

Association between left ventricular hypertrophy with retinopathy and renal dysfunction in patients with essential hypertension

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ABSTRACT

Introduction: It has been suggested that hypertension (HTN) is associated with certain target organ damage (TOD) and related clinical conditions. On the other hand, left ventricular hypertrophy (LVH) has been considered as an independent risk factor of cardiovascular events and death. The aim of this study was to examine the relationship between HTN-induced LVH and TOD (retinopathy and renal failure).

Methods: We assessed 102 hypertensive subjects (43 males and 59 females) with a mean age of 60.2 \pm 8.8 (range 35–81) years. LVH was defined as a left ventricular mass index (LVMI) of more than 51 and 47 g/(m [to the power of 2.7]), in men and women, respectively. The degree of retinopathy on ophthalmological examination was defined according to the Keith-Wagener classification. Serum creatinine, blood urea nitrogen and urine protein concentrations were also measured.

Results: Hypertensive retinopathy was found in 94 (92.2 percent) cases (Grades I 55.9 percent; II 28.5 percent; III 3.9 percent; IV: 3.9 percent). The mean systolic and diastolic blood pressures and serum creatinine concentration showed significant correlation with the severity of LVH. There was no significant relationship between LVH severity and retinopathy or proteinuria.

Conclusion: The tight control of systolic and diastolic blood pressures in the first step of essential hypertension can assist to postpone LVH. Furthermore, routine measurement of serum creatinine can predict the risk of cardiovascular complications in the hypertensive patient.

Keywords: essential hypertension, left ventricular hypertrophy, renal dysfunction, retinopathy

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INTRODUCTION

Hypertension (HTN) is the most common cardiovascular disease.⁽¹⁾ The disease which was considered to be rare outside of Europe and America in the early 1900s, is now diagnosed in more than 25% of the population throughout the world.^(1,2) Although HTN is often asymptomatic, the disease is related to different types of target organ damage (TOD) and associated clinical conditions.⁽²⁾ Subtle TOD, such as left ventricular (LV) hypertrophy (LVH), retinopathy, microalbuminuria and cognitive dysfunction, occurs early in the course of hypertensive disease, while catastrophic events, such as stroke, heart attack, renal failure and dementia, are usually a result of a long period of uncontrolled HTN complications.^(3,4) On the other hand, echocardiographically-determined LV mass (LVM) indices, corrected for either body surface area or patients' height, are independent risk predictors of cardiovascular disease and chronic heart failure.⁽⁵⁻⁹⁾ Hence, these indices as well as other factors, such as the severity of retinopathy and renal dysfunction (all evidences of TOD), were confirmed to be major predictors of cardiovascular mortality and morbidity among hypertensive patients.⁽¹⁰⁻¹²⁾

In selected populations such as those with HTN, renal dysfunction was found to be related to LVH.⁽¹¹⁾ Some authors also claimed that LVH is an independent predictor for extracardiac TODs in essential HTN.⁽¹³⁾ In fact, some of the previous reports revealed that there is a significant association between different types of TOD in hypertensive populations.⁽¹⁴⁻¹⁶⁾ Unfortunately, discordant conclusions on this matter emphasise the need for further investigation on such relationships.^(17,18) Therefore, the aim of this study was to examine the relationship between LVH and other signs of TODs (retinopathy and renal failure) secondary to systemic HTN.

METHODS

The study was carried out from January to September 2006 in the heart clinic of our university hospital. 102 consecutive patients (mean age 60.2 \pm 8.8 years; range 35–81 years) with the diagnosis of HTN-induced LVH (based on electrocardiography [ECG] and echocardiography

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Table I. Prevalence of left ventricular hypertrophy on electrocardiography in different classes of left ventricular hypertrophy on echocardiography.

Severity of LVH on echocardiography	No. (%) of patients with LVH on ECG	No. (%) of patients without LVH on ECG	Total
Mild	12 (20.3)	47 (79.7)	59
Moderate	13 (36.1)	23 (63.9)	36
Severe	4 (57.1)	3 (42.9)	7
Total	29 (28.4)	73 (71.6)	102

LVH: left ventricular hypertrophy; ECG: electrocardiography

findings and ruling out other possible aetiologies of LVH) were evaluated. All the patients were newly diagnosed and untreated. Cases with the following conditions were excluded from the study: echocardiographic features or positive family history indicative of hypertrophic cardiomyopathy; and the presence of any other known disease, which was completely or partially responsible for renal dysfunction or retinal abnormality (such as diabetes mellitus and genetic or autoimmune diseases affecting retinal or renal integration).

The blood pressure (BP) was measured with an arm-cuff and a mercury sphygmomanometer after the patient had been resting in a sitting position for five minutes. Systolic and diastolic BP measurements were taken as the first and fifth phase of the Korotkoff sounds, respectively. HTN was defined as a systolic BP \geq 140 mmHg and/or diastolic BP \geq 90 mmHg on two measurements taken with a one-day interval.

M-mode, two-dimensional echocardiographic examinations were performed for all the subjects in the partial left decubitus position, using a Esaote Caris Plus machine (Caris Plus, Esaote SpA, Genoa, Italy) and a 2.5–3.5 MHz electrical transducer (Carius Plus, Esaote SpA, Genoa, Italy). End-diastolic left ventricular internal diameter (LVIDd), septal wall thickness (SWT) and posterior wall thickness (PWT) were calculated from the two-dimensionally-guided M-mode tracings and measured in five consecutive cardiac cycles, according to the Penn Convention.⁽¹⁹⁾

LVM was determined by Devereux's formula: $LVM = 1.04 \times \{[(LVIDd + PWT + SWT)^3 - LVIDd^3] - 13.6\}$. Subsequently LVM was divided by height^{2.7} in order to evaluate the LVM index (LVMI) in terms of $g/m^{2.7}$.⁽²⁰⁾ LVH was respectively defined as LVMI $>$ 51 $g/m^{2.7}$ in men and $>$ 47 $g/m^{2.7}$ in women.^(17,21) On the basis of the SWT, LVH was stratified into no LVH ($6 < SWT \leq 11$ mm), mild ($11 < SWT \leq 15$ mm), moderate ($15 < SWT \leq 18$ mm), and severe LVH ($SWT > 18$ mm).⁽²²⁾ For detecting LVH, two different ECG criteria were used: the Sokolow-Lyon voltage (sum of amplitude of S-wave in V1 and R-wave in V5 or V6 $>$ 35 mm) and LV strain pattern (ST-segment

depression or T-wave inversion in leads V5–V6).^(23,24)

All the patients, whose records were blinded, were referred to an ophthalmologist for the retinal examination. Based on the Keith-Wagener classification,⁽²⁵⁾ the retinopathy was categorised into four grades. Serum creatinine and blood urea nitrogen (BUN) were measured for all the patients, according to the routine laboratory policy. Data was expressed as means \pm standard deviation (SD). The analysis of variance test was used to assess the relationship between the different variables and the three groups of LVH severity. Statistical analysis was performed via the Statistical Package for Social Sciences version 11.5 (SPSS Inc, Chicago, IL, USA).

RESULTS

Out of 102 patients, 43 (42.2%) were male and 59 (57.8%) were female. Based on the LVH classification on echocardiographical evaluation, 59, 36 and seven patients had mild, moderate and severe LVH, respectively. Out of the 102 patients with LVH on echocardiography, only 29 (28.4%) showed characteristic features of LVH on ECG (Table I). The relationship between echocardiographically-diagnosed and ECG-detected LVH was statistically significant ($p < 0.01$). There were significant associations between the severity of LVH on echocardiography and the mean systolic and diastolic BPs (both p -values $<$ 0.01) (Table II). There was also a significant correlation between the severity of LVH and the patients' age (p -values $<$ 0.01) (Table III).

Only eight patients (7.8%) showed a normal retinal examination, while 55.9%, 28.4%, 3.9% and 3.9% of the patients respectively revealed Grades 1, 2, 3 and 4 retinopathy. As shown in Table IV, there was no statistically-significant relationship between the grade of LVH and the severity of retinal hypertensive disease ($p >$ 0.05). As shown in Table V, by increasing the LVH grading on echocardiography, the serum creatinine and BUN also increased, and this was statistically significant ($p = 0.001$). Although 23 patients showed elevated urine protein levels, there was no significant statistical relationship between the severity of LVH on

Table II. Association between systolic and diastolic blood pressures and severity of left ventricular hypertrophy on echocardiography.

Severity of LVH on echocardiography	No. of patients	Mean \pm SD systolic BP (mmHg)	Mean \pm SD diastolic BP (mmHg)
Mild	59	147.4 \pm 18.4	87.2 \pm 10.1
Moderate	36	159.3 \pm 23.8	90.5 \pm 11.8
Severe	7	157.1 \pm 25.0	88.5 \pm 10.7
Total	102	152.3 \pm 21.5	88.5 \pm 10.8

LVH: left ventricular hypertrophy; SD: standard deviation; BP: blood pressure

echocardiography and the severity of proteinuria ($p > 0.05$).

DISCUSSION

The present study showed a positive correlation between LVH and age. This important correlation can be due to a long duration of undiagnosed HTN (even though all the patients were newly diagnosed). This possible explanation of the study findings should be kept in mind in future investigations. LVH is one of the most serious complications of HTN, and it has been strongly associated with an increased incidence of heart failure, coronary artery disease, myocardial infarction, cardiac arrhythmias and sudden death.^(7,26) Based on these facts, its early detection is mandatory in order to obtain LVH regression, using certain adequate antihypertensive drugs.^(27,28)

Conventional ECG has been thought to be a less accurate method than echocardiography for detecting well-established LVH.⁽²⁹⁾ It is striking that even the more accurate method using echocardiography failed to detect 70%–80% of patients suffering from LVH in non-selected hypertensive patients and also in those with mild to moderate HTN.^(29,30) Hence, previous reports have emphasised that relying on ECG to diagnose LVH in hypertensive patients, with its satisfactory specificity but low sensitivity, is not logical.^(18,29,32) Based on our study findings (Table I), the more severe the LVH is on echocardiography, the more likely it would be diagnosed on ECG. Hence, ECG is not a reliable method for screening hypertensive patients for LVH, particularly in mild to moderate cases.

The existing correlation between the LVMI and systolic and diastolic BPs, as well as the mean arterial pressure, had been previously evaluated by other authors via 24-hour ambulatory BP monitoring (ABPM) or home BP monitoring, and compared with LVMI.^(14,33-42) These studies found a significant correlation of LVMI with systolic and diastolic BPs, and most of them concluded

Table III. Association between patients' age and severity of left ventricular hypertrophy on echocardiography.

Severity of LVH on echocardiography	No. of patients	Mean \pm SD age (year)
Mild	59	58.7 \pm 8.3
Moderate	36	61.1 \pm 9.2
Severe	7	67.0 \pm 8.2
Total	102	60.1 \pm 8.8

LVH: left ventricular hypertrophy; SD: standard deviation

that if the BP was well-controlled, a normal LVM would be expected. Their findings also seemed to suggest that the association of BP with LVM in hypertensive patients may partially explain the increased cardiovascular risk. However, in a few investigations, there was no significant correlation between the LVMI and diastolic BP, or even the systolic BP.⁽⁴²⁻⁴⁴⁾ Some investigators concluded that diastolic BP was not a reliable parameter in association to LVH,^(43,44) and others suggested that although the office or home BP did not have a remarkable correlation with the LVM, the 24-hour ambulatory BP had a stronger correlation to the LV structural indices.⁽⁴⁵⁾

On the other hand, some studies revealed a definite, although weak association between the 24-hour BP and LVM in hypertensive patients.^(17,46) These researchers were convinced that systolic BP, mean heart rate and standard deviation over 24 hours contributed to LVM in hypertensive subjects. Schillaci et al asserted that even in patients with well-controlled HTN, the LVM was greater than that of normotensive individuals who were matched by confounding factors (such as the patient's age, gender, obesity, and clinic and 24-hour BPs). This finding is compatible with the fact that during antihypertensive therapy, a reduction in the coronary heart disease risk is lower than expected, and that in treated patients with essential HTN, some factors (haemodynamic and/or non-haemodynamic) other than BP may affect the LVM.⁽⁴⁷⁾ The results from the current research were consistent with the majority of the previous studies that showed positive associations between the systolic and diastolic BPs and LVMI in hypertensive patients. Our investigation confirmed that the more severe and uncontrolled the BP, the more severe the LVH. Additionally, the older the patient, the more severe the LVH was on echocardiographical analysis.

In Palatini et al's study, 51% of hypertensive patients were affected by retinopathy,⁽¹⁷⁾ compared to 92.1% of patients in our study. This difference between the two studies was most likely because our subjects were those who had LVH. This evidence could be indirectly indicative of an increased prevalence of retinopathy in hypertensive

Table IV. Association between severity of retinopathy and left ventricular hypertrophy on echocardiography.

Severity of LVH on echocardiography	Retinal examination, no. (%) of patients					Total
	Normal	Grade 1	Grade 2	Grade 3	Grade 4	
Mild	6 (10.2)	36 (61.0)	13 (22.0)	1 (1.7)	3 (5.1)	59
Moderate	2 (5.6)	14 (38.9)	16 (44.4)	3 (8.3)	1 (2.8)	36
Severe	0 (0.0)	7 (100.)	0 (0.0)	0 (0.0)	0 (0.0)	7
Total	8 (7.8)	57 (55.9)	29 (28.4)	4 (3.9)	4 (3.9)	102

LVH: left ventricular hypertrophy

patients who suffer from LVH.⁽¹⁷⁾ In Dahlöf et al's study, a positive correlation between the vascular involvement of the retina in the untreated hypertensive patients and left ventricular wall thickness on echocardiography was reported.⁽⁴⁸⁾ This study was in contrast with the results of our study, which showed no significant relationship between LVH and retinopathy, although it did indicate that the retinopathy severity increases with increasing LVH grading. This difference between the two studies could be due to the study criteria of retinopathy used by Dahlöf et al, which were not based on the standard modified Keith-Wagener classification system, and their conclusion was based only on the presence or absence of any retinal abnormality regardless of its severity.⁽⁴⁸⁾

In Cuspidi et al's study in 2001 on 800 hypertensive patients, the prevalence of Grades 1 and 2 retinopathy among hypertensive patients was 46% and 32%, respectively, and only a few patients (< 2%) showed Grades 3 and 4 abnormalities.⁽¹⁶⁾ In our study, the prevalence of Grades 1 and 2 retinopathy was 55.9% and 28.4%, respectively, which approximately correlated with Cuspidi et al's report. However, in our study, the frequency of patients who had Grades 3 and 4 retinopathy was less than those with Grades 1 and 2, but it was still more than that in Cuspidi et al's study. This difference could be due to our LVH patient population which had more severe and prolonged HTN compared to Cuspidi et al's study population, and it is therefore logical to expect higher grades of retinopathic disorder to be more prevalent among our study population.

In 2002, Cuspidi et al again investigated the relationship between TOD and LV concentric remodelling. Two groups of never-treated essential hypertensive patients, 31 with normal LV geometry (Group I, relative wall thickness 0.39) and 31 with LV concentric remodelling (Group II, relative wall thickness 0.47), were included in the study. These groups were matched for age, gender, body mass index and mean 24-hour systolic BP. No significant difference was found between the two groups regarding the prevalence of retinal changes and microalbuminuria. The authors suggested that in hypertensive patients with similar BP and LVMI levels,

Table V. Blood urea nitrogen and serum creatinine in left ventricular hypertrophy on echocardiography of hypertensive patients.

LVH on echocardiography	No. of patients	Mean \pm SD BUN (mg/dL)	Mean \pm SD Cr (mg/dL)
Mild	59	18.7 \pm 7.2	0.9 \pm 0.2
Moderate	36	21.8 \pm 10.3	1.2 \pm 1.6
Severe	7	30.2 \pm 25.9	1.8 \pm 2.1
Total	102	20.6 \pm 10.8	1.1 \pm 1.1

BUN: blood urea nitrogen; Cr: serum creatinine; SD: standard deviation

the existing LV concentric remodelling did not affect the occurrence of TODs.⁽⁴⁹⁾ Our results were similar to those in this study. Although increasing the LVH grading led to increasing the severity of retinopathy and proteinuria, the association between LVH severity and these two forms of TOD was statistically not significant. The authors also asserted that 14.9% of their HTN patients showed a normal retinal pattern, while arteriolar narrowing and arteriovenous crossing were respectively observed in 42.4% and 42.7% of patients.⁽⁵⁰⁾ In another study by the same group, two independent ophthalmologists examined the same group of hypertensive patients with the following results: Examiner 1: normal 15.2%; Group I 25.4%; Group II 58.9%; Group III 0.5%; and Examiner 2: normal 14.7%; Group I 27.9%; Group II 56.8%; Group III 0.5%.⁽³⁾ The results of this study was approximately similar to their previous research conducted in 2001. In contrast, the prevalence of normal retina in our investigated population (7.8%) was less than that in the previous study, but the prevalence of Grade 1 and 2 retinopathies was relatively similar. This difference was again due to the difference in study criteria between the patient populations.

In accordance with our findings, Grosso et al also examined the relationship between retinal arteriolar narrowing and LVH in patients with HTN. The researchers found no significant correlation between the arteriole-to-venule ratios and LVM. However, they suggested that further clinical studies were required to clarify the correlation between early microvascular

changes and other clinical indicators of hypertensive organ damage.⁽¹⁾ Recently, Cuspidi et al described the prevalence of advanced retinal microvascular lesions. They also determined the associations of retinal microvascular lesions with cardiac and extracardiac signs of TOD in a large selected hypertensive population. In a multivariate logistic regression analysis, although advanced retinopathy was significantly associated with LVH (odds ratio 4.0), no correlation was detected between retinopathy and microalbuminuria. They concluded that retinal microvascular lesions and cardiac and macrovascular markers of TOD were strongly related to each other.⁽³⁾ Our study confirmed the results of this investigation.

Torun et al aimed to determine the frequency of TOD in never-treated, mild-to-moderate HTN. They also evaluated the beneficial properties of ABPM for detecting patients who were at high risk for TOD and cardiovascular disease in these groups. In this study, the frequency of the combination of TOD signs (microalbuminuria, LVH and hypertensive retinopathy) was higher in patients with HTN than in normal subjects (71.4% vs. 30%). They suggested that ABPM may provide useful clinical information to detect patients who are at high risk for cardiovascular diseases and TOD in newly-diagnosed, mild-to-moderate HTN.⁽¹⁵⁾ In our study, although proteinuria and retinopathy were not correlated exactly with the severity of HTN, the LVM and creatinine levels were significantly and positively associated with systolic and diastolic BPs. Ayodele et al confirmed these results in the same year and showed a positive association between systolic BP and TOD. They suggested that an early detection of patients with HTN and strict BP control should help in reducing TOD and other clinical complications in hypertensive patients.⁽²⁾

Leoncini et al investigated the relationship between creatinine clearance and subclinical organ damages in 957 patients who were afflicted with primary HTN and had never been previously treated. They found that the risk of acquiring LVH or retinal vascular changes increased significantly with each SD decrease in creatinine clearance, regardless of the traditional cardiovascular risk factors. They suggested that the routine evaluation of creatinine clearance might be helpful for identifying HTN patients with a higher cardiovascular risk.⁽⁵¹⁾ This corroborated with our current study, where there was a significant relationship between LVH grading and elevation creatinine. In 2005, Smilde et al studied the relationship between renal dysfunction and LVH in a cross-sectional study in 8,592 patients, and found a positive relationship between LVH and mild renal dysfunction.⁽⁵²⁾

Viazzi et al in 2005 showed that the relationship between urinary albumin excretion and cardiovascular risk was well below the threshold of 2.5 mg/mmol in women and 3.5 mg/mmol in men. Thus, using a value of 1.8 mg/mmol of albumin to creatinine ratio, they were able to identify a significantly greater percentage of TOD in patients with HTN. They asserted that albuminuria measurement was a suitable first step work-up in patients with HTN as well as a very cost-effective screening test.⁽⁵³⁾ In our study, although the protein excretion did not correlate with the severity of LVH (as TOD), the increase in serum creatinine was compatible with the LVH grading.

Hence, we conclude that firstly, a strong relationship exists between BP and LVH. Therefore, a tight control of systolic and diastolic BPs in the first step of essential HTN can assist to postpone LVH. Secondly, the classic ECG criteria for the detection of LVH is not a reliable method for screening hypertensive patients for LVH, particularly in mild to moderate degrees of the disease, due to its low sensitivity. Lastly, there is no significant correlation between retinopathy and LVH among essential hypertensive patients. However, the serum levels of BUN and creatinine show a significant association with LVH.

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