SPECIAL SITUATIONS

Assessment of End Organ Damage in Hypertension—Left Ventricular Hypertrophy

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ABSTRACT

Left ventricular Hypertrophy (LVH) is an important consequence of systemic hypertension and is considered as target organ damage. LVH has significant impact on the prognosis and regression of LVH correlates with better outcomes in hypertensive individuals. Electrocardiography (ECG) remains the basic tool to diagnose LVH in hypertension although it has significant limitations in terms of sensitivity and specificity. Echocardiography not only provides a better estimate of LVH but also allows better quantification of left ventricular mass and volumes, while providing clues for other causes of LVH. Cardiac magnetic resonance Imaging (CMR) is considered the gold standard for estimation and characterization of LVH, but is limited due to its availability and cost. Computed Tomography of heart also offers reliable estimate of LVH at the cost of high radiation exposure and is not recommended for this purpose. Assessment of LVH should be done using ECG in every patient with hypertension while echocardiography and CMR should be reserved for specific indications

Keywords: Electrocardiography, Hypertension, Left ventricular hypertrophy.

INTRODUCTION

Hypertension is an important health challenge, which is the principal cause of death and disability. A systematic analysis which included 135 population-based studies of more than 9 lakh adults from 90 countries observed that prevalence of hypertension decreased by 2.6% in high-income group countries during 2000 to 2010, whereas it increased by 7.7% in the low- and middle-income countries.[1] This is because of improvements in public health interventions in high-income countries. India belongs to low- to middle-income group countries and shows high prevalence of hypertension, which is steadily increasing.

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The age for standardized prevalence of hypertension is 26.6% for men and 24.7% for women.[2] Overall burden of hypertension in India is estimated to be approximately 118.2 million.[3]

HYPERTENSIVE HEART DISEASE

Hypertension has a detrimental effect on almost all organs of the body, and its effect on the heart is called as hypertensive heart disease or hypertensive cardiopathy. Hypertension leads to the remodeling of the myocardium in response to chronically elevated blood pressure and wall stress.[4]

Hypertension leads to changes in both structure and function of the heart (Flow Chart 1).[5] Hypertensive heart disease has several recognizable stages, such as LVH and systolic and diastolic dysfunction, which progress to clinical heart failure and ischemic heart disease.[6] The LVH typically has the distinct importance due to being associated with a 3- to 15-fold increase in cardiovascular events.[7]

Hypertensive heart disease is asymptomatic in its initial stages. In its advanced stage, it can manifest as angina pectoris, dyspnea, and arrhythmias as a result of reduced coronary reserve, impaired systolic and diastolic function, and atrial and ventricular arrhythmias.[7] It further leads to inappropriate activation of the renin–angiotensin–aldosterone system, which has been identified as a key pathologic pathway contributing to fibrosis, cardiomyocyte abnormalities, inflammation, and endothelial dysfunction.[8]

The LVH is defined as increased indexed LV mass and classified as concentric or eccentric based on the ratio of LV wall thickness to chamber dimension. The LVH is concentric if the ratio is increased, else it is eccentric (Fig. 1).[9] It takes months to years in order to develop LVH, and likewise regression is also a slow process.

Common tools to detect cardiac sequel of hypertension, most importantly LVH, include ECG and echocardiography, computed tomography (CT) scan, and CMR imaging. The CMR is considered to be the gold standard today, but is limited due to unavailability and cost.

ELECTROCARDIOGRAPHY

The ECG is an inexpensive, initial screening tool to assess target organ damage in a hypertensive patient. It can be

Flow Chart 1: Structural and functional changes in heart due to hypertension
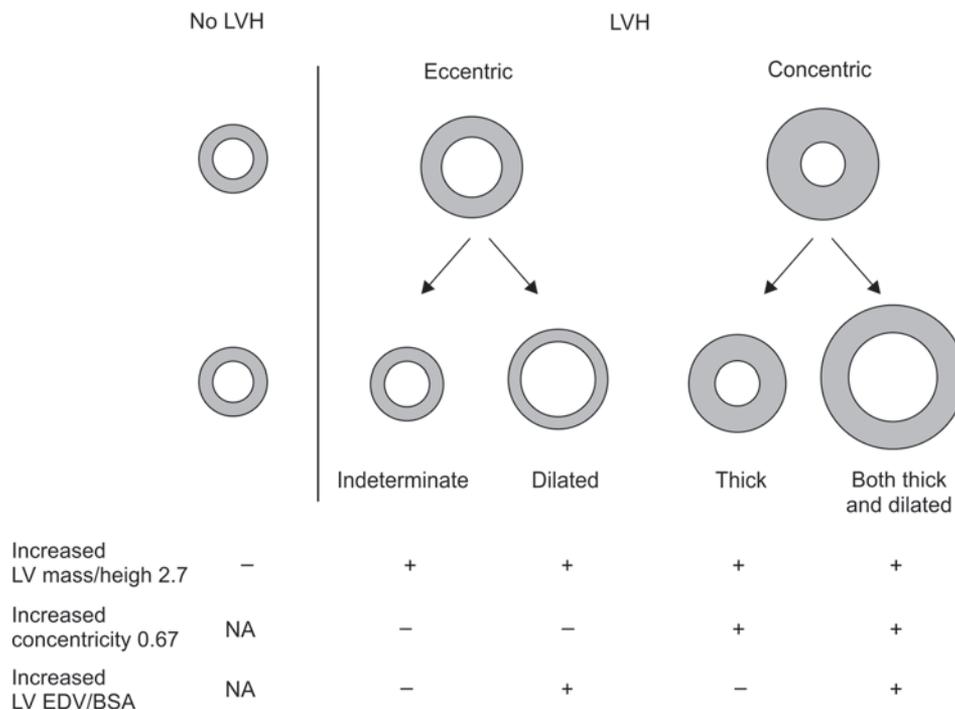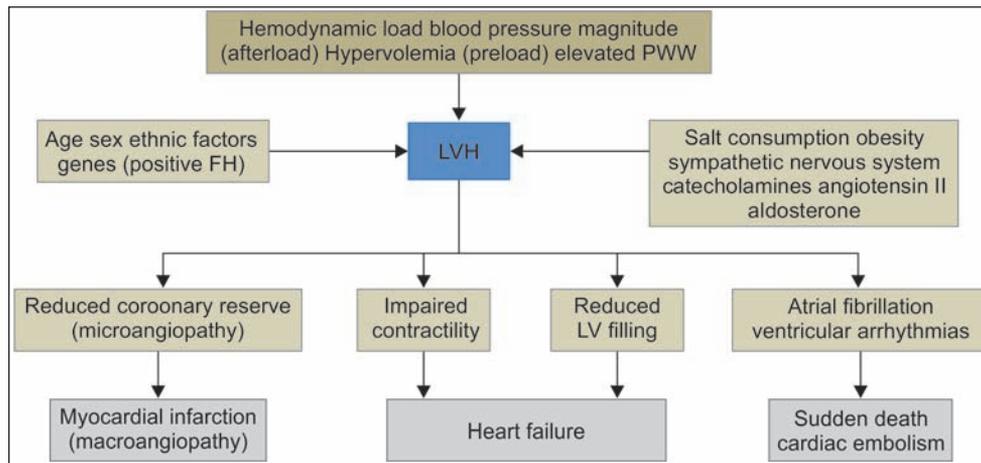(Adapted from: Schmieder[5])

Fig. 1: Types of LV hypertrophy (Adapted from: Khouri et al[9])

used to assess the presence of left atrial enlargement, LVH, myocardial ischemia or infarction, ventricular premature beats, and atrial fibrillation. The sensitivity and specificity of ECG vary widely depending upon the gold standard used [echo or magnetic resonance imaging (MRI) or necropsy] and severity of LVH. Overall, sensitivity of ECG in detecting moderate-to-severe LVH ranges from 30 to 60%, while specificity ranges from 80 to 90%. Despite its relative insensitivity, ECG does have prognostic significance. Hypertensive patients with ECG-documented LVH, who meet ECG criteria, have a greater LV mass than those who do not meet ECG criteria.[10] Associated abnormalities of ST-T changes signify high LV mass in patients with LVH.

LEFT VENTRICULAR HYPERTROPHY

The LVH produces five major changes in the ECG, which include increased QRS voltage, increased QRS duration, left axis deviation, repolarization (ST-T) changes, and left atrial enlargement.

Increased QRS Voltage and Duration

Increased LV mass augments amplitude of voltage generated, which is reflected on the surface ECG as positive forces on the left precordial leads (increased R waves) and negative forces on the right precordial leads (S waves). The R wave amplitude is also increased in leads I and aVL. Widening of QRS duration is also known to occur

with development of LVH, which may be subtle or pronounced. Widening of QRS eventually may result into complete left bundle branch block (LBBB) pattern on the ECG. However, LBBB may result from other pathological changes like calcification or fibrosis of the proximal conduction system. A number of criteria have been suggested for diagnosis of LVH.

Cornell Criteria

Add the R wave in aVL and the S wave in V3. If the sum is greater than 28 mm in males or greater than 20 mm in females, LVH is present.

Modified Cornell Criteria

Examine the R wave in aVL. If the R wave is greater than 12 mm in amplitude, LVH is present.

Sokolow–Lyon Criteria

Add the S wave in V1 plus the R wave in V5 or V6. If the sum is greater than 35 mm, LVH is present.

Romhilt-Estes LVH Point Score System

If the score equals 4, LVH is present with 30 to 54% sensitivity. If the score is greater than 5, LVH is present with 83 to 97% specificity.
- Amplitude of largest R or S in limb leads ≥ 20 mm = 3 points
- Amplitude of S in V1 or V2 ≥ 30 mm = 3 points
- Amplitude of R in V5 or V6 ≥ 30 mm = 3 points
- ST and T wave changes opposite QRS without digoxin = 3 points
- ST and T wave changes opposite QRS with digoxin = 1 point
- Left atrial enlargement = 3 points
- Left axis deviation = 2 points
- QRS duration ≥ 90 ms = 1 point
- Intrinsicoid deflection in V5 or V6 > 50 ms = 1 point

These scores are not full proof and there are fallacies associated with these scores. The QRS voltage increases with both thickening of the wall (pressure overload) and dilatation of the chamber (volume overload) of the left ventricle. There is significant day-to-day variability in QRS voltage due to lead placement, respiration, and body position. In addition, young black males may have increased voltage in the absence of hypertension.[11]

The LVH is also seen in aortic stenosis and aortic insufficiency, mitral valve insufficiency, some congenital cardiac defects, and hypertrophic obstructive cardiomyopathy in addition to hypertension. Classical ECG criteria for detection of LVH have a satisfactory specificity, but low sensitivity. The sensitivity declines dramatically in the presence of obesity. The most sensitive, but least specific criteria are high voltages in the precordial leads.[11]

Repolarization Abnormalities

Severe pressure overload is often associated with ST depression and T wave inversion in the leads with relatively tall R waves. This pattern may be a result of primary alteration in the repolarization of the hypertrophied muscle or due to relative subendocardial ischemia.[12]

The "strain pattern" is characterized by ST depression ≥1 mm in lateral leads I, aVL, and V4 to V6 (most commonly just V5 or V6 is used). The direction of the T wave is in the opposite of the direction of the upright QRS complex (Fig. 2). Furthermore, the T wave is asymmetric with a gradual down slope (upward convex) followed by a rapid up slope and a terminal positive overshoot. The presence of a "strain pattern" implies a poor prognosis. Increased LVM and coronary artery disease are associated with the strain pattern.

The ECG LVH with "strain pattern" is the most lethal classic Framingham cardiovascular risk factor (Graph 1).

Fragmented QRS on ECG

Fragmented QRS complexes (fQRS) on surface ECG are defined as an rSR' pattern in the absence of typical bundle branch block. Morphologically, it represents an altered QRS complex that has a duration <120 ms and has either an additional R wave, notching in the nadir of the S wave, or an additional R' wave.[13] In one study, 24-hour ambulatory blood pressure monitoring and ECG screening were done in 548 "healthy" persons without cardiac hypertrophy. It was observed that fQRS pattern was significantly higher in patients with hypertension and prehypertension as against those with normal blood pressure. The fQRS on a 12-lead ECG has been demonstrated as a marker of myocardial fibrosis. The fQRS
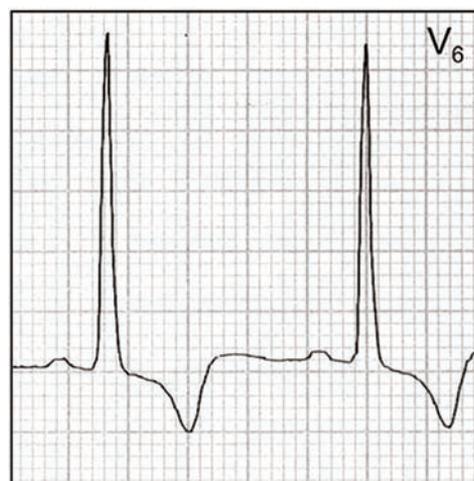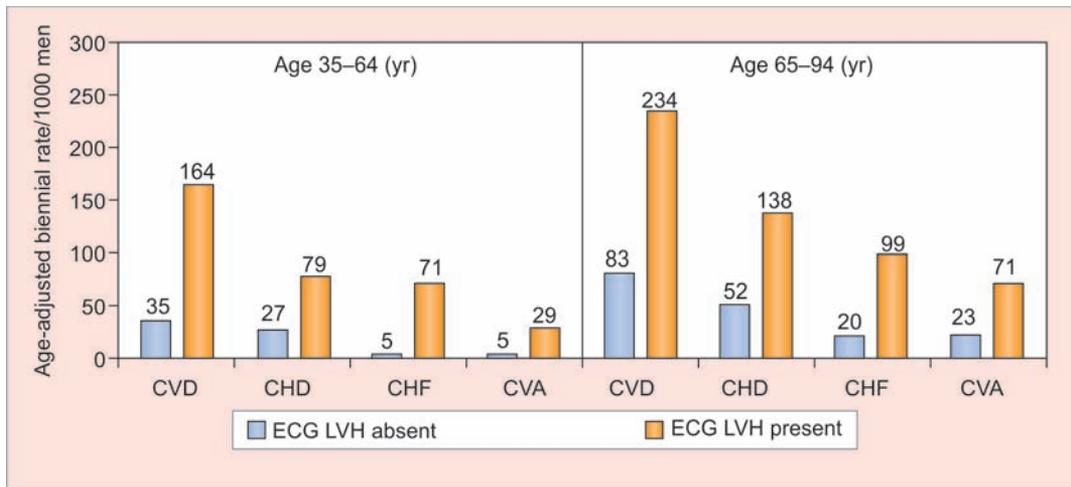

Fig. 2: The LVH with strain pattern (Adapted from: Cífková[11])

Graph 1: The LVH and Framingham cardiovascular risk (Adapted from: Cífková[11])
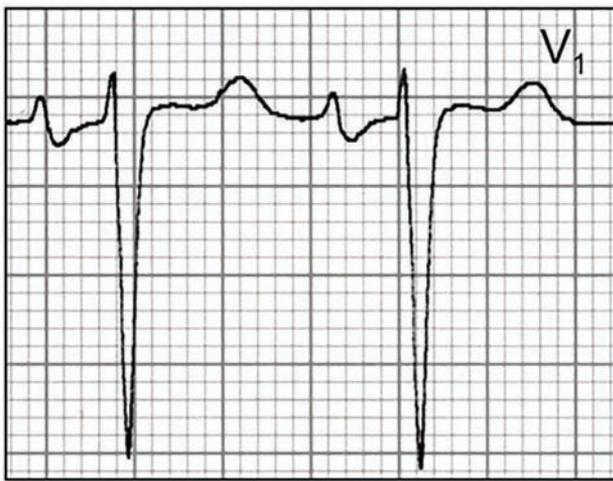

Fig. 3: The LA enlargement on ECG (Adapted from: Cífková[11])

has been shown to be an independent predictor of new onset atrial fibrillation in postoperative period in patients undergoing coronary artery bypass graft.[14]

Left Atrial Enlargement

Left atrial enlargement is one of the early change seen in hypertensive heart disease. Surface ECG finding of increased duration of terminal portion of P wave and amplitude of P wave is one of the earliest finding of hypertensive heart disease. P wave duration more than 0.04 seconds and depth of more than 1 mm or their product > −0.04mm sec is indicative of left atrial enlargement[11] are indicative of left atrial enlargement (Fig. 3).

ECHOCARDIOGRAPHY

The LVH on echocardiography may be detected in 20 to 40% patients with arterial hypertension. Two-dimensional (2D) echocardiography allows more accurate and reproducible measurements of LV volumes and mass and is most commonly calculated using the Devereux equation.[15]

Echocardiography offers more reliable detection of LVH as compared with ECG in women,[16] in obese individuals[17] with body mass index > 30 kg/m^2, and in smokers.[18] The Devereux formula for calculating LV mass is

$$LV\ mass = 0.8 \times (1.04\ [(LVIDd + PWTd + SWTd)\ 3 - (LVIDd)\ 3]) + 0.6\ gm$$

where LVIDd is the LV internal diameter in diastole, PWTd is the posterior wall thickness in diastole, and SWTd is the septal wall thickness in diastole. This formula is applicable only to patients without major distortion of their LV geometry (e.g., LV aneurysm). For patients with an increased LV mass (LV mass > 125 gm/m^2 in men and > 110 gm/m^2 in women), calculation of relative wall thickness (RWT) using the equation ($2 \times$ PWTd/LVIDd) will aid in classification of concentric or eccentric LVH. Patients with an increased RWT (RWT ≥ 0.42) have concentric hypertrophy, whereas patients with a normal value (RWT ≤ 0.42) have eccentric hypertrophy. Patients with concentric remodeling are those with normal LV mass, but increased RWT. Echocardiography-derived LV mass and RWT measurements have been shown to carry prognostic significance in hypertensive patients, even those without LVH.[19]

Septal bulge (basal septal wall thickness ≥ 2 mm thicker than midseptal wall thickness) is an early echocardiographic sign in patients with hypertension. In a study, it was observed that when resting blood pressure (BP) was used to diagnose hypertension, septal bulge was a reasonable predictive sign with a sensitivity of 73% and specificity of 76%. However, when cycle ergometer test or ambulatory BP monitoring was used to diagnose hypertension, septal bulge strongly predicted arterial hypertension with sensitivity of 93% and specificity of 86%.[20]

The LVH is seen many other conditions apart from hypertension like hypertrophic cardiomyopathy (HCM).
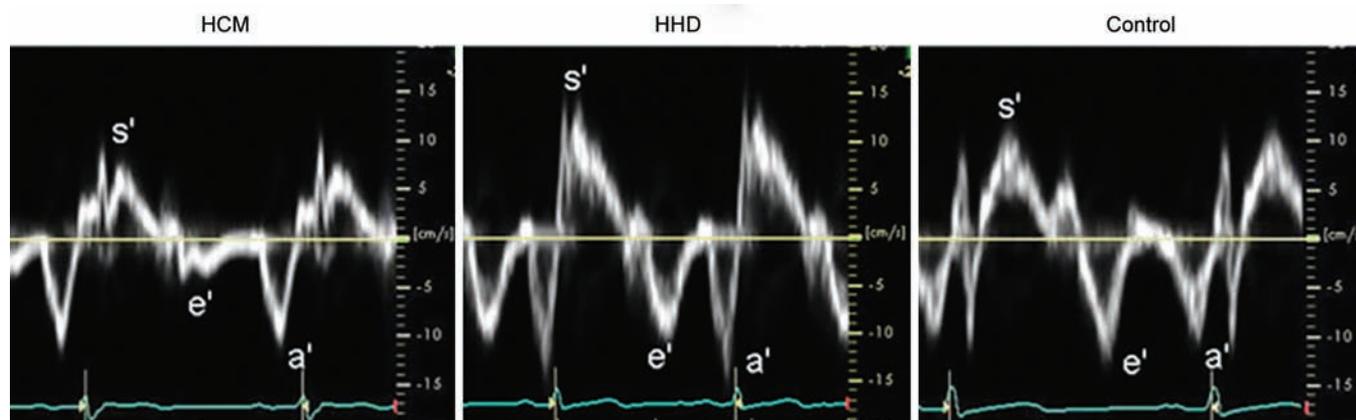
Fig. 4: Tricuspid annular velocity (Adapted from: Hayashi et al[21])

Echocardiography can differentiate the two conditions. Apart from other echocardiographic signs, RV wall thickness is greater in HCM than in hypertensive patients. Tricuspid annular motion velocity determined by pulsed tissue Doppler echocardiography can be used to detect right ventricular dysfunction in HCM. Early diastolic tricuspid annular motion velocity (TAM-e') was found to be significantly lower in HCM than those with hypertension (Fig. 4).[21]

Strain rate (SR) imaging derived from tissue Doppler imaging is able to discriminate HCM from hypertensive LVH. The septum/posterior wall thickness ratio and systolic strain (ε sys) are able to discriminate HCM from hypertensive LVH. An ε sys cutoff value of –10.6% discriminated between HCM and H-LVH with a sensitivity of 85.0%, specificity of 100.0%, and predictive accuracy of 91.2%. The combination of the septum/posterior wall thickness ratio and ε sys discriminates HCM from H-LVH with a predictive accuracy of 96.1%.[22] Strain rate imaging can also be used to distinguish between individuals with hypertensive LVH and those with strength-training athletic LVH. Hypertensive LVH has significant longitudinal strain, peak systolic strain rate [SR (S)], peak early diastolic strain rate [SR (E)], reductions *vs* control. The lack of these reductions in athletes suggests that SR imaging may have clinical use in discerning the physiologic LVH state.[23]

Implication of LVH on Echocardiography

Levy et al[24] studied the relation of LV mass to the incidence of cardiovascular disease, mortality from cardiovascular disease, and mortality from all causes in 3,220 subjects enrolled in the Framingham Heart Study, who were 40 years of age or older and free of clinically apparent cardiovascular disease, in whom LV mass was determined echocardiographically. During a 4-year follow-up period, there were 208 incident cardiovascular events, 37 deaths from cardiovascular disease, and 124 deaths from all causes. Left ventricular mass (corrected for height) was associated with death from all causes with a relative risk of 1.49 in men and 2.01 in women. Increase in LV mass was associated with all outcome events, and the relation was seen in LV mass not considered as "hypertrophic." Cardiovascular disease and death rates had a 1.5-fold increase for each 50 gm/m of LV mass indexed by height. Thus, it is hypothesized that LVH is an independent risk marker of long-term exposure to the combined effects of various risk factors for atherosclerosis, especially in context of cerebrovascular disease.[25] Further, regression of LVH has been shown to confer protection from cardiovascular disease.[26] In the Losartan Intervention for End-Point reduction (LIFE) study carried out in hypertensive patients with LVH, patients randomized to losartan showed greater regression of LVH and lesser risk of stroke.[27,28] A prespecified analysis of the LIFE trial participants for prognostic effects of serial changes in ECG and echocardiographic indices of LVH confirmed its independent value.[29,30]

Three-dimensional Echocardiography

Three-dimensional (3D) echocardiography has several advantages over M-mode and 2D methods, as it does not rely on geometric assumptions. It is highly reproducible for assessment of LV mass and volumes, but as with any echocardiography technique, it relies on adequate acoustic windows and an experienced practitioner.[31] The availability of 3D echocardiography is still limited to selected few centers and its use in hypertensive patients is limited.

Computed Tomography

The CT is used when a patient has contraindications for CMR, offering an excellent spatial resolution and unrestricted field of view. However, the relatively low temporal resolution and the radiation exposure (ranging from 5 to 20 mSv) make cardiac CT the least preferred technique among the three for LVH assessment.[32]

In a study, multidetector row computed tomography (MDCT) was compared with MRI in the assessment LV wall thickness. It was observed that in assessable segments by both modalities, a significant correlation between MDCT and MRI was found for end-diastolic wall thickness (EDWT) and end-systolic wall thickness (ESWT) and percent systolic wall thickening %SWT. However, mean EDWT and ESWT values by MDCT were slightly lower than those by cine MRI.[33]

Cardiac Magnetic Resonance Imaging

The MRI has emerged as a powerful imaging modality for assessment of hypertensive heart disease, as it is not restrained by acoustic windows, provides accurate and reproducible measures of LV function and mass, and enables myocardial fibrosis assessment.[34] It is also a reliable and reproducible measurement of cardiac parameters like volume, ejection fraction, and cardiac mass. It can also differentiate the etiology of LVH by providing information about tissue characterization.

Presently, the methodology of choice for measuring LVM by CMR is steady-state free precession (SSFP) cine imaging. The absolute values of LVM measured by CMR tend to be lower than those for echocardiography because SSFP cine imaging allows the visualization of myocardial trabeculae and thus, includes trabeculae in the LV volume measurement excluding it from the mass. Echocardiography, however, generally includes trabeculations in the measurement of LV mass. Although CMR has excellent reproducibility for measuring LVM and is widely perceived as the gold standard, its accuracy has not been validated against necropsy LV weight in humans.[35]

The MRI is useful in differentiating hypertrophy because of hypertension from other causes like HCM. When the EDWT is ≥ 15 mm, indexed LV mass was significantly greater in hypertensive patients as HCM. However, midwall late gadolinium enhancement and systolic anterior motion of mitral valve were present in HCM as compared with hypertensive patients.[36]

Hypertension leads to myocardium remodeling due to cardiomyocyte hypertrophy, fibroblast stimulation, and increased collagen stimulation, which leads to fibrosis. The MRI is useful to detect this fibrosis. In a study, it was observed that hypertensive patients with LVH exhibited greater diffuse fibrosis and reduced circumferential strain and circumferential SRs compared with hypertension without LVH and control subjects. Hypertensive patients with LVH had higher ECV (extracellular volume), and higher ADC (apparent diffusion coefficient). Based on these observations, it was suggested that ADC measurement may be a novel target to monitor hypertensive patients.[37]

Evaluation of LVH—How and When?

Although LVH is important end organ damage due to hypertension, and its regression is shown to improve outcomes, no current guidelines recommend monitoring of its progression/regression. Since most of the currently recommended first-line therapeutic agents for hypertension also reduce LVH significantly (except diuretics), the focus of the current guidelines is adequate control of BP rather than LVH regression. Serial ECG monitoring may help to demonstrate changes in the ECG voltage over time, which correlates with regression of LVH. However, loss of ECG voltage could be due to many other factors like alteration in the leads position, development of anasarca, pericardial or pleural effusion, weight gain, and increased severity of chronic obstructive pulmonary disease. Thus, the investigation to monitor LVH regression today is echocardiography rather than ECG.

Baseline evaluation of hypertensive patient includes biochemistry along with ECG for detection of any preexisting abnormality at the onset of the treatment. Follow-up ECG is indicated only when the clinical situation demands evaluation for additional supportive information regarding development of ischemic heart disease. Routine follow-up ECG monitoring is not indicated in uncomplicated hypertension. Echocardiography, on the contrary, is not indicated for measurement of LVH/mass routinely for hypertensive patients owing to its cost and availability. Indications for echo in hypertensive patient include:

- Patients with mild diastolic hypertension without any other risk factors or end organ damage (no LVH on ECG). Demonstration of LVH by echo is generally an indication for instituting medical therapy, while lack of LVH generally supports nonpharmacologic therapy.
- Patients with severely elevated blood pressure in the clinic (suspected white coat hypertension) without evidence of end organ damage. Absence of LVH on echo in these patients suggests either white coat hypertension or hypertension of recent onset. Ambulatory blood pressure monitoring would be the most important in this situation.
- Patients with suspected or documented heart disease, which needs further evaluation.
- Patients with bundle branch blocks.

Since the indications of echocardiography for detection of LVH are very few and limited even at baseline, routine follow-up echo for monitoring LVH regression is not recommended. A significant change in the clinical scenario should, however, prompt repeat echo evaluation.

SUMMARY

The LVH is an important target organ damage in hypertension and correlates with increased risk of morbidity

and mortality. The ECG and echocardiography are the two common tools to detect LVH in clinical practice, which are widely available to most of the clinicians today. Although MRI is the gold standard to evaluate LVH, its use is restricted to research settings. Documentation of LVH regression although satisfying has no bearing on the treatment of hypertension and, thus, routine follow-up ECG/ECHO for LVH monitoring are not currently recommended. Documenting good BP control using either clinic or home BP monitoring or ambulatory BP monitoring is the more important part of follow-up of hypertensive patients than monitoring LVH, as adequate control of hypertension is the key to improve long-term outcomes.

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