients in the UK. Heart 2016. Doi: 10.1136/heartjnl-2016-309843.

25.   Papadakis M., Carre F., Kervio G., et al. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. Eur Heart J 2011;32(18):2304–13. Doi: 10.1093/eurheartj/ehr140.

26.   Johnson JN., Grifoni C., Bos JM., et al. Prevalence and clinical correlates of QT prolongation in patients with hypertrophic cardiomyopathy. Eur Heart J

2011;32(9):1114–20. Doi: 10.1093/eurheartj/ehr021.

27.   Coppini R., Ferrantini C., Yao L., et al. Late Sodium Current Inhibition Reverses Electromechanical Dysfunction in Human Hypertrophic Cardiomyopathy. Circulation 2013;127(5):575–84. Doi: 10.1161/CIRCULATIONAHA.112.134932.

28.   Gray B., Ingles J., Medi C., Semsarian C. Prolongation of the QTc interval predicts appropriate implantable cardioverter-defibrillator therapies in hypertrophic cardiomyopathy. JACC Heart Fail 2013;1(2):149–55. Doi: 10.1016/j.jchf.2013.01.004.

29.   Rapezzi C., Arbustini E., Caforio ALP., et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34(19):1448–58. Doi: 10.1093/eurheartj/ehs397.

30.   Rapezzi C., Lorenzini M., Longhi S., et al. Cardiac amyloidosis: the great pretender. Heart Fail Rev 2015;20(2):117–24. Doi: 10.1007/s10741-015-9480-0.

31.   Sharma S., Merghani A., Mont L. Exercise and the heart: the good, the bad, and the ugly. Eur Heart J 2015;36(23):1445–53. Doi: 10.1093/eurheartj/ehv090.

32.   Papadakis M., Carre F., Kervio G., et al. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. Eur Heart J 2011;32(18):2304–13. Doi: 10.1093/eurheartj/ehr140.

33.   Wilson MG., Sharma S., Carre F., et al. Significance of deep T-wave inversions in asymptomatic athletes with normal cardiovascular examinations: practical solutions for managing the diagnostic conundrum. Br J Sports Med 2012;46(Suppl_1):i51–8.

Doi: 10.1136/bjsports-2011-090838.

34. Panza JA., Maron BJ. Relation of electrocardiographic abnormalities to evolving left ventricular hypertrophy in hypertrophic cardiomyopathy during childhood. Am J Cardiol 1989;63(17):1258–65.

35. Montgomery J V., Harris KM., Casey SA., Zenovich AG., Maron BJ. Relation of electrocardiographic patterns to phenotypic expression and clinical outcome in hypertrophic cardiomyopathy. Am J Cardiol 2005;96(2):270–5. Doi: 10.1016/j.amjcard.2005.03.058.

36. Calore C., Cianfrocca C., Iacovella I., et al. Hypertrophic Cardiomyopathy with Normal ECG: Clinical Meaning and Prognostic Implications. Circulation 2018;124:A15703.

37. Sherrid M V., Cotiga D., Hart D., et al. Relation of 12-Lead Electrocardiogram Patterns to Implanted Defibrillator-Terminated Ventricular Tachyarrhythmias in Hypertrophic Cardiomyopathy. Am J Cardiol 2009;104(12):1722–6. Doi: 10.1016/j.amjcard.2009.07.056.

38. Konno T., Nagata Y., Teramoto R., et al. Usefulness of Electrocardiographic Voltage to Determine Myocardial Fibrosis in Hypertrophic Cardiomyopathy. Am J Cardiol 2016;117(3):443–9. Doi: 10.1016/j.amjcard.2015.11.015.

39. Biagini E., Pazzi C., Olivotto I., et al. Usefulness of Electrocardiographic Patterns at Presentation to Predict Long-term Risk of Cardiac Death in Patients With Hypertrophic Cardiomyopathy. Am J Cardiol 2016;118(3):432–9. Doi: 10.1016/j.amjcard.2016.05.023.

40. Östman-Smith I., Wisten A., Nylander E., et al. Electrocardiographic amplitudes: A

new risk factor for sudden death in hypertrophic cardiomyopathy. Eur Heart J 2010;31(4):439–49. Doi: 10.1093/eurheartj/ehp443.

41.   Rowin EJ., Hausvater A., Link MS., et al. Clinical Profile and Consequences of Atrial Fibrillation in Hypertrophic Cardiomyopathy. Circulation 2017;136(25):2420–36. Doi: 10.1161/CIRCULATIONAHA.117.029267.

42.   Adabag AS., Casey SA., Kuskowski MA., Zenovich AG., Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;45(5):697–704. Doi: 10.1016/j.jacc.2004.11.043.

43.   Maron BJ., Savage DD., Wolfson JK., Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol 1981;48(2):252–7.

44.   Elliott PM., Poloniecki J., Dickie S., et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36(7):2212–8.

45.   Elliott PM., Kaski JC., Prasad K., et al. Chest pain during daily life in patients with hypertrophic cardiomyopathy: an ambulatory electrocardiographic study. Eur Heart J 1996;17(7):1056–64.

46.   Efthimiadis GK., Giannakoulas G., Parcharidou DG., et al. Chronotropic incompetence and its relation to exercise intolerance in hypertrophic cardiomyopathy. Int J Cardiol 2011;153(2):179–84. Doi: 10.1016/j.ijcard.2010.08.026.

47.   Maurizi N., Faragli A., Imberti J., et al. Cardiovascular screening in low-income settings

using a novel 4-lead smartphone-based electrocardiograph (D-Heart®). Int J Cardiol 2017;236:249–52. Doi: 10.1016/j.ijcard.2017.02.027.

48. Maron BJ., Casey SA., Olivotto I., et al. Clinical Course and Quality of Life in High-Risk Patients With Hypertrophic Cardiomyopathy and Implantable Cardioverter-Defibrillators. Circ Arrhythm Electrophysiol 2018;11(4):e005820. Doi: 10.1161/CIRCEP.117.005820.

49. Bardy GH., Smith WM., Hood MA., et al. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med 2010;363(1):36–44. Doi: 10.1056/NEJMoa0909545.

50. Burke MC., Gold MR., Knight BP., et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol 2015;65(16):1605–15. Doi: 10.1016/j.jacc.2015.02.047.

51. Lambiase PD., Gold MR., Hood M., et al. Evaluation of subcutaneous ICD early performance in hypertrophic cardiomyopathy from the pooled EFFORTLESS and IDE cohorts. Hear Rhythm 2016;13(5):1066–74. Doi: 10.1016/j.hrthm.2016.01.001.

52. Maurizi N., Olivotto I., Olde Nordkamp LRA., et al. Prevalence of subcutaneous implantable cardioverter-defibrillator candidacy based on template ECG screening in patients with hypertrophic cardiomyopathy. Hear Rhythm 2016;13(2):457–63. Doi: 10.1016/j.hrthm.2015.09.007.

53. Francia P., Adduci C., Palano F., et al. Eligibility for the Subcutaneous Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy. J

Cardiovasc Electrophysiol 2015;26(8):893–9. Doi: 10.1111/jce.12714.

54. Srinivasan NT., Patel KH., Qamar K., et al. Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy. Circ Arrhythm Electrophysiol 2017;10(4). Doi: 10.1161/CIRCEP.117.004801.

Tables 1. Prevalence of ECG abnormalities in HCM and prognostic role of the ECG in patients with HCM.

Study	n	% abnormal ECG	Main abnormalities	(%)
Rowin et al.(14)	114	90	Non-voltage criteria for LV hypertrophy	54
			Isolated Sokolow-Lyon criteria for LVH	1
			Isolated Cornell criteria for LVH	1
			Pathologic Q waves	43
			ST-segment depression or elevation	25
			T-wave inversion	56
Calore et al.(16)	247	96	Isolated Sokolow-Lyon criteria for LVH	2
			ST-T alterations	82
			Pathologic Q waves	35
			T wave inversion	50
McLeod et al.(3)	2485	94	/	
Delcre' et al.(11)	257	94	Romhilt-Estes criteria for LVH ≥ 5	60
			ST segment depression	7
			T wave inversion	18
			Pathological Q waves	53
			ST convex segment elevation≥2 mm in V1-V2 leads	36
Sheikh et al.(24)	425	93	Sokolow-Lyon voltage criteria for LVH	43
			ST-segment depression	49
			ST-segment elevation	44
			T wave inversion in the lateral leads	73
			Pathologic Q waves	18
Montgomery et al. (35)	448	96	Romhilt-Estes (≥ 4 points)	53
			Cornell voltage score	41
			LVH with strain	37
Prognostic studies				
Study	**n**	**Type of outcome**	**Main ECG predictors**	
Biagini et al.(39)	1004	Sudden death/ICD discharge	QRS duration > 120 msec (HR: 1.78 (1.05 - 3.03))	
			Low QRS voltages (HR: 2.26 (1.01 - 5.07))	
			"Pseudo STEMI"pattern (HR: 2.28 (1.38 - 3.77))	
Östman-Smith et al.(40)	116	Cardiac arrest	Pathological T-wave inversion precordial leads	
			ST-segment depression 2 mm	
			Dominant S in V4	
			Limb-lead QRS-amplitude sum ≥ 12 mV	
			12-lead amplitude–duration product ≥ 2.5 mV	
Mcleod et al. (3)	2485	Mortality	Abnormal ECG	
Mongomery et al.(35)	448	Mortality	Abnormal delayed precordial R-wave progression	

Abbreviations: TWI: T wave inversion.

FIGURE LEGENDS:

Figure 1. The interpretation of standard ECG in HCM must necessarily reconsider traditional concepts such as "hypertrophy", "necrotic waves" and "ischaemic abnormalities" derived from patients with hypertensive, valvular and ischaemic heart disease (A) and integrate them with other specific ECG categories within a cardiomyopathy-specific mindset (B).

Figure 2. Giant T waves inversion in a patient with apical HCM. The CMR images show significant apical LVH in the end-diastolic frame (left), apical obliteration in the end-systolic farme (center) and apical late gadolinium enhancement (right).

Figure 3. Short PR and pre-excitation in a patient with Danon disease.

Figure 4. A: Low QRS voltages and pseudo-necrosis pattern in V1-V4 in a patient affected by cardiac amyloidosis. The CMR shows a concentric increase of the LV wall thickening (left) and typical LGE pattern at the short axis (center) and 4 chamber view (right) with difficulty in nulling of myocardial signal on the LGE images. B: Low QRS voltages suggesting high fibrosis burden in "end-stage" HCM The CMR shows mild LVH on the 4 chamber and short axis cine images (left) and diffuse LGE pattern (right).

Figure 5. ECG of a 32 year-old athlete of Afro-Caribbean descent. Note the anterior (V1-V4) T wave inversion accompanied by J point and ST elevation with superior concavity. This pattern is recognized as physiological in black athletes and not suggestive of pathological hypertrophy.

Figure 6. Patient with MYH7 mutation and paediatric onset hypertrophic cardiomyopathy. The patient was transplanted due to repetitive arrhythmias not amenable to treatment (slow VT below optimal defibrillation threshold). The patient showed evidence of microvascular ischemia during relative tachycardia on Holter monitoring (arrows) (A) and received multiple ICD shocks due to ischemia-induced VT/VF(B). Histological examination of the heart showed severe LVH, diffuse fibrosis and microvascular remodelling (C). Pathology images courtesy of Ornella Leone.

Figure 7. Summary of the role of ECG in the diagnosis and management of HCM.

The Electrocardiogram in the Diagnosis and Management of Patients with Hypertrophic Cardiomyopathy

Gherardo Finocchiaro[a] MD, PhD, Nabeel Sheikh[a] MRCP, PhD, Elena Biagini[b] MD, Michael Papadakis[c] MBBS, MRCP, MD, Nicolo' Maurizi [d] MD, Gianfranco Sinagra[e] MD, Antonio Pelliccia[f] MD, Claudio Rapezzi[b] MD, Sanjay Sharma[c] BSc, MBChB, MD, Iacopo Olivotto[d] MD

Institutions:

[a] Cardiothoracic Centre, Guy's and St Thomas' Hospital, London, United Kingdom

[b] Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum, University of Bologna, Italy

[c] Cardiology clinical and academic group. St George's, University of London, London and St George's University Hospital NHS Foundation Trust. United Kingdom

[d] Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy

[e] Cardiovascular Department, A.O.U. Ospedali Riuniti, Trieste, Italy

[f] Sports Medicine and Science Institute, CONI, Rome, Italy

Word count: 4020

Author for correspondence:

Gherardo FInocchiaro MD, PhD Consultant Cardiologist,

Guy's and St. Thomas's Hospital, London, United Kingdom

Westminster Bridge Rd, Lambeth, London SE1 7EH

E-mail: gherardo.finocchiaro@nhs.net

Abstract

In an era of rapid technological development and evolving diagnostic possibilities, the electrocardiogram (ECG) is living an authentic "renaissance" in myocardial diseases. To date, the ECG remains an irreplaceable first step when evaluating patients with hypertrophic cardiomyopathy (HCM) and an abnormal ECG may be the only manifestation of disease at an early stage. In some instances specific electrical anomalies may differentiate HCM from phenocopies such as cardiac amyloidosis and glycogen storage diseases. The exponential growth in knowledge of the complexity of HCM has led to new challenges in terms of early identification of the disease, differential diagnosis, risk stratification and development of targeted therapies. In this scenario the apparently "old fashioned" ECG and the array of ECG-based techniques, ranging from Holter monitoring and loop recorders to exercise testing, are as contemporary as ever. In the present review, we discuss the current role of the ECG in the diagnosis and management of HCM, focusing on various clinical settings where its appropriate use and interpretation can make a difference.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetically determined heart muscle disease characterized by left ventricular (LV) hypertrophy in the absence of a cardiac or systemic cause and has an estimated prevalence of 1:500(1) in the general population. Disease-causing mutations in the genes encoding structural components of the cardiac sarcomere are identified in 40 to 60% of cases. The pathological hallmarks of the disease include myocyte hypertrophy and disarray, interstitial and replacement fibrosis, small-vessel abnormalities and electrical remodelling of the cardiomyocyte. Although patients may have a normal life expectancy, a significant proportion develop HCM-related complications including heart failure, atrial fibrillation and cardioembolic stroke, while a minority exhibit life-threatening ventricular arrhythmias or die suddenly(2).

The diagnosis of HCM relies on the detection of increased LV wall thickness by imaging modalities, such as echocardiography or cardiovascular magnetic resonance (CMR). The recent technological advances in cardiovascular imaging have permeated every aspect of clinical practice, and allow a comprehensive phenotypic and functional cardiac characterization including tomographic assessment of myocardial mechanics, wall motion, chamber size and function. Emerging possibilities include tissue characterization to identify oedema, fibrosis or infiltration. In such scenarios, it is easy to consider the old-fashioned electrocardiogram (ECG) as obsolete. Far from that, the ECG remains a cornerstone in the assessment of patients with HCM. Even more, it is undergoing a "renaissance" in the field of cardiomyopathies, not only because of its inexpensive nature and wide availability, but because it provides details that are related to morphology, function and genetic substrate at

the same time. In this review, we will discuss the current role of the ECG in the diagnosis, risk stratification and management of HCM, focusing on various settings where its correct interpretation can be decisive, in an increasingly high-tech and expensive clinical arena.

Systematic ECG interpretation: a cardiomyopathy-oriented framework

Electrocardiographic interpretation requires a systematic approach that examines every aspect of the electrical activity of the heart in its clinical context, taking into consideration demographic and clinical variables such as age, gender, ethnicity, family history and genotype. Another fundamental premise is that there is a need to reconsider traditional concepts such as "hypertrophy", "Q waves" and "ischaemic abnormalities" derived from patients with hypertensive, valvular and ischaemic heart disease (Figure 1 A) and to integrate them with other, specific electrocardiographic categories belonging to a cardiomyopathy-specific mindset (Figure 1 A and B). As a normal ECG is observed only in 5 to 10% of patients with echocardiographic evidence of HCM (usually at the milder end of the clinical spectrum)(3), the 12-lead ECG is the quintessential screening tool for this disease (Table 1). While certain patterns may be highly suggestive, there is no such thing as pathognomonic ECG for HCM.

Atrial abnormalities

The atria are often dilated in HCM. Left atrial enlargement reflects diastolic dysfunction, high filling pressures, outflow obstruction and functional mitral regurgitation, and may herald progression towards the end-stage phase. Left atrial dilatation and dysfunction is *per se* a marker of adverse prognosis(4). ECG signs of left and right

enlargement and P-wave prolongation (a known predictor of atrial fibrillation - AF) may be observed in HCM patients, rarely occurring in isolation: other ECG abnormalities as repolarization changes or signs of left ventricular hypertrophy (LVH) generally concur.

Ventricular pre-excitation

Ventricular pre-excitation manifests on the 12-lead ECG with a short PR interval and a delta wave at the origin of the QRS complex(5). When this feature is associated with cardiac symptoms as palpitations, syncope or arrhythmias, it is referred to as the Wolff-Parkinson-White (WPW) syndrome. Although ventricular pre-excitation is a primary electrical disorder, it may be associated with structural heart disease, as HCM. The association of LVH, often severe, with ventricular pre-excitation should raise suspicion of a glycogen-storage disease produced by *LAMP2* or *PRKAG2* mutations, or Anderson-Fabry disease, with important therapeutic and prognostic implications both for the patient and the family members(6).

Q waves

The lack of consensus regarding the definition of a pathological Q wave, with multiple proposed diagnostic criteria, constitutes a source of confusion. Q wave duration ≥40 ms or an absolute depth of >3 mm are considered pathological criteria by some, whereas others recommend an amplitude ≥25% of the ensuing R wave(7). Early studies showed that Q waves occur most frequently in patients with an unusual pattern of ventricular hypertrophy, lacking typical asymmetric septal hypertrophy(8). In histopathologic studies, abnormal Q waves were associated with transmural myocardial fibrosis, similar to that seen in myocardial infarction(9). Koga et al.(10) performed intracoronary electrocardiograms and showed two potential mechanisms for Q waves in

patients with HCM. One reflected loss of local electrical forces due to transmural fibrosis and the other was the result of initial QRS vector abnormalities due to disproportionate hypertrophy of the basal interventricular septum and/or basal left ventricular free wall. Recent studies investigating the correlation between Q waves on the ECG and myocardial LGE at CMR have reached discordant results(11). While some suggest that late gadolinium enhancement (LGE) may indeed correlate with pathological Q waves in HCM(12), others have failed to demonstrate a significant relationship(13).

The QRS complex and ventricular hypertrophy

While increased QRS voltages are often identified in isolation in young healthy individuals, this feature is generally associated with other abnormalities in HCM. In a study by Rowin et al.(14), the ECG was abnormal in 90% of patients with HCM according to the 2010 ESC recommendations for interpretation in athletes(15) and only 2% exhibited isolated QRS voltage criteria for LV hypertrophy (Sokolow-Lyon and Cornell voltage score). These findings were confirmed in a recent study by Calore et al.(16) where the ECG was abnormal in 96% of patients with HCM and increased QRS voltages occurred in isolation in only 2%. Low limb lead voltages are defined as a QRS amplitude ≤5 mm in each of the limb leads. The combination of low voltages with significant increase in wall thickness on the echocardiogram or CMR should raise the possibility of cardiac amyloidosis(17).

Complete bundle branch block is relatively uncommon in HCM and is often secondary to invasive interventions for alleviating left ventricular outflow obstruction. Septal myectomy often results in a left and alcohol septal ablation may cause right bundle branch block(18). Left bundle branch block may also be seen in advanced stages of disease progression with extensive, often transmural anteroseptal scar(19). Lesser degrees of

intraventricular conduction delay are non-specific and may be observed in healthy individuals and athletes. Similarly, isolated axis deviation is rare in patients with HCM and should not prompt further investigations in asymptomatic individuals without a family history of cardiac disease or sudden cardiac death (SCD)(20). Fragmentation of the QRS complexes (f-QRS), defined as presence of an additional R wave (R') or notching in the nadir of the S wave, reflects intraventricular conduction delay and may be a marker of myocardial fibrosis(21). Although F-QRS have been used to predict arrhythmic events in HCM patients with implantable cardioverter defibrillators (ICDs) for primary or secondary prophylaxis(1), its prognostic role remains unclear.

Finally, although some degree of right ventricular (RV) primary or secondary involvement may be present in HCM(22), isolated voltage criteria for right ventricular hypertrophy is extremely uncommon. ECG findings suggestive of RV strain suggest rare HCM phenocopies, such as storage diseases, where RV hypertrophy may be identified by cardiac imaging.

Repolarization abnormalities

ST-T segment abnormalities are common in HCM. Deep T wave inversion (TWI) in the lateral leads is a recognized feature of apical HCM (Figure 2) and should prompt an accurate evaluation of this morphologic variant with available imaging techniques(23). In patients with HCM, TWI commonly involves the inferior and lateral leads, T waves are deep (≥-0.2 mV) and often preceded by ST segment depression (24). Both TWI and ST depression appear to be even more common in black individuals with HCM (25). Abnormalities of the ST segment are notoriously poorly predictive of epicardial coronary artery disease in HCM patients.

Isolated inferior TWI in the absence of LVH has been reported in up to 6% of healthy black athletes and 2% of white athletes(25). However, TWI in the lateral leads may pre-date the development of a full phenotypic expression of HCM in highly trained athletes(23). Therefore, clinical surveillance with annual follow-up is prudent in this context.

QTc prolongation

Significant QT prolongation (QTc > 480 ms) has been described in 1 out of 8 HCM, a prevalence that is significantly higher compared to healthy individuals(26). QTc prolongation likely reflects the interplay of cardiac hypertrophy, fibrosis and outflow tract obstruction, although electrophysiological remodelling of cardiomyocytes, characterized by marked enhancement in the late sodium current and delayed repolarization, is also considered a major determinant(26,27). Recently, QTc prolongation on baseline ECG was reported as a key clinical predictor of appropriate ICD therapies in patients with HCM(28).

The standard ECG in the diagnosis of HCM

HCM is generally diagnosed by demonstrating LVH with a wall thickness >15 mm at echocardiogram or CMR. However, this magnitude of LVH is not specific for HCM and may be secondary to various other pathological conditions. In this setting, the ECG is extremely useful in guiding the differential diagnosis between sarcomeric HCM and its phenocopies. A "red flag approach" should be part of routine assessment of patients with cardiomyopathies(29).

While Q waves with positive T waves in the same leads (Q/T discordance) and giant (>10 mm) T wave inversion in the anterolateral leads support the diagnosis of sarcomeric

HCM, short P-R and/or ventricular pre-excitation are common findings in storage diseases like glycogenosis, Danon disease (Figure 3), *PRKAG2*, and Anderson-Fabry disease, and can also be found in mitochondrial disease(29). These ECG abnormalities should be evaluated in the clinical context including inheritance pattern and specific signs and symptoms such as renal impairment, hearing impairment, diabetes, muscle weakness or mental retardation. In the long-term, storage and mitochondrial diseases may all progress to atrioventricular (AV) conduction delay and ultimately to high degree AV block; the latter is also a common complication of infiltrative disorders as cardiac amyloidosis. Storage diseases are invariably accompanied by strikingly high amplitude QRS complexes with voltage criteria for LVH with ST segment depression and T wave inversion in the lateral leads(29). Conversely, the expansion of myocardial interstitium secondary to extracellular infiltration (in conjunction with direct toxic of the myocyte by circulating precursor proteins) typically causes low QRS voltages in amyloidosis (Figure 4A). However, absolute reduction in voltage amplitude is seen in only 20% of patients with *ATTR*-amyloidosis (as compared to 60% with AL-amyloidosis) and therefore its absence does not rule out the disease. Rather, suspicion should arise in the presence of *relative* QRS voltage reduction compared to the degree of hypertrophy on echo or MRI (i.e. when electro-morphological discordance is present)(30). Low QRS voltages may be rarely seen in patients with end-stage sarcomeric HCM and represent an ominous sign of diffuse fibrosis(2) (Figure 4B).

Differential diagnosis with athlete's heart and normal variants

Long-term athletic training is associated with a series of alterations in cardiac structure, function and electrical activity that are collectively termed athlete's heart(31).

ECG changes observed in athletes often overlap with those of patients with cardiac conditions as channelopathies and cardiomyopathies including HCM. Recent international recommendations for ECG interpretation in athletes underscore which abnormalities should be considered as reflective of physiological adaptation to exercise and which instead should be regarded as highly suggestive of pathology(20). Isolated voltage criteria for LVH or left axis deviation are highly suggestive of a normal process, while repolarization abnormalities such as TWI (especially in the lateral leads) and ST depression or pathological Q waves are more likely expression of HCM. Occasionally, athletes may exhibit TWI in the absence of underlying structural disease, often creating a conundrum in differential diagnosis. Lateral TWI should always be considered pathological until proven otherwise. Notably, they may precede the full expression of HCM in otherwise healthy athletes and therefore mandate annual monitoring with echocardiogram and potentially CMR(23). TWI in leads V1-V4 is relatively common especially in black athletes commonly preceded by convex ST segment elevation (Figure 5) (32). TWI in V1-V2 may be present in up to 3-5% of white athletes and does not warrant investigation in the absence of symptoms or a relevant family history(33).

ECG changes along the natural history of HCM

HCM is associated with favourable mid-term prognosis in most patients, although various trajectories of disease progression may be observed and long-term studies are uncovering considerable late morbidity. The ECG may change significantly during this time, reflecting long-term morpho-functional evolution. In the phase of phenotypic development, commonly during adolescence, increase in QRS voltages and development of ST-segment and T-wave abnormalities may occur over a short time frame. Over following decades, the

11

most common changes are represented by the progressive evidence of left atrial enlargement and various degrees of QRS prolongation reflecting septal fibrosis and conduction tissue involvement. In the later stages, when myocardial fibrosis burden becomes significant, left bundle block may develop. Rarely, there is a decrease in the amplitude of the QRS voltages leading to a true "low-voltage pattern" in conjunction with end-stage disease, when transmural replacement fibrosis is predominant(2) (Figure 6). In a limited subset, the appearance of ST-segment elevation with negative T waves may mark the development of apical aneurysms, usually in the setting of mid-ventricular obstruction.

The standard ECG in gene carriers without LVH

Increased availability of genetic testing for HCM has led to emergence of a novel patient subset including genetically affected family members without LVH. Genotype-positive(+)-LVH-negative(-)(G+LVH-) individuals raise unresolved issues such as the optimal follow-up strategy to monitor conversion to overt HCM(1). Although no specific ECG pattern is characteristic of this status, certain ECG abnormalities may precede the development of LVH in children(34), most commonly increased precordial voltages and deep Q waves. These probably reflect microstructural rearrangement (myocardial disarray, interstitial fibrosis and microvascular remodeling) that can also precede LVH development. Hence, the ECG is more sensitive than echocardiography as a screening tool in HCM families.

The standard ECG for risk stratification and management

Despite its unquestionable use in the diagnosis of HCM and family screening, the role of the 12-lead ECG in risk stratification and management is less well established (Table 1). McLeod et al.(3) retrospectively examined the clinical phenotype and prognosis of HCM patients with a normal ECG in a cohort of 2,486 individuals. A normal tracing was identified in 6% of patients (n=135), who experienced a lower rate of cardiac-related mortality (including sudden cardiac death), compared to patients with an abnormal ECG. Montgomery et al.(35) failed to demonstrate the prognostic role of the ECG in a cohort of 448 patients with HCM. In a cohort of 245 Italian patients in which 7% exhibited a normal ECG(36) none of these patients experienced arrhythmic events or SCD, compared with 8% of patients with an abnormal tracing during a follow-up period of 8±6 years. Conversely, Sherrid et al(37) demonstrated no value for ECG abnormalities in predicting appropriate ICD intervention or SCD in a cohort of 330 patients with HCM.

Other studies have suggested correlations between various ECG parameters, phenotype and outcome in HCM. Konno et al(38) found low ECG voltages to be predictive of myocardial fibrosis on CMR. Delcrè et al(11) observed the number and severity of ECG changes to be directly related to phenotypic expression on CMR. Biagini et al(39) found an independent predictive value between certain ECG changes, including low QRS voltage, increased QRS duration and a "pseudo-ST-segment elevation myocardial infarction" pattern and SCD in HCM. Östman-Smith et al(40) assessed ECG patterns as predictors of SCD in 116 adult HCM patients, finding a correlation between cardiac arrest and TWI, ST-segment depression and a dominant S-wave in V4. They proposed an ECG risk score based on these parameters, combined with QRS amplitude and QTc measurements. Conflicting results from all these studies suggest that larger, multicenter studies with substantial follow up analysis

are required to assess the prognostic role of ECG patterns in HCM. Currently , no pattern alone or in combination can be used for clinical decision-making regarding prognosis or therapy with the exception of potential reassurance for patients with normal tracings.

Last but not least, the role of serial ECG testing in clinical practice is instrumental in considering cardiac resynchronization therapy in highly symptomatic individuals with wide QRS complexes who are in the end-stage phase of the disease(2) and in monitoring of the QTc in HCM patients taking QT-prolonging drugs such as disopyramide or amiodarone.

ECG-based techniques

ECG-based investigations such as 24-48 hour Holter monitoring and exercise tolerance test are widely used in the assessment of patients with HCM and for risk stratification and clinical management. Holter monitoring is indicated to assess supraventricular and ventricular arrhythmic burden, but may also prove useful for identifying bradyarrhythmias (e.g. in patients with history of syncope) and signs of microvascular ischemia.

AF is the most common arrhythmia in patients with HCM and a main predictor of heart failure-related mortality. AF is four- to six fold more common in HCM than in similarly aged individuals in the general population, with an incidence from 2 to 5% per year and a prevalence that ranges from 18% to 28%(41). However, its true prevalence is difficult to evaluate because of frequent silent occurrences. Detection of clinically silent AF, identified only by extended periods of monitoring, raises important implications for treatment strategy and stroke prophylaxis, as HCM patients with AF have 8 time greater risk of ischemic stroke compared with those in sinus rhythm[3,8]. Cardiac rhythm monitoring devices

like implantable cardioverter defibrillator (ICD), 24-hour Holter monitoring or loop recorder are useful in this context(42).

Non-sustained ventricular tachycardia (NSVT), defined as three or more consecutive ventricular beats at a rate of greater than 100 beats/min with a duration of less than 30 seconds, is detected in up to 54% of patients with HCM(1). A number of studies have reported an association between NSVT and risk of SCD in patients with HCM(43,44). NSVT is included both in the ESC and AHA/ACC guidelines among the risk factors that should be considered in primary prevention of SCD.

ST-T segment depression may be detected frequently at Holter monitoring in patients with HCM, but has not been consistently linked with chest pain or perfusion abnormalities on SPECT imaging(45). The exercise tolerance test provides important information regarding functional capacity, investigation of symptoms and risk stratification. Exercise-induced arrhythmias and blunted blood pressure response predict risk for SCD especially in adults aged ≤ 40 years-old. Exercise may be helpful in unmasking microvascular ischemia by showing ST-segment depression (18).

Finally, exercise testing and Holter monitoring may be instrumental to diagnosing chronotropic incompetence which is present in up to 25% of patients with HCM(4). Chronotropic incompetence is likely multifactorial, including excessive doses of AV node blocking drugs. Autonomic dysfunction is frequent amongst patients with HCM and linked to the high prevalence of abnormal sinus-node function and His–Purkinje conduction in up to 2/3 of HCM patients undergoing electrophysiological study(46). Deranged autoregulation of the microvascular myocardial network may also play a role in abnormal chronotropic response(46).

Novel personal ECG devices

A wide range of novel personal portable devices have been developed recently with the aim of providing continuous patient monitoring. Smartphone technologies generally involve a single-lead ECG obtained on a small device that communicates with a smartphone. Various companies currently offer different versions of the smartphone ECG that generally operate using a similar principle of a collection device, consisting of two to six electrodes, and an application on a smartphone that processes data(47). The use of these affordable and easy-to-use technologies has not been established in HCM, but there is a potential for employing them for widespread screening in otherwise healthy individuals or for tele-monitoring of patients with an established diagnosis.

The ECG in the choice of the implantable cardioverter defibrillator

HCM patients at risk of SCD may require primary prophylaxis with an implantable cardioverter defibrillator (ICD)(1). However, in young individuals , the benefit of ICD protection must be weighed against the considerable likelihood of long-term device-related complications(48). The subcutaneous ICD (S-ICD) represents an advantageous alternative in this setting, avoiding intravascular leads related complications(49), as reflected in the IDE study and EFFORTLESS registry(50,51). The S-ICD continuously senses the surface ECG with a morphology-based rhythm discrimination algorithm and QRS complexes and T wave abnormalities – frequently observed in HCM - can cause sensing issues resulting in inappropriate shocks. In order to avoid these complications, ECG vector screening protocols using unconventional leads have been implemented to exclude patients with unsuitable ECG morphologies. Based on this strategy, from 11 to 16% of patients with HCM are not eligible

for S-ICD implantation- a greater proportion compared to other cardiac diseases, largely due to marked T wave inversion with ST-T segment depression, an R/T wave amplitude <3 and large amplitude of QRS complexes (52–54). These screening failure rates could be reduced by the development of novel interpretation algorithms.

Conclusions

The ECG remains a cornerstone in the diagnosis and management of patients with HCM (Figure 7). Despite the recent exponential development of imaging techniques, a learned interpretation of the ECG provides invaluable clues in the early identification of the disease, the differential diagnosis with other cause of LVH or with physiological adaptation in highly trained athletes and detection of features that may suggest a high risk of adverse outcomes. A combined assessment of the ECG with the most advanced imaging techniques is particularly useful in clinical practice, contributing to the enduring youth of this ancient instrument as cardiovascular medicine evolves.

REFERENCES:

1. Authors/Task Force members., Elliott PM., Anastasakis A., et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35(39):2733–79. Doi: 10.1093/eurheartj/ehu284.

2. Olivotto I., Cecchi F., Poggesi C., Yacoub MH. Patterns of Disease Progression in Hypertrophic Cardiomyopathy: An Individualized Approach to Clinical Staging. Circ Hear Fail 2012;5(4):535–46. Doi: 10.1161/CIRCHEARTFAILURE.112.967026.

3. McLeod CJ., Ackerman MJ., Nishimura R, Tajik a. J., Gersh BJ., Ommen SR. Outcome of Patients With Hypertrophic Cardiomyopathy and a Normal Electrocardiogram. J Am Coll Cardiol 2009;54(3):229–33. Doi: 10.1016/j.jacc.2009.02.071.

4. Finocchiaro G., Haddad F., Knowles JW., et al. Cardiopulmonary responses and prognosis in hypertrophic cardiomyopathy: a potential role for comprehensive noninvasive hemodynamic assessment. JACC Heart Fail 2015;3(5):408–18. Doi: 10.1016/j.jchf.2014.11.011.

5. Levitin DJ., Created B., Nature H. ScienceDirect Wolff – Parkinson – White syndrome (WPW) and athletes : Darwin at play ? 2015;48:356–61.

6. Maron BJ., Maron MS., Semsarian C. Genetics of Hypertrophic Cardiomyopathy After 20 Years. J Am Coll Cardiol 2012;60(8):705–15. Doi: 10.1016/j.jacc.2012.02.068.

7. Sharma S., Drezner JA., Baggish A., et al. International recommendations for

electrocardiographic interpretation in athletes. Eur Heart J 2017. Doi: 10.1093/eurheartj/ehw631.

8. Maron BJ., Wolfson JK., Ciró E., Spirito P. Relation of electrocardiographic abnormalities and patterns of left ventricular hypertrophy identified by 2-dimensional echocardiography in patients with hypertrophic cardiomyopathy. Am J Cardiol 1983;51(1):189–94.

9. Maron BJ., Epstein SE., Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. Am J Cardiol 1979;43(6):1086–102.

10. Koga Y., Yamaga A., Hiyamuta K., Ikeda H., Toshima H. Mechanisms of abnormal Q waves in hypertrophic cardiomyopathy assessed by intracoronary electrocardiography. J Cardiovasc Electrophysiol 2004;15(12):1402–8. Doi: 10.1046/j.1540-8167.2004.04314.x.

11. Delcrè SDL., Di Donna P., Leuzzi S., et al. Relationship of ECG findings to phenotypic expression in patients with hypertrophic cardiomyopathy: a cardiac magnetic resonance study. Int J Cardiol 2013;167(3):1038–45. Doi: 10.1016/j.ijcard.2012.03.074.

12. Maron MS. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2012;14:13. Doi: 10.1186/1532-429X-14-13.

13. Papavassiliu T., Flüchter S., Haghi D., et al. Extent of myocardial hyperenhancement on late gadolinium-enhanced cardiovascular magnetic resonance correlates with q

waves in hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2007;9(3):595–603. Doi: 10.1080/10976640600945465.

14.   Rowin EJ., Maron BJ., Appelbaum E., et al. Significance of false negative electrocardiograms in preparticipation screening of athletes for hypertrophic cardiomyopathy. Am J Cardiol 2012;110(7):1027–32. Doi: 10.1016/j.amjcard.2012.05.035.

15.   Corrado D., Pelliccia A., Heidbuchel H., et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. Eur Heart J 2010;31(2):243–59. Doi: 10.1093/eurheartj/ehp473.

16.   Calore C., Melacini P., Pelliccia A., et al. Prevalence and clinical meaning of isolated increase of QRS voltages in hypertrophic cardiomyopathy versus athlete's heart: relevance to athletic screening. Int J Cardiol 2013;168(4):4494–7. Doi: 10.1016/j.ijcard.2013.06.123.

17.   Finocchiaro G., Pinamonti B., Merlo M., et al. Focus on cardiac amyloidosis : a single-center experience with a long-term follow-up 2009. Doi: 10.2459/JCM.0b013e3283536534.

18.   Maron BJ., Maron MS., Wigle ED., Braunwald E. The 50-Year History, Controversy, and Clinical Implications of Left Ventricular Outflow Tract Obstruction in Hypertrophic Cardiomyopathy. From Idiopathic Hypertrophic Subaortic Stenosis to Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2009;54(3):191–200. Doi: 10.1016/j.jacc.2008.11.069.

19.   Cappelli F., Morini S., Pieragnoli P., et al. Cardiac Resynchronization Therapy for End-

Stage Hypertrophic Cardiomyopathy: The Need for Disease-Specific Criteria. J Am Coll Cardiol 2018;71(4):464–6. Doi: 10.1016/j.jacc.2017.11.040.

20.   Sharma S., Drezner JA., Baggish A., et al. International Recommendations for Electrocardiographic Interpretation in Athletes. J Am Coll Cardiol 2017;69(8):1057–75. Doi: 10.1016/j.jacc.2017.01.015.

21.   Pietrasik G., Zaręba W. QRS fragmentation: diagnostic and prognostic significance. Cardiol J 2012;19(2):114–21.

22.   Finocchiaro G., Knowles JW., Pavlovic A., et al. Prevalence and Clinical Correlates of Right Ventricular Dysfunction in Patients With Hypertrophic Cardiomyopathy. Am J Cardiol 2013. Doi: 10.1016/j.amjcard.2013.09.045.

23.   Pelliccia A., Di Paolo FM., Quattrini FM., et al. Outcomes in athletes with marked ECG repolarization abnormalities. N Engl J Med 2008;358(2):152–61. Doi: 10.1056/NEJMoa060781.

24.   Sheikh N., Papadakis M., Panoulas VF., et al. Comparison of hypertrophic cardiomyopathy in Afro-Caribbean versus white patients in the UK. Heart 2016. Doi: 10.1136/heartjnl-2016-309843.

25.   Papadakis M., Carre F., Kervio G., et al. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. Eur Heart J 2011;32(18):2304–13. Doi: 10.1093/eurheartj/ehr140.

26.   Johnson JN., Grifoni C., Bos JM., et al. Prevalence and clinical correlates of QT prolongation in patients with hypertrophic cardiomyopathy. Eur Heart J

2011;32(9):1114–20. Doi: 10.1093/eurheartj/ehr021.

27. Coppini R., Ferrantini C., Yao L., et al. Late Sodium Current Inhibition Reverses Electromechanical Dysfunction in Human Hypertrophic Cardiomyopathy. Circulation 2013;127(5):575–84. Doi: 10.1161/CIRCULATIONAHA.112.134932.

28. Gray B., Ingles J., Medi C., Semsarian C. Prolongation of the QTc interval predicts appropriate implantable cardioverter-defibrillator therapies in hypertrophic cardiomyopathy. JACC Heart Fail 2013;1(2):149–55. Doi: 10.1016/j.jchf.2013.01.004.

29. Rapezzi C., Arbustini E., Caforio ALP., et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34(19):1448–58. Doi: 10.1093/eurheartj/ehs397.

30. Rapezzi C., Lorenzini M., Longhi S., et al. Cardiac amyloidosis: the great pretender. Heart Fail Rev 2015;20(2):117–24. Doi: 10.1007/s10741-015-9480-0.

31. Sharma S., Merghani A., Mont L. Exercise and the heart: the good, the bad, and the ugly. Eur Heart J 2015;36(23):1445–53. Doi: 10.1093/eurheartj/ehv090.

32. Papadakis M., Carre F., Kervio G., et al. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. Eur Heart J 2011;32(18):2304–13. Doi: 10.1093/eurheartj/ehr140.

33. Wilson MG., Sharma S., Carre F., et al. Significance of deep T-wave inversions in asymptomatic athletes with normal cardiovascular examinations: practical solutions for managing the diagnostic conundrum. Br J Sports Med 2012;46(Suppl_1):i51–8.

Doi: 10.1136/bjsports-2011-090838.

34. Panza JA., Maron BJ. Relation of electrocardiographic abnormalities to evolving left ventricular hypertrophy in hypertrophic cardiomyopathy during childhood. Am J Cardiol 1989;63(17):1258–65.

35. Montgomery J V., Harris KM., Casey SA., Zenovich AG., Maron BJ. Relation of electrocardiographic patterns to phenotypic expression and clinical outcome in hypertrophic cardiomyopathy. Am J Cardiol 2005;96(2):270–5. Doi: 10.1016/j.amjcard.2005.03.058.

36. Calore C., Cianfrocca C., Iacovella I., et al. Hypertrophic Cardiomyopathy with Normal ECG: Clinical Meaning and Prognostic Implications. Circulation 2018;124:A15703.

37. Sherrid M V., Cotiga D., Hart D., et al. Relation of 12-Lead Electrocardiogram Patterns to Implanted Defibrillator-Terminated Ventricular Tachyarrhythmias in Hypertrophic Cardiomyopathy. Am J Cardiol 2009;104(12):1722–6. Doi: 10.1016/j.amjcard.2009.07.056.

38. Konno T., Nagata Y., Teramoto R., et al. Usefulness of Electrocardiographic Voltage to Determine Myocardial Fibrosis in Hypertrophic Cardiomyopathy. Am J Cardiol 2016;117(3):443–9. Doi: 10.1016/j.amjcard.2015.11.015.

39. Biagini E., Pazzi C., Olivotto I., et al. Usefulness of Electrocardiographic Patterns at Presentation to Predict Long-term Risk of Cardiac Death in Patients With Hypertrophic Cardiomyopathy. Am J Cardiol 2016;118(3):432–9. Doi: 10.1016/j.amjcard.2016.05.023.

40. Östman-Smith I., Wisten A., Nylander E., et al. Electrocardiographic amplitudes: A

new risk factor for sudden death in hypertrophic cardiomyopathy. Eur Heart J 2010;31(4):439–49. Doi: 10.1093/eurheartj/ehp443.

41. Rowin EJ., Hausvater A., Link MS., et al. Clinical Profile and Consequences of Atrial Fibrillation in Hypertrophic Cardiomyopathy. Circulation 2017;136(25):2420–36. Doi: 10.1161/CIRCULATIONAHA.117.029267.

42. Adabag AS., Casey SA., Kuskowski MA., Zenovich AG., Maron BJ. Spectrum and prognostic significance of arrhythmias on ambulatory Holter electrocardiogram in hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;45(5):697–704. Doi: 10.1016/j.jacc.2004.11.043.

43. Maron BJ., Savage DD., Wolfson JK., Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol 1981;48(2):252–7.

44. Elliott PM., Poloniecki J., Dickie S., et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000;36(7):2212–8.

45. Elliott PM., Kaski JC., Prasad K., et al. Chest pain during daily life in patients with hypertrophic cardiomyopathy: an ambulatory electrocardiographic study. Eur Heart J 1996;17(7):1056–64.

46. Efthimiadis GK., Giannakoulas G., Parcharidou DG., et al. Chronotropic incompetence and its relation to exercise intolerance in hypertrophic cardiomyopathy. Int J Cardiol 2011;153(2):179–84. Doi: 10.1016/j.ijcard.2010.08.026.

47. Maurizi N., Faragli A., Imberti J., et al. Cardiovascular screening in low-income settings

using a novel 4-lead smartphone-based electrocardiograph (D-Heart®). Int J Cardiol 2017;236:249–52. Doi: 10.1016/j.ijcard.2017.02.027.

48.   Maron BJ., Casey SA., Olivotto I., et al. Clinical Course and Quality of Life in High-Risk Patients With Hypertrophic Cardiomyopathy and Implantable Cardioverter-Defibrillators. Circ Arrhythm Electrophysiol 2018;11(4):e005820. Doi: 10.1161/CIRCEP.117.005820.

49.   Bardy GH., Smith WM., Hood MA., et al. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med 2010;363(1):36–44. Doi: 10.1056/NEJMoa0909545.

50.   Burke MC., Gold MR., Knight BP., et al. Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator: 2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry. J Am Coll Cardiol 2015;65(16):1605–15. Doi: 10.1016/j.jacc.2015.02.047.

51.   Lambiase PD., Gold MR., Hood M., et al. Evaluation of subcutaneous ICD early performance in hypertrophic cardiomyopathy from the pooled EFFORTLESS and IDE cohorts. Hear Rhythm 2016;13(5):1066–74. Doi: 10.1016/j.hrthm.2016.01.001.

52.   Maurizi N., Olivotto I., Olde Nordkamp LRA., et al. Prevalence of subcutaneous implantable cardioverter-defibrillator candidacy based on template ECG screening in patients with hypertrophic cardiomyopathy. Hear Rhythm 2016;13(2):457–63. Doi: 10.1016/j.hrthm.2015.09.007.

53.   Francia P., Adduci C., Palano F., et al. Eligibility for the Subcutaneous Implantable Cardioverter-Defibrillator in Patients With Hypertrophic Cardiomyopathy. J

Cardiovasc Electrophysiol 2015;26(8):893–9. Doi: 10.1111/jce.12714.

54.	Srinivasan NT., Patel KH., Qamar K., et al. Disease Severity and Exercise Testing Reduce Subcutaneous Implantable Cardioverter-Defibrillator Left Sternal ECG Screening Success in Hypertrophic Cardiomyopathy. Circ Arrhythm Electrophysiol 2017;10(4). Doi: 10.1161/CIRCEP.117.004801.

Tables 1. Prevalence of ECG abnormalities in HCM and prognostic role of the ECG in patients with HCM.

Study	n	% abnormal ECG	Main abnormalities	(%)
Rowin et al.(14)	114	90	Non-voltage criteria for LV hypertrophy	54
			Isolated Sokolow-Lyon criteria for LVH	1
			Isolated Cornell criteria for LVH	1
			Pathologic Q waves	43
			ST-segment depression or elevation	25
			T-wave inversion	56
Calore et al.(16)	247	96	Isolated Sokolow-Lyon criteria for LVH	2
			ST-T alterations	82
			Pathologic Q waves	35
			T wave inversion	50
McLeod et al.(3)	2485	94	/	
Delcre' et al.(11)	257	94	Romhilt-Estes criteria for LVH ≥ 5	60
			ST segment depression	7
			T wave inversion	18
			Pathological Q waves	53
			ST convex segment elevation≥2 mm in V1-V2 leads	36
Sheikh et al.(24)	425	93	Sokolow-Lyon voltage criteria for LVH	43
			ST-segment depression	49
			ST-segment elevation	44
			T wave inversion in the lateral leads	73
			Pathologic Q waves	18
Montgomery et al. (35)	448	96	Romhilt-Estes (≥ 4 points)	53
			Cornell voltage score	41
			LVH with strain	37

Study	n	Outcome	Main ECG predictors
Biagini et al.(39)	1004	Sudden death/ICD discharge	QRS duration > 120 msec (HR: 1.78 (1.05 - 3.03))
			Low QRS voltages (HR: 2.26 (1.01 - 5.07))
			"Pseudo STEMI"pattern (HR: 2.28 (1.38 - 3.77))
Östman-Smith et al.(40)	116	Cardiac arrest	Pathological T-wave inversion precordial leads
			ST-segment depression > 2 mm
			Dominant S in V4
			Limb-lead QRS-amplitude sum ≥ 12 mV
			12-lead amplitude–duration product ≥ 2.5 mV
Mcleod et al. (3)	2485	Mortality	Abnormal ECG
Mongomery et al.(35)	448	Mortality	Abnormal delayed precordial R-wave progression

Abbreviations: TWI: T wave inversion.

FIGURE LEGENDS:

Figure 1. The interpretation of standard ECG in HCM must necessarily reconsider traditional concepts such as "hypertrophy", "necrotic waves" and "ischaemic abnormalities" derived from patients with hypertensive, valvular and ischaemic heart disease (A) and integrate them with other specific ECG categories within a cardiomyopathy-specific mindset (B).

Figure 2. Giant T waves inversion in a patient with apical HCM. The CMR images show significant apical LVH in the end-diastolic frame (left), apical obliteration in the end-systolic farme (center) and apical late gadolinium enhancement (right).

Figure 3. Short PR and pre-excitation in a patient with Danon disease.

Figure 4. A: Low QRS voltages and pseudo-necrosis pattern in V1-V4 in a patient affected by cardiac amyloidosis. The CMR shows a concentric increase of the LV wall thickening (left) and typical LGE pattern at the short axis (center) and 4 chamber view (right) with difficulty in nulling of myocardial signal on the LGE images. B: Low QRS voltages suggesting high fibrosis burden in "end-stage" HCM The CMR shows mild LVH on the 4 chamber and short axis cine images (left) and diffuse LGE pattern (right).

Figure 5. ECG of a 32 year-old athlete of Afro-Caribbean descent. Note the anterior (V1-V4) T wave inversion accompanied by J point and ST elevation with superior concavity. This pattern is recognized as physiological in black athletes and not suggestive of pathological hypertrophy.
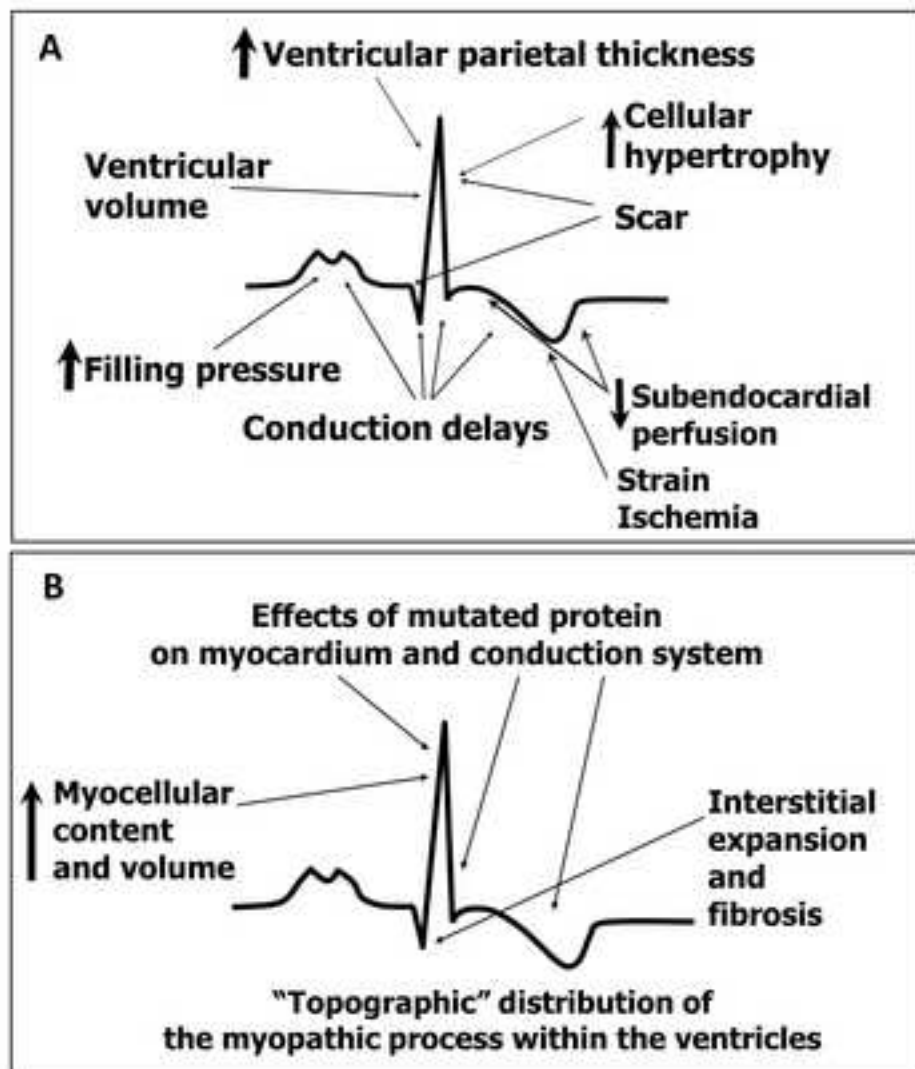
Figure 6. Patient with MYH7 mutation and paediatric onset hypertrophic cardiomyopathy. The patient was transplanted due to repetitive arrhythmias not amenable to treatment

(slow VT below optimal defibrillation threshold). The patient showed evidence of microvascular ischemia during relative tachycardia on Holter monitoring (arrows) (A) and received multiple ICD shocks due to ischemia-induced VT/VF(B). Histological examination of the heart showed severe LVH, diffuse fibrosis and microvascular remodelling (C). Pathology images courtesy of Ornella Leone.

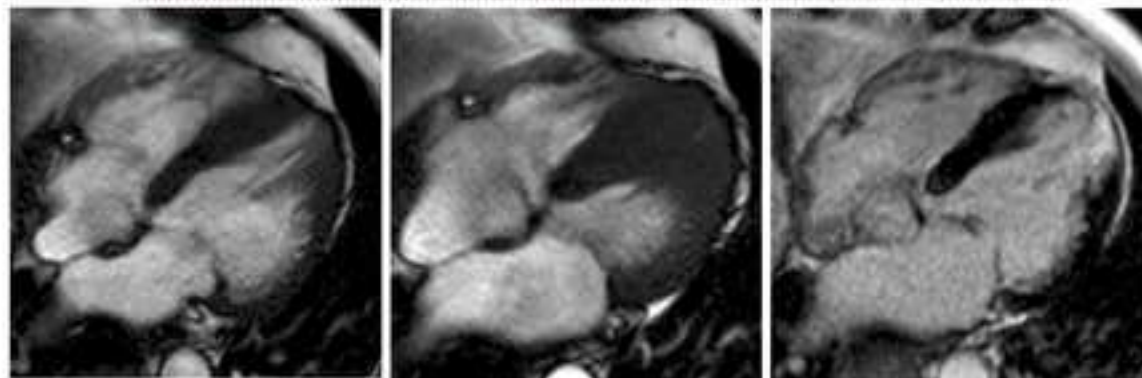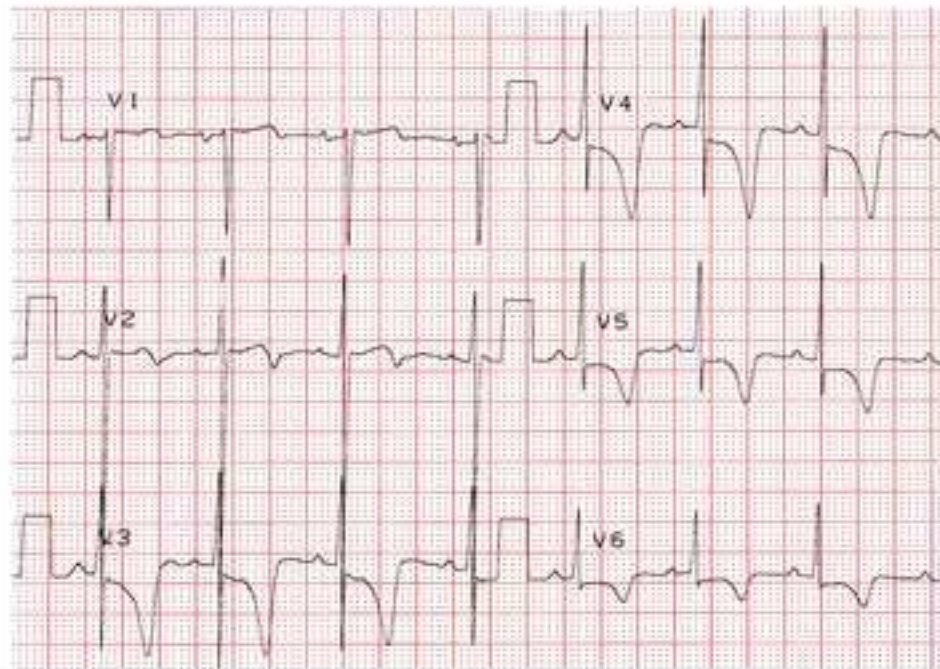**Figure 7**. Summary of the role of ECG in the diagnosis and management of HCM.

Figure

A

↑Ventricular parietal thickness

↑Cellular hypertrophy

Ventricular volume

Scar

↑Filling pressure

Conduction delays

↓Subendocardial perfusion

Strain Ischemia

B

Effects of mutated protein on myocardium and conduction system

↑Myocellular content and volume

Interstitial expansion and fibrosis

"Topographic" distribution of the myopathic process within the ventricles