

Hypertrophic cardiomyopathy; main ECG/VCG features and Cardiovascular Magnetic Resonance Image

Andrés Ricardo Pérez-Riera MD PhD & Raimundo Barbosa-Barros MD

Hypertrophic cardiomyopathy(HCM) is defined clinically as unexplained hypertrophy of the left ventricle (**Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997; 336:775–785.**) The hypertrophy is most commonly asymmetric and involves the interventricular septum.

Prevalence 1:500 in the general population. Most HCM is familial. Systemic evaluation of first-degree relatives has revealed that HCM is familial in over 90% of cases. The pattern of inheritance is autosomal-dominant; thus, each child has a 50% chance of inheriting the gene. Major advances in mutation identification have been achieved over the last decade in family screening programs. HCM is caused by mutations in genes for cardiac sarcomeric contractile proteins (**Mogensen J, Klausen I, Pedersen A, et al. Alpha-cardiac actin is a novel disease gene in familial HCM. J Clin Invest 1999; 103: r39–r43.**). In adult disease, disease-causing mutations have been identified in the genes for 10 proteins, including β -myosin heavy-chain, essential and regulatory myosin light-chain, α -tropomyosin, cardiac troponin T, troponin I, myosin-binding protein C, and actin. Rarer mutations in α -myosin, troponin C, and titin have also been described. To date, more than 200 different mutations have been reported since the first genetic mutation was identified in 1989; many of them are private mutations confined to the proband and immediate family. About 10% of cases seem to be nonfamilial (sporadic) but are also caused mostly by sarcomeric protein gene mutations (usually new or “de novo” mutations). β -myosin heavy-chain genetic mutations account for about 40% of adult cases, with more than 50 different mutations described. Cardiac myosin-binding protein C mutations occur in about 30% to 40%, especially in patients with late-onset HCM, in whom ECG or ECHO features of HCM may not always appear before the age of 40. The other mutations each account for 1% to 15% of adult cases.

The diagnosis of HCM in an infant has different genetic implications than in an adult, and storage disorders and metabolic defects predominate in childhood HCM. These are genetic defects but are usually recessive.

Presenting symptoms can include chest pain, palpitations, or syncope, but the disease can also be asymptomatic and discovered as a result of an incidental finding such as a murmur, eg, during a medical examination for insurance coverage or during clinical evaluation of a family. HCM It is a genetic paradigm of cardiac hypertrophy. Cardiac hypertrophy and interstitial fibrosis are important risk factors for sudden cardiac death (SCD) and morbidity in HCM. The entity is characterized by substantial genetic and phenotypic heterogeneity, leading to considerable diversity in clinical course including the most common cause of SCD among young athletes and in young people and a determinant of heart failure symptoms in patients of any age. Oxidative stress is implicated in the pathogenesis of cardiac hypertrophy and fibrosis.

HCM is characterized by marked myocardial thickening predominantly affecting the interventricular septum and/or the apex of the LV. ECG evidence of LVH is found in 50% of patients. A characteristic abnormality is the presence of abnormal Q waves in the anterolateral or inferior chest leads, which may mimic the appearance of myocardial infarction. As the LV becomes increasingly less compliant, there is increasing resistance to atrial contraction, and signs of left atrial enlargement are commonly seen. Atrial fibrillation and supraventricular tachycardias are common. Ventricular tachycardias may also occur and are a cause of sudden death.

Main electrocardiographic changes associated with HCM

I. P-wave:

Left atrial enlargement: Patients with HCM and impaired LV relaxation develop progressive LAE and P wave modifications. This ECG feature is observed in approximately 20% of cases as a consequence of augmentation of left ventricle (LV) end diastolic pressure and diminution of LV compliance (Savage 1978). Impaired relaxation in HCM results in a reduced rate and volume of filling during the rapid filling

period of diastole, with a resultant compensatory increase in atrial systolic filling, which results in a loud and often palpable fourth heart sound. In LAE, the P wave of increased duration is ≥ 110 ms in adults, ≥ 120 ms in seniors, and 90 ms in children. Chronic LAE can produce AF eventually in its evolution, which results in severe hemodynamic deterioration because of the importance of atrial systole in the presence of the impaired relaxation (Wigle 1985). Biatrial enlargement (BAE) is observed in the dilated phase with right ventricular heart failure (**Biolato M, Montalto M, Sestito A, Gallo A, Grieco A. ECG signs of biatrial enlargement in a young adult. Intern Emerg Med. 2010 Oct; 5: 441-442**). Asymmetric septal hypertrophy is a common cause of LVOTO. In these cases, mitral valve regurgitation is present in 30% of those patients as well as BAE (**Opfermann UT, Doll N, Walther T, Mohr FW. Combined mitral valve repair, LVOT myectomy and left atrial cryoablation therapy. Interact Cardiovasc Thorac Surg. 2003 Dec; 2: 501-502.**). Right atrial enlargement (RAE) is observed in the so-called Bernheim's syndrome characterized by right ventricular hypertrophic cardiomyopathy leading to right ventricular outflow tract dynamic obstruction by right eccentric hypertrophy of the right side of ventricular septum (**Sanen FJ. Stenosis of the right ventricle caused by excentric hypertrophy of the left ventricle or ventricular septum (Bernheim's syndrome). Z Kreislaufforsch. 1960 Apr; 49: 331-336.**

Sanen 1960).

II. PR or PQ interval duration

In HCM it is possible to observe normal, short and prolonged PR interval, AV blocks of different degrees and even total AV block. PRKAG2 mutations are responsible for a diverse phenotype such as HCM, familial occurrence of right bundle branch block (RBBB), sinus bradycardia and the familial forms of the WPW syndrome. A short PR interval should raise suspicion of a mutant PRKAG2 gene (**MacAlpin RN. The fragmented QRS: does it really indicate a ventricular abnormality? J Cardiovasc Med (Hagerstown). 2010 Nov; 11: 801-9.**). Additionally, the possibility of Anderson-Fabry's disease (Chen 1979), a sex linked recessive entity, should be considered in patients with cardiomegaly of unknown cause and the following ECG abnormalities: PR interval ≤ 120 ms without δ wave, high voltage QRS complexes in the left precordial

leads, prolonged QRS interval, giant negative T waves suggestive of Ap-HCM, supraventricular and ventricular arrhythmias, concentric LVH without subaortic obstruction. Anderson-Fabry's disease is a relatively prevalent cause of LVH mimicking HCM. In this entity the 12-lead ECG amplitude/duration product is the most successful at describing the severity of cardiac involvement (**Pérez Riera AR, Ferreira C, Ferreira Filho C, et al. Electrovectorcardiographic diagnosis of left septal fascicular block: anatomic and clinical considerations. Ann Noninvasive Electrocardiol. 2011 Apr; 16:196-207.**)

Cornell voltage-duration product ($RaVL + SV3$ with 6 mm added in women \times QRS duration). Values ≥ 2440 mm/ms are diagnostic of LVH (Positive criteria of LVH CP ≥ 2440 mm \times ms). The Cornell product is a useful ECG marker, reflecting left ventricular mass (**Haghjoo M, Mohammadzadeh S, Taherpour M, et al. ST-segment depression as a risk factor in hypertrophic cardiomyopathy. Europace. 2009 May; 11: 643-9.**)

QRS duration is an independent ECG predictor of the presence of LVH, and the simple product of either Cornell voltage or 12-lead voltage and QRS duration significantly improves identification of LVH relative to other ECG criteria that use QRS duration and voltages in linear combinations (**Migliore F, Zorzi A, Michieli P, et al. Prevalence of Cardiomyopathy in Italian Asymptomatic Children with Electrocardiographic T-Wave Inversion at Pre-Participation Screening. Circulation. 2012 Jan 24;125(3): 529-38.; Maron BJ. Distinguishing hypertrophic cardiomyopathy from athlete's heart physiological remodelling: clinical significance, diagnostic strategies and implications for preparticipation screening. Br J Sports Med.2009 Sep; 43: 649-656.**)

Namdar et al (**Namdar M, Steffel J, Jetzer S, et al. Value of Electrocardiogram in the Differentiation of Hypertensive Heart Disease, Hypertrophic Cardiomyopathy, Aortic Stenosis, Amyloidosis, and Fabry Disease. Am J Cardiol. 2012;109(4):587-93**) demonstrated that a corrected QT interval duration < 440 ms in combination with a PQ interval minus P wave duration in lead II < 40 ms was 100% sensitive and 99% specific for the diagnosis of Anderson-Fabry's disease, whereas a corrected QT duration > 440 ms and a Sokolow-Lyon index ≤ 1.5 mV were found to have a sensitivity and specificity of 85% and 100%, respectively, for the diagnosis of amyloidosis and differentiation from NOHCM, aortic stenosis, and

hypertensive heart disease. The incidence of Anderson-Fabry's disease in the US is 1 in 40000. It is an X-linked lysosomal storage disorder caused by mutations of the α -galactosidase A gene, and progressive intracellular accumulation of globotriaosylceramide. Hemizygous men and heterozygous women can develop cardiac disease. Whereas men experience the most severe clinical phenotype, clinical presentation in women varies from asymptomatic to severely symptomatic and the genetic testing is the gold standard for the diagnosis (**Gambarin FI, Disabella E, Narula J, et al. When should cardiologists suspect Anderson-Fabry disease? Am J Cardiol. 2010 Nov 15; 106:1492-1499.**).

IV) QRS axis or SÂQRS

The QRS axis located between 0° and $+90^\circ$ is the rule in NOHCM forms. SÂQRS between 0° and -90° is observed in 30% of cases.

Left anterior fascicular block (LAFB) and extreme left QRS axis deviation is eventually observed after percutaneous septal ethanol ablation in association with complete RBBB pattern.

Rarely, QRS axis is perpendicular to frontal plane in HCM. In this circumstance, isodiphasic QRS complexes are observed in this plane (Kilicaslan 2007).

V) QRS complexes

LVH systolic or strain pattern is characteristic in patients with HCM. Additionally, the QRS/ST/T angle is wide, near 180° .

The terms systolic and diastolic LVH are used in electrovectorcardiography.

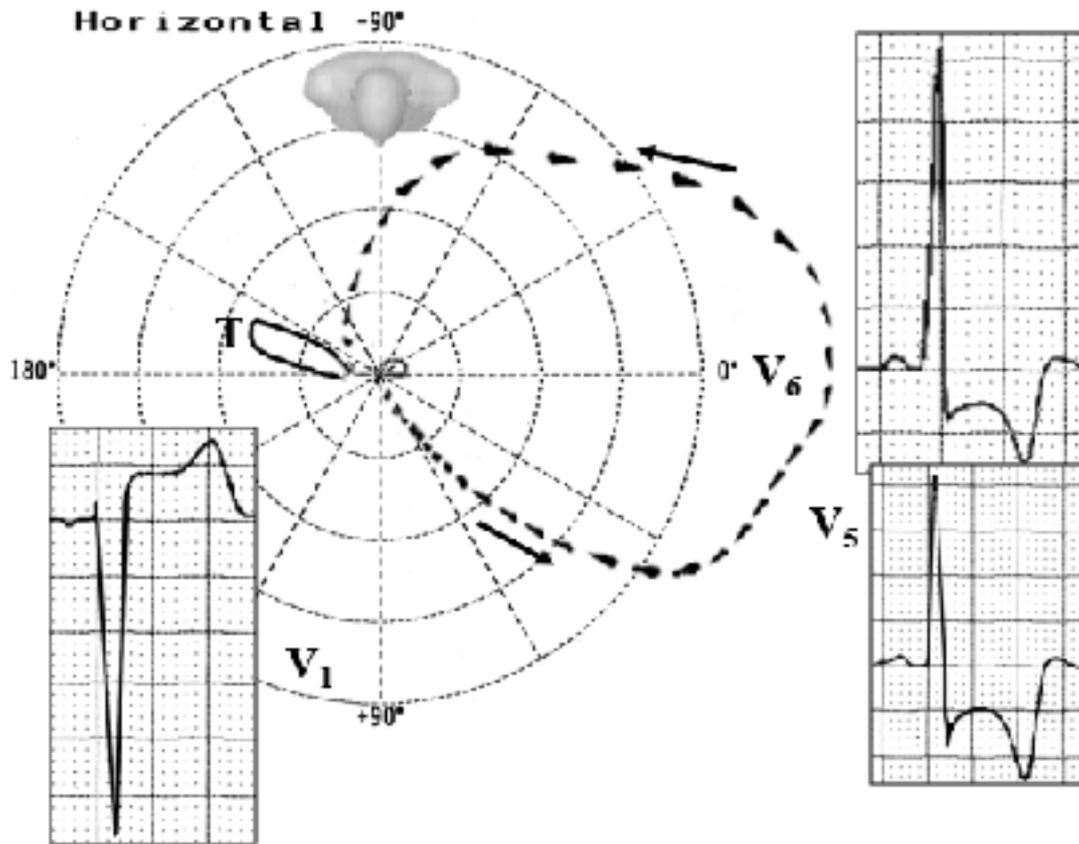
Electrocardiogram features in Apical Hypertrophic cardiomyopathy(ApCM)

- Giant negative T waves in the precordial ECG leads: Giant negative T waves negativity ≥ 1.0 mV (10 mm). Giant negative T waves are more common in Japanese patients than in American patients: 15% in Japan vs. 3% in the US (Kitaoka 2003). The significant posterior and rightward shift of the ST/T vector is responsible for the characteristic giant negative T wave (>10 mm) in the leads of the horizontal plane from V2 to V5. T waves at the onset, may not present a significant voltage and may appear later with the evolution of the disease (**Bielli M, Parravicini U, Zanetta M, Zenone F.** [Apical hypertrophic cardiomyopathy: description of a case in advanced age with documentation of electrocardiographic course. *G Ital Cardiol.* 1991;21(12):1325-9.).
- The depth of negative T waves is related to craniocaudal asymmetry and apical late enhancement (**Dumont CA, Monserrat L, Soler R, et al.** Interpretation of electrocardiographic abnormalities in hypertrophic cardiomyopathy with cardiac magnetic resonance. *Eur Heart J.* 2006;27(14):1725-31.).
- Stress test may decrease the depth of T waves (**Tilmant PY, Lablanche JM, Laurent JM, Héthuin JP, Folliot JP, Bertrand ME.** [Non-obstructive hypertrophic myocardopathy. Apropos of 5 cases. *Arch Mal Coeur Vaiss.* 1980;73(11):1269-78.).
- Three hypotheses emerged to explain these negative T waves: 1) apical subendocardial ischemia.; 2) apical cell disorder; 3) greater duration of action potential of hypertrophied cells, thus conditioning the area to have a slower repolarization (**Tsunakawa H, Wei D, Mashima S, Harumi K.** Study on the genesis of giant negative T wave in apical hypertrophic cardiomyopathy using a three-dimensional computer model. *Jpn Heart J.* 1991;32(6): 799-809.).
- The prevalence in the western world of this form of HCM is approximately 0.02 to 0.2% and it constitutes 8% of the cases of the entity. In Japan, the apical form of HCM constitutes 25% of HCM (**Maron BJ.** Apical hypertrophic cardiomyopathy: the continuing saga. *J Am Coll Cardiol.* 1990;15(1):91-3.).

- Sometimes R-wave voltage and T-wave negativity progressively decreased in magnitude in serial ECGs.
- Prominent R waves in intermediate precordial leads are observed in ≈80% of cases of Ap-HCM subtype.
- NSVT can be observed in patients that developed apical aneurysm with normal coronary arteries; to clarify the mechanisms of ECG abnormalities in hypertrophic cardiomyopathy, 102 patients were examined with CMR. Distribution and magnitude of hypertrophy and late enhancement were correlated with ECG abnormalities:
- Abnormal Q waves reflect the interrelation between upper anterior septal thickness and other regions of the LV and RV, and wider Q waves are associated with late enhancement;
- Conduction disturbances and absent septal Q waves are associated with late enhancement;

Figure below shows the main ECG/VCG features in a typical case of NOHCM in the apical region: ApHCM.

Horizontal plane



Initial vectors of QRS loop heading forward and to the left; Anteriorization of QRS loop predominantly located in the left anterior quadrant; Maximal vector that increases voltage; Final vectors located to the right and backward with ST/T vector in the right posterior quadrant; E point that does not match the 0 point and is located backward and rightward from the latter.

Figure shows ApCM structure with the characteristic ace-of-spades sign

Apical hypertrophic cardiomyopathy

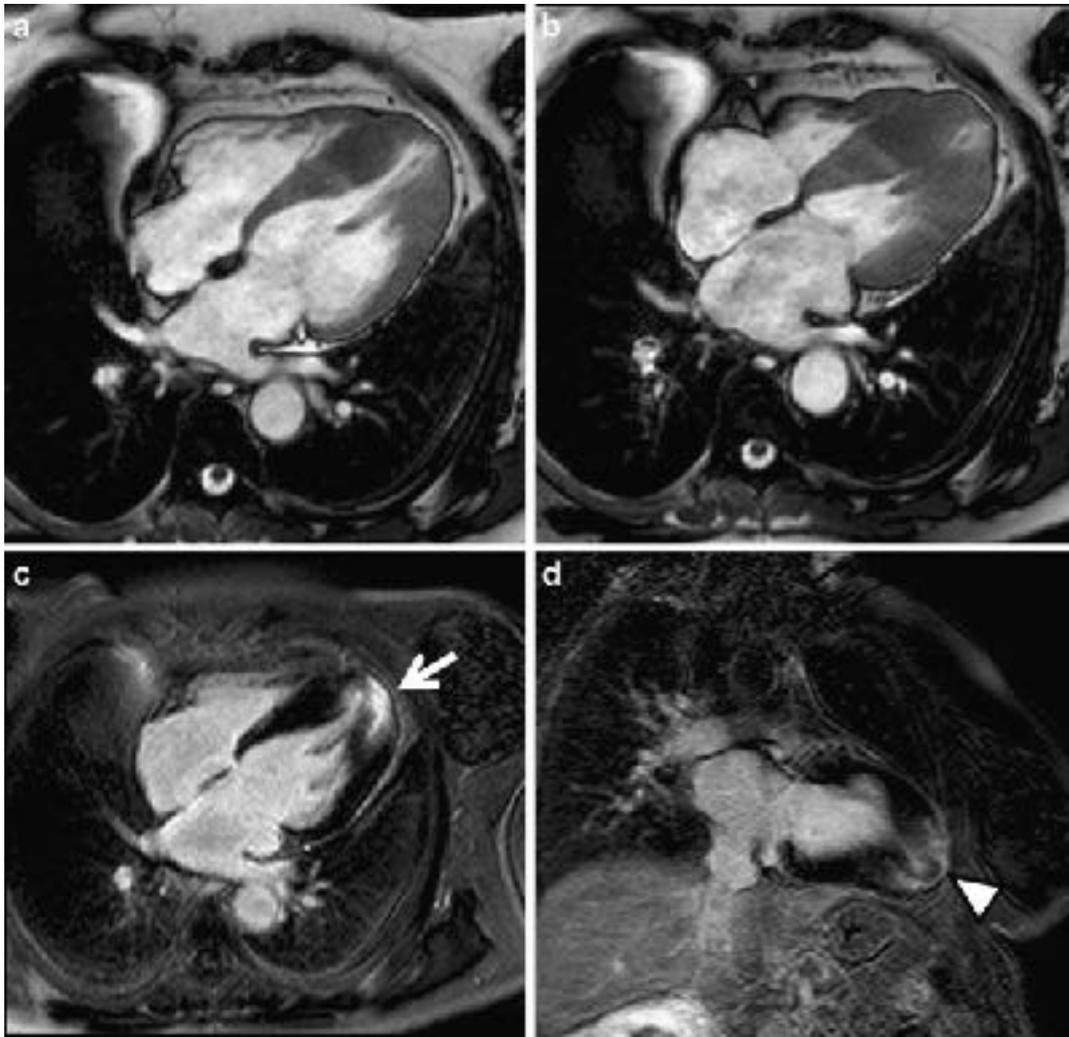


Case of ApHCM

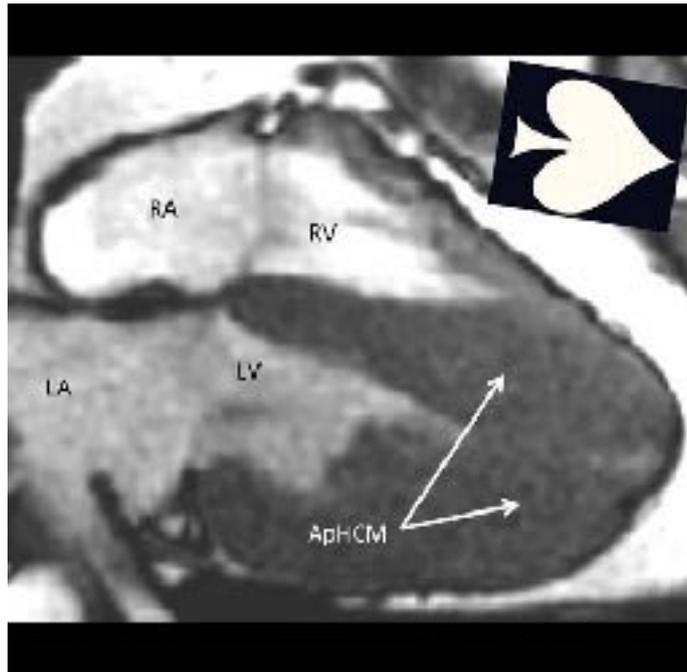


Two-dimensional echocardiogram in an apical 4-chamber view shows apical hypertrophy in the apical one third of the ventricle, with apical left ventricle cavity obliteration. RV = right ventricle RA = right atrium LA = left atrium LV= left ventricular cavity

Cardiovascular magnetic resonance (CMR) or Cine MRI

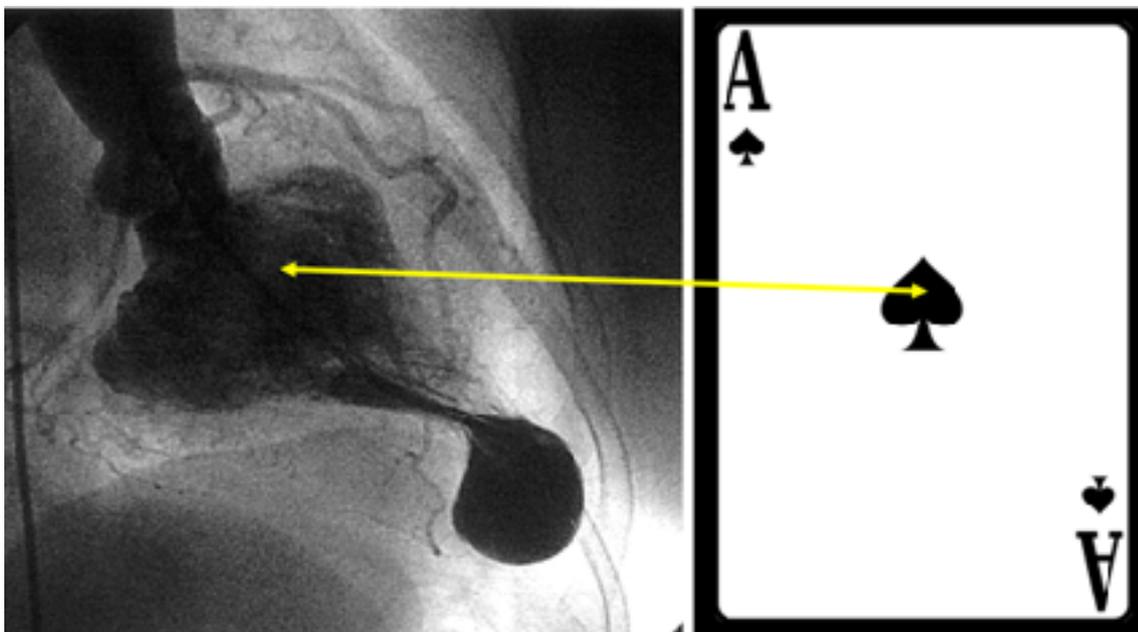


ApHCM. Cine MRI in the four-chamber view shows progressive thickening of the ventricular walls towards the apex in diastole (a) and systole (b). Late enhancement in a four-chamber view (c) and vertical long axis (d) demonstrates strong enhancement in the hypertrophied myocardium (arrow). Note the presence of “pseudo diverticulum” in the most apical myocardium (arrowhead).



Four-chamber CMR SSFP image demonstrating asymmetrical left ventricular apical thickening. (LV = left ventricle; RV = right ventricle; LA = left atrium; RA = right atrium; ApHCM = apical hypertrophy).

Left Ventriculography characteristic of Ap-HCM



The "ace-of-spades" sign on left ventriculography is pathognomonic (Olearczyk B, Gollol-Raju N, Menzies DJ. Apical hypertrophic cardiomyopathy mimicking acute

coronary syndrome: a case report and review of the literature. *Angiology*. 2008; 59:629-631.).

Any increase in LV mass above these values is considered normal: 134 g/m² of body surface for men and 109 g/cm² for women with or without cavity dilatation.

In absolute terms the LV weight is from 120 to 240 g in men and 20% less in women: 100 to 200 g.

The mass calculation is performed in echocardiography.

V-b) Prolonged QRS duration or width in HCM

Bongiovanni *et al* found in 241 patients with HCM that a QRS duration \geq 120 ms in the ECG is directly related to cardiovascular mortality and is a strong and independent predictor of prognosis in patients with HCM. Biventricular pacing can restore synchronous contraction and shorten QRS duration. Biventricular pacing reduced QRS duration compared to right ventricular pacing (**Bongioanni S, Bianchi F, Migliardi A, *et al*. Relation of QRS duration to mortality in a community-based cohort with hypertrophic cardiomyopathy. *Am J Cardiol* 2007; 100: 503-6.**).

V-c) Abnormal non-infarction deep-narrow Q waves

Prominent deep-narrow Q waves in the ECG are considered characteristic of HCM (**Rao U, Agarwal A. Importance of Q waves in early diagnosis of hypertrophic cardiomyopathy. *Heart*. 2011; 97: 1993-4.**) and significant in early diagnosis (**Ohmoto-Sekine Y, Suzuki J, Shimamoto R, Yamazaki T, Tsuji T, Nagai R, Ohtomo K. Gender-specific clinical characteristics of deep Q waves in hypertrophic cardiomyopathy. *Gend Med*. 2007;4(3):274-83.**).

Abnormal Q waves may mimic myocardial infarction and at times reflect septal hypertrophy.

Of the 200 consecutive patients with HCM who underwent CMR imaging, 10 male and 8 female patients had deep Q waves. Deep Q waves were more prevalent in females with HCM than in their male counterparts (28.6% vs 5.8%, respectively; $P < 0.001$). Of the 18 patients with deep Q waves, maximum wall thickness was localized at either the

basal anterior wall or the mid-ventricular septum in 9 (90%) of the 10 male patients and 6 (75%) of the 8 female patients. In both sexes, the Q wave distribution pattern of I and aVL and of II and aVF indicated location of maximum hypertrophy at the mid-ventricular septum in 6 (75%) of the 8 patients with the former pattern, and at the basal anterior wall in 9 (90%) of the 10 patients with the latter pattern. Diagnostic deep Q waves were detected more frequently in female patients with HCM than in their male counterparts. In HCM with deep Q waves in limb leads, the morphologic and electrocardiographic analysis showed similar features in both sexes (**Godballe C, Hoeck HC, Sørensen JA. Transient abnormal Q-waves. Ugeskr Laeger. 1990;152(2):92-4.**). Abnormal Q-waves observed in the ECG are divided in infarction Q-waves and non-infarction Q-waves. This last group is divided in transient abnormal Q waves and permanent non-infarction Q-waves. Transient abnormal Q waves are defined as abnormal Q waves, which disappear within ten days. They are most often seen in patients with ischemic heart disease but are also seen in other conditions (**Zhang ZM, Prineas RJ, Eaton CB. Evaluation and comparison of the Minnesota Code and Novacode for electrocardiographic Q-ST wave abnormalities for the independent prediction of incident coronary heart disease and total mortality (from the Women's Health Initiative). Am J Cardiol. 2010 Jul 1; 106:18-25.**) such as advanced hyperkalemia, septic shock, acute pancreatitis, localized metabolic and electrolyte disturbances and hypothermia.

Possible mechanisms of permanent non-infarction Q-waves are: Loss of viable myocardium, altered distribution of myocardial mass, altered sequence of depolarization, and altered position of the heart.

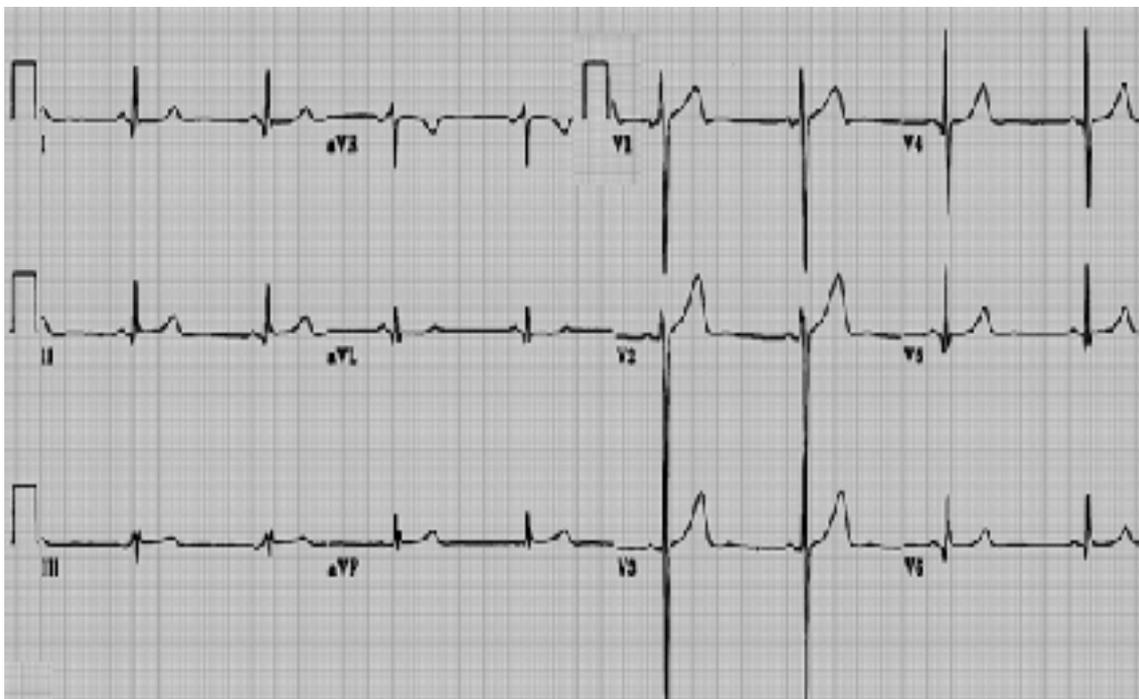
Infarction Q-waves are characterized by Q duration ≥ 40 ms (in VCG ≥ 30 ms) and with ST-T abnormalities which are stronger events predictors and total mortality than isolated Q-wave abnormalities (**Chatterjee S, Changawala N. Fragmented QRS complex: a novel marker of cardiovascular disease. Clin Cardiol. 2010 Feb; 33: 68-71.**).

Permanent non-infarction Q-waves are characterized by Q-wave duration ≤ 35 ms (those of infarction ≤ 40 ms), "clean" and deep Q-wave aspect (those of true infarction present notches and are usually accompanied of injury current and ischemia).

Additionally, they may be observed in children and young people (those of infarction are found in adults and elderly people), are frequently asymptomatic and serum enzymes and troponin are normal (those of infarction in the acute phase, with increased CKMB, TGO, DHL and Troponin).

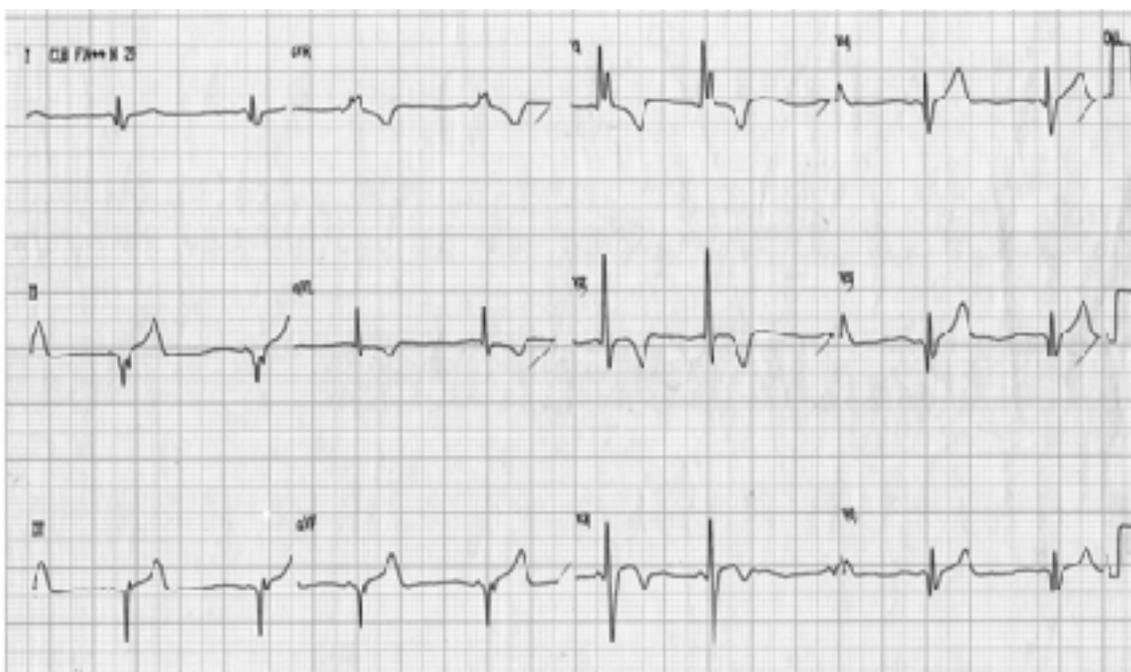
In $\approx 10\%$ of HCM cases, very wide R waves in V1 and aVR associated to deep and "clean" Q waves in V5 and V6 and/or in inferior leads are observed as a consequence of augmented first left septal vector.

Example of HCM with conspicuous Q waves on ECG



Note "clean" deep and narrow Q waves in left leads I, aVL, and V4 to V6. A voltage of V1 is greater than V2 the R: R reverse progression in the precordial lead. The increased voltage of the first vector (septal vector) is indicative of septal hypertrophy that justifies the higher voltage of R wave in V1 and concomitant increase in the depth of Q wave in the left leads I, aVL, V5 and V6.

Male, 23-year-old patient, with history of tiredness at strain and syncope episode



NOHCM Note deep clean q waves and prominent anterior forces in right precordial lead

V-d) Fragmented (fQRS): Myocardial scar causes heterogeneous ventricular activation, is a substrate for reentrant ventricular arrhythmias and is associated with

poor prognosis. Fragmented QRS (fQRS) on 12-lead ECG represents myocardial conduction delays due to myocardial scar in patients with coronary artery disease. The presence of a fragmented QRS (fQRS) complex on a routine 12-lead ECG is another marker of depolarization abnormality together with SAECG. fQRS is not specific for CAD and is also encountered in other myocardial diseases such as cardiomyopathy and congenital heart disease. fQRS is associated with increased mortality and arrhythmic events in patients with CAD. fQRS has also been defined as a marker of arrhythmogenic right ventricular dysplasia/cardiomyopathy and Brugada syndrome. In Brugada syndrome, the presence of fQRS predicts episodes of ventricular fibrillation during follow-up.

fQRS is defined as changes in QRS morphology with different RSR' patterns (QRS duration <120 ms), additional R waves, notched S wave, or $>1R'$ wave (Das 2010).

fQRS included various RSR' patterns (QRS duration <120 ms), such as ≥ 1 R prime or notching of the R wave or S wave present in at least two contiguous leads of those representing anterior (V1-V5), lateral (I, aVL, V6), or inferior (II, III, aVF) myocardial segments (Das 2008).

The significance of fQRS has not been defined in the presence of a wide QRS (wQRS; duration ≥ 120 ms).

Fragmented wQRS (f-wQRS) is due to bundle branch block, premature ventricular contractions (PVCs), or paced rhythms (f-pQRS). f-wQRS on a standard 12-lead ECG is a moderately sensitive and highly specific sign for myocardial scar in patients with known or suspected coronary artery disease. f-wQRS is also an independent predictor of mortality (Bsaran 2010).

Myocardial fibrosis in patients with nonischemic cardiomyopathy can be identified as late gadolinium enhancement areas on cardiac magnetic resonance studies. fQRS complexes on ECG are associated with intraventricular systolic dyssynchrony and subendocardial fibrosis in nonischemic cardiomyopathy patients with a narrow QRS interval and sinus rhythm (Chen 1979). The usefulness of fQRS varies with the incidence of ventricular disease in the population studied. This ECG sign is commonly

associated with ventricular abnormalities with and without demonstrable myocardial scar, but also occurs in the absence of clinical heart disease (Pérez-Riera 2011).

VI) Repolarization abnormalities

They are the most common abnormalities, occurring in more than 80% of cases.

ST-segment abnormalities: In a retrospective study of 173 consecutive patients with a diagnosis of HCM multivariate analysis demonstrated that ST-segment depression in the high lateral leads and syncope were the predictors of SD or appropriate ICD therapy in patients with HCM. Consequently, in addition to generally accepted risk factors, ST-segment depression in the high lateral leads could be of prognostic significance in HCM patients (Maron 2009).

T-waves abnormalities: T-wave inversion in the ECG is usually dismissed in young people as normal persistence of the juvenile pattern. The prevalence of T-wave inversion decreases significantly after puberty; however, is a common ECG feature of HCM and arrhythmogenic right ventricular cardiomyopathy, which are the main causes of SD in athletes. Echocardiographic investigation in athletes with post-pubertal persistence of T-wave inversion at pre-participation screening is warranted because it may lead to pre-symptomatic diagnosis of an abnormality of cardiomyopathies at risk of SD (Papadakis 2011). It is characteristic in patients with HCM. Additionally, the QRS/ST/T angle is wide, near 180°.

Prolonged QRS duration or width in HCM: Bongiovanni *et al* found in 241 patients with HCM that a QRS duration ≥ 120 ms in the ECG is directly related to cardiovascular mortality and is a strong and independent predictor of prognosis in patients with HCM. Biventricular pacing can restore synchronous contraction and shorten QRS duration. Biventricular pacing reduced QRS duration compared to right ventricular pacing (Bongiovanni S, Bianchi F, Migliardi A, Gnani R, Pron PG, Casetta M, Conte MR. Relation of QRS duration to mortality in a community-based cohort with hypertrophic cardiomyopathy. *Am J Cardiol.* 2007;100(3): 503-6.).

V-a) Criteria based in increase of amplitude voltage of QRS

The most frequently used criteria for LVH in epidemiological trials is the Sokolow-Lyon index: S wave of V1 + R of V5 \geq 35 mm or 3.5 mV in adults older than 30 years of age, > 40 mm or 4.0 mV between 20 and 30 years old (Sokolow-Rapaport), > 60 mm between 16 and 20 years and > than 65 mm between 11 and 16 years. Sensitivity: 25%. Specificity: 95%. Modified Sokolow-Lyon index uses a close lead (V2) and a distant one (V6). This is the reason why it has the same value as the Sokolow-Lyon index, which uses a distant lead (V1) and a close one (V5).

III. Abnormal inferior and anterior and/or lateral Q waves

Prominent deep-narrow Q waves in the ECG are considered characteristic of HCM (Rao U, Agarwal A. **Importance of Q waves in early diagnosis of hypertrophic cardiomyopathy.** *Heart.* 2011; 97 (23): 1993-4.) and significant in early diagnosis (Ohmoto-Sekine 2007 Ohmoto-Sekine Y, Suzuki J, Shimamoto R, et al. **Gender-specific clinical characteristics of deep Q waves in hypertrophic cardiomyopathy.** *Gend Me.* 2007; 4(3): 274-83.). Abnormal Q waves may mimic myocardial infarction and at times reflect septal hypertrophy. Of the 200 consecutive patients with HCM who underwent CMR imaging, 10 male and 8 female patients had deep Q waves. Deep Q waves were more prevalent in females with HCM than in their male counterparts (28.6% vs 5.8%, respectively; $P < 0.001$). Of the 18 patients with deep Q waves, maximum wall thickness was localized at either the basal anterior wall or the mid-ventricular septum in 9 (90%) of the 10 male patients and 6 (75%) of the 8 female patients. In both sexes, the Q wave distribution pattern of I and aVL and of II and aVF indicated location of maximum hypertrophy at the mid-ventricular septum in 6 (75%) of the 8 patients with the former pattern, and at the basal anterior wall in 9 (90%) of the 10 patients with the latter pattern. Diagnostic deep Q waves were detected more frequently in female patients with HCM than in their male counterparts. In HCM with deep Q waves in limb leads, the morphologic and electrocardiographic analysis showed similar features in both sexes (Godballe C, Hoeck HC, Sørensen JA. **Transient abnormal Q-waves.** *Ugeskr Laeger.* 1990;152(2):92-4.). Abnormal Q-waves observed in the ECG are divided in infarction Q-waves and non-infarction Q-waves. This last group is divided in transient abnormal Q waves and permanent non-infarction Q-waves. Transient abnormal Q waves are defined as abnormal Q waves, which disappear within

ten days. They are most often seen in patients with ischemic heart disease but are also seen in other conditions (**Zhang ZM, Prineas RJ, Eaton CB. Evaluation and comparison of the Minnesota Code and Novacode for electrocardiographic Q-ST wave abnormalities for the independent prediction of incident coronary heart disease and total mortality (from the Women's Health Initiative). Am J Cardiol. 2010 Jul 1; 106:18-25.**) such as advanced hyperkalemia, septic shock, acute pancreatitis, localized metabolic and electrolyte disturbances and hypothermia. Possible mechanisms of permanent non-infarction Q-waves are: Loss of viable myocardium, altered distribution of myocardial mass, altered sequence of depolarization, and altered position of the heart.

Bizarre QRS complexes masquerading, for example, as pre-excitation and bundle branch block.

In HCM, the right or left ventricular free walls or both become thick because of chronic pressure overload. The interventricular septum can also become hypertrophied and can lead to LVOT obstruction. When the septum hypertrophies, normal septal forces that travel left to right through the septum are exaggerated on the ECG because of the enlarged septal mass. Septal hypertrophy can produce larger-than-normal Q waves in lateral leads I, aVL, V5, and V6 that can mimic lateral wall MI and can result in larger-than-normal R waves in V1 and V2 that mimic lateral (old dorsal) wall MI. If the LV free wall is hypertrophied, a QS complex can be recorded in V1, V2, and sometimes V3, which can mimic anteroseptal MI. If the ST segment is not elevated or shows an upward concave elevation and the T wave is upright in the presence of a QS complex in V1 or V2, this favors LVH. If the ST segment shows convex elevation with an inverted T wave, anteroseptal MI is more likely.

Differentiating physiological LVH in athletes from that in patients with HCM

Athlete's heart consequence of intensive athletic training is associated with a spectrum of morphologic and functional cardiac changes, considered to be physiologic adaptations to increased hemodynamic load and neurohormonal changes (**Pelliccia, A., Maron, B. J., Spataro, A., Proschan, M. A., & Spirito, P. The upper limit of**

physiologic cardiac hypertrophy in highly trained elite athletes.1991; *N Engl J Med*, 324(5), 295-301.) In most athletes, morphologic cardiac changes are mild and do not raise clinical concern, but in some highly trained athletes, LV remodeling may be substantial, prompting differential diagnosis with hypertrophic cardiomyopathy (HCM) (Sharma, S., Maron, B. J., Whyte, G., Firoozi, S., Elliott, P. M., & McKenna, W. J. (2002). **Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 40(8), 1431-1436.**) Accurate identification of HCM in athletes has relevant clinical implications, because this disease is one of the most common causes of sudden cardiac death(SCD) (Pelliccia, A., Fagard, R., Bjornstad, H. H., Anastassakis, A., Arbustini, E., Assanelli, D. **Pericardial Diseases of the European Society of, C. (2005). Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*, 26(14), 1422-1445.**)

Distinguishing athlete's heart from HCM may prove particularly difficult when absolute LV wall thickness is in the range of 13 to 15 mm, which identifies the "gray zone" of overlap between these 2 clinical entities. Although previous studies have proved useful in aiding this differential diagnosis,

In the pediatric group the most common cause of diastolic or volume load is athletic training which causes a physiological hypertrophy that needs to be differentiated against HCM. In endurance athletes there can be a considerable enlargement in ventricular cavity size, with a proportional increase in wall thickness so that wall-to-cavity ratios remain normal. This results in both increases in QRS voltage, and sometimes more widespread T-wave inversion in precordial leads beyond V1 (because of the larger RV). The voltage increases in precordial leads are greater in male than female athletes, and about 50% of male athletes (Ostman-Smith, I. **Differential diagnosis between left ventricular hypertrophy and cardiomyopathy in childhood.2014; *J Electrocardiol*, 47(5), 661-8.**)

Diffuse T-wave inversion on ECG proved useful for discriminating the 2 conditions. Inverted T waves were present in about 1/2 of patients with HCM; their presence was associated with 52% of sensitivity, but normal T waves excluded HCM with 92% of specificity. Diffuse negative T-wave may represent subtle expression of HCM, which may precede the full phenotypic expression of the disease for years but ultimately be associated with adverse clinical events (Pelliccia, A., Di Paolo, F. M., Quattrini, F. M., Basso, C., Culasso, F., Popoli, G., . . . Maron, B. J. (2008). Outcomes in athletes with marked ECG repolarization abnormalities. 2008; *N Engl J Med*, 358(2), 152-161.)

Athletes with such ECG patterns should be viewed with great caution and merit continued clinical surveillance. Conversely, voltage criteria for LVH (i.e., Sokolow-Lyon) were not reliable in discriminating athletes from patients with HCM. Therefore, isolated increase of QRS voltages, in absence of other ECG abnormalities, should not be considered, per se, as evidence for a pathologic condition. Additionally, left-axis deviation or P-wave compatible with atrial enlargement, were found with similar prevalence in athletes and in patients with HCM(Caselli, S., Maron, M. S., Urbano-Moral, J. A., Pandian, N. G., Maron, B. J., & Pelliccia, A. Differentiating left ventricular hypertrophy in athletes from that in patients with hypertrophic cardiomyopathy. 2014; *Am J Cardiol*, 114(9), 1383-1389.)

The ECG is very important in risk assessment in patients with HCM. It has been shown that the risk of SCD is incremental at 6-limb lead voltages ≥ 10 mV in 128 patients with childhood HCM (39 with SCD, (Ostman-Smith, I., Wettrell, G., & Riesenfeld, T. A cohort study of childhood hypertrophic cardiomyopathy: improved survival following high-dose beta-adrenoceptor antagonist treatment.1999; *J Am Coll Cardiol*, 34(6), 1813-22.)(Ostman-Smith, I., Wettrell, G., Keeton, B., Riesenfeld, T., Holmgren, D., & Ergander, U. Echocardiographic and electrocardiographic identification of those children with hypertrophic cardiomyopathy who should be considered at high-risk of dying suddenly.2005; *Cardiol Young*, 15(6), 632-42.)and ≥ 7.7 mV in 116 adult HCM patients (29 with sudden death) (Ostman-Smith, I., Wisten, A., Nylander, E., Bratt, E. L., Granelli, A., Oulhaj, A., & Ljungstrom, E.. Electrocardiographic amplitudes: a new risk factor for sudden death in

hypertrophic cardiomyopathy. *Eur Heart J,2010; 31(4), 439-49.*) an additional voltage risk cut-off in the adult patients was a 12-lead duration product $\geq 2.2 \text{ mV} \cdot \text{s}$ with a sensitivity of 92% and a negative predictive value of 97% (Ostman-Smith et al., 2010).

It was also shown that morphological ECG-changes may indicate excessive risk: both QRS-axis deviation, T-wave inversion, ST depression $\geq -2 \text{ mm}$, a dominant S-wave in lead V4, and a QTc $\geq 440 \text{ ms}$ were all individually associated with a significantly increased risk of SCD arrhythmia death in HCM. This observation led to the construction of an ECG risk score (Table below).

Table X Calculation of the ECG risk score validated for HCM

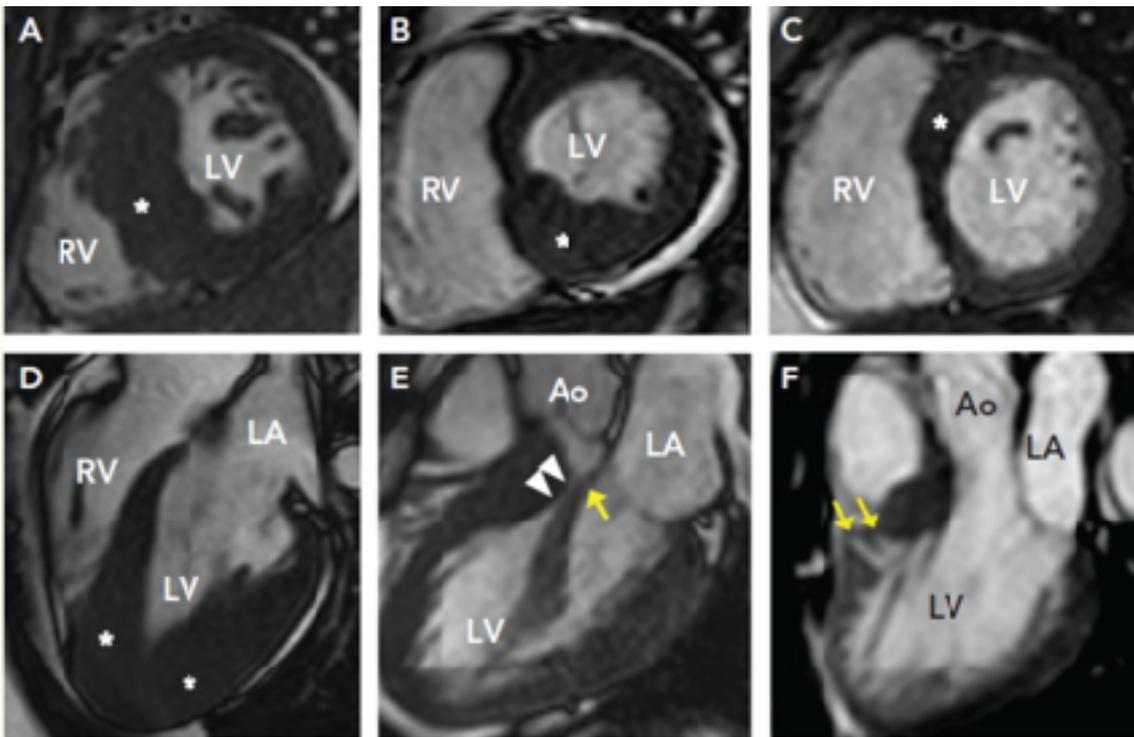
Feature	Cut-offs	Points
Any deviation in QRS-axis		1
T-wave inversion in limb lead other than III	$\geq 1 \text{ mm}$	1
Precordial T-wave inversion in V4, V5 or V6: (does not get added to limb-lead score, so max 2 points for T-waves)	$\geq 1 \text{ mm}$	2
ST-segment depression	$\geq 2 \text{ mm}$	2
S-wave \geq R-wave in V4 (dominant S-wave)		2
QTc:	$\geq 440 \text{ ms}$	2
Limb-lead QRS-amplitude	$\geq 7.7 \text{ mV}$	1
sum	$\geq 10.0 \text{ mV}$	2
	$\geq 12.0 \text{ mV}$	3
12-lead amplitude-duration product	$\geq 2.2 \text{ mV} \cdot \text{s}$	1
	$\geq 2.5 \text{ mV} \cdot \text{s}$	2
	$\geq 3.0 \text{ mV} \cdot \text{s}$	3

Maximum score 14 points; High-risk score consists of N5 points (Ostman-Smith et al., 2010). A score of N5 points, in other words 6 points or above, constitutes a high-risk score and that cut-off gives the best ROC-curve and a higher specificity (85% versus 78%) than the 12-lead amplitude × duration

The Role of Cardiac MRI in the Diagnosis and Risk Stratification of HCM

HCM, is the most frequent genetic cardiomyopathy characterized by substantial heterogeneity. Although the majority of patients with HCM remain asymptomatic with near-normal longevity, a small, but important, subset remain at risk for a wide range of clinical outcomes including SCD. CMR, has emerged as an imaging modality particularly well suited to characterize the phenotypic expression of HCM. CMR helps in the diagnosis of HCM by identifying areas of hypertrophy not well visualized by echo, providing more accurate wall thickness measurements and differentiating HCM from other causes of LVH. CMR has led to the identification of novel subgroups of patients with HCM, including those with LV apical aneurysms (a subgroup at increased risk for ventricular arrhythmias and thromboembolic stroke), as well as abnormalities that contribute to LVOTO. Additionally, contrast-enhanced CMR with LGE has recognized patients with extensive LGE (≥ 15 % LV myocardium) as individuals who may be at increased risk of SCD, independent of other high-risk features, with implications on management strategies including consideration for primary prevention ICDT. These observations justify an expanded role of CMR in the routine clinical assessment of patients with HCM (**Rowin EJ, Maron MS. The Role of Cardiac MRI in the Diagnosis and Risk Stratification of Hypertrophic Cardiomyopathy. Arrhythm Electrophysiol Rev. 2016;5(3):197-202.**)

Examples

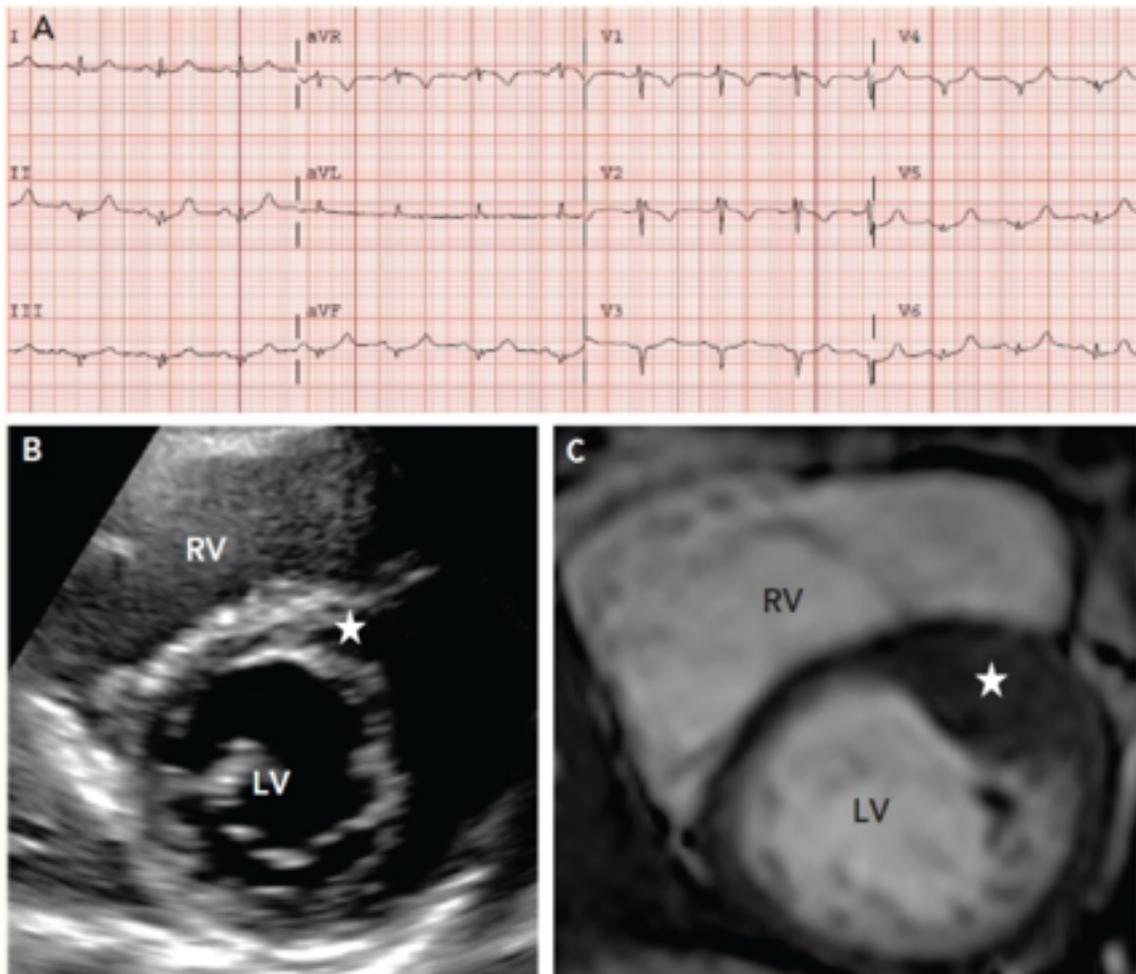


CMRIs in 6 patients carrying HCM with several phenotypic expression

A–C: Short-axis CMRIs demonstrating: (A) massive LVH (31 mm of wall thickness) confined to the IVS (asterisk), (B) massive LVH (wall thickness =30 mm) in the inferior septum and inferior wall (asterisk) and (C) mild asymmetric hypertrophy of the septum (asterisk; wall thickness =16 mm) in a patient with a disease-causing sarcomere mutation in the myosin-binding protein C gene. D: Four-chamber long-axis view demonstrating hypertrophy localized to the LV apex (asterisks). E: Three-chamber long-axis view demonstrating muscular midcavitary obstruction attributable to the insertion of anomalous anterolateral papillary muscle directly into anterior leaflet (arrow) contacting the midventricular septum in systole (arrowheads). F: A 24-year-old

genotype-positive phenotype-negative man with two deep, narrow myocardial crypts (arrows) in the anterior septum, considered a morphological marker for affected status. Ao = aorta; CMR = cardiovascular magnetic resonance; HCM = hypertrophic cardiomyopathy; LA = left atrium; LV = left ventricle; RV = right ventricle.

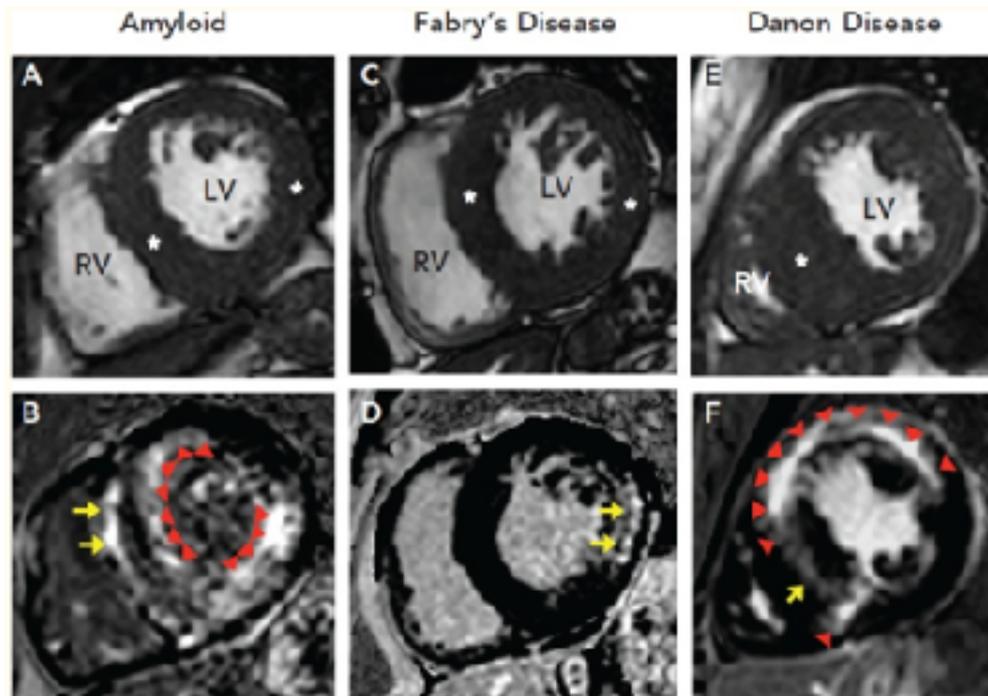
Figure



CMR for HCM Diagnosis

An asymptomatic 36-year-old woman with a family history of HCM. A: Twelve-lead ECG: incomplete RBBB and anterior and inferior Q waves. B: 2D echo demonstrated normal LV wall thickness. C: Given abnormal ECG, patient underwent CMR, which reveals an area of segmental hypertrophy in the anterolateral LV wall (asterisk) consistent with a diagnosis of HCM.

Figure



CMR for differentiation of etiology of LVH

- I. **Cardiac Amyloidosis confirmed by cardiac biopsy:** A: Pre-contrast short-axis CMR image in a 64-year-old man with increased LV wall thickness in both septum and lateral wall (maximum wall thickness of 18 mm in septum and 14 mm in lateral wall). B: Post-contrast images in the same patient demonstrates early contrast washout with epicardial LGE in septum (arrows) and global subendocardial LGE (arrowheads) leading to concern for amyloidosis.
- II. **Fabry's disease (α -galactosidase A deficiency) confirmed by genetic testing (pathogenic mutation in the galactosidase α gene).** C: Pre-contrast short-axis CMR image in a 44-year-old woman with increased LV wall thickness in both IVS and lateral wall (maximum wall thickness of 16 mm in septum and 13 mm

in the lateral wall). D: Post-contrast images in the same patient demonstrate LGE confined to the basal inferolateral wall leading to concern for Fabry's disease may account for up to 5% of cases of adult HCM. This new observation is important, as Fabry disease is potentially reversible if treated with enzyme replacement therapy (**Sachdev B, Takenaka T, Teraguchi H, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002; 105:1407–1411.**). A serum enzyme assay may suffice as a screening test.

III. **Danon Disease. Genetic testing was thereby sent and revealed a pathogenic mutation in the lysosomal-associated membrane protein 2 gene.** E: Pre-contrast short-axis CMR image in a 21-year-old man demonstrated massive LVH (wall thickness of 32 mm) confined to the IVS (asterisk). F: Post-contrast images in the same patient demonstrated transmural LGE throughout the anterior and lateral walls with mid-myocardial LGE throughout the IVS in a pattern atypical for HCM.

Other causes of adult hypertrophic cardiomyopathy

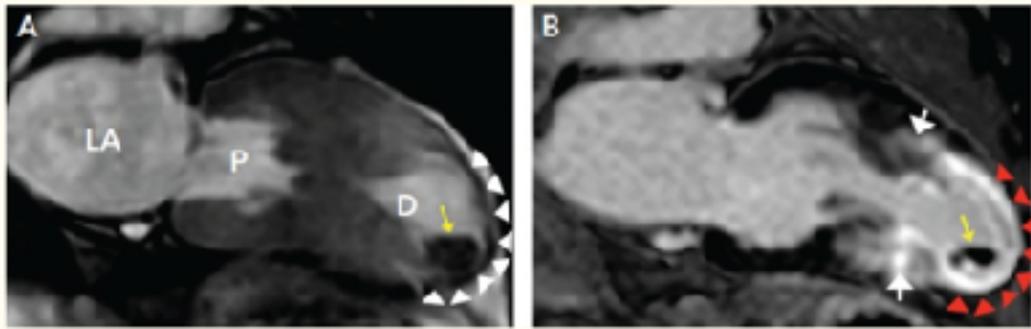
Though most cases of adult HC, are due to sarcomere defects, patients with other disorders may also present with cardiac hypertrophy.

Friedreich ataxia an autosomal-recessive disease involving sclerosis of the spinal cord, is often associated with HCM, and its cardiovascular manifestations may precede the neurological symptoms by up to a decade in some cases.

Noonan syndrome (male Turner syndrome) is marked by short stature, a webbed neck, ptosis, and hypogonadism along with cardiac hypertrophy.

Wolff-Parkinson-White syndrome with hypertrophic cardiomyopathy, a no sarcomere disease with features of a storage disorder in the myocardium, is caused by mutations in the adenosine monophosphate kinase gene.

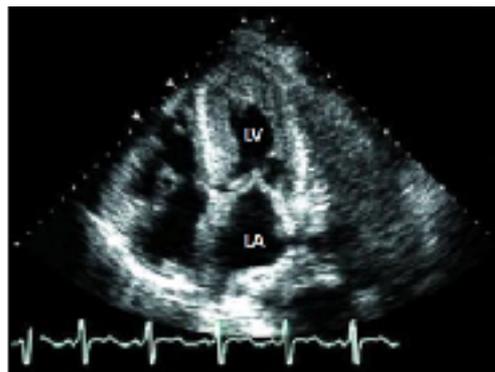
Figure



LV Scarring associated with apical aneurysm in a patient with HCM

Hypertrophic cardiomyopathy at a glance

- I. The risk of inheritance in HCM is 50%.
- II. Screening with ECG and ECHO is recommended for all first-degree relatives of patients with HCM.



Two-dimensional transthoracic echocardiographic image in the apical four-chamber view of a patient with HCM showing severe LVH. LV = left ventricle, LA = left atrium.

- III. There are 10 genes, and currently > 200 mutations
- IV. The genotype-phenotype relationship is not reliable.
- V. Screen for Fabry disease (treat with enzyme replacement therapy).