Hypertrophic Cardiomyopathy

Andrés Ricardo **Pérez-Riera, MD PhD;** Raimundo **Barbosa-Barros, MD;** Rodrigo **Daminello Raimundo, PhD;** Luiz Carlos **de Abreu, PhD;** Kjell **Nikus, MD PhD**

Abbreviations/acronyms

ACS: Acute Coronary Syndrome; AD: Autosomal Dominant Inheritance; AF: Atrial Fibrillation; Ap-HCM: Apical Hypertrophic Cardiomyopathy; AR: Autosomal Recessive; ARVC/D: Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia; ASA: Alcohol Septal Ablation; AVB: Atrioventricular Block; BAE: Biatrial Enlargement; CAD: Coronary Artery Disease; CAVB: Complete Atrioventricular Block; CCT: Cardiac Computed Tomography; CHB: Complete Heart Block; ICD: Implantable Cardioverter Defibrillator; CHF: Congestive Heart Failure; CMRI: Cardiovascular Magnetic Resonance Imaging; ECG: Electrocardiogram/ Electrocardiographic; EMF: Endomyocardial Fibrosis; FD: Fabry Disease; fQRS: Fragmented QRS; GVUS: Genetic Variants of Unknown Significance; HCM: Hypertrophic Cardiomyopathy; HR: Heart Rate; IVS: interventricular septum; LA: Left Atrial/Atrium; LAE: Left Atrial Enlargement; LBBB: Left Bundle Branch Block; LGE-CMRI: Late Gadolinium Enhancement on CMRI; LoF: Loss of function; LV: Left Ventricle/Ventricular; LVH: Left Ventricular Hypertrophy; LVNC: Left Ventricular Non-Compaction; LVOT: Left Ventricular Outflow Tract; LVOTO: Left Ventricular Outflow Tract Obstruction; MACE: Major Adverse Cardiac Events; MVOHCM: Mid-Ventricular Hypertrophic Obstructive Cardiomyopathy; MWT: Maximal Wall Thickness; NOHCM: Non-Obstructive Hypertrophic Cardiomyopathy; NSVT: Non-Sustained Ventricular Tachycardia; OHCM: Obstructive Hypertrophic Cardiomyopathy; OHCA: Out-of-

Hospital Cardiac Arrest; PET: Positron Emission Tomography; PTSMA: Percutaneous Transluminal Septal Myocardial Ablation; RAE: Right Atrial Enlargement; RBBB: Right Bundle Branch Block; RV: Right Ventricle/Ventricular; RVOTO: Right Ventricular Outflow Obstruction; S: Sensitivity; SAM: Systolic Anterior Motion; SAN: Sinoatrial Node; SMVT: Sustained Monomorphic Ventricular Tachycardia, SP Specificity; STSE: ST-Segment Elevation: STSD: ST Segment Depression; SSS: Sick Sinus Syndrome; TTE: Transthoracic Echocardiography; TWI: T-Wave Inversion; WPW-S: Wolff-Parkinson-White Syndrome.

Introduction

HCM is a worldwide, relatively frequent, genetic heart disease that often does not affect life expectancy macroscopically, characterized by abnormal LV wall thickness and/or heart weight (a heart weight >500 g has pathological significance).[1] The average gross weight of the heart was 289.6 g for men at an age of 31-40 years, 284.7 g for women at the same age. At an age of 61-70 years, the average weight was 345.9 g for men and 285.1 g for women. HCM has normal or supernormal systolic function and impaired diastolic function, including chamber stiffness and impaired relaxation.[2] Active relaxation is an energy-consuming process, and its impairment in HCM may be related to abnormal calcium kinetics,[3] subendocardial ischemia,[3] no uniform temporal and regional distribution of load and inactivation.[4]

In HCM the LVH is typically asymmetrical, but it can also be symmetrical and can involve only delimited regions, such as the apex: Ap-HCM.

The diagnostic microscopic features include:

Myofibrillar disarray: in which the myocardial cells are arranged in a disorganized pattern[5] (the loss of the normal parallel alignment of the myocytes), associated with interstitial fibrosis. Additionally, myofibrillar disarray may be produced by abnormal stress vectors resulting from alterations in the sequence of depolarization, and therefore the pattern of contraction. This unifying concept to explain the development of myofibrillar disarray could be observed in a variety of conditions such as in normal hearts by chronic electrical pacing.[6]

Dysfunction of the coronary microvasculature: normal epicardial arteries on coronary angiography, increased wall thickening leading to luminal narrowing, silent myocardial ischemia, myocardial injury and fibrosis[7] are some features. In summary, myocardial ischemia could be secondary to microcirculation disease, decrease of vasodilator capacity, systemic compression of septal and subepicardial vessels, fall of pressure in aorta root, difficulty in coronary filling by hypertrophy, coronary atherosclerosis in >50 year-old patients, offer/demand imbalance by excessive increase of ventricular mass, **c) Striking increase in interstitial connective tissue**: replacement fibrosis may be pericellular, patchy, or extensive and often is more prominent in the ventricular septum.[5, 8] LVH and/or myocardial fibrosis without myocardial disarray are features of uncertain significance.[9]

Mitral valve abnormalities, including aberrant papillary muscles, abnormal papillary muscle insertion into the anterior mitral leaflet, and enlargement and elongation of mitral leaflets are common in HCM and responsible for the creation of a pathologic dynamic LVOT gradient.[10] In 5 to 10% of patients, in the late phase, they evolve into dilatation and systolic dysfunction resulting from myocardial fibrosis secondary to microinfarctions and possible associated to CAD.

The anatomopathological substrate is an important septal cell disorder (95%) and hypertrophy of the middle layer with narrowing of light of the intramural branches responsible of ventricular dysfunction as well as arrhythmias.

HCM and its variable phenotypic expression classifications

Genotype-positive and phenotype-negative HCM, subclinical HCM "near normal variant". Related to relatives of individuals' genetic mutation for HCM, or those who should be followed up for the risk of developing any other variant such as the presence of crypts: genotype-positive and phenotype-negative HCM,[11] abnormal trabeculation, and anterior mitral valve leaflet elongation. Some studies have pointed at the presence of myocardial crypts (ie, narrow, blood-filled invaginations within the LV wall) as a prephenotypic marker of HCM in the absence of LVH. LV myocardial crypts represent a distinctive morphological expression of HCM, occurring with different frequency in HCM patients with or without LVH. Crypts are a novel CMRI marker, which may identify individual HCM family members who should also be considered for diagnostic genetic testing. These data support an expanded role for CMRI in early evaluation of HCM families. Single or paired inferobasal myocardial crypts were an occasional and by no means rare finding among patients referred for CMRI without a pretest suspicion of HCM. This, together with similar previous findings in a cohort of healthy volunteers, supports their being regarded, in such individuals, as incidental variants of local myocardial structure, unlikely to require further investigation. It is necessary a larger registry-type study may be justified to investigate the clinical implications of multiple crypts, especially if associated with HCM family history.[12] Phenotype-negative HCM suggests that HCM is more common than previously estimated, which may enhance its

recognition in the practicing cardiovascular community, allowing more timely diagnosis and the implementation of appropriate treatment options for many patients.[13]

Septal asymmetrical variant with resting LVOTO and "S" shape or sigmoid septum (obstruction at subaortic level: septal basal thickness). This variant is the most frequent and is found in approximately 20% of the patients and is associated with mitral valve SAM and dynamic LVOT, however, in 75% of cases HCM is not associated with LVOT, hence the name change from OHCM to HCM.

Asymmetrical HCM: Basal septal thickness ≥15 mm; ratio of septal thickness to thickness of inferior wall at midventricular level >1.5. The asymmetric septal form is the most common morphologic variant of HCM and accounts for up to 60–70% of cases. In asymmetric HCM, the ventricular septum is disproportionately enlarged, with the anteroseptal myocardium most commonly involved. The septal hypertrophy can be limited to the subaortic, midventricular, or apical regions. In some patients, the hypertrophy can be focal and may involve only one or two LV segments, hypertrophy involving the basal anterior septum, anterolateral free wall, posterior septum, and apex. At times, it may involve the entire length of the septum from base to apex or may extend and involve anterior or inferior walls of the LV. The normal thickness of the LV is 12 mm or less, measured during diastole. Figure 1 shows septal basal hypertrophy, the most frequent anatomical variant.

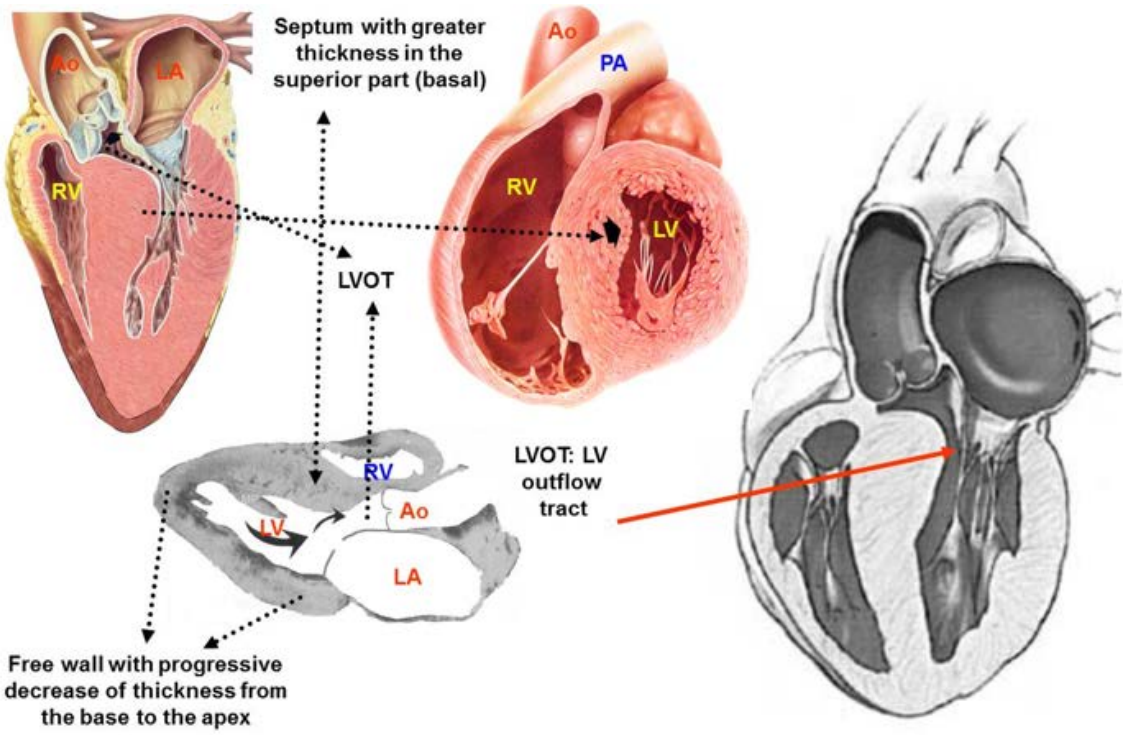

Figure 1. Obstructive HCM: severe peak gradient in the LVOT or mid LV cavity ≥30 mm.

Scheme to assess the Wigle's score

"The Wigle's score" is a point score system which takes into account the thickness of the ventricular septum, the presence of septal hypertrophy at papillary or apical levels, and the presence of anterolateral wall extension of hypertrophy; the score is the sum of these factors, spanning from 0 to 10 (Table 1).

Location thickness	Thickness	Points
Septal basal	15-19 mm	1
	20-24 mm	2
	25-29 mm	3
	≥ 30 mm	4
Extension to papillary muscle		2

Extension to apex		2
Extension to lateral wall		2

Table 1. Total 10. The total score is the sum of these individual factors and spans from 0 to 10. The magnitude and distribution of LVH, assessed by Wigle's score, is related to invasive indexes of passive diastolic dysfunction. HCM patients with severe LVH (Wigle's score ≥8) showed higher pulmonary capillary wedge pressure, LV end-diastolic pressure, and constant of chamber stiffness.[14]

Figure 2 is a typical ECG example of septal basal thickness, "S" shape or sigmoid septum (obstruction at subaortic level), and Figure 3 shows a comparison between the first vector in a normal heart and in HCM with sigmoid septum. Figure 4 shows the same comparison in the horizontal plane.

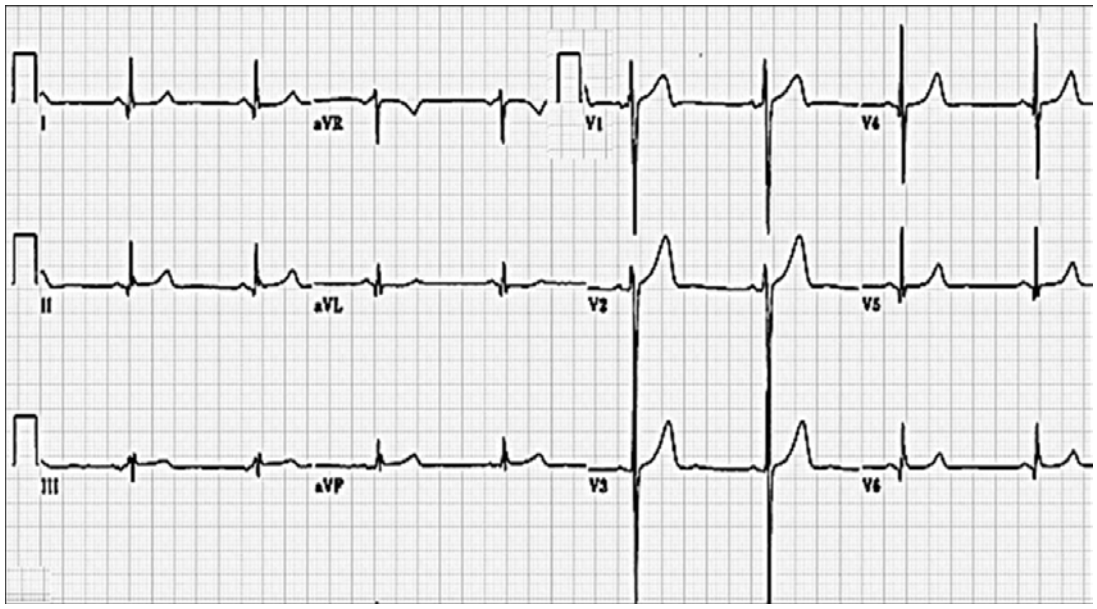

Figure 2. Note the "clean dagger shape deep" and narrow Q waves in lateral leads I, aVL, and V4 to V6. Concomitantly, a R voltage of V1 is greater than V2: R reverse progression in the precordial leads. The increased voltage of the first vector (septal vector) is indicative of selective left septal hypertrophy 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.

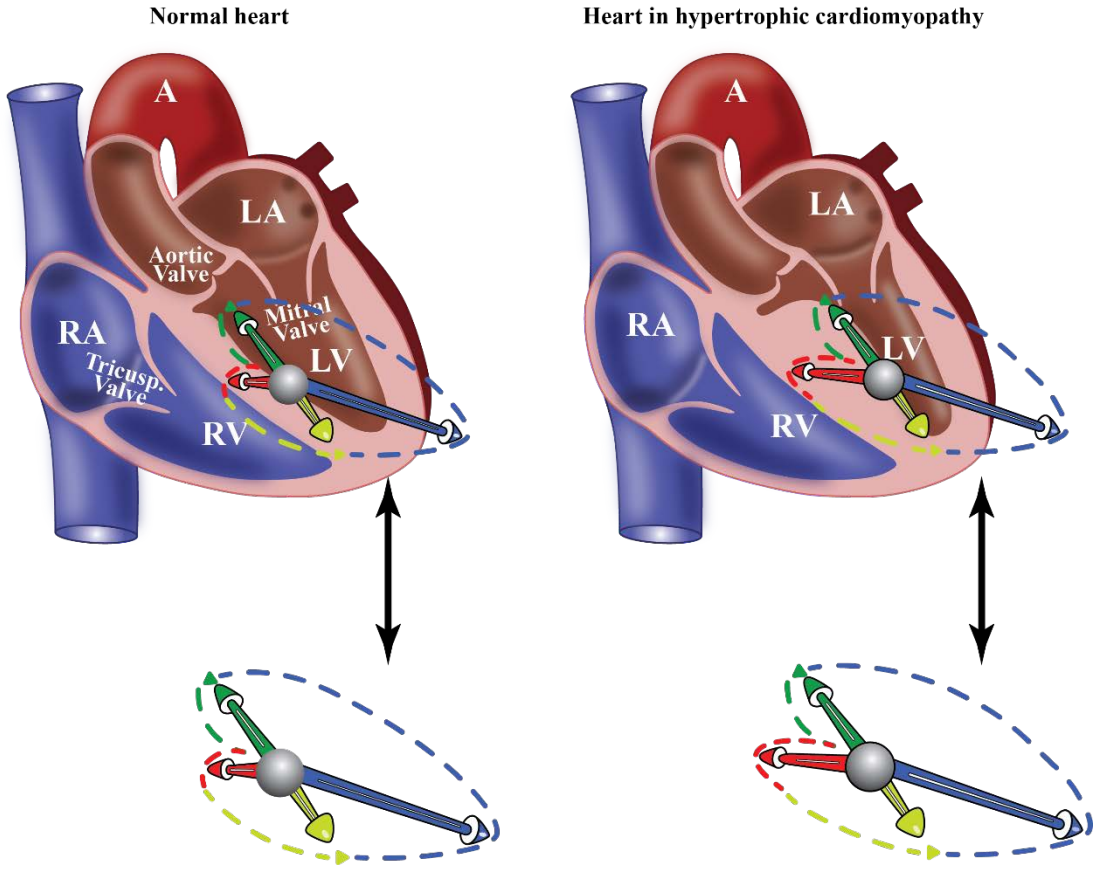

Figure 3. Ludic figure in the frontal plane showing different magnitudes of the first septal vector in a normal heart and in sigmoid basal hypertrophy.

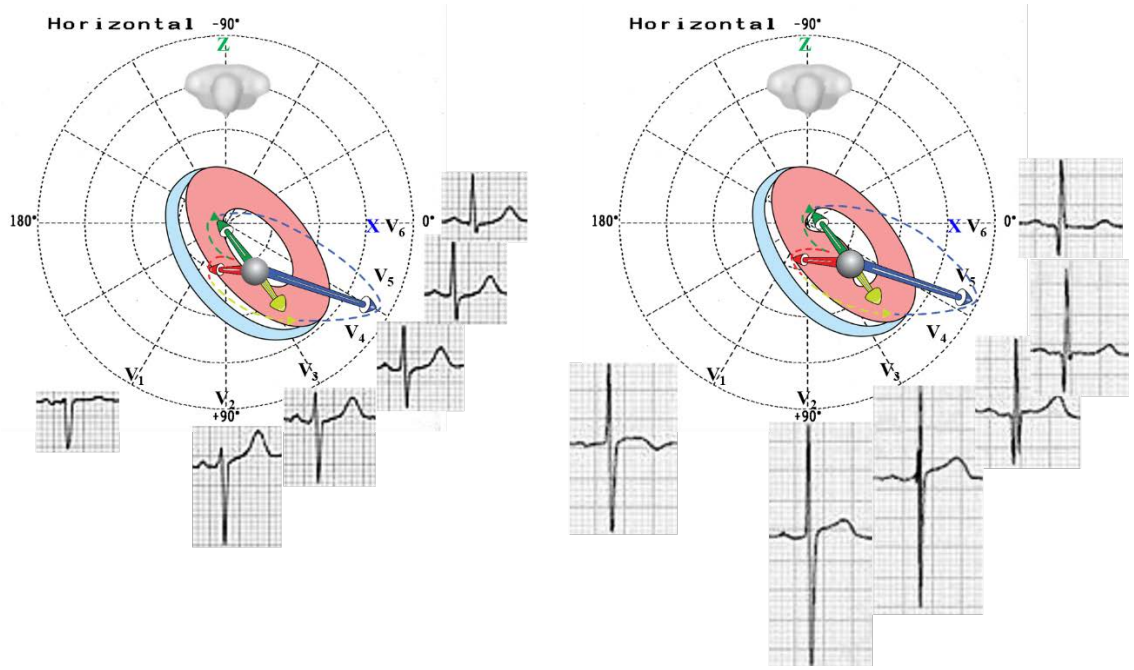

Figure 4. The ECG phenotype of HCM depends on the anatomical variety, thus, the most frequent form (OHCM) is characterized by dynamic obstruction - of varying degrees - in the LVOT consequence of abnormal selective hypertrophy located in the high left IVS responsible for the first septal vector of ventricular activation, septal vector, or "Peñaloza-and Transchesi vector"[15] that activates the middle third of the left septal surface, which explains the presence of increased of R waves voltage in the right precordial leads (V1 and/or V1-V2) and concomitant " large dagger-like septal Q waves" in the lateral wall leads (I, aVL, and V4 to V6) and sometimes in the inferior wall (II, II, and aVF). This phenotype is explained by the presence of a longer-lasting septal vector that points to the right precordial lead s and moves away from the left ones.

Q wave >3 mm in depth and/or >40 ms in duration in at least two leads except aVR showed the highest sensitivity (50% in the young, 29% in adults) while retaining a high specificity (90% in the young, 97% in adults), resulting in the highest accuracy (69% in the young, 52% in adults). Using this criterion, abnormal Q waves were present in 27.6% of preclinical carriers, and in 5.4% of non-carriers. This Q wave type is caused by

transmural fibrosis and or disproportionate hypertrophy of the basal IVS and/or basal LV free wall.[16] In normal hearts small ‘septal’ q waves are typically registered in the lateral leads (I, aVL, V5 and V6). The absence of small septal q waves in leads V5-6 should be considered abnormal. Absent q waves in V5-6 is most commonly due to LBBB. Deeper Q waves (>2 mm) may be seen in leads III (+120°) and aVR (-150°) as a normal heart. Q waves are considered abnormal if >40 ms (1 mm) wide, >2 mm deep, >25% of depth of the QRS complex. These need to be present in at least two contiguous leads to be considered abnormal (leads II and III for example, and not leads II and aVF). The exception is the lateral leads V6, I, and aVL where the Q wave duration only needs to be 30 ms to be deemed abnormal.

Non-obstructive forms

Septal asymmetrical with reverse septal curvature (NOHCM) *c*haracterized by a septal hypertrophy as a reversed "S", more distant from the LVOT. This presentation does not cause obstruction to the LVOT. The identification of this variant by CMRI is characterized by a septal/free wall thickness ratio greater than 1.3 in the short-axis.[17] Changes in rotation and back-rotation at the LV basal level in HCM patients with a typical reverse septal curvature are mainly caused by regional changes in the basal septal and anterior segments, the LV segments mostly involved in the hypertrophic process. At the apical level changes in rotation and back-rotation are more homogeneous. counter-clockwise rotation at the basal LV level were seen, in particular in the septal segment.[18] Sigmoid septum (focal and isolated hypertrophy of the basal interventricular is defined as a septum ≥13 mm in men and ≥12 mm in women, exceeding ≥50% of the median septum thickness) was classified as Type 1 (≤14 mm) and Type 2 (≥15 mm). Regarding the HCM, patients with type 2 sigmoid septum are older and generally hypertensive;

otherwise, often they have no clear differences in their clinical, ECG or TTE characteristics. Therefore, CMRI is helpful in the differential diagnosis.[19]

MVOHCM or mid-ventricular obstruction with or without LV apical diverticulum. MVHOCM is a rare variant that occurs in ≈1% of HCM patients.[20] It could be complicated by apical aneurysm.[21] It characterized by a MVHOCM that causes a local narrowing and, in severe cases, apical dilatation. In ≈10% of patients, there may be apical aneurysm formation.[17] Apical aneurism is better diagnosed by CRMI than TTE which, in turn, can fail to detect this change in 10% of cases.[22] MVHOCM with secondary formation of apical aneurysm is a rare variant of HCM. They have a unique behavior because unlike other variants it causes SMVT, which makes it particularly severe.[23]

Example: A 53 year-old Caucasian male presented a sudden discomfort and syncope ≈1 hour before, he started with profuse diaphoresis, dyspnea at rest, followed by syncope. The patient reported to be accompanied by a cardiologist and informed to be a carrier of familial HCM. He also reported a son who suddenly died at age of 18 during cycling. He is using β-blockers. *Physical*: cold sweating, unconscious, and dyspnea. Tachycardia, regular cardiac rhythm (heart rate: 185 bpm), without cannon "a" waves, changes in beat-to-beat systolic blood pressure or variations in the first heart sound intensity. Blood pressure: 80 × 60 mmHg. Peripheral pulses present without edema. Bilateral crackles in both lungs. Figure 6 shows a 12-lead ECG during the event and Figure 7 immediately after the reversion.

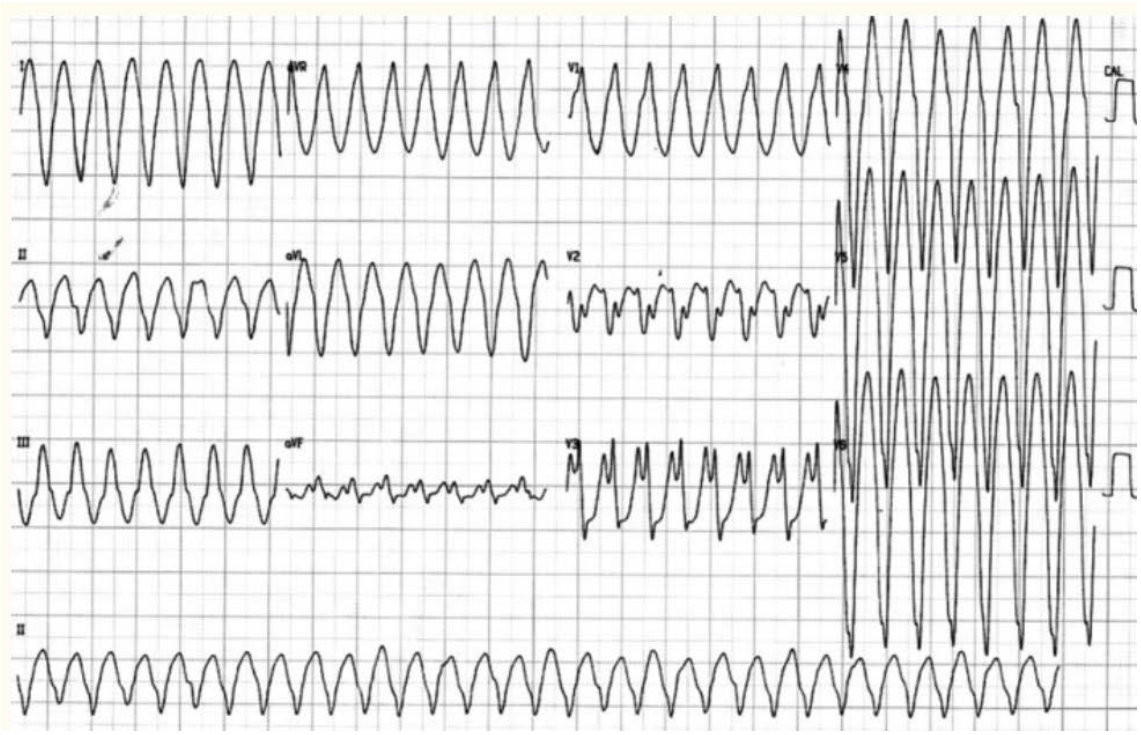

Figure 6. SMVT, 187 bpm, QRS axis in the right superior quadrant “no man's land or Northwest axis” (≈−175°), absence of fusion and/or capture beats, R wave in V_1, and QS pattern from V_2 to V_6. Conclusion: SMVT originated from apical focus.

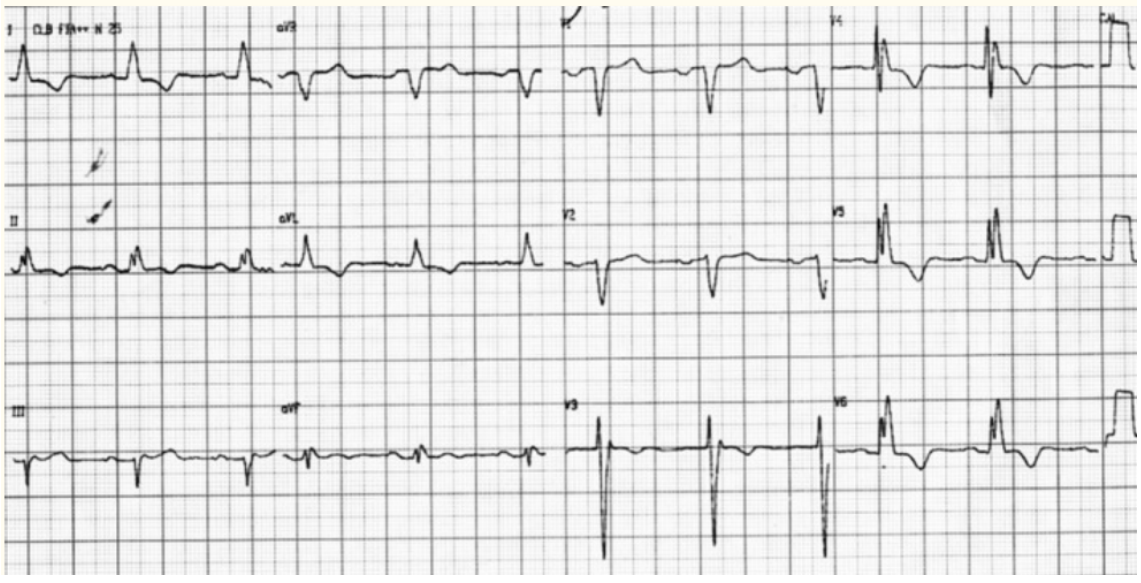

Figure 7. ECG performed immediately after SMVT reversion. Sinus rhythm, prolonged P wave duration (P = 145 ms), P, augmented P-terminal forces (PTF-V_1): LAE, first degree AV block. PR interval (260 ms): QRS duration 115 ms, fQRS. The ST segment

and T wave are in an opposite direction to the preceding QRS complexes in the lateral leads: strain pattern.

MVHOCM, when in association with apical aneurysm, frequently is complicated with SMVT, unlike other forms of HCM, the VTs of which are usually NSVT. This difference makes the MVHOCM more severe, which indicates the need of implanting an automatic ICD as a secondary prevention for SCD, in association with β-blockers. The latter are aimed at decreasing the number of shocks by the device.

An overview of Ap-HCM or Yamaguchi syndrome: Invigorating the value of the Electro-Vectorcardiogram

Ap-HCM or Yamaguchi syndrome is a non-obstructive subtype of HCM which predominantly affects the LV apex of the heart. The apex (the most inferior, anterior, and lateral part as the heart lies in situ) is located in the midclavicular line, in the fifth intercostal space, formed by the LV. The base of the heart, the posterior part, is formed by both atria, but mainly the LA. Ap-HCM is a rare form of HCM which usually involves the apex of the LV, but rarely the RV or both.[24] Ap-HCM was thought to be confined to the Japanese population but it is also found in other populations. Of all the HCM patients in Japan the prevalence of Ap-HCM was 15%, whereas in the USA the prevalence was only 3%.[25] Due to the nature of its presentation that mimics ACS and also to the unfamiliarity of the condition by some physicians, the diagnosis of Ap-HCM is frequently missed or delayed.[26, 27] This variant causes in 2%, 3% to 8%; obliteration of LV cavity at the apex together with an apical wall thickness >15 mm or a ratio between apical and basal LV wall thicknesses ≥1.3-1.5 cm.[4] This variant has a better prognosis than the other

variants, although it has been more associated with ischemia and apical myocardial infarction.[28]

The relevance of the ECG/VCG in Ap-HCM

ECG features in Ap-HCM

- Giant negative T waves in the precordial leads with negativity ≥1.0 mV (10 mm). The significant posterior and rightward shift of the ST/T vector is responsible for the characteristic giant negative T wave from V2 to V5 in the horizontal plane. T waves at the onset may not present a significant voltage and may appear later with the evolution of the disease.[29]
- The depth of negative T waves is related to craniocaudally asymmetry and apical late enhancement.[30]
- Exercise stress test may decrease the depth of T waves.[31]
- Three hypotheses emerged to explain these negative T waves: apical subendocardial ischemia, apical cell disorder, and greater duration of action potential of hypertrophied cells, thus conditioning the area to have a slower repolarization.[32]
- The prevalence of Ap-HCM in the western world is approximately 0.02 to 0.2% and constitutes 8% of HCM, while in Japan the apical form represents about 25%.[32]
- Prominent R waves in intermediate precordial leads are observed in ≈80% of Ap-HCM.
- Sometimes R-wave voltage and T-wave negativity progressively decrease in magnitude in serial ECGs.
- NSVT can be observed in patients who developed apical aneurysm with normal coronary arteries. In order to clarify the mechanisms of ECG abnormalities in HCM, 102 patients were examined with CMRI. 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.

VCG in Ap-HCM: type IV vectorcardiographic LVH of our classification

Figure 8 shows an ECG/VCG correlation in Ap-HCM in the horizontal plane.

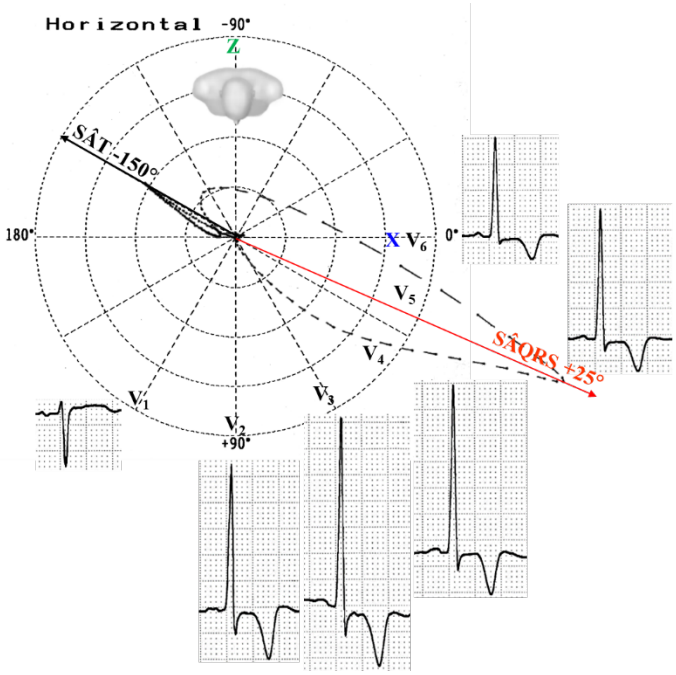

Figure 8. Vectorcardiogram in Ap-HCM (type IV vectorcardiographic LVH): initial vectors of QRS loop heading forward and to the left; QRS loop predominantly located in the left anterior quadrant; maximal vector that increases voltage; final vectors located in the right posterior quadrant; the **E** point (beginning of the QRS loop) is not coincident with the **0** point (end of the QRS loop) and located backward and rightward related the 0 point. This pattern is considered by us a type IV vectorcardiographic LVH.

We divided the vectorcardiographic LVH into five subtypes in the HP (modified from Varrriale)[33] (Figure 9).

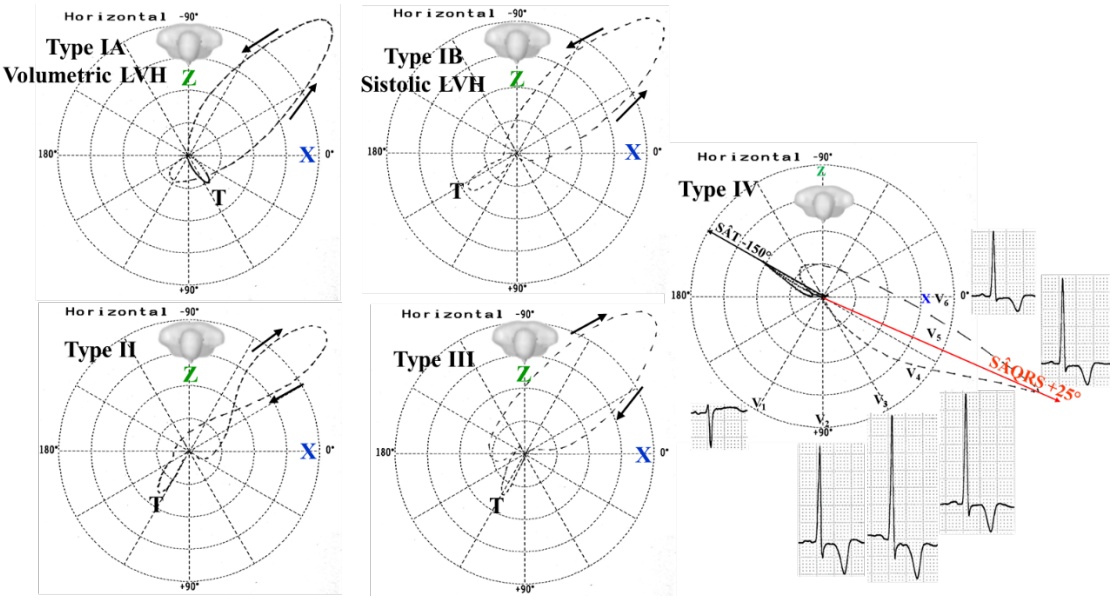

Figure 9. The diagnosis is based on the following elements in Ap-HCM (type IV LVH): giant (≥10mm) and negative T waves from V2 to V4; prominent R waves in intermediate precordial leads: QRS-loop predominantly located on anterior left quadrant (HP); T-wave axis in the right posterior quadrant in the HP and right superior quadrant in the FP: extreme axis deviation = QRS axis between -90° and ±180° ("Northwest Axis");[34] mild symptoms and benign course; aspect of spade cards in left ventriculography (pathognomonic?); absence of ventricular gradient; the incidence increases significantly the more advanced the age of the group under study, since typical ECG manifestations may appear late and with evolution.

Figures 10-16 illustrate a typical example of ECG/VCG in Ap-HCM.

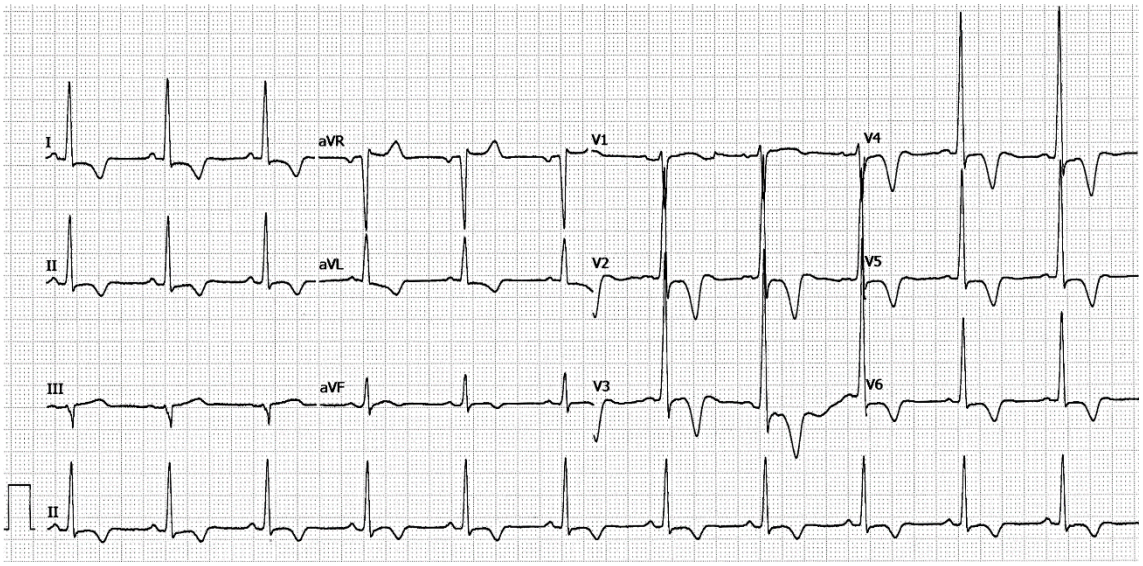

Figure 10. Prominent R waves in intermediate precordial leads, giant negative T waves only in V3 (T-wave ≥10 mm deep). By definition giant negative T wave is considered when ≥ 10 mm deep. In the present case only V3 meets this criterion. T wave is negative in I, II, aVL, and from V1 to V6. LVH criteria based on increase of amplitude or voltage of the QRS complexes. Positive Sokolow-Lyon index: S of V1 + R of V5 ≥35 mm in adults. Positive point score system for LVH or Romhilt-Estes Score = 6 points. ST-T vector opposite to QRS without digitalis. R wave in V5 or V6 ≥30 mm. 5 or more points: certain LVH.

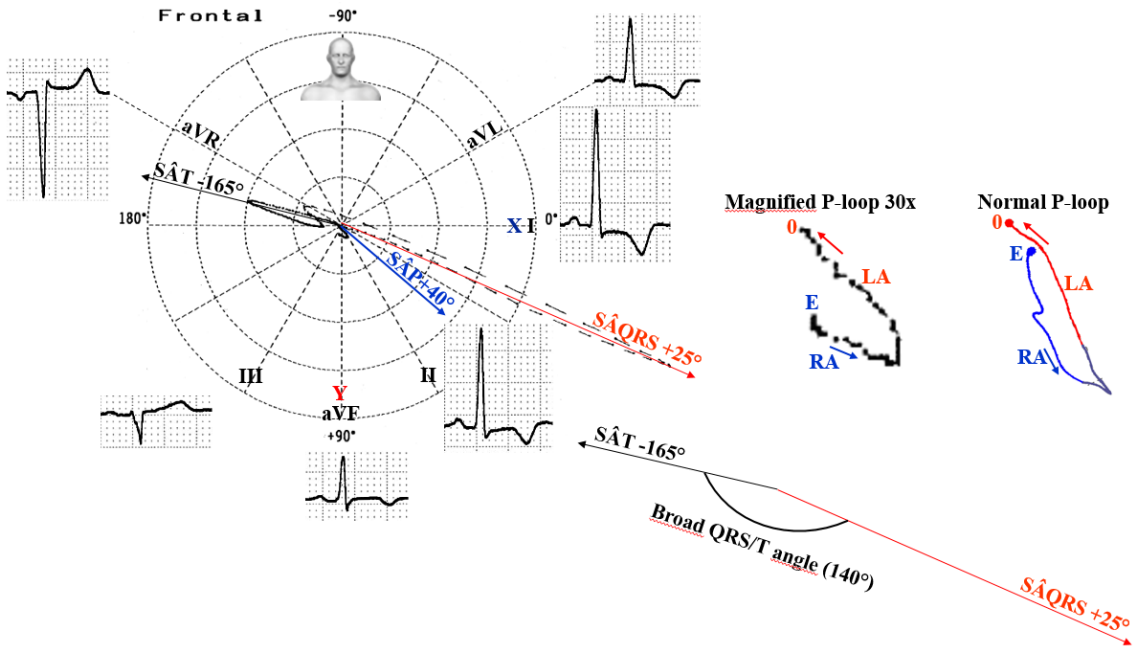

Figure 11. ECG/VCG correlation in the FP. Normal P- wave/loop, very broad QRS/T angle (140°): SÂQRS + 25°/ SÂT -165°.

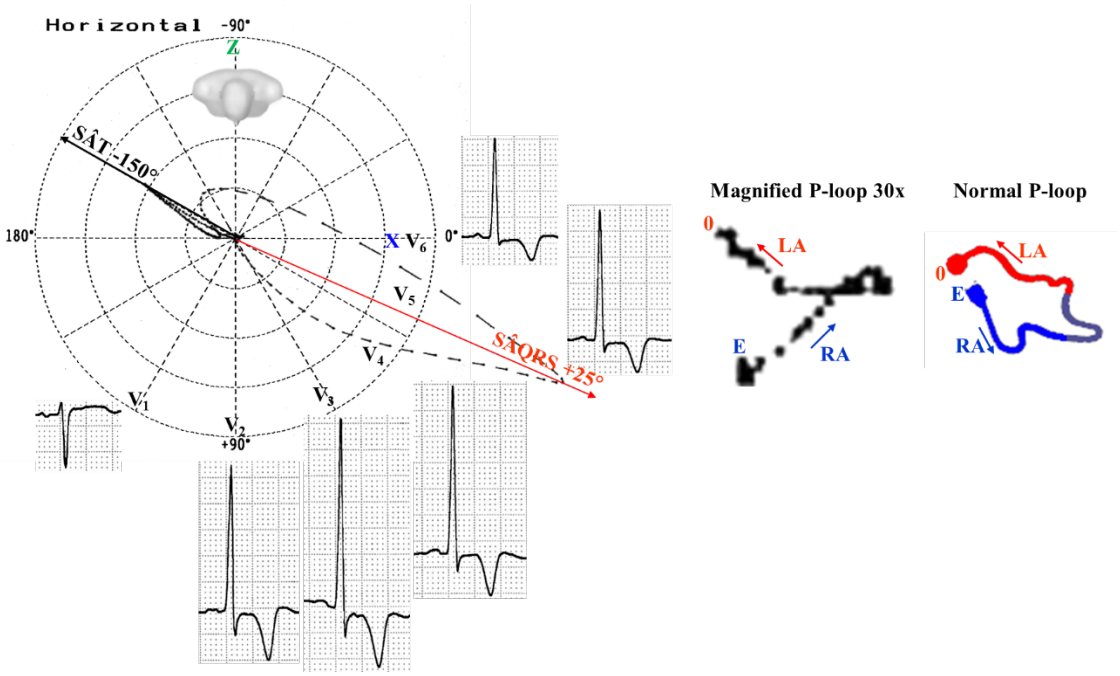

Figure 12. ECG/VCG correlation in the HP. QRS-loop predominantly located in the anterior left quadrant (≈25°, clockwise rotation), giant R wave from V2 to V5, and deep negative T-waves from V2 to V6. T-loop located in the right posterior quadrant (SÂT -165°). Very broad QRS/T angle near 160°). Wide QRS-T angle (>90°) in the 12-lead ECG is associated with an increased risk of SCA independent of the left ventricular ejection fraction.[35]

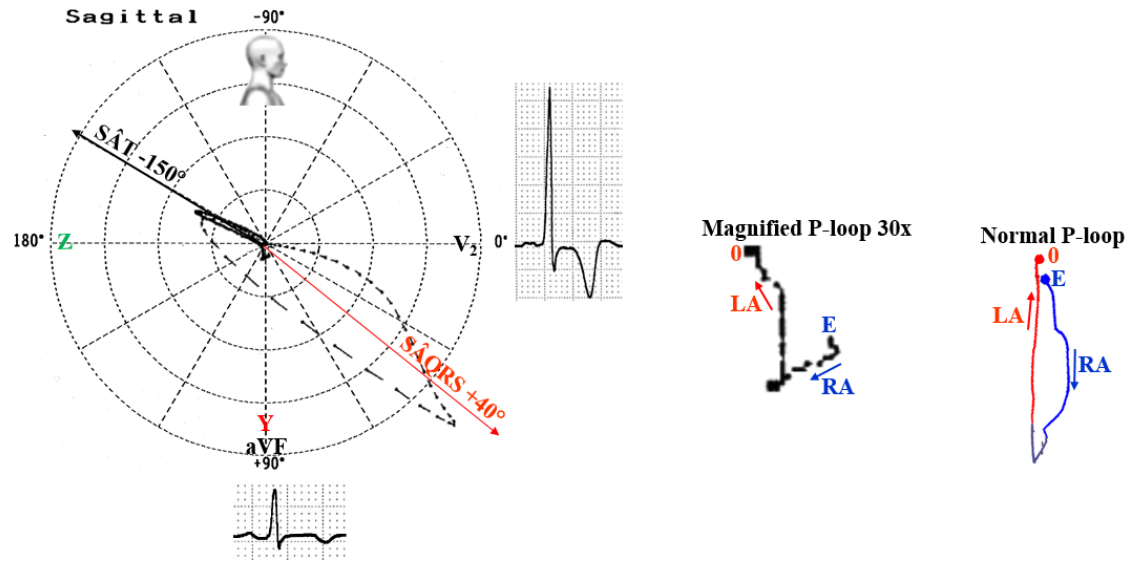

Figure 13. ECG/VCG correlation in the Right Sagittal Plane. Magnified P-loop shows normal (or near normal) P- wave/loop, very broad QRS/T angle (140°): SÂQRS + 40°/ SÂT -150°. Negative T-wave in V2 because T loop is directed to back and upward.

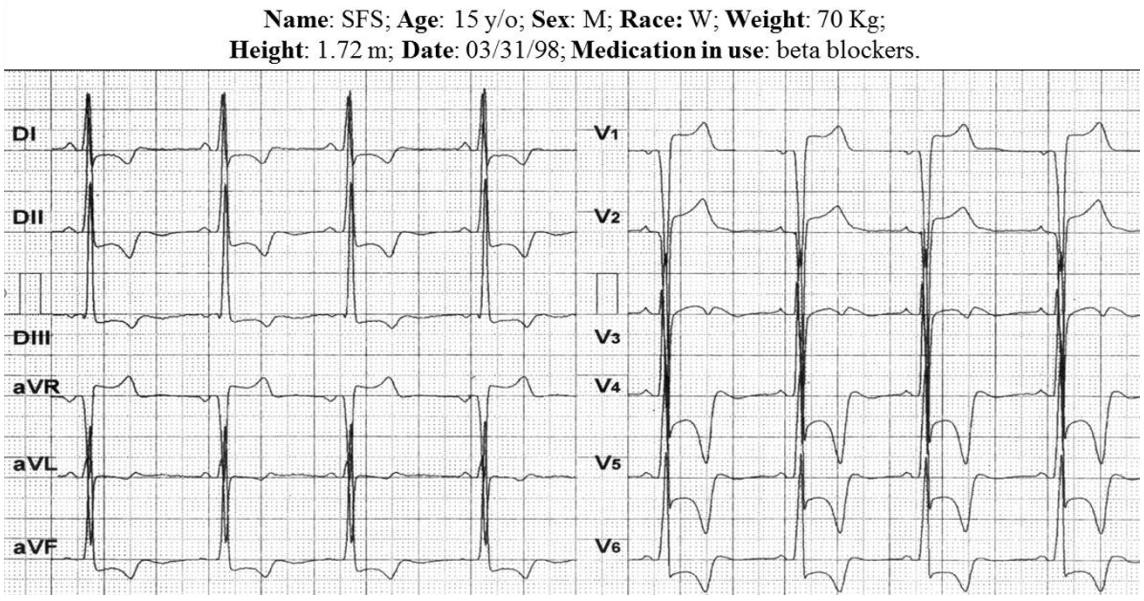

Figure 14. Clinical/echocardiographic diagnosis: Ap-HCM. Diastolic thickness of IVS in the apical region greatly increased (32 mm): Ap-HCM.

ECG diagnosis: sinus rhythm, LAE, normal QRS axis in the FP (+50º), LVH (positive Sokolow-Lyon index: S of V1 + R of V5 ≥ 35 mm or 3.5 mV in adults older than 30, 40 mm or 4.0 mV between 20 and 30 years (Sokolow-Rapaport), >60 mm between 16 and 20 years, and >65 mm between 11 and 16 years), QS pattern in V1-V2 contrasting with abruptly prominent QRS anterior QRS forces in intermediate leads (V3-V4), R wave of V5 or V6 >26 mm and strain pattern of ventricular repolarization from V4-V6, high lateral (I aVL), and inferior wall (II-III-aVF) leads with wide QRS/ST/T angle near ±180º.

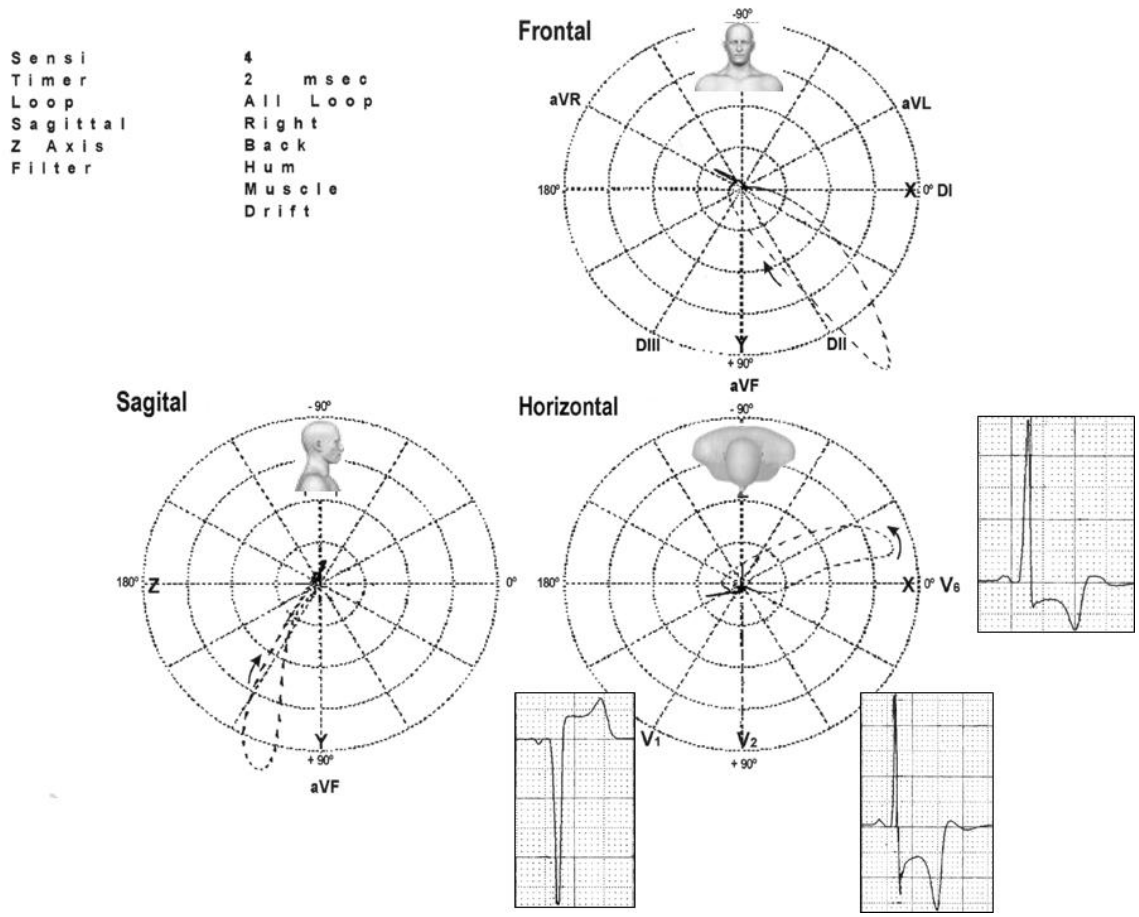

Figure 15. ECG/VCG correlation of the same patient: The main body of the QRS loop located in the left, inferior, and posterior quadrant, the magnitude of maximal QRS vector is clearly increased (>2.2 mV): LVH. Giant negative T wave from V4 to V6 (Ap-HCM).

Clinical case

A 41-year-old male patient with history of chest pain and exhaustion in strain. He mentioned systemic hypertension currently without treatment. He does not smoke or have diabetes. His father died with 77 years of age due to AMI? His brother died suddenly when he was 37 y/o while sleeping.

Cardiac auscultation: regular heart rhythm, HR=68 bpm + fourth heart sound without murmur, normal pulmonary artery and limbs, blood pressure = 140/100 mmHg.

The ECG was performed, and also TTE was suggested to rule out Ap-HCM. Several ECGs with the same morphology.

Supplementary tests. **TTE**: LV end diastolic diameter: 49 mm. LV end systolic diameter: 26 mm. Septal diastolic thickness: 14 mm; LV posterior wall diastolic diameter: 14 mm; aorta: 29 mm; LA: 40 mm; EF=78%; mass: 355 g.

Conclusion: moderate concentric LVH (moderate LV diastolic dysfunction, heart valves with normal morphological aspect, absence of gradient in the LVOT, mild mitral reflux). Holter monitoring: predominantly sinus rhythm, asymptomatic isolated ventricular ectopic beats (210), absence of NSVT.

Left heart catheterization: presence of myocardial bridge in the proximal $^{1}/_{3}$ of the LAD. LV with ap-HCM with apical predominance (ventriculography shows spade-like morphology). Normal coronary arteries.

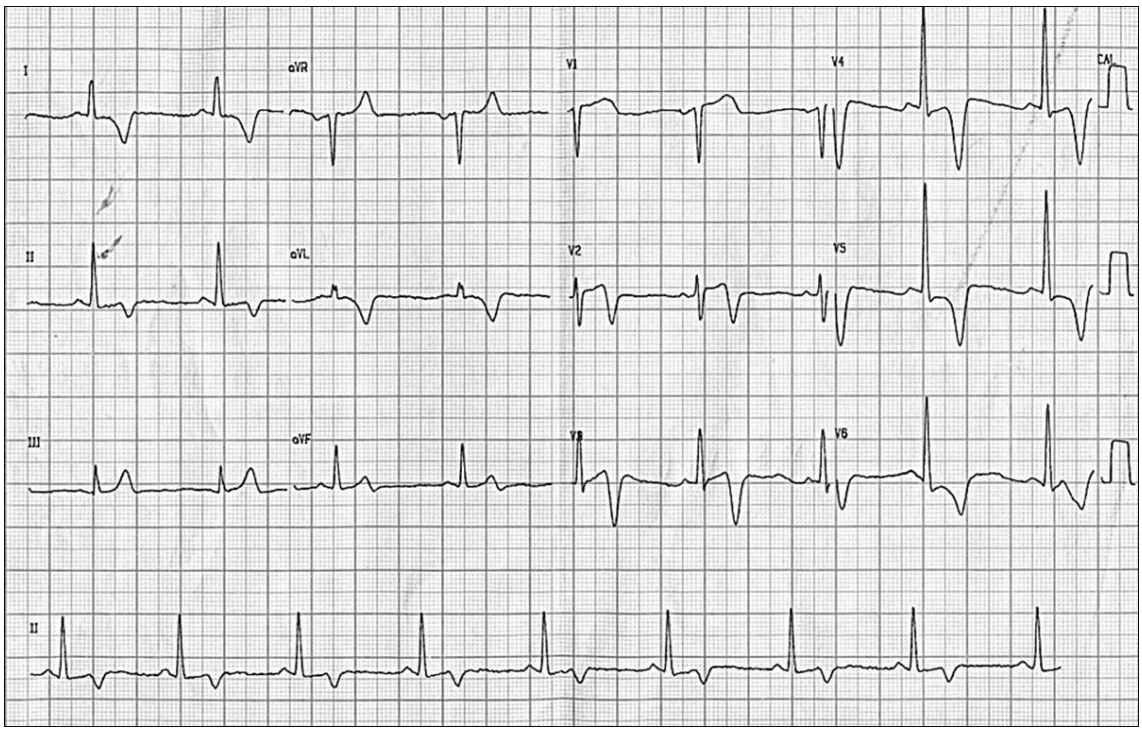

Figure 16. Deep TWI, asymmetric T-wave in I, aVL and from V2 to V6 in the inferior leads, biphasic T-wave in aVF, negative symmetric T-wave in II, V2-V3.

Vectorcardiogram features in Ap-HCM

In the apical form we find type IV vectorcardiographic LVH of our classification; nevertheless, it is not exclusive since other non-apical forms of HCM may display this pattern by presenting: initial vectors of the QRS loop heading to the front and the left; 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. This is the only case of LVH without CAD associated to T loop in this quadrant. A curious fact is constituted by the association of apical infarction and T loop in right posterior position; E point not coincident with the 0 point of the QRS-loop, and located backward and to the right from the latter.

Genetic background in Ap-HCM

HCM is inherited as an AD trait and is attributed to mutations in one of a number of genes that encode for one of the sarcomere proteins.

About 50-60% of patients with a high index of clinical suspicion for HCM will have a mutation identified in at least 1 of 9 sarcomeric genes. Approximately 45% of these mutations occur in the β myosin heavy chain gene on chromosome 14 q11.2-3, while approximately 35% involve the cardiac myosin binding protein C gene. Since HCM is typically an autosomal dominant trait, children of an HCM parent have 50% chance of inheriting the disease-causing mutation. Whenever a mutation is identified through genetic testing, family-specific genetic testing can be used to identify relatives at risk for the disease. In individuals without a family history of HCM, the most common cause of the disease is a de novo mutation of the gene that produces the β-myosin heavy chain. HCM is a myocardial disease with variable phenotypes and genotype. Non-obstructive

HCM localized to the cardiac apex (wall thickening is confined to the most distal region at the apex)

Ap-HCM is a specific variant of HCM. This variant has been first described in Japan where the prevalence is much higher than in the western world.

Ap-HCM, occurs in only 1 to 2% of the non-Japanese population.

Only a limited number of sarcomere gene defects (e.g., cardiac actin Glu101Lys) are consistently produce Ap-HCM.[36]

De novo cases are frequent. A single amino acid substitution in actin causes either CHF or maladaptive cardiac hypertrophy, depending on its effect on actin structure and function. De novo mutations in cardiac actin gene were identified in two patients with sporadic HCM who presented with syncope in early childhood. Patients were heterozygous for missense mutations resulting in Pro164Ala and Ala331Pro amino acid substitutions, adjacent to regions of actin-actin and actin-myosin interaction, respectively. A mutation that cosegregated with familial HCM was also found, causing a Glu99Lys substitution in a weak actomyosin binding domain. The cardiac phenotype in many affected patients was characterized by an Ap-HCM.[37]

Differential diagnosis with disorders that may involve the LV apex

There are many disorders that may involve the LV apex; however, they are sometimes difficult to differentiate. The spectrum of diseases that most frequently affect the apex of the LV include:

LV apical cardiac tumors: Primary tumors of the heart are rare, with an incidence of between 1.7 and 190 per 100 000 at unselected necropsy, the majority of which are benign.[38] Cardiac myxomata account for approximately half of these, occurring most frequently in the atria (75% LA and 20% RA), and rarely in the LV or RV (3–4% on

either side). Other benign primary cardiac tumors include papillary fibroelastomas, fibromas and lipomas. Diagnostic tool to establish diagnosis TTE with contrast/ CCT: CCT/CMRI.

LV apical thrombus: Mobility of LV apical thrombi was the most important parameter associated with early thrombus resolution. Late resolution of LV apical thrombi was associated with poor long-term clinical outcomes.[39] Diagnostic tool to establish diagnosis: TTE with contrast/CCT/CMRI.

Isolated LVNC: very unusual congenital cardiomyopathy. It is a disease of endomyocardial trabeculations that increase in number and prominence. This cardiomyopathy carries a high risk of malignant arrhythmias, thromboembolic phenomenon and LV dysfunction. Diagnostic tool to establish diagnosis CMRI/CCT.[40]

Endomyocardial fibrosis (EMF): an idiopathic disorder of the tropical and subtropical regions of the world that is characterized by the development of restrictive cardiomyopathy and fibrotic changes in the endocardium, usually limited to the cardiac apex. Diagnostic tool to establish diagnosis: CMRI/CCT. A LV angiogram shows apical obliteration during both systole and diastole in EMF, whereas in Ap-HCM obliteration occurs only in systole and also there is an absence of significant ventricular hypertrophy in EMF patients.[41]

CAD: Physicians caring for patients with chest pain should consider Ap-HCM in their differential diagnosis in case of a patient with chest pain and ECG changes suggestive of CAD.[42] Diagnostic tool to establish diagnosis: TTE/coronary angiogram and LVG.

Takotsubo cardiomyopathy ("octopus trap"): also known as transient apical ballooning syndrome, apical ballooning cardiomyopathy, stress-induced cardiomyopathy, Gebrochenes-Herz-Syndrome, broken heart, or simply stress cardiomyopathy. A bulging

out of the LV apex with a hypercontractile base of the LV is often noted. Its hallmark is bulging out of the apex of the heart with preserved function of the base.

LV false tendons: fibrous or fibromuscular bands that stretch across the LV from the septum to the free wall. They can also tether to a papillary muscle, but unlike the chordae tendineae, do not connect to the mitral leaflets. They are anatomic variants that should not be mistaken for abnormalities such as tumors, subaortic membranes, thrombus borders, septal hypertrophy.

Chronic Chagasic cardiomyopathy: the apical aneurysm with thrombus in it is a frequent and distinctive finding.[43] The apical aneurysm more frequent in men, unrelated to age, and heart weight. Patients dying of the cardiac consequences of Chagas's cardiomyopathy were more likely to have an apical aneurysm than those whose death was unrelated to the disease but the mode of death (SCD or with CHF) was unconnected with its presence. Trans illumination from within the ventricle at necropsy was not only useful in demonstrating the aneurysm but also showed areas of myocardial thinning elsewhere. Thrombosis within the lesion are frequent[44] (Figure 17).

LV aneurysms.

LV pseudo aneurysms.

Apical diverticula.

Apical ventricular remodeling.

ARVC/D with LV involvement.

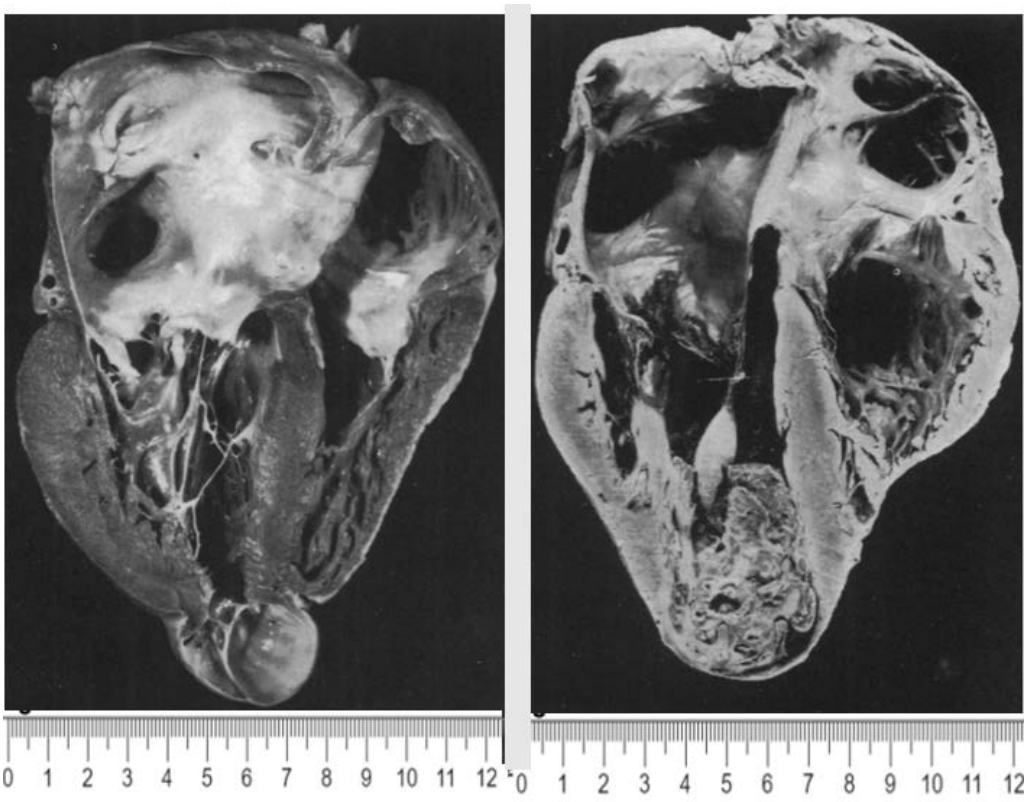

Figure 17. A) Chronic Chagasic cardiomyopathy with apical aneurysm. B) Thrombosis of the apical aneurysm.

Ap-HCM[45] with an emphasis on the diagnostic criteria and imaging features. In this setting cardiac imaging methods can provide the clue to obtaining the diagnosis.

Figure 18 shows a pathognomonic left ventriculography in Ap-HCM.

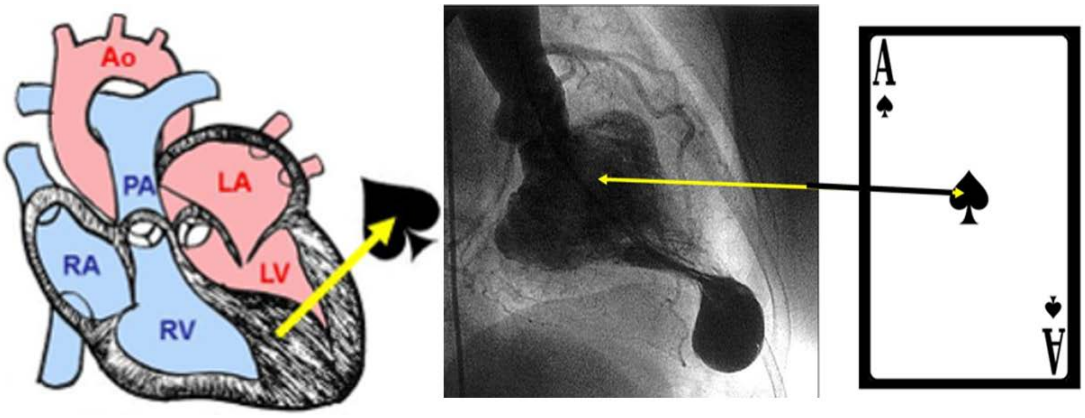

Figure 18. Left ventriculography pathognomonic of Ap-HCM: Ace-of-spades sign refers to the pathognomonic configuration of the LV as seen in Ap-HCM.[46]

Ap-HCM complications

Specific complications of apical HCM include:

1) **Apical infarctions** with resultant aneurysm formation, the so called burned-out apex. An apical aneurysm further increases the risk of
2) **Thrombi formation and thromboembolic phenomena.**
3) **MACE:** The presence of apical aneurysms or a significant amount of delayed enhancement (>5%) are major predictors of MACE and survival in Ap-HCM.
4) **AF:** common in HCM with a prevalence of 22-32 %. The impact of AF on overall survival, LV function, thromboembolic stroke and quality of life is crucial.

Prognosis

The prognosis of Ap-HCM regarding to SCD is believed to be better than that of OHCM. Patients with the Ap-HCM had a benign clinical course. However, the mutation Arg719Trp in the cardiac beta-myosin heavy chain (beta MHC) gene is a high risk factor for sudden death and can be associated with an unusual Ap-HC.[47] Current evidence suggests that these patients experience severe symptoms and are at increased risk of

ventricular arrhythmias and death, especially in the presence of an apical akinetic chamber. A large LV end diastolic dimension may predict cardiac events in Ap-HCM patients.[48]

Morbid sequel, and other extra-cardiac disorders such as: AF, diastolic dysfunction, LAE, apical thrombi, ventricular aneurysms/apical akinetic chamber, myocardial infarction, CHF, high incidence of coronary fistulae and morbid AF.[49]

Neuromuscular disorders (NMDs): Ap-HCM is rarely associated with NMDs, such as limb girdle muscular dystrophy, glycogen storage disease, metabolic myopathy, myopathy of unknown significance, or eosinophilia-myalgia syndrome. The rare association of NMDs with Ap-HCM might be due to absence of systematic neurological investigations of patients with Ap=HCM and vice versa.[50]

The probability of survival without morbid events at 10 years was 77±4%.

Three independent predictors of cardiovascular morbidity were identified: age at diagnosis ≥60 years, LA diameter ≥36 mm, and New York Heart Association class ≥III at baseline.[51]

ICD has been used in Ap-HCM patients with cardiac arrest and NS-VT.[17]

Unlike other variants of HCM, the prognosis of ApHCM is relatively benign. The overall mortality rate of Ap-HCM patients was 10.5% and cardiovascular mortality was 1.9% after a follow-up of 13.6 ± 8.3 years.[52]

Management

Currently available therapies for HCM have been effective in reducing morbidity, there remain important unmet needs in the treatment of both the obstructive and non-obstructive phenotypes. Novel pharmacotherapies directly target the molecular underpinnings of HCM. The recent developments in the treatment of HCM including pharmacotherapy. Medications used to treat symptomatic patients with Ap-HCM include

verapamil, beta-blockers and antiarrhythmic agents such as amiodarone and procainamide.

ICD: HCM patients with LV apical aneurysms are at high risk for arrhythmic sudden death and thromboembolic events. Identification of this phenotype expands risk stratification and can lead to effective treatment interventions for potentially life-threatening complications.[53] An ICD is recommended for high risk patients. In HCM, unlike CAD, prevention of SCD with ICD therapy is unassociated with significant increase in cardiovascular morbidity or mortality, or transformation to CHF deterioration. ICD therapy does not substantially impair overall psychological and physical well-being.[54] Ap-HCM, VTs of which are usually NSVT. This difference makes more severe, which indicates the need of implanting automatic ICD as a secondary prevention for SCD, in association to β-blockers. The latter are aimed at decreasing the number of shocks by the device.

Figure 19 shows image comparisons of TTE without and with contrast, and CRMI for the diagnosis, expanded risk stratification, and management implications in HCM. Patients with high-risk LV apical aneurysms.

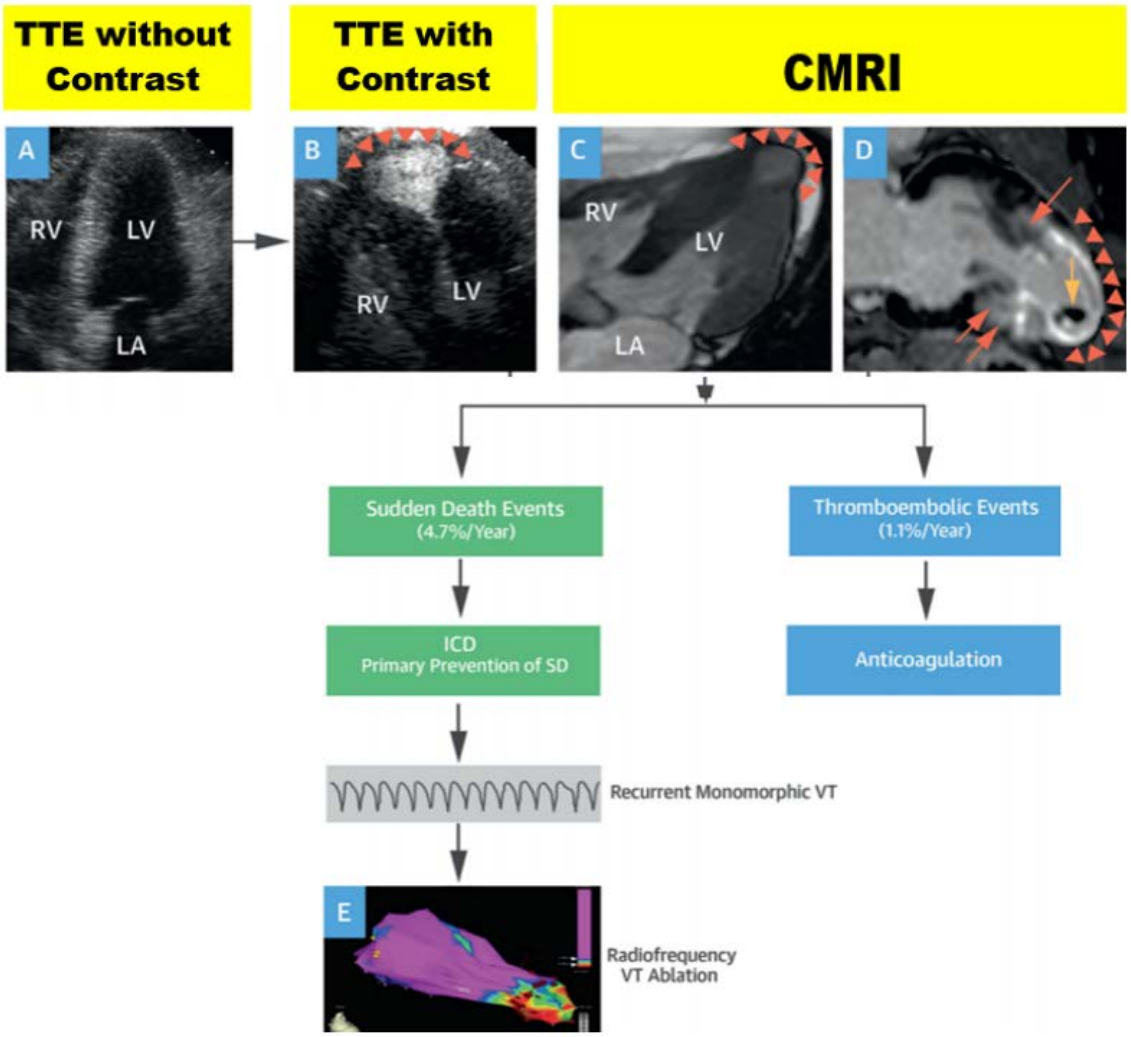

Figure 19. (A to D) Aneurysms more reliably identified by CMRI and contrast with TTE. (A) in 4-chamber view shows normal apical contour without evidence of apical aneurysm, whereas TTE (Echo) with contrast (B) and CMRI (C) in the same patient demonstrates medium-sized, thin-wall apical aneurysm (arrowheads) with associated hour-glass–shaped LV chamber (D). Aneurysms can raise risk of SD. (D) In another patient, contrast-enhanced CMR image shows transmural LGE of aneurysm rim (arrowheads) with contiguous cho into the inferior (short arrows) and anterior LV walls (long arrow), a potential nidus of MVT. Aneurysms are sources of thromboemboli. Marked signal intensity contrast between the bright aneurysm rim and hypointense mass (yellow arrow) confirms presence of a thrombus in the apical aneurysm. Below are management

implications and effect of treatment interventions, including prevention of SD with ICDs, radiofrequency ablation of arrhythmic focus for refractory monomorphic VT (E). and stroke prophylaxis with anticoagulation. (E) Electroanatomic endocardial voltage map in the right anterior oblique view of an apical aneurysm patient with recurrent VT. The red dots represent the ablation lesions delivered around the rim of the scarred aneurysm. ICD ¼; LA ¼; LV ¼; RV ¼; SD ¼ SCD; VT ¼.[53]

Ablation: Patients with Ap-HCM or non-Ap-HCM had similar success rate of AF ablation after single procedure and lower success rate after multiple procedure compared with the control group;[55] Long-term outcome of catheter ablation for AF was worse in patients with Ap-HCM, as compared to controls, but was similar to patients with asymmetric septal obstructive HCM.[56] Ap-HCM has a better prognosis than asymmetric septal HCM. However, the outcome of catheter ablation for AF in patients with Ap-HCM is similar. In patients with Ap-HCM, AF Is frequent and associated with a substantial risk for strokes and mortality suggesting that AF should be carefully managed in Ap-HCM.[57]

Monomorphic VT in Ap-HCM can be due to endocardial, epicardial or intramural reentry in areas of apical scar. ICD indications in HCM if one or more of the acknowledged SCD risk factors were present: family history of premature HCM-related death particularly if sudden, in a close relative, or multiple in occurrence, unexplained syncope, particularly in young patients, or if demonstrated to be arrhythmia-based, frequent, multiple, or prolonged episodes of NSVT documented in serial ambulatory, Holter monitoring and hypotensive or attenuated blood pressure response to exercise.

Concentric, symmetrical, diffuse or homogeneous HCM: This variant is characterized by thickening of the myocardium and a reduction of the LV cavity in absence of an identifiable cause such as hypertensive heart disease, aortic stenosis, athletes heart syndrome or infiltrative disease or n storage disorder (Danon's disease (X-linked), familial transthyretine-related amyloidosis (ATTR) (autosomal dominant). sarcoidosis, FD, etc), which represent ≈ 20% 5-10% [1-4] to 42% of all cases.[58] It is also characterized by diffuse parietal hypertrophy of the LV with reduction of LV cavity. This variant may also be present in the so called HCM phenocopies: amyloidosis, sarcoidosis and FD.[59] Danon disease (clinical triad of cardiomyopathy, skeletal myopathy, and intellectual disability). It is caused by genetic mutations in the lysosome-associated membrane 2 (LAMP2) gene, with most mutations leading to an absence of LAMP2 protein, and hypertensive heart disease; about 10 to 30% of black African/Afro-Caribbean athletes had abnormal ECG. R/S voltage criteria exceeding hypertrophic indices in about 60 to 89% of black African/Afro-Caribbean athletes. ST-segment elevation (17%-90%) and TWI are frequent findings among this ethnicity. About 10 to 12% of black African/Afro-Caribbean athletes had a LV wall thickness ranging from 13 to 15 mm. Cavity dimensions ranged from 40 to 66 mm in black African/Afro-Caribbean athletes with a relative wall thickness >0.44.[60]

Athletic training may lead to cardiac remodeling, both electrophysiologically and structurally. Depending on the training intensity and duration, the size of the cardiac cavities often increases, in particular that of the LV. In addition, LV wall thickness may eventually reach the level of LVH mainly in Afro-descendants. However, this remodeling process mainly affects males; at a comparable training intensity and duration, male athletes, on average, develop a higher degree of LVH than females.[61, 62] The LVH is occasionally hard to distinguish from pathological HCM, however, in the athlete's heart,

the diastolic function usually remains normal, yet subtle changes may occur, in particular in males.[63] In addition, evidence also suggests that athletic training may lead to adverse RV remodeling, even towards a RV cardiomyopathy phenotype.[64]

Focal HCM: Characterized by hypertrophy located in the myocardium. CMRI helps distinguishing focal HCM from other cardiac masses, by identifying evidence of myocardial contractility in the former case.[17]

HCM in RV or biventricular: This variant occurs in 18% of HCM patients, generally involving the mid- and apical portion of the RV, which may cause RVOTO in severe cases. Increased maximum thickness of the RV wall (>8 mm) has been shown by CMRI in approximately 20% of HCM patients.[59] Areas with increased wall thickness are commonly observed in the insertion of the RV wall into anterior and posterior septum, although the entire RV may be involved. Figure 20 shows an ECG example of pseudo LVH and Figure 21 RVH associated to LVH (biventricular hypertrophic pattern).

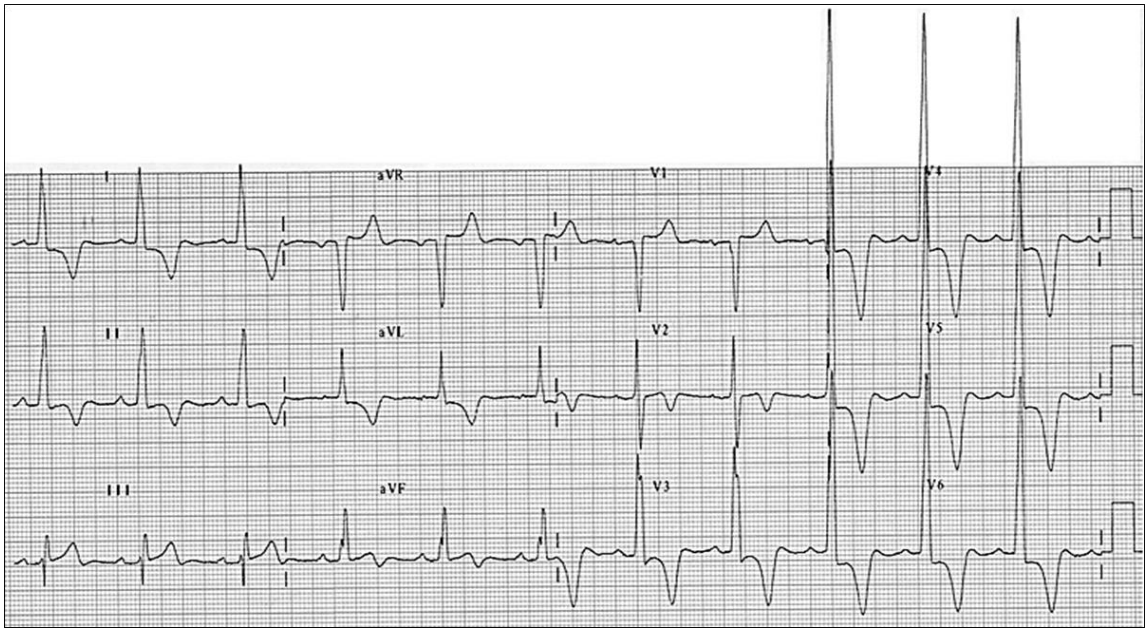

Figure 20. Note signs of severe LVH, pure and discreetly wide R in I, aVL, V5 and V6 with STSD followed by negative asymmetrical TWI suggesting incomplete LBBB. The

precordial transition zone is dislocated to right (isodiphasic QRS in V2) with abrupt onset of pure R with high voltage in V3 indicating counterclockwise rotation of the heart around the longitudinal axis of the heart. Strain pattern of repolarization: STSD convex to the top followed by asymmetrical giant TWI wave, although in some leads (as II) T wave tends to be symmetrical (this tendency to symmetry indicates severe degree of LVH).

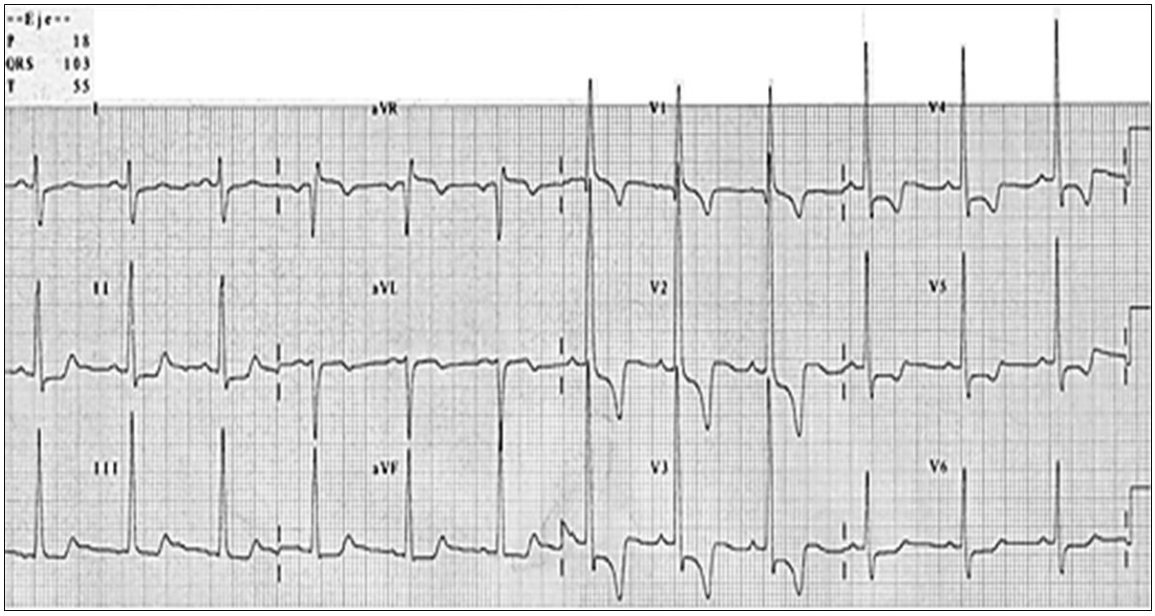

Figure 21. Clinical diagnosis: HCM with mutation in troponin I and RVH associated to LVH. ECG diagnosis: Note elements of biventricular LVH associated with RVH: electrical QRS axis +100° qR pattern in V1 with R of high voltage in right precordial leads. This shaft right into I with rS pattern in leads I and aVL might erroneously suggest left posterior fascicular block. But remember that the postulate by Rosenbaum says, "the diagnosis of LPFB is only possible in the absence of clinical RVH, vertical heart or lateral myocardial infarction."

Lateral and/or posterolateral HCM: Multiple clinical, genetic, and morphologic features, such as risk of SCD from arrhythmia, diastolic dysfunction, or LVOTO, the major determinant of progressive CHF. Consequently, HCM is a complex heart disease

with variable hypertrophy location in the LV and/or RV. Additionally, HCM is the most frequent and prototypic monogenic cardiovascular entity or single-gene disease, with most often AD inherited with variable expressivity and incomplete penetrance.[65] HCMs are heterogeneous group of pathophysiological mechanisms and etiologies, which lead to the development of LVH, not explained by a significant and prolonged increase in post-load. OHCM is an inherited myocardial disease defined by cardiac hypertrophy (wall thickness ≥15 mm) that is not explained by abnormal loading conditions, and LVOT ≥30 mmHg, diastolic dysfunction, myocardial ischemia, and mitral regurgitation.

HCM: epidemiology and genetic background

HCM is the most common monogenic cardiovascular disorder.

Prevalence: in the general population around the world is 0.2% (1 in 500 adults), 1 case per 200 to 500 persons.[66]

Sex ratio: M/F ratio 1:1. Genetic inheritance does not follow sex predilection as consequence of AD pattern of inheritance**.** It is a way a genetic trait or condition can be passed down from parent to child. One copy of a mutated (changed) gene from one parent can cause the genetic condition. A child who has a parent with the mutated gene has a 50% chance of inheriting that mutated gene. Men and women are equally likely to have these mutations and sons and daughters are equally likely to inherit them.

Age presentation: The most common presentation is in the third decade of life but may be present at any age, from newborns to elderly patients.

The morphologic evidence is found in ≈25% of first-degree relatives of patients with HCM.

Global distribution: So far it has been described in 122 countries, 20 million peoples affected worldwide, accounting for 88% of world population.

Clinically identified individuals: only 10%, Unidentified: 90%; Symptomatic: 6%, Asymptomatic: 4%,

Inherited pattern: AD inheritance.[67]

Genes mutations: HCM is caused by mutations in genes encoding the tree different myofilament contractile components of the sarcomere: The thin (≈ 5%), thick(≈ 45%) and Z disc (≈ 1%) with 11 mutations or more genes sarcomere genes mutations, with β-myosin heavy chain and myosin-binding protein C genes most commonly involved.[68-70] There are more than 2000 sarcomere pathogenic or with uncertain pathogenicity mutations. Many mutations are confined to single families.[71, 72]

Figure 22 shows the main sarcomere gene mutation locations in HCM in thick, thin, contractile myofilaments and Z disk protein. Pathogenic variants (PVs) in genes encoding protein constituents of the sarcomeres are the main causes of HCM. PVs exhibit a gradient of effect sizes, as reflected in their penetrance and variable phenotypic expression of HCM. MYH7 and MYBPC3, encoding β-myosin heavy chain and myosin binding protein C, respectively, are the two most common causal genes and responsible for ≈40% of all HCM cases but a higher percentage of HCM in large families. PVs in genes encoding protein components of the thin filaments are responsible for ≈5% of the HCM cases.[73]

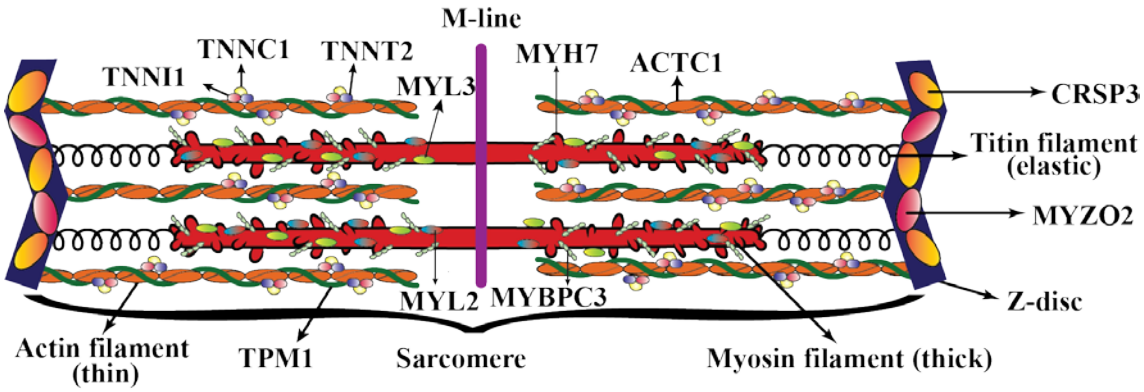

Figure 22. Thick contractile myofilament proteins (≈ 45%): MYBPC3 (20%), MYH7(20%), MYL2(<1%), MYL3(<1%). Thin contractile myofilament proteins (≈ 5%): ACT1 gene (Actin), TPM1(Tropomiosin1), TNNI3, TNNC1, TNNT2. Z disk protein (≈ 1%) CRSP3, MYZ02.

HCM is caused by a mutation in a group of related genes that make up the cardiac sarcomere. More than 2000 mutations in any of at least 11 genes encoding the molecular components of the sarcomere can lead to development of HCM. One or more of these genetic mutations are found in up to 60% of individuals with a family history of HCM and 30% of those without a family history. Table 2 lists genes implicated in HCM.

Gene	Protein	Function
Established causal gene HCM (large families)		
MYH7	β-Myosin heavy chain	ATPase activity, force generation
MYBPC3	Myosin-binding protein C	Cardiac contraction
TNNT2	Cardiac troponin T	Regulator of actomyosin interaction
TNNI3	Cardiac troponin I	Inhibitor of actomyosin interaction
TPM1	α-Tropomyosin	Places the troponin complex on cardiac actin
ACTC1	Cardiac α-actin	Actomyosin interaction

MYL2	Regulatory myosin light chain	Myosin heavy chain 7–binding protein
MYL3	Essential myosin light chain	Myosin heavy chain 7–binding protein
CSRP3	Cysteine- and glycine-rich protein 3	Muscle LIM protein (MLP), a Z disk protein
Likely causal genes for HCM (small families)		
FHL1	Four-and-a-half LIM domains 1	Muscle development and hypertrophy
MYOZ2	Myozenin 2 (calsarcin 1)	Z disk protein
PLN	Phospholamban	Regulator of sarcoplasmic reticulum calcium
TCAP	Tcap (telethonin)	Titin capping protein
TRIM63	Muscle ring finger protein 1	E3 ligase of proteasome ubiquitin system
TTN	Titin	Sarcomere function
Genes associated with HCM (small families and sporadic cases)		
ACTN2	Actinin, α2	Z disk protein
ANKRD1	Ankyrin repeat domain 1	A negative regulator of cardiac genes
CASQ2	Calsequestrin 2	Calcium-binding protein
CAV3	Caveolin 3	A caveolae protein
JPH2	Junctophilin-2	Intracellular calcium signaling

LDB3	Lim domain binding 3	Z disk protein
MYH6	Myosin heavy chain α	Sarcomere protein expressed at low levels in the adult human heart
MYLK2	Myosin light chain kinase 2	Phosphorylate myosin light chain 2
NEXN	Nexilin	Z disc protein
TNNC1	Cardiac troponin C	Calcium-sensitive regulator of myofilament function
VCL	Vinculin	Z disk protein

Table 2. Genes Implicated in HCM.

The Z score for each gene reflects deviation of the observed variants in the ExAC database from the expected number. A higher positive *Z* score indicates that the gene is intolerant to variation. Likewise, pLI indicates probability of intolerance to LoF variants with 1 indicating total intolerance. HCM indicates hypertrophic cardiomyopathy; and LoF, loss of function.

Methodologies used for the diagnosis of HCM

ECG:[74-76] In an era of fast technological development and evolving diagnostic possibilities, the ECG is living an authentic "rebirth" in cardiomyopathies. Currently, the ECG remains an irreplaceable first step when evaluating patients with 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 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.[77] The ECG in the diagnosis and management of patients with HCM is altered in > 90% of cases. In presence of HCM diagnosis a normal ECG is indicative of good prognosis.[78]

TTE: It is the first-line imaging test to confirm the diagnosis of HCM. Diagnosis of HCM: wall thickness > 15 mm at the end of diastole in at least one LV myocardial segment or ≥13 mm in patients with a first-degree relative with confirmed HCM, and a septal to lateral wall thickness ratio ≥1.3 in a non-dilated LV, and in the absence of other conditions that may explain such abnormality.[79] . Different studies done on athletes to assess the morphological changes of the LV show that the thickness of the IVS rarely exceeds 12 mm in men and 11 mm in women; also, when present, LVH is typically symmetric. African-American athletes have a higher prevalence of LVH. Only 2% of healthy Caucasian athletes show an IVS between 13 and 16 mm, and none above 16 mm; in healthy black athletes though, LV hypertrophy (IVS ≥ 13 mm) is detected in 18% of males and (IVS > 11 mm) in 3% of females. Although a minority, athletes in the “gray zone” of LVH with an IVS between 13 and 15 mm constitute a diagnostic challenge for differentiating an adaptive LVH from an initial expression of HCM. Some TTE parameters should be assessed to help in differential diagnosis. TTE: the most available method to assess morphological and functional changes of HCM.

Limitations: patients with poor acoustic window, poor visualization of basal anterolateral wall of LV, apex and RV.[80]

Ambulatory ECG Holter monitoring: It should be performed for 24 to 48 hours in all patients diagnosed with HCM for risk assessment of atrial and ventricular arrhythmias and SCD.

Kawasaki et al, aimed to examine Holter findings in relation to the long-term prognosis in patients with HCM.[81] Ambulatory Holter monitoring were performed in 106 HCM patients with sinus rhythm. All were prospectively followed for the composite endpoint of SCD, cardiovascular death, and hospitalization for CHF stroke associated with AF. Cardiovascular events occurred in 19 patients during a mean follow-up of 10.1 years. Neither arrhythmia information nor autonomic information as assessed by HR variability and turbulence significantly differed between HCM patients with and without cardiovascular events. Average heart rates were lower in HCM patients with cardiovascular events than in those without. Multivariate Cox proportional hazards regression analysis after adjustment for baseline characteristics showed that lower average HR remained an independent predictor of cardiovascular events.

Exercise stress testing: Its provides useful information regarding functional capacity, efficacy of treatment, blood pressure response to exercise and inducible ischemia). On the other hand, the utility of exercise stress testing in the evaluation of the arrhythmic risk in HCM patients appears to be limited to the identification of low-risk patients. Exercise stress testing in controlled environment seems to be safe in properly selected patients with HCM, and benefits of the diagnostic and prognostic information obtained outweigh the small risks,.[82]

Exercise echocardiography: This resource can be helpful to study induction of arrhythmias, abnormal blood pressure response to exercise, and induced LVOT gradient in patients with HCM and may aid in differential diagnosis, although the non-existence of these features does not exclude the diagnosis of MCH. Maximal oxygen uptake would

not help in the differential diagnosis.[83] The exercise echocardiogram evidences latent obstruction easily induced by exercise in 60 to 75% of NO-HCM. The determination of the gradient under this condition must be considered in routine investigation of patients with mild or no obstruction at rest. The evaluation of HCM incorporates methods based on the ultrasound image, which, along with CMRI, allow recognizing ventricular obstruction generating mechanisms, thus facilitating the diagnosis and management of NO-HCM and latent obstructive forms.

Exercise TTE: A significant number of patients without resting LVOTO develop mechanical obstruction with exercise due to mitral-septal contact). Hypotensive blood pressure response to exercise can be an arbitrator in risk stratification decisions. Exercise testing with a variety of methods has become an integral and powerful component of the noninvasive evaluation of HCM, and in some patients can determine treatment strategy.[84]

LGE-CMRI: A reliable, accurate, quantitative analysis of LV wall thickness is fundamental, since a measurement >30 mm increases the risk of SCD.[85] Therefore, this may be a crucial information for the implant of ICD to prevent SCD in some patients. Measurements of LV wall thickness should be performed in the short-axis, at the end of diastole.[59] LV mass, quantified by CMRI (indexed for body surface area), >2 standard deviations above the normal range is a sensitive predictor of favorable clinical outcomes in HCM. The normal range for LV mass index is 62.5 ± 9.0 g/m2 for men and 54.6 ± 12.0 g/m2 for women.[59] However, the measurement of LV mass lacks specificity as an indicator of clinical outcomes, probably because in many HCM patients, hypertrophy is limited to a small number of segments of the LV.[85] CMRI is more accurate than TTE in diagnosing ventricular hypertrophy, its magnitude and distribution.[86] Consequently, the method is decisive for stratifying the risk of HCM. In addition, CMRI provides a better evaluation of hypertrophy distribution, mainly when it is localized in the anterolateral

region, and in posterior and apical septum of LV,[80] and a more reliable quantification of the myocardial mass in case of asymmetric HCM.[59] Myocardial fibrosis can be detected by LGE-CMRI. This method is based on the property of gadolinium to distribute in the extracellular space between normal and fibrotic tissue, leaving the latter tissue in a slower rate.[87] There is no standard of reference for LGE in HCM, although its presence in the IVS, particularly in the mid- and basal anteroseptal segment, is suggestive of HCM.[59] LGE can also occur in LV free wall and hypertrophied segments of the ventricles. These data indicate that analysis of the segments by delayed enhancement CMRI is an important parameter for differential diagnosis of HCM.[88] LGE is found in 65% of patients and the distribution of fibrosis typically follows a multifocal, heterogeneous and mid-wall pattern. LGE is not commonly found in non-HCM, except in advanced stages, and can be associated with increased myocardial stiffness and reverse remodeling of the LV. An inverse relationship between LGE and LV function was verified.[17] The presence of LGE predicts a worse prognosis for HCM patients due to higher risk of SCD, systolic dysfunction and NSVT.[89] Areas of LGE may represent the substrate for MACE. LGE-CMRI is a supporting tool in the decision-making process for primary prevention ICDs in patients in whom high-risk for SCD remains uncertain after assessment of conventional risk factors.[90]

Contraindications for CMRI: previous ICD implant, implanted pacemaker, (Currently, the test can be performed in some pacemakers and patients.[91]) brain clips, cochlear implants, and metallic fragments in the eyes.[87]

Limitations for CRMI: nephrogenic systemic fibrosis (which causes systemic tissue fibrosis and is associated with the use of gadolinium in patients with stage 4 and 5 chronic renal failure) and patients with hepatorenal syndrome.[92]

CCT: Its provides a precise delineation of the myocardium and measurement of cardiac wall thickness, ventricular volumes, and LVEF, which are well correlated with the CMRI findings. Additionally, CCT allows the assessment of coronary trees and cardiac valves. CCT should be considered in patients with poor acoustic window for TTE or contraindications for CMRI (class IIa).[80] CCT has a wide range of clinical applications due to anatomic and functional properties. However, they are indicated only in case of diagnostic doubt, poor acoustic window to perform TTE or contraindications to perform CMRI. Therefore, CCT is rarely used as the first method of choice for patients with HCM.[93] Both CMRI and CCT are important tools for the assessment of HCM patients.[88]

Bone scintigraphy in the event of suspected amyloidosis: There are two main subtypes of cardiac amyloidosis: transthyretin-related cardiac amyloidosis (ATTR) and cardiac light-chain (AL) amyloidosis.[94] Differentiating the two is important for both prognosis and management, and this was only possible through invasive biopsy procedures. Additionally, bone scintigraphy is able to reliably distinguish between the two.[95]

Genetic analysis and/or counselling should be systematically considered.

HCM is defined as abnormal thickening of the LV myocardium without dilatation and in the absence of any other systemic disease leading to afterload augmentation, such as aortic stenosis or hypertension (unexplained LVH). Hypertrophy is typically asymmetric and sometimes exuberant.[96] HCM has with a maximum wall thickness ≥15 mm in adults or a z-score >3 in children.[80, 90] If there is a family history of HCM, or if genetic testing confirms that a relative has inherited the family's pathogenic sarcomere variant, a maximum LV wall thickness ≥13 mm supports diagnosis. Such LVH occurs in a non-dilated ventricle in the absence of other cardiac or systemic disease capable of producing the observed magnitude of increased LV wall thickness, such as hypertension or

storage/infiltrative disorders. The diagnosis of HCM is most often established with TTE and/or CMRI.

Clinical history

Often, patients with HCM remain asymptomatic or mildly symptomatic, and present to medical attention after identification of a suggestive family history, detection of a murmur on physical examination, or an abnormal ECG. The most common presenting symptom is dyspnea (90% of cases). Dyspnea is a consequence of elevated LV diastolic filling pressures (and transmission of those elevated pressures back into the pulmonary circulation). The elevated LV filling pressures principally are caused by impaired diastolic compliance as a result of marked LVH. chest discomfort presyncope, syncope. Syncope is a very common symptom, resulting from inadequate cardiac output upon exertion or from cardiac arrhythmia. It occurs more commonly in children and young adults with small LV chamber size and evidence of VT upon ambulatory monitoring, palpitations, angina, orthopnea, paroxysmal nocturnal dyspnea, dizziness, CHF, and SCD. Important historical clues include progressive exertional intolerance and lightheadedness or syncope during or immediately following exertion or when dehydrated. It has the highest incidence in preadolescent and adolescent children and is particularly related to extreme exertion. The risk of SCD in children is as high as 6% per year in >80% of cases, the arrhythmia that causes SCD is VF. Many of these cases degenerate into VF from fast atrial arrhythmias, such as AG, supraventricular tachycardia, or WPW syndrome, while others result from VT and low cardiac output hemodynamic collapse. A multigenerational family history should be elicited at initial evaluation focusing on relatives with any cardiac diagnoses, "thick" hearts, "heart attack" or stroke early in life, abnormal heart rhythms, permanent pacemakers or ICDs, CHF, or heart

transplantation. Reported history of SCD should trigger focused questions regarding relatives with premature or unexpected death, death associated with exertion, and availability of autopsy or postmortem genetic testing.

Physical examination

The presence of a harsh crescendo–decrescendo systolic murmur at the lower left sternal border, a mid–late systolic apical murmur or holosystolic apical murmur, and/or paradoxically split S2 should alert clinicians to the possibility of HCM fatigue, Findings are characterized by, laterally displaced apical impulse, and double carotid pulse. A double apical impulse due to forceful LA contraction against a highly noncompliant LV, normal S1 and split S2, S3 due to CHF, prominent "a wave" of jugular venous pressure. A systolic ejection murmur is present as follows: diminished intensity with increase preload (squatting) or afterload (handgrip) and increased intensity with a decrease in preload (Valsalva maneuver, Orthostatic position and post premature ventricular contraction increase Gradient and cardiac murmur), and with any decrease in afterload (vasodilator administration, squatting position and hangrip maneuver decrease the gradient and cardiac murmur).

ECG phenotypes in HCM

The most common abnormalities are LVH, ST-segment alterations, TWI, deep narrow Q waves in lateral leads or inferolateral leads and the peculiar diminution of R waves in the lateral precordial leads seen in this patient.

Presence of deep S waves in V1 and V2 and large R waves in V5 and V6 strain repolarization changes are common findings. Another ECGs frequently registered are pathological Q waves in the inferior and lateral leads with ≥40 ms duration and ≥3 mm

depth suggest LV asymmetric septal hypertrophy, P-wave abnormalities related to LAE (duration >120 ms, notch P-wave mitrale, Morris index).

WPWS is observed in a glycogen-storage disease produced by LAMP2 or PRKAG2 mutations or FD.

Sinus Node Dysfunction/ SSS: The characterization consists in periods of inappropriate and often severe sinus bradycardia. Sinus pauses, sinus arrests and sinus exits blocks that can happen with and without appropriate escape rhythm, alternating tachycardia and bradycardia, referred to as a tachy-brady syndrome, which could also be associated with supraventricular tachycardia. *Meaning:* Abnormal automaticity, conduction, or both of the SAN and surrounding tissues. Patients with HCM may have SSS together or SSS may develop in later years. Antiarrhythmic drug therapy should be given carefully and 24-hour ambulatory electrocardiogram monitoring should be done in certain periods.[97]

Abnormal His-Purkinje conduction: These are observed in 15-30% of HCM patients.[98] *Meaning:* Abnormal His-Purkinje system conduction may result in CHB.[99]

P-wave. ***Characterization possibilities****:* Normal, **LAE, RAE** or **BAE** patterns.

LAE: is characterized by broad, bifid P wave in lead II "P mitrale", In lead II bifid P wave with inter peaks of P wave >40 ms, P wave duration >110 ms in adults, ≥120 ms in seniors, and 90 ms in children and biphasic P wave with terminal negative portion >40 ms duration and >1mm deep: Morris index: S= 69%; SP=93%[100] (P terminal force in V1 mm/s) (0.04 mm/s). SÂP beyond +30°.[101] In V1 LAE pattern reflects diastolic dysfunction, high filling pressures, LVOTO, functional mitral regurgitation and progression toward the end-stage phase. 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 this hemodynamic situation is frequent registered left atrial

enlargement (LAE) (“P mitrale”) consequence of the left ventricular diastolic dysfunction that may lead to compensatory LAE. In LAE, the Chronic LAE can produce AF eventually in its evolution, which results in severe hemodynamic deterioration, systemic embolism, because of the importance of atrial systole in the presence of the impaired relaxation.[102] The presence of LAE is a marker of poor prognosis,[103] augmentation of LV end diastolic pressure and diminution of LV compliance.[104]

RAE: It is characterized by peaked P wave (“P pulmonale”) with amplitude >2.5 mm in the inferior leads (II, III and aVF), Sensitivity (S)= 7%, Specificity (SP)=100 %), positive part of P wave in V1-V2 >1.5mm (S= 7%; SP=100 %), and combined criteria: positive part of P wave in V2 >1.5mm + SÂQRS>+90° + R/S>1 in V1: S=49% SP=100%.

RAE is present in 14% t of patients with HCM, and reflects increased pulmonary pressures because of severe diastolic and/or systolic LV dysfunction. Patients have a higher prevalence of sarcomeric gene mutations, troponin T mutations and complex genotypes. RAE is a marker of disease progression and adverse outcome in sarcomeric HCM.[105] RAE as an independent predictor of MACE. Finally, RAE is observed in the so-called Bernheim's syndrome characterized by RVH cardiomyopathy leading to RVOT dynamic obstruction by right eccentric hypertrophy of the right side of ventricular septum.[106]

BAE: lead II (amplitude ≥2.5 mm + duration ≥120 ms), lead V1 or a combination of leads. lead V1 or a combination of leads. Biphasic P waves with initial positive deflection ≥1.5 mm tall + terminal negative deflection ≥1 mm deep + terminal negative deflection ≥40 ms duration. The diagnosis of BAE requires criteria for LAE and RAE to be met BAE is diagnosed when criteria for both RAE and LAE are present on the same ECG. Poor prognosis when present in HCM. 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: **Diastolic dysfunction** is dangerous and is believed to be associated with CHF symptoms in patients who have what's called preserved LVEF. **High filling pressures:** Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure is >12 mmHg or when the LVEDP is >16 mmHg. HCM is a primary myocardial disease, characterized by LVH, normal or supernormal **systolic function** and impaired **diastolic function**, including chamber stiffness and impaired relaxation.[2, 107] LVOTO is a recognized feature of HCM. It is caused by the thickened heart muscle and the abnormal movement of the mitral valve. This is the main mechanism of debilitating symptoms in HCM patients. About two-thirds of patients have obstructive form. In most patients, LVOTO occurs via systolic anterior motion (SAM) of the mitral valve in which the elongated leaflets contact the septum in mid-systole due to the high-velocity flow of blood directly on the leaflets. The narrower diameter of the LVOT due to increased septal wall thickness contributes to this obstruction. This leads to increased intraventricular pressures that over time can lead to LV dysfunction. Symptoms may include chest pain, dyspnea, exertional fatigue, dizziness, palpitation, and other symptoms of heart failure. Patients may experience near-syncope or syncope due to outflow obstruction or arrhythmia. A systolic ejection murmur may be heard at the lower left sternal border and apex that varies with the subaortic gradient. **Functional mitral regurgitation:** The systolic anterior motion of the mitral valve contributes to the development of mitral regurgitation and further narrows the LVOT, leading to more severe symptomatology. Cardiac magnetic resonance imaging accurately measures the left ventricular mass, the degree of diastolic function and it may also be used to distinguish phenotypic variants.

BAE is observed in the dilated phase with RV heart failure.[108] 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.[109]

PR interval: possibilities are normal PR interval, prolonged/first-degree AVB, or short PR interval. First-degree AVB is observed in ≈ 20% of the cohort demonstrated PR prolongation ≥200 ms, which associated in multivariable analyses with HCM-related death as well as a secondary end point of SCD or potentially lethal arrhythmic events. Higuchi et al demonstrates an association between first-degree AVB and cardiac outcomes among patients with HCM, even after moderate risk adjustment for common risk factors.[110, 111] Short PR interval (<120 ms) is considered an early detectable marker of myocardial storage diseases mainly FD. mild cardiac phenotype with symmetric distribution of LVH is suggestive of FD.[112-114] A definite diagnosis of FD was defined as follows: a GLA mutation with ≤5% GLA activity (leucocytes, mean of reference value, males only) with ≥ 1 characteristic FD symptom or sign: Periodic crisis of neuropathic pain in extremities, cornea verticillata, corneal whirling, angiokeratomas, hypohidrosis, proteinuria & progressive deterioration of renal function, heat/cold, exercise intolerance, GI distress, and early ischemic stroke.

Characteristics Favoring HCM and Athlete's Heart

In favor of HCM: asymmetrical hypertrophy, diastolic dysfunction, LGE-CRMI.

In favor of athlete's heart: homogeneous hypertrophy with maximal thickness of 15mm, ellipsoid LV shape, regression with deconditioning.

Most common 12-lead ECG abnormalities reported in athletes: early repolarization 22–100%, increased QRS voltages (suggestive of LVH) 14–85%, prolonged PR interval 10–

35%, TWI 3–30%, prolonged QTc <10%, LAE/RAE <7%, abnormal precordial R wave progression <5%, LBBB or RBBB <2%.

Proposed algorithm management for athletes identified with a genetic mutation for HCM in the context of a family screening.

Prolonged QRS duration: RBBB after ASA (37-70% of patients), LBBB after septal myectomy (50-100% of patients), and fQRS complex is a myocardial conduction abnormality that indicates myocardial scar. It is defined as additional spikes, R' wave, notching of R or S wave within the QRS complex in two contiguous leads corresponding to a coronary territory in a ECG (0.5 150 Hz).[115] Though initially fQRS was defined in the setting of normal QRS duration (<120 ms), later it has been expanded to include conditions with wide QRS complexes, ventricular ectopy and paced rhythm, when more than 2 notches are present. It is an important, yet often overlooked marker of mortality and arrhythmic events in many cardiac diseases. Several demonstrated the role of fQRS in predicting ventricular arrhythmias in the setting of HCM. In a prospective study of 167 HCM patients, ventricular arrhythmias and SCD were considered as the major arrhythmic events. The study established that fQRS is significantly associated with MACE and. fQRS was identified to be an independent predictor of VA and major arrhythmic events in HCM.[22]

Ogura et al. investigated associations between baseline fQRS and MACE, as well as the new appearance of fQRS and MACE in HCM patients. The results showed that baseline fQRS was associated with the occurrence of MACEs and all-cause death, but not with CHF-related hospitalization. Additionally, baseline ECG fQRS is associated well with LGE-CMRI findings. In patients without fQRS, the new appearance of fQRS during the follow-up was associated with MACE and CHF-related hospitalization.[116] Rattanawong et al in a systematic review and meta-analysis showed that baseline fQRS

significantly increased the risk of MACE in HCM patients.[117] An observational study showed that a myocardial scar visualized by LGE-CMRI predicted MACE in HCM patients.[118] fQRS is expected to be a useful predictor of MACEs because fQRS can be obtained from a standard normal resting ECG; however, problems remain for patients without baseline fQRS. In some HCM patients without baseline fQRS, Ogura et al saw the new appearance of fQRS during follow-up. An association between the new appearance of fQRS and MACEs has been reported in adult congenital heart disease. To use fQRS as a risk predictor for HCM patients, the association between the new appearance of fQRS and MACEs must be clarified.

ST-segment depression: STSD in the I and aVL leads could be of prognostic significance in HCM patients.[119]

Pseudo–ST-SE myocardial infarction: the ECG finding of convex ST-segment elevation and abnormal Q waves could be valuable for detection of disease progression in patients with HCM.[120]

TWI: Anterior TWI could be a variant in athletes of African/Afro Caribbean origin and some endurance athletes; however, the presence of this specific repolarization anomaly also raises the possibility of HCM or ARVC. The combination of J-point elevation and TWI The association of J-point elevation and TWI on right precordial lead V1-V4 offers the potential for an accurate differentiation between 'physiologic' and 'cardiomyopathic' anterior TWI, among athletes of both white/Caucasian or black/Afro Caribbean descent. Conversely, ST-SE without J-point elevation preceding anterior TWI may reflect cardiomyopathy. Conversely, ST-segment elevation without J-point elevation preceding anterior TWI may reflect cardiomyopathy.[121]

Figures 23 and 24 show ECG tracings of healthy athlete with anterior TWI from V1–V4 in a 21-year-old Caucasian athlete.

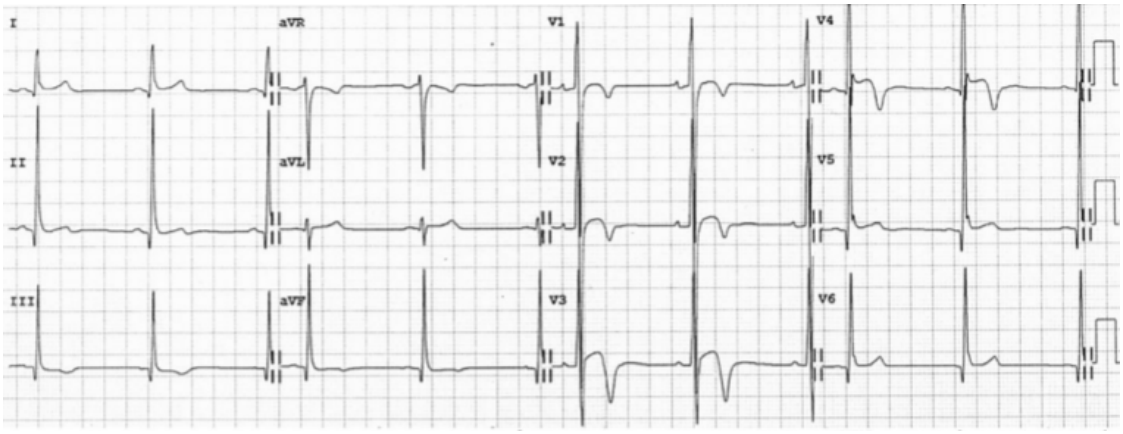

Figure 23. TWI from V1–V4. Note the TWI in V3–V4 are preceded by J-point elevation and STSE.

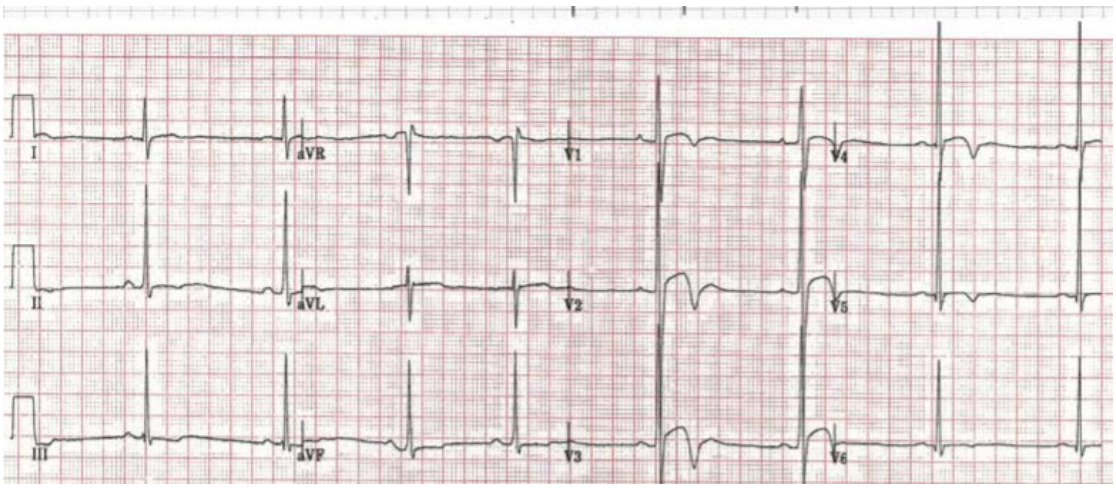

Figure 24. ECG diagnosis: Anterior TWI extending to inferolateral leads in a 19-year-old black athlete. Negative T-waves in V2–V4 are preceded by J-point elevation and STSE.

Table 4 shows the main features for differential diagnosis between HCM and black athlete's heart[122]

	HCM	Athlete's Heart
Symptoms	±	No
Family history	Yes	No

Voltage criteria for LVH example Sokolow-Lyon	When positive Without significance	When in isolation positive without significance
Pathological Q waves	Q/R ratio ≥ 0.25 or ≥ 40 ms in duration in ≥ 2 contiguous leads excluding III and aVR and ST depression ≥ 0.5 mm in depth ≥ 2 contiguous leads are seen 20% of HCM.[123]	Absent
Pathologic ECG	>90% of cases	20-30%
ECG repolarization modifications	ST-SE without J-point elevation preceding anterior TWI may reflect cardiomyopathy. TWI (≥1 mm in depth in ≥2 contiguous leads; excludes leads aVR, III, and V1	2% in Caucasian and 10% in Black. ST-SE followed by TWI from V1 to V4 is considered normal in African-American.[121]
TTE	Maximum thickness >16 mm and asymmetric LVED <45mm Abnormal diastolic function with Ele´`>14 and e´ septal <11	Harmonic enlargement of the four chambers Maximum thickness < 16mm and symmetric LVEDD>55 mm Normal diastolic function with Ele´`<14

	Myocardial dispersion at rest and decreased GLS in exercise	Improvement of EF and GLS in exercise
CMRI	LGE LV thickness/LV diastolic volume ≥0.15 Maximum diastolic thickness/minimum diastolic thickness ≥1.3	Absence of LGE. Normal o decreased T1 mapping and ECV, LV thickness/LV diastolic volume <0.15, Maximum diastolic thickness/minimum diastolic thickness <1.3, Improvement of rest LVEF >11% stress CRM.

Table 4.

QTc prolongation: Predict appropriate ICD therapies in patients with HCM.[124] QTc prolongation is an independent predictor of arrhythmia recurrence in HCM patients undergoing AF ablation, and might identifying those HCM patients likely to have a better outcome after the procedure.[125] In HCM patients undergoing AF ablation, QTc >448 ms, and presence of fQRS are independent risk factors for arrhythmia recurrence at follow-up. The combination of these two parameters has greater predictive value and would help to identify patients who are at the highest risk of procedural failure.[126]

Supraventricular arrhythmias: AF is the most common arrhythmia observed in HCM. AF is present in 5 % of HCM patients at the time of diagnosis. AF >8 times higher risk of ischemic stroke. Causes: significant septal hypertrophy, significant mitral valve

regurgitation, SAM, and LVOT obstruction. AF is the most common supraventricular arrhythmia observed in HCM and is frequently associated with acute and/or long-term clinical deterioration, embolic complications, and increased cardiovascular mortality due to heart failure and stroke.[127] Factors that predispose to AF: significant septal hypertrophy, significant mitral valve regurgitation, systolic anterior motion (SAM), and LVOT obstruction. HCM is related to ischemic stroke and AF is under-recognized and consequently, many patients who should be on oral anticoagulation for stroke prevention go untreated. The consequences of AF on the long-term prognosis of HCM patients are not uniformly unfavorable; however, and in ≈30% of patients the arrhythmia is compatible with an uneventful course. AF is a common sustained arrhythmia in HCM patients and is primarily related to LAE and remodeling. There are several clinical, ECG, and TTECG features that have been associated with development of AF in HCM patients; strongest predictors are left atrial size, age, and heart failure class. AF can lead to progressive functional decline, worsening heart failure and increased risk for systemic thromboembolism. The management of AF in HCM patient focuses on symptom alleviation (managed with rate and/or rhythm control methods) and prevention of complications such as thromboembolism (prevented with anticoagulation). Finally, evidence suggests that early rhythm control strategy may result in more favorable short- and long-term outcomes.[128] Twenty-seven patients diagnosed with HCM and having a history of documented AF attack were compared with 53 age- and gender-matched patients who had no such history. LA diameter was significantly greater and gradient in the LVOT was lower in patients with AF than those without AF. Maximum P-wave duration (Pmax), P wave dispersion (PWD) and P-Terminal Force (PTF-V1) (normal PTF-V1 does not exceed 0.04 s in width and 1 mm in depth, i.e., 0.04 mm/s) values were significantly higher in patients with AF. A Pmax>134.5 ms separated the patients with

AF from controls with a sensitivity of 92%, specificity of 89% and a positive predictive value of 80%. A PWD value > 52.5 ms separated patients from controls with a sensitivity of 96%, a specificity of 91% and a positive predictive accuracy of 84%. An LA diameter >4.2 cm separated patients from controls with a sensitivity of 96% and a specificity of 81%. The authors concluded that LA diameter and PWD values are the most significant predictors for AF occurrence in patients with HCM, and simply measuring Pmax and PWD values, could easily identify the patients with high risk, and prescribe the necessary treatment and follow-up protocols for such patients [129]. Sinus rhythm is present in most cases. Possible acute AF is observed in ≈10% of cases as a consequence of LV impairment of relaxation, compliance diminution or diastolic stiffness of the LV and augmentation of end diastolic LV pressure and consequently augmentation of medium intra LA pressure, leading to LAE. In a large cohort of patients with HCM, a marked increase in LA dimension was a novel and independent marker of prognosis in HCM, particularly relevant to the identification of patients at risk of death related to heart failure.[130]

Ventricular arrhythmias: NSVT is defined as an episode of ventricular tachycardia that involves a heart rate of >100 bpm, lasts for at least three heartbeats and persists ≤30 sec. Most often, this either does not cause any symptoms at all or it causes palpitations. Occasionally, can produce lightheadedness, dizziness, or, more rarely, syncope.[131] NSVT should be considered in the primary prevention of SCD. McKenna et al. found that NSVT was significantly associated with an increased risk of SCD during a mean follow-up period of 2.6 years.[132] In a large HCM cohort with no or only mild symptoms, myocardial fibrosis detected by CMRI was associated with greater likelihood and increased frequency of ventricular tachyarrhythmia's (including NSVT) on ambulatory

Holter ECG. Therefore, contrast-enhanced CMRI identifies HCM patients with increased susceptibility to ventricular tachyarrhythmias.[133]

Exercise-induced arrhythmias and blunted blood pressure response predict the risk of SCD, especially in ≤40 years HCM patients.

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. Signs of WPW (short PR, delta wave) - ECG features of WPW were seen in 33% of patients with HCM in one study, and at least one genetic mutation has been identified that is associated with both conditions. Data concerning the familial occurrence of ventricular preexcitation, i.e. WPW syndrome, indicate autosomal dominant inheritance with a gene mutation on chromosome 7q3 has been described in familial HCM coexisting with WPW syndrome.[134]

Bobkowski et al[135] presented a case of a 7-year-old boy with HCM and coexisting WPW syndrome. On his chromosome 14, molecular diagnostics revealed a C 9123 mutation (arginine changed into cysteine in position 453) in exon 14 in a copy of the gene for β-myosin heavy chain (MYH7). It was the first known case of mutation of the MYH7 gene in a child with both HCM and WPW. Since no linkage between MYH7 mutation and HCM with WPW syndrome has been reported to date, we cannot conclude whether the observed mutation is a common cause for both diseases, or this patient presents an incidental co-occurrence of HCM (caused by MYH7 mutation) and WPW syndrome.

Association of HCM and WPW has been reported, but whether the prognosis or severity of arrhythmia is different compared to the individual disorders remains unsettled. Talle et al reported a case of HCM with WPW syndrome in a 28-year-old male Nigerian soldier presenting with recurrent syncope and lichen planus.[136] Concurrence of HCM and WPW in a consecutive series of patients presenting with preexcitation, 7.62% were found

to have HCM.[137] Of the many phenocopies of HCM, cardiac hypertrophy and preexcitation are typically caused by a mutation of the γ 2 subunit of the adenosine monophosphate-activated protein kinase (PRKAG2) Gollob et al identified a novel mutation (Arg531Gly) in the gamma-2 regulatory subunit (PRKAG2) of AMP-activated protein kinase (AMPK) to be responsible for a syndrome associated with ventricular preexcitation and early onset of AF and conduction disease.[138] These observations confirm an important functional role of AMPK in the regulation of ion channels specific to cardiac tissue. The identification of the cardiac ion channel(s) serving as substrate for AMPK not only would provide insight into the molecular basis of AF and heart block but also may suggest targets for the development of more specific therapy for these common rhythm disturbances. Although both HCM and WPW are independently associated with various forms of arrhythmias and SCD, whether their concurrence will result in more frequent and severe arrhythmias or fatalities remains conjectural, and to our knowledge, this has not been reported in SSA. We present a case of HCM with WPW in a young African soldier presenting with recurrent syncope.

Figures 25 and 26 show ECGs belonging to a young man with HCM who was admitted with poorly tolerated VT. He had SCD waiting for an ICD.

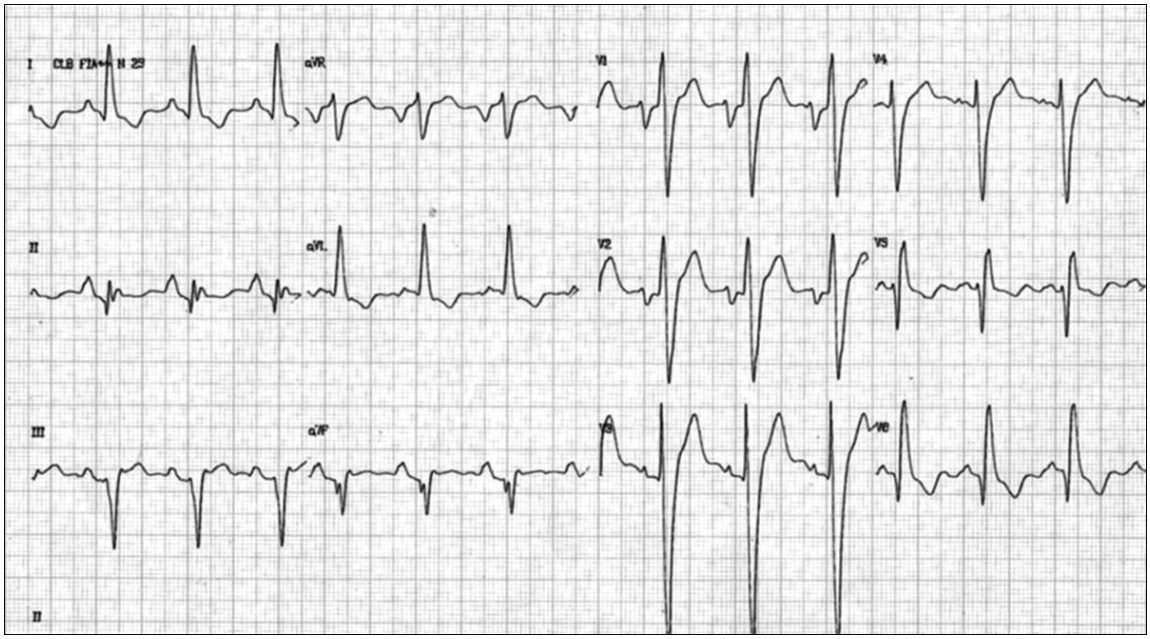

Figure 25. LAE: P duration 120 ms, bimodal shape and the P wave terminal forces in V1 lead very augmented and deep (PTF-V1) indicating elevated filling pressure of the LV), LVH with strain pattern of repolarization, QRS axis deviated to left (-35º), deep narrow Q-waves in inferolateral leads and fQRS.

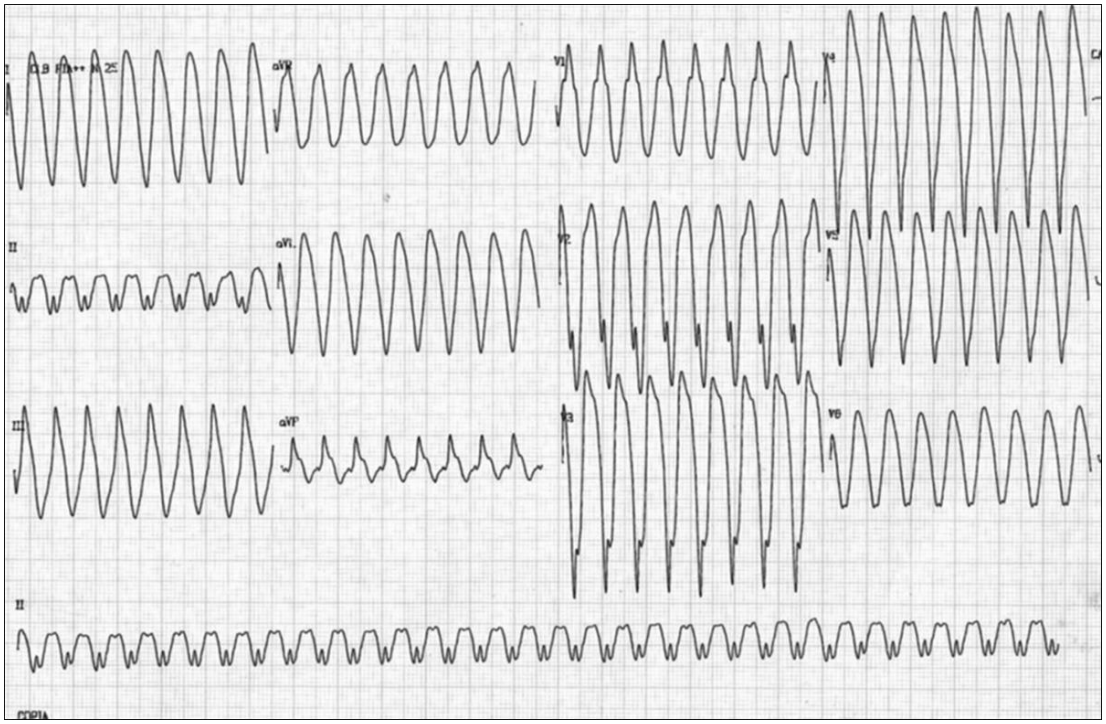

Figure 26. The same patient during sustained monomorphic VT.

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.[139] Additionally, the possibility of FD,[140] 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. FD 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.[141] It is the product of Cornell: QRS voltage and QRS duration (QRS voltage-duration product); Cornell voltage-duration product (RaVL + SV3 with 6 mm added in women x QRS duration). Values ≥ 2440 mm/ms are diagnostic of LVH (Positive criteria of LVH CP ≥ 2440 mm x ms). The Cornell product is a useful ECG marker, reflecting left ventricular mass.[119] 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.[142 143]

Namdar et al[144] demonstrated that a corrected QT interval duration <440 ms in combination with a PR interval minus P wave duration in lead II <40 ms was 100% sensitive and 99% specific for the diagnosis of FD, whereas a corrected dQT 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 FD 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. Homozygous 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.[145]

QRS axis or SÂQRS: The QRS axis located between 0º and +90º is the rule in NOHCM forms. SÂQRS between 0º and –90º is observed in 30% of cases. LAFB and extreme left QRS axis deviation is eventually observed after ASA 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.[146]

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.[147]

Abnormal non-infarction deep-narrow Q waves: Prominent deep-narrow Q waves("dagger-like") in the ECG are considered characteristic of HCM [148] and significant in early diagnosis.[149] Q waves are registered in lateral (I, aVL, V5-6) ± inferior (II, III, aVF) leads. Abnormal Q waves may mimic myocardial infarction and at times reflect septal hypertrophy. Of the 200 consecutive patients with HCM who underwent CMRI, 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.[150] 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[151] 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.

QRS complexes: LVH with systolic or strain pattern is characteristic in patients with HCM. Additionally, the QRS/ST/T angle is wide, near 180º. We use the term LVH when the LV receives in the diastole, a blood volume greater than normal (diastolic or volumetric LVH) or when there is a greater difficulty in the systole to empty its content (systolic or strain pattern LVH) or both at the same time. The terms systolic and diastolic LVH are used as an old nomenclature in ECG-VCG.

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.

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 ≥ 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 >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).

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.[152]

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 ≈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.

Prominent R waves in intermediate precordial leads are observed in ≈80% of cases of Ap-HCM.

fQRS: Myocardial scar causes heterogeneous ventricular activation, is a substrate for reentrant ventricular arrhythmias and is associated with poor prognosis. fQRS on 12-lead ECG represents myocardial conduction delays due to myocardial scar in patients with coronary artery disease. The presence of a fQRS complex on a routine 12-lead ECG is another marker of depolarization abnormality together with signal-averaged ECG. 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 ARCD/C and Brugada syndrome. In Brugada syndrome, the presence of fQRS predicts episodes of VF during follow-up.

fQRS included various RSR' patterns (QRS duration <120 ms), such as ≥1R'[153] 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.[154]

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 CAD. f-wQRS is also an independent predictor of mortality.

Myocardial fibrosis in patients with nonischemic cardiomyopathy can be identified as LGE-CMRI 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.[140] 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.[141]

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 lateral leads and syncope were the predictors of SCD or appropriate ICD therapy in patients with HCM. Consequently, in addition to generally accepted risk factors, ST-segment depression in the lateral leads could be of prognostic significance in HCM patients.[143]

T-waves abnormalities: TWI 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 ARVD/C, which are the main causes of SCD in athletes. TTE in athletes with post-pubertal persistence of TWI at pre-participation screening is warranted because it may lead to pre-symptomatic diagnosis of an abnormality of cardiomyopathies at risk of SCD.[155]

Since the phenotypic expression of HCM is variable, and not uncommonly includes patients with mild and localized LVH, the differential diagnosis with physiological remodeling of athlete's heart arises not uncommonly.[156]

Athletic training in male Afro-descendants is associated with marked ECG repolarization changes that overlap with HCM. Differentiating between both is prudent since Afro-descendants exhibit a higher prevalence of exercise-related SCD from HCM compared with Caucasians. TWIs in anteroseptal wall appear to represent an ethnic

variant of ‘athlete’s heart’. Conversely, TWIs in the apical/ lateral leads may represent the initial expression of underlying HCM.[157]

An ECG finding of giant negative T waves in the precordial leads is characteristic of Ap-HCM.[158] This specific variant is a NOHCM located in the cardiac apex that has been first described in Japan where the prevalence is much higher than in the western world.

Corrected QT interval (QTc): QT interval duration and its dispersion can be clinical markers of electrophysiological instability and ventricular arrhythmias. QT interval prolongation in surface ECG shows significant association with mechanical dyssynchrony and LV dysfunction in HCM.[159]

Corrected QT dispersion: QT dispersion is defined as the difference between the maximum and minimum QT values, and corrected QT dispersion is calculated according to the Bazett formula. For patients with HCM, measurement of baseline corrected QT dispersion from surface ECG may be used to identify those at risk for clinical deterioration in long-term follow-up. QT dispersion and corrected QT dispersion were significantly different between patients with and without clinical endpoints defined as cardiac death and hospitalization due to worsening in heart failure. Corrected QT dispersion >80 ms detected patients with clinical endpoints with sensitivity and specificity of 79% and 75%, respectively. Patients with corrected QT dispersion <80 ms were significantly free of clinical endpoints.[160]

ECG after ASA: Complete RBBB pattern: after ASA in the first septal perforating ramus of the left descending artery is very frequent. Septal fibrosis following ASA caused a predominance of complete RBBB; on the other hand, LBBB is very frequently produced by myectomy (>90% of cases). A possible requirement of a permanent pacemaker should always be considered before intervention when patients have preexisting RBBB or

LBBB. Additionally, ASA cause frequently new Q waves, new RBBB, transient anterior STSE, and several degrees of AV blocks. Predictors of permanent complete AV block after ASA are female gender, older age and pre-existing LBBB. A pre-existing LBBB is a risk factor for the development of complete AV block and may merit prophylactic pacemaker implantation. Atrioventricular and intraventricular conduction disturbances are common after ASA. Other frequent ECG disorders after ASA are: fascicular blocks, transient prolongation of QT interval, significant and persistent prolongation of corrected QT interval, QT dispersion.

The JT interval and corrected JT dispersion are not significantly changed after ASA. ASA for OHCM induces significant delayed ECG changes in most patients. The changes include QRS prolongation, new RBBB, persistent QT prolongation, transient QT dispersion, PR prolongation and changes in heart rate variability.[161]

Ventricular arrhythmias: The most frequent ones are MVTs triggered by late-coupled PVCs in more than 85% of cases. In patients with implanted ICD, they are frequently terminated by anti-tachycardia pacing, which does not reduce the frequency of ICD shocks. Younger HCM patients have more rapid heart rate VTs, which may explain the peak of SCD in early adulthood. The circadian periodicity of VT peaked at midday (with 20% occurring between 11:00 PM and 7:00 AM). It is different from that observed in ischemic heart disease, and is likely to relate to the distinct character of the arrhythmogenic substrate in HCM and its modulators.

From a cohort of 330 patients with HCM selected because of their high risk for SD, ECG did not predict subsequent appropriate ICD intervention for VTs and was not useful in risk stratification for SD. No differences in the ECG characteristics of patients with and without appropriate device interventions were identified. Markedly increased ECG voltages, QRS duration, left or rightward QRS axis, abnormal Q waves, and QTc or

QT dispersion were not associated with appropriate ICD discharge. Conversely, normal ECGs except for a repolarization abnormality in only 1 anatomic distribution were not associated with freedom from ICD discharge. Moreover, no combination of ECG variables was associated with the likelihood of an appropriate ICD discharge.[162]

The association between SCD and NSVT in young patients is striking; however, the majority of SCDs, even in young patients, occurred in patients without NSVT. This clearly shows that Holter monitoring identifies only a subset of subjects at higher risk. Clearly we need to rule out other contributing risk factors before reassuring an individual patient based on this non-invasive modality only.

The five main risk factors in the primary prevention of SCD in HCM are: family history of SCD, syncope, massive wall thickness ≥30 mm, NSVT in Holter Monitoring, and abnormal blood pressure response to exercise.

In HCM, as a genetic cardiac disease, the risk for SCD may also exist from birth.

Figure 27 shows an ECG of an elderly patient with severe LVOTO and Figures 28 and 29 immediately after ASA.

.

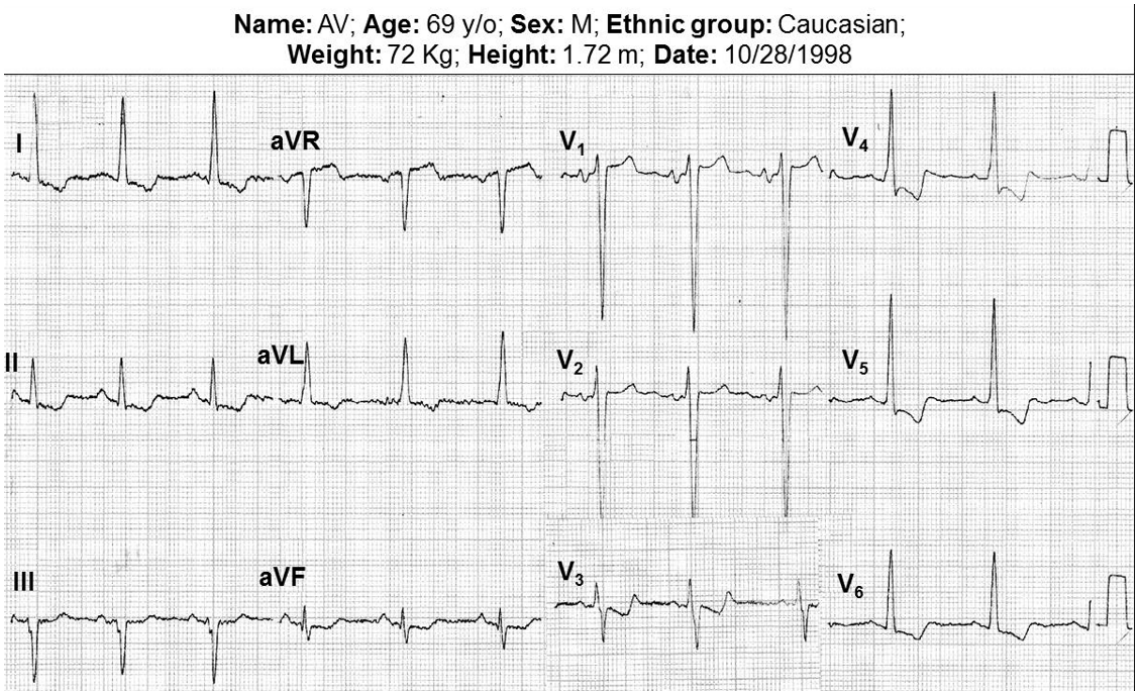

Figure 27. Clinical diagnosis: OHCM with gradient in LVOT of 80 mmHg and clinically in NYHA functional group IV (dyspnea in rest), even with medication. ECG diagnosis: LAE+LVH with strain pattern. Reduction of hypertrophic septum is chosen, by ASA in the first perforating artery, anterior descending artery branch.

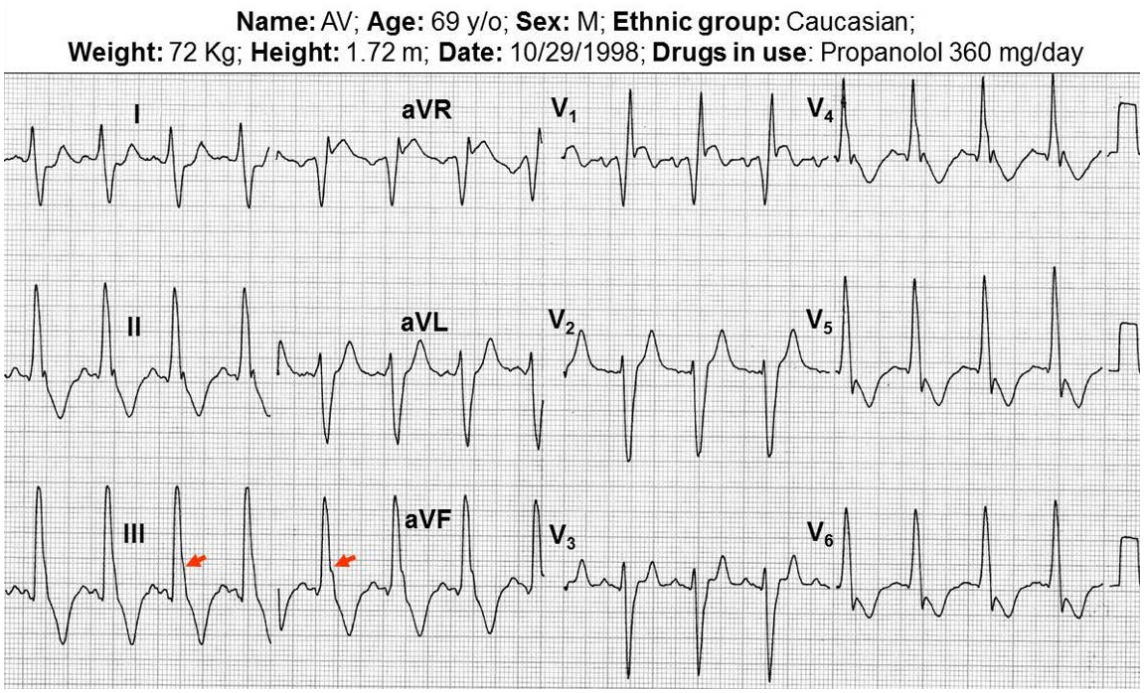

Figure 28. Clinical data: the same patient immediately after ASA in the first perforating artery, branch of the anterior descending artery. ECG: ST + LAE + LVH + CRBBB + LPFB + septal MI: QR in V1 and ST segment elevation of subepicardial lesion type + LPFB, I and aVL rS, qR in III, RIII>RII, notch in descending limb of R wave of III and aVF (red arrows) and ÂQRS shifted to the right (+110º).

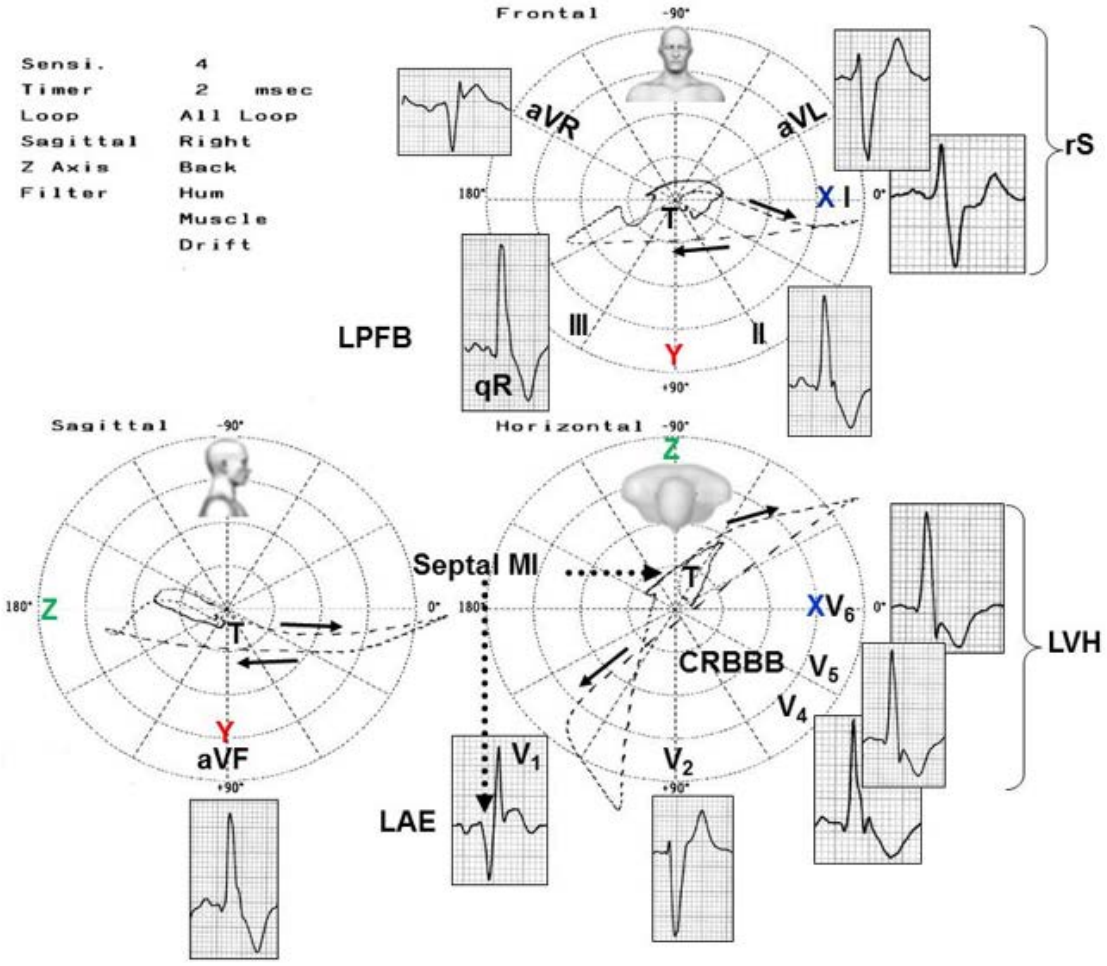

Figure 29. ECG/VCG correlation immediately after ASA procedure of the same patient that shows LAE, LVH, LPFB, CRBBB and septal infarction.

Figures 30-33 show another ECG belonging to a patient with severe LVOTO.

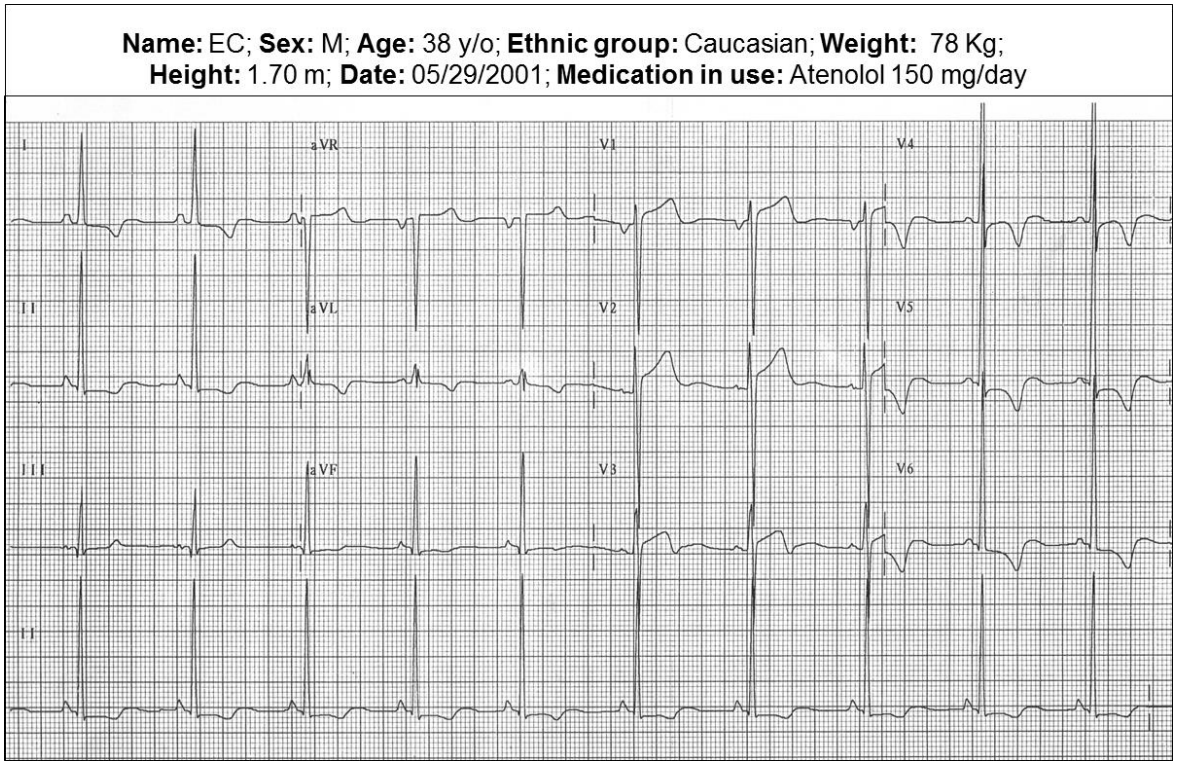

Figure 30. Clinical diagnosis: severe O-HCM, which does not respond to drugs. Septal thickness is 30 mm; gradient in rest is 80 mmHg. Functional class IV. ECG diagnosis: left chambers hypertrophy. Cabrera systolic pattern of ventricular repolarization ("strain pattern").

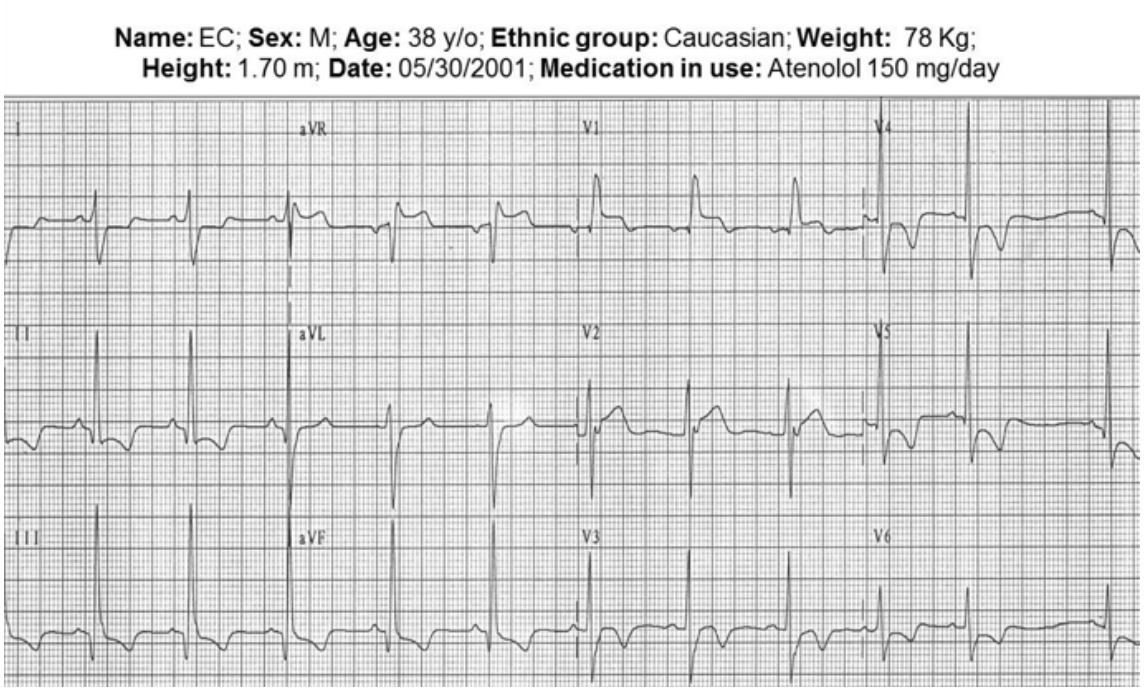

Figure 31. Clinical diagnosis: the same patient after ASA in the first septal perforator artery. Great relief of dyspnea. Significant reduction of septal thickness. ECG diagnosis: CRBBB + LPFB + lesion current and septal subepicardial ischemia (LV). SÂQRS close to +120°; SI-QIII-TIII pattern; RIII > 15 mm RII; qIII > qII > q aVF. Clinical absence of asthenic biotype, RVH or lateral infarction: LPFB. QRSD: 153 ms. Broader S wave in left leads; qR in V1: complete RBBB.

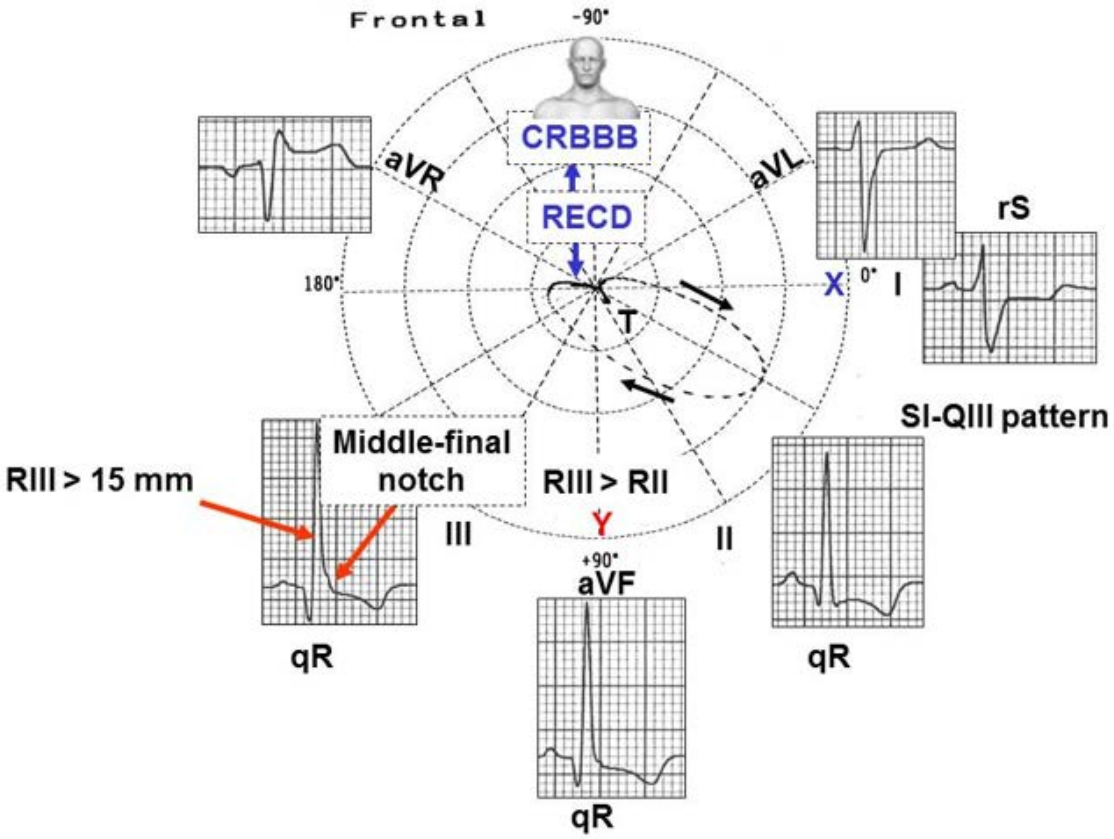

Figure 32. ECG/VCG correlation in the frontal plane. SÂQRS: around + 120º; I & aVL: rS pattern; clinical absence of vertical heart, RVH or lateral infarction; qR pattern in inferior leads; qIII > qaVF > qII; QRSD: 153 ms; Right End Conduction Delay (RECD) in the right X orthogonal lead. Conclusion: complete RBBB + LPFB.

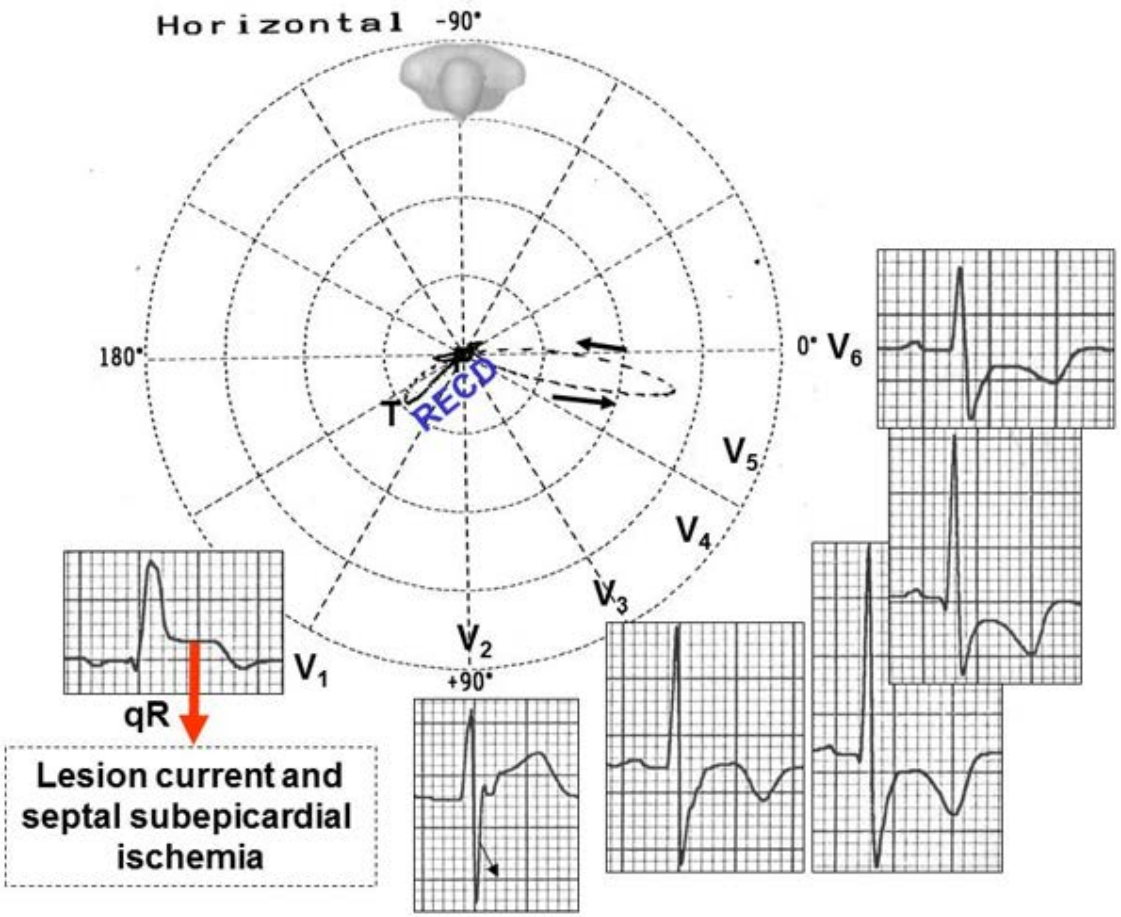

Figure 33. ECG/VCG correlation of the same patient in the horizontal plane: Afferent limb behind the efferent one: Grishman-type CRBBB; ECD in “glove finger” in the right anterior quadrant: CRBBB; “Epsilon like wave”; QRSD: 153 ms; CRBBB; broader S in left leads → CRBBB. Conclusion: CRBBB, Grishman or Kennedy type I in VCG.

Figures 34-37 show another case of severe OHCM.

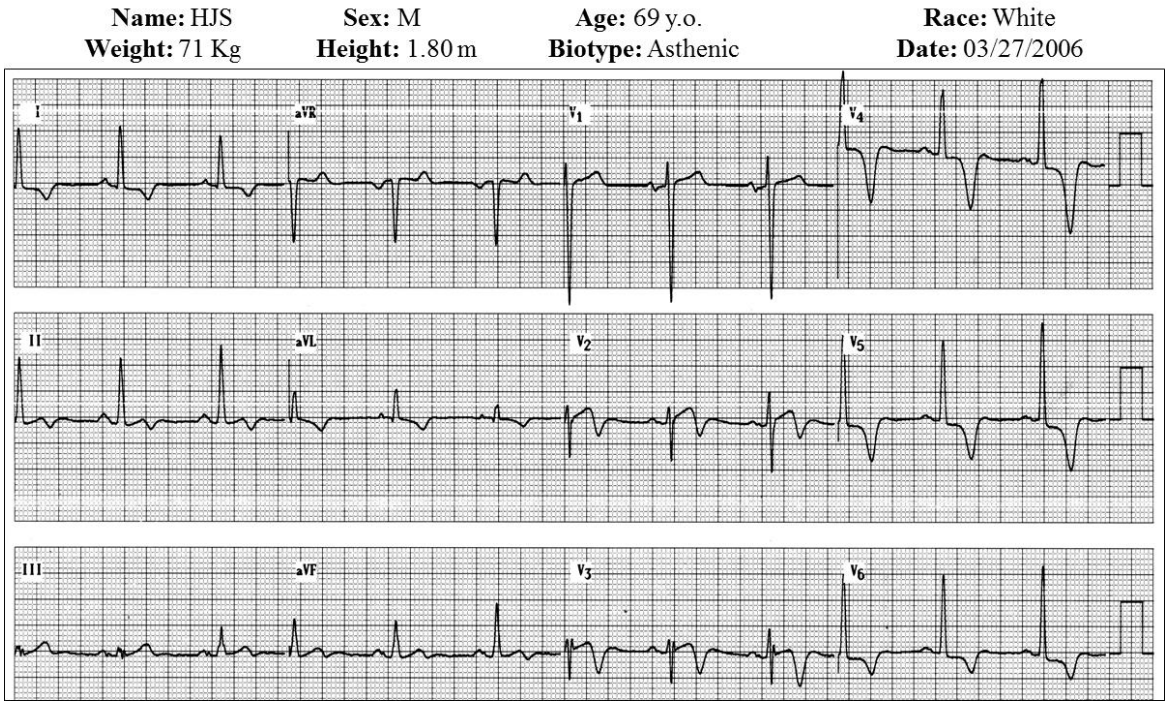

Figure 34. Clinical diagnosis: OHCM with gradient of 35 mmHg, associated with systemic high blood pressure. ECG diagnosis: LVH, ventricular repolarization systolic pattern. TWI from V2 to V6 and in I, II and aVL. T waves at times with a tendency to symmetry in intermediate leads (V2 to V4).

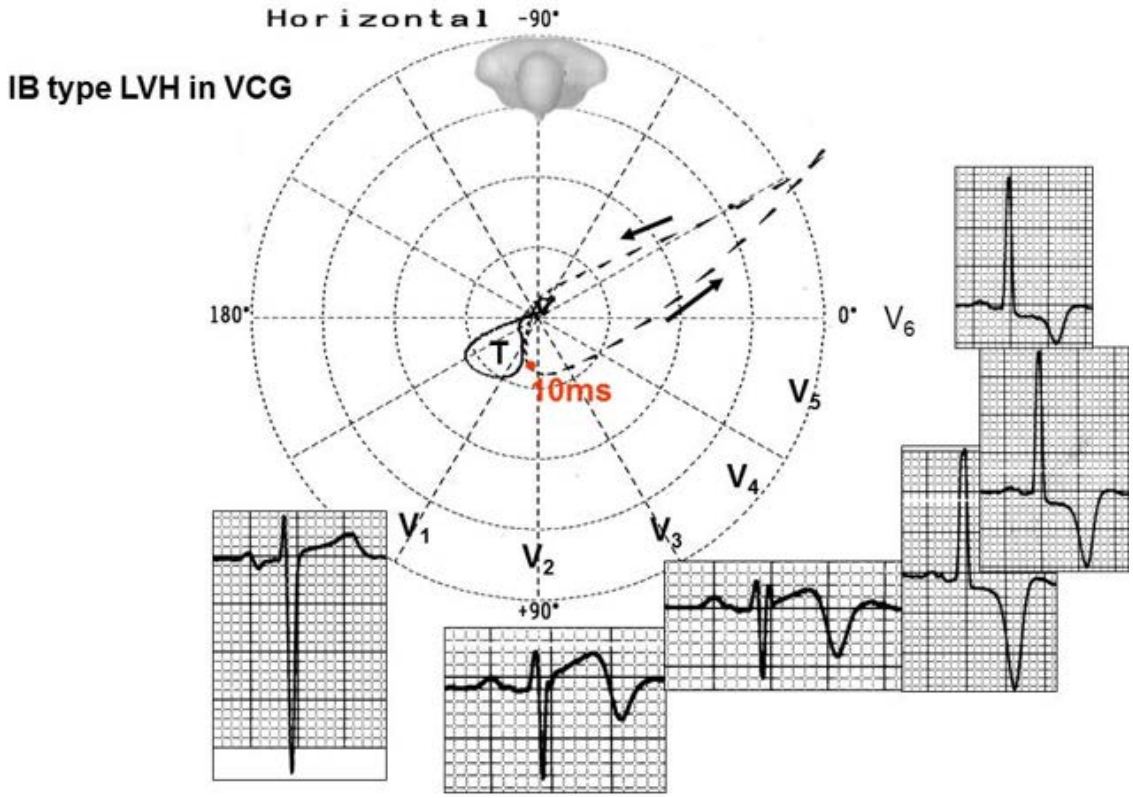

Figure 35. ECG/VCG correlation of an elderly patient (69 years old) in the horizontal planr, carrier of moderate OHCM, associated with high blood pressure. T loop opposite to the QRS loop and rounded (primary?); QRS loop with elongated morphology; TWI from V2 to V6; maximal vector >2 mV; counterclockwise rotation; QRS/T angle close to +180º; initial 10 ms vector heading forward and to the left: absence of Q wave from V4 to V6.

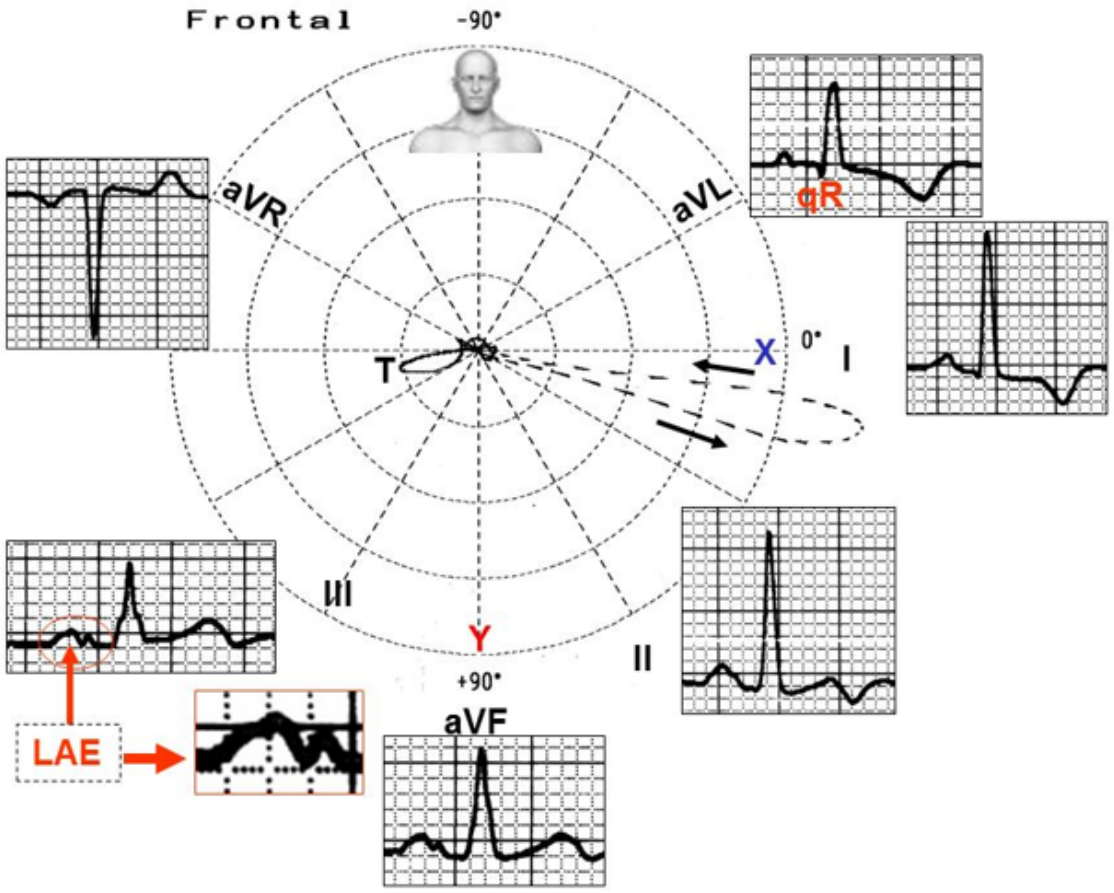

Figure 36. ECG/VCG correlation in the frontal plane. QRS/T angle not matching; preserved septal vector; SÂQRS +10°; maximal vector >2 mV.

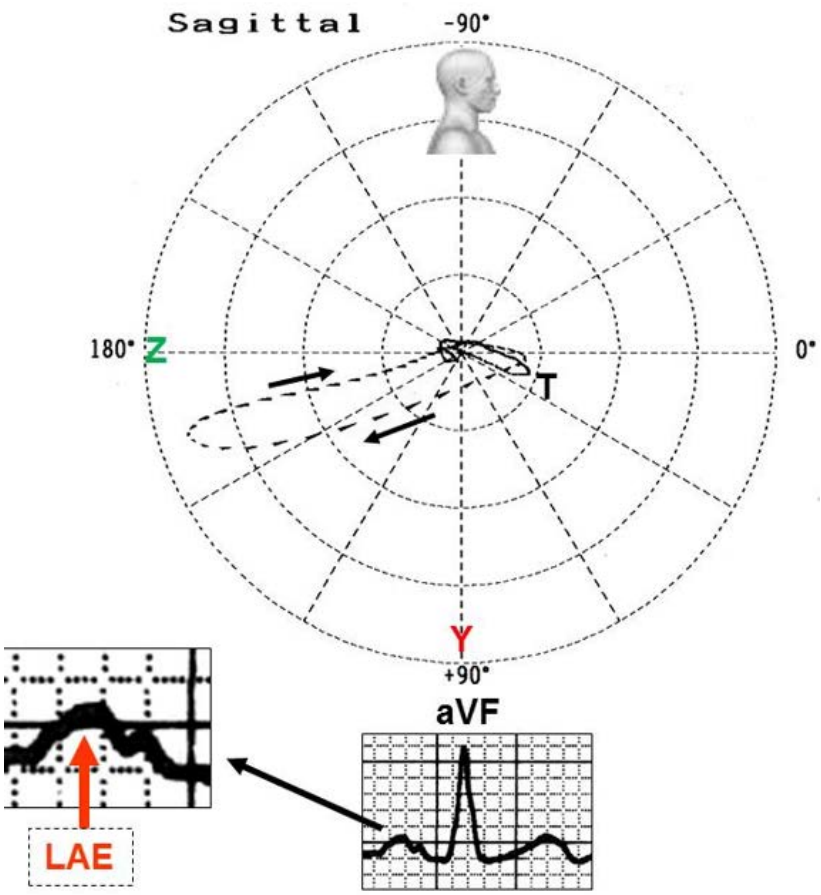

Figure 37. ECG/VCG correlation in the right sagittal plane. QRS loop located in the inferoposterior quadrant.

Differential diagnosis of HCM

Athlete's heart, aortic stenosis, amyloidosis, FD, glycogen storage disease, hypertensive heart disease, mucopolysaccharide storage disease, restrictive cardiomyopathy, sarcoidosis.

Risk factors associated to SCD in HCM

Obesity is highly prevalent among patients with HCM and is associated with increased likelihood of obstructive physiology and adverse prognosis. Strategies aimed at preventing obesity and weight increase may play an important role in management and prevention of disease-related complications.[163]

Extreme increase of septal thickness: LVH (>30 mm) in young patients;

Very increased estimation of myocardial mass;

Progression of the disease to LV wall thinning and decrease of ejection fraction;

History of recovery from SCD;

Recurrent syncope in young people;

The presence of extensive; LGE-CMRI in the IVS and RV anterior and posterior insertions may be a biomarker of SCD.[164] Brazilian authors recommend that quantification of myocardial fibrosis should be performed with visual assessment.[165]

Type I HCM: with genetic alteration with mutations in locus 1q of the long arm of chromosome 14, which alters the heavy chain of cardiac beta-myosin (beta-MyHC), high penetrance, severe hypertrophy and sudden cardiac death present in approximately 50% of affected patients. The locations Arg403 (substitution of the amino acid arginine by glycine in position 403), Arg453Cys (substitution of the amino acid arginine by cysteine in position 453), and Arg719Trp (substitution of the amino acid argynine by tryptophan in position 719) are considered malignant.

Type II HCM: (15%) alteration in chromosome 1: locus 1q3. It modifies cardiac troponin T (cTnT). These patients present little hypertrophy and high arrhythmic mortality in young people under 30 years old. To this moment, 8 mutations have been described. Note: in patients in whom a genetic diagnosis has been made of malignant form, even in absence of symptoms and hypertrophy, implantable cardioverter defibrillators are indicated.

HCM due to mutations in genes encoding sarcomere proteins is most commonly inherited as an AD trait. ≈50% of HCM cases occur in the absence of a family history, a recessive inheritance pattern may be involved A pedigree was identified with suspected AR transmission of HCM. Twenty-six HCM-related genes were comprehensively screened

for mutations in the proband with targeted second generation sequencing, and the identified mutation was confirmed with bi-directional Sanger sequencing in all family members and 376 healthy controls. A novel missense mutation (c.1469G>T, p.Gly490Val) in exon 17 of MYBPC3 was identified. Two siblings with HCM were homozygous for this mutation, whereas other family members were either heterozygous or wild type. Clinical evaluation showed that both homozygotes manifested a typical HCM presentation, but none of others, including 5 adult heterozygous mutation carriers up to 71 years of age, had any clinical evidence of HCM. These data identified a MYBPC3 mutation in HCM, which appeared AR inherited in this family. The absence of a family history of clinical HCM may be due to not only a de novo mutation, but also AR mutations that failed to produce a clinical phenotype in heterozygous family members. Therefore, consideration of recessive mutations leading to HCM is essential for risk stratification and genetic counseling.[166]

AF can lead to progressive functional decline, worsening hf and increased risk for systemic thromboembolism. The management of AF in HCM patient focuses on symptom alleviation (managed with rate and/or rhythm control methods) and prevention of complications such as thromboembolism (prevented with anticoagulation. Evidence suggests that early rhythm control strategy may result in more favorable short- and long-term outcomes.[167]

Presence of NSVT on Holter in patient with alteration of conscience. Recording of NSVT on Holter monitoring and massive LVH with a maximum wall thickness >30 mm are considered predictors of SCD in HCM patients.[168]

History of HCM associated myocardial infarction.[169] Morphologic abnormalities of the intramural coronary arterioles represent the primary morphologic substrate for microvascular dysfunction and its functional consequence-that is, blunted myocardial

blood flow (MBF) during stress. PET and CMRI have led to an enhanced understanding of the role that myocardial ischemia and its sequelae fibrosis play on clinical outcome. Studies with PET have shown that HCM patients have impaired myocardial blood flow after dipyridamole infusion and that this blunted MBF is a powerful independent predictor of cardiovascular mortality and adverse LV remodeling associated with LV systolic dysfunction. Stress LGE-CMRI has also shown that MBF is reduced in relation to magnitude of wall thickness and in those LV segments occupied by LGE (i.e., fibrosis). These CMRI observations show an association between ischemia, myocardial fibrosis, and LV remodeling, providing support that abnormal MBF caused by microvascular dysfunction is responsible for myocardial ischemia-mediated myocyte death, and ultimately replacement fibrosis. Efforts should now focus on detecting myocardial ischemia before adverse LV remodeling begins, so that interventional treatment strategies can be initiated earlier in the clinical course to mitigate ischemia and beneficially alter the natural history of HCM.

NSVT is associated with a substantial increase in sudden death risk in young patients with HCM. A relation between the frequency, duration, and rate of NSVT episodes could not be demonstrated.[170]

SVT induction in electrophysiological study.

The development of a malignant arrhythmia requires the coalescence of triggers at a critical moment in time as well as a pro-arrhythmic substrate.

Vectorcardiogram in HCM

According to Ellison and Restieaux, the method displays: usefulness to quantify severity; usefulness to estimate the magnitude of left ventricular mass (normal 50 to 90 g/m^2 in children and young adults).

The following VCG elements stand out:

Increased voltage of LV maximal spatial vector in QRS loop: Normal values in the HP = 1.35 mv (0.75 to 2.2 mv), FP = 1.55 mv (0.9 to 2.3 mV), and SP = 1.5 mv (0.5 to 2.3 mV). The degree of this increase is directly related to ventricular mass. Thus, values of 3 mV correspond to the LV mass of 150 g/m^2, values of 4 mV correspond to a mass of 275 g/m^2 and 5 mV and are equivalent to LV mass of 400 g/m^2.

T loop opposite to the QRS loop: This element is an indication of severity in HCM; thus, the greater the severity, the more obtuse the QRS-T angle (normal maximal value of QRS-T angle in the three planes = 75º). In children and young people, the QRS-T angle is usually normal. In adults almost always exceeding 75º.

In severe forms and in elderly patients, the angle is close to 180º.

Dromotropic disorders: Frequent.

LAFB: maybe by inclusion of anterior fascicle in the septal muscle with disorder.

LSFB: particularly in NOHCM of the middle and low regions of the septum. Marked anterior shift of QRS loop is observed in the HP in absence of initial convexity to the right of the 20 ms vector.

CLBBB: it is very frequent after septectomy surgery (80% of cases).

CRBBB: it is very frequent after ASA injected in the first septal perforator artery of the LADA.

Middle age man with high blood pressure, moderate symmetrical LVH, normal coronary arteries and pathognomonic LV shape: The "ace-of-spades" sign on left ventriculography. Figure 38 shows an ECG with biventricular hypertrophy.

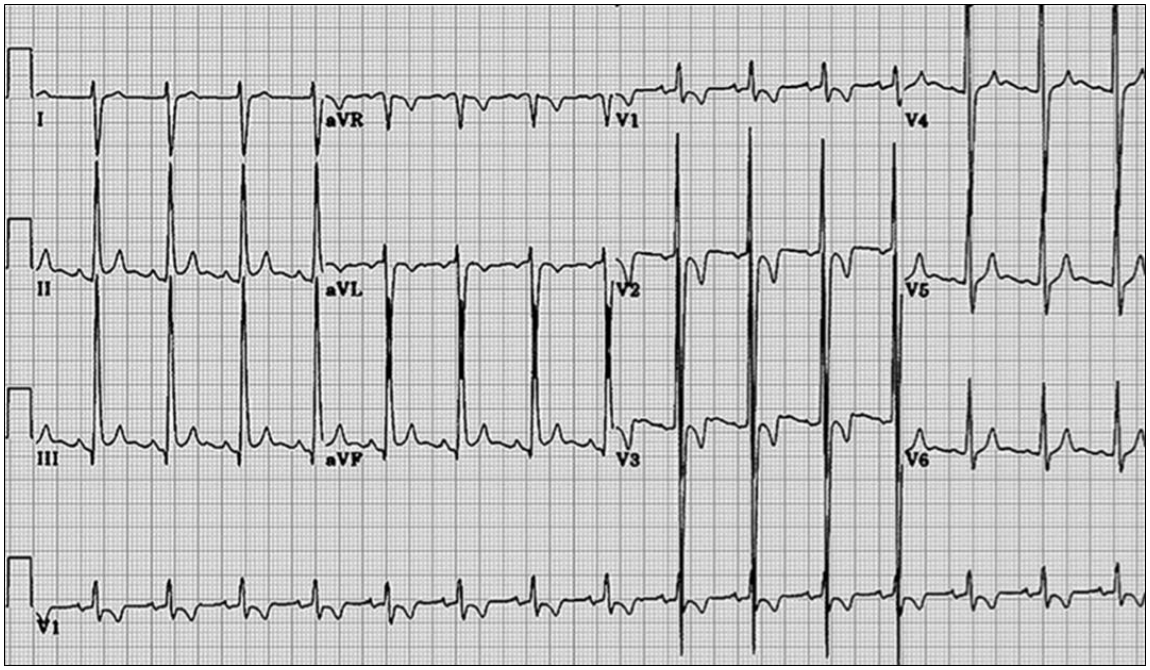

Figure 38**.** Note the pattern of biventricular overload (LVH + HVD) and more dilated left atrium. Electrical axis of the QRS right at +110º, broad pattern of isodiphasic RS from V2 to V4; a phenomenon known as Katz-Watchtel wide QRS complexes consisting of V2-5 that are a sign of biventricular hypertrophy described by these authors in 1935 in carriers of interventricular communication with BVH. The near absence of ST segment with very short QT interval (330 ms next) is remarkable. We have no explanation for this phenomenon in the present case, however we know well the causes are congenitally acquired short QT interval as acidosis alterations in autonomic tone, digitalis toxicity and effect, hypercalcemia, hyperkalemia and hyperthermia.

Figures 39-44 show a typical example of Ap-HCM.

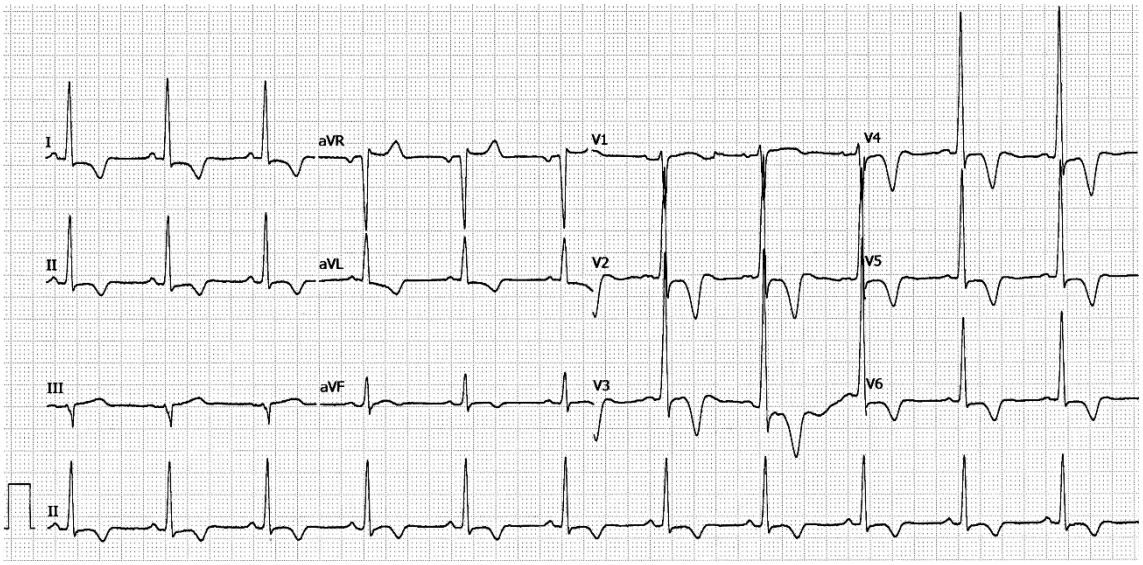

Figure 39. Clinical diagnosis: Apical Hypertrophic Cardiomyopathy. ECG diagnosis: LVH. Giant negative T waves only in V3. By definition giant negative T wave is considered when ≥10 mm deep. In the present case only V3 meets this criterion. T wave is negative in I, II, aVL, and from V1 to V6. LVH criteria based on increase of amplitude or voltage of the QRS complexes. Positive Sokolow-Lyon index: S of V1 + R of V5 ≥35 mm in adults. Following the point score system for LVH or Romhilt-Estes Score = 6 points. ST-T vector opposite to QRS without digitalis. R wave in V5 or V6 ≥30 mm. 5 or more points: certain LVH.

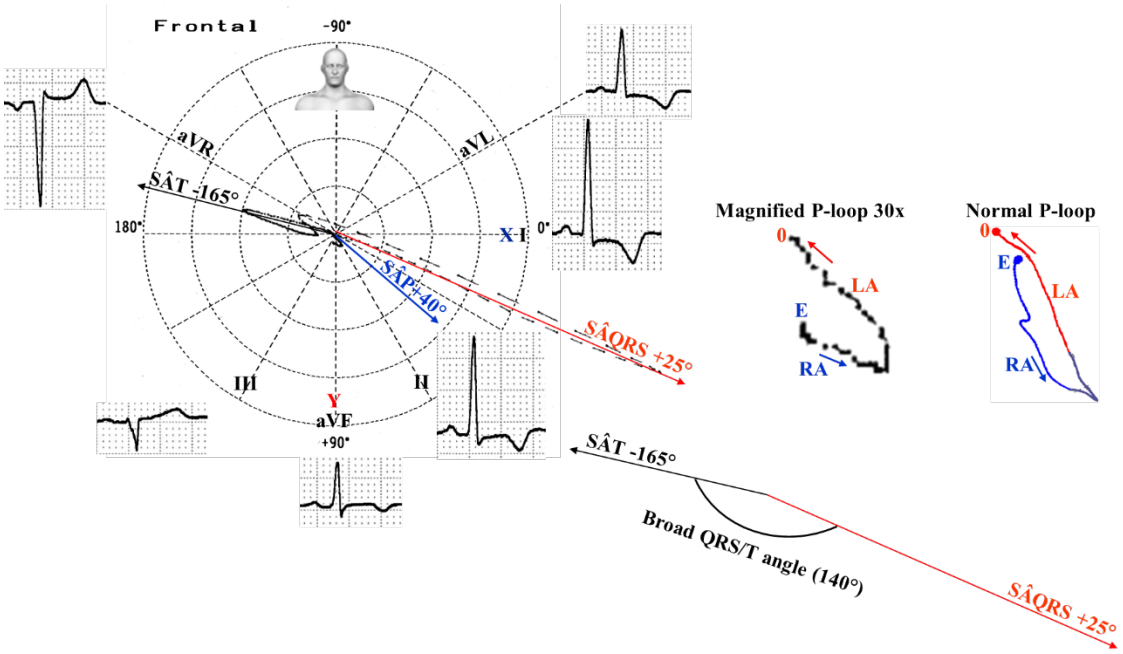

Figure 40. ECG/VCG correlation in the frontal plane.

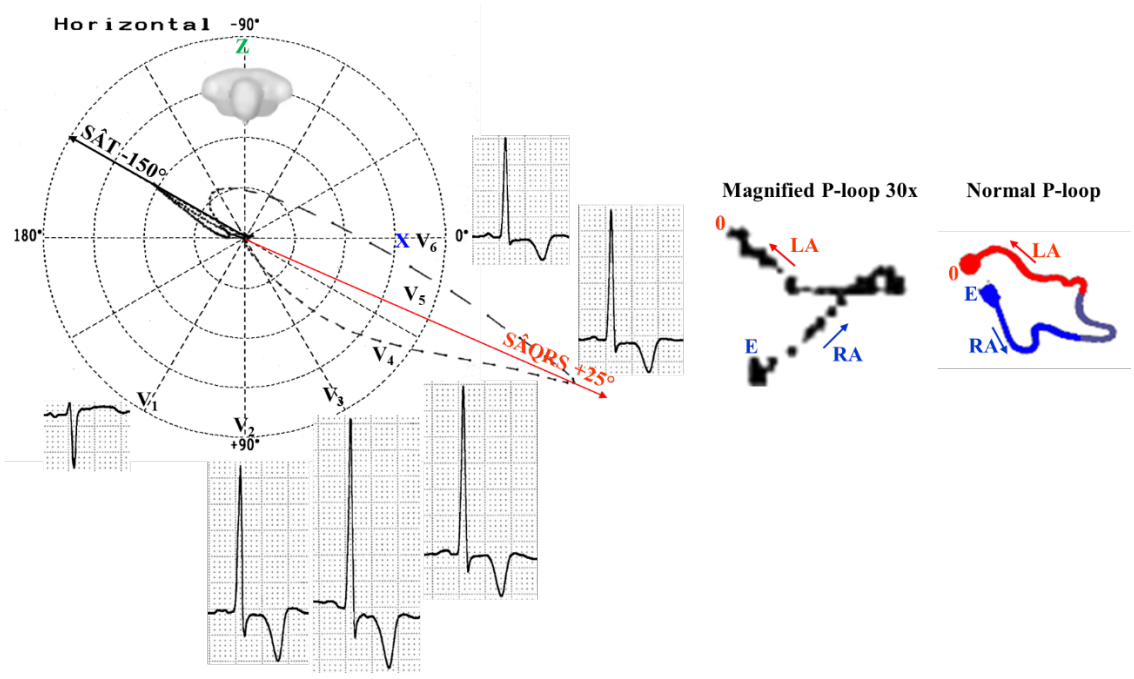

Figure 41. ECG/VCG correlation in the horizontal plane.

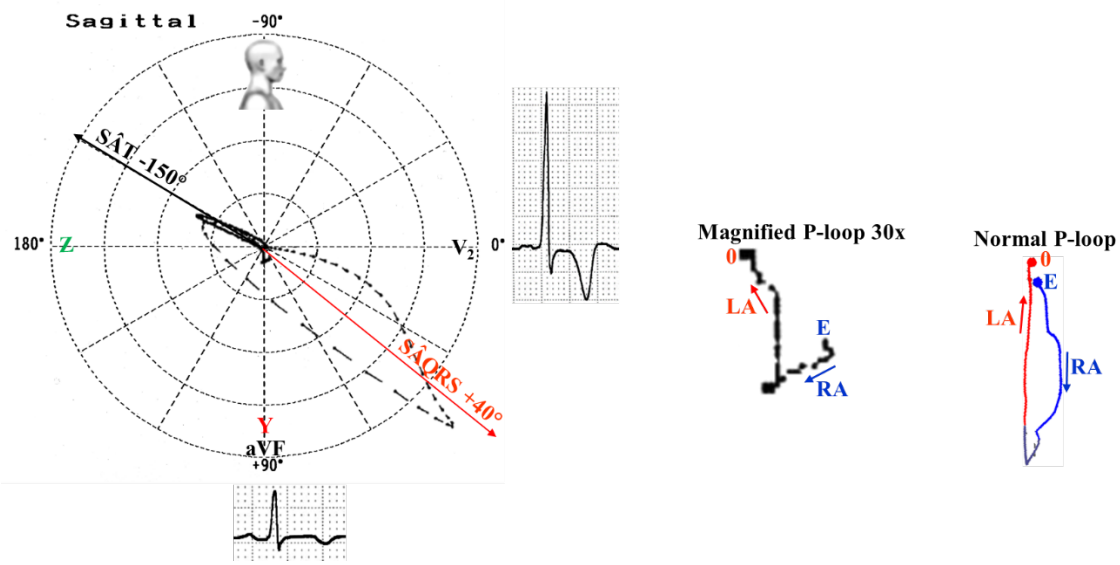

Figure 42. ECG/VCG correlation in the right sagittal plane.

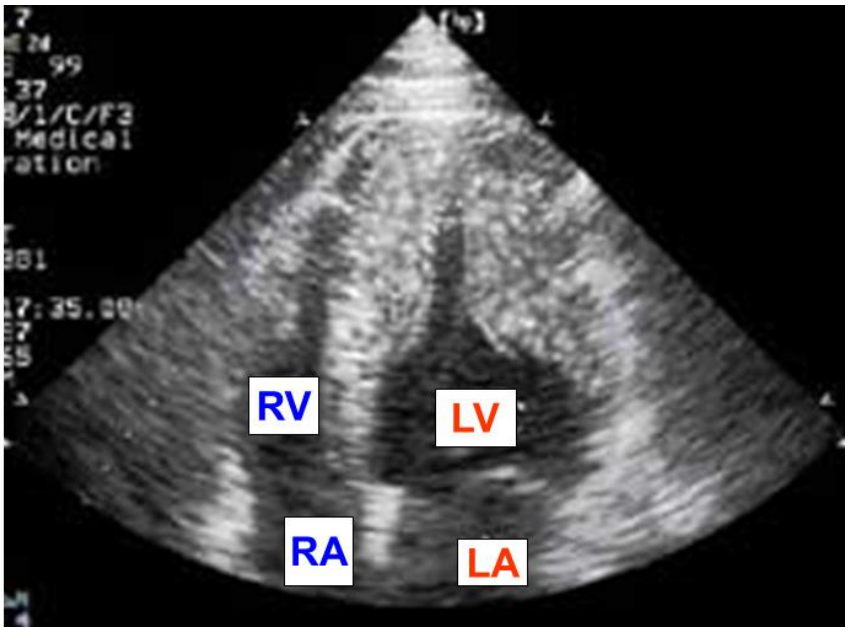

Figure 43. Two-dimensional echocardiogram. Apical 4-chamber view shows apical hypertrophy in the apical one third of the ventricle, with apical LV cavity obliteration. **RV** = right ventricle **RA** = right atrium **LA** = left atrium **LV**= left ventricular cavity

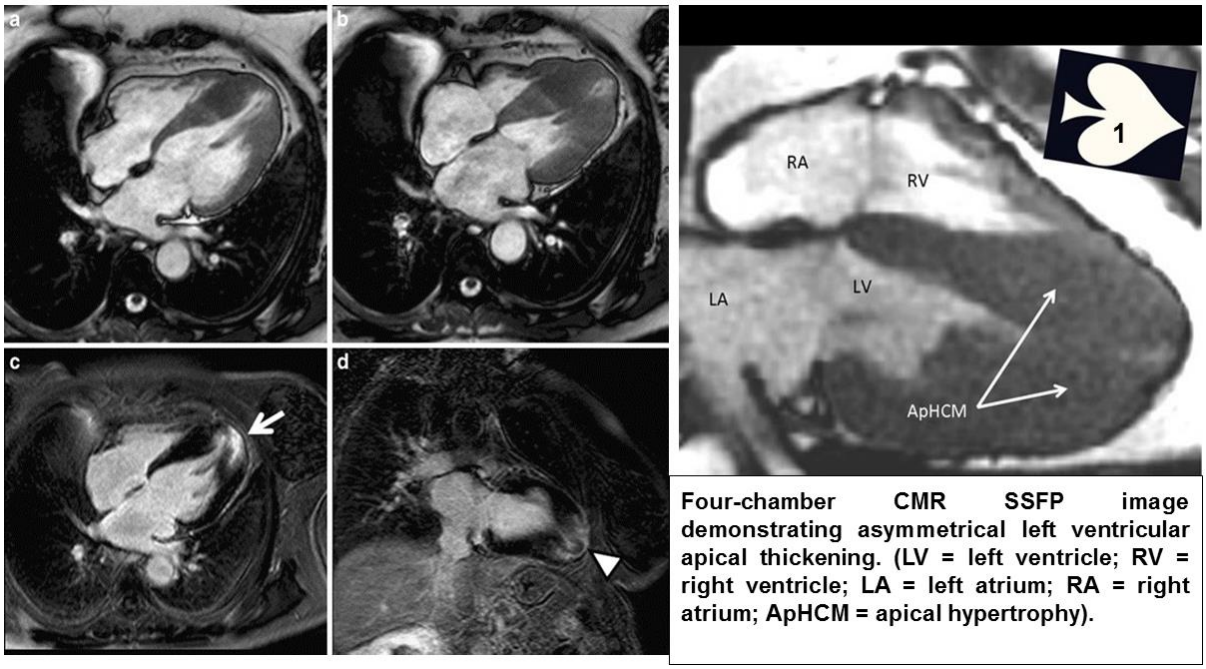

Figure 44. Ap-HCM. Cine MRI in the four-chamber view shows progressive thickening of the ventricular walls towards the apex in diastole (a) and systole (b). Late enhancement in a four-chamber view (c) and vertical long axis (d) demonstrates strong enhancement in the hypertrophied myocardium (arrow). Note the presence of "pseudo diverticulum" in the most apical myocardium (arrowhead).

HCM is characterized by substantial genetic and phenotypic heterogeneity, leading to considerable diversity in clinical course including the most common cause of SCD in young athletes and a determinant of HF symptoms in patients of any age.

Two-dimensional echocardiography has been the most reliable method for establishing a clinical diagnosis of HCM. However, CMRI, with its high spatial resolution

and tomographic imaging capability, has emerged as a technique particularly well suited to characterize the diverse phenotypic expression of this complex disease.

CMRI is often superior to TTC for HCM diagnosis, by identifying areas of segmental hypertrophy (i.e., anterolateral wall or apex) not reliably visualized by echocardiography (or underestimated in terms of extent).

High-risk HCM patient subgroups identified with CMRI include those with thin-walled scarred LV apical aneurysms (which prior to CMRI in HCM remained largely undetected).

End-stage systolic dysfunction, and massive LVH. CMRI observations also suggest that the cardiomyopathic process in HCM is more diffuse than previously regarded, extending beyond the LV myocardium to include thickening of the RV wall as well as substantial morphologic diversity with regard to papillary muscles and mitral valve. These findings have implications for management strategies in patients undergoing invasive septal reduction therapy.

Among HCM family members, CMRI has identified unique phenotypic markers of affected genetic status in the absence of LVH including: myocardial crypts, elongated mitral valve leaflets and late gadolinium enhancement. The unique capability of LGE-CMRI to identify myocardial fibrosis has raised the expectation that this may represent a novel marker, which may enhance risk stratification. LGE appears to be an important determinant of adverse LV remodeling associated with systolic dysfunction. However, the predictive significance of LGE for SCD is incompletely resolved and ultimately future large prospective studies may provide greater insights into this issue. These observations underscore an important role for CMRI in the contemporary assessment of patients with HCM, providing important information impacting diagnosis and clinical management strategies.

Prognosis

Mortality rates of 1 to 4% have been reported in patients with HCM, but these numbers have greatly improved in the past two decades.

Even though most patients with HCM have no symptoms, the first clinical presentation is often SCD from malignant arrhythmias. The highest mortality is in young people.

Early diagnosis is important as it allows the healthcare provider is to prescribe an appropriate level of safe physical activity

Besides SCD, patients can have atrial and ventricular arrhythmias.

Those who have concomitant mitral regulation and diastolic dysfunction are also prone to recurrent episodes of CHF.

Management of HCM

There are currently no disease-specific medications for HCM.

For patients with HCM without symptoms, lifestyle changes and medications for conditions that may contribute to cardiovascular disease are recommended.

For those with symptoms, the focus is on symptom management using medications and procedures.

Medications

β-blockers, metoprolol (Lopressor, Toprol-XL), propranolol (Inderal, Innopran XL) or atenolol (Tenormin).

Calcium channel blockers such as verapamil (Verelan, Calan SR,) or diltiazem (Cardizem, Tiazac).

Heart rhythm drugs such as amiodarone (Pacerone) or disopyramide (Norpace).

Blood thinners such as warfarin (Coumadin, Jantoven), dabigatran (Pradaxa), rivaroxaban (Xarelto) or apixaban (Eliquis) to prevent blood clots in cases of AF.

Diuretics offer limited and varying relief of symptoms. They may help with function but may also have adverse side effects.

Procedures

A range of surgical and nonsurgical procedures can be used to treat HCM:

Surgical Septal Myectomy: It is an open-heart surgery considered for people with obstructive HCM and severe symptoms. This is generally reserved for younger patients and for people whose medications are not working well. A surgeon removes part of the thickened septum that is bulging into the LV. Septal myectomy helps improve blood flow out of the heart and reduces backward flow of blood through the mitral valve (mitral regurgitation). The surgery may be done using different approaches, depending on the location of the thickened heart muscle. In one type, called apical myectomy, surgeons remove thickened heart muscle from near the tip of the heart. Sometimes the mitral valve is repaired at the same time. Currently, surgical septal myectomy is regarded as the "gold standard" treatment for most patients with OHCM and drug-refractory symptoms. However, the best results are obtained by those surgeons who have extensive experience with this operation at a small number of referral centers.

ASA: In this procedure, ethanol (a type of alcohol) is injected through a tube into the small artery that supplies blood to the area of heart muscle thickened by HCM. The alcohol causes these cells to die. The thickened tissue shrinks to a more normal size. The risks and complications of heart surgery increase with age. For this reason, ASA may be preferred to myectomy in older patients with other medical conditions. Possible complications include heart block, which requires implantation of a pacemaker.[171]

ASA requires selection of patients with a suitable clinical profile.

The US/Canada (ACC/AHA) guidelines suggest limiting ASA to patients of advanced age, those at an unacceptably high operative risk as a result of important comorbidities or those with a strong aversion to surgery.[90] The limitation of ASA to patients >60 years can be justified by the low rate of SCD in elderly HCM patients[172] and their shorter period of potential risk compared to young patients. Additionally, patients with concomitant diseases that would independently warrant surgical correction, such as CAD or mitral valve repair for ruptured chordae, cannot be candidates for ASA.

Long-term mortality and (aborted) SCD rates after ASA and myectomy are similarly low. Patients who undergo ASA have more than twice the risk of permanent pacemaker implantation and a 5 times higher risk of the need for additional septal reduction therapy compared with those who undergo myectomy.[173]

Surgically implanted devices: Surgeons can implant several types of devices to help the heart work better, including:

ICD: it reduces the risk of SCD. An ICD helps maintain a normal heartbeat by sending an electric shock to the heart if an irregular heartbeat is detected. This reduces the risk of SCD. An ICD is a small device that continuously monitors the heartbeat. It is implanted in the chest like a pacemaker. If a life-threatening arrhythmia occurs, the ICD delivers precisely calibrated electrical shocks to restore a normal heart rhythm. ICD has been shown to help prevent SCD, which occurs in a small number of people with HCM. Delayed enhancement CMRI is a supporting tool in the decision-making process for primary prevention ICDs in patients in whom high-risk for SCD remains uncertain after assessment of conventional risk factors.[174]

Pacemaker: This device uses electrical pulses to prompt the heart to beat at a normal rate.

CRT: A dilated/end-stage phase of HCM is rare but well-recognized. The role for CRT in this subset of patients remains unexplored. This device coordinates contractions between the LV and RV. CRT in patients with dilated/end-stage HCM does not appear to confer a benefic effect on ventricular function. In medium-term follow-up, however, LV function did not appear to deteriorate further, yet advanced CHF therapy was common in this group. In a large tertiary referral practice for HCM, progressive LV dysfunction reaching an endstage is rare. In lieu of this, biventricular pacing is rarely indicated.

This therapeutic tool was utilized specifically in those patients with CHF despite maximal medical therapy. Remarkable is the relatively young age of these patients, nearly all of whom are male, a finding in keeping with an earlier report.[175, 176] Patients with HCM, in use of iCDs, cannot be followed-up by CMRI, since the presence of ICD implant may be a contraindication for the exam. In this context, CCT is a useful alternative in the assessment and management of these patients.

Heart transplantation in patients with HCM: In HCM patients with advanced, end-stage disease or patients showing refractory CHF signs and symptoms, a heart transplant may be considered. A minority of patients (around 3.5%) can progress to an end-stage state, characterized by systolic dysfunction and restrictive ventricular filling, related to extensive fibrotic replacement and chamber remodeling. In these cases, life expectancy is significantly reduced: a mean 3-year survival time has been reported. In this procedure, a person's diseased heart is replaced with a healthy donor heart. The 1-year survival rate after cardiac transplantation is as high as 84%, with a 5-year survival rate of 75% and 10-year survival rate of 59%. The functional status of the recipient after the procedure is generally excellent.[177]

An average age of transplant recipients (45 years) is associated with a survival rate that is similar to the rate for transplantation in patients with other cardiomyopathies or

ischemic heart disease (i.e., 85%, 75%, and 61%, at 1, 5, and 10 years, following data from the United Network for Organ Sharing),[178] with potentially superior survival (92% at 5 years) at centers that specialize in the treatment of HCM.[179]

References

1. Sheppard MN. Practical Cardiovascular Pathology. 2nd ed. London, UK: Hodder Arnold; 2011.
2. Wigle ED, Rakowski H, Kimball BP*, et al.* Hypertrophic cardiomyopathy. Clinical spectrum and treatment. Circulation. 1995;92:1680-1692.
3. Gwathmey JK, Warren SE, Briggs GM*, et al.* Diastolic dysfunction in hypertrophic cardiomyopathy. Effect on active force generation during systole. J Clin Invest. 1991;87:1023-1031.
4. Betocchi S, Hess OM, Losi MA*, et al.* Regional left ventricular mechanics in hypertrophic cardiomyopathy. Circulation. 1993;88:2206-2214.
5. Hughes SE. The pathology of hypertrophic cardiomyopathy. Histopathology. 2004;44:412-427.
6. Adomian GE, Beazell J. Myofibrillar disarray produced in normal hearts by chronic electrical pacing. Am Heart J. 1986;112:79-83.
7. Camici PG, Olivotto I, Rimoldi OE. The coronary circulation and blood flow in left ventricular hypertrophy. J Mol Cell Cardiol. 2012;52:857-864.
8. Gutierrez-Barrios A, Camacho-Jurado F, Diaz-Retamino E*, et al.* Invasive assessment of coronary microvascular dysfunction in hypertrophic cardiomyopathy: the index of microvascular resistance. Cardiovasc Revasc Med. 2015;16:426-428.
9. Papadakis M, Raju H, Behr ER*, et al.* Sudden cardiac death with autopsy findings of uncertain significance: potential for erroneous interpretation. Circ Arrhythm Electrophysiol. 2013;6:588-596.
10. Jain CC, Newman DB, Geske JB. Mitral Valve Disease in Hypertrophic Cardiomyopathy:Evaluation and Management. Curr Cardiol Rep. 2019;21:136.
11. Captur G, Lopes LR, Mohun TJ*, et al.* Prediction of sarcomere mutations in subclinical hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 2014;7:863-871.
12. Petryka J, Baksi AJ, Prasad SK*, et al.* Prevalence of inferobasal myocardial crypts among patients referred for cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2014;7:259-264.
13. Semsarian C, Ingles J, Maron MS*, et al.* New perspectives on the prevalence of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2015;65:1249-1254.
14. Ciampi Q, Betocchi S, Losi MA*, et al.* Effect of hypertrophy on left ventricular diastolic function in patients with hypertrophic cardiomyopathy. Heart Int. 2006;2:106.
15. Penaloza D, Tranchesi J. The three main vectors of the ventricular activation process in the normal human heart. I. Its significance. Am Heart J. 1955;49:51-67.
16. Konno T, Shimizu M, Ino H*, et al.* Diagnostic value of abnormal Q waves for identification of preclinical carriers of hypertrophic cardiomyopathy based on a molecular genetic diagnosis. Eur Heart J. 2004;25:246-251.
17. Noureldin RA, Liu S, Nacif MS*, et al.* The diagnosis of hypertrophic cardiomyopathy by cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012;14:17.
18. Kauer F, van Dalen BM, Soliman OI*, et al.* Regional left ventricular rotation and back-rotation in patients with reverse septal curvature hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2013;14:435-442.
19. Gentille-Lorente D, Salvado-Usach T. [Sigmoid septum: A variant of the ventricular hypertrophy or of the hypertrophic cardiomyopathy?]. Arch Cardiol Mex. 2016;86:110-122.
20. Harada K, Shimizu T, Sugishita Y*, et al.* Hypertrophic cardiomyopathy with midventricular obstruction and apical aneurysm: a case report. Jpn Circ J. 2001;65:915-919.
21. Tse HF, Ho HH. Sudden cardiac death caused by hypertrophic cardiomyopathy associated with midventricular obstruction and apical aneurysm. Heart. 2003;89:178.
22. Kang KW, Janardhan AH, Jung KT*, et al.* Fragmented QRS as a candidate marker for high-risk assessment in hypertrophic cardiomyopathy. Heart Rhythm. 2014;11:1433-1440.

23. Perez-Riera AR, Barbosa-Barros R, de Lucca AA, Jr.*, et al.* Mid-ventricular Hypertrophic Obstructive Cardiomyopathy with Apical Aneurysm Complicated with Syncope by Sustained Monomorphic Ventricular Tachycardia. Ann Noninvasive Electrocardiol. 2016;21:618-621.
24. Albanesi Filho FM, Castier MB, Lopes AS*, et al.* [Is the apical hypertrophic cardiomyopathy seen in one population in Rio de Janeiro city similar to that found in the East?]. Arq Bras Cardiol. 1997;69:117-123.
25. Kitaoka H, Doi Y, Casey SA*, et al.* Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. Am J Cardiol. 2003;92:1183-1186.
26. Abdin A, Eitel I, de Waha S*, et al.* Apical hypertrophic cardiomyopathy presenting as acute coronary syndrome. Eur Heart J Acute Cardiovasc Care. 2016;5:289-291.
27. Payus AO, Sholeh FM, Mustafa N. Yamaguchi syndrome – A pseudoacute coronary syndrome of the young: A case report on apical hypertrophic cardiomyopathy. J Med Sci. 2019;39:197-199.
28. Wigle ED. Cardiomyopathy: The diagnosis of hypertrophic cardiomyopathy. Heart. 2001;86:709-714.
29. Bielli M, Parravicini U, Zanetta M*, et al.* [Apical hypertrophic cardiomyopathy: description of a case in advanced age with documentation of electrocardiographic course]. G Ital Cardiol. 1991;21:1325-1329.
30. Dumont CA, Monserrat L, Soler R*, et al.* Interpretation of electrocardiographic abnormalities in hypertrophic cardiomyopathy with cardiac magnetic resonance. Eur Heart J. 2006;27:1725-1731.
31. Tilmant PY, Lablanche JM, Laurent JM*, et al.* [Non-obstructive hypertrophic myocardiopathy. Apropos of 5 cases]. Arch Mal Coeur Vaiss. 1980;73:1269-1278.
32. Maron BJ. The giant negative T wave revisited ... in hypertrophic cardiomyopathy. J Am Coll Cardiol. 1990;15:972-973.
33. Varriale P, Alfenito JC, Kennedy RJ. The vectorcardiogram of left ventricular hypertrophy. Analysis and criteria (Frank Lead system). Circulation. 1966;33:569-576.
34. Pérez-Riera AR, Yanowitz F, Barbosa-Barros R*, et al.* Electrocardiographic "Northwest QRS Axis" in the Brugada Syndrome: A Potential Marker to Predict Poor Outcome. JACC: Case Reports. 2020;2:2230-2234.
35. Chua KC, Teodorescu C, Reinier K*, et al.* Wide QRS-T Angle on the 12-Lead ECG as a Predictor of Sudden Death Beyond the LV Ejection Fraction. J Cardiovasc Electrophysiol. 2016;27:833-839.
36. Arad M, Penas-Lado M, Monserrat L*, et al.* Gene mutations in apical hypertrophic cardiomyopathy. Circulation. 2005;112:2805-2811.
37. Olson TM, Doan TP, Kishimoto NY*, et al.* Inherited and de novo mutations in the cardiac actin gene cause hypertrophic cardiomyopathy. J Mol Cell Cardiol. 2000;32:1687-1694.
38. Reynen K. Cardiac myxomas. N Engl J Med. 1995;333:1610-1617.
39. Oh JK, Park JH, Lee JH*, et al.* Shape and Mobility of a Left Ventricular Thrombus Are Predictors of Thrombus Resolution. Korean Circ J. 2019;49:829-837.
40. Spirito P, Autore C. Apical hypertrophic cardiomyopathy or left ventricular non-compaction? A difficult differential diagnosis. Eur Heart J. 2007;28:1923-1924.
41. Hassan WM, Fawzy ME, Al Helaly S*, et al.* Pitfalls in diagnosis and clinical, echocardiographic, and hemodynamic findings in endomyocardial fibrosis: a 25-year experience. Chest. 2005;128:3985-3992.
42. Duygu H, Zoghi M, Nalbantgil S*, et al.* Apical hypertrophic cardiomyopathy might lead to misdiagnosis of ischaemic heart disease. Int J Cardiovasc Imaging. 2008;24:675-681.
43. Elizari MV. [Chagasic myocardiopathy: historical perspective]. Medicina (B Aires). 1999;59 Suppl 2:25-40.
44. Oliveira JS, Mello De Oliveira JA, Frederigue U, Jr.*, et al.* Apical aneurysm of Chagas's heart disease. Br Heart J. 1981;46:432-437.

45. Cisneros S, Duarte R, Fernandez-Perez GC*, et al.* Left ventricular apical diseases. Insights Imaging. 2011;2:471-482.
46. Yusuf SW, Bathina JD, Banchs J*, et al.* Apical hypertrophic cardiomyopathy. World J Cardiol. 2011;3:256-259.
47. Dohlemann C, Hebe J, Meitinger T*, et al.* Apical hypertrophic cardiomyopathy due to a de novo mutation Arg719Trp of the beta-myosin heavy chain gene and cardiac arrest in childhood. A case report and family study. Z Kardiol. 2000;89:612-619.
48. Suganuma Y, Shinmura K, Hasegawa H*, et al.* [Clinical characteristics and cardiac events in elderly patients with apical hypertrophic cardiomyopathy]. Nihon Ronen Igakkai Zasshi. 1997;34:474-481.
49. Chung T, Yiannikas J, Freedman SB*, et al.* Unusual features of apical hypertrophic cardiomyopathy. Am J Cardiol. 2010;105:879-883.
50. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. Circulation. 1996;93:372-379.
51. Yan L, Wang Z, Xu Z*, et al.* Two hundred eight patients with apical hypertrophic cardiomyopathy in china: clinical feature, prognosis, and comparison of pure and mixed forms. Clin Cardiol. 2012;35:101-106.
52. Eriksson MJ, Sonnenberg B, Woo A*, et al.* Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002;39:638-645.
53. Rowin EJ, Maron BJ, Haas TS*, et al.* Hypertrophic Cardiomyopathy With Left Ventricular Apical Aneurysm: Implications for Risk Stratification and Management. J Am Coll Cardiol. 2017;69:761-773.
54. 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:e005820.
55. Chen X, Dong JZ, Du X*, et al.* Long-term outcome of catheter ablation for atrial fibrillation in patients with apical hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2018;29:951-957.
56. Roh SY, Kim DH, Ahn J*, et al.* Long-Term Outcome of Catheter Ablation for Atrial Fibrillation in Patients With Apical Hypertrophic Cardiomyopathy. J Cardiovasc Electrophysiol. 2016;27:788-795.
57. Lee SE, Park JK, Uhm JS*, et al.* Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. Heart. 2017;103:1496-1501.
58. Sultan FAT, Saadia S. Patterns of Left Ventricular Hypertrophy and Late Gadolinium Enhancement on Cardiac MRI in Patients with Hypertrophic Cardiomyopathy and their Prognostic Significance - An Experience from a South Asian Country. J Clin Imaging Sci. 2021;11:14.
59. Hoey ET, Teoh JK, Das I*, et al.* The emerging role of cardiovascular MRI for risk stratification in hypertrophic cardiomyopathy. Clin Radiol. 2014;69:221-230.
60. Pambo P, Scharhag J. Electrocardiographic and Echocardiographic Findings in Black Athletes: A General Review. Clin J Sport Med. 2021;31:321-329.
61. Rowland T, Roti M. Influence of sex on the "Athlete's Heart" in trained cyclists. J Sci Med Sport. 2010;13:475-478.
62. Whyte GP, George K, Sharma S*, et al.* The upper limit of physiological cardiac hypertrophy in elite male and female athletes: the British experience. Eur J Appl Physiol. 2004;92:592-597.
63. Pelliccia A, Maron MS, Maron BJ. Assessment of left ventricular hypertrophy in a trained athlete: differential diagnosis of physiologic athlete's heart from pathologic hypertrophy. Prog Cardiovasc Dis. 2012;54:387-396.
64. Heidbuchel H, La Gerche A. The right heart in athletes. Evidence for exercise-induced arrhythmogenic right ventricular cardiomyopathy. Herzschrittmacherther Elektrophysiol. 2012;23:82-86.

65. Christiaans I, Birnie E, Bonsel GJ*, et al.* Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. Eur J Hum Genet. 2008;16:1201-1207.
66. Atteya G, Lampert R. Sudden Cardiac Death in Genetic Cardiomyopathies. Card Electrophysiol Clin. 2017;9:581-603.
67. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. N Engl J Med. 2018;379:1977.
68. Alfares AA, Kelly MA, McDermott G*, et al.* Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. Genet Med. 2015;17:880-888.
69. Cirino AL, Harris S, Lakdawala NK*, et al.* Role of Genetic Testing in Inherited Cardiovascular Disease: A Review. JAMA Cardiol. 2017;2:1153-1160.
70. Fourey D, Care M, Siminovitch KA*, et al.* Prevalence and Clinical Implication of Double Mutations in Hypertrophic Cardiomyopathy: Revisiting the Gene-Dose Effect. Circ Cardiovasc Genet. 2017;10.
71. Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol. 2012;60:705-715.
72. Richards S, Aziz N, Bale S*, et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-424.
73. Marian AJ. Molecular Genetic Basis of Hypertrophic Cardiomyopathy. Circ Res. 2021;128:1533-1553.
74. Afanasyev A, Bogachev-Prokophiev A, Lenko E*, et al.* Myectomy with mitral valve repair versus replacement in adult patients with hypertrophic obstructive cardiomyopathy: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2019;28:465-472.
75. Robyns T, Nuyens D, Lu HR*, et al.* Prognostic value of electrocardiographic time intervals and QT rate dependence in hypertrophic cardiomyopathy. J Electrocardiol. 2018;51:1077-1083.
76. Walsh R, Mazzarotto F, Whiffin N*, et al.* Quantitative approaches to variant classification increase the yield and precision of genetic testing in Mendelian diseases: the case of hypertrophic cardiomyopathy. Genome Med. 2019;11:5.
77. Finocchiaro G, Sheikh N, Biagini E*, et al.* The electrocardiogram in the diagnosis and management of patients with hypertrophic cardiomyopathy. Heart Rhythm. 2020;17:142-151.
78. Abstract 15703:: Hypertrophic cardiomyopathy with normal ECG: clinical meaning and prognostic implications [Internet]. Circulation. 2018.
79. Elliott P, Andersson B, Arbustini E*, et al.* Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29:270-276.
80. Authors/Task Force m, 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;35:2733-2779.
81. Kawasaki T, Sakai C, Harimoto K*, et al.* Holter monitoring and long-term prognosis in hypertrophic cardiomyopathy. Cardiology. 2012;122:44-54.
82. Argulian E, Chaudhry FA. Stress testing in patients with hypertrophic cardiomyopathy. Prog Cardiovasc Dis. 2012;54:477-482.
83. Sheikh N, Papadakis M, Schnell F*, et al.* Clinical Profile of Athletes With Hypertrophic Cardiomyopathy. Circ Cardiovasc Imaging. 2015;8:e003454.
84. Rowin EJ, Maron BJ, Olivotto I*, et al.* Role of Exercise Testing in Hypertrophic Cardiomyopathy. JACC Cardiovasc Imaging. 2017;10:1374-1386.
85. Zhang L, Mmagu O, Liu L*, et al.* Hypertrophic cardiomyopathy: Can the noninvasive diagnostic testing identify high risk patients? World J Cardiol. 2014;6:764-770.

86. Rickers C, Wilke NM, Jerosch-Herold M*, et al.* Utility of cardiac magnetic resonance imaging in the diagnosis of hypertrophic cardiomyopathy. Circulation. 2005;112:855-861.
87. Sara L, Szarf G, Tachibana A*, et al.* [II Guidelines on Cardiovascular Magnetic Resonance and Computed Tomography of the Brazilian Society of Cardiology and the Brazilian College of Radiology]. Arq Bras Cardiol. 2014;103:1-86.
88. Bogaert J, Olivotto I. MR Imaging in Hypertrophic Cardiomyopathy: From Magnet to Bedside. Radiology. 2014;273:329-348.
89. Harrigan CJ, Peters DC, Gibson CM*, et al.* Hypertrophic cardiomyopathy: quantification of late gadolinium enhancement with contrast-enhanced cardiovascular MR imaging. Radiology. 2011;258:128-133.
90. Gersh BJ, Maron BJ, Bonow RO*, et al.* 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:2761-2796.
91. Nordbeck P, Ertl G, Ritter O. Magnetic resonance imaging safety in pacemaker and implantable cardioverter defibrillator patients: how far have we come? Eur Heart J. 2015;36:1505-1511.
92. Leite CC. Gadolinium and nephrogenic systemic fibrosis: every physician should know. Radiol Bras. 2007;40:iv-iv.
93. Nagueh SF, Bierig SM, Budoff MJ*, et al.* American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: Endorsed by the American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2011;24:473-498.
94. Westermark P, Benson MD, Buxbaum JN*, et al.* Amyloid: toward terminology clarification. Report from the Nomenclature Committee of the International Society of Amyloidosis. Amyloid. 2005;12:1-4.
95. Gillmore JD, Maurer MS, Falk RH*, et al.* Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133:2404-2412.
96. Hensley N, Dietrich J, Nyhan D*, et al.* Hypertrophic cardiomyopathy: a review. Anesth Analg. 2015;120:554-569.
97. Yalim Z, Dural I, Emren V*, et al.* Coexistence of Sick Sinus Syndrome and Hypertrophic Cardiomyopathy in Patient with Syncope. IJCMR. 2016;3:77.83.
98. Fitzgerald P, Kusumoto F. The effects of septal myectomy and alcohol septal ablation for hypertrophic cardiomyopathy on the cardiac conduction system. J Interv Card Electrophysiol. 2018;52:403-408.
99. Fananapazir L, Tracy CM, Leon MB*, et al.* Electrophysiologic abnormalities in patients with hypertrophic cardiomyopathy. A consecutive analysis in 155 patients. Circulation. 1989;80:1259-1268.
100. Morris JJ, Jr., Estes EH, Jr., Whalen RE*, et al.* P-Wave Analysis in Valvular Heart Disease. Circulation. 1964;29:242-252.
101. Bayes de Luna A. Clinical Electrocardiography A Textbook. 4th ed. Hoboken, NJ: Wiley-Blackwell; 2012.
102. Wigle ED, Sasson Z, Henderson MA*, et al.* Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. Prog Cardiovasc Dis. 1985;28:1-83.
103. 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;3:408-418.
104. Savage DD, Seides SF, Clark CE*, et al.* Electrocardiographic findings in patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Circulation. 1978;58:402-408.

105. Limongelli G, Masarone D, Frisso G*, et al.* Clinical and genetic characterization of patients with hypertrophic cardiomyopathy and right atrial enlargement. J Cardiovasc Med (Hagerstown). 2017;18:249-254.
106. Sanen FJ. [Stenosis of the right ventricle caused by excentric hypertrophy of the left ventricle or ventricular septum (Bernheim's syndrome)]. Z Kreislaufforsch. 1960;49:331-336.
107. Maron BJ, Bonow RO, Cannon RO, 3rd*, et al.* Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (2). N Engl J Med. 1987;316:844-852.
108. Biolato M, Montalto M, Sestito A*, et al.* ECG signs of biatrial enlargement in a young adult. Intern Emerg Med. 2010;5:441-442.
109. Opfermann UT, Doll N, Walther T*, et al.* Combined mitral valve repair, LVOT myectomy and left atrial cryoablation therapy. Interact Cardiovasc Thorac Surg. 2003;2:501-502.
110. Higuchi S, Minami Y, Shoda M*, et al.* Prognostic Implication of First-Degree Atrioventricular Block in Patients With Hypertrophic Cardiomyopathy. J Am Heart Assoc. 2020;9:e015064.
111. Wong TC. First-Degree Atrioventricular Block and Hypertrophic Cardiomyopathy: "I Have a Bad Feeling About This". J Am Heart Assoc. 2020;9:e015911.
112. Maron MS, Xin W, Sims KB*, et al.* Identification of Fabry Disease in a Tertiary Referral Cohort of Patients with Hypertrophic Cardiomyopathy. Am J Med. 2018;131:200 e201-200 e208.
113. Pochis WT, Litzow JT, King BG*, et al.* Electrophysiologic findings in Fabry's disease with a short PR interval. Am J Cardiol. 1994;74:203-204.
114. Seo J, Kim M, Hong GR*, et al.* Fabry disease in patients with hypertrophic cardiomyopathy: a practical approach to diagnosis. J Hum Genet. 2016;61:775-780.
115. Jain R, Singh R, Yamini S*, et al.* Fragmented ECG as a risk marker in cardiovascular diseases. Curr Cardiol Rev. 2014;10:277-286.
116. Ogura S, Nakamura K, Morita H*, et al.* New Appearance of Fragmented QRS as a Predictor of Ventricular Arrhythmic Events in Patients With Hypertrophic Cardiomyopathy. Circ J. 2020;84:487-494.
117. Rattanawong P, Riangwiwat T, Kanitsoraphan C*, et al.* Baseline fragmented QRS increases the risk of major arrhythmic events in hypertrophic cardiomyopathy: Systematic review and meta-analysis. Ann Noninvasive Electrocardiol. 2018;23:e12533.
118. Ratheendran AC, Subramanian M, Bhanu DK*, et al.* Fragmented QRS on electrocardiography as a predictor of myocardial scar in patients with hypertrophic cardiomyopathy. Acta Cardiol. 2020;75:42-46.
119. Haghjoo M, Mohammadzadeh S, Taherpour M*, et al.* ST-segment depression as a risk factor in hypertrophic cardiomyopathy. Europace. 2009;11:643-649.
120. Furuki M, Kawai H, Onishi T*, et al.* Value of convex-type ST-segment elevation and abnormal Q waves for electrocardiographic-based identification of left ventricular remodeling in hypertrophic cardiomyopathy. Kobe J Med Sci. 2009;55:E16-29.
121. Calore C, Zorzi A, Sheikh N*, et al.* Electrocardiographic anterior T-wave inversion in athletes of different ethnicities: differential diagnosis between athlete's heart and cardiomyopathy. Eur Heart J. 2016;37:2515-2527.
122. Abuli M, de la Garza MS, Sitges M. Differentiating Athlete's Heart from Left Ventricle Cardiomyopathies. J Cardiovasc Transl Res. 2020;13:265-273.
123. Sharma S, Drezner JA, Baggish A*, et al.* International Recommendations for Electrocardiographic Interpretation in Athletes. J Am Coll Cardiol. 2017;69:1057-1075.
124. Gray B, Ingles J, Medi C*, et al.* Prolongation of the QTc interval predicts appropriate implantable cardioverter-defibrillator therapies in hypertrophic cardiomyopathy. JACC Heart Fail. 2013;1:149-155.
125. Wen SN, Liu N, Li SN*, et al.* QTc Interval Prolongation Predicts Arrhythmia Recurrence After Catheter Ablation of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy. Circ J. 2015;79:1024-1030.

126. Wen SN, Zhu HJ, Sun PY*, et al.* Depolarization and repolarization parameters on ECG predict recurrence after atrial fibrillation ablation in patients with hypertrophic cardiomyopathy. J Cardiovasc Electrophysiol. 2019;30:2405-2413.
127. Olivotto I, Cecchi F, Casey SA*, et al.* Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517-2524.
128. Garg L, Gupta M, Sabzwari SRA*, et al.* Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical impact, and management. Heart Fail Rev. 2019;24:189-197.
129. Ozdemir O, Soylu M, Demir AD*, et al.* P-wave durations as a predictor for atrial fibrillation development in patients with hypertrophic cardiomyopathy. Int J Cardiol. 2004;94:163-166.
130. Nistri S, Olivotto I, Betocchi S*, et al.* Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol. 2006;98:960-965.
131. Al-Khatib SM, Stevenson WG, Ackerman MJ*, et al.* 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2018;138:e210-e271.
132. McKenna WJ, England D, Doi YL*, et al.* Arrhythmia in hypertrophic cardiomyopathy. I: Influence on prognosis. Br Heart J. 1981;46:168-172.
133. Adabag AS, Maron BJ, Appelbaum E*, et al.* Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51:1369-1374.
134. MacRae CA, Ghaisas N, Kass S*, et al.* Familial Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome maps to a locus on chromosome 7q3. J Clin Invest. 1995;96:1216-1220.
135. Bobkowski W, Sobieszczanska M, Turska-Kmiec A*, et al.* Mutation of the MYH7 gene in a child with hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome. J Appl Genet. 2007;48:185-188.
136. Talle MA, Buba F, Bonny A*, et al.* Hypertrophic Cardiomyopathy and Wolff-Parkinson-White Syndrome in a Young African Soldier with Recurrent Syncope. Case Rep Cardiol. 2019;2019:1061065.
137. Perosio AM, Suarez LD, Bunster AM*, et al.* Pre-excitation syndrome and hypertrophic cardiomyopathy. J Electrocardiol. 1983;16:29-40.
138. Gollob MH, Seger JJ, Gollob TN*, et al.* Novel PRKAG2 mutation responsible for the genetic syndrome of ventricular preexcitation and conduction system disease with childhood onset and absence of cardiac hypertrophy. Circulation. 2001;104:3030-3033.
139. MacAlpin RN. The fragmented QRS: does it really indicate a ventricular abnormality? J Cardiovasc Med (Hagerstown). 2010;11:801-809.
140. Chen CH, Nobuyoshi M, Kawai C. ECG pattern of left ventricular hypertrophy in nonobstructive hypertrophic cardiomyopathy: the significance of the mid-precordial changes. Am Heart J. 1979;97:687-695.
141. Perez Riera AR, Ferreira C, Ferreira Filho C*, et al.* Electrovectorcardiographic diagnosis of left septal fascicular block: anatomic and clinical considerations. Ann Noninvasive Electrocardiol. 2011;16:196-207.
142. Migliore F, Zorzi A, Michieli P*, et al.* Prevalence of cardiomyopathy in Italian asymptomatic children with electrocardiographic T-wave inversion at preparticipation screening. Circulation. 2012;125:529-538.
143. 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;43:649-656.

144. 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;109:587-593.
145. Gambarin FI, Disabella E, Narula J*, et al.* When should cardiologists suspect Anderson-Fabry disease? Am J Cardiol. 2010;106:1492-1499.
146. Kilicaslan F, Kirilmaz A, Bayturan O*, et al.* Indeterminate QRS axis in a patient with hypertrophic cardiomyopathy. Int J Cardiol. 2007;114:e5-6.
147. 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;100:503-506.
148. Rao U, Agarwal A. Importance of Q waves in early diagnosis of hypertrophic cardiomyopathy. Heart. 2011;97:1993-1994.
149. Ohmoto-Sekine Y, Suzuki J, Shimamoto R*, et al.* Gender-specific clinical characteristics of deep Q waves in hypertrophic cardiomyopathy. Gend Med. 2007;4:274-283.
150. Godballe C, Hoeck HC, Sorensen JA. [Transient abnormal Q-waves]. Ugeskr Laeger. 1990;152:92-94.
151. 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;106:18-25 e12.
152. Chatterjee S, Changawala N. Fragmented QRS complex: a novel marker of cardiovascular disease. Clin Cardiol. 2010;33:68-71.
153. Das MK, Maskoun W, Shen C*, et al.* Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm. 2010;7:74-80.
154. Das MK, Suradi H, Maskoun W*, et al.* Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol. 2008;1:258-268.
155. 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;32:2304-2313.
156. Yamaguchi H, Ishimura T, Nishiyama S*, et al.* Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. Am J Cardiol. 1979;44:401-412.
157. Badran HM, Elnoamany MF, Soltan G*, et al.* Relationship of mechanical dyssynchrony to QT interval prolongation in hypertrophic cardiomyopathy. Eur Heart J Cardiovasc Imaging. 2012;13:423-432.
158. Bayrak F, Kahveci G, Mutlu B*, et al.* Usefulness of surface electrocardiogram in predicting the clinical course of patients with hypertrophic cardiomyopathy. Anadolu Kardiyol Derg. 2007;7 Suppl 1:178-181.
159. Riera AR, de Cano SJ, Cano MN*, et al.* Vector electrocardiographic alterations after percutaneous septal ablation in obstructive hypertrophic cardiomyopathy. Possible anatomic causes. Arq Bras Cardiol. 2002;79:466-475.
160. Qin JX, Shiota T, Lever HM*, et al.* Conduction system abnormalities in patients with obstructive hypertrophic cardiomyopathy following septal reduction interventions. Am J Cardiol. 2004;93:171-175.
161. O'Mahony C, Lambiase PD, Rahman SM*, et al.* The relation of ventricular arrhythmia electrophysiological characteristics to cardiac phenotype and circadian patterns in hypertrophic cardiomyopathy. Europace. 2012;14:724-733.
162. Sherrid MV, 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;104:1722-1726.
163. Fumagalli C, Maurizi N, Day SM*, et al.* Association of Obesity With Adverse Long-term Outcomes in Hypertrophic Cardiomyopathy. JAMA Cardiol. 2020;5:65-72.

164. Klopotowski M, Kukula K, Malek LA*, et al.* The value of cardiac magnetic resonance and distribution of late gadolinium enhancement for risk stratification of sudden cardiac death in patients with hypertrophic cardiomyopathy. J Cardiol. 2016;68:49-56.
165. Oliveira DC, Assuncao FB, Santos AA*, et al.* Cardiac Magnetic Resonance and Computed Tomography in Hypertrophic Cardiomyopathy: an Update. Arq Bras Cardiol. 2016;107:163-172.
166. Wang Y, Wang Z, Yang Q*, et al.* Autosomal recessive transmission of MYBPC3 mutation results in malignant phenotype of hypertrophic cardiomyopathy. PLoS One. 2013;8:e67087.
167. Vaidya K, Semsarian C, Chan KH. Atrial Fibrillation in Hypertrophic Cardiomyopathy. Heart Lung Circ. 2017;26:975-982.
168. Spirito P, Bellone P, Harris KM*, et al.* Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000;342:1778-1785.
169. Maron MS, Olivotto I, Maron BJ*, et al.* The case for myocardial ischemia in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2009;54:866-875.
170. Monserrat L, Elliott PM, Gimeno JR*, et al.* Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol. 2003;42:873-879.
171. Spirito P, Rossi J, Maron BJ. Alcohol septal ablation: in which patients and why? Ann Cardiothorac Surg. 2017;6:369-375.
172. Maron BJ, Rowin EJ, Casey SA*, et al.* Risk stratification and outcome of patients with hypertrophic cardiomyopathy >=60 years of age. Circulation. 2013;127:585-593.
173. Liebregts M, Vriesendorp PA, Mahmoodi BK*, et al.* A Systematic Review and Meta-Analysis of Long-Term Outcomes After Septal Reduction Therapy in Patients With Hypertrophic Cardiomyopathy. JACC Heart Fail. 2015;3:896-905.
174. Gersh BJ, Maron BJ, Bonow RO*, et al.* 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e783-831.
175. Killu AM, Park JY, Sara JD*, et al.* Cardiac resynchronization therapy in patients with end-stage hypertrophic cardiomyopathy. Europace. 2018;20:82-88.
176. Thaman R, Gimeno JR, Murphy RT*, et al.* Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. Heart. 2005;91:920-925.
177. Torres MF, Perez-Villa F. Heart transplantation in patients with hypertrophic cardiomyopathy. Glob Cardiol Sci Pract. 2018;2018:32.
178. Maron MS, Kalsmith BM, Udelson JE*, et al.* Survival after cardiac transplantation in patients with hypertrophic cardiomyopathy. Circ Heart Fail. 2010;3:574-579.
179. Rowin EJ, Maron BJ, Abt P*, et al.* Impact of Advanced Therapies for Improving Survival to Heart Transplant in Patients with Hypertrophic Cardiomyopathy. Am J Cardiol. 2018;121:986-996.