Left Ventricular Hypertrophy in Mild Essential Hypertension
Its Progression, Prediction and Treatment Strategy

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SUMMARY
Since the pathogenesis of left ventricular hypertrophy (LVH) in hypertension is thought to be multifactorial, the antihypertensive strategy also has to be multifaceted. Diagnosis of LVH is more reliable than ever with echocardiography either of the M-mode or 2D method. Diagnostic criteria have already been proposed by Ganau et al who classified LV morphology into 4 different sectors based on the standard values of left ventricular mass index (LVMI) and relative wall thickness in diastole (RWTd): normal, concentric remodeling, concentric hypertrophy and eccentric hypertrophy. The concentric hypertrophy pattern is the most risky with regard to prognosis. Therefore, its detection and prediction for further progression have to be conducted with relatively easy routine work-up procedures such as echocardiography and maximal exercise testing. The prediction of LVH progression has already been proposed based on several studies conducted in patients with borderline or mild hypertension. The following two predictors were defined as LVMI > 124 g/m² and peak Ps at maximal exercise testing > 200 mmHg. Therefore, the patient who meets these criteria has to be treated with medications that are appropriately selected on an individualized basis. Both hyperinsulinemia and insulin resistance are thought to be involved in the initiation, promotion and potentiation of remodeling of the LV in hypertension. Physical fitness also seems to be decreased in a parallel manner. Selection of the most appropriate drug for a given patient has to be individually determined based on the risks that have to be corrected. Finally, arteriosclerosis, which is almost always initiated and progresses in concert with hypertension, must also be targeted with regard to such prognostic aspects as cardiovascular morbidity and mortality. Arteriosclerosis is pathogenetically independent from hypertension, but usually behaves in concert with it. Selection of medication must be focussed on an individualized basis not only for LVH, but also for improvement in arterial elasticity. Further
clinical research is still needed to provide more reasonable approaches to patients with hypertension. (Jpn Heart J 1996; 37: 417-429)

**Key words:** Mild hypertension Left ventricular hypertrophy Hemodynamic mechanism Neurohumoral mechanism Concentric hypertrophy Eccentric hypertrophy Left ventricular mass index Relative wall thickness LVH progression Arteriosclerosis

In recent years mild hypertension has accounted for a large part of cardiovascular disease. It has also been one of the most important threats to good health, especially in the elderly. In the pathogenesis of essential hypertension both genetic and environmental factors affect the adaptation mechanisms not only of the cardiovascular regulatory system, but also of the intracellular mechanisms of the target tissue or organs, culminating in proliferative changes of arteriolar smooth muscle cells, cardiac myocytes and interstitial fibroblasts. These changes in target tissues or organs are thought to be an adaptation mechanism accounted for by shear stress, including increased pre-and afterloads and/or neurohumoral influences.

Several epidemiological studies have demonstrated that these changes clearly increase morbidity and mortality, not necessarily accompanied by premonitory symptoms or signs. The data of the prospective Framingham study established that left ventricular hypertrophy (LVH) and blood pressure are risk factors for cardiovascular events independent from each other. Still remaining to be demonstrated are the influences of electrical instability and reduced coronary reserve due to LVH and interstitial deposition of collagen materials on malignant arrhythmias, myocardial ischemia and/or congestive heart failure. Whatever the sequence of cardiovascular events, mild hypertension associated with LVH has to be treated with medical regimens that effectively regress LVH.

However, there are also several other questions that have to be answered; (1) what is the best way to detect LVH, (2) how can the progression of LVH be predicted, (3) how can we determine the appropriate time for medical intervention and (4) what kind of medication has to be chosen. To solve these problems, one has to know the precise natural progression of LVH in the unmedicated state. Also of clinical interest are arteriosclerosis that progresses in concert with hypertension, and what are the best procedures for its detection and evaluation.

These topics are of common interest among physicians who are engaged in daily clinical practice. This paper will review and offer a descriptive perspective on some basic concepts for understanding LVH in patients with borderline and mild hypertension.
MECHANISM OF THE DEVELOPMENT OF LVH

Page’s mosaic theory for the pathogenesis of essential hypertension seems also to be applicable to the developmental mechanism of LVH in mild hypertension. It can often be seen in daily clinical practice that some patients develop a rather rapid progression of LVH while others do not, even in very similar clinical situations with regard to demographic, anthropometric and other clinical profiles. These differences clearly indicate that multifactorial mechanisms are involved in the development of LVH in a fairly complex manner. Traditionally, the following mechanisms have been postulated; (1) hemodynamic factors including pressure and volume overloads and (2) nonhemodynamic factors. The latter seem to have been more intensely and widely examined in its various facets particularly regarding such coexisting pathologies as arteriosclerosis, hyperlipidemia and diabetes mellitus; demographic profiles such as age and gender; celluoproliferative neurohormonal factors and growth factors, and antihypertensive medication itself.

Hemodynamic mechanisms

Transformation of mechanical stimuli

When cardiomyocytes deform in shape, a diffuse intracellular cascade is activated to elicit signals which accelerate or promote synthesis and degradation of RNA and protein. There are mechanotransducers in the cellular membrane responsible for activation of \( Na^+ \) and \( Ca^{2+} \) channels, the precise roles of which in the developmental processes of LVH have not been established. Other signal transducing mechanisms that respond to mechanical stimuli are involved in accelerating protein synthesis. \(^9\) Shear stress induced activation of phospholipase C provokes (1) adenylyl cyclase activity in an increased intracellular concentration of cyclic AMP and (2) increased protein kinase C. In summary, shear stress to cardiac myocytes augments their contractile force due to the Frank-Starling mechanism and culminates in increased protooncogene c-fos that promotes DNA related protein synthesis and develops hypertrophy of myocytes.

Autocrine and paracrine mechanisms

Shear stress also induces other protooncogenes, including TGF-beta 1, PDGF, bFGF, aFGF, and IGF-I that evoke the development of gene expression of contractile protein in the fetus. \(^10\) These growth factors have also shown a wide range of regulatory activity producing ANP and suppressing the \( Ca^{2+}\)-ATPase related gene in the sarcoplasmic reticulum. More importantly, GFs such as TGF-beta 1, PDGF and IGF-I also stimulate fibroblast-related collagen synthesis. Locally produced angiotensin II resulting from shear stress again plays some role and participates in the development of myocyte hypertrophy. \(^11\) In addition, in
vitro studies of hypertrophy of human myocytes have revealed myotropine that could increase protein synthesis and mRNA levels of such protooncogenes as c-myc, c-fos and c-jun. Those may play some genetic role in cellular growth processes.

**Other modulatory and environmental factors**

Development of myocyte hypertrophy has long been attributed to genetic factors, the precise mechanisms of which have gradually been revealed. Among them deletion-insertion polymorphism corresponding to the ACE related gene code intron 16 has been reported, and the ACE-DD genotype has been thought to be a particularly strong risk factor for LVH development. Na+ itself has also been reported as an independent factor producing myocyte hypertrophy, although its precise mechanism has not been clearly elucidated.

**Nonhemodynamic mechanisms**

Since blood pressure level and LVH have often been dissociated in daily clinical practice, nonhemodynamic mechanisms have been strongly implicated in the development of LVH.

**Norepinephrine**

Increases in gene expression of such protooncogene as c-myc and beta MHC, or alpha-actin genetic type of skeletal muscle are mediated through the alpha adrenergic nervous system. Although the precise mechanism of intracellular transmission cascade still remains to be revealed, inositol triphosphate and diacylglycerol might increase intracellular calcium concentration culminating in activation of protein kinase C. On the other hand, the membrane receptors of myocytes have strong connections to beta-adrenergic stimuli that increase cyclic AMP, predicting the development of myocytic hypertrophy in which protein kinase A may play an important role.

**Angiotensin II (AGT-II)**

It has already been demonstrated that AGT-II directly stimulates myocytic proliferation. The effects on protein synthesis and fibroblastic collagen production are promoted in a dose-dependent manner through the AT1 receptor. Increased AGT-II due to stimulation of phospholipase-C and protein kinase C might play important roles in the development of such genetic expression induced by AGT-II as nuclear protooncogenes including c-fos, c-mic, Erg-1 and especially c-jun.

On the other hand, it is well known that AGT-II suppresses the activity of collagenase, an enzyme responsible for collagen degeneration. It is also known that this suppression of AGT-II induced collagenase activity could be completely eliminated by AT2 receptor antagonists.
**Aldosterone and other hormones**

It is well known that aldosterone is related to interstitial fibrosis of the myocardium with regard to excess sodium intake. Aldosterone directly affects cardiac fibroblasts through its connection with corticoid type I receptors and the effect is inhibited by spironolactone. It has been postulated that myocardial fibrosis induced by excess aldosterone might be related to Na⁺ overload in myofibroblasts.

Various other hormones, including thyroid hormone, insulin, endothelin (ET), growth hormone and sex hormones have also been shown to be related to the development of LVH. ET has been suggested to play a role in the regulation of production and the degeneration of fibroblastic collagen in the myocardium. It has been postulated that ET-1 and ET-3 promote type I and type III collagen synthesis in cultured rat myocytes.

**Clinical Aspects of LVH**

**Diagnosis of LVH**

**Standardization of LVH diagnosis**

Until the recent introduction of echocardiography into daily clinical practice, the diagnosis of LVH had long been performed with a standard 12 lead ECG. Despite its relatively high specificity, the sensitivity of ECG diagnosis for LVH is too low to be accepted for routine clinical use. Now, both M-mode and 2D echocardiography have been widely used as reliable tools for morphological determination of the heart. The former is classified into two different methods; the standard and Penn Convention methods. In the Penn Convention method the endocardial echogram is not included in the measurement of the internal diameter of the left ventricle. Therefore, values underestimate the LV dimension compared to the standard method. It has also been noted that the M-mode method results in higher values than 2D echocardiography. However, dimensional values obtained by both methods are sufficiently correlated with those of autopsied hearts and mutual correlation between the two methods is also reasonable. When the shape of the left ventricle is largely deformed, 2D echocardiography is thought to be superior and more stable than the M-mode method. Either method, however, could be applied in sequential comparisons of the LV morphology, if both reproducibility and reliability are assured within reasonable limits.

**Problems in ECG diagnosis of LVH**

Although ECG diagnosis of LVH is still a useful tool for epidemiological study because of its relatively high specificity, its usefulness in clinical practice is greatly limited because of its low sensitivity. Prospective studies performed over
3 years on unmedicated patients with borderline and mild hypertension disclosed progression of LVH characterized by increased LVMI and/or RWTd without significant changes in blood pressure levels both at rest and peak systolic pressure during maximal exercise testings. On the other hand, QRS voltages during this period were characterized by a significant decrease, especially in subjects who developed concentric hypertrophy. In addition ECG voltage determined by several voltage dependent diagnostic criteria did not correlate well with changes in LVMI during 5 years of observation. Therefore, these findings indicate that conventional ECG voltage criteria are entirely inappropriate for the diagnosis of LVH or for the assessment of its progression in patients with borderline and mild hypertension.

**Morphology of LVH and its progression**

Ganau et al (1992) proposed 4 morphological patterns of LVH in hypertensive subjects based on two parameters represented by LVMI and RWTd; normal (NL 52%), concentric remodeling (CR 13%), concentric hypertrophy (CH 8%) and eccentric hypertrophy (EH 27%). Each pattern is hemodynamically and morphologically characterized as follows: CH revealed the largest total peripheral resistance (TPR) with a spherical LV; EH the largest cardiac index (CI) with an ellipsoid LV; and CR revealed slightly reduced CI, that is, within the lower normal limit. Thus, LV morphology in borderline or mild hypertension is clearly related to the state of hemodynamic loads, either volume and/or pressure load.

Our data on 69 unmedicated patients with borderline or mild hypertension who were observed over 5 years disclosed the following findings. At the initial observation, the distribution of each LV pattern was almost identical to that reported by Ganau et al as seen in the following: NL 53%, CR 12%, CH 11% and EH 23%. After 5 years, there were significant increases in LVMI and RWTd as a whole, even with no significant increases in systolic and diastolic pressures. Morphologically, NL remained within the normal dimension, most of the CR moved to the CH dimension, CH revealed an augmented CH pattern and EH remained the same EH dimension with a significant increase in RWTd tending toward the CH pattern. Hemodynamically CH revealed significant increases in systolic and diastolic pressures (Ps & Pd) associated with significant increases in TPR and decreases in CI.

**Prediction of LVH progression**

Since LVH in hypertension is one of the most important risk factors for cardiovascular events, it is imperative to predict accurately the progression of LVH at the initial evaluation of hypertensive patients. Our data collected from 155 unmedicated males with borderline and mild hypertension demonstrated that there is a significant correlation between LVMI and peak systolic pressure
during symptom limited maximal exercise testing \((r = 0.57, p < 0.0001)\), and between LVMI and systolic pressure after a 20 minute rest \((r = 0.48, p < 0.0001)\).\(^{25}\) Observation after 5 years without medication also demonstrated that the most reliable predictive factors for the progression of LVH were initial LVMI and peak systolic pressure at the initial maximal exercise testing. We have presently been using the following criteria as tentative predictors of its progression; LVMI > 124g/m\(^2\) and peak systolic pressure at maximal exercise testing > 200 mmHg. Thus, those patients satisfying these criteria have to be treated with the most appropriate medication and followed up under careful observation with echocardiography.

**Other factors responsible for LVH**

Other factors related to the pathogenesis and severity of hypertension were micro albuminuria, hyperinsulinemia and exercise tolerance. Our observation of 55 borderline and mild hypertensive patients without overt diabetes mellitus, obesity or renal dysfunction demonstrated that all values including plasma norepinephrine and epinephrine, ANP, daily urinary C-peptide excretion, and daily urinary microalbumin were within the normal ranges. Significant correlations to LVMI, however, were noted with both daily urinary C-peptide \((r = 0.35, p < 0.01)\) and microalbumin \((r = 0.33, p < 0.02)\) (Figure 1). Multiple logistic regression analyses revealed that both peak Ps at maximal exercise testing (RxR:47.5\%) and daily urinary C-peptide excretion (RxR:15.3\%) strongly contributed to the LVMI phenotype. On the other hand, only daily urinary C-peptide excretion (RxR:3.45) contributed significantly to daily urinary

![Figure 1](image-url)  
*Figure 1.* Correlations between LVMI (g/m\(^2\)) and urinary C-peptide (microgr/day), and maximal systolic pressure (mmHg) at the peak exercise stage.
It has long been known that dynamic exercise alters insulin sensitivity, resulting in improvement of glucose metabolism. On the other hand, hyperinsulinemia is thought to play some role in the pathogenesis of hypertension with regard to hypertrophy of smooth muscle cells and intraluminal diminution of arterioles. In addition, hyperinsulinemia also might act as a promotor for myocardial cellular growth and have some role in the pathogenesis of LVH. Our study conducted with 156 unmedicated male patients with borderline and mild hypertension clearly revealed a weak, but significant negative correlation between RWTd and normalized treadmill time (TMTn) \( r = -0.38, p < 0.01 \) (Figure 2). Normalized treadmill time is thought to be a useful indicator in the evaluation of physical fitness or exercise tolerance. After 5 years of observation, 27 patients who developed overt LVH out of 64 unmedicated patients revealed a clear decrease in physical fitness associated with increased casual Ps and Pd, increased TPR and decreased CI. Multiple logistic regression analysis also identified casual blood pressure and RWTd as explanatory variables of TMTn.

Therefore, we can safely conclude that the borderline and mild hypertensive patients without medication who showed remarkable progression in LVH within 5 years were characterized by increased casual blood pressure and TPR, and decreased CI along with an obvious decrease in physical fitness. Hyperinsulinemia and/or insulin resistance might be common denominators.
among these phenomena, and LVMI > 124 g/m² and peak Ps of more than 200 mmHg during maximal exercise stress testing were identified as predictors of progression of LVH.

It is still unclear whether the mechanism for decreased physical fitness is dependent on central and/or peripheral effects. In patients with the CH type of LVH, blood flow through skeletal muscle may not increase in conjunction with increased metabolic demand. In addition, the skeletal muscle type might be changed: fast twitch type II muscle fibers may be decreased. Moreover, the numbers of capillaries per muscle fiber may not increase and capillary rarefaction might occur in the insulin resistant situation. The mechanisms still remain to be clarified.

**The regression of LVH**

*Can the concentric nature of LVH be naturally regressed?*

As mentioned above, untreated borderline and mild hypertension as a whole reveal progression of LVH within several years. There are, however, some subjects who do not show any progression or even show evidence of regression of LVH. Of 155 male patients with borderline and mild hypertension, 56 subjects (average age: 44 ± 5 years) who completed the second check-up after 3.7 years were selected for the study. Subjects were divided into three groups based on changes in RWTd; progressive (delta RWTd > 0.1), less progressive (0.1 > delta RWTd > 0) and regressive (delta RWTd < 0). Comparisons with BP levels at rest, BP at maximal exercise testing, and echocardiographic parameters were made among 14 subjects with progression (Group A) and 13 subjects with regression (Group B). While no significant differences were noted on entry between the two groups with regard to resting BP, CI, EF, mVcf, TPRI, LVDd or WTd, significant differences were noted in maximal exertional Ps, IVSTd and several echocardiographic parameters indicating diastolic functions. After 3.7 years, increased RWTd in Group A was associated with significant increases in IVSTd, PWTd and TPRI, and decreases in LVDd and LVDs without significant changes in blood pressure levels. On the other hand, decreased RWTd in Group B was characterized not by blood pressure levels, but by increased LVDd, and decreased IVSTd and TPRI. LVMI increased in the former and does not change in the latter. Therefore, it can be stated that about 1/4 of the borderline and mild hypertensive subjects revealed repression of the concentric nature of LV pattern without changes in blood pressure levels. LVMI, however, did not show a significant decrease in Group B, probably because of an age-dependent increase in LV volume.

**LVH regression due to medication**

Results of TOMHS have clearly demonstrated that any medication tested in the study significantly decreased the BP level more than life style modification
alone did.\textsuperscript{29} It is well known that changes in BP do not correlate with the amount of LVH regression. If the medication stimulates the sympathetic nervous system and results in activation of the renin-angiotensin-aldosterone axis, the regression of LVH that is expected as a result of decreased BP might be canceled out to some extent. Therefore, there is theoretical support in drug selection for those without inherent sympathetic stimulation. Actually, however, regression of LVH can be obtained with most antihypertensive drugs with minor exceptions, if a certain degree of BP decrease is reached.\textsuperscript{30}

Since the differences in effects observed among various antihypertensive drugs is subtle and the results of TOMHS have supported this position, different view points for the evaluation of treatment effects have to be sought. Our data on 67 patients with borderline and mild hypertension have demonstrated the difference in treatment effects with regard not only to regression of LVH, but also to physical fitness. Twenty five of 67 patients received medication after 4.5 years of unmedicated observation and another 42 cases were also followed up thereafter, without medication. Among the medicated group, 15 patients received a dihydropyridine calcium channel antagonist, and 10 received the beta-blocker acebutolol. These three groups were followed for 3.4 years, with the two groups with medication revealing an almost identical decrease in BP and regression of LVH. Only the unmedicated group did not show any changes in BP or LV morphology. There were, however, great differences observed among these three groups with regard to physical fitness. Physical fitness did not change in the unmedicated group, increased in subjects on calcium channel antagonists and decreased in subjects on beta-blockers. The precise mechanisms for these differ-
ences have not been elucidated. It is postulated that blood flow to skeletal muscle may be decreased in subjects receiving beta-blockers, while blood flow may be increased in subjects receiving calcium channel antagonists. Thus, it is safe to say that antihypertensive agents have to be given without causing hypoperfusion of vital tissues or organs.

**LVH and arteriosclerosis**

It has long been known that hypertension and arteriosclerosis are parallel phenomena which influence each other. At the very beginning of these two different pathologies, the major site for hypertension resides in the smooth muscle layer of the arterioles, while arteriosclerosis takes place in the arterial intima. Triggering factors, including both hemodynamic and nonhemodynamic ones, are shared by these two different phenomena. Therefore, these two pathologies develop and progress in parallel with each other, so treatment has to focus not only on hypertension, but also on arteriosclerosis.\(^{31}\)

The diastolic function of LV (A/E ratio) and vascular elasticity of the common carotid artery were assessed in 55 cases with normal BP. Based on the M-mode echocardiogram of the LV, the subjects were divided into two groups; 44 cases with normal LV morphology (RWTd < 0.4) and 11 cases with LV concentric remodeling (RWTd > 0.4). Comparisons between the two groups demonstrated that the latter had higher casual Ps, and a lower A/E ratio and lower carotid arterial elastance than the former. RWTd in the normotensive population as a whole revealed a weak, but significant (either positive or negative) correlation to A/E ratio or carotid arterial elastance (Figure 3). Therefore, subjects with a high normal range of BP, defined using the criteria proposed by JNC-V, may show the concentric remodeling pattern of LV associated with depressed diastolic LV function and arteriosclerosis.

Another study was performed on 52 patients under treatment with a dihydropyridine class calcium channel antagonist to evaluate the effectiveness of reducing LVH and improving carotid arterial elasticity. These subjects were divided into two groups; Group A with LVMI > 124 g/m² and Group B with LVMI < 124 g/m². There were no significant differences between the two groups with regard to age, casual BP, fractional shortening, and systolic and diastolic diameters of the carotid artery. Interestingly enough, A/E ratio and carotid wall thickness in Group A were significantly larger than those in Group B, while there was no significant difference noted in the elastance index between the two groups. Thus, treatment with calcium channel antagonists could not improve carotid arterial elasticity, even though it might maintain diastolic function within a reasonable range in patients without LVH. Other effective approaches for the treatment of arteriosclerosis have to be sought for patients with hypertension.\(^{31}\)
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