Left Ventricular Hypertrophy in Patients with Coronary Artery Disease

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Abstract:

Coronary artery disease is the most common cause of death in the general population. Left ventricular hypertrophy (LVH) is an independent risk factor for CV events.

Keywords: Left Ventricular Hypertrophy, Coronary Artery Disease, LVH.

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Introduction

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 **(1).**

Etiology

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

1. Essential 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**(1).**

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**(2)**

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 **(3)**.

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**(1)**

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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. 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**(1)**.

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(**4**).

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. Regression analysis also showed that the most important element was angiotensin II levels, which appears closely related in part to stimulation of myocardial fibrosis**(1)**.

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**(5)**.

Evaluation

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. Various criteria for LVH by ECG have been suggested over the years. Most criteria utilize the voltage in one or more leads, QRS duration, secondary ST-T wave abnormalities, or left atrial abnormalities.

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 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. While electrocardiography is not sensitive and cannot be used to definitively exclude the diagnosis of LVH, it still plays a diagnostic and management role**(6)**

Voltage Criteria

Limb Leads

- R wave in lead I + S wave in lead III > 25 mm
- R wave in aVL > 11 mm
- R wave in aVF > 20 mm
- S wave in aVR > 14 mm

Precordial Leads

- R wave in V4, V5 or V6 > 26 mm
- R wave in V5 or V6 plus S wave in V1 > 35 mm
- Largest R wave plus largest S wave in precordial leads > 45 mm **(7).**

Non-Voltage Criteria

- Increased R wave peak time > 50 ms in leads V5 or V6
- ST segment depression and T wave inversion in the left-sided leads: *AKA the left ventricular 'strain' pattern* **(8).**

An Echocardiogram

Echo 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 **(9)**.

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 **(10)**.

2D-LV mass

It was obtained using the ASE/EACVI-recommended formula for the estimation of LV mass from LV linear dimensions based on modeling the left ventricle as a prolate ellipse of revolution: **LV mass (g) = 0.8(1.04(LVIDD + IVST + PWT)3 LVIDD3) + 0.6** where LVIDD is LV internal end-diastolic dimension, IVST is the end-diastolic interventricular septal wall thickness, and PWT is end-diastolic LV posterior wall thickness**(11)** .

Left Ventricular Mass Index

Left ventricular mass is an important determinant of diagnosis and prognosis in patients with heart disease (cardiovascular morbidity and mortality) in specific for determination of severity and type of cardiac hypertrophy. The formulas used are the following:

- **LV Mass** = 0.8 x (1.04 x (((LVEDD + IVSd +PWd)^3 - LVEDD^3))) + 0.6
- **LVMI (LV Mass Indexed to Body Surface Area)** = LV Mass / BSA
- **RWT (Relative Wall Thickness)** = 2 x PWd / LVEDD

For BSA, Mosteller's formula is employed: BSA = (((Height in cm) x (Weight in kg))/ 3600) ^{½} **(12)**

Relative wall thickness (RWT) allows classification of LV mass increase as either:

- Concentric hypertrophy (RWT >0.42);
- Eccentric hypertrophy (RWT ≤0.42).**(13)**

Cardiac magnetic resonance imaging (MRI)

CMR 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.

LV wall-thickness measured from an end-diastolic cine image in the short-axis plane is the most commonly used measurement to define and quantify LVH. Normal LV myocardial thickness is <11 mm.5 LVH is considered mild if it measures 11-13 mm, moderate if it measures 14-15 mm, and severe if it measures >15 mm. LVH can also be defined and quantified in terms of absolute and BSA-indexed LV mass values, with values over the 95th percentile considered abnormal (91 g/m2 in males and 77 g/m2 in females).**(14)**

The late gadolinium enhancement (LGE) sequence is the standard technique used for myocardial tissue characterization.Noncontract enhanced T1 and T2 values, which appears to be more robust than qualitative assessment of signal intensity. Furthermore, contrast-enhanced T1 mapping, in conjunction with the hematocrit value, is useful for calculating the extracellular volume fraction (ECV), a measure of the proportion of extracellular space within the myocardium. An increased ECV is a marker of myocardial remodeling and is most often due to excessive collagen deposition (in the absence of amyloid or edema). The modified look locker (MOLLI) and shortened MOLLI (ShMOLLI) sequences are the most commonly used techniques for acquisition of T1 mapping values. Less applicable in the context of LVH are T2-weighted sequences, which can be used for acquisition of T2 mapping values. Absolute T1 and T2 values for normal LV myocardium vary across different MRI systems and manufacturers. Furthermore, several studies have shown that numerous factors can affect the native T1 relaxation time, including the implemented imaging pulse sequence, magnetic field strength (T1 values increase with increasing field strength), acquisition plane (eg 2-chamber vs 4-chamber); region of myocardium being sampled, and the patient's heart rate, age, and sex. In general, a large native myocardial T1 value is encountered in various disease states that result in edema or fibrosis, and in amyloid deposition. Reduced native T1 relaxation time can be seen in siderosis, Anderson-Fabry disease (AFD), and

fat deposition. T2 relaxation times are increased in disease states associated with myocardial inflammation and edema**(14)**.

Morbidity and Mortality

LVH can be a strong predictor of cardiovascular morbidity and mortality in patients without underlying CAD even after adjusting other major cardiovascular risk factors such as age, smoking, obesity, dyslipidemia, blood pressure, and diabetes. A directly proportional relationship is established between LVH and mortality Moreover, LVH can cause an increase in mortality due to ventricular arrhythmia, and diastolic dysfunction by itself can cause neurohormonal changes predisposing to arrhythmia. Additionally, LVH can be a marker in patients with coronary heart disease who can develop arrhythmia due to atherosclerosis, endothelial dysfunction, or remodeling**(2).**

, so pathologic LVH can be the cause of adverse cardiovascular events. Hence, the need arises to focus on drug development targeted to inhibit its growth.

CAD and LVH

LVH as a Cause of CAD

LVH has been linked to a variety of negative cardiovascular outcomes including death, myocardial infarction, and heart failure, regardless of whether it is detected by an ECG or echocardiography. Although there has been much debate about why LVH is such an important risk factor , the basic mechanisms that predispose patients with LVH to develop atherosclerosis and consequent CAD are not well understood. Abnormalities in the coronary arteries, platelets, increased blood viscosity, and a prothrombotic condition have all been proposed as possible mechanisms. In addition to these variables, which may also lead to a reduction in myocardial oxygen delivery, individuals with LVH have a higher myocardial oxygen demand. Another basic explanation for the link between LVH and CAD is that LVH acts as a noninvasive sensor of the amount of atherosclerosis and CAD since it reflects target organ damage from concomitant risk factors like hypertension. This idea is supported by the fact that LVH is linked to atherosclerosis in other vascular regions, such as the carotid artery. Another developing theory is that LVH on its own acts as a low-level inflammatory condition, as evidenced by recent animal and human research. If this is the case, the proinflammatory state linked to LVH could raise the risk of atherosclerosis, CAD, and myocardial infarction**(15).**

Association of LVH and CAD

The Framingham study, which included 4976 participants, was one of the first to prove the association between LVH and CAD. It has demonstrated that in both sexes, a history of myocardial

infarction increases the chance of LVH by more than three fold, whereas angina pectoris without a history of myocardial infarction doubles the risk in males**(15).**

The LIFE study, which focused on left ventricle structural and functional abnormalities in a large group of hypertensive patients, found that patients with CAD exhibited higher LV cavity dimensions and mass than their control group. Although both groups presented with eccentric LV hypertrophy, patients with CAD had a more significant prevalence of eccentric hypertrophy than concentric hypertrophy or remodeling. Additionally, lower LV systolic function and greater myocardial afterload and peripheral resistance were found in the CAD group. As a result, patients with CAD exhibited reduced cardiac output and index values**(15).**

Another interesting finding of this study is that patients with symptomatic CAD had about 80% higher LV mass and 20% higher LV wall stress than healthy people. As a result, the estimated myocardial oxygen demand index in patients with CAD was 1.2 times higher than patients without CAD and 2.15 times higher than the average healthy population.

The large Dallas Heart Study established that concentric ventricular hypertrophy (LV wall thickness, concentricity, and indexed LV mass) was independently associated with coronary atherosclerosis measured by coronary artery calcium, which implies the presence of CAD. However, ventricular dilation was not associated with the coronary atherosclerotic burden. These links were especially strong among black patients. Moreover, the study demonstrates a correlation between concentric hypertrophy and higher c-reactive protein levels; however, this link appears to be mediated by LVH risk factors rather than the disease itself. As a result, the synergistic combination of increasing atherosclerotic burden in the presence of concomitant risk factors linked to a proinflammatory environment, patients with concentric LVH may be at greater risk for incident atherothrombotic events **(16)**.

Prognosis of patients with CAD and LVH

It was found that an increase of 20 units in LV mass increased the adjusted hazard ratio of death by 22% and hazard ratio of sudden or arrhythmic death by 40% .

Total mortality was also higher in patients with LVH. Furthermore, LVH in CAD patients had adverse outcomes even after PCI with drug-eluting stents. after accounting for LVH as an independent factor in STEMI, the all-cause mortality risk was found to be higher cardiac disease to sudden cardiac death or arrhythmia. LVH has also been associated with an increased risk of long-term cardiac death. and total mortality**(17).**

Management of LVH in patients with CAD

LVH in patients with CAD should be treated with a combination of lifestyle changes and active management of the comorbidities that cause it. In patients with hypertension, lifestyle measures such as weight loss and sodium restriction have been shown to diminish ECG LVH. Treatment of elevated blood pressure slows the progression of LVH. This can be achieved by using drugs that contain an angiotensin-converting enzyme inhibitor. Angiotensin-converting enzyme inhibitors were the most efficient antihypertensive agents in lowering LV mass. It is well established that angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel blockers reduced LV mass by reducing wall thickness, while diuretics reduced LV mass by reducing LV volume. However, LV mass was not reduced by alpha-adrenergic blockers or direct-acting vasodilators**(18**).

In normotensive patients with CAD, very few studies have looked into the management of LVH. It has been suggested that we will need to achieve lower than traditional blood pressure targets (e.g., a systolic blood pressure of 120 mm Hg) or even a personalized blood pressure target level that guarantees full LVH regression in that population. The E4 study examined the possibility of adding an aldosterone blocker (eplerenone, enalapril, and eplerenone/enalapril) . Lastly, trientine, which is a copper chelating agent, has been shown to reduce LVH in diabetic normotensive patients**(18**)

LVH Regression and cardiovascular system

clinical trials have demonstrated that LVH regression during antihypertensive treatment reduces cardiovascular morbidity and mortality. Thus, LVH regression is considered a therapeutic target and a reversible risk marker in hypertension. Some studies indicate that different classes of antihypertensive medication might differ in their ability to promote LVH regression. However, most interesting, a number of studies have demonstrated that LVH regression is not always achieved, even when blood pressure (BP) is optimally controlled, in particular, in women and obese subjects. Recently, results from the Strong Heart Study, a population-based cohort, including hypertensive patients with multiple cardiovascular risk factors and comorbidities, demonstrated an average increase in LV mass (LVM) during follow-up, even in the subpopulation with optimal BP control. These findings suggest that in the real world, there might be problems in achieving effective LVH regression, which are not explored in clinical trials that are conducted in selected hypertensive populations**. (19).**

References:

1. BORNSTEIN, A. B., RAO, S. S. & MARWAHA, K. 2020. Left ventricular hypertrophy.
2. YILDIZ, M., OKTAY, A. A., STEWART, M. H., MILANI, R. V., VENTURA, H. O. & LAVIE, C. J. 2020. Left ventricular hypertrophy and hypertension. *Progress in cardiovascular diseases,* 63**,** 10-21.
3. NWABUO, C. C. & VASAN, R. S. 2020. Pathophysiology of hypertensive heart disease: beyond left ventricular hypertrophy. *Current hypertension reports,* 22**,** 1-18.
4. SAHEERA, S. & KRISHNAMURTHY, P. 2020. Cardiovascular changes associated with hypertensive heart disease and aging. *Cell transplantation,* 29**,** 0963689720920830.
5. SINGH, A., MISHRA, R. & BILLEY, A. 2023. CARDIAC LESIONS IN SUDDEN DEATH: INSIGHTS FROM AUTOPSY AND HISTOPATHOLOGICAL ANALYSIS. *Int J Acad Med Pharm,* 5**,** 1567-1573.
6. YAKYMENKO, O., KOLOMIIETS, S., SMAL, V., SEBOV, D. & TBILIELI, V. 2022. Electrocardiography: a manual.
7. PEGUERO, J. G., LO PRESTI, S., PEREZ, J., ISSA, O., BRENES, J. C. & TOLENTINO, A. 2017. Electrocardiographic criteria for the diagnosis of left ventricular hypertrophy. *Journal of the American College of Cardiology,* 69**,** 1694-1703.
8. BAYRAM, N., AKOĞLU, H., SANRI, E., KARACABEY, S., EFEOĞLU, M., ONUR, O., DENIZBASI, A. & ONUR, Ö. E. 2021. Diagnostic Accuracy of the Electrocardiography Criteria for Left Ventricular Hypertrophy (Cornell Voltage Criteria, Sokolow-Lyon Index, Romhilt-Estes, and Peguero-Lo Presti Criteria) Compared to Transthoracic Echocardiography. *Cureus,* 13.
9. CUSPIDI, C., RESCALDANI, M., SALA, C. & GRASSI, G. 2014. Left-ventricular hypertrophy and obesity: a systematic review and meta-analysis of echocardiographic studies. *Journal of hypertension,* 32**,** 16-25.
10. BARBIERI, A., BURSI, F., MANTOVANI, F., VALENTI, C., QUAGLIA, M., BERTI, E., MARINO, M. & MODENA, M. G. 2012. Left ventricular hypertrophy reclassification and death: application of the Recommendation of the American Society of Echocardiography/European Association of Echocardiography. *European Heart Journal–Cardiovascular Imaging,* 13**,** 109-117.

11. GREBE, S. J., MALZAHN, U., DONHAUSER, J., LIU, D., WANNER, C., KRANE, V. & HAMMER, F. 2020. Quantification of left ventricular mass by echocardiography compared to cardiac magnet resonance imaging in hemodialysis patients. *Cardiovascular Ultrasound,* 18**,** 1-9.
12. HAYCROFT, B., STEVENSON, A., STORK, R., GAFFNEY, S., MORGAN, P., PATTERSON, K. & JOVANOVIC, A. 2023. Targeted literature review exploring the predictive value of estimated glomerular filtration rate and left ventricular mass index as indicators of clinical events in Fabry disease. *Orphanet Journal of Rare Diseases,* 18**,** 322.
13. Barbieri, A., Albini, A., Maisano, A., De Mitri, G., Camaioni, G., Bonini, N., ... & Boriani, G. (2021). Clinical value of complex echocardiographic left ventricular hypertrophy classification based on concentricity, mass, and volume quantification. *Frontiers in Cardiovascular Medicine*, *8*, 667984.
14. GRAJEWSKI, K. G., STOJANOVSKA, J., IBRAHIM, E.-S. H., SAYYOUH, M. & ATTILI, A. 2020. Left Ventricular Hypertrophy: Evaluation With Cardiac MRI. *Current Problems in Diagnostic Radiology,* 49**,** 460-475.
15. KHALID, K., PADDA, J., ISMAIL, D., ABDULLAH, M., GUPTA, D., PRADEEP, R., HAMEED, W., COOPER, A. C. & JEAN-CHARLES, G. 2021. Correlation of coronary artery disease and left ventricular hypertrophy. *Cureus,* 13.
16. HUANG, B.-T., LU, Y., BO-SEN, Y., HUANG, F.-Y., QIAN-FENG, X., XIAO-BO, P., YONG, P. & MAO, C. 2022. Relationship of body fat and left ventricular hypertrophy with the risk of all-cause death in patients with coronary artery disease. *Journal of Geriatric Cardiology: JGC,* 19**,** 218.
17. STEWART, M. H., LAVIE, C. J., SHAH, S., ENGLERT, J., GILLILAND, Y., QAMRUDDIN, S., DINSHAW, H., CASH, M., VENTURA, H. & MILANI, R. 2018. Prognostic implications of left ventricular hypertrophy. *Progress in cardiovascular diseases,* 61**,** 446-455.
18. REICHEK, N. 2018. LVH and CAD: New Steps Down an Old Path. American College of Cardiology Foundation Washington, DC.

19. KIM, H. M., HWANG, I.-C., CHOI, H.-M., YOON, Y. E. & CHO, G.-Y. 2022. Prognostic implication of left ventricular hypertrophy regression after antihypertensive therapy in patients with hypertension. Frontiers in Cardiovascular Medicine, 9, 1082008.