Electro/Vectorcardiogram in Left Ventricular Hypertrophy/Enlargement (LVH)

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Left ventricular hypertrophy (LVH) is a condition in which there is an increase in left ventricular mass, either due to an increase in wall thickness or due to left ventricular cavity enlargement, or both. Most commonly, the left ventricular wall thickening occurs in response to pressure overload, and chamber dilatation occurs in response to the volume overload. (**Cuspidi C, Sala C, Negri F, Mancia G, Morganti A., Italian Society of Hypertension. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. J Hum Hypertens. 2012 Jun;26(6):343-9**.). LVH is a powerful, independent predictor of cardiovascular events and is considered a "silent killer"; however, it is modifiable and reversible. LVH is associated with an increased incidence of AF VT/VF, and SCD. Hypertension and hypertensive heart disease results in inflammation and fibrosis, which produces a substrate for inhomogeneity and an increase in the risk of arrhythmias. Myocardial fibrosis dissociates the excitable myocardial fibers and changes the biophysical properties of impulse propagation, which is known to increase the anisotropic conduction that predisposes to arrhythmias(**R. Cardinal, M. Vermeulen, M. Shenasa, et al., Anisotropic conduction and functional dissociation of ischemic tissue during reentrant ventricular tachycardia in canine myocardial infarction, Circulation 77 (5) (1988) 1162–1176**). Inflammation, fibrosis and remodeling that is produced by Hypertension are different from changes that result in diabetes mellitus,

ischemia, etc. Thus, each pathology should be investigated and managed separately. HTN begets LVH, LVH begets remodeling, arrhythmias, and SCD.

Cardiac hypertrophy is the abnormal enlargement, or thickening, of the heart muscle, resulting from increases in cardiomyocyte size and changes in other heart muscle components, such as extracellular matrix. Causes can be physiological – for example, the amount of exercise performed by an athlete – or pathological – for example, as a result of hypertension or valvular disease.

Importance of ECG for LVH

Electrocardiography (ECG) is the least expensive and most readily available test for the diagnosis of LVH. While its specificity is relatively high, its low sensitivity makes the clinical utility somewhat limited. Numerous criteria for LVH by ECG have been suggested over the years. Most criteria utilize the voltage or amplitude in one or more leads, R-wave peak time, prolonged QRS duration, secondary ST-T wave abnormalities, ”strain pattern” or left atrial enlargement(LAE). The best recognized established ECG criteria are the Cornell voltage, the Cornell product, the Sokolow-Lyon index, as well as the Estes-Romhilt point scoring system.

ECG is relatively insensitive in diagnosing LVH because it relies on the measurement of the electrical activity of the heart by electrodes placed on the surface of the skin to predict the left ventricular mass. The intracardiac electrical signal is problematic to measure in this way because the voltage measurements are impacted by all elements that lie between the heart muscle and the ECG electrodes, specifically fat, fluid, and air. Because of the variations in these elements, ECG underdiagnoses LVH in patients with pleural effusions, pericardial effusions, anasarca, obesity as well as chronic obstructive pulmonary disease (COPD). Also, LVH diagnosed by ECG is strongly impacted by both age and ethnicity. A malignant subphenotype of LVH has been described, in which minimal elevations in cardiac biomarkers identify individuals with LVH at high risk for developing heart failure (HF). Lewis et al tested the hypothesis that a higher prevalence of malignant LVH among blacks may contribute to racial disparities in HF risk. Participants (n=15 710) without prevalent cardiovascular disease were pooled from the ARIC Study (Atherosclerosis Risk in Communities), the DHS (Dallas Heart Study), and the MESA (Multi-Ethnic Study of Atherosclerosis). Participants were classified into 3 groups: those without ECG-LVH, those with ECG-LVH and normal biomarkers (hs-

cTnT (high sensitivity cardiac troponin-T) <6 ng/L and NT-proBNP (N-terminal pro-B-type natriuretic peptide) <100 pg/mL), and those with ECG-LVH and abnormal levels of either biomarker (malignant LVH). The outcome was incident HF. Over the 10-year follow-up period, HF occurred in 512 (3.3%) participants, with 5.2% in black men, 3.8% in white men, 3.2% in black women, and 2.2% in white women. The prevalence of malignant LVH was 3-fold higher among black men and women versus white men and women. Compared with participants without LVH, the adjusted hazard ratio for HF was 2.8 (95% CI, 2.1-3.5) in those with malignant LVH and 0.9 (95% CI, 0.6-1.5) in those with LVH and normal biomarkers, with similar findings in each race/sex subgroup. Mediation analyses indicated that 33% of excess hazard for HF among black men and 11% of the excess hazard among black women was explained by the higher prevalence of malignant LVH in blacks. Of black men who developed HF, 30.8% had malignant LVH at baseline, with a corresponding population attributable fraction of 0.21. The proportion of HF cases occurring among those with malignant LVH, and the corresponding population attributable fraction, were intermediate and similar among black women and white men and lowest among white women. A higher prevalence of malignant LVH may in part explain the higher risk of HF among blacks versus whites. Strategies to prevent development or attenuate risk associated with malignant LVH should be investigated as a strategy to lower HF risk and mitigate racial disparities.(**Alana A Lewis 1, Colby R Ayers 1, Elizabeth Selvin 2, Ian Neeland 1, Christie M Ballantyne 3, Vijay Nambi 3 4 5, Ambarish Pandey 1, Tiffany M Powell-Wiley 6, Mark H Drazner 1, Mercedes R Carnethon 7, Jarett D Berry 1, Stephen L Seliger 8, Christopher R DeFilippi 9, James A de Lemos 1Racial Differences in Malignant Left Ventricular Hypertrophy and Incidence of Heart Failure: A Multicohort StudyCirculation. 2020 Mar 24;141(12):957-967. doi: 10.1161/CIRCULATIONAHA.119.043628**.)

While electrocardiography is not sensitive and cannot be used to definitively exclude the diagnosis of LVH, it still plays a diagnostic and management role. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, LVH regression (diagnosed by ECG utilizing the Sokolow-Lyon index or the Cornell product criteria) in response to losartan improved clinical cardiovascular outcomes independent of blood pressure response.

Advantages of the ECG for Left Ventricular Hypertrophy diagnosis

- Low cost;
- Easy application in a great universe;
- High specificity (close to 99%);
- Simple diagnostic criteria;
- Possibility of identifying ischemia, necrosis, arrhythmias and associated dromotropic disorders;
- Independent from the experience of the observer and the quality of the equipment;
- Irreplaceable in apical hypertrophic cardiomyopathy when revealing the typical giant negative T waves from V2 to V5 accompanied by positive voltage criteria.
- Preparticipation screening is a life-saving and cost-effective strategy in young athletes in whom SCD is mostly caused by ECG-detectable heart muscle diseases (Anderson, Exeter et al. 2012, Corrado, Basso et al. 2012, Schwartz and Corrado 2012, Thorolfsson, Thordardottir et al. 2012). Addition of ECG to preparticipation screening saves 2.06 life-years per 1000 athletes at an incremental total cost of $89 per athlete and yields a cost-effectiveness ratio of $42 900 per life-year saved (95% CI, $21 200 to $71 300 per life-year saved) compared with Cardiovascular-focused history and physical examination alone (Wheeler, Heidenreich et al. 2010).

Drawbacks of ECG for LVE/LVH diagnosis

- Electrocardiography is too insensitive to be used alone to screen for LVH. Sensitivity: 20% to 60%. Only 3% of the general population and 5% of hypertensive patients show LVE in ECG. ECG criteria should not be used to rule out LVH in patients with hypertension (Pewsner, Juni et al. 2007).
- Low specificity to determine the enlargement modality; (**Goldberger AL, Goldberger ZD, Shvilkin A. Goldberger's Clinical Electrocardiography: A Simplified Approach, 9th ed, Elsevier/Saunders, Philadelphia 2017**.)
- Inverse ratio between sensitivity and specificity of ECG criteria for LVE: the greater the sensitivity, the smaller the specificity and vice-versa;
- Sensitivity and specificity are affected in concomitance of: RVE/RVH, myocardial infarction, bundle branch block by use of drugs.

Value of Echocardiogram for the diagnosis of LVH

An echocardiogram is the test of choice in establishing the diagnosis of LVH. Its sensitivity is significantly higher than ECG, and the test can also diagnose other abnormalities such as left ventricular dysfunction (both systolic as well as diastolic) and valvular heart disease. Cardiac ultrasound utilizes transthoracic or transesophageal positioning of the transducer to measure the left ventricular end-diastolic diameter, posterior wall thickness, and interventricular septum thickness. From these measurements and the patient's height and weight, the LV mass index can be determined. According to the American Society of Echocardiography and/European Association of Cardiovascular Imaging, LVH is defined as an increased left ventricular mass index (LVMI) to greater than 95 g/m in women and increased LVMI to greater than 115 g/m in men. Despite the advantages of echocardiography and Doppler analysis, an important consideration in using this tool as a screening test in all hypertensive patients is its significant cost when compared to ECG.

Echocardiography is the test of choice

Echocardiography, if available, should be the test of choice to assess for LVH. It is much more sensitive than ECG and can also detect other abnormalities such as LV dysfunction and valvular disease. This test uses transthoracic or transesophageal ultrasonography to measure the LV end-diastolic diameter, posterior wall thickness, and interventricular septum thickness. From these measurements and the patient's height and weight, the LV mass index can be calculated. (Devereux, Kramer-Fox et al. 1986)

Several different cutoff values for the LV mass index have been proposed; the LIFE study used values of >104 g/m2 in women and >116 g/m2 in men to define LVH.

When using echocardiography to assess for LVH, it is imperative that the LV mass index be used and not just the LV wall thickness, as it often happens in clinical practice. This is necessary because diagnosis by wall thickness alone is not a good indicator of LVH, with a concordance between wall thickness and a LV mass index of only 60% (Leibowitz, Planer et al. 2007). In addition, wall thickness tends to underestimate LVH in women and overestimate it in men.

Is echocardiography cost-effective?

Despite its clear advantages, an important consideration about echocardiography as a screening test for all hypertensive patients is its cost.

A suggested way to reduce cost is to measure the left ventricular mass index only. A limited echocardiographic examination is much less expensive than a complete two-dimensional echocardiogram ($255 vs $431 per the 2009 Medicare Ambulatory Payment Classification) and should be the examination performed if the patient has no other clinical indication for echocardiography.

Another way to control cost is to stratify patients by risk and to do echocardiography only in those who would benefit most from it. Based on the prevalence of LVH, one study concluded that echocardiography is most cost-effective in men 50 years or older (Cuspidi, Meani et al. 2006) (Cuspidi, Meani et al. 2006).

Further study is necessary to define more precisely the cost-effectiveness of echocardiographic screening for LVH in terms of potentially preventable cardiovascular morbidity and death. Echocardiogram performed in a 68-year-old man being evaluated for uncontrolled hypertension and symptoms of congestive heart failure. LVH was diagnosed by an elevated left ventricular mass index, which is calculated from the interventricular septal thickness (IVSd), posterior wall thickness (PWTd), and left ventricular end-diastolic internal diameter (LVIDd).

Cardiac Magnetic Resonance Imaging (MRI)

In terms of specific testing for LVH, cardiac magnetic resonance imaging (MRI) is now considered the gold standard as it is even more precise and reproducible than cardiac ultrasound. It can accurately estimate LV mass and determines if other structural cardiac abnormalities are present. The widespread use of MRI is severely restricted in clinical practice due to its cost, logistics, and limited availability. While it may never be useful in screening for LVH, it has a significant role in clinical research and in the assessment

of cardiovascular anatomy in certain clinical situations.(**Ruilope LM, Schmieder RE. Left ventricular hypertrophy and clinical outcomes in hypertensive patients. Am. J. Hypertens. 2008 May;21(5):500-8**.)

The main method to diagnose LVH is echocardiography, which allows measuring the thickness of the muscle of the heart. Two dimensional echocardiography can produce images of the left ventricle. The thickness of the LV as visualized in echocardiography correlates with its actual mass. Normal thickness of the LV myocardium is from 6 to 11 mm (as measured at the very end of diastole). If the myocardium is more than 1.1 cm thick, the diagnosis of LVH can be made by echocardiography.

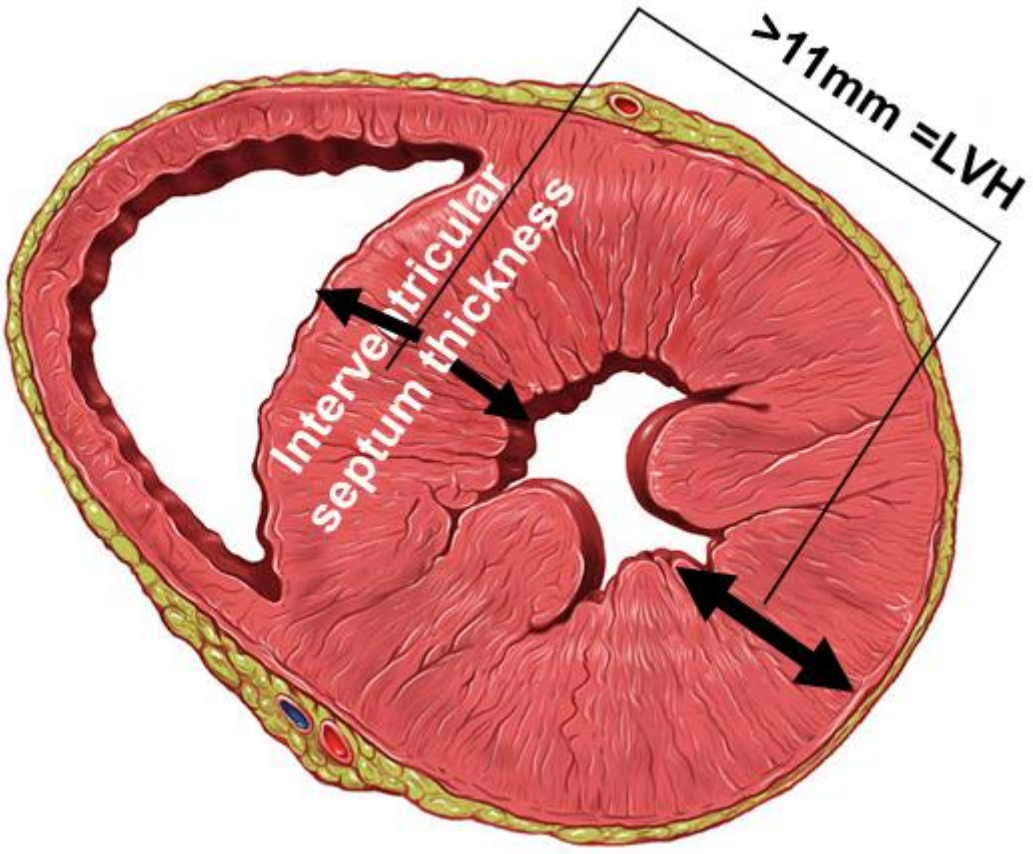


Figure 3. Left Ventricular Enlargement/Hypertrophy.

Cardiac MRI: The costly gold standard

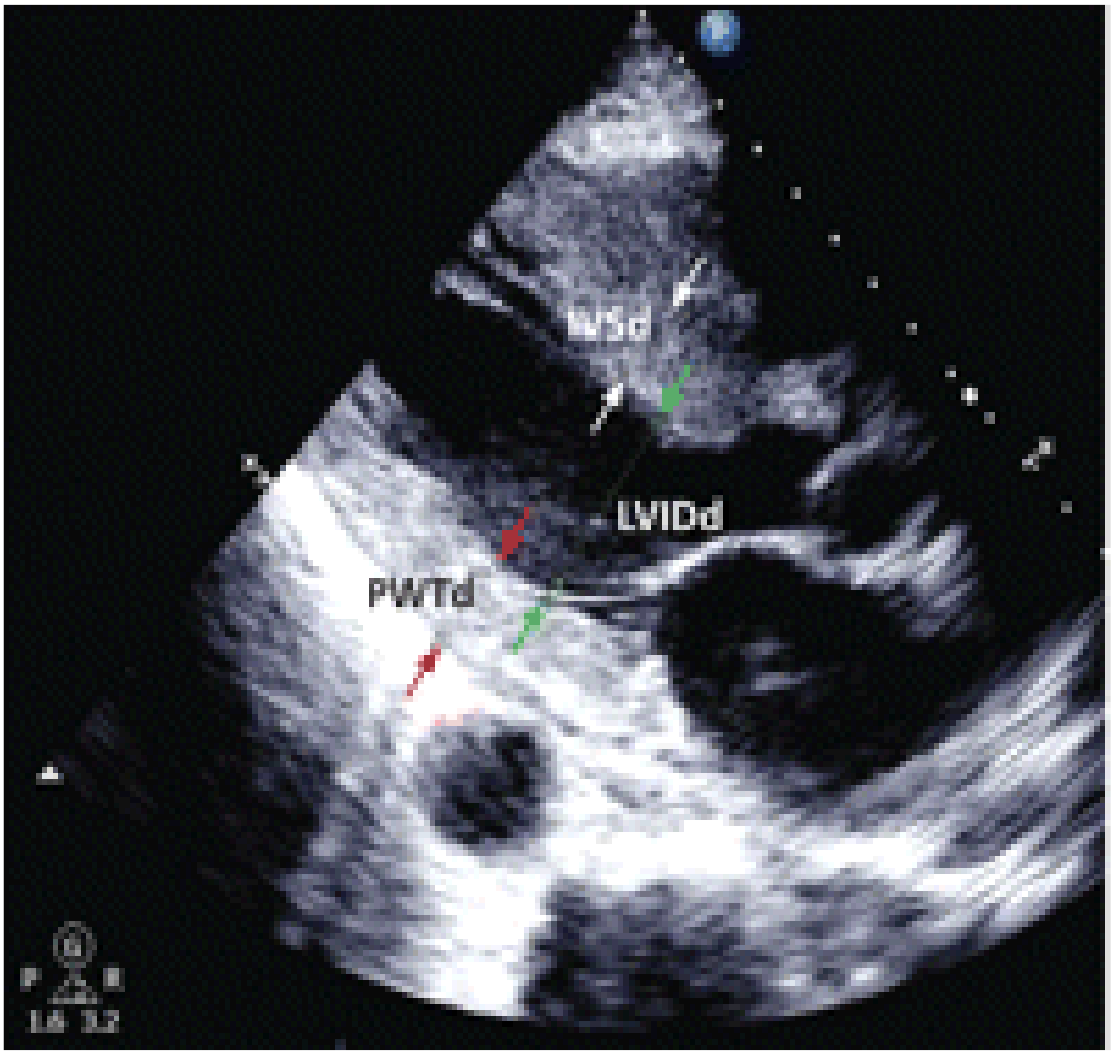


Figure 4. Cardiac MRI is the gold standard test for LVH, as it is even more accurate and reproducible than echocardiography (Bottini, Carr et al. 1995). It can precisely estimate a patient's left ventricular mass and assess for other structural cardiac abnormalities. MRI's use, however, is severely restricted in clinical practice due to its high cost and limited availability. While it may never be used for general screening for LVH, it certainly has a role in clinical research and for assessing cardiac anatomy in special clinical situations.

Although the varying phenotypic spectra of hypertensive heart disease (HHD) can be assessed by ECG, echocardiography and cardiovascular magnetic resonance (CMR), ECG criteria for LVH are insensitive, while echocardiography and CMR are expensive, less readily available and often lack requisite expertise. Consequently, the use of circulating biomarkers in the diagnosis and prognostication of HHD beyond the traditional N-terminal pro- b-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) have become an attractive alternative. Dike Ojji et al. carried out a PubMed and Google Scholar databases' search of original articles on circulating biomarkers used in the diagnosis of the different spectrum of HHD over the last 10

years [2005-2015] in humans. Fourteen studies met the inclusion criteria with NT-pro BNP being the most studied circulating biomarker in HHD followed by soluble ST2 (sST2). There is a lack of data on the use of circulating biomarkers in HHD. There is a need to explore further this area of investigative cardiology.(**Dike Ojji 1, Elena Libhaber 2, Kim Lamont 2, Friedrich Thienemann 3 4 5, Karen Sliwa 2 3Circulating biomarkers in the early detection of hypertensive heart disease: usefulness in the developing worldCardiovasc Diagn Ther. 2020 Apr;10(2):296-304. doi: 10.21037/cdt.2019.09.10**.)

Etiology of LVH

There are various clinical conditions that can lead to the development of LVH. The most common of these include the following:

1. Essential hypertension high blood pressure (hypertension).
2. Renal artery stenosis
3. Athletic heart with physiological LVH
4. Aortic valvar stenosis
5. Coarctation of the aorta
6. Hypertrophic cardiomyopathy without or with outflow tract obstruction (HOCM)
7. Subaortic stenosis (left ventricular outflow tract obstruction by muscle or membrane)
8. Aortic regurgitation
9. Mitral regurgitation
10. Dilated cardiomyopathy
11. Ventricular septal defect.
12. Infiltrative cardiac processes (e.g., Amyloidosis, Fabry disease, Danon disease)

Hypertension and aortic valve stenosis are the most common causes of LVH. In both of these conditions, the heart is contracting against an elevated afterload. Another cause is increased filling of the left ventricle inducing diastolic overload, which is the underlying mechanism for eccentric LVH in patients with regurgitant valvular lesions such as aortic regurgitation or mitral regurgitation and also seen in dilated cardiomyopathy. Coronary artery disease has been demonstrated to play a role in the pathogenesis of LVH, as the normal myocardium tries to compensate for tissue that has become ischemic or infarcted. Athletic heart with physiological LVH is a relatively benign condition. Intensive training results in increased left ventricular muscle mass, wall thickness, and chamber size, but the systolic function and diastolic function remain normal.

Causes of LVH according to the age group

- **Infants:**
    - Fibroelastosis;
    - Tricuspid atresia;
    - Single left ventricle;
    - Pulmonary Atresia without Ventricular Septal Defects;
    - Patent D*uctus Arteriosus* in premature babies;
    - Children of diabetic mothers;
    - Severe Aortic Stenosis (Ao.S.);
    - Pompe's disease.

- **Children:**
    - Ventricular Septal Defect (VSD);
    - Patent Ductus Arteriosus (PDA);
    - Endocardial Cushion Defects (ECD);
    - Aortic Stenosis (Ao.S.);
    - Coarctation of the Aorta (Co.A);
    - Systemic Hypertension (SHT).

- **Young people:**

- Athletes;
- Mitro-aortic injuries.
- Co.A;
- Systemic hypertension (SHT).

- **Adults:**
  - SHT;
  - Ao.S.;
  - Mitro-aortic injuries;
  - Myocardial sclerosis.
  -
- **Elderly people:**
  - Systemic hypertension (SHT). Secondary;
  - Myocardial sclerosis;
  - SHT;
  - Bicuspid Ao.S.

Left Ventricular Hypertrophy classification according to hemodynamic modality and substrate

- Systolic, of pressure or concentric left ventricular hypertrophy: It results from the heart pumping against an elevated afterload, as
  - Systemic hypertension (SHT)/Hypertensive heart disease (HHD)
  - Aortic stenosis (AOS): valvular, subvalvular and supravalvular.
  - Coarctation of the aorta (CoA).
- Diastolic, volume/volumetric or eccentric left ventricular hypertrophy/overload
  - Aortic Regurgitation / Insufficiency (AoI).
  - Mitral Valve Regurgitation (MVI).
  - Dilated Cardimyopathy
  - Patent Ductus Arteriosus (PDA)
  - Ventricular Septal Defect (VSD), hemodynamic group II.
  - Anemia.

The major conditions associated with LV volume overload are aortic or mitral valve regurgitation and dilated cardiomyopathy.

- Primary or hypertrophic cardiomyopathy by myocardial diseases that dilate the heart:
    - Ischemic heart disease.
    - Cardiomyopathies
    - Myocarditis.
    - Congestive heart failure.

Epidemiology

Left ventricular hypertrophy (LVH) is present in 15% to 20% of the general population. It is more often prevalent in blacks, the elderly, the obese, and in patients with hypertension. A review of echocardiographic data of 37700 individuals revealed 19%-48% prevalence of LVH in untreated hypertensives and 58%-77% in high-risk hypertensive patients. The presence of obesity also causes 2 -fold increased risk of developing LVH. The prevalence of LVH ranges from 36% (conservative criteria) to 41% (lesser conservative criteria) in the population, depending on the criteria used for defining it. LVH prevalence is not reported to be different between men and women (range 36.0% versus 37.9% (conservative criteria) and 43.5% versus 46.2% (lesser conservative criteria).The prevalence of eccentric LVH is relatively more compared to concentric hypertrophy.

Pathophysiology

Left ventricular hypertrophy (LVH) and remodeling early on, are very important compensatory processes that develop over time in response to wall stress or any significant hemodynamic pressure or volumetric burden. The increased mass of muscle fibers or wall thickness serves initially as a compensatory mechanism that helps to maintain contractile forces and counteracts the increased ventricular wall stress. The benefits of increased wall thickness to compensate for elevated wall stress are offset by a significant increase in the degree of stiffness of the hypertrophied walls associated with a significant increase in diastolic ventricular pressures, which are subsequently transmitted back into the left atrium as well as the pulmonary vasculature.

As previously indicated, LVH is a compensatory but ultimately, an abnormal increase in the mass of the myocardium of the left ventricle induced by a chronically elevated workload on the heart muscle. But, pathologic LVH once developed, puts the patient at significant risk for the development of heart failure, dysrhythmias, and sudden death. The most common etiologic cause is the heart contracting against an elevated afterload, as seen in hypertension and also seen in valvar aortic stenosis. Another cause is increased filling of the left ventricle inducing diastolic overload, which is the underlying mechanism for eccentric LVH in patients with regurgitant valvular lesions such as aortic regurgitation or mitral regurgitation and also seen in dilated cardiomyopathy. Coronary artery disease has been demonstrated to play a role in the pathogenesis of LVH, as the normal myocardium tries to compensate for tissue that has become ischemic or infarcted. One key pathophysiologic component in LVH is the concomitant development of myocardial fibrosis. Initially, fibrosis is clinically manifested by diastolic dysfunction, but systolic dysfunction will also develop with progressive disease. **Marketou ME, Parthenakis F, Vardas PE. Pathological Left Ventricular Hypertrophy and Stem Cells: Current Evidence and New Perspectives. Stem Cells Int. 2016;2016:5720758**.)

Based on relative wall thickness (posterior wall thickness x 2 / LV internal diameter at end-diastole), and the left ventricular mass (LVM) index (left ventricular mass normalized for body surface area or height), the left ventricular hypertrophy can be categorized into 2 types; concentric hypertrophy (increased LWM index and relative wall thickness (RWT) more than 0.42) or eccentric hypertrophy (increased LWM index and RWT less than or equal to 0.42).

Concentric left ventricular hypertrophy is an abnormal increase in left ventricular myocardial mass caused by chronically increased workload on the heart, most commonly resulting from pressure overload-induced by arteriolar vasoconstriction as occurs in, chronic hypertension or aortic stenosis.

Eccentric left ventricular hypertrophy is induced by an increased filling pressure of the left ventricle, otherwise known as diastolic overload, which represents the underlying mechanism for volumetric or diastolic overload in patients with regurgitant valve lesions such as aortic or mitral regurgitation as well as in the case of dilated cardiomyopathy. In patients with coronary artery disease, these mechanisms can play a

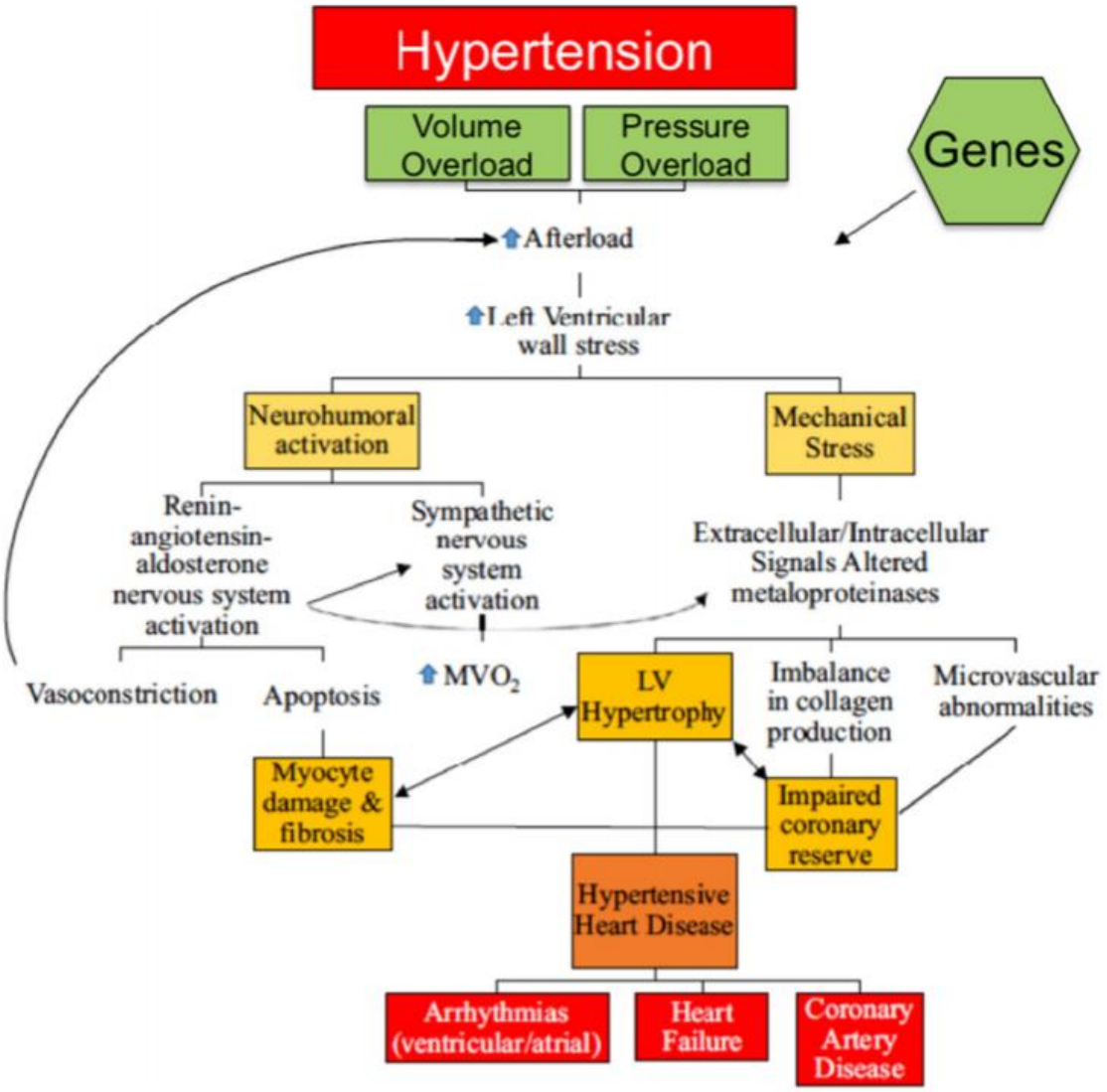
role in an attempt to compensate for ischemic or infarcted myocardial tissue. This type of sustained increase in wall stress along with cytokine and neuro-activation stimulates the development of myocardial hypertrophy or increasing muscle thickness with the deposition of the extracellular matrix. This increased mass of muscle fibers or wall thickness serves initially as a compensatory mechanism that helps to maintain contractile forces and counteracts the increased ventricular wall stress. The benefits of increased wall thickness to compensate for elevated wall stress are offset by a significant increase in the degree of stiffness of the hypertrophied walls associated with a significant increase in diastolic ventricular pressures, which are subsequently transmitted back into the left atrium as well as the pulmonary vasculature.

One key pathophysiologic component in LVH is the concomitant development of myocardial fibrosis. Initially, fibrosis is clinically manifested by diastolic dysfunction, but systolic dysfunction will also develop with progressive disease.

Myocardial fibrosis appears to be pathophysiologically linked to the renin-angiotensin-aldosterone system (RAAS). Evidence has been established that angiotensin II produces a profibrotic effect in the myocardial tissue of hypertensive patients. This explains why angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are among the most potent agents in the treatment of hypertension, especially from the standpoint of morbidity and mortality. LVH has been shown to be a consistent predictor of cardiovascular morbidity as well as mortality in hypertensive patients.(**Jia G, Aroor AR, Hill MA, Sowers JR. Role of Renin-Angiotensin-Aldosterone System Activation in Promoting Cardiovascular Fibrosis and Stiffness. Hypertension. 2018 Sep;72(3):537-548**.) Certain antihypertensive therapies that induce regression of LVH decrease rates of major adverse cardiovascular events and enhance survival, regardless of the degree of blood pressure reduction. The clinical importance is two-fold: 1) recognizing that LVH can be a modifiable risk factor and 2) that management choices are significantly more complex than just controlling the blood pressure**.(Sciarretta S, Paneni F, Palano F, Chin D, Tocci G, Rubattu S, Volpe M. Role of the renin-angiotensin-aldosterone system and inflammatory processes in the development and progression of diastolic dysfunction. Clin. Sci. 2009 Mar;116(6):467-77**.)

Genomics may also play a significant role in the pathogenesis of LVH. Mutated genes that encode proteins of the sarcomere have a direct etiologic relationship in patients who

present with hypertrophic cardiomyopathy. Also, there seems to be a genetic predisposition evidenced by the fact that some mildly hypertensive patients develop LVH while others do not.(**Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. Circ. Res. 2017 Sep 15;121(7):749-770**.) Increased availability of genetic testing for HCM has led to the emergence of a novel patient subset, consisting of asymptomatic genetically affected family members with normal cardiac function without LVH.(**Maron BJ, Semsarian C. Emergence of gene mutation carriers and the expanding disease spectrum of hypertrophic cardiomyopathy.**Eur Heart J**. 2010; 31:1551–1553. doi: 10.1093/eurheartj/ehq111**). In a multicenter cohort, G+LVH– individuals demonstrated a benign clinical course with virtually no demonstrable risk for disease-related morbidity/mortality, including almost 20% who have already achieved relatively advanced age. This observation and uncommon conversion to the HCM phenotype suggest that many gene carriers can anticipate normal longevity. These genotype-positive (+)–LVH-negative (–) (G+LVH–) individuals raise unresolved clinical issues concerning conversion to HCM phenotypes and risk for cardiovascular complications. **(Christiaans I, Birnie E, Bonsel GJ, Mannens MM, Michels M, Majoor-Krakauer D, Dooijes D, van Tintelen JP, van den Berg MP, Volders PG, Arens YH, van den Wijngaard A, Atsma DE, Helderman-van den Enden AT, Houweling AC, de Boer K, van der Smagt JJ, Hauer RN, Marcelis CL, Timmermans J, van Langen IM, Wilde AA. Manifest disease, risk factors for sudden cardiac death, and cardiac events in a large nationwide cohort of predictively tested hypertrophic cardiomyopathy mutation carriers: determining the best cardiological screening strategy.**Eur Heart J**. 2011; 32:1161–1170. doi: 10.1093/eurheartj/ehr092)(Gray B, Ingles J, Semsarian C. Natural history of genotype positive-phenotype negative patients with hypertrophic cardiomyopathy.**Int J Cardiol**. 2011; 152:258–259. doi: 10.1016/j.ijcard.2011.07.095**)



Pathophysiological pathways of hypertensive heart disease and LVH that lead to arrhythmias, heart failure, and coronary artery disease. Abbreviations: LV-left ventricle; MV02- mixed venous oxygen saturation. With permission from Shenasa M, et al. Card Electrophysiol Clin 2015;7:207–220 **[14].(M. Shenasa, H. Shenasa, N. El-Sherif, Left ventricular hypertrophy and arrhythmogenesis, Card. Electrophysiol. Clin. 7 (2) (2015) 207–220.)**

Histopathology

A heart undergoing hypertrophy usually exhibits changes in architecture as well as histology depending on the cause and stage of hypertrophy. Various histologic changes have been demonstrated and include volume fraction of fibrous tissue, degree of myocyte diameter, as well as ultrastructural changes in mitochondria. It has also been

postulated that the cardiac renin-angiotensin system, as well as angiotensin-converting enzyme function, may be important factors in the hypertrophic response. The fact that myocardial hypertrophy may develop independently of hypertension suggests that angiotensin II may play a role as it induces myocardial fibrosis as well. Recent studies where regression analysis was performed showed that plasma angiotensin II, ACE, and renin levels correlated with left ventricular mass independent of blood pressure. (**Jia G, Aroor AR, Hill MA, Sowers JR. Role of Renin-Angiotensin-Aldosterone System Activation in Promoting Cardiovascular Fibrosis and Stiffness. Hypertension. 2018 Sep;72(3):537-548.**) Regression analysis also showed that the most important element was angiotensin II levels, which appears closely related in part to stimulation of myocardial fibrosis.

Other factors that have been implicated in the development of myocardial hypertrophy include endothelin, heterotrimeric G proteins, as well as the role of cardiac sodium-potassium pumps. There may also be a pro-LVH genotype that has been demonstrated. Finally, other factors that may have a role in the degree of LVH include concomitant coronary disease or valvular heart disease as well as inflammatory cytokines calcium/calmodulin-dependent protein kinase II signal transducer and activator of transcription-3.(**Maillet M, van Berlo JH, Molkentin JD. Molecular basis of physiological heart growth: fundamental concepts and new players. Nat. Rev. Mol. Cell Biol. 2013 Jan;14(1):38-48.**)

Toxicokinnetics

When the heart is exposed to long periods of increased workload, it undergoes hypertrophic enlargement secondary to the increased demand. Various cardiovascular pathologies such as myocardial infarction, stimulant drug abuse, or obesity have been shown to induce cardiac cell hypertrophy, which may lead to heart failure. Various signaling modulators in the cardiovascular system have been demonstrated to regulate cardiac mass, including an influence on gene expression, apoptosis, cytokines, as well as stimulation of growth factor. Recent studies suggest that pathological hypertrophy can be reversed or prevented altogether. Other molecular mechanisms potentially causing cardiac hypertrophy include the aberrant re-expression of a fetal gene program. A variety of molecular pathways that potentially induce a coordinated control of the

program that induces hypertrophy include the following: natriuretic peptides, adrenergic nervous system, adhesion, and cytoskeletal proteins, IL-6 cytokines, MEK-ERK1/2 signaling, histone acetylation, calcium-mediated modulation and the role of microRNAs in controlling the cardiac hypertrophic response. At a cellular level, cardiomyocyte hypertrophy is characterized by an increase of cell size, up-regulation of protein synthesis, and intensified organization of the sarcomere. Mechanical stress induces a hypertrophic response downstream of mechanosensitive molecular structures. The sarcomeric Z-disc and its proteins seem to drive mechanical stress-induced signal transduction or mechanotransduction. An example of mechanosensitive molecules includes a family of Z-disc-specific proteins, calsarcins, or myozenins. Calsarcins have been demonstrated to attach the cardiac skeletal apparatus to signaling molecules that directly impact gene expression by binding to the Z-disc myofilament anchor proteins, a-actinin, and telethonin, and then attaching them to calcineurin, a calcium-dependent phosphatase demonstrated to induce cardiomyocyte hypertrophy by transcriptional pathways downstream.(**Samak M, Fatullayev J, Sabashnikov A, Zeriouh M, Schmack B, Farag M, Popov AF, Dohmen PM, Choi YH, Wahlers T, Weymann A. Cardiac Hypertrophy: An Introduction to Molecular and Cellular Basis. Med Sci Monit Basic Res. 2016 Jul 23;22:75-9.)**

History and Physical

Patients may have had long-standing hypertension without even knowing it. After hypertension is confirmed on at least three different occasions based on the average of two or more readings taken at each of the subsequent visits, clinicians should assess the patient for evidence of end-organ damage involving the heart, brain, eyes, and kidneys. Most cases of hypertension are essential hypertension. However, secondary causes, such as renal artery stenosis, coarctation of the aorta, and/or metabolic disorder such as pheochromocytoma or hyperaldosteronism, hyperparathyroidism, hypothyroidism, as well as hyperthyroidism must be excluded. Sleep apnea syndrome has been linked to both pulmonary hypertension as well as systemic hypertension. Also, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines, the patient should be assessed for cardiovascular risk factors other than hypertension, including metabolic

syndrome, tobacco use, increased LDL-cholesterol, diabetes mellitus, obesity, family history of premature cardiovascular death, lack of exercise, and microalbuminuria. Social history should include the patient's use of over-the-counter medications since herbal medications such as licorice or ephedrine could cause left ventricular hypertrophy. The patient should also be asked about the use of oral contraceptives, excess alcohol intake, as well as the use of cardiac stimulants such as cocaine or amphetamines.

A funduscopic exam in long-standing hypertension reveals hypertensive retinopathy. These signs usually develop later in the course of the disease. The exam will often show arteriovenous nicking, arteriolar constriction, cotton, wool spots, flame-shaped hemorrhages, yellow hard exudates, as well as edema of the optic disc. Signs and symptoms of hypertensive heart disease depend most commonly on the severity and duration as well as type of hypertrophy. Once left ventricular hypertrophy is established, the patient commonly manifests an S4 gallop, which reflects diastolic dysfunction or diminished left ventricular compliance, which can lead to initially diastolic heart failure and, ultimately, systolic heart failure. Another manifestation of left ventricular hypertrophy includes a sustained apical impulse shifted to the left or towards the axilla, reflecting hypertrophied heart muscle. Patients who have hypertensive heart disease secondary to coarctation of the aorta will manifest a systolic ejection murmur, radiating to the back as well as diminished or virtually absent lower extremity peripheral pulses. (**Agabiti-Rosei E, Muiesan ML, Salvetti M. Evaluation of subclinical target organ damage for risk assessment and treatment in the hypertensive patients: left ventricular hypertrophy. J. Am. Soc. Nephrol. 2006 Apr;17(4 Suppl 2): S104-8**.)

Hemodynamic valvular lesions can lead to hypertrophy with signs of concentric or eccentric remodeling of the left ventricle. Although initially compensatory, a thicker myocardial wall that reduces left ventricular radial and circumferential wall stress will benefit the systolic function of the left ventricle. With aortic stenosis, there would be a harsh systolic ejection murmur peeking in mid-to-late systole radiating from the aortic area into the carotid arteries associated with pulsus parvus et tardus. Patients with aortic insufficiency, especially if long-standing, will manifest a diastolic blowing murmur, heard over the aortic area radiating down the left lower sternal border. Other clinical signs of severe chronic aortic insufficiency are often the result of an increased or

widened pulse pressure because the incompetent aortic valve allows a more significant fall in the diastolic pressure when compared to normal. Bounding or pistol-shot pulses may also be present. Because of the volumetric alterations of the left ventricle resulting hypertrophy is eccentric. This type of eccentric hypertrophy is also seen in patients with chronic mitral regurgitation.

Old Systolic and Diastolic Overload concept of Left Ventricular Hypertrophy

Since Cabrera and Monroy (Cabrera and Monroy 1952) we use the term LVE/LVH when the left ventricle (LV) receives in diastole, a volume of blood greater than normal –diastolic, eccentric or volumetric overload of the LV– or when it has a greater difficulty during systole to empty its content –pressure, systolic or strain pattern overload of the LV– or both at the same time. This term is the one used in electro-vectorcardiography.

	LV Systolic Overload	**LV Diastolic Overload**
Main causes	Systemic Hypertension Aortic Stenosis Coarctation of Aorta	Aortic valve insufficiency Mitral valve insufficiency Ventricular septal deffect Patent ductus arteriosus
Initial r wave in V1 lead	Absent or minimal	Greater R wave
Q waves in left leads	Absent	Present
Intrinsicoid deflection, R peak time or ventricular activation time in V5-V6	Shorter	Longer
QRS -ST/T relationship	Discordant significant ST-segment and T-wave depression in the anterolateral leads	Concordant

Systolic and diastolic overload ECG/VCG patterns/modalities of Left Ventricular Hypertrophy

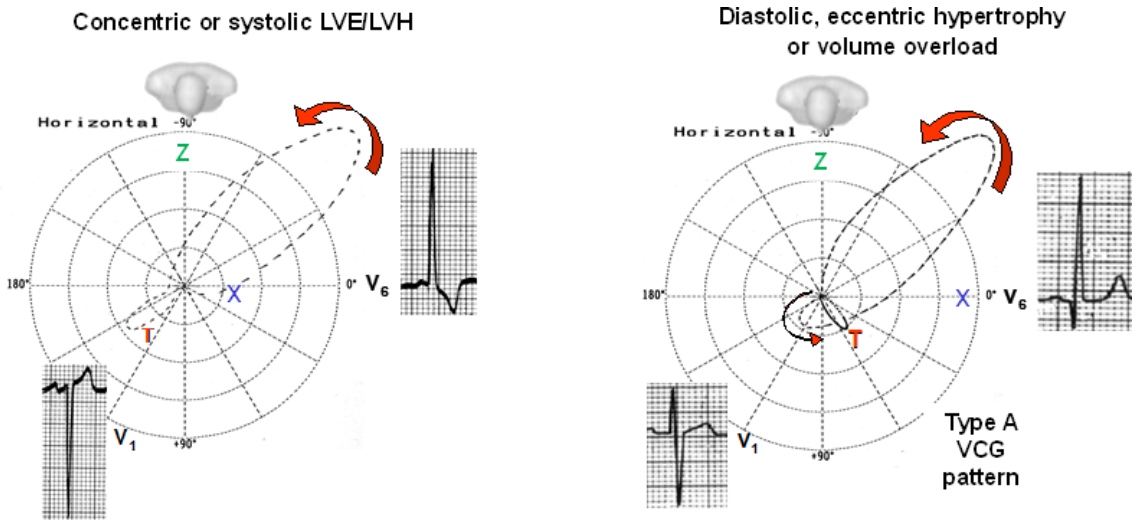


Figure 1. As electrocardiographic correlate for concentric LVH as compared with eccentric LVH, a shorter intrinsicoid deflection and a significant ST-segment and T-wave depression in the anterolateral leads was noted. In patients with advanced acquired heart disease, severe dilatation and left ventricular hypertrophy, the hemodynamic and ECG correlation is low. In congenital heart disease it is better.

Systolic or concentric LVH – ECG/VCG correlation in the Horizontal Plane

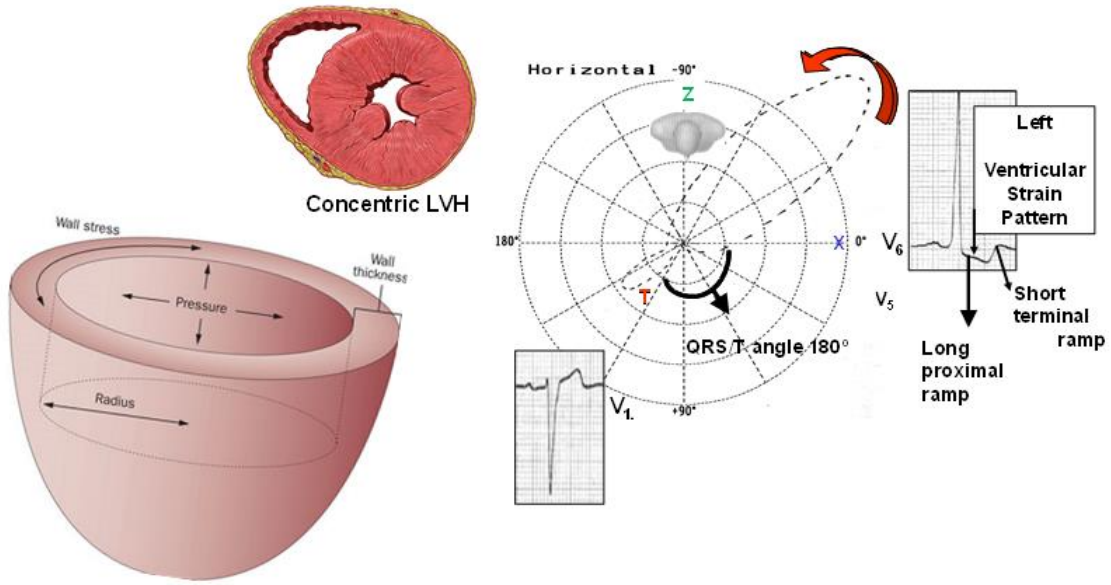


Figure 2. Repolarization abnormalities: Deviation of the ST segment and the T wave in the opposite direction to the main QRS vector causes widening QRS amplitude and wide QRS/T angle.

Left Ventricular Enlargement/Hypertrophy

Any increase in LV mass above the values 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. This term is used in echocardiography. (Echocardiography-based left ventricular mass estimation).

Representation of normal ventricular activation with four vectors in the FP and HP

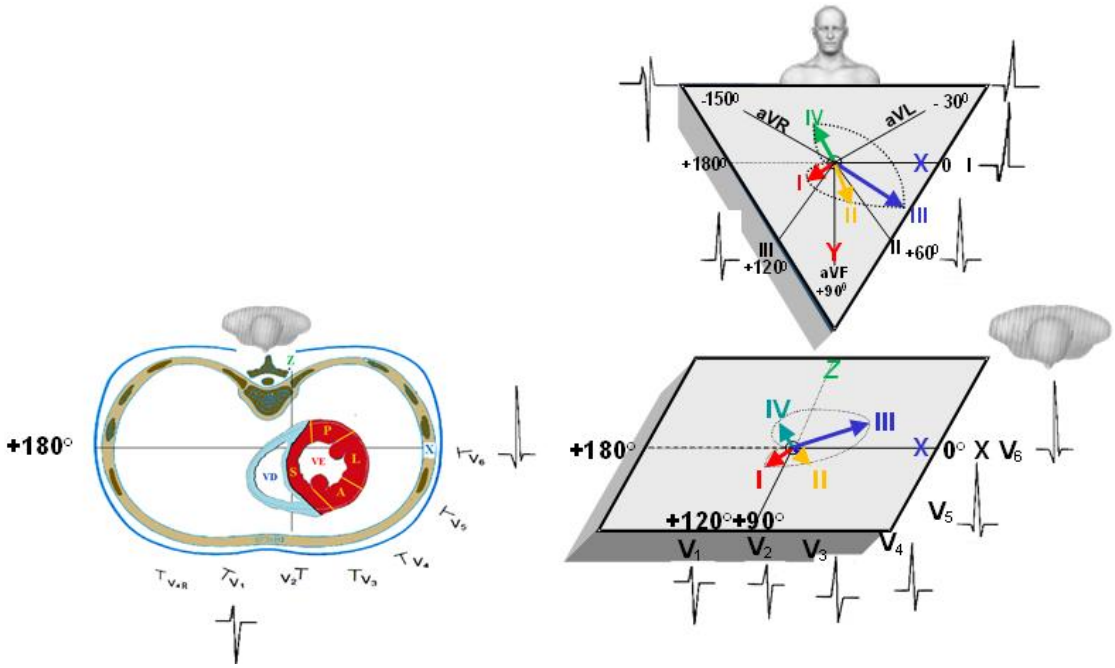


Figure 5. The four vectors of ventricular depolarization in the frontal and horizontal planes and ECG/VCG correlation.

Vectors of ventricular activation in Left Ventricular Hypertrophy

- **Vector I, I_{AM}, (anteromedial) septal or of the middle 1/3 of interventricular septum:**
  - **Normal:** of small magnitude (initial 10 to 20 ms). To the front and the right (85% of cases), above or below, according to the position of the heart (horizontal or vertical).
  - **Systolic LVH pattern:** Vector I, I_{AM}, decreases or even disappears.
  - **Diastolic LVH pattern:** Vector I, I_{AM}, increases. Consequently, it causes increase in the initial R wave voltage of V_1 and V_2 (however the R/S ratio always remains in $V_1<1$) and concomitantly, deep Q waves (≥2 mm) in V_5 and V_6. These Q waves are clean and do not last longer than 35 ms.

Modification in the direction of the I_{AM} vector or septal vector in LVH: in the middle third of interventricular septum (IVS). Frontal view.

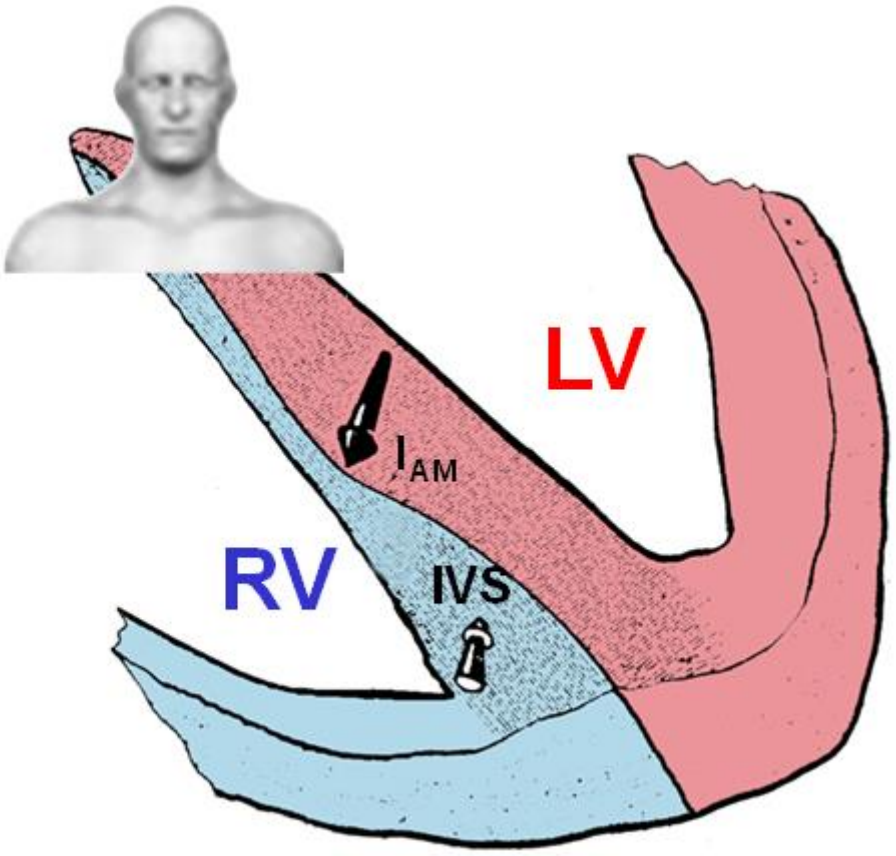


Figure 6. This is a vector of small magnitude, which represents the initial 10 to 20 ms of depolarization. It heads to the front and the right (85%) or the left (15%), above or below according to the position of the heart (horizontal or vertical).

Characteristics of normal I_{AM} vector in the Horizontal Plane

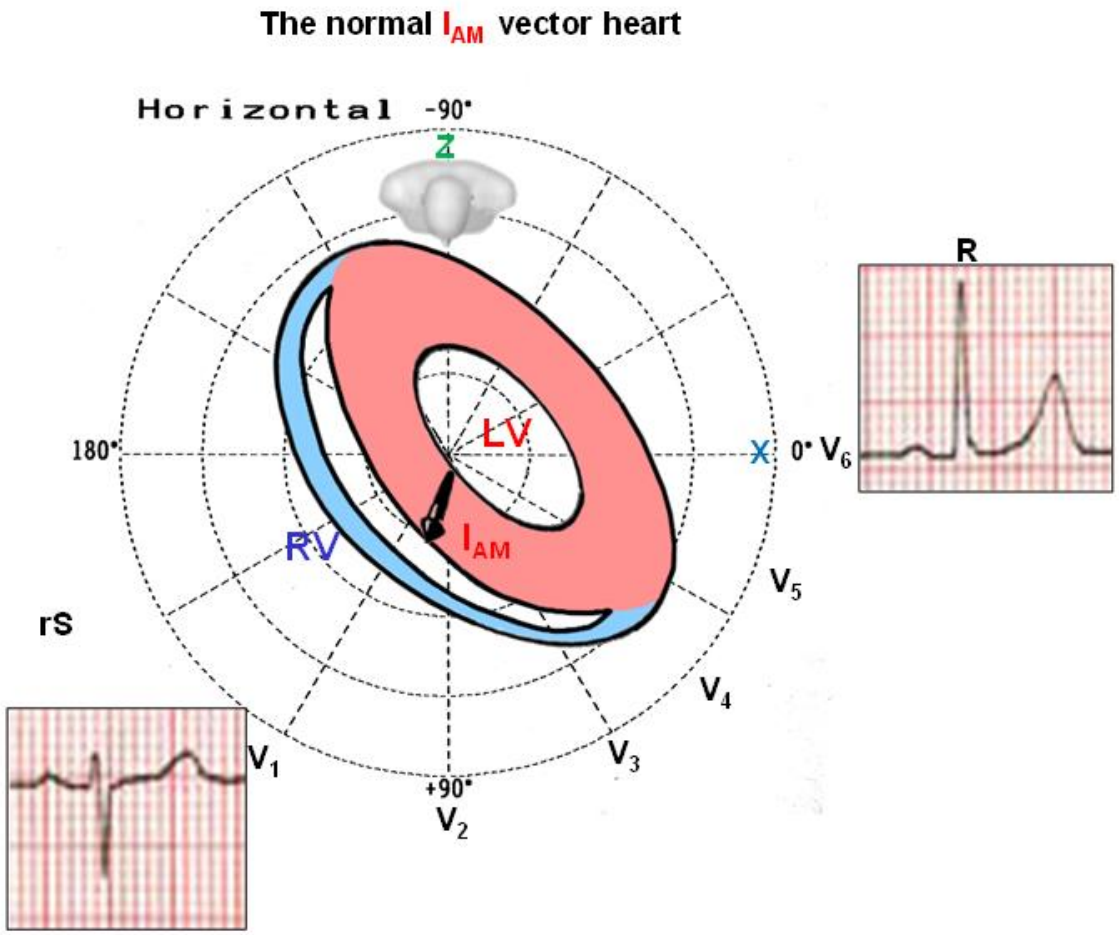


Figure 7. First normal I_{AM} vector in the Horizontal Plane is directed to the front and rightward in 85% of cases and to the front and leftward in 15%.

Characteristics of I_{AM} vector in diastolic, volumetric or eccentric LVH/ Overload

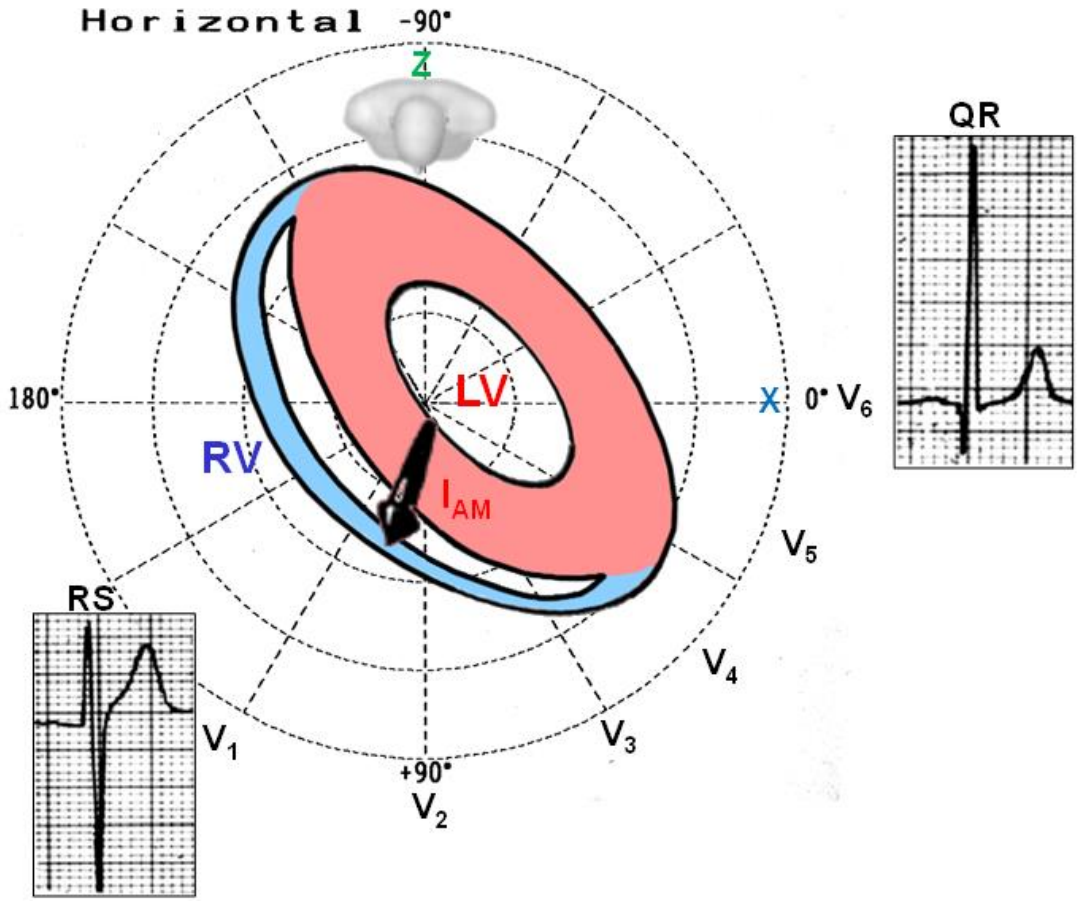


Figure 8. Characteristic of the first I_{AM} vector in diastolic, volumetric or eccentric Left Ventricular Hypertrophy/Overload. Vector I, IAM, increases. Consequently, it causes increase in initial R wave voltage of V1 and V2 (however the R/S ratio always remains in V1<1) and concomitantly, deep Q waves (≥2 mm) in V5 and V6. These Q waves are clean and do not last longer than 35 ms.

Vector II or of low interventricular septum (IVS)

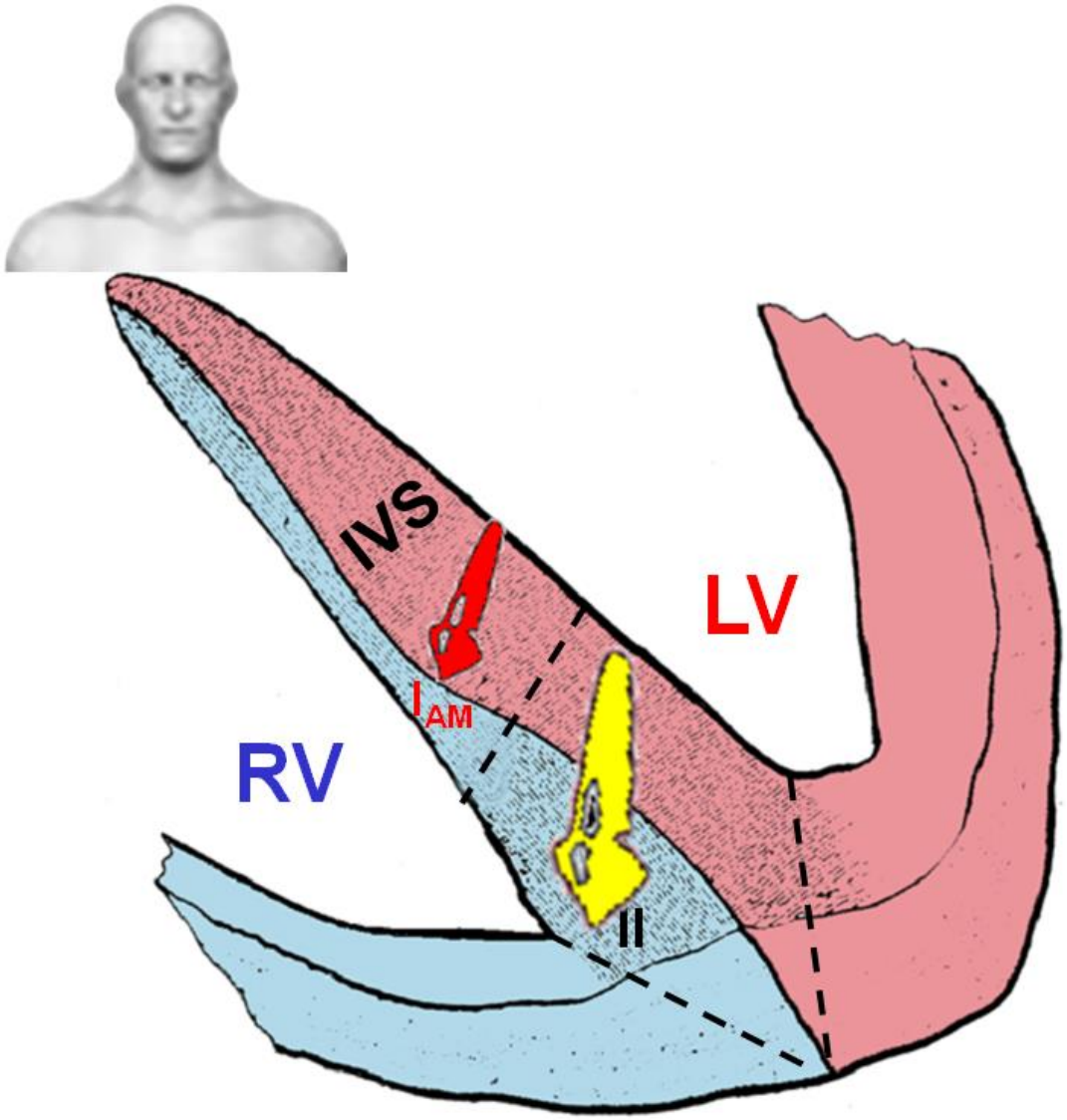


Figure 9. Vector II of low interventricular septum (when explained with four vectors) from 20 to 40 ms. It represents the activation of low paraseptal regions of the interventricular septum (IVS) until the apex (II). It stretches from 20 ms to 40 ms and it heads to the front. Hypertrophy of these areas manifests in the opposite leads: V2-V4 or V3 to V4 (transitional leads); thus, in the case of selective enlargement of these regions, we record in these leads, complexes of great voltage of the R/S type. This pattern is typically found in VSD as an element of biventricular enlargement and known as Katz-Wacthel sign/phenomenon.

Ventricular activation vectors in LVH: Vector III or of the free wall

- **Vector III or of the free wall:**
    - Normal: activation of free walls of both ventricles (from 40 to 60 ms). It is directed toward the predominant ventricle (LV), i.e. backward, to the left and below. Instantaneous maximal QRS vector of loop is normally <2.2 mV.
    - LVH: The R waves show increased voltage in the leads that face the Left Ventricle: I, aVL, V_5 and V_6 and concomitantly, deep S waves in the opposite leads from which vector III moves away: V_1 and V_2. Instantaneous maximal vector > 2.2 mV with pear-shaped narrowing of QRS loop in the HP.

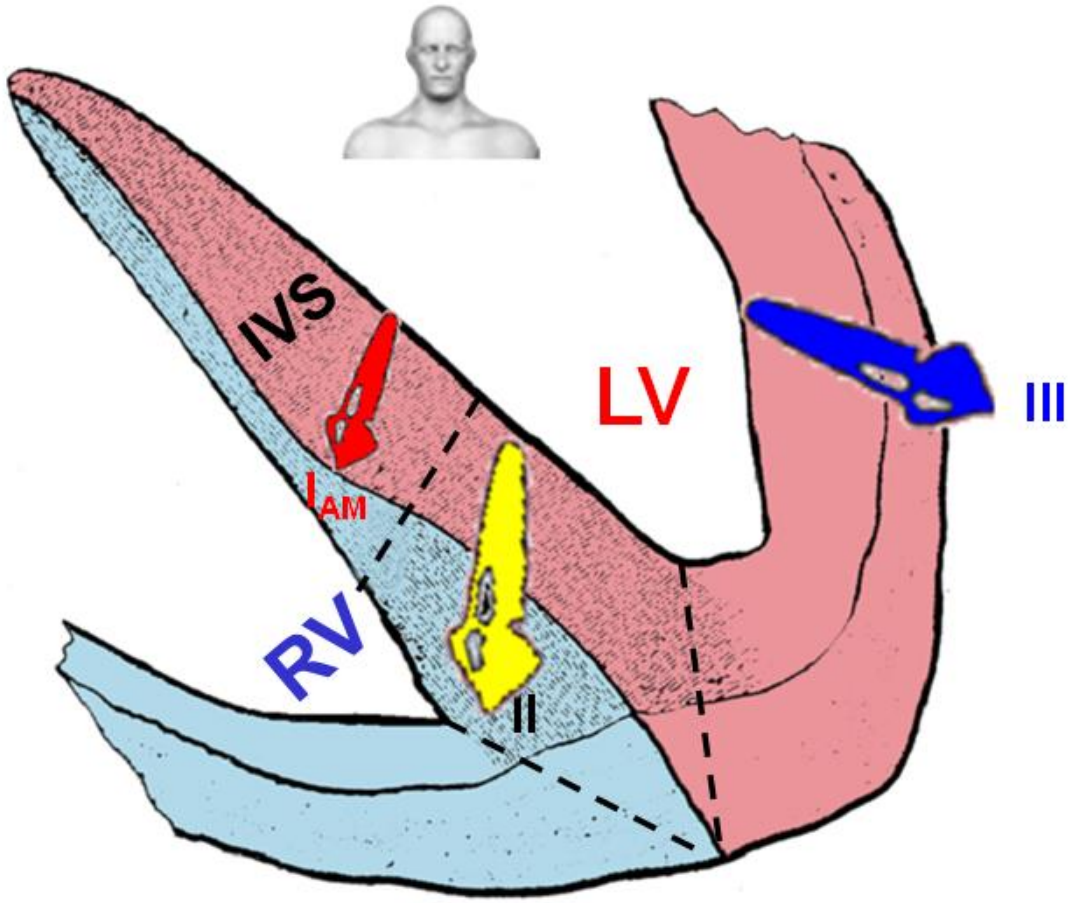


Figure 10. It is the vector (III) that represents the activation of the endo and epicardium of the free walls of both ventricles, and its direction is heading to the predominant

ventricle (LV), i.e. backward, to the left and below. It stretches between 40 ms and 60ms.

Representation of vector III in the Horizontal Plane in Left Ventricular Hypertrophy

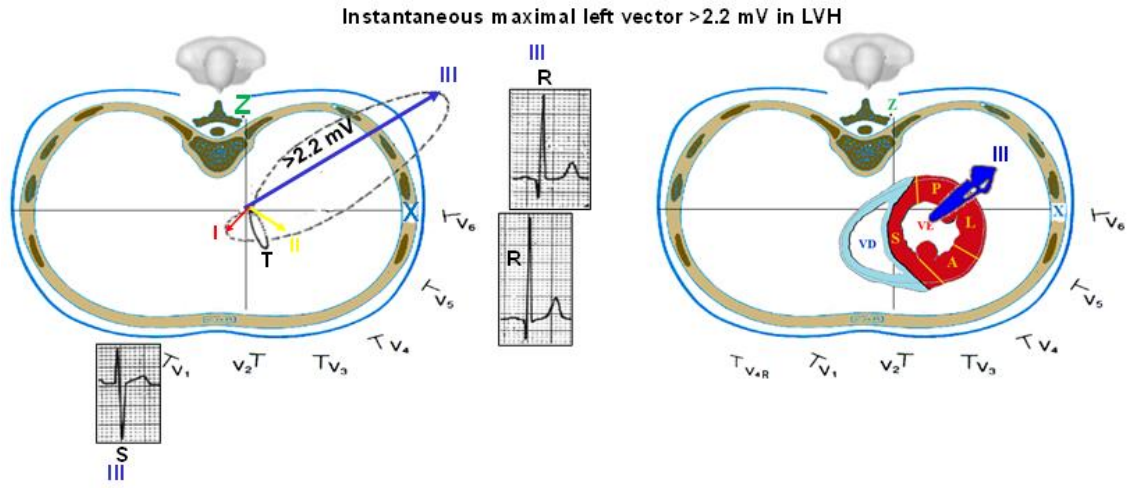


Figure 11. Representation of vector III of free wall in the horizontal plane in diastolic, volumetric or excentric LVH.

Vector IV or basal in normal heart and in Left Ventricular Hypertrophy

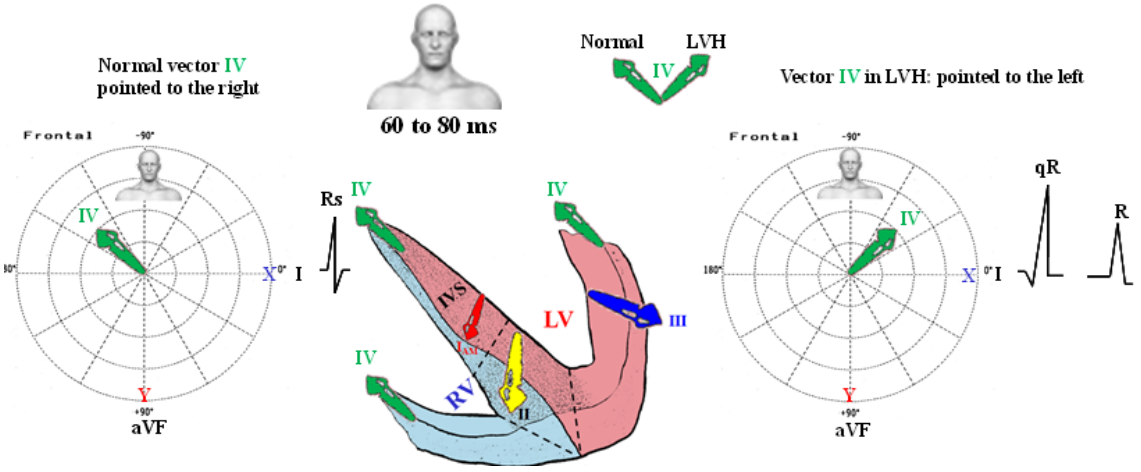


Figure 12.

- Normal: activation of basal portions of the septum and free wall of both ventricles (60 and 80 ms). Upward, backward and to the right.

- LVH: vector III more to the left. The left superior and posterior orientation of the middle vector of QRS in LVE is due in part to hypertrophy of the posterior basal portion of the LV that activates later and without opposite forces from the RV.

It represents the activation of the basal portions of the septum and free wall of both ventricles. It heads backward, upward and to the right. It is situated between 60 and 80 ms.

Possible modifications in the direction of the initial septal vector (Vector I_{AM}) in Left Ventricular Hypertrophy in the HP

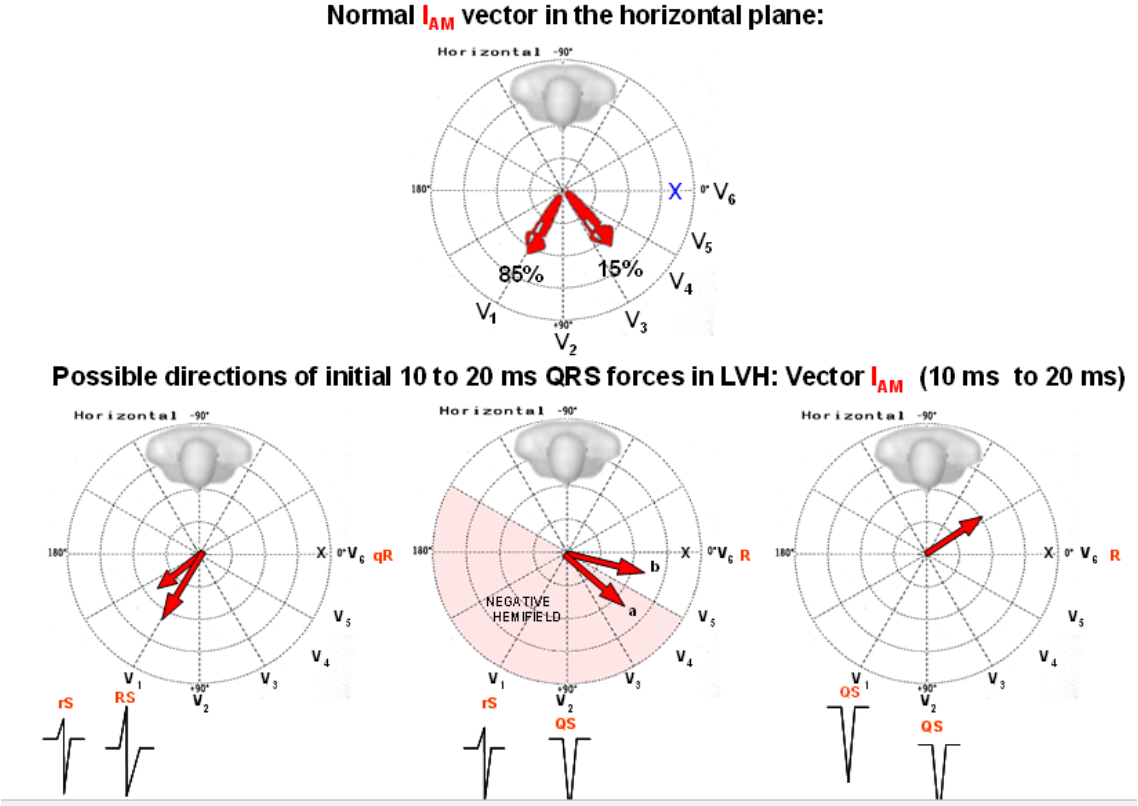


Figure 13. It heads to the front and to the right (85% cases), and it may even point to the left (15%). Rarely backward. Possible modifications in the direction of the septal I_{AM} vector in LVH in the horizontal plane. It may suffer modifications both in direction and magnitude.

Modifications in the magnitude of the I_{AM} septal vector in Left Ventricular Hypertrophy

It may increase (volume or diastolic enlargement) or decrease or even disappear (pressure or systolic enlargement). In the first case (diastolic LVE), it causes increase in initial R wave voltage in V_1 and V_2 (however the R/S ratio always remains in V_1<1) and causes deep Q waves (≥2 mm) in V_5 and V_6. These Q waves are "clean" and do not last longer than 35 ms.

The main entities where we may observe a significant increase in the magnitude of the septal vector are aortic regurgitation/insufficiency, ventricular septal defect and hypertrophic heart disease.

Differential diagnosis between q waves of diastolic LVH and infarction q waves

- Q duration: LVH: ≤35 ms. Those of infarction: ≥40 ms (except aVR and V1 leads). In the vectorcardiogram where the duration of the Q wave can be measured more precisely, the Q wave is considered abnormal with ≤30ms. In infants and children with anomalous origin of coronary artery, the pathological Q-wave duration ≥30ms.
- Q wave aspect: LVH: "clean" and deep. Those of infarction with notches and usually accompanied of injury current (ST) and ischemia (T).
- Cause: LVH: Altered distribution of myocardial mass. Myocardial Infarction: transmission of the cavity potentials to the surface of the heart or new balance of electrical forces that become oriented away from the region affected. They are the result of absence of electrical activity.
- Serum enzymes and troponin: LVH: normal. Those of infarction in acute phase, with increased CKMB, TGO, DHL and Troponin;
- Age group: LVH: they may be observed in children and young people (those of infarction are found in adults and elderly people with the exception of anomalous origin of coronary artery from pulmonary artery where Q waves are observed in infanst and children also).
- In HCM, the right or left ventricular free walls or both become thick because of chronic pressure overload. The interventricular septum can also become hypertrophied and can lead to LVOT obstruction. When the septum hypertrophies, normal septal forces that travel left to right through the septum are exaggerated on the ECG because of the enlarged septal mass. Septal hypertrophy can produce larger-than-normal Q waves in lateral leads I, aVL, V5, and V6 that can mimic lateral wall MI and can result in larger-than-normal R waves in V1 and V2 that mimic dorsal wall MI. If the LV free wall is hypertrophied, a QS complex can be recorded in V1, V2, and sometimes V3, which can mimic anteroseptal MI. If the ST segment is not elevated or shows an upward concave elevation and the T wave is upright in the presence of a QS complex in V1 or V2, this favors LVH. If the ST

segment shows convex elevation with an inverted T wave, anteroseptal MI is more likely.

The precise criteria for pathologic Q waves have been debated. The latest definition is accepted by the ESC and ACC (Thygesen, Alpert et al. 2007, Thygesen, Alpert et al. 2007, Thygesen, Alpert et al. 2007).

Definition of a pathologic Q wave

- Any Q wave in leads V2–V3 ≥0.02 s or QS complex in leads V2 and V3
- Deep Q wave ≥0.03 s and >0.1 mV or QS complex in leads I, II, aVL, aVF, or V4–V6 in any two leads of a contiguous lead grouping (I, aVL,V6; V4–V6; II, III, and aVF).
- R wave ≥0.04 s in V1–V2 and R/S ≥1 with a concordant positive T wave in the absence of a conduction defect.

Notes

- The absence of pathologic Q waves does not exclude a myocardial infarction!
- Lead III often shows Q waves, which are not pathologic as long as Q waves are absent in leads II and aVF (the contiguous leads).
- For those interested: the Minnesota Code Classification System for Electrocardiographic Findings contains a very extensive definition of pathologic Q waves.
- The Novacode system further classifies ischemic abnormalities in patients with no known history of myocardial infarction. (Rautaharju, Park et al. 1998) (Rautaharju, Park et al. 1998)
- The presence of a Q wave does not indicate any specific electrophysiological mechanism. To the contrary, Q waves can be related to one or more of the following four factors (Goldberger 2006) (Goldberger 2006).
- Physiologic and positional effects.
- Myocardial injury or replacement.
- Ventricular enlargement.
- Altered ventricular conduction.

- Clinicians should be aware of three principles with respect to Q waves: 1) not all Q waves are pathologic; 2) not all pathologic Q waves are due to myocardial infarction caused by fixed coronary artery occlusion; and 3) there is no firm consensus on the criteria for the diagnosis of pathologic Q waves (Bonow 2011) (Bonow, Maurer et al. 2011) (Bonow and Holly 2011).
- A broader discussion of the electrocardiogram in MI is found elsewhere.
- If there is a Q wave in I, II, aVL or aVF it should not be more than a quarter of the size of the R wave.
- Larger Q waves may be found in III and aVR.
- Abnormal Q waves suggest MI, old or recent.
- Pathological (abnormal) Q waves are defined as greater than 1/3 the height of the R wave, greater than 0.04 sec (40 msec) in duration, or present in the right precordial leads.

Electrocardiographic criteria for Left Ventricular Hypertrophy diagnosis

- Criteria based on increase of amplitude voltage of the QRS complexes;
- Criteria based on the discrete increase in QRS complex duration at the expense of a delay in the time of appearance of R wave apex: ventricular activation time, "R peak time" or intrinsicoid deflection in the leads that are opposite to the left ventricle (I, Avl, V5-V6), initial time of intrinsic deflection or ventricular activation time (VAT);
- Criteria based on $^{QRS}/_{ST\text{-}T}$ angle broadening: ST segment depression and T wave inversion in the left precordial leads and in the limb leads in which major QRS deflections are upright;
- Tendency to SÂQRS deviation to the left, backward and upward;
- Association: Ex Point score systems
- Indirect criteria.

LVH criteria based on increase of amplitude or voltage of the QRS complexes

- **LVH criteria on precordial leads**
  - Sokolow and Lyon index: S of V1 + R of V_5 ≥35 mm or 3.5 mV in adults older than 30, 40 mm or 4.0 mV between 20 and 30 years (Sokolow-Rapaport) and >60 mm between 16 and 20 years and >65 mm between 11 and 16 years. Modified Sokolow and Lyon index: S wave of V_2 + R of V_5 or V_6 ≥35 mm.
  - R wave of greater voltage + S wave deeper than any precordial lead ≥45 mm or 4.5 mV.
  - R wave of V_5 or V_6 ≥26 mm (2.6 mV).
  - S wave of V_1 ≥23 mm.
  - S wave of V_2 ≥ of 29 mm or greater.
  - If any S wave of V_1, V_2 or V_3 ≥30 mm.
  - If any R wave of V_4, V_5 or ≥27 mm.
  - R wave of V6 > than R wave of V_5 when both have an increased voltage.
- **LVH criteria on limb leads**
  - S wave of aVR ≥15 mm;
  - R wave of I ≥14;
  - R wave of aVL ≥11 (1.1 mV);
  - R wave of aVF ≥20 mm (2.0 mV);
  - Any R wave or S wave in the frontal plane leads ≥20 mm;
  - Lewis index (LI): (RI+SIII-RIII-SI>1.7 mV) LI = (RI - I) - (RIII - SIII) >17 mm;
  - Gubner-Ungerleider index = (RI+SIII>2.5 mV) R of I + S of III ≥25 mm (2.5 mV);
  - White-Bock index W-B = (R1 + R3) -- (R3 + S1) >17 mm.
- **LVH criteria using both planes**
  - Cornell index (CI) or Casale criteria or Cornel criteria: CI = RaVL + S V3 > than 28 mm in men or > 20 mm in women indicates LVH.

Sokolow index and Sokolow index modified for LVH (Sokolow and Lyon 1949)

S wave 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 > than 65 mm between 11 and 16 years. Sensitivity: 25%. Specificity: 95%.

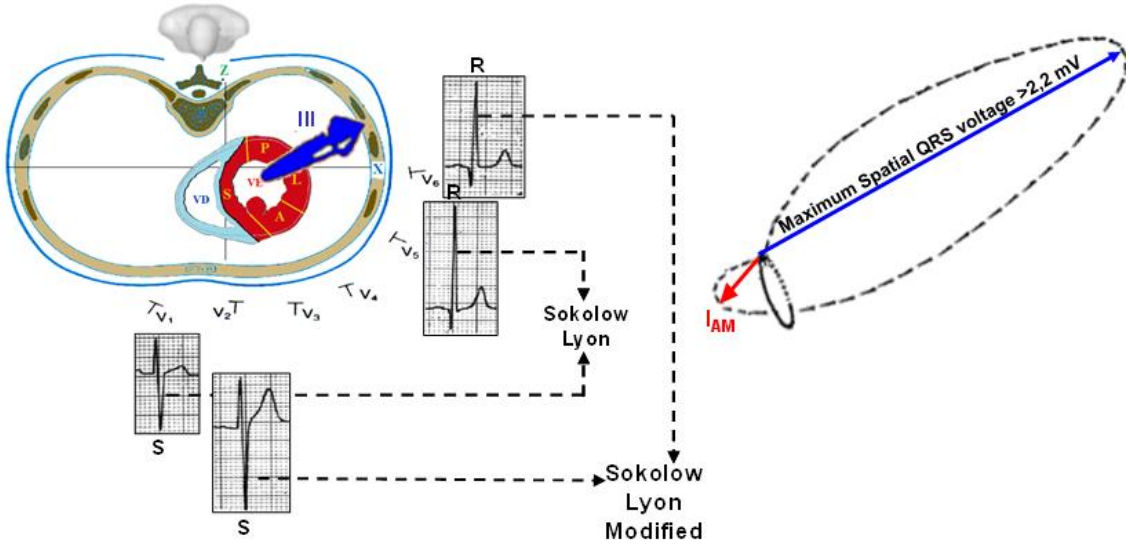


Figure 14. Modified index: S wave of V2 + R of V5 or V6 ≥35 mm. This index uses a close lead (V2) and a distant one (V6). This is the reason why it has the same value as the Sokolow-Lyon index, which uses a distant lead (V1) and a close one (V5).

R wave voltage in V6 taller than R wave voltage in V5 when both are increased: RV6>RV5

The presence of this sign suggests LV dilatation, i.e. diastolic, eccentric or volumetric LVH. (Talbot 1979)

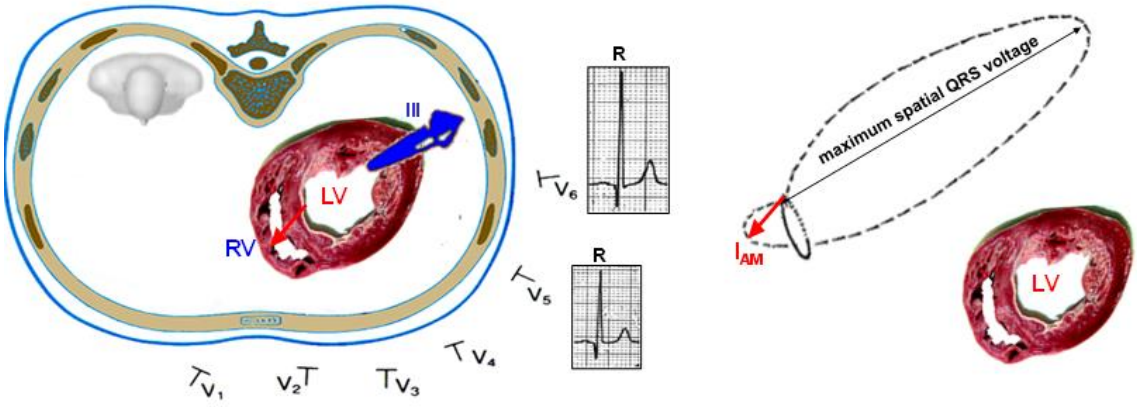


Figure 15. Additionally, left ventricular volumes were estimated in 59 patients, who were investigated by single plane ventriculography and coronary arteriography. The relation of the left ventricular end-diastolic volumes to the QRS voltage of the 12-lead ECGs and Frank VCGs was examined. It was found that the maximum spatial QRS voltage and the R wave voltage of leads V5 and V6 in patients without LVH were inversely correlated with end-diastolic volume. This inverse relation of QRS voltage and left ventricular volume may explain the loss of QRS voltage with dilatation of the heart. In patients with left ventricular hypertrophy, QRS voltage is usually positively correlated with the degree of LVH. (Talbot, Kilpatrick et al. 1977).

Ventricular Activation Time (VAT), intrinsicoid deflection, or "R peak time" in left leads I, aVL, V5-V6

Left Ventricular Activation Time (VAT): it is the time from QRS complex onset to peak of R wave on left leads (time of appearance of R peak). The normal value of VAT is <0.05 sec or 50 ms in V5 or V6. This parameter is prolonged in diastolic, volumetric, or eccentric LVH. VAT is shorter in systolic or concentric LVH than in diastolic LVH (Buchner, Debl et al. 2009). The prolongation of VAT is associated with diastolic dysfunction in patients with newly diagnosed untreated hypertension (Boles, Almuntaser et al. 2010).

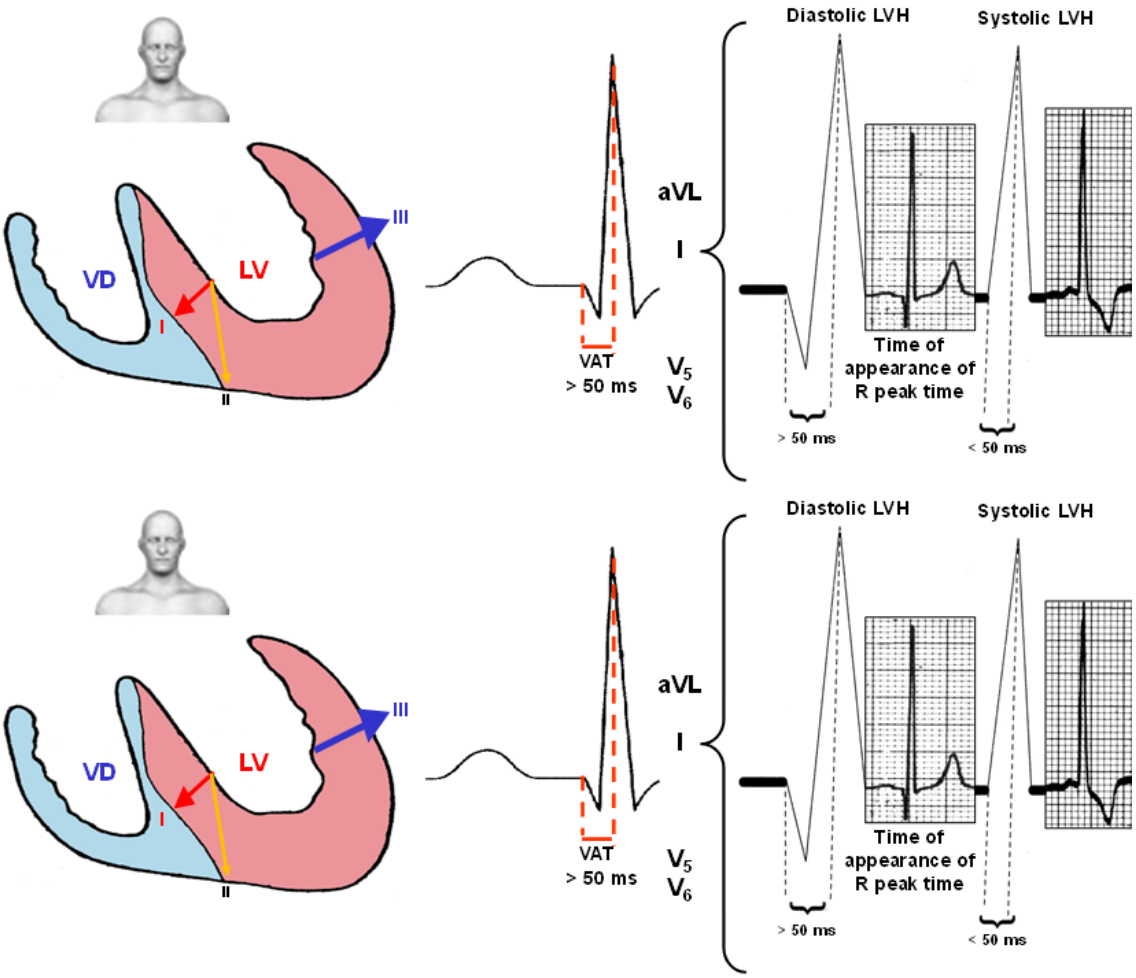


Figure 16. Ventricular Activation Time (VAT), intrinsicoid deflection, or "R peak time" in left leads I, aVL, V5-V6.

Criteria based on QRS/T angle prolongation: Systolic, concentric Cabrera type or LVH Strain pattern

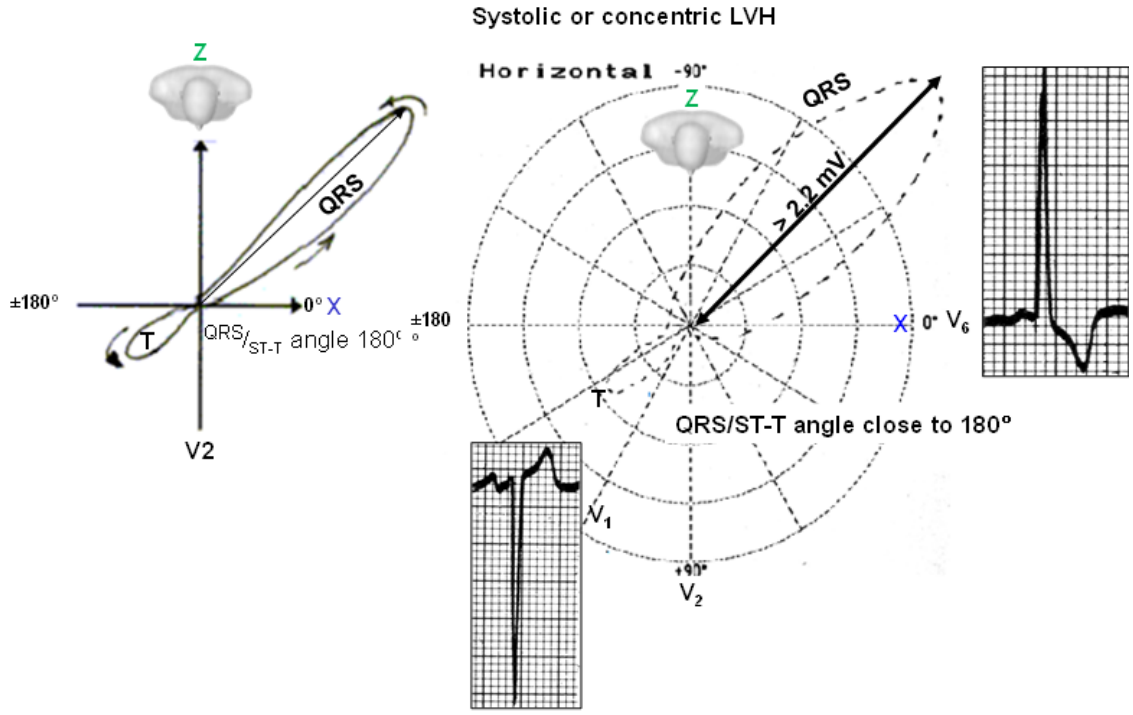


Figure 17. QRS/ST-T angle >100º and a T wave upright in V2 and more negative than -01 mV in V6. ST segment depression with upward convexity and T wave inversion in the left precordial leads.

Tendency to SÂQRS deviation to the left, backward and upward

In adults SÂQRS beyond -30^0 is considered left axis deviation. Axes between 0^0 and -30^0 may be observed in endomorphs and pregnant women.

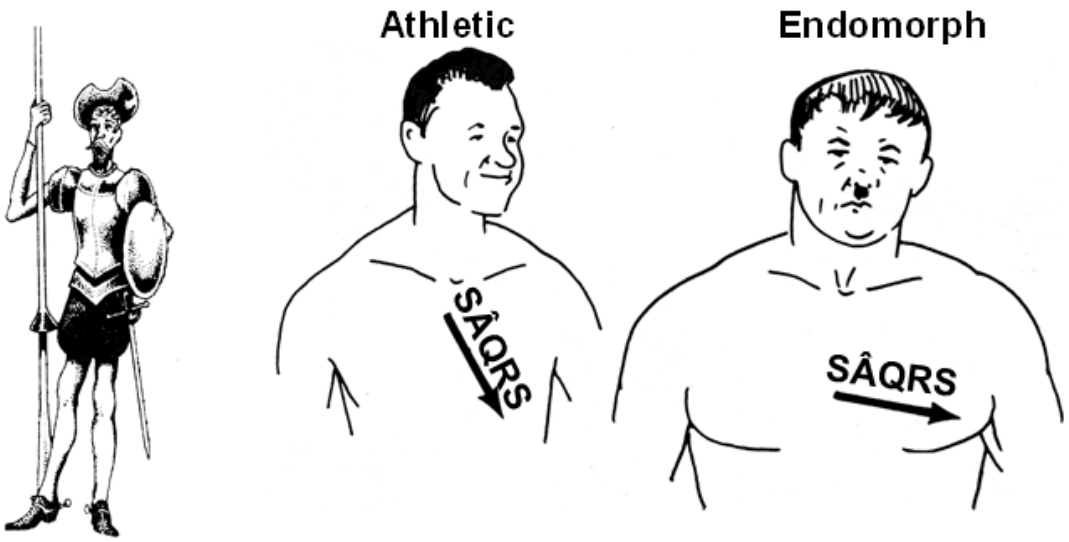


Figure 18. Electrical axis according to biotype and the causes for axis deviation in LVH.

In LVH, SÂQRS may be deviated to the left as a consequence of:

- Levorotation of the heart in its longitudinal axis
- Deviation to the left of basal vector **IV**

LVH in young people and children, usually presents non-deviated SÂQRS on frontal plane.

LVH associated to Left Anterior Fascicular Block (LAFB), extremely deviates SÂQRS to the left beyond - 45^0.

SÂQRS in LVH in the Frontal Plane

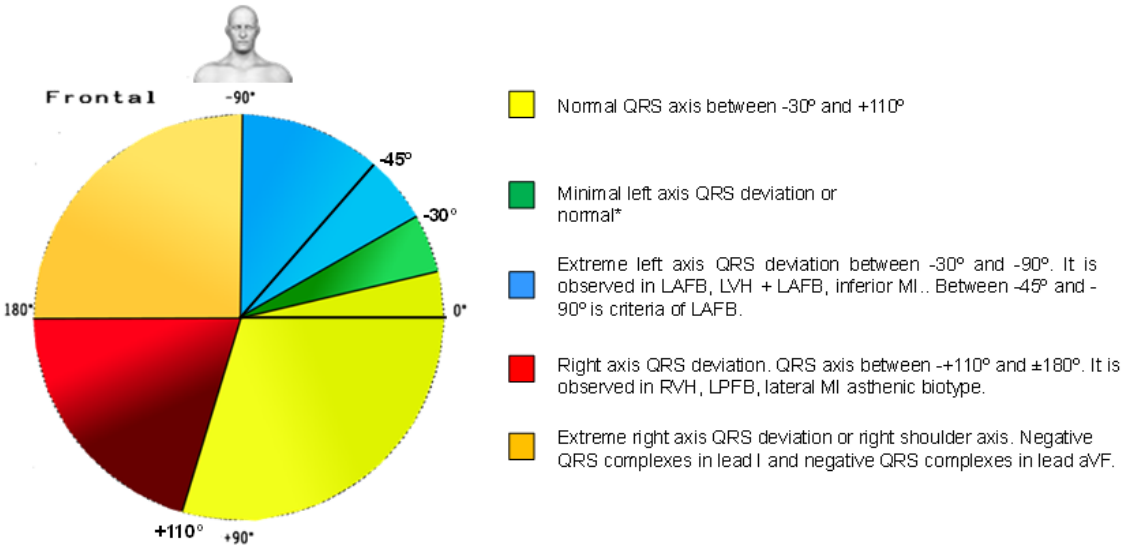


Figure 19. *Note: Axes between 0º and –30º may be observed in endomorphs and pregnant women. When the axis is between 0 and -30 degrees, it is sometimes referred to as a physiological (as opposed to pathological) left axis deviation. Axis of QRS in LVH in the frontal plane is considered with left axis deviation when ≥30º. Romhilt-Estes Score (Romhilt and Estes 1968) (Romhilt, Greenfield et al. 1968) (Romhilt, Greenfield et al. 1968).

Main causes of extreme left axis deviation in the Frontal Plane

- Left anterior fascicular block of the his bundle: LAFB;
- End conduction delay by the superior division of the right branch: ECD (block of the superoanterior zone of the right ventricle)
- Advanced left bundle branch block: ALBBB or complete LBBB
- Wolff-Parkinson-White syndrome: WPW
- Inferior or diaphragmatic infarction
- Association of inferior infarction, LAFB or Complete LBBB
- Certain types of emphysema: pseudo deviation of AQRS to the left
- Hyperpotassemia;
- Acute pulmonary embolism (APE);
- Right ventricular ectopic rhythm;
- Congenital heart diseases: endocardial cushion defects, tricuspid atresia, 15% of VSD, single ventricle, anomalous onset of coronary artery of pulmonary artery, giant AV fistulae;
- Left ventricular hypertrophy.

Point score system for LVE/LVH or Romhilt-Estes Score (Romhilt and Estes 1968, Romhilt, Greenfield et al. 1968)

The authors attribute values from 1 to 3 points to the different existing criteria, 5 or more points: certain LVH; 4 points: probable LVH.

ECG finding	Scoring
Voltage criteria **Voltage Criteria (any of):** **R or S wave in limb leads ≥20 mm** **S wave in V1 or V2 ≥30 mm** **R wave in V5 or V6 ≥30 mm**	**3 points**
ST-T vector opposite to QRS without digitalis	**3 points**
ST-T vector opposite to QRS without digitalis	**1 point**
Left atrial abnormality; terminal negativity of the P wave in V1 >1 mm in depth with a duration of ≥0.042	**3 points**
Left axis deviation ≥30º	**2 points**
QRS duration >90 ms	**1 point**
Delayed ventricular activation time, R peak time or intrinsicoid deflection in V5 or V6 (>0.05 sec) or ≥50 ms	**1 point**

Cornell limb lead criterion, Cornell index (CI) (Casale, Devereux et al. 1985) or Casale criterion for LVH

***Cornell criteria*:** Add the R wave in aVL and the S wave in V3. If the sum is >28 mm in males or >20 mm in females, then LVH is present.

CI = R aVL + SV3: >28 mm (>2.8 mV) in men or >20 mm (>2.0 mV) in women suggests LVH.

Gender-specific Cornell voltage (SV3 + RaVL >2.8 mV in men and >2.0 mV in women.

The criterion has high sensitivity and specificity for LVH, and is the best ECG criterion to evaluate LVH.

Modified Cornell Criteria: Examine the R wave in aVL. If the R wave is >12 mm in amplitude, then LVH is present.

Cornell product (Molloy, Okin et al. 1992); (CorP.)*Cornell voltage-duration product

It is the product of 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 not only left ventricular mass but also LV geometry and diastolic function in Japanese hypertensive patients.

Reduction in Cor P ECG LVH during antihypertensive therapy is associated with fewer hospitalizations for HF, independent of blood pressure lowering, treatment method, and other risk factors for HF (Okin, Devereux et al. 2007).

Perugia Score System for LVH (Verdecchia, Schillaci et al. 1998) (Verdecchia, Schillaci et al. 1998)

- The Perugia score[1] carried the highest population-attributable risk for cardiovascular morbidity and mortality compared with classic methods for detection of LVH. Traditional interpretation of standard electrocardiography maintains an important role for cardiovascular risk stratification in essential hypertension. ECG-LVH.
- Perugia Score requires positivity of one or more of the following criteria:
  - ***SV3+ RaVL >2.4 mV (men) or >2.0 mV (women);***
  - ***Left ventricular strain pattern***
  - ***Romhilt-Estes score of ≥5 points.***
- The Perugia score has low sensitivity. They showed that the prevalence of LVH in the hypertensive population is highest using the Perugia score, followed by the Sokolow-Lyon voltage criteria.
- When compared with traditional criteria for ECG diagnosis of LVH, the Perugia score showed the highest sensitivity (34%) at the expense of a slight decrease in specificity (93%), whereas, for example, the Cornell voltage yielded a sensitivity of 16% and a specificity of 97%.

Cornell/strain index (Verdecchia, Angeli et al. 2003) (Verdecchia, Sleight et al. 2003) (Verdecchia, Angeli et al. 2003)

The Cornell/strain [C/S] index, a simple electrocardiographic (ECG) index for left ventricular hypertrophy (LVH) defined by the presence of either a classic strain pattern or a Cornell voltage (sum of R in aVL + S in V(3) >2.0 mV in women or 2.4 mV in men, or both).

After adjustment for age, sex, smoking, and other confounders, the C/S index identified subjects with hypertension at increased risk of events (relative risk 1.76; 95% confidence interval 1.32-2.33). The C/S index achieved the highest population-attributable risk (16.1%) for cardiovascular events in hypertensive patients.

Framingham criterion (Levy, Garrison et al. 1990, Manyari 1990) (Levy, Wilson et al. 1990) (Levy, Labib et al. 1990)

Coexistence of a definite strain pattern and at least one of the following voltage criteria:

- Sum of the amplitudes of the R wave on lead I and the S wave on lead III ≥2.5 mV
- Sum of the amplitudes of the S wave on lead V1 or V2 and the R wave on lead V5 or V6 ≥3.5 mV,
- The S wave on the right precordial lead ≥2.5 mV and the R wave on the left precordial lead ≥2.5 mV

Combination criteria of LVH (Erice, Romero et al. 2009)

The combination of Cornell (RaVL+SV3>2.8 mV in men and>2.0 mV in women) with Lewis (RI+SIII-RIII-SI>1.7 mV) and Gubner-Ungerleider (RI+SIII>2.5 mV) indices displayed the highest net sensitivity (80.0% and 76.7%, respectively) while retaining excellent specificity (88.9% and 91.6%, respectively).

The combination of the Cornell and the Lewis or Gubner voltage criteria showed the greatest net sensitivity and specificity for the LVH diagnosis of HCM in a cardiovascular examination conducted in young people.

Peguero-Lo Presti citeria (Peguero, Lo Presti et al. 2017)

The goal of this study was to test a new method to improve the diagnostic performance of the electrocardiogram. The study was divided into 2 groups, a test and a validation cohort. In the test cohort, 94 patients were analyzed, including 47 with the diagnosis of hypertensive crisis and 47 with normal blood pressure at admission. Echocardiography was used to estimate the left ventricular mass index. Area under the curve (AUC) analysis was used for comparison of single and combined leads. The McNemar test was used to assess agreement among the ECG criteria against the LV mass index.

The proposed ECG criteria involved measuring the amplitude of the deepest S wave (S_D) in any single lead and adding it to the S wave amplitude of lead V_4 (SV_4). Currently accepted LVH ECG criteria such as Cornell voltage and Sokolow-Lyon were used for comparison. The validation cohort consisted of 122 consecutive patients referred for an echocardiogram regardless of the admitting diagnosis. The S_D was the most accurate single lead measurement for the diagnosis of LVH (AUC: 0.80; $p < 0.001$). A value of SD + SV 4 ≥2.3 mV in women and ≥2.8 mV in men is considered positive for SVI. When both cohorts were analyzed, the $S_D + SV_4$ criteria outperformed Cornell voltage with a significantly higher sensitivity (62% [95% confidence interval [CI]: 50% to 72%] vs. 35% [95% CI: 24% to 46%]). The specificities of all the criteria were ≥90%, with no significant difference among them. The proposed criteria for the ECG diagnosis of LVH improved the sensitivity and overall accuracy of the test.

Value of the Peguero-Lo Presti criteria at LVH
A systematic review and meta-analysis by researchers from the People's Republic of China that addressed the issue of Peguero-Lo Presti criteria for the diagnosis of left ventricular hypertrophy was published in the June 29, 2021 issue of PLoS Left Ventricular Hypertrophy (LVH) it is one of the main causes of arrhythmia, heart failure and sudden cardiac death. Early diagnosis and therapy can reverse its mechanism and improve the clinical course of patients. The electrocardiogram (ECG) is the most common diagnostic tool for immediate screening due to its established clinical value, wide availability and low cost. In clinical practice, several electrocardiographic criteria (at least 35) have been proposed; however, they all have low sensitivity. Therefore, exploration of new criteria with greater sensitivity is necessary.

In 2017, Peguero et al. introduced a new ECG criterion (called the Peguero-Lo Presti criterion), which is the sum of the amplitude of the deepest S wave in any lead with the S wave in lead V4 (SD + SV4), to diagnose HVI. They demonstrated that this criterion had a greater sensitivity (62% vs 35%) and a similar specificity (90% vs 92%) than the Cornell voltage index, which is the most used criterion. This finding has been confirmed by many studies. However, many scholars argue that the Peguero-Lo Presti criteria may not be a better screening tool for LVH in certain populations (obese patients and Asian populations). Thus, the last study by Ricciardi et al. verified that the Cornell index had a more accurate diagnostic performance than the Peguero-Lo Presti criteria. In contrast, a more recent meta-analysis by Noubiap et al. demonstrated that the Peguero-Lo Presti criteria have better diagnostic performance than the Cornell voltage index and the Sokolow-Lyon criteria and may be more useful in routine clinical practice as a screening tool for LVH. substantial heterogeneity was observed. Unfortunately, the authors did not carry out an exploratory analysis of the sources of such heterogeneity. After a careful reading of that study, the authors found that the different reference standards used for diagnosis (echocardiography and cardiovascular cardiac magnetic resonance) and the inclusion of abstracts of some studies for analysis may have been the main cause of the heterogeneity. Based on the above, it is still difficult to reach a consensus on the true diagnostic efficacy of the Peguero-Lo Presti criteria in LVH. Therefore, the authors conducted a systematic review and meta-analysis to assess the accuracy and clinical value of the above criteria to guide clinical practice and pave the way for future research. To this end, electronic databases from Medline, Web of Knowledge, Embase, and Cochrane Library were searched from inception to May 18, 2020. Trials written in English that investigated Peguero's criteria were included in Presti to detect LVH. Data were extracted and analyzed independently by two researchers. A total of 51 records were examined and 6 studies involving 13,564 patients were finally included. A bivariate analysis showed that the sensitivity of the analyzed criteria (0.52, 95% confidence interval (CI) 0.46-0.58) was greater than the Cornell voltage index (0.29, 95% CI % 0.23-0.36) and Sokolow-Lyon (0.24, 95% CI 0.21-0.27); the diagnostic accuracy (0.69, 95% CI 0.65-0.73) was also higher than the Cornell voltage index (0.67, 95% CI 0.62-0.71) and the Sokolow-Lyon (0.28, 95% CI 0.25-0.32); and specificity (0.85, 95% CI 0.79-0.90) was similar to the voltage index (0.92, 95% CI 0.89-0.95) and Sokolow- Lyon (0.94, 95% CI 0.88-0.97). Two studies (involving 12,748 patients) were excluded because they included partially healthy

individuals and represented substantial heterogeneity. Pooled analysis of the remaining 4 trials (including 816 patients) showed that the sensitivity of the Peguero-Lo Presti criteria (0.56, 95% CI 0.51-0.61) was also greater than that of the strain test. of Cornell index (0.36, 95% CI 0.31). –0.42) and the Sokolow-Lyon criteria (0.24, 95% CI 0.18–0.31); diagnostic accuracy (0.84, 95% CI 0.80-0.87) was also higher than the voltage index (0.54, 95% CI 0.50-0.58) and Sokolow's criteria - Lyon (0.38, 95% CI 0.34-0.42); and the specification***Yu Z, Song J, Cheng L, Li S, Lu Q, Zhang Y, Lin X, Liu D. Peguero-Lo Presti criteria for the diagnosis of left ventricular hypertrophy: A systematic review and meta-analysis. PLoS One. 2021 Jan 29;16(1):e0246305. doi: 10.1371/journal.pone.0246305. PMID: 33513186; PMCID: PMC7846009.***

The Shao criteria for hypertensive Chinese population

The ECG criteria currently available for the diagnosis of LVH have low in sensitivity. Thus, Shao et al (Shao 2018) compared the diagnostic performance of newly proposed ECG criteria to the existing criteria in a Chinese population. A total of 235 consecutive hypertensive patients, hospitalized between May 2017 and April 2018, were included. They were divided into two groups based on the gold standard echocardiogram: those with (n = 116) and without LVH (n = 119). The newly proposed ECG criteria were calculated by summating the amplitude of the deepest S wave (SD) in any single lead and the S-wave amplitude of lead V4 (SV4).

The area under the curve was calculated and compared against the sex-specific Cornell limb lead and Sokolow-Lyon criteria. ECG analysis of the cohort showed that the newly proposed criteria had the highest sensitivity in diagnosing LVH (male: 65.5%; female: 81%), followed by the Cornell limb lead criteria (male: 55.2%; female: 56.9%). The specificities of both sets of criteria were higher than 70%, with no significant differences between them. Receiver operator curve analysis showed an optimal cutoff of ≥2.1 mV for females (AUC: 0.832; 95% CI: 0.757-0.906) and ≥2.6 mV for males (AUC: 0.772; 95% CI: 0.687-0.856).The newly proposed SD + SV4 criteria provide an improved sensitivity for the ECG diagnosis of LVH compared to existing criteria, but its routine use will require further validation in larger populations.

Indirect criteria for Left Ventricular Hypertrophy/Overload

- Left atrial enlargement (LAE) in absence of right ventricular hypertrophy/enlargement;

- Left anterior fascicular block (LAFB);
- Incomplete left bundle branch block (ILBBB);
- Advanced LBBB or Complete LBBB;
- Morphology of left ventricle in multiple leads;
- Deep and narrow (<40 ms) q waves in inferior leads, mainly leads III and aVF and less often in lead II;
- Absence of q waves in left leads;
- Notching and prolongation of QRS complexes or complexes in "M" in I and aVL or V_3 and $V_{4;}$
- Poor R wave progression in precordial leads. Absence of growth of r wave in the right precordial leads from V_1 to V_3, with sudden increase in $V_{4;}$
- Pseudo septal or anteroseptal infarction pattern;
- R wave of increased voltage in V2 by dislocation of transition zone to the right;
- Secondary alteration of T wave;
- Negative U wave in left precordial leads;
- Acute atrial fibrillation in myocardiosclerosis;

Common electrocardiographic criteria for the diagnosis of left ventricular hypertrophy (LVH) (Okin, Devereux et al. 2004) (Okin, Roman et al. 2004) (Okin, Devereux et al. 2004) (Okin, Devereux et al. 2004)
Cornell voltage criteria SV3 + RaVL ≥ 2.0 mV (28 mm) in men SV3 + RaVL ≥ 2.8 mV (20 mm) in women (some variations use a lower cutoff value in men)
Cornell product criteria SV3 + RaVL (+8 in women A) × QRS duration ≥ 2.440 mm × ms
Sokolow-Lyon voltage criteria SV1 + RV5 or RV6 ≥3.5 mV (35 mm) B or RaVL ≥1.1 mV (11 mm)
Romhilt-Estes point score system (a score ≥5 is diagnostic of LVH, a score of 4 is "probable" LVH). Voltage criteria (3 points): Any S or R in limb leads ≥20 mm SV1, SV2, RV5, or RV6 ≥30 mm ST-T wave changes of LVH (3 points, 1 point on digitalis) Left atrial abnormality (3 points):

Terminal component of the P wave in V1 ≥1 mm and ≥40 ms Left axis deviation (2 points): QRS axis of ≥ -30^0 Prolonged QRS duration (1 point): ≥90 ms Prolongation of ventricular activation time or delayed intrinsicoid deflection time (1 point): ≥50 ms in V5 or V6

A systematic review of 21 studies (Pewsner, Juni et al. 2007), published in 2007, found that all the criteria were less sensitive than specific:

Of note, the ranges of the published values were extremely broad. For example, the ranges in sensitivity were:

Cornell voltage—median sensitivity 15%, median specificity 96%

Cornell product—median sensitivity 19.5%, median specificity 91%

Sokolow-Lyon voltage—median sensitivity 21%, median specificity 89%

Romhilt-Estes point score—median sensitivity 17%, median specificity 95%.

The ranges in sensitivity were:

Cornell voltage—2% to 41%

Cornell product—8% to 32%

Sokolow-Lyon voltage—4% to 51%

Romhilt-Estes point score—0% to 41%.

Indirect criteria of LVH

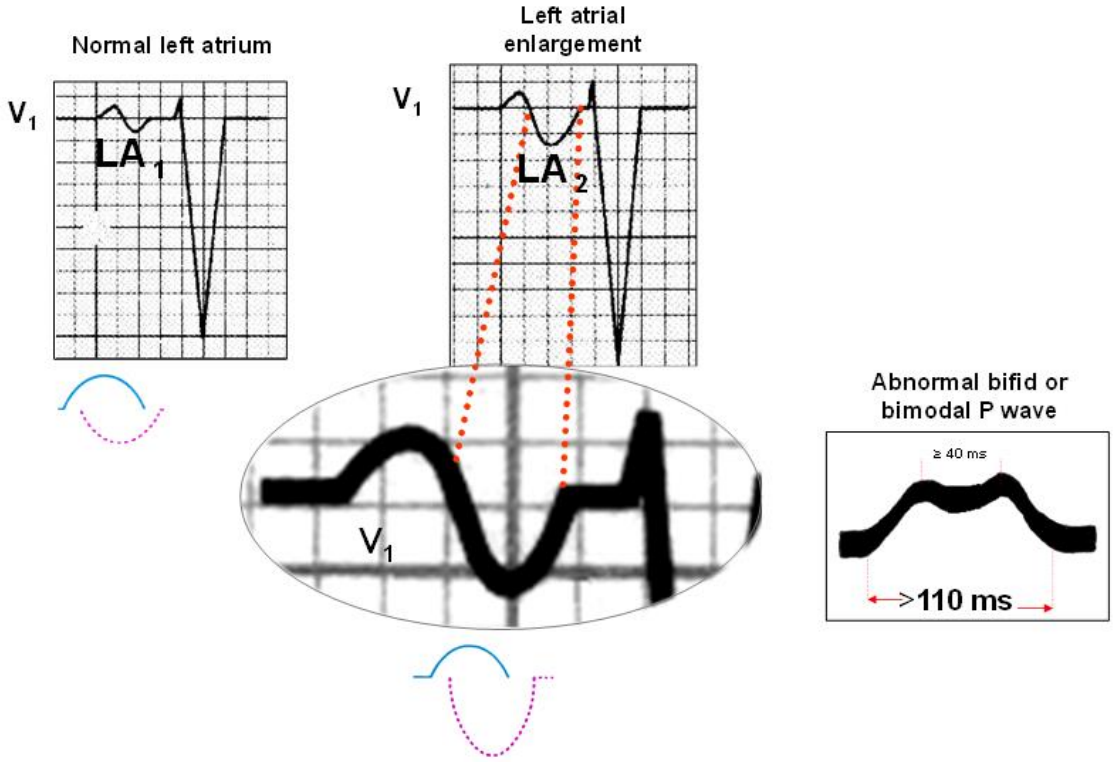


Figure 20. Increase in depth and duration of final negative component of the wave in V1 (left atrial enlargement Morris' index) (Morris, Estes et al. 1964); slow and deep of P in V1 or V1-V2. PTFV1. P terminal force in lead V1 equal or more negative than 0.04 mm/s. Greater than 0.03 mm/s: product of the duration of the final negative component (duration expressed in seconds; while depth is expressed in mm). Values above 0.03 mm per second constitute a highly sensitive criterion for the diagnosis of LAE.

Electrocardiographic diagnosis of LVH in the presence of LBBB

The presence of LBBB on 12-lead ECG may obscure the diagnosis of LVH.

The criterion of SV2 + RV6 greater than 4.5 mV demonstrated a sensitivity of 86% and a specificity of 100% for LVH diagnosis in the presence of LBBB.

QRS duration greater than 160 ms plus left atrial enlargement strongly supports the diagnosis of LVH in the presence of LBBB (Klein, Vera et al. 1984).

There are no differences in limb lead voltage, intrinsicoid deflection, or mean frontal plane QRS axis.

The following criteria can be helpful in left bundle branch block: QRS voltage increase, left atrial enlargement, QRS duration >155 ms (Oreto, Saporito et al. 2007).

LVH can be diagnosed in the presence of LBBB with an accuracy at least similar to that observed in patients without this conduction defect. Computer-assisted

interpretation of the ECG may be useful in the diagnosis of LVH as it enables the implementation of more accurate algorithms. Diagnostic algorithms, voltage-duration products, and certain compound criteria had the best sensitivities (Rodriguez-Padial and Bacharova 2012) (Rodriguez-Padial, Rodriguez-Picon et al. 2012)

LA abnormality is significantly diagnostic of LVH in the presence of LBBB. Age, body mass index, body surface area, frontal axis, and QRS duration are also significant predictors of LV mass.

Kafka parameters for the diagnosis of LVH in presence of LBBB

Kafka et al (Kafka, Burggraf et al. 1985) selected and used 5 ECG parameters in cumulative fashion for the diagnosis of LVH in the presence of LBBB:

- RaVL ≥11 mm;
- QRS axis ≤40º or SII greater than RII;
- SV1 + RV5 to RV6 ≥40 mm;
- SV2 ≥30 mm
- SV3 ≥25 mm.

This cumulative approach was superior to using single conventional criterion such as SV1 + RV5 or RV6. When LVH was defined as an M-mode index of at least 115 g/m2, the sensitivity was 75% and specificity 90%. Using M-mode, a mass of at least 215 g was the standard, the sensitivity was 73% and the specificity 66%.

LVH can be diagnosed by ECG criteria in the presence of LBBB at least as reliably as in normal conduction.

LVH criteria in the presence of Complete Left Bundle Branch Block

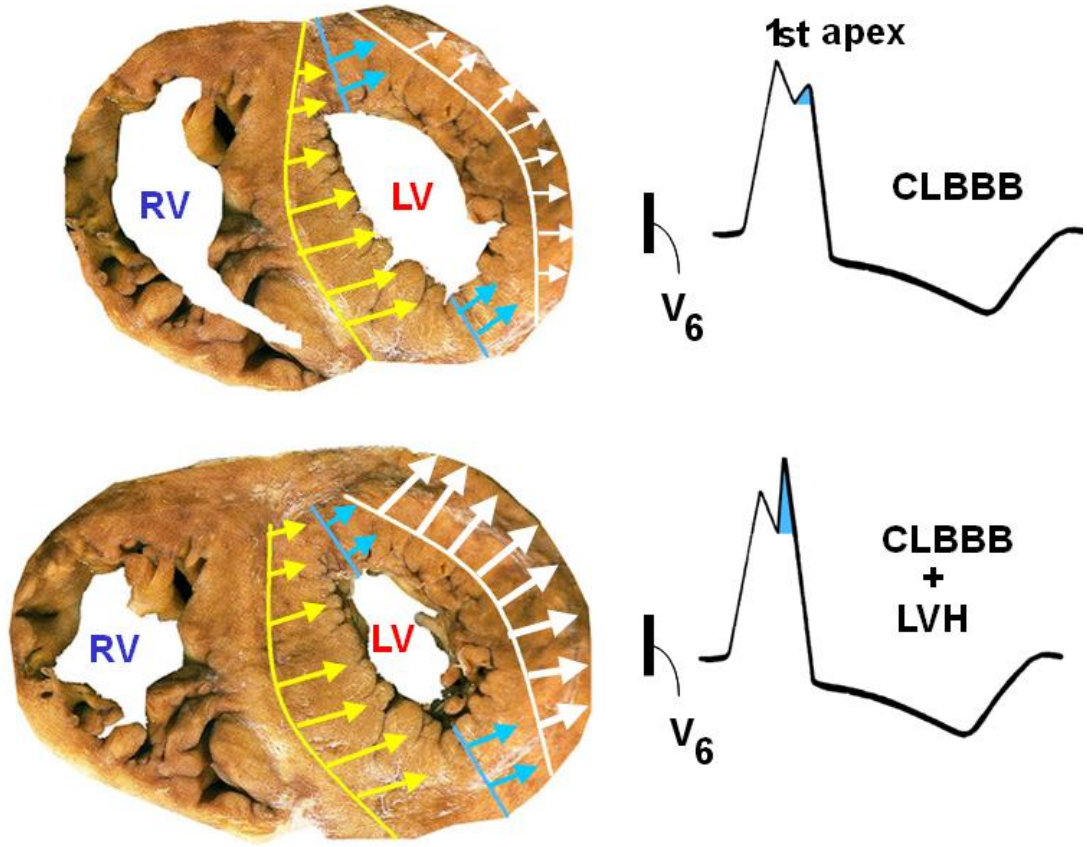


Figure 21. According to the apex of R wave in V6, of greater amplitude than the first apex. As the LV free wall has more mass to be depolarized, the last apex is of greater voltage than the first.

ECG Diagnosis of LVH in the Presence of RBBB

With RBBB, ECG criteria for LVH using right precordial S waves and combination criteria of right precordial S waves and left precordial R waves have a marked reduction in sensitivity, whereas left precordial R wave criteria have modestly reduced sensitivity. Limb lead criteria for LVH have increased sensitivity in the presence of RBBB. Acceptable sensitivity for the diagnosis of LVH in patients with bundle branch block requires a combination of limb and precordial lead voltage criteria and/or other nonvoltage ECG criteria, since the prevalence of LVH in the presence of RBBB appears higher than the sensitivity of individual criteria.

- Presence of Morris criteria for left atrial enlargement in absence of mitral valve stenosis. Specificity: 90%, sensitivity: 32%;

- SÂQRS deviation to the left beyond -30°: specificity: 68%, sensitivity: 61%;
- Voltage of R wave of I > than 10 mm. Specificity: 90%, sensitivity: 39%;
- Voltage of R wave of aVL > than 7 mm. Specificity: 74%, sensitivity: 50%;
- In I and aVL, qRs pattern, with q and R wave of greater voltage and s wave of reduced voltage;
- rSr' pattern in the leads of the inferior wall: II, III and aVF;
- Unipolar morphology of right precordial leads observed in intermediary precordial leads V3 and V4;
- Increase in S wave depth in V1: rSr'. The S corresponds to vector III of the hypertrophic LV free wall that gets away from V1;
- Voltage of R wave of V5 ≥ than 20 mm. Specificity: 90%, sensitivity: 20%;
- S wave of V1 + R of V5 or V6 > 35 mm. Specificity: 100%, sensitivity: 4%;
- Intrinsicoid deflection of V5 and V6 ≥ than 50 ms.

In right bundle branch block, LVH is suggested by a left atrial enlargement pattern, secondary repolarization changes, and a sum of S wave in lead III plus the maximal R+S in a precordial lead ≥ 35 mm (Oreto, Saporito et al. 2007).

Chan et al (Chan, Logue et al. 2006), examined the instantaneous effect of RBBB on QRS amplitudes and LVH voltages in 40 patients who had intermittent complete RBBB during a single 10 s standard 12-lead ECG recording. RBBB was associated with an increase in initial QRS forces (RV1, RV2, and QV6) but significant decreases in mean mid-QRS amplitudes that reflect LV depolarization (RaVL, SV1, SV3, RV5, and RV6).

All late QRS forces were increased with RBBB (R' V1, SV5, SI). As a result, combined voltages used for LVH criteria were significantly reduced by RBBB: Sokolow-Lyon voltage decreased from 1520 to 1014 microvolts ($p < 0.001$), and Cornell voltage decreased from 1438 to 746 microvolts ($p < 0.001$).

The authors conclude that RBBB is associated with significant reduction in "left ventricular" QRS amplitudes of the standard ECG, consistent with cancellation, rather than unmasking, of left ventricular mid-QRS forces by altered septal and delayed RV depolarization. Because QRS voltages that are routinely combined for the detection of LVH are reduced in RBBB, standard LVH criteria will perform with lower sensitivity in patients with RBBB.

VCG criteria for left ventricular hypertrophy

VCG has a superior sensitivity and specificity than ECG to detect LVH (Vine, Finchum et al. 1971).

From 100 autopsied cases with LVH studied by Abbott-Smith and Chou (Abbott-Smith and Chou 1970), VCG was capable of diagnosing 50% with just 11.7% of false positives.

It enables to clarify doubtful cases of association with septal or anteroseptal electrically inactive areas, which certain LVHs of the systolic type may cause in ECG (LVH with QS in V_1, V_1 and V_2 or V_1, V_2 and V_3). Thus, in absence of anterior electrically inactive area, the VCG shows the dashes from the initial 10 to 20 ms of the QRS loop without delay.

When there is a possible septal inactive area, the vector of the initial 20 ms is located in the left posterior quadrant.

Frequently, the vector of the initial 10 ms in LVH of high blood pressure is heading backward or to the front and the left, originating complexes of the QS type in V1 or V1-V2 simulating septal inactive area (Hugenholtz, Ryan et al. 1963).

The VCG seems to be superior to the ECG and the echocardiogram for the diagnosis of ventricular hypertrophies associated to electrically inactive areas, besides having a greater correlation with the echocardiogram than ECG when estimating the LV mass.

In our service, we follow the criteria by Varriale et al (Varriale, Alfenito et al. 1966) (Varriale, Alfenito et al. 1966), modified, which take into account the

characteristics of the QRS loop in the horizontal plane (HP); thus, five types are described: IA, IB, II, III and IV.

Type IA: vector of the initial 20 ms heading to the front and the right (Type IA) or to the front and the left (Type IB), oval morphology, counterclockwise rotation, and most of the QRS loop located in the left posterior quadrant.

T loop matching QRS (IA) or not matching QRS (IB).

Type IB: very similar to the QRS loop of CLBBB: vector of the initial 20 ms heading to the front and the left, (rare to the right), rotation in eight with counterclockwise proximal portion and clockwise distal portion, and E point that does not coincide with the 0 point, and located to the front and the right from the latter.

T loop to the front and right, opposite to the QRS loop.

Note: it is differentiated from CLBBB by the absence of middle-final delay.

Type II: this is the variant frequently found in LVE with high blood pressure, characterized by initial vectors heading to the right and discretely to the front, clockwise rotation (inverted), simulating antero-lateral infarction, narrow morphology and QRS loop located mostly in the left posterior quadrant.

Type III: Initial vectors of QRS loop heading to the front and the left; QRS loop more anterior and predominantly located in the left anterior quadrant; increased voltage of maximal vector;

Final vectors located to the right and backward with the ST/T vector in the right posterior quadrant;

E point not matching 0 point and located backward and to the right of the latter.

Type IV: Characterized by:

- Initial vectors of QRS loop heading to the front and the left;
- QRS loop more anterior and predominantly located in the left anterior quadrant;
- Increased voltage of maximal vector;

- Final vectors located to the right and backward with the ST/T vector in the right posterior quadrant;
- E point not matching 0 point and located backward and to the right of the latter.

The five vectorcardiographic types of LVH in the HP: IA, IB, II, III and IV

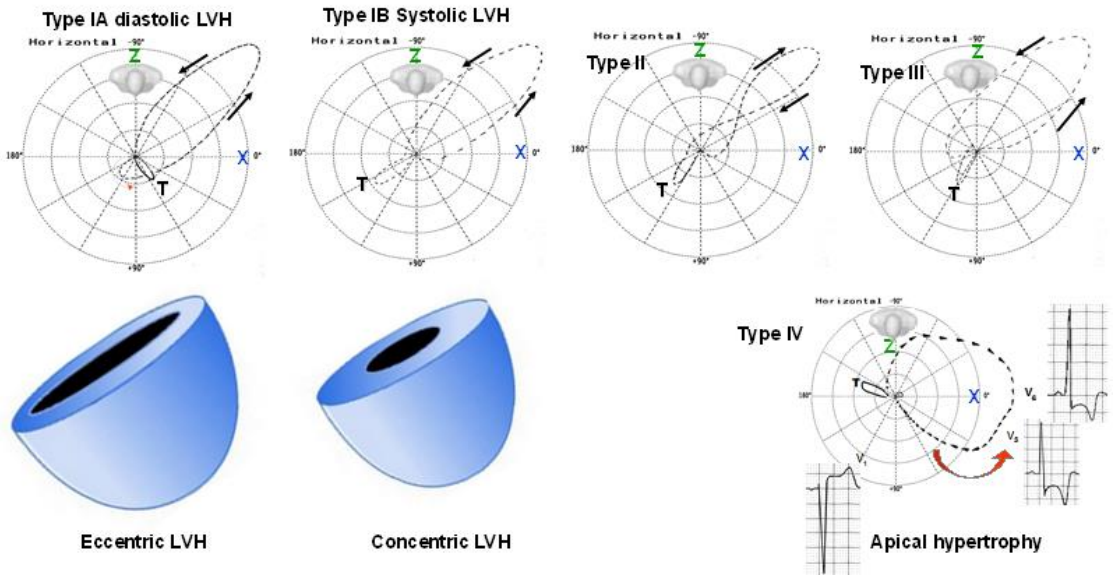


Figure 22. The five vectorcardiographic types of LVH in the HP: IA, IB, II, III and IV.

Vectorcardiographic characteristics of type IA LVH in the HP

- 10 to 20 ms vector of QRS loop directed to the front and rightward with increased magnitude.
- QRS morphology ovoid or elongated.
- Counterclockwise rotation.
- QRS loop predominantly located in the the left posterior quadrant.
- Left ventricular maximal vector >2 mV.

- "Clean" deep and narrow Q waves in left leads I, aVL, V5-V6 and eventually in inferior leads; consequently the I_{AM} vector is increased.
- Frequent ST segment elevation concave to the top followed by positive T wave in left leads.
- T loop with polarity concordant with the precedent QRS complex.

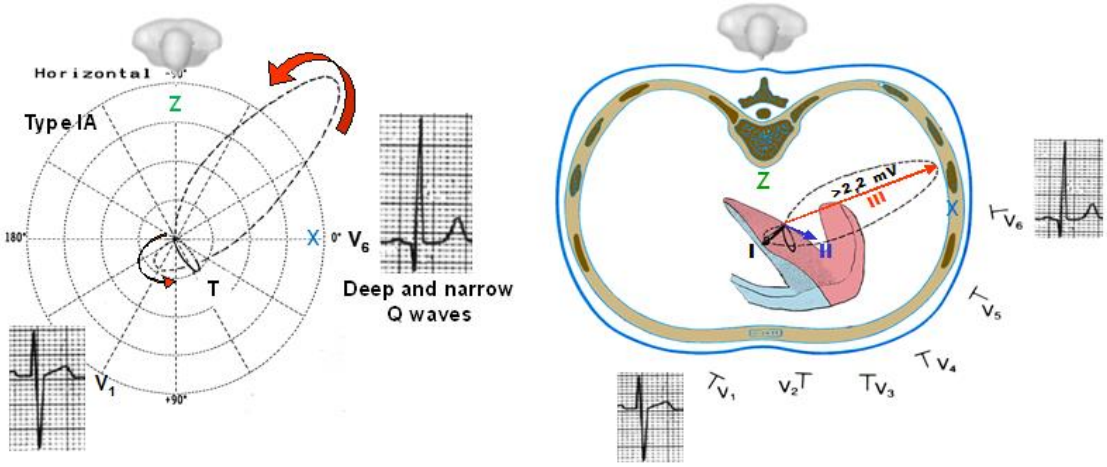


Figure 23. Vectorcardiographic characteristics of type IA LVH in the HP.

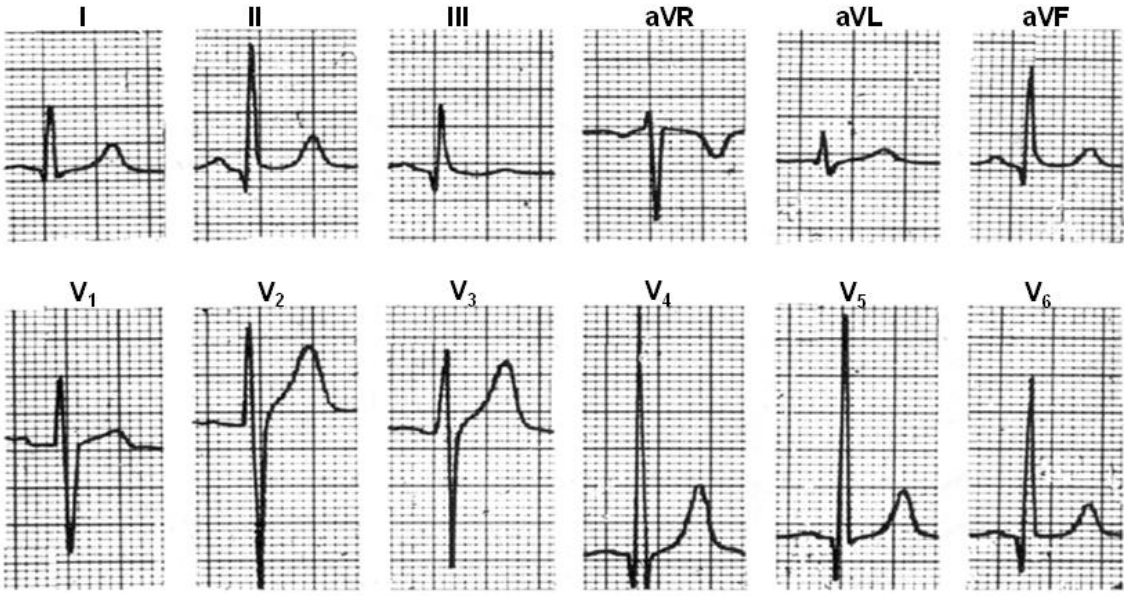


Figure 24. Clinical diagnosis: Marfan syndrome with severe aortic regurgitation. ECG diagnosis: Typical diastolic, volumetric or eccentric LVH pattern (it corresponds to type 1A VCG LVH): magnified septal vector manifested by prominent R wave in V1 and V2 and deep narrow Q waves fromV4 to V6 and inferior leads. T waves polarity matching with QRS complex and ST segment concave to the top and elevated in V5 and V6.

Systolic, concentric ECG/VCG LVH in the HP: VCG type IB

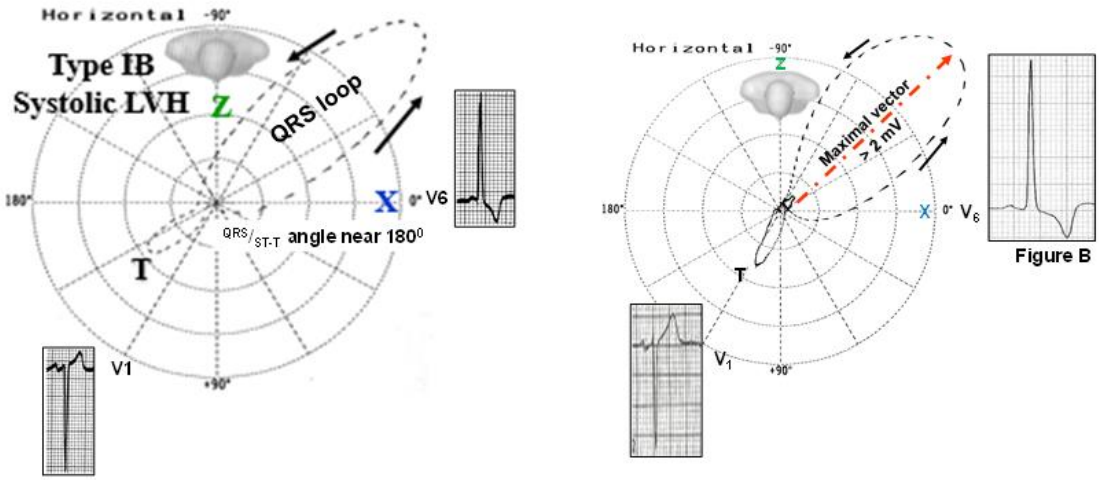


Figure 25. Type IB: vector of initial 20 ms of QRS loop heading to the front and the left, oval morphology, counterclockwise rotation, location predominant in left posterior quadrant and maximal vector of increased magnitude: >2 mV. Characteristically the ST segment and T wave are opposite related to QRS polarity (strain pattern). The T wave remains asymmetric with slow initial ramp and rapid terminal ramp. T loop opposite to QRS loop (not matching) heading to the front and the right: QRS/ST-T angle near 180^0.

Comparison of normal QRS and T loops / waves with ECG/VCG type IB LVH in the FP

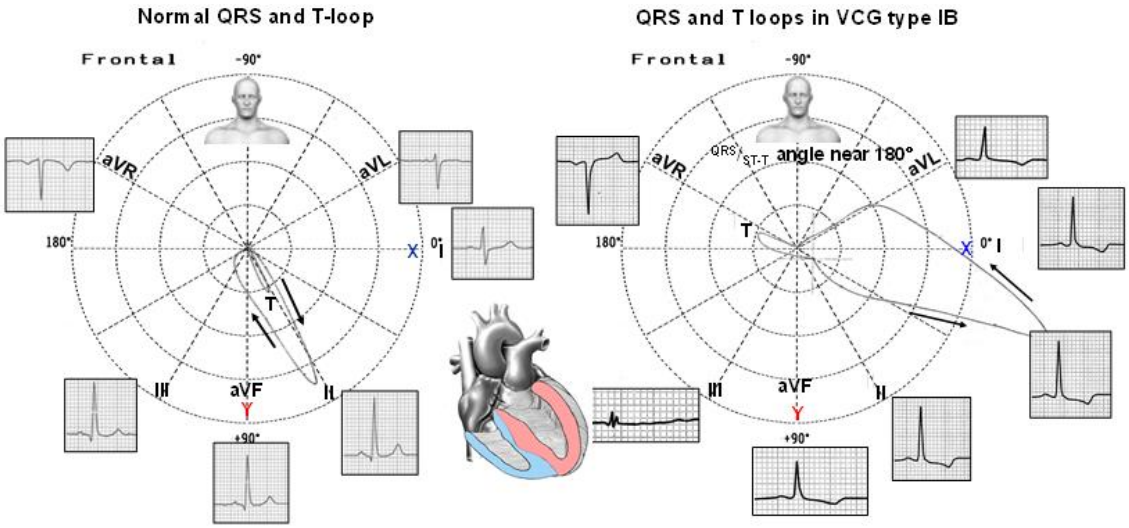


Figure 26. Comparison of normal QRS and T loops / waves with ECG/VCG type IB LVH in the FP.

ECG/VCG correlation in the frontal and horizontal planes

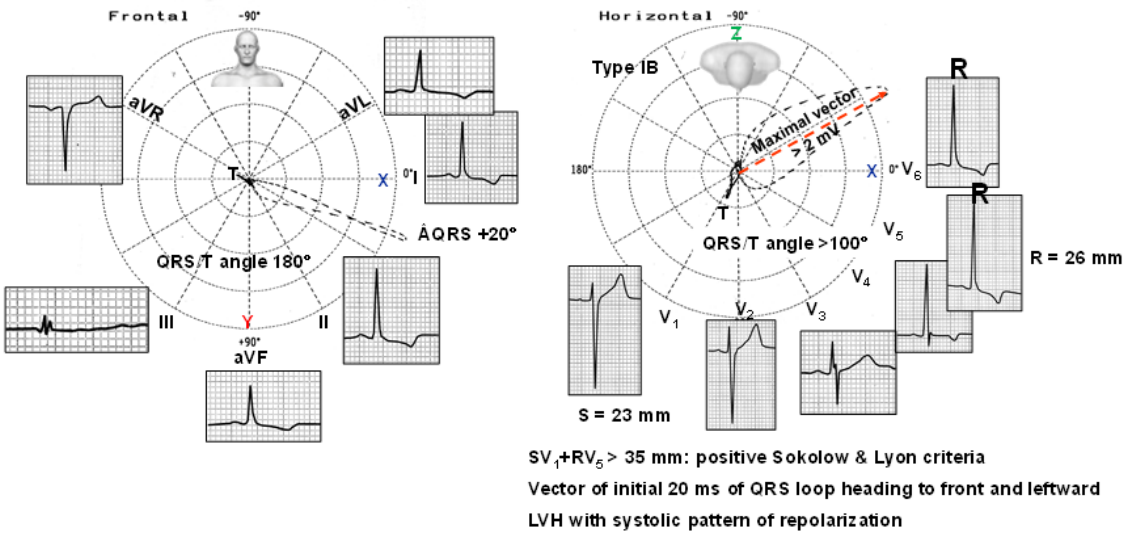


Figure 27. ECG/VCG correlation in the frontal and horizontal planes.

Name: EJS. **Age:** 30 y.o. **Sex:** M.
Height: 1.70 m. **Weight:** 72 Kg. **Biotype:** athletic.

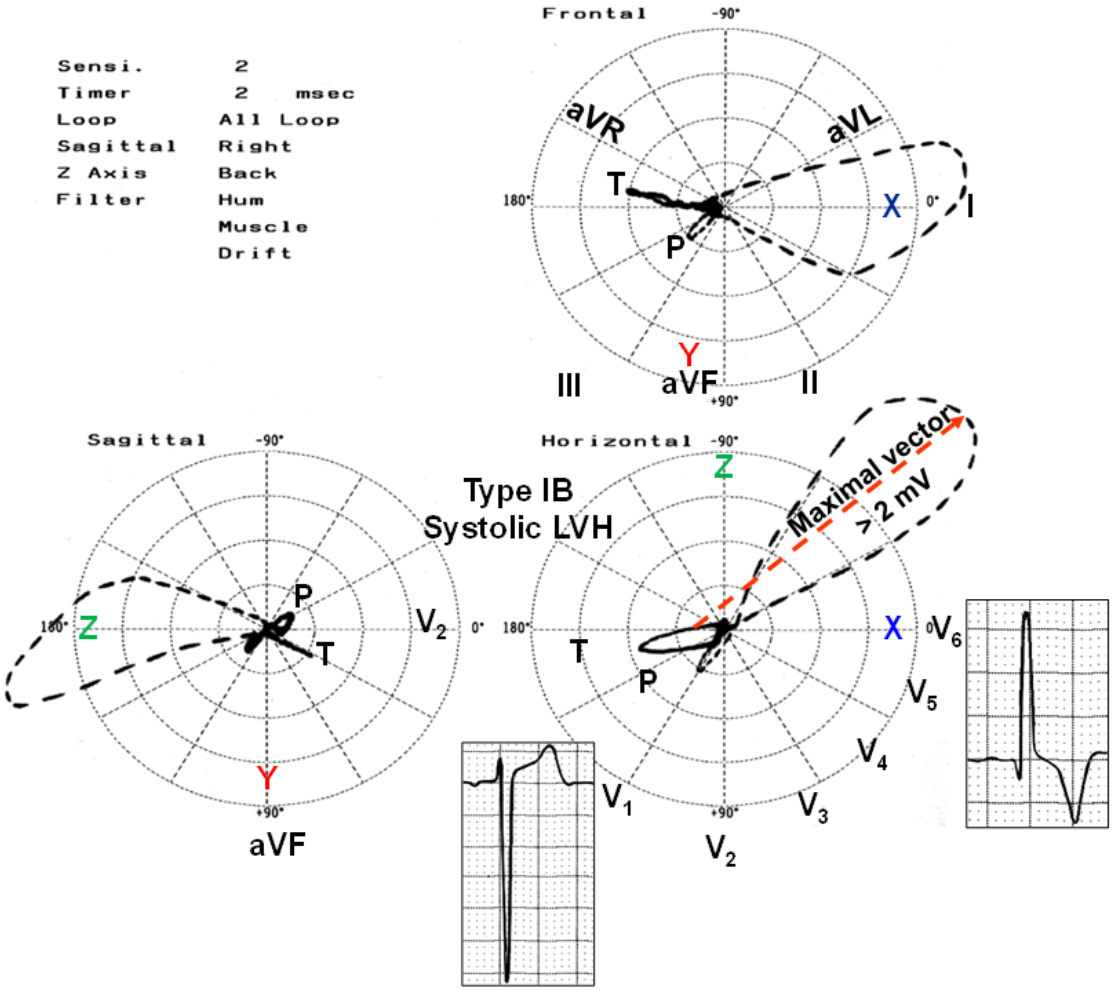


Figure 28. ECG/VCG correlation.

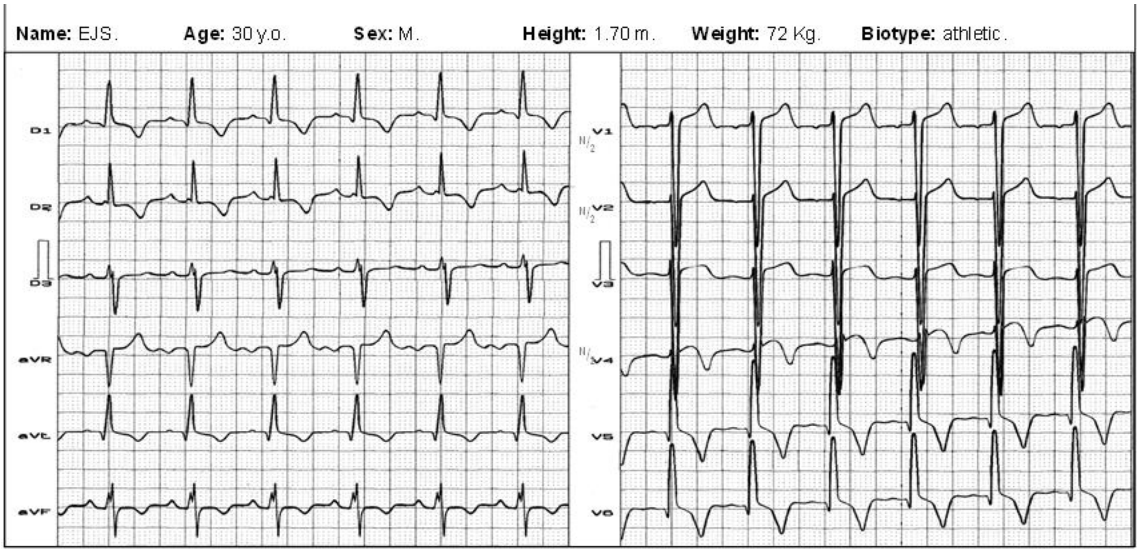


Figure 29. Clinical diagnosis: bivalvular aortic stenosis. ECG diagnosis: SR, HR: 98 bpm, SAQRS: 0^0. LVH of the systolic, concentric type of Cabrera: "systolic overloading pattern". Positive Sokolow-Lyon index: S of V1 + R of V5 > 35 mm, and T loop opposite to QRS loop (not matching) heading to the front and the right: QRS/ST-T angle near 180^0.

Left Ventricular Hypertrophy vectorcardiographic type II. ECG/VCG correlation V1-V6

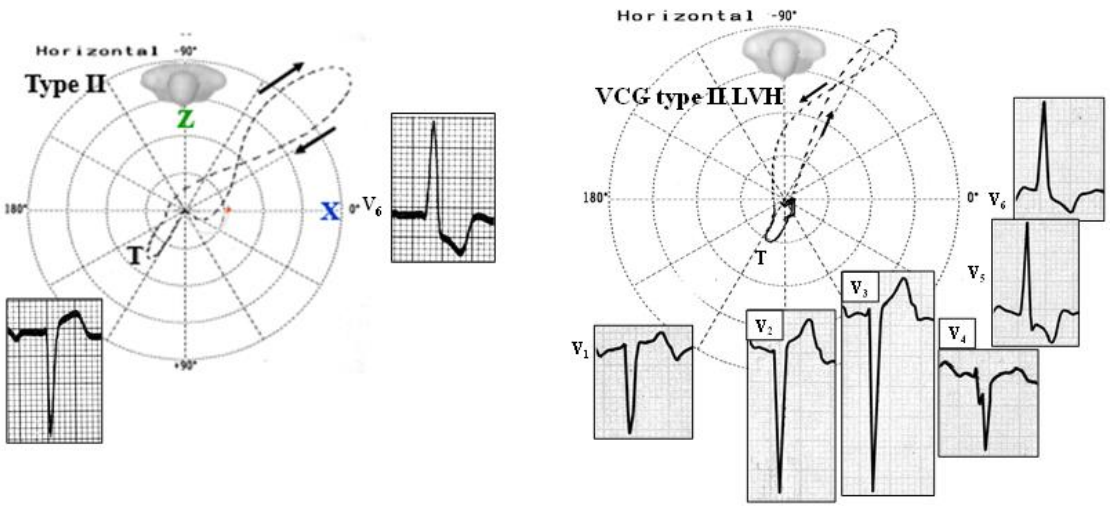


Figure 30. Type II LVH: Very similar to QRS loop of Complete Left Bundle Branch Block: Vector of initial 20 ms heading to the front and the left (rarely to the right), rotation in eight with counterclockwise proximal portion and clockwise distal portion, and E point not matching 0 point and located to the front and the right of this. T loop to the front and the right, opposite to QRS loop. The maximal left vector >2 mV. Note: it differentiates from Complete Left Bundle Branch Block by absence of middle-final delay.

ECG/VCG correlation in the Frontal and Right Sagittal Planes

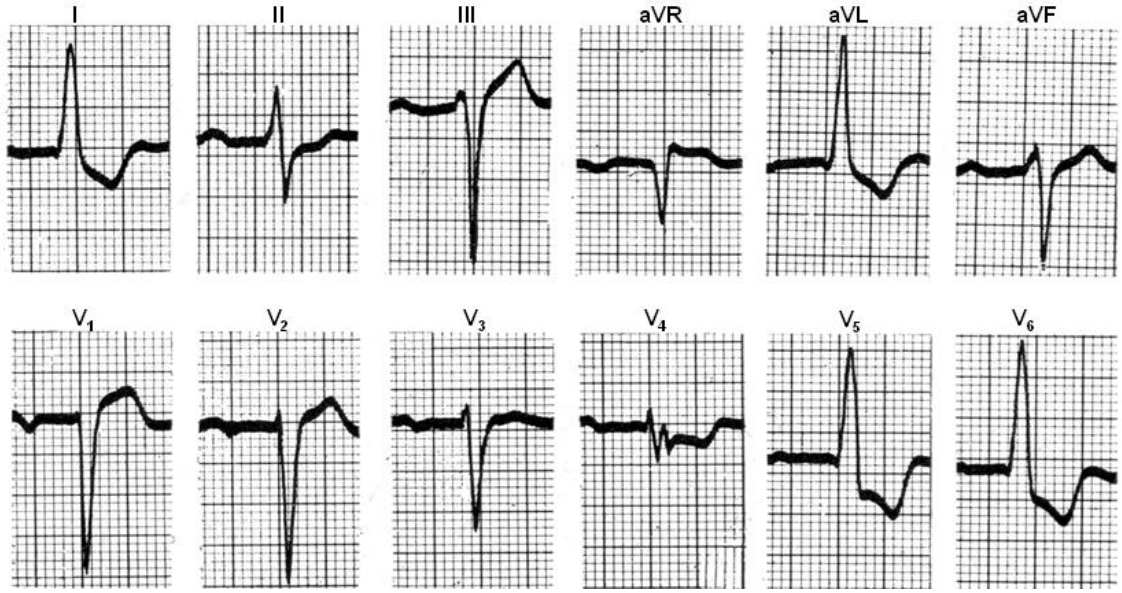


Figure 31. ECG/VCG correlation in the Frontal and Right Sagittal Planes.

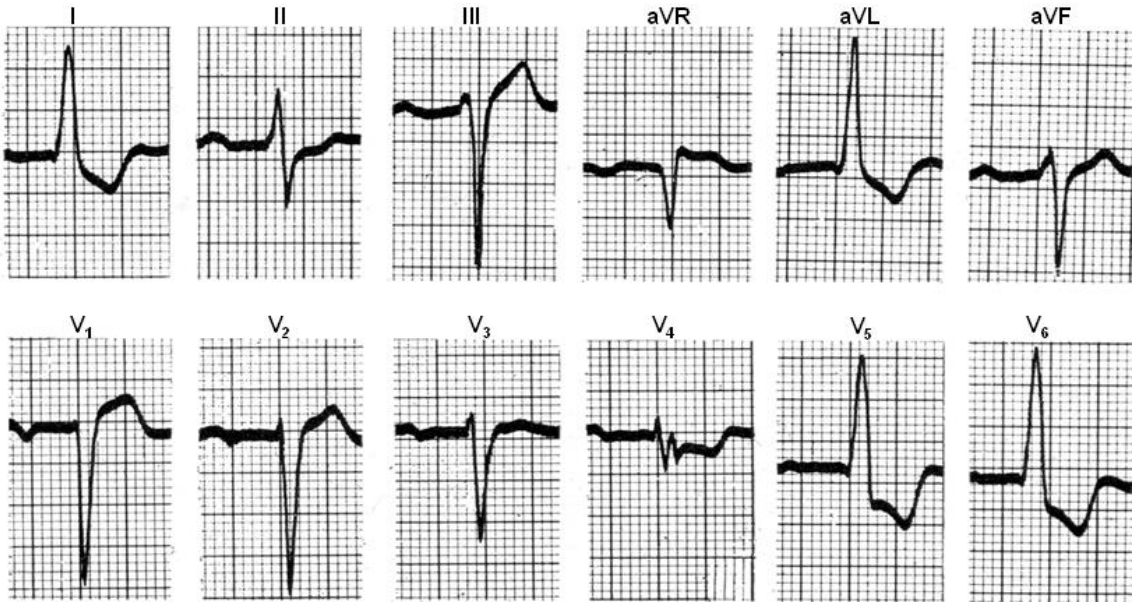


Figure 32. LAE (Morris criteria) + 1st degree AVB; PR= 24º ms; AQRS – 30^0 , QRS duration: 110 ms, LVH systolic pattern: SÂT + 120^0 in the FP and to the front and the right in the HP. ILBBB? Initial embryonic q wave in left leads I, aVL, V5-V6.

VCG differential diagnosis between LVH type II from genuine CLBBB

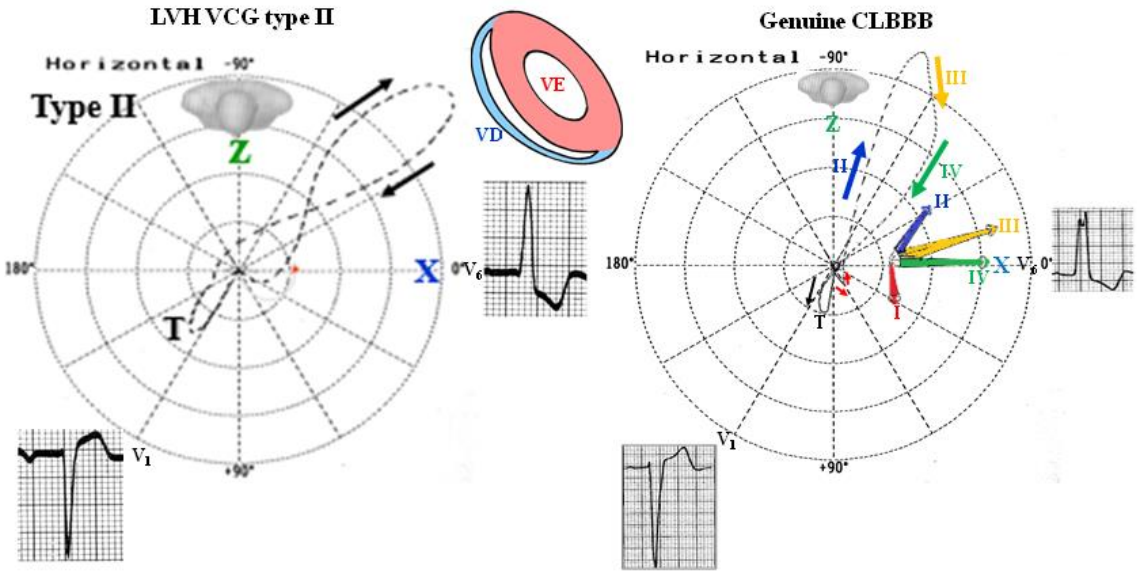


Figure 33. VCG differential diagnosis between LVH type II from genuine CLBBB.

LVH VCG type II: Absence of middle final conduction delay of QRS loop (dashes closer to one another).	**Genuine CLBBB:** Characteristic middle final conduction delay of QRS loop (tear closer one to another) (vector IV).

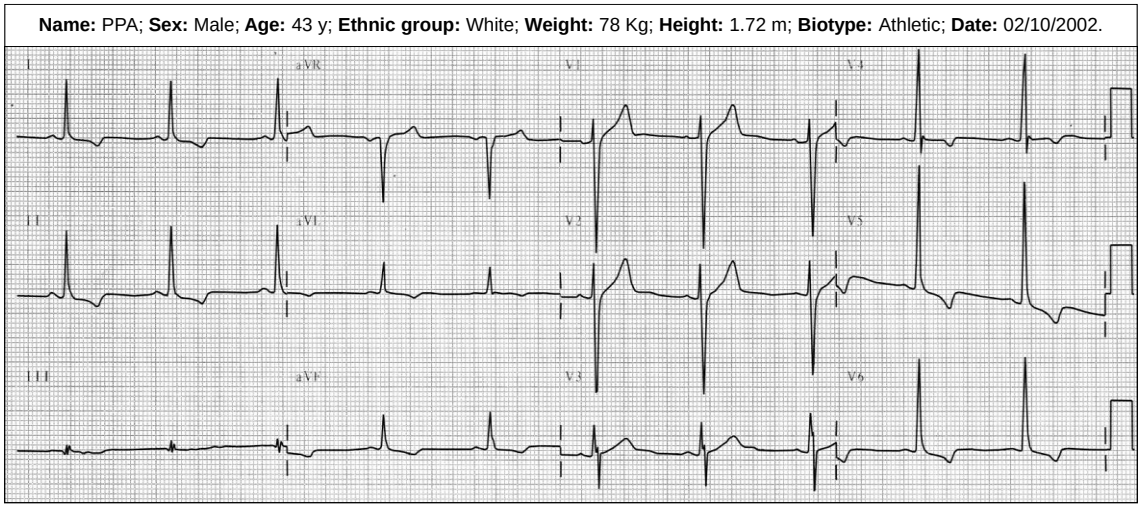


Figure 34. Clinical diagnosis: hypertensive heart disease. Essential systemic hypertension. ECG diagnosis: Typical systolic LVH pattern: secondary alteration of ventricular repolarization (I, aVL, V5 and V6) and in inferior wall. Wide QRS/T angle >100º: depressed ST segment, upwardly convex followed by inverted T waves with asymmetrical branches: the first descending portion with slow inscription and fast

ascending final portion in left leads (V5, V6, I, aVL), and in inferior leads II and aVF (vertical heart). Absence of Q wave in V5 and V6.

Left Ventricular Hypertrophy vectorcardiographic type III

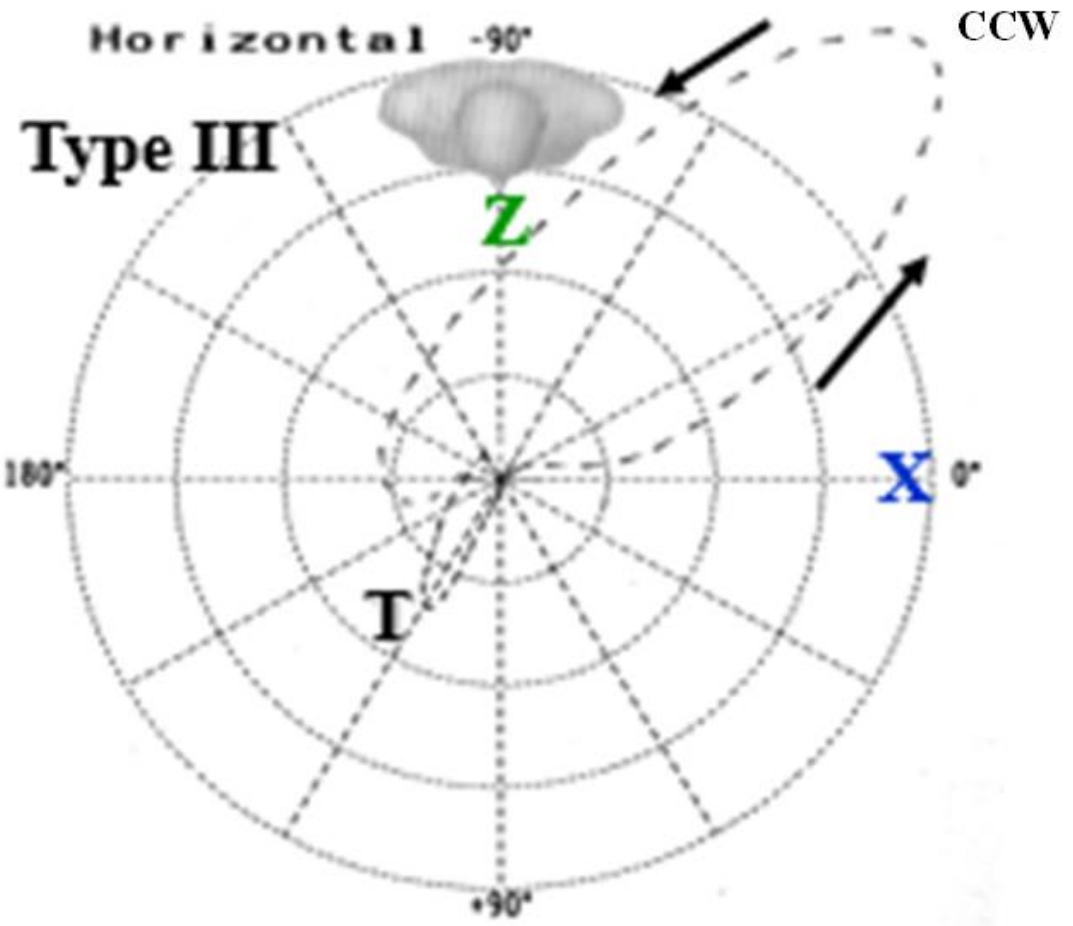


Figure 35. Type III: This is the variant frequently found in LVH and high blood pressure characterized by initial vectors heading to the right and discretely to the front, counterclockwise rotation (CCW) (inverted) simulating anterolateral myocardial infarction. Narrow aspect and QRS loop located mostly in the left posterior quadrant. T loop opposite: located in the anterior right quadrant.

VCG differential diagnosis between type III LVH from Anterolateral Myocardial Infarction

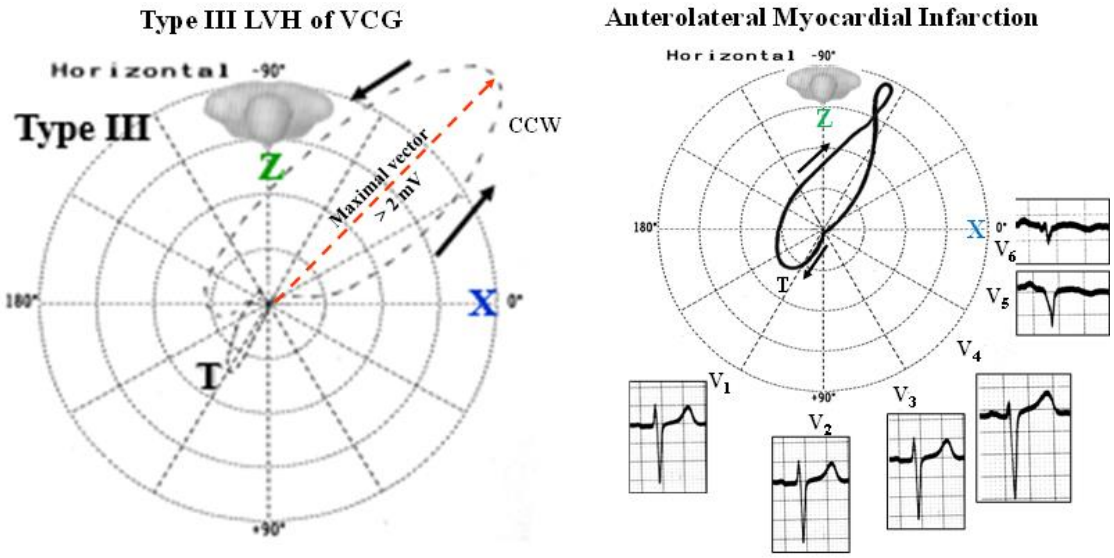


Figure 36. VCG differential diagnosis between type III LVH from Anterolateral Myocardial Infarction.

QRS loop with CCW rotation LV Maximal Vector >2 mV Rs pattern in the left leads	QRS loop with CW rotation LV Maximal Vector <2 mV QS or Qr pattern in the left leads

Left Ventricular Hypertrophy vectorcardiographic type IV. ECG/VCG correlation V1-V6

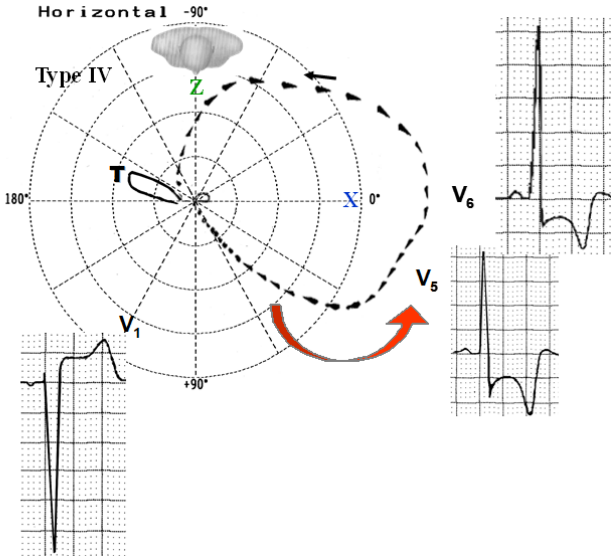


Figure 37. Initial vectors of QRS loop heading to the front and the left; QRS loop more anterior and predominantly located in the left anterior quadrant; Increased voltage of maximal vector; Final vectors located to the right and backward with the ST/T vector in the right posterior quadrant; E point not matching 0 point and located backward and to the right of the latter

Left Ventricular Hypertrophy, vectorcardiographic type IV

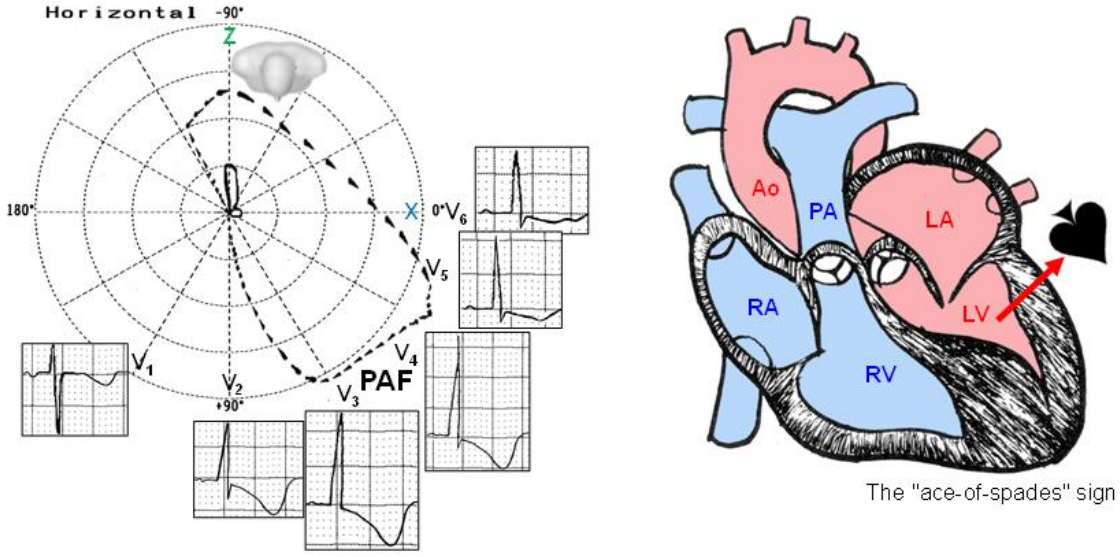


Figure 38. Clinical diagnosis: non-obstructive apical hypertrophic cardiomyopathy of the inferior and apical region of the septum. ECG/VCG diagnosis: LVH type IV: Prominent QRS loop Anterior Forces (PAF). The QRS-loop is located predominantly in the left anterior quadrant. The initial 10 to 20 ms forces without convexity to the right. The R waves are predominant across precordial leads. The T loop is located in the posterior quadrants on orthogonal Z line; consequently, T waves are negative, deep and giant in precordial leads.

ECG LVH typical of Non-obstructive Apical Hypertrophic Cardiomyopathy

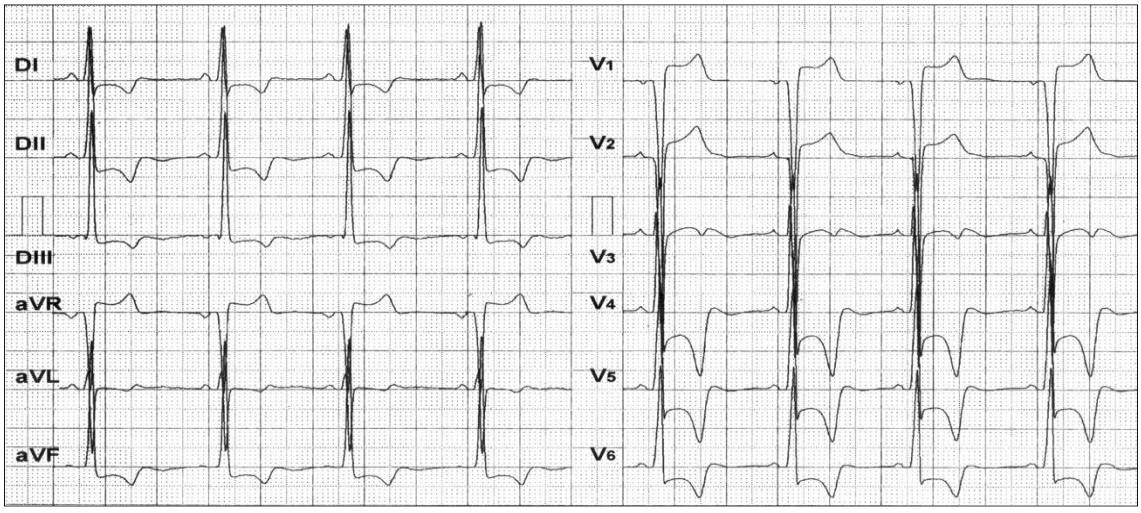


Figure 39. Clinical diagnosis: Non-obstructive Apical Hypertrophic Cardiomyopathy. Apical portion of the septum with 32 mm of diastolic thickness. ECG diagnosis: LAE. LVE: systolic pattern by important alteration secondary to ventricular repolarization in anterolateral and inferior wall. This pattern corresponds to type IV VCG pattern.

VCG LVH typical of Non-obstructive Apical Hypertrophic Cardiomyopathy

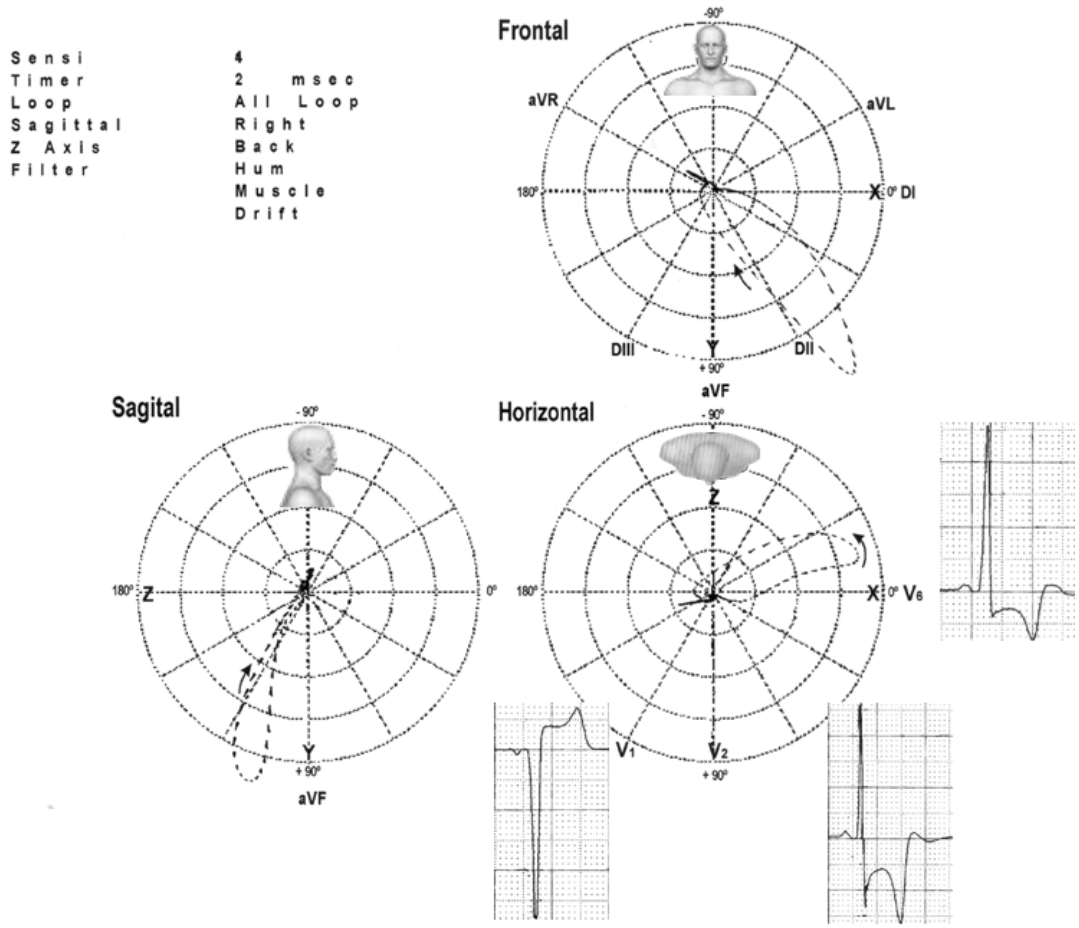


Figure 40. VCG: LVE type IV in a patient with non-obstructive apical hypertrophic cardiomyopathy. Note giant negative T waves and significant ST segments depression from V4 to V6 and ST segment elevation in V1.

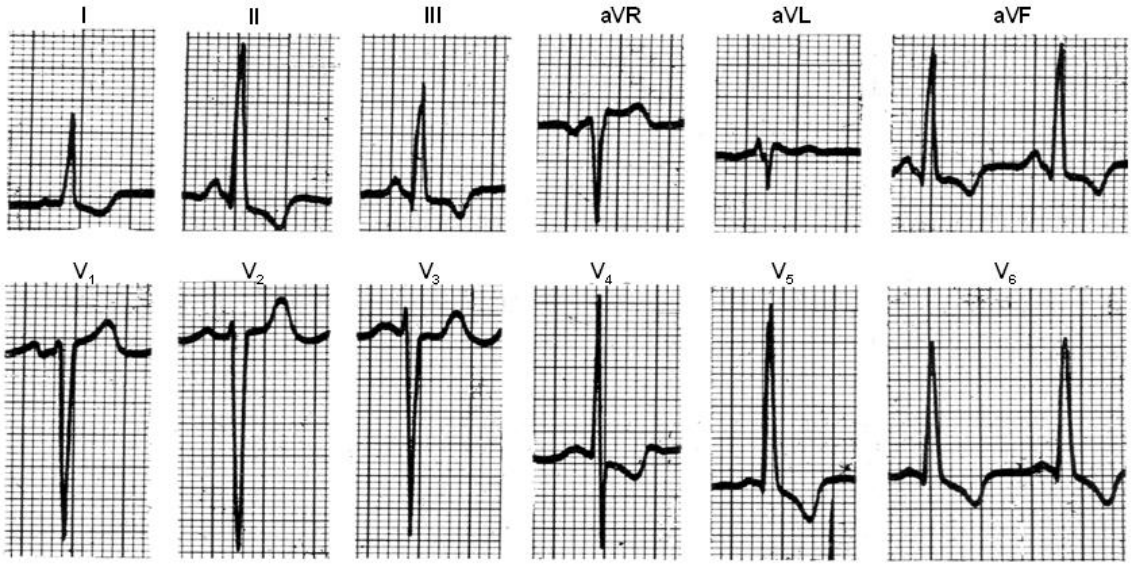


Figure 41. ECG diagnosis: LVH systolic pattern, voltage criteria present: R or S ≥30 mm in the HP or 20 mm in the FP. SÂQRS not deviated and near $+50^0$: ST-T vector opposite to QRS complex; "strain pattern".

Systolic LVH associated with Rosenbaum's type IV LAFB

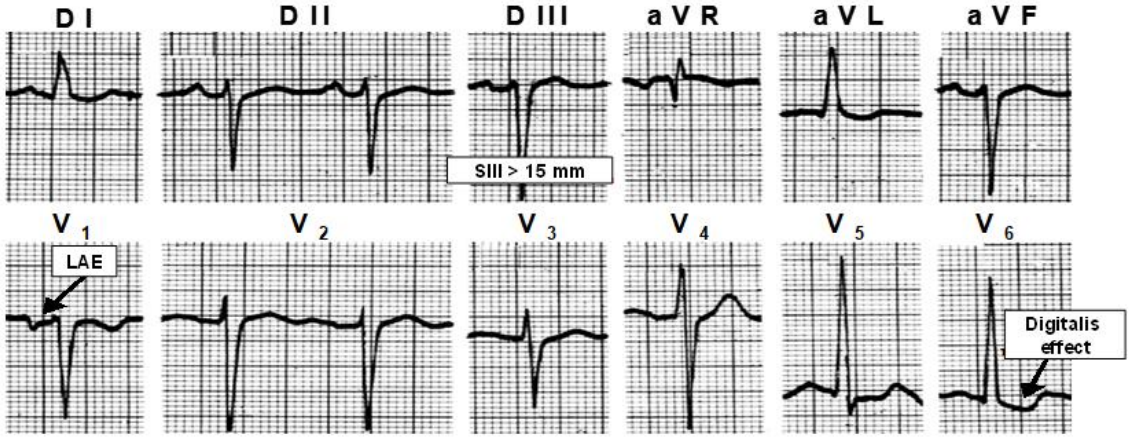


Figure 42. ECG diagnosis: There are criteria of left atrial enlargement (final negative P-wave component deep and slow), extreme QRS left axis deviation on FP (QRS axis -60°), SIII > SII (SIII >15 mm: Rosenbaum's type IV LAFB): T wave possibly inverted in one or more of the left leads in I, V5 and V6. Short QT interval and "spoon" aspect of ST segment in V6 (digitalis effect).

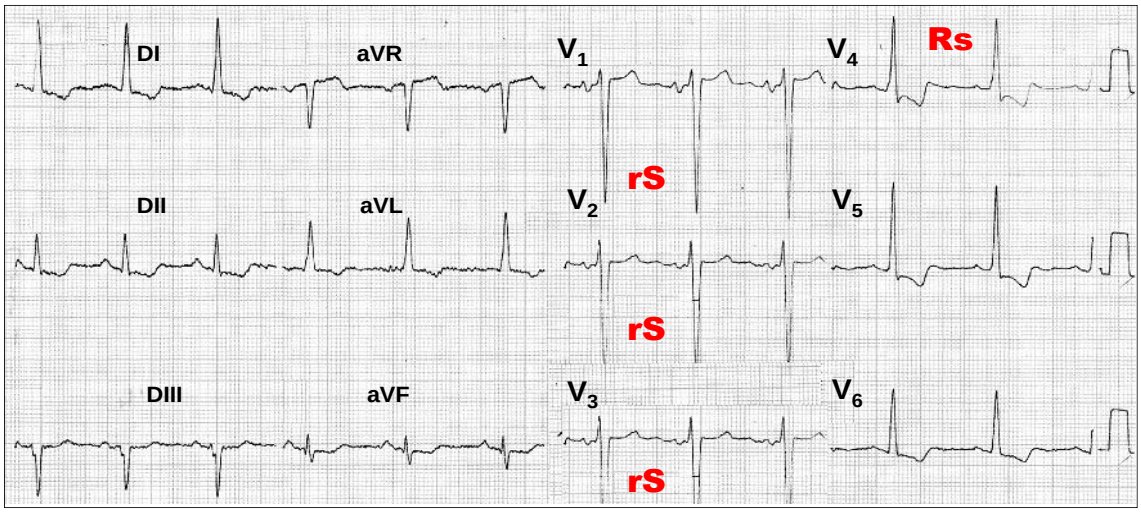


Figure 43. Clinical diagnosis: obstructive hypertrophic cardiomyopathy. ECG diagnosis: Sinus rhythm, left atrial enlargement, QRS axis 0°, sudden shift from rS type to Rs type complexes with no recording of transitional R/S. The phenomenon occurs by posterior dislocation of QRS loop in the HP. Systolic or strain pattern of ventricular repolarization.

Athletic heart with physiological LVH

Almost all athletes with physiological LVH have concomitant enlargement of the left ventricular cavity. Typical values of left ventricular cavity size in athletes with LVH range between 55 and 65 mm,(**Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes, Ann Intern Med, 1999, vol. 130 (pg. 23-31**) ~10% of athletes with LVH exhibit normal left ventricular cavity size. Clinical features indicative of pathological left ventricular hypertrophy in the assessment of an athlete with a left ventricular wall thickness between 13 and 16 mm

I. **Symptoms:** Unexplained syncope—particularly during exercise, palpitations, shortness of breath disproportionate to the exercise performed, dizziness, chest pain
II. **Family history:** HCM in a first-degree relative in an athlete with LVH should raise the suspicion of HCM, because the disorder is inherited as an autosomal dominant trait. (Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. American College of Cardiology/European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy:

a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines, J Am Coll Cardiol, 2003, vol. 42 (pg. 1687-713))

III. **Demographic:** Age <16 years old, female sex, participation in purely isometric sport, small body surface area

IV. **Echocardiographic:** Left ventricular wall thickness >16 mm, asymmetrical septal hypertrophy, small left ventricular cavity diameter in end-diastole, presence of systolic anterior motion of the mitral valve leaflet and associated left ventricular outflow obstruction, abnormal indices of diastolic function.

V. **12-leads ECG:** Pathological Q-waves, ST segment depression, T-wave inversions in the lateral/inferior leads, Left bundle branch block Role of 12-lead ECG, cardiopulmonary exercise stress testing, and cardiac magnetic resonance imagingThe cause of LVH in an athlete may remain equivocal despite thorough echocardiographic evaluation. Enormous advances in the molecular genetics of HCM in the past two decades raise the potential role of genetic testing to resolve the diagnostic dilemma. Unfortunately, the condition exhibits marked genetic heterogeneity with over 200 mutations in 12 different genetic loci and is time consuming, labour-intensive, and expensive. 16 The results of genetic testing are not available to the athlete in a timely fashion and the diagnostic yield is only 60–70%, therefore a negative gene test does not exclude HCM. 34 In the current era, differentiation between physiological LVH and HCM continues to rely on non-invasive clinical investigations aimed at identifying the broader phenotype of HCM. Information obtained from a 12-lead ECG, cardiopulmonary exercise testing, and cardiac MRI provides invaluable adjunctive information (*Table 1*). With respect to the 12-lead ECG, although both physiological LVH and HCM are associated with large QRS complexes in left ventricular leads, the additional presence of ST segment depression, deep (more than −0.2 mV) T-wave inversions in the lateral or inferior leads, pathological Q-waves, and left bundle branch block are highly indicative of HCM.(**Ryan MCJ, Fench J, Joshi J, Choudhury L, Chojnowska L, Michalak E, et al. The standard electrocardiogram as a screening test for hypertrophic cardiomyopathy, Am J Cardiol, 1995, vol. 76 (pg. 689-94)**(**Savage DD, Seides SF, Clark CE, et al. Electrocardiographic findings in patients with obstructive and non-obstructive hypertrophic cardiomyopathy, Circulation, 1978, vol. 58 (pg. 402**-8) The identification of deep T-wave inversions in the

anterior and/or lateral leads is a recognized feature of apical HCM (**Montgomery JV, Harris KM, Casey SA, Zenovich AG, Maron BJ. Relation of electrocardiographic patterns to phenotypic expression and clinical outcome in hypertrophic cardiomyopathy, Am J Cardiol, 2005, vol. 96 (pg. 270-5)** and should prompt detailed assessment of the left ventricular apex at echocardiography, employing the use of a contrast agent to define the endocardial borders if necessary. (**Thanigaraj SPJ. Apical hypertrophic cardiomyopathy: echocardiographic diagnosis with the use of intravenous contrast image enhancement, J Am Soc Echocardiogr, 2000, vol. 13 (pg. 146-9)** In this regard, additional imaging with cardiac magnetic resonance will provide better definition of the left ventricular apex and also prove useful in the demonstration of LVH affecting the antero-lateral free wall (which may not be visualized clearly at echocardiography). (**Moon JCFN, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography, Heart, 2004, vol. 90 (pg. 645-9)** Gadolinium enhanced magnetic resonance may identify myocardial fibrosis in the left ventricle in some affected individuals with HCM. (**Popović ZB, Kwon DH, Mishra M, Buakhamsri A, Greenberg NL, Thamilarasan M, et al. Association between regional ventricular function and myocardial fibrosis in hypertrophic cardiomyopathy assessed by speckle tracking echocardiography and delayed hyper-enhancement magnetic resonance imaging, J Am Soc Echocardiogr, 2008, vol. 21 (pg. 1299-305)**)The measurement of peak oxygen consumption during an exercise test is a useful method of differentiating physiological LVH from HCM. Athletes, participating in endurance sports have large peak oxygen consumption. A peak oxygen consumption of >50 mL/kg/min (or >120% of that predicted for age) in an athlete with mild LVH favours physiological adaptation.(**Sharma S, Elliott PM, Whyte G, Mahon N, Virdee MS, Mist B, et al. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes, J Am Coll Cardiol, 2000, vol. 36 (pg. 864-70)** In contrast, most individuals with HCM have a sub-normal peak oxygen consumption irrespective of the magnitude of LVH and functional capacity, since the combination of impaired myocardial relaxation associated with a small left ventricular cavity, exercise related myocardial ischaemia, and dynamic left ventricular outflow obstruction is not conducive to the

generation of large and sustained increase in stroke volume (and therefore cardiac output). By virtue of the diversity of the morphological and functional manifestations of HCM, there is no single investigation that will identify all athletes with HCM and diagnostic uncertainty may persist despite a plethora of cardiac investigations. In these circumstances, it is our practice to attempt to persuade the athlete to detrain for 3 months followed by echocardiographic reassessment to ensure an accurate diagnosis, on the understanding that physiological LVH should regress completely back to normal, whereas pathological LVH will persist, **(Pelliccia A, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F. Remodelling of left ventricular hypertrophy in elite athletes after long-term de-conditioning, Circulation, 2002, vol. 105 (pg. 944-9)(Basavarajaiah SWM, Junagde S, Jackson G, Whyte G, Sharma S, Roberts WO. Physiological left ventricular hypertrophy or hypertrophic cardiomyopathy in an elite adolescent athlete: role of detraining in resolving the clinical dilemma, Br J Sports Med, 2006, vol. 40 (pg. 727-9)** albeit to a lesser extent. The detraining process is understandably associated with anxiety, and costs fitness and future team selection; however, it could be argued that it is a relatively small price to pay given the risks involved with on-going participation in strenuous exercise in an individual with HCM. ECG is used to screen for LVH, but common ECG-LVH criteria have been found less effective in athletes. Hedman et al. evaluated the value of ECG for identifying athletes with LVH or a concentric cardiac phenotype. A retrospective analysis of 196 male Division I college athletes routinely screened with ECG and echocardiography within the Stanford Athletic Cardiovascular Screening Program was performed. LV mass and volume were determined using echocardiography. LVH was defined as LV mass (LVM) >102 g/m²; a concentric cardiac phenotype as LVM-to-volume (M/V) ≥1.05 g/mL. Twelve-lead ECGs including high-resolution time intervals and QRS voltages were obtained. Thirty-seven previously published ECG-LVH criteria were applied, of which the majority have never been evaluated in athletes.

37 ECG used for Detecting Left Ventricular Hypertrophy

	Ia. Limb lead(s)	Ib. Precordial lead(s)
Single lead	• R I >15 mm	• S V1 >23 mm

	• R aVL >11 mm • R aVF >20 mm • Q or S aVR >19 mm R or S in any limb lead >19 mm	• S V2 >25 mm • R V5 >33 mm • R V6 >25 mm • R in any precordial lead >26 mm • R + S in any precordial lead >35 mm
Multiple leads	• R I + S III >25 mm • (R I - S I) + (S III - R III) >16 mm	• S V1 + R V5 >35 mm • S V1 + R V5/V6 >35 mm • S V2 + R V4/V5 >45 mm • S V2 + R V5/V6 >45 mm • S V1/V2 + R V6 >40 mm • S V1/V2 + R V5/V6 >35 mm • R V5/V6 >26 mm • R V6 : V5-ratio >1.0 • Either of: S V1 >23 mm; R V5 >33 mm; R V6 >25 mm

Ic. Limb + Precordial leads

- R aVL + S V3 >28 mm (males); >20 mm (females)
- R aVL + S V3 adjusted for BMI/age >28 mm (males); >20 mm (females)
- Sum of QRS in aVF, V2, V6 >93 mm (≤30 years); >59 mm (>30 years)
- Sum of (R+[S or Q]) in all 12 leads ≥179 mm
- Sum of (max of Q, R or S) in all 12 leads ≥179 mm
- Max S any lead + S V4 ≥28 mm (males), ≥23 mm (females)
- Either of: R aVL >11 mm; S V1+R V5 >35 mm; R V5/V6 >26 mm
- Either of: R aVL >12 mm; R I/II/III/aVF >20 mm; R V5/V6 >26 mm

II. **Including QRS-duration**
• QRS-duration >114 ms (males); >97 ms (females)
• (R aVL + S V3) * QRS-dur, ≥2436 mm/ms
• Sum of (R+[S or Q]) in all 12 leads * QRS-duration ≥17472 mm/ms
• Sum of (max of Q, R or S) in all 12 leads * QRS-duration ≥17472 mm/ms
IV. LV mass Equation
• Rautaharju LV mass Equation

Figure 1 Summary of the 37 different ECG criteria for detecting LVH applied in the 196 male athletes of the current report.

C-statistics, including area under the receiver operating curve (AUC) and likelihood ratios were calculated. ECG lead voltages were poorly associated with LVM (r = 0.18-0.30) and M/V (r = 0.15-0.25). The proportion of athletes with ECG-LVH was 0%-74% across criteria, with sensitivity and specificity ranging between 0% and 91% and 27% and 99.5%, respectively. The average AUC of the criteria in identifying the 11 athletes with LVH was 0.57 (95% confidence interval [CI] 0.56-0.59), and the average AUC for identifying the 8 athletes with a concentric phenotype was 0.59 (95% CI 0.56-0.62). The authors concluded that the diagnostic capacity of all ECG-LVH criteria were inadequate and, therefore, not clinically useful in screening for LVH or a concentric phenotype in athletes. This is probably due to the weak association between LVM and ECG voltage. None of the 37 major evaluated ECG criteria were clinically useful in detecting LVH in athletes. This challenges the common belief among physicians that ECG voltage is correlated to left ventricular mass (LVM).These findings could impact how physicians involved in the clinical care of athletes interpret and evaluate the athletes' ECG in regard to LVH.(**Kristofer Hedman 1, Kegan J Moneghetti 2, David Hsu 2, Jeffrey W Christle 2, Alessandro Patti 3, Euan Ashley 2, David Hadley 4, Francois Haddad 5, Victor Froelicher 2Limitations of Electrocardiography for Detecting Left Ventricular Hypertrophy or Concentric Remodeling in AthletesAm J Med. 2020 Jan;133(1):123-132.e8. doi: 10.1016/j.amjmed.2019.06.028**.)

VI. Cardiopulmonary exercise testing Peak $V_{O2\ max}$ <50mL/kg/min or <120% of predicted maximum.

VII. CMRI; Demonstration of apical hypertrophy, demonstration of significant myocardial fibrosis with gadolinium enhancement

VIII. Detraining Failure of regression of left ventricular hypertrophy

REFERENCES

1. Abbott-Smith, C. W. and T. C. Chou (1970). "Vectorcardiographic criteria for the diagnosis of left ventricular hypertrophy." Am Heart J **79**(3): 361-369.
2. Anderson, L., D. Exeter and L. Bowyer (2012). "Sudden cardiac death: mandatory exclusion of athletes at risk is a step too far." Br J Sports Med **46**(5): 331-334.
3. Boles, U., I. Almuntaser, A. Brown, R. R. Murphy, A. Mahmud and J. Feely (2010). "Ventricular activation time as a marker for diastolic dysfunction in early hypertension." Am J Hypertens **23**(7): 781-785.
4. Bonow, R. O. (2011). "Surgical ventricular reconstruction for heart failure: is there life after STICH?" JACC Cardiovasc Imaging **4**(7): 771-773.
5. Bonow, R. O. and T. A. Holly (2011). "Myocardial viability testing: still viable after stich?" J Nucl Cardiol **18**(6): 991-994.
6. Bonow, R. O., G. Maurer, K. L. Lee, T. A. Holly, P. F. Binkley, P. Desvigne-Nickens, J. Drozdz, P. S. Farsky, A. M. Feldman, T. Doenst, R. E. Michler, D. S. Berman, J. C. Nicolau, P. A. Pellikka, K. Wrobel, N. Alotti, F. M. Asch, L. E. Favaloro, L. She, E. J. Velazquez, R. H. Jones, J. A. Panza and S. T. Investigators (2011). "Myocardial viability and survival in ischemic left ventricular dysfunction." N Engl J Med **364**(17): 1617-1625.
7. Bottini, P. B., A. A. Carr, L. M. Prisant, F. W. Flickinger, J. D. Allison and J. S. Gottdiener (1995). "Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient." Am J Hypertens **8**(3): 221-228.
8. Buchner, S., K. Debl, J. Haimerl, B. Djavidani, F. Poschenrieder, S. Feuerbach, G. A. Riegger and A. Luchner (2009). "Electrocardiographic diagnosis of left ventricular hypertrophy in aortic valve disease: evaluation of ECG criteria by cardiovascular magnetic resonance." J Cardiovasc Magn Reson **11**: 18.
9. Cabrera, E. and J. R. Monroy (1952). "Systolic and diastolic loading of the heart. II. Electrocardiographic data." Am Heart J **43**(5): 669-686.
10. Casale, P. N., R. B. Devereux, P. Kligfield, R. R. Eisenberg, D. H. Miller, B. S. Chaudhary and M. C. Phillips (1985). "Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria." J Am Coll Cardiol **6**(3): 572-580.

11. Chan, P. G., M. Logue and P. Kligfield (2006). "Effect of right bundle branch block on electrocardiographic amplitudes, including combined voltage criteria used for the detection of left ventricular hypertrophy." Ann Noninvasive Electrocardiol **11**(3): 230-236.
12. Corrado, D., C. Basso and G. Thiene (2012). "Sudden cardiac death in athletes: what is the role of screening?" Curr Opin Cardiol **27**(1): 41-48.
13. Cuspidi, C., S. Meani, C. Valerio, V. Fusi, C. Sala, M. Maisaidi and A. Zanchetti (2006). "Effects of angiotensin II receptor blockade-based therapy with losartan on left ventricular hypertrophy and geometry in previously treated hypertensive patients." Blood Press **15**(2): 107-115.
14. Cuspidi, C., S. Meani, C. Valerio, V. Fusi, C. Sala and A. Zanchetti (2006). "Left ventricular hypertrophy and cardiovascular risk stratification: impact and cost-effectiveness of echocardiography in recently diagnosed essential hypertensives." J Hypertens **24**(8): 1671-1677.
15. Devereux, R. B., R. Kramer-Fox, W. T. Brown, M. K. Shear, N. Hartman, P. Kligfield, E. M. Lutas, M. C. Spitzer and S. D. Litwin (1986). "Relation between clinical features of the mitral prolapse syndrome and echocardiographically documented mitral valve prolapse." J Am Coll Cardiol **8**(4): 763-772.
16. Erice, B., C. Romero, M. Anderiz, E. Gorostiaga, M. Izquierdo and J. Ibanez (2009). "Diagnostic value of different electrocardiographic voltage criteria for hypertrophic cardiomyopathy in young people." Scand J Med Sci Sports **19**(3): 356-363.
17. Goldberger, J. J. (2006). "Atrial fibrillation ablation: location, location, location." J Cardiovasc Electrophysiol **17**(12): 1271-1273.
18. Goldberger, J. J. (2006). "Unraveling the mysteries of the AV node." Heart Rhythm **3**(9): 1001-1002.
19. Hugenholtz, P. G., T. J. Ryan, T. Woerner and H. D. Levine (1963). "Recognition of anterior wall infarction in patients with left ventricular hypertrophy. A study by the Frank vector-cardiogram." Circulation **27**: 386-396.
20. Kafka, H., G. W. Burggraf and J. A. Milliken (1985). "Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block: an echocardiographic study." Am J Cardiol **55**(1): 103-106.
21. Klein, R. C., Z. Vera, A. N. DeMaria and D. T. Mason (1984). "Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of left bundle branch block." Am Heart J **108**(3 Pt 1): 502-506.
22. Leibowitz, D., D. Planer, F. Ben-Ibgi, D. Rott, A. T. Weiss and M. Bursztyn (2007). "Measurement of wall thickness alone does not accurately assess the presence of left ventricular hypertrophy." Clin Exp Hypertens **29**(2): 119-125.
23. Levy, D., R. J. Garrison, D. D. Savage, W. B. Kannel and W. P. Castelli (1990). "Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study." N Engl J Med **322**(22): 1561-1566.
24. Levy, D., S. B. Labib, K. M. Anderson, J. C. Christiansen, W. B. Kannel and W. P. Castelli (1990). "Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy." Circulation **81**(3): 815-820.
25. Levy, D., P. W. Wilson, K. M. Anderson and W. P. Castelli (1990). "Stratifying the patient at risk from coronary disease: new insights from the Framingham Heart Study." Am Heart J **119**(3 Pt 2): 712-717; discussion 717.

26. Manyari, D. E. (1990). "Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study." N Engl J Med **323**(24): 1706-1707.
27. Molloy, T. J., P. M. Okin, R. B. Devereux and P. Kligfield (1992). "Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product." J Am Coll Cardiol **20**(5): 1180-1186.
28. Morris, J. J., Jr., E. H. Estes, Jr., R. E. Whalen, H. K. Thompson, Jr. and H. D. McIntosh (1964). "P-Wave Analysis in Valvular Heart Disease." Circulation **29**: 242-252.
29. Okin, P. M., R. B. Devereux, K. E. Harris, S. Jern, S. E. Kjeldsen, S. Julius, J. M. Edelman, B. Dahlof and L. S. Investigators (2007). "Regression of electrocardiographic left ventricular hypertrophy is associated with less hospitalization for heart failure in hypertensive patients." Ann Intern Med **147**(5): 311-319.
30. Okin, P. M., R. B. Devereux, S. Jern, S. E. Kjeldsen, S. Julius, M. S. Nieminen, S. Snapinn, K. E. Harris, P. Aurup, J. M. Edelman, H. Wedel, L. H. Lindholm, B. Dahlof and L. S. Investigators (2004). "Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events." JAMA **292**(19): 2343-2349.
31. Okin, P. M., R. B. Devereux, J. E. Liu, L. Oikarinen, S. Jern, S. E. Kjeldsen, S. Julius, K. Wachtell, M. S. Nieminen and B. Dahlof (2004). "Regression of electrocardiographic left ventricular hypertrophy predicts regression of echocardiographic left ventricular mass: the LIFE study." J Hum Hypertens **18**(6): 403-409.
32. Okin, P. M., R. B. Devereux, M. S. Nieminen, S. Jern, L. Oikarinen, M. Viitasalo, L. Toivonen, S. E. Kjeldsen, S. Julius, S. Snapinn, B. Dahlof and L. S. Investigators (2004). "Electrocardiographic strain pattern and prediction of cardiovascular morbidity and mortality in hypertensive patients." Hypertension **44**(1): 48-54.
33. Okin, P. M., M. J. Roman, E. T. Lee, J. M. Galloway, B. V. Howard and R. B. Devereux (2004). "Combined echocardiographic left ventricular hypertrophy and electrocardiographic ST depression improve prediction of mortality in American Indians: the Strong Heart Study." Hypertension **43**(4): 769-774.
34. Oreto, G., F. Saporito, F. Messina, S. Lanteri and F. Luzza (2007). "[Electrocardiographic diagnosis of left ventricular hypertrophy in the presence of intraventricular conduction disturbances]." G Ital Cardiol (Rome) **8**(3): 161-167.
35. Peguero, J. G., S. Lo Presti, J. Perez, O. Issa, J. C. Brenes and A. Tolentino (2017). "Electrocardiographic Criteria for the Diagnosis of Left Ventricular Hypertrophy." J Am Coll Cardiol **69**(13): 1694-1703.
36. Pewsner, D., P. Juni, M. Egger, M. Battaglia, J. Sundstrom and L. M. Bachmann (2007). "Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review." BMJ **335**(7622): 711.
37. Rautaharju, P. M., L. Park, F. S. Rautaharju and R. Crow (1998). "A standardized procedure for locating and documenting ECG chest electrode positions: consideration of the effect of breast tissue on ECG amplitudes in women." J Electrocardiol **31**(1): 17-29.
38. Rautaharju, P. M., L. P. Park, B. R. Chaitman, F. Rautaharju and Z. M. Zhang (1998). "The Novacode criteria for classification of ECG abnormalities and their

clinically significant progression and regression." J Electrocardiol **31**(3): 157-187.
39. Rodriguez-Padial, L. and L. Bacharova (2012). "Electrical remodeling in left ventricular hypertrophy-is there a unifying hypothesis for the variety of electrocardiographic criteria for the diagnosis of left ventricular hypertrophy?" J Electrocardiol **45**(5): 494-497.
40. Rodriguez-Padial, L., B. Rodriguez-Picon, M. Jerez-Valero, J. Casares-Medrano, F. O. Akerstrom, A. Calderon, V. Barrios, A. Sarria-Santamera, J. R. Gonzalez-Juanatey, A. Coca, J. Andres and J. Ruiz-Baena (2012). "Diagnostic accuracy of computer-assisted electrocardiography in the diagnosis of left ventricular hypertrophy in left bundle branch block." Rev Esp Cardiol (Engl Ed) **65**(1): 38-46.
41. Romhilt, D. W. and E. H. Estes, Jr. (1968). "A point-score system for the ECG diagnosis of left ventricular hypertrophy." Am Heart J **75**(6): 752-758.
42. Romhilt, D. W., J. C. Greenfield, Jr. and E. H. Estes, Jr. (1968). "Vectorcardiographic diagnosis of left ventricular hypertrophy." Circulation **37**(1): 15-19.
43. Schwartz, P. J. and D. Corrado (2012). "Sudden cardiac death in young competitive athletes." Eur Heart J **33**(16): 1986-1988.
44. Sokolow, M. and T. P. Lyon (1949). "The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads." Am Heart J **37**(2): 161-186.
45. Talbot, S., D. Kilpatrick, A. Jonathan and M. J. Raphael (1977). "QRS voltage of the electrocardiogram and Frank vectorcardiogram in relation to ventricular volume." Br Heart J **39**(10): 1109-1113.
46. Thorolfsson, B., F. R. Thordardottir, G. T. Gunnarsson and A. F. Sigurdsson (2012). "[Screening for risk factors of sudden cardiac death in young athletes]." Laeknabladid **98**(2): 83-88.
47. Thygesen, K., J. S. Alpert, H. D. White and E. S. C. A. A. H. A. W. H. F. T. F. f. t. R. o. M. I. Joint (2007). "Universal definition of myocardial infarction." Eur Heart J **28**(20): 2525-2538.
48. Thygesen, K., J. S. Alpert, H. D. White and E. S. C. A. A. H. A. W. H. F. T. F. f. t. R. o. M. I. Joint (2007). "Universal definition of myocardial infarction." J Am Coll Cardiol **50**(22): 2173-2195.
49. Thygesen, K., J. S. Alpert, H. D. White, E. S. C. A. A. H. A. W. H. F. T. F. f. t. R. o. M. I. Joint, A. S. Jaffe, F. S. Apple, M. Galvani, H. A. Katus, L. K. Newby, J. Ravkilde, B. Chaitman, P. M. Clemmensen, M. Dellborg, H. Hod, P. Porela, R. Underwood, J. J. Bax, G. A. Beller, R. Bonow, E. E. Van der Wall, J. P. Bassand, W. Wijns, T. B. Ferguson, P. G. Steg, B. F. Uretsky, D. O. Williams, P. W. Armstrong, E. M. Antman, K. A. Fox, C. W. Hamm, E. M. Ohman, M. L. Simoons, P. A. Poole-Wilson, E. P. Gurfinkel, J. L. Lopez-Sendon, P. Pais, S. Mendis, J. R. Zhu, L. C. Wallentin, F. Fernandez-Aviles, K. M. Fox, A. N. Parkhomenko, S. G. Priori, M. Tendera, L. M. Voipio-Pulkki, A. Vahanian, A. J. Camm, R. De Caterina, V. Dean, K. Dickstein, G. Filippatos, C. Funck-Brentano, I. Hellemans, S. D. Kristensen, K. McGregor, U. Sechtem, S. Silber, M. Tendera, P. Widimsky, J. L. Zamorano, J. Morais, S. Brener, R. Harrington, D. Morrow, M. Lim, M. A. Martinez-Rios, S. Steinhubl, G. N. Levine, W. B. Gibler, D. Goff, M. Tubaro, D. Dudek and N. Al-Attar (2007). "Universal definition of myocardial infarction." Circulation **116**(22): 2634-2653.

50. Varriale, P., J. Alfenito and R. J. Kennedy (1966). "The simultaneous occurrence of ventricular pre-excitation, left bundle branch block, and delayed A-V conduction." Am Heart J **71**(6): 803-806.
51. Varriale, P., J. C. Alfenito and R. J. Kennedy (1966). "The vectorcardiogram of left ventricular hypertrophy. Analysis and criteria (Frank Lead system)." Circulation **33**(4): 569-576.
52. Verdecchia, P., F. Angeli, C. Borgioni, R. Gattobigio, G. de Simone, R. B. Devereux and C. Porcellati (2003). "Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: a meta-analysis." Am J Hypertens **16**(11 Pt 1): 895-899.
53. Verdecchia, P., F. Angeli, G. Reboldi, E. Carluccio, G. Benemio, R. Gattobigio, C. Borgioni, M. Bentivoglio, C. Porcellati and G. Ambrosio (2003). "Improved cardiovascular risk stratification by a simple ECG index in hypertension." Am J Hypertens **16**(8): 646-652.
54. Verdecchia, P., G. Schillaci, C. Borgioni, A. Ciucci, R. Gattobigio, I. Zampi and C. Porcellati (1998). "Prognostic value of a new electrocardiographic method for diagnosis of left ventricular hypertrophy in essential hypertension." J Am Coll Cardiol **31**(2): 383-390.
55. Verdecchia, P., G. Schillaci, C. Borgioni, A. Ciucci, R. Gattobigio, I. Zampi, G. Reboldi and C. Porcellati (1998). "Prognostic significance of serial changes in left ventricular mass in essential hypertension." Circulation **97**(1): 48-54.
56. Verdecchia, P., P. Sleight, F. Avanzini, G. de Simone, S. Pede, F. Perticone, G. Schillaci, D. Vanuzzo, F. Angeli, G. P. Reboldi and A. P. Maggioni (2003). "Hypertrophy at ECG and its regression during treatment survey (HEART survey). Rationale, design and baseline characteristics of patients." Ital Heart J **4**(7): 479-483.
57. Vine, D. L., R. N. Finchum, H. T. Dodge, W. H. Bancroft, Jr. and D. C. Hurst (1971). "Comparison of the vectorcardiogram with the electrocardiogram in the prediction of left ventricular size." Circulation **43**(4): 547-558.
58. Wheeler, M. T., P. A. Heidenreich, V. F. Froelicher, M. A. Hlatky and E. A. Ashley (2010). "Cost-effectiveness of preparticipation screening for prevention of sudden cardiac death in young athletes." Ann Intern Med **152**(5): 276-286.